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- **When will the time come? The criteria for withdrawing treatment from terminally ill children – in the context of the recurring problem of "passive euthanasia"**
- **Interplay between EDA-EDAR and WNT signalling pathways in the development of skin appendages in hypohidrotic ectodermal dysplasia**

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Maria Boratyńska[1,2]

When is that moment? The criteria for withdrawing treatment from terminally ill children – in the context of the recurring problem of "passive euthanasia"

Kiedy jest ten moment? O kryteriach zaprzestania leczenia u terminalnie chorych dzieci – w kontekście powracającego problemu „eutanazji biernej"

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Abstract

Introduction and objective: The article aims to formulate criteria determining the right moment to discontinue life support to a terminally ill child at the end of life. The argument refers to two standards guiding critical decision-making: medical futility and the patient's best interests. When a child demonstrates discernment, account must also be taken of their reasoning. The deterioration of a child's health, which precedes the decision to stop further therapeutic efforts, is a clinical condition that immediately precedes torment that can only lead to death, or a situation of complete and definitive exclusion of positive perception and feeling. **Materials and methods:** The case review covers the specificity of birth in conditions of extreme prematurity, with lethal malformations and with neurodegenerative diseases. **Results:** This study shows that it is possible to draw a line between lawful consent to the death of a patient and unlawful passive euthanasia. **Conclusions:** The individual quality of life perceived by the child in question is crucial. In the final phase of terminal disease, there is no medical or moral reason for pain and suffering. Nor is there support for vital functions in a state of deep collapse caused by irreversible brain damage. The insistence of parents to continue such care is more a question of satisfying their own emotional needs and can be judged as a violation of the child's right to die in peace and dignity.

Keywords: child, terminal illness, passive euthanasia, best interests, futile treatment

Streszczenie

Wprowadzenie i cel: Artykuł ma na celu sformułowanie kryteriów ustalających właściwą chwilę, by zaprzestać czynności wspomagających życie dziecka nieuleczalnie chorego i u schyłku życia. Argumentacja odwołuje się do dwóch standardów kierujących podejmowaniem krytycznych decyzji – daremności terapeutycznej i najlepiej pojętego interesu pacjenta. Gdy dziecko wykazuje własne rozeznanie, uwzględnienia wymagają ponadto podawane przez nie własne racje. Pogorszenie zdrowia dziecka, które stawia przed decyzją o zaprzestaniu dalszych wysiłków leczniczych, to stan kliniczny, który bezpośrednio poprzedza męczarnie prowadzące już tylko do śmierci, albo sytuacja całkowitego i definitywnego wyłączenia pozytywnego postrzegania i odczuwania. **Materiał i metody:** Przegląd przypadków obejmuje specyfikę narodzin w warunkach skrajnego wcześniactwa, z wadami letalnymi i z chorobami neurodegeneracyjnymi. **Wyniki:** Opracowanie dowodzi, że możliwe jest wytyczenie granicy między zgodnym z prawem przyzwoleniem na śmierć pacjenta a niedozwoloną eutanazją bierną. **Wnioski:** Kluczowe znaczenie ma indywidualna jakość życia postrzegana przez dziecko, o które chodzi. Jedną z istotnych wskazówek powinien stanowić stosunek cierpień i dolegliwości do korzyści odnoszonych z życia w takim stanie. W schyłkowej fazie śmiertelnej choroby dla bólu i cierpienia nie ma żadnej medycznej ani moralnej racji. Nie ma jej

również podtrzymywanie czynności życiowych w stanie głębokiej zapaści wywołanej nieodwracalnym uszkodzeniem mózgu. Naleganie rodziców, by kontynuować taką opiekę, zaspokaja bardziej ich własną potrzebę emocjonalną oraz może być oceniane jako naruszenie prawa dziecka do umierania w spokoju i godności.

Słowa kluczowe: dziecko, choroba terminalna, eutanazja bierna, najlepiej pojęty interes, terapia daremna

PREFACE. THE LEGAL INTEREST OF A MEDICAL SUBJECT IN A CASE FOR THE DISCONTINUATION OF TREATMENT

Ethical and legal reflection on the comfort of dying children is one of the most painful experiences, and at the same time seems to violate a kind of social taboo. The death of a child is presented as an event contrary to nature, arousing violent emotional opposition, and often also a reflex of denial from society, leading to the desire to fight to extend the child's life, even for just one day. It is therefore all the more difficult to discuss the meaning of intensive life support for critically ill children. Parents are inevitably led by their own views when assessing the situation. In the context of their decisions, reference is made to the category of rights, autonomy, and respect for private life. A doctor is allowed to stop futile treatment, the continuation of which would contradict current medical knowledge. However, the indications may be ambiguous.

The discontinuation of futile treatment should be a medical decision, dictated by medical knowledge and the best interests of the patient, without the need for judicial involvement. Strictly speaking, the rationale for the withdrawal of futile treatment is the lack of medical indications for its continuation and, consequently, the absence of any obligation on the part of the medical practitioner to maintain unsuccessful treatment. However, the balance of health benefits and side effects or other ailments does not always present itself clearly. The child's parents, in particular, may find it difficult to come to terms with the fact that their child's life is inevitably coming to an end and medicine has no means of stopping this. The so-called "protocol for the cessation of futile treatment", which is drawn up collegially in such circumstances, is sometimes perceived by the patient's relatives as a death sentence, even though this "sentence" was in fact issued by the incurable disease. This, in turn, can often lead to desperate protests, which may take the form of reports to law enforcement authorities that doctors intend to kill the patient or have already done so by withholding resuscitation or disconnecting life support. In the event of a disagreement between doctors and the child's parents about further treatment, the guardianship court should have the casting vote. However, under Polish civil procedure, adjudication is filled with formal obstacles. While substantive legal grounds for adjudication exist in the relevant acts, there are no defined criteria for decision-making, no clear formal basis for granting the doctor or the hospital the status of a party to the proceedings (as an entity having a separate interest in a particular decision), and thus no procedural instruments for filing motions for evidence, receiving court documents, or the right to appeal against unfavourable decisions. Perhaps this accounts for the lack of spectacular rulings that would set precedents and provide directional guidance for other cases of this nature.

The substantive legal basis for seeking substitute authorisation from the guardianship court for the treatment of a decisionally incapable patient is Article 32(2) of the UZL (Ustawa o zawodach lekarza i lekarza destysty/Act on the Professions of Doctor and Dentist)[1], which applies equally to adults and children. Formally speaking, the court's competencies extend only to giving consent to the implementation of treatment, and not to its cessation. This argument was made by a family court chairwoman when the hospital's legal adviser alerted her to a problem with stopping futile treatment in a patient whose relatives, unable to accept it, occupied the patient's room in the intensive care unit. The problem is therefore not contrived. The literal wording of the law suggests the decision is up to the judge, but one has to resort to a functional interpretation of the provision. It is supposed to supersede the will of the patient, and that can, after all, be both positive and negative. Polish courts have already issued rulings showing that such a negative will of a patient who is incompetent at the time of adjudication, and documented by a previously made statement called an advance directive, needs to be respected[2]. The mechanism of the court's refusal to authorise treatment is not sufficient for this, as the subject of the request may well be the demand raised on behalf of the patient to stop the unwanted treatment. While it is true that rulings have been made in positive treatment authorisation proceedings (i.e. blood transfusions for Jehovah's Witnesses), formally preventing a ruling in the opposite direction through this route presents itself as a concept bearing marks of absurdity. This is because accepting it would lead to the conclusion that, in a guardianship case, the medical entity has no way to establish under the authority of the court that it is not bound

1. Ustawa z dnia 5 grudnia 1996 r. o zawodach lekarza i lekarza dentysty (t.j. Dz. U. z 2021 r., poz. 790, 1559).
2. See: Postanowienie SN z 27.10.2005 r., III CK 155/05. Orzecznictwo Sądu Najwyższego Izba Cywilna 2006; 7–8: 137; Postanowienie Sądu Okręgowego w Warszawie z 23.01.2008 r., sygn. VI Ca 582/07; Karcz R: Zgoda pacjenta na zastosowanie metody leczenia; status procesowy zakładu opieki zdrowotnej w postępowaniu sądowym z urzędu. Glosa do postanowienia z 23 stycznia 2008 r. Sądu Okręgowego w Warszawie, VI Ca 582/07. Państwo i Prawo 2008; 11: 143–146; Postanowienie Sądu Rejonowego z 12.12.2006 r., II RNs 580/06 – follow: Karcz R: Obrona pacjenta przed niechcianą transfuzją w praktyce sądowej. Prawo i Medycyna 2007; 4: 39.

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by a duty of care, or that, under equivocal circumstances, it does have such a duty.

With all this in mind, the question of the legal interest on the part of the medical practitioner or the hospital in obtaining an adverse decision needs to be assessed. In non-prejudicial guardianship proceedings for the authorisation of medical treatment, the medical subject usually acts in the role of notifying the court of the need to initiate proceedings *ex officio*. The scope for presenting one's own arguments is limited to the content of the notice[3]. Conversely, the status of a full participant in proceedings concerning a person's significant affairs provides much greater opportunities. In practice, however, the courts deny this to doctors, although there are times when they grant such attributes to a hospital[4]. A party to a civil lawsuit or a participant in a non-litigious proceeding is an entity that has a legal interest in obtaining a specific outcome in its favour. The source of misunderstandings and the denial of such status to medical entities seems to be the conviction that they do not have a substantive legal interest on their side. Only initially can the view be defended that a medical entity does not have its own interest in obtaining a ruling permitting the implementation of a specific treatment, because only the patient has such an interest[5]. This applies when the patient is legally independent and retains factual competence. The Warsaw Regional Court rightly ruled that courts are not authorised to rule on the treatment of a person with full legal capacity who has consciously opposed a particular method of treatment. In other words, the court cannot adjudicate a "dispute" between a doctor and such a patient. However, the evaluation changes when it comes to a patient who is legally dependent or actually incapable of making decisions, is in serious danger to life or health, and whose preferences remain unknown. The object of the judicial authorisation is then to undertake necessary treatment beyond the urgent case or to stop futile treatment – when the patient would otherwise lose their life as a result. As a rule, doctors have a duty to save their patients in the event of a life-threatening emergency, which arises from Article 30 of the UZL, while the treatment provider, on the basis of Article 15 of the UDL (Ustawa o działalności leczniczej/Act on Medical Activity)[6], may not refuse treatment to a patient who needs it because of a life-threatening emergency. Failure to fulfil these duties risks criminal and civil liability on the part of the direct perpetrators and, on the part of the hospital, entails the sanction of compensation. The medics therefore have a substantive legal interest and a statutory basis to establish that, under the circumstances, they were not under such obligations, i.e. the omission was lawful. They also have a substantive legal interest in confirming that it is their duty in the given circumstances to treat an incompetent patient, including a child, despite parental objections. Examples from foreign case law provided later in this article show that the hospital is not denied the status of a party to the proceedings, even though it is a guardianship procedure conducted *in re*. However, Polish procedural regulations on this matter are exceedingly laconic and practically confined to two provisions: Article 570 of the KPC (Kodeks postępowania cywilnego/Code of Civil Procedure): The guardianship court may initiate proceedings *ex officio* (i.e. also on request – MB) – and Article 572 of the KPC (§ 1. Anyone to whom an event justifying the initiation of proceedings *ex officio* is known is obliged to notify the guardianship court of it). The structure of the legislation thus implies that the medical entity may choose whether to limit its role to neutral notification of the court or to act as an applicant representing its own interest and claiming the attributes of a party in the proceedings.

Further complicating the adjudication of such cases is the fact that medical substantive law does not even provide decision-making criteria according to which adjudication should take place. This is bluntly described by practising judges as a "legal wilderness", consisting of unknown adjudication criteria, unclear status of the medical subject in the proceedings, the impossibility of appointing an *ex officio* representative for the patient, and even reasonable doubt as to whether service of a copy of the order is due to the medical subject, since the latter is not a participant in the proceedings[7]. *De lege ferenda*, it would seem useful to appoint either an *ex officio* representative[8], or a guardian *ad litem* for the patient. This applies in particular to situations where consent to treatment is refused by the legal representative of a legally dependent person, including the child's parent. Polish law does not even provide such an elementary solution as the application of the criterion of the child's welfare in all official decisions concerning the child. This principle

3. As Rylski points out, an application to initiate guardianship proceedings should be distinguished from a notice under Article 572 of the Code of Civil Procedure, which initiates proceedings *ex officio* (Rylski P: Uczestnik postępowania nieprocesowego – zagadnienia konstrukcyjne. Wolters Kluwer Polska, Warszawa 2017: 332).
4. An example is provided by a research report on the subject conducted and commented on by Jerzy Słyk. The author himself presents, in effect, a shaky and undecided position. At one time he is opposed to granting medical entities and physicians a legal interest in the adjudication, elsewhere he states that the physician's legal interest in the court's adjudication "appears to be capable of being grasped". He concludes, however, that the practice of treating the hospital as a participant in the proceedings "must be assessed critically in terms of its compliance with the procedural rules" (Słyk J: Zezwolenie [zgoda] sądu opiekuńczego na udzielenie świadczenia zdrowotnego dorosłemu pacjentowi. Prawo w Działaniu 2023; 54: 7–49).
5. Karcz R: Zgoda pacjenta na zastosowanie metody leczenia; status procesowy zakładu opieki zdrowotnej w postępowaniu sądowym z urzędu. Glosa do postanowienia z 23 stycznia 2008 r. Sądu Okręgowego w Warszawie, VI Ca 582/07. Państwo i Prawo 2008; 11: 143–146.
6. Ustawa z 15 kwietnia 2011 r. o działalności leczniczej (t.j. Dz. U. z 2022 r., poz. 633, 655, 974, 1079, 2280, 2705, 2770).
7. The doubt is resolved positively, but only for pragmatic and common-sense reasons. At most, the incompetent patient could be given a copy of the order on the duvet.
8. Such a demand was made by the judicial community. See: Blikowska J: Zabieg medyczny na nieświadomym pacjencie tylko za zgodą sądu. Rzeczpospolita 29.08.2016. Available from: https://www.rp.pl/prawo-dla-ciebie/art3257681-zabieg-medyczny-na-nieswiadomym-pacjencie-tylko-za-zgoda-sadu; Strus-Wołos M: Ochrona praw osób z zaburzeniami psychicznymi w postępowaniach z zakresu prawa osobowego dotyczących bezpośrednio stanu zdrowia psychicznego (Work in process of publication, provided as a courtesy).

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can only be derived from international documents, where it is commonly present.

Examples of foreign cases show that treatment entities there use litigation procedure to gain assurance that the patient treatment under review will be lawful. The designations of some cases highlight the litigation aspect by explicitly naming the treatment entity in the case title: *Airedale NHS Trust v. Bland* (1993); *Portsmouth NHS Trust v. Wyatt & Ors* (2004); *An NHS Trust v. MB* (2006); *Alder Hey Children's NHS Foundation Trust v. Evans* (2018). In the well-known *Anthony Bland* case, the hospital declared that its concern was precisely to ensure that doctors would act lawfully and that withholding aggressive life-sustaining treatment from the patient would not expose them to a charge of manslaughter. Such a determination is all the more important when objections to the manner of medical care are raised by the patient's relatives, who may seriously decide to notify law enforcement authorities of a suspected crime. Then the case for determining the obligation or lack thereof is the only way to obtain certainty about the law, and therefore the medical entity cannot be denied a legal interest in a ruling addressed to it, either permitting the cessation of treatment or ordering it to be maintained.

This article seeks to address the question of the criteria whereby medical due diligence and medical ethics would suggest terminating life support for a child with a fatal prognosis. In professional medical recommendations, bioethical literature, and judicial practice, two standards are usually used to guide critical decision-making: medical futility and the patient's best interests. Kazimierz Szewczyk, proposes interpreting "best interests" as "best understood interests", arguing that the term "best" erroneously implies the need to determine some ideal best interest of the patient in question, while it is only the interest best understood by the parties involved – the doctors and the parents representing the child[(1)]. The use of the plural in the original, on the other hand, captures what seems to be the key aspect of this criterion: the need to consider the balance of multiple factors[(2)]. When a child shows an understanding of their circumstances, the decision is additionally complicated, as their own reasoning must be acknowledged. The subject of consideration here are specific cases of birth in circumstances of extreme prematurity, with lethal defects, neurodegenerative illnesses, and other incurable diseases. Each of these groups has its own specificity in terms of identifying the right moment when further medical intervention would be pointless and merely interfere with a peaceful passing.

The analyses were carried out on the basis of case studies, most of which were settled by court rulings. Some of these have already been analysed in my earlier studies, so I take the liberty of citing extracts taken from them. I also return to the terminological issues considered earlier, because the blurring of the boundaries of certain concepts is sometimes used to create a "chilling effect": coercion to continue futile treatment out of fear of being charged with deliberately killing the patient. Before this happens, however, doctors, hospitals, and their lawyers may be advised at the outset to apply to the guardianship court for substitute authorisation to discontinue treatment in the event of disagreement between medical personnel and the child's parents regarding the issue of futile treatment, clearly emphasising and specifying in the application their own legal interest. That legal interest lies in establishing that the medical personnel are not obliged to maintain treatment deemed futile for the child in question, and that its discontinuation will therefore be lawful, in particular that it will not violate the obligations arising from Article 30 UZL and Article 15 UDL. The legal interest is thus to legalise the planned omissions. In the background of such cases, there is usually a fear on the part of doctors of being accused of failing to provide medical assistance in circumstances requiring it – i.e. failing to fulfil basic duties towards an incompetent patient. Such a clear formulation of the claim is likely to make the judiciary aware that not only the welfare of the child, in the broad sense of the term, but also the legal security of the doctors caring for him or her, needs to be taken into account in adjudication, and may contribute to the unification of practice in the application of civil procedures. In turn, the status of the applicant would enable the medical party to appeal decisions in which the courts attempt to evade taking a substantive position.

CESSATION OF FUTILE TREATMENT IS NOT EUTHANASIA

The conceptual distinction between the medically justified cessation of futile treatment and the offences of intentional homicide, euthanasia murder, or assisted suicide can be made mainly by referring to the therapeutic purpose of the treatment and to the indications of current medical knowledge. The same applies to demonstrating the fundamental difference between withholding futile treatment and euthanasia, which is reprehensible from the point of view of medical ethics. A thorough comparative analysis of these concepts was first conducted in 2019[(3)], except that it referred to the then-current wording of the Code of Medical Ethics (Kod Etyki Lekarskiej, KEL) and the anachronistic terms "extraordinary therapeutic measures"[9] and "persistent

9. A critical dissection of the criteria for dividing therapeutic measures into ordinary and extraordinary has long been carried out by the American bioethicists Tom L. Beauchamp and James F. Childress. Referring to the literature and the judgements of the courts, they proved the vagueness and utter unhelpful relativisation in this now ancient division. Ordinary measures were initially referred to as standard and generally recognised in the medical community, while extraordinary measures were referred to as experimental or novel. Thus, the evaluation was only concerned with the mode of treatment; the degree of prevalence and recognition of the method among medical practitioners were decisive, without taking into account the condition of the individual patient, including possible benefit. (In re Quinlan, The Supreme Court of New Jersey, 31.03. 1976, 70 N.J. 10 (1976), 355 A.2d 647, https://law.justia.com/cases/new-jersey/supreme-court/1976/70-n-j-10-0.html). The doctors claimed that the ventilator was a routine device, while the clergy considered it to be an extraordinary therapeutic measure, the use

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treatment" used therein. Consequently, the deliberations on this topic were characterised by strong criticism, dictated primarily by the KEL's use of inadequate and therefore inappropriate concepts, and by the acknowledged penetration of these flawed concepts into legal discourse. Further references to the problems considered took place in connection with the high-profile 2021 case involving a Polish patient with the initials RS, for whom life-sustaining measures were discontinued in a UK hospital[4]. Subsequently, the interdisciplinary team at the Patient Ombudsman produced a position paper in 2021, confusingly titled "Standards". However, instead of clarifying the issues, it introduced confusion between the concepts of futile and persistent treatment[5]. The terminology was reordered in the bioethics collective work "Konsultacje etyczne w praktyce klinicznej", aimed primarily at doctors, published in early 2024[6]. A detailed comparative analysis of the terms "futile treatment" and "persistent treatment" was carried out by Małgorzata Świderska[7], while Anna Alichniewicz analysed the very definition of futile treatment from a bioethical perspective, showing that it is not unambiguous[8]. Over the years, clinical practice guidelines have been developed by successive groups of medical specialists, where the term "futile treatment" has been used more and more widely in place of the rightly criticised term "persistent treatment". Three key documents were developed in paediatrics.

"Rekomendacje dotyczące postępowania z matką oraz noworodkiem urodzonym na granicy możliwości przeżycia z uwzględnieniem aspektów etycznych" is a document concerning perinatal care[9]. It mainly describes the medical criteria that provide the basis for clinical decision-making. Some of the basic criteria when deciding on resuscitation of the newborn in the delivery room are the gestational age and the strictly defined duration of the resuscitation – as prolonging resuscitation may cause significant and irreversible damage to many organs. On the other hand, it was pointed out that, although the doctor is not appointed to assess the quality of life of the child, they should not be indifferent to the child's suffering resulting from what is described as "persistent" treatment. It was emphasised there that doctors are not obliged to continue inexpedient treatment, while pushing for further treatment will require the approval of the guardianship court and overcoming the parents' lack of consent by this means. Parents, on the other hand, have the legitimacy to oppose a course of treatment, but they cannot bindingly insist on a particular treatment. Disputes arising between doctors and the child's parents should be resolved by the court. The medical balance sheet is only a starting point[10,11].

The guidelines "Wytyczne na temat terapii daremnej na oddziałach anestezjologii i intensywnej terapii dziecięcej"[12] (OAITD – paediatric departments of anaesthesiology and intensive therapy) state that it is the duty of the doctor treating a child with an advanced, incurable chronic disease to periodically assess the balance of benefits and losses that result for the patient from the treatment provided. It is very important that the treatment team is guided by the best interests of the child, taking into account current medical knowledge, therapeutic options and taking into account the opinion of other specialists. The legal representative, on the other hand, should be the representative of the interests of their child but often, being unable to come to terms with the separation, may more or less consciously seek to keep them alive at all costs, contributing to the child's suffering. Therefore, the doctor has the task of encouraging the patient's loved ones to try to understand the child's position and to adopt the child's point of view rather than their own. The guidelines include a list of procedures that need to be continued as palliative care. These include gastrointestinal feeding (also via gastric tube, PEG – if tolerated), hydration, and intravenous glucose supply. On the other hand, the list of therapeutic procedures that will not be undertaken or will be discontinued in the OAITD consists of cardiopulmonary resuscitation, mechanical respiratory support, pharmacological and electrical circulatory support, antibiotic treatment, parenteral nutrition, blood product transfusion, surgery and other invasive procedures (which does not apply to procedures that improve patient comfort), mechanical circulatory support, extracorporeal respiratory support such as ECMO, renal replacement treatment, and extracorporeal liver function support. ECMO, renal replacement treatment and extracorporeal support of liver function. The guidelines therefore prescribe palliative surgery to improve comfort in living (or dying), allow no artificial ventilation, but require continued feeding as long as the body is receiving it.

In comparison, the comprehensive 2011 paediatric guidelines[13], which were published a decade earlier, use the term "persistent treatment" and list the criteria for this: acting against the best interests of the patient, acting against the

of which was not obligatory and the patient's father had the moral right to decide to disconnect it. Thus, as can be seen, the ways of understanding the same concepts were clearly diverging. The court recognised this problem and, in its reasoning, drew attention to the "vagueness" of their understanding in the case at hand and the possible relativisation when the same procedure is considered ordinary for a patient with a chance of recovery (e.g. a ventilator for a child undergoing a critical phase of polio), but extraordinary in view of the enforced maintenance of vital processes in a terminal or vegetative state. The usefulness of this distinction for decisions on the continuation of life-sustaining procedures is therefore presented as highly questionable. In the 1983 report of the Presidential Commission for the Study of Ethical Problems in Medicine, Biology and the Behavioural Sciences, Deciding to Forego Life-Sustaining Treatment, it was stated that the distinction between ordinary and extraordinary therapeutic measures had already become so confusing that, for the sake of those involved in resolving difficult situations, these formulations should be avoided. From a moral point of view, it only makes sense if it is based on an analysis of the benefits and burdens experienced by the patient: ordinary measures produce more benefits than burdens, while extraordinary measures produce significantly more burdens than benefits. See: Beauchamp TL, Childress JF: Zasady etyki medycznej. 4th ed., Książka i Wiedza, Warszawa 1996: 212–214; Boratyńska M, Konieczniak P: Persistent treatment. In: Safjan M (ed.): Medical Law. Cases and Commentaries. Wolters Kluwer Polska, Warszawa 2011: 406–416; Boratyńska M, Malczewski J: Niewspółmierne środki terapeutyczne. In: Zielińska E (ed.): System prawa medycznego. Tom II. Regulacja prawna czynności medycznych. Część 2. Wolters Kluwer Polska, Warszawa 2019: 597–602.

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patient's beliefs, acting against the dignity of a human being, and acting against nature – the consequences of which are prolonged dying, undue suffering, and violation of dignity. While they aptly recognise the vagueness and ambiguity of the term "persistent treatment", they do not call for its amendment or clarification[8: at 11].

In 2010, Magdalena Rutkowska and Slawomir Szczepaniak reported that Poland lacks a real field for discussion of this issue. Concrete decisions are not made based on the criteria of the good – which characterise the attitude of an ethicist – but rather with reference to the principles shaped by one's worldview. As a result, they are presented as absolute – which corresponds to an ideological stance[14].

The 2011 guidelines certainly aimed to change mindsets, as evidenced by the passage in the introduction: "In paediatrics, in particular, the recognition of a child's right to die with dignity and to stop treatment is extremely difficult. The currently formulated statement that a doctor in a no-chance situation should withdraw from a treatment that prolongs the life and suffering of the child – is often not fully understood and applied. Therapeutic persistence, which makes it impossible according to ethical principles to 'accept death' and affects its natural course, is a moral and legal transgression"[13: at 9]. Nevertheless, the abandonment of artificial nutrition in children with dysphagia due to neurological diseases is considered unethical there – as leading to "cachexia and death by starvation"[13: at 117]. As Kazimierz Szewczyk rightly pointed out, the guidelines do not address situations where treatment is futile or those that carry an unbearable burden. According to him, the "all-round good idea of the document" has been largely destroyed by the confusion of concepts of different provenance: the terms "futile treatment", "extraordinary measures", and "disproportionate" are used in the document as *de facto* synonyms for "persistent treatment". The guidelines thus reproduce the narrowly defined and only locally used concept of therapeutic persistence, and the omission of artificial nutrition in children with neurological swallowing loss is therein principally regarded as unethical[1]. It is not a new argument that more progressive jurists raise the need for statutory regulation of these issues and accentuate the *de lege lata* inconsistencies at a systemic level[15,16]. Regarding the case of the Polish RS patient in the UK, where futile treatment was withheld, I argued that the law should in no way replace medical knowledge, which is paramount, but could establish procedural safeguards, mandate collegial decision-making, and formulate a list of factors to be taken into account[3: at 222]. This would increase doctors' sense of security and give them the confidence to decide; however, as foreign cases show, it will not resolve violent conflicts with some of the patient's relatives[10]. In the absence of specific statutory solutions, professional guidelines and recommendations serve as decision-making criteria in accordance with the principles of medical knowledge. However, they lack consistency and uniformity. While the 2021 guidelines present a state-of-the-art approach, their scope of application remains limited.

The reduction of therapeutic futility to terminal procedures is also reflected in the "Raport zespołu ekspertów przy Rzeczniku Praw Pacjenta": "This paper adopts the term futile treatment to describe end-of-life medical therapies that offer no benefit to the patient. [...] It seems that the term futile treatment more clearly captures the essence of the problem: to do something that is pointless, that is futile, is a waste of energy and time, and ultimately remains harmful because it increases suffering, prolongs agony"[5: at 16]. Attempts to narrow the concept of futile treatment to end-of-life care only perpetuate conceptual confusion and, in doing so, represent a regression in relation to the findings of modern medical knowledge. The same confusion and misrepresentation have long prevailed in various legal studies which still refer to the concepts of "persistent treatment" and "extraordinary measures". This refers to works that either date back to or were rediscovered[11] at a time when, for at least two years (i.e. as of 2014), the "Guidelines for dealing with the ineffectiveness of sustaining organ function (futile treatment) in patients deprived of the ability to make conscious declarations of will in intensive care units" had already been in circulation, using the appropriate terminology of "futile treatment" and referring comparatively to the term "persistent treatment", highlighting differences and pointing out inaccuracies[17]. The inconsistency between the terminology adopted in medical science and non-substantive legal studies urgently needs to be rectified to ensure legal security for doctors.

The guidelines in question immediately address these terminological discrepancies in the introduction by recognising that the phrase "futile treatment" more accurately describes management that does not achieve the intended therapeutic benefit than the term "persistent treatment". The phrase "futile treatment" more accurately describes the decision regarding the maintenance of organ function in patients treated in intensive care units. The term "futile treatment" was used to describe the maintenance of organ function without benefit to the patient and without the possibility of achieving the intended therapeutic goals.

10. One example in particular is the case of Vincent Lambert, recognised on several occasions by numerous national authorities and by the ECtHR, which examined respect for human rights in the French Law on the Rights of the Sick and the End of Life in its 2005 version, known as Loi Leonetti.

11. Posted on the Medycyna Praktyczna portal in 2018, the sweeping study by W. Wróbel from 2009: Rezygnacja z uporczywej terapii w świetle polskiego prawa. Available from: https://www.mp.pl/etyka/kres_zycia/46416,rezygnacja-z-uporczywej-terapii-w-swietle-polskiego-prawa. The term "persistent treatment" is also used by Sroka T: Article 38, In: Safjan M, Bosek L (eds.): Konstytucja RP. Tom. 1. Komentarz do art. 1–86. C.H.Beck, Warszawa 2016: thesis 115. Both authors refer to the definition of persistent treatment still taken from the draft law on the protection of the human genome and the human embryo and the Polish Bioethics Council (known as Gowin's draft) – 6th Sejm, Druk No. 3467, 2009, modelled on the consensus of the illegitimate Working Group on Ethical Problems of the End of Life.

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Its continuation was considered a "medical malpractice", with the understanding that decisions to limit futile treatment should be made collegially.

The concept of "persistent treatment" has taken deep roots and its eradication requires intensive persuasive efforts within the medical community as well. Experience shows that in Poland the legislature cannot be relied upon, so the new Code of Medical Ethics must play a substitute role, supporting the existing laconic legal provisions. Contrary to appearances and the declared impossibility by some lawyers[12], these provisions offer a reasonably consistent legal framework for medical conduct in conditions of therapeutic futility, but they require thoughtful interpretation, and the new solution adopted in the KEL is likely to greatly facilitate it.

Under Polish law, a doctor is obliged to provide medical assistance in any case where delay could cause danger of loss of life, grievous bodily harm, or serious disorder of health (Article 30 of the UZL), but also – to perform the profession in accordance with the indications of current medical knowledge, methods and means available to them, in accordance with the principles of professional ethics, and with due diligence (Article 4 of the UZL). Criminal law, on the other hand, criminalises both intentional and unintentional exposure to direct danger of loss of life or serious disorder of health, as well as intentional failure to render assistance in danger. From this, it follows that, under Polish law, the obligation to take and continue therapeutic measures is determined by the indications of medical knowledge. There is no such obligation without positive indications, so in a particular case, a sufficient justification for refusal or cessation of treatment is the lack of indications for its maintenance. On the other hand, there is an obligation to provide medical assistance in any case of imminent danger to life. In medical law, however, what is fundamental to the evaluation of medical actions and omissions is the therapeutic purpose of the intervention. The norms of medical law function as special provisions that take precedence over the norms of criminal law. If circumstances justifying lawful injury to a human being – up to and including a fatal outcome – are regulated by medical law, then these norms determine the abrogation of unlawfulness of such an act or omission. Thus, in the legal relationship between the doctor and the patient, criminal law and the Criminal Code do not apply directly, but only in an auxiliary manner[13]. The science of criminal law has developed the construct of the countertype of a therapeutic act, which consists of a set of four prerequisites that legalise medical intervention in a patient's body. Without their fulfilment, such an act would constitute a violation of numerous personal rights and, under criminal law, would amount to intentional bodily harm with the use of a dangerous instrument. These justifying circumstances are: a therapeutic purpose, conformity of the action with current medical knowledge, proper consent provided by the patient (or, alternatively, by a person or body appointed to represent his interests), and the doctor's possession of the appropriate, formally confirmed qualifications[14]. In the same way, the countertype theory applies equally to the cessation of treatment: there is no obligation to continue it, so the omission is legal, as long as at least one of the premises legalising the prior action is no longer valid. This means: the absence of the therapeutic purpose of the interference, failure to observe the laws of medical knowledge, referred to simplistically as medical malpractice, or the patient's autonomic discord. In other words, the failure to provide medical assistance in circumstances involving the risk of at least grave bodily harm can be qualified, for example, as the crime of failure to render aid in distress or exposure to imminent danger of at least grave bodily harm. However, only if there are no special circumstances justifying the failure to act – namely, the lack of indications for treatment, the futility of further treatment, or the lack of patient consent. Therefore, due to the auxiliary nature of criminal law in this legal sphere, the typification of crimes against life should not be a premise for clinical decisions in medicine. Medical law determines the scope of permissibility of such actions independently – albeit with the necessary reference to the body of medical knowledge, practice, and ethics. It is therefore crucial to define professional rules for initiating or withholding treatment in cases commonly referred to as hopeless. These rules make up the objective criterion of medical due diligence. Thus, the rules of medical knowledge are a subset of the rules of professional due diligence, which are referred to in general in Article 355 of the Civil Code, and, with regard to medical professionals, in Article 4 of the UZL and other medical professional laws[(18)].

The new Code of Medical Ethics has officially introduced the concept of futile treatment into the rules of medical ethics, finally abandoning the term "persistent treatment". The change in nomenclature is not insignificant in its implications. Therapeutic futility also defines the limits of medical care for patients who are clinically stabilised, but with permanent cognitive incontinence as a result of irreversible loss of most brain functions, and whose lives depend (quite literally) on numerous tubes supplying water, food, and oxygen. Limiting the assessment of either persistence or futility solely to terminal conditions would not resolve the most important and, at the same time, most difficult questions. Meanwhile, it is crucial to determine the advisability of further treatment in light of the chances of improving or maintaining health. With regard

12. For example Tymiński R: In: Walewski P: Daremny ból. Polityka 2025: 10: 41.
13. See also Boratyńska M: Tak zwana eutanazja bierna w świetle nowych technologii. Gubernaculum et Administratio (in work).
14. Buchała K: Prawo karne materialne. Państwowe Wydawnictwo Naukowe, Warszawa 1980: 314; Andrejew I: Polskie prawo karne w zarysie. 5th ed., Państwowe Wydawnictwo Naukowe, Warszawa 1978: 222.

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to terminal conditions, it is pointless, because all that matters is the alleviation of pain and other distressing symptoms accompanying dying. The limits of duty are initially defined by the indications of current medical knowledge. Beyond the indications, there is no duty. What is futile lies beyond those indications and is not only non-obligatory, but rightly considered medical malpractice and, according to the current wording of the KEL, constitutes an ethical prohibition. And finally – via Article 4 of the UZL – it falls under the criteria of professional propriety. The introduction of the notion of futility, which is widely accepted in the medical community, into the KEL sends back into oblivion the previous ideas of defining "persistent treatment", and with them – the revolving implications echoed by legal scholars in commentaries on the Criminal Code or the Constitution.

The World Medical Association defines futile treatment as treatment that "offers no reasonable hope of recovery or improvement" or from which "the patient is permanently unable to experience any benefit"[19]. Within such defined boundaries, the maintenance of a patient's vital functions using specialised apparatus may be considered futile. At this point, a terminological problem arises. Many people refer to the abandonment of life-sustaining treatment as "passive euthanasia", either approvingly or in a decidedly pejorative context.

Medical ethics generally do not permit euthanasia. The World Medical Association Code of Medical Ethics defines euthanasia as "a physician deliberately administering a lethal substance or carrying out an intervention to cause the death of a patient with decision-making capacity at the patient's own voluntary request"[20]. Such a restrictive understanding of euthanasia – as an active intervention – may resolve the issue at the level of medical ethics, but the problem remains when the interpretation of criminal law does not follow the same direction. The message from Catholic circles is that all euthanasia is evil. The term "passive euthanasia" as a prohibition is frequently used by principled proponents of the idea of the sanctity of life. The word "euthanasia" is thus becoming a tool of oppression and a means of exerting pressure on physicians. This conceptual confusion, on the other hand, is conducive to arguing that when a case is "one of euthanasia"[21], it refers to any cessation of keeping a patient alive and can be used as a charge of intentional homicide. The "use of euthanasia", regardless of how the term is defined, is considered incompatible with the medical ethos, and the same problem may arise in legal assessment.

Sometimes the omission of life-sustaining treatment is called "passive euthanasia" in good faith by some bioethicists as well. An attempt at ethical evaluation of such cases was made as far back as 1984 by Zbigniew Szawarski with regard to children suffering from incurable conditions[22]. The cases cited by Szawarski also remain relevant in light of current medical developments. One of Szawarski's staunchest critics, Rev. Tadeusz Biesaga, has portrayed his views as "brutal" and as an "emotive persuasion" in favour of, among other things, euthanasia, to which Szawarski is said to be urging suffering humanity"[15]. This criticism lacks merit and is based on winning emotions, and the vocabulary used reflects the heated nature of the polemic. I have posted a discussion and update of Szawarski's case studies in another paper[23]. Jacek Hołówka, on the other hand, argues that passive euthanasia is practiced in any hospital when it abandons another attempt to restore a heartbeat using electrodes, and it is clear from the context that the author sees nothing wrong with this[24], as did Szawarski or James Rachels earlier[22,25]. Such generalisations, however, can prove dangerous when the term "passive euthanasia" is used in a commentary to the Criminal Code concerning the crime of murder[16]. While this is accompanied by the caveat that it is not a crime to discontinue treatment in end-stage conditions, there is no explicit reference to the criterion of therapeutic futility, despite the fact that the 2014 medical guidelines should have long since normalised this concept[17]. It is free to argue that this will only result in a change in the Code of Medical Ethics as more noticeable.

Using the term "passive euthanasia" in the context of crime multiplies doubts instead of removing them. This is illustrated by the following case study. A patient with amyotrophic lateral sclerosis (SLA) had entered the advanced stage of the disease, at which point he was offered mechanical ventilation. The patient refused. When he lost consciousness, doctors soon intubated him, ignoring his earlier refusal. After waking up, the patient continued to protest, but his wishes were ignored. Using this example, the doctors explained to the students that turning off artificial ventilation would constitute "euthanasia".

Withdrawal of life-sustaining treatment thus needs to be confronted with the category of euthanasia and the penal law.

The concept of "passive euthanasia" cannot, therefore, be abandoned altogether, but for legal evaluation, it is worth narrowing down the boundaries of unlawful omission according to the criterion of actual breaches of medical duty. For the sake of legal certainty, which generally prohibits euthanasia, the adoption of reasonably clear criteria for passive euthanasia is therefore dictated by a legal rather than a moral necessity. Doctors need guidelines which, at the same time, define the boundaries of legal security. In other words, they need to know what behaviours – with particular reference to omissions – cannot expose them to criminal charges. Let us, therefore, try to clarify what unauthorised passive euthanasia is in medical terms. Passivity means

15. Biesaga T: Bioetyka utylitarystyczna Zbigniewa Szawarskiego. In: Biesaga T (ed.): Bioetyka polska. Wydawnictwo Naukowe PAT, Kraków 2004: 146.
16. See: Kokot R: Art. 150 III/2. In: Stefański R (ed.): Kodeks karny. Komentarz. C.H.Beck, Warszawa 2020.
17. The concept of "persistent treatment" and "passive euthanasia" is used nomen omen persistently and inadequately and in bad faith, because using arbitrary assumptions by Roszkiewicz in an article with a biased title: Czy można uśmiercić pacjenta z powodu niskiej jakości życia? Uwagi na tle orzecznictwa Europejskiego Trybunału Praw Człowieka. Forum Prawnicze 2023: 1: 16–36.

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the omission of certain acts. A person can be charged with omission when they remained passive despite having a duty to act. The primary duty of a physician is to save the life of a threatened patient using medical means but following current medical knowledge. However, interpretations of such general formulations diverge. Acting or neglecting to act outside of these indications is not obligatory. Because of this, the consent to the patient's death through the omission of medical actions can be regarded as reprehensible only if there is an obligation on the part of the doctor to act, which was omitted with the merciful intention of hastening the patient's death[26].

Passive euthanasia, on the part of the doctor, would therefore have to be an omission dictated by compassion for the patient's suffering and hastening their death, which breaches medical duties: failure to resuscitate, administer medicine, or perform life-saving surgery – but only when it violates the obligations. However, when the obligations cease, there are no grounds for alleging infringement. Therefore, a decision is made to classify the activities as either mandatory or optional (based on the balance of positive and negative consequences of treatment)[27]. A legally unacceptable, punishable omission that meets the criteria for passive euthanasia will therefore be an infringement of medical duty – that is to say, a medically unjustified abandonment of treatment that would have been of benefit to the patient, motivated by compassion for the suffering person and intended to hasten their death. Situations meeting these criteria are extremely rare, but the point is precisely to show, by way of contrast, that a failure to provide medical care in accordance with medical knowledge cannot be considered unlawful.

A completely separate issue is the suspension of life-sustaining treatment when, due to the patient's condition, it does not benefit them. Withdrawal of life-sustaining treatment, when it does not bring benefits to the patient in a particular condition, as a rule, is considered medically and morally justified and legally permissible. Futile treatment is not a subject of obligation. Refraining from continuing it does not constitute misconduct, and continuing it would be an error of medical procedure. It is crucial to determine the desirability of further treatment in terms of the chances of improving or maintaining health, or at least keeping the patient in a relatively stable state with a satisfactory quality of life. Discontinuing treatment in circumstances of therapeutic futility is legally grounded. If it spares further suffering, it is a humanitarian act.

Practising the profession in accordance with current medical knowledge is one of the obvious criteria for the appropriateness of medical activities. However, it requires clarification of which activities count as mandatory. The answer is provided by the state of medical knowledge translated into the clearest possible professional guidelines and an assessment of the clinical condition of the patient in question. Clinical practice guidelines supported by the authority of medical societies are important. They are conducive to good practice, and their additional function is considered to provide doctors with a sense of legal security. Compliance with the criteria formulated therein makes it possible to avoid the allegation of infringement of the rules and liability. They contain many valuable directives and valuable findings[see e.g. in Britain: 28], but they cannot be regarded as a universal recipe for every circumstance. Critical moments in the dynamics of the disease and symptoms, entailing the need for decisive decisions, are easier to grasp in specific situations.

The literature provides evidence of parents insisting on aggressive and invasive life-prolonging treatment for critically ill newborns. There is a growing tendency to honour such wishes, even for children born with Edwards syndrome, heart disease, or prematurity under 26 weeks of pregnancy. There is talk of the "ethics of abdicating" doctors from difficult decisions in favour of the parents' preferences. This is thought to be a by-product of respect for patient autonomy, which extends to "parental autonomy" in decision-making[29]. Parents, due to their exceptional closeness to the child, are usually best positioned to determine the child's best interests, assess the quality of life, and predict the ability to cope with treatment[30,31]. They are also held accountable for their care and thus bear the main consequences of the decisions taken[32]. In the well-known *Charlie Gard* case, his parents argued that state intrusion into such a private area of life as child upbringing means an erosion of fundamental constitutional values and renders their parental rights ineffective[18]. In *Williamson,* Lady Hale J ruled that, in a free society, parents should have a high degree of autonomy in the way they perform their duties[19]. Privacy also includes the right to autonomy, and parental autonomy requires the freedom and independent decision-making of children. Any restrictions may be seen as undermining this right, causing some parents to feel disempowered in their "parental rights". However, parental rights are not absolute and have never been treated as such[33]. Emotional involvement can lead parents to evaluate a child's best interests from their own perspective rather than empathising with the child's situation. *Alfie Evans*' parents understood the importance of their son's brain scan but avoided confronting its implications[20]. The "necessary balance is ensured by the best interests test", but it is sometimes assessed as minimally protecting the right of parents to respect for privacy and family life. Opponents argue that this task is better met by the competitive concept of "serious harm" proposed in relation to critically ill children[34]. It requires the state to refrain from interfering until a defined risk arises on the part of the child. According to some, it is supposed to safeguard the most vital goods and interests of the child – physical health, vitality, integrity and normal functioning

18. *UKSC, In the matter of Charlie Gard (Permission to Appeal Hearing)* (2017).
19. *R. (on the application of Williamson) v. Secretary of State for Education and Employment* [2005] UKHL 15, at 72.
20. *Alder Hey Children's NHS Foundation Trust v. Evans* [2018] EWHC 308 (Fam) at 38.

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of the body, lack of pain, suffering or grotesque disfigurement, intellectual efficiency, and emotional stability[35]. Others justify external intervention only by the need for immediate action[36] or when children do not have their basic needs met[37].

This problem seems to be somewhat misplaced. Parents, understandably, would like to make decisions according to their own conviction and without the intervention of state authorities. However, they often have in mind their own privacy rather than the privacy of a child who is not their own, but a vulnerable person requiring proper care, in the context of which the word "power" is completely out of place. Parental rights are not independent but serve the proper fulfilment of parental responsibilities and are subordinated in individual legislations to either the "welfare of the child" or the "best interests of the child". Third-party interference can be felt privately by parents as a perception of agency. However, allowing "autonomous" decision-making about the child in the context of respect for privacy respects the personal beliefs and values of the parents (or the convictions of those around them who submit out of fear of social condemnation) more than the best interests of the child. Meanwhile, the best interests test is about what a child patient needs as a person, i.e. to care only about their feelings. The quality of life perceived by that child is crucial, when it proves to be "unbearable". One important consideration should be whether suffering is commensurate with the expected benefits of treatment. Parents would like to keep their child with them for as long as possible and cherish their presence and life. If they hear about a parenteral probe or mechanical ventilation, they will probably give their consent without thinking. However, the question is what benefits it brings in the terminal phase of the disease and whether those benefits outweigh the ailments associated with surgical tracheostomy. It is therefore necessary to define what constitutes the privacy of that child, considering in the first place the symptoms of their critical illness. This requires empathy with the child and their position only: what else is the child able to feel and how is the child affected by the current condition? With serious damage and a lack of successful forecasts, intensive life support actually prevents a peaceful passing.

Representation of a child's rights by parents is sometimes erroneously equated with the rights and freedoms of the parents themselves, and restricting decisions on the child's case is treated as an attack on civil liberties. However, rights and freedoms are legislated to protect self-interest. The Polish Constitution guarantees parents "the right to provide their children with moral and religious upbringing and instruction in accordance with their beliefs" (Article 53(3)). The misunderstanding stems from the erroneous treatment of medical care in terms of upbringing. Deciding on medical care is included in the satisfaction of health needs, and these fall into the strictly custodial category and are listed in the KRO (Kodeks rodzinny i opiekuńczy/Family and Guardianship Code)[21] separately from upbringing – as custody of the person: "Parental authority includes, in particular, the duty and right of parents to exercise custody over the person and property of the child and to raise the child, with respect for the child's dignity and rights" (Article 95 § 1 KRO). Deciding on health matters is not part of upbringing activities and is not covered by constitutional freedom. Therefore, it is not possible to decide autonomously on these matters and be guided by personal beliefs. Parental authority here does not give room for free choice: it should be exercised as the child's welfare and the public interest require (Article 95 § 3 of the KRO)[38]. According to Article 17 of the UPP (Ustawa o prawach pacjenta i Rzeczniku Praw Pacjenta/Act on Patient Rights and the Patient Rights Ombudsman)[22], consent to a health care service "has the right" of both the patient and the legal representative of a legally dependent patient, and the identity of the wording of the two provisions creates the risk of interpreting self-consent and surrogate consent in the same way. However, there is no symmetry between the two. Self-consent is a sovereign right of the patient, while surrogate consent is a competence whose executor is strictly bound by the criterion of the ward's welfare[39,40].

The decision on the child's health care is not a manifestation of the parent's own freedom. The parent is only granted the authority to represent the interests of the ward. This requires consideration of many factors, but not one's own point of view. The right to give surrogate consent to medical treatment and to perform other medical activities on the child cannot be treated as independent and autonomous. Therefore, operating in this context with the concept of "parental autonomy" is a misunderstanding.

The only genuine parental right is the right to personal contact with the child, because it also satisfies the self-interest of the entitled person. Other prerogatives are reduced to duties of due care and are exercised in the interest of the child. Their side effect can be the satisfaction of the personal need to care and a sense of moral and emotional satisfaction from the duty fulfilled. There is undoubtedly an element of the right to privacy in the sense of enjoying undisturbed family life, but only within the limits set by the child's welfare. The disruption of harmony can be more distressing when there is interference with surrogate critical health decisions, such as continuing or discontinuing futile treatment. It is then possible for family life to be ruined or paralysed, convoluted and disintegrated, caused by the loss of a beloved child, the despair of watching their prolonged torment or the sacrifice of everyone, including siblings, to care for severe disabilities[38: 52–53].

Determining what medical care will be appropriate for a child, taking into account their clinical condition, the prognosis of improvement, and various therapeutic options,

21. Ustawa z dnia 25 lutego 1964 r. Kodeks rodzinny i opiekuńczy (t.j. Dz. U. z 2023 r. poz. 2809).
22. Ustawa z 6 listopada 2008 r. o prawach pacjenta i Rzeczniku Praw Pacjenta (t.j. Dz. U. z 2024 r. poz. 581).

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is not the domain of one decision-making group – neither parents nor doctors – and has been repeatedly reviewed by guardianship courts in different countries over the years. This is a typical way of protecting the rights of dependents in care, and there is nothing unusual about it. Decisions on critical issues are the most difficult, the most prone to error, and have irreversible consequences for another person; therefore, they cannot be of a quasi-discretionary nature. Parents' opinions are listened to with attention and empathy, but their decision is not predominant. The review powers of the court represent the state supervision of the proper exercise of parental care. Physicians do not, of course, have the right to positively decide on the treatment of children as a substitute or against the views of their parents, unless it is a medically dictated urgent action necessary to save life or seriously endangered health. However, medical duty does not include futile treatment. This creates a triangle of decision-making interdependencies, where parents have the power to oppose specific treatments, but cannot legally insist on specific treatments. However, medical indications can be vague and uncertain due to many uncertainties about the prognosis. Therefore, the views of doctors and parents may differ, and there is nothing unusual in this, because finding the right answer requires a balancing of many factors. If doctors, contrary to the parents' wishes, insist on continuing treatment, they must seek the approval of the court and thus overcome the parents' lack of consent to medical activities perceived as *bona fides* in accordance with the best interests of the child.

The final straw in the process of gradual deterioration that precedes the decision to cease further efforts is the clinical state that immediately precedes unbearable suffering that can only lead to death, or a situation of complete and definitive exclusion of positive perception and feeling. Physicians can be expected to take a rational and pragmatic approach, representing the current state of medical knowledge, but their judgment can only be trusted if they are not influenced by their own philosophical beliefs or use moral evasions so as not to endanger anyone.

DISCONTINUATION OF NUTRITION AND HYDRATION

The cessation of futile therapeutic measures, however, leaves open the question of how to proceed with feeding and hydration using specialised techniques. Artificial nutrition for an "otherwise healthy" and independently breathing patient in a vegetative state is a procedure on which their life directly depends. As a result, the crucial decision is not to stop futile treatment in the strict sense – understood as fighting the disease – but to remove the feeding tube. The recognition of nutrition as futile renders it non-obligatory, but it is difficult to establish criteria for the futility of nutrition. Dissent prevails even in the highest adjudicatory bodies, as shown by the minority opinion of the European Court of Human Rights (ECHR) in the famous *Vincent Lambert* case (2015). Although the court ruled that the cessation of a patient's life support in a Persistent Vegetative State (PVS) was lawful and did not violate human rights, the dissenting opinion included the words: "a severely disabled person who is unable to communicate his wishes about his present condition may, based on a number of questionable assumptions, be deprived of two basic life-sustaining necessities, namely food and water […] The case before this court is one of euthanasia, even if under a different name"[23]. Despite repeatedly using all the collegial procedures required by French law to adjudicate and decide on treatment, appeal proceedings continued for four more years. After Lambert's death in 2019, Dr Vincent Sanchez, the physician who led the medical team, was accused by the patient's mother of failing to help him in danger. Both court instances handed down acquittals, but the mere fact of a criminal case does not encourage doctors to make firm decisions about incompetent patients without the support of their relatives. Vincent Lambert was the patient whose life essentially hung on a feeding tube at a crucial moment. Treatment for the root cause of the VS had been completed, and independent breathing regained, but consciousness and decision-making competence had not returned, nor could he swallow food. The patient could not decide for himself, and the withholding of CANH (clinically assisted nutrition and hydration) by third parties is equated with a sentence of death by starvation. In this reasoning, key issues of law and medical ethics converge: when it is legal and ethical to stop treating a patient, and whether assisted feeding is a form of treatment and thus subject to its rules, or whether it belongs to the unshakeable principles of primary care. Decisions of this kind are sometimes referred to as euthanasia.

The well-known and oft-cited clash between two perspectives: the concept of feeding and hydration as either part of compulsory primary care or as a specialised medical procedure justified within the limits of therapeutic expediency seems to have brought the discussion to a dead end. The main arguments can be summarised as follows. The classification of artificial nutrition as a therapeutic activity implies, in principle, an obligation to continue, but allows for its discontinuation when it proves futile. The classification of CANH as a non-medicinal activity, on the other hand, makes it an obligation falling within the scope of so-called primary care.

It is considered that artificial nutrition is too different from other medical measures to allow the establishment of a moral standard that could provide a common basis for evaluation. Accordingly, certain medical measures may be dispensed with, but the administration of food and liquids may not be disregarded. Feeding the hungry is one of the "simplest gestures that show care" and "an excellent symbol of the fact that human life is always inscribed in the life of the whole society and community"[27: 217,41,42]. Withholding

23. *Lambert and Others v. France*, judgement ECHR, June 5, 2015, 46043/14; http://hudoc.echr.coe.int/fre?i=002-10758.

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CANH is therefore considered tantamount to killing. The cause of death is then not the fatal disease, at some stage depriving the patient of the ability to feed themselves, but the omission of physicians who fail to provide food and fluids. Such statements appear as an issue in the discussion on the lack of difference between killing and letting die[24](See polemically: 27: 160–162,43,44).

These claims have been extensively analysed over the years, but the unshakeable principles are, one might say, evergreen. They do not change or evolve. They just bloom in the same shape from time to time: Beauchamp and Childress cited the view of C. Everett Koop (U.S. Surgeon General) who, in 1982, declared that the death of children born with severe defects by the withdrawal of nutrition was a kind of infanticide by starvation to death[25]. In Poland, Zbigniew Szawarski argued against such a view(22). Nevertheless, a Koop-like thesis is present in the paediatric guidelines of 2011. "Discontinuation and withdrawal of persistent life-sustaining treatment in children. The abandonment of artificial nutrition in children with dysphagia in the course of neurological diseases is considered unethical there as leading to 'cachexia and death by starvation'"(13). The 2015 minority opinion in the *Vincent Lambert* case strikes the same tone.

However, one could just as well argue the opposite: a patient who is no longer fed and hydrated artificially dies as a result of the progression of the disease or an injury resulting in an inability to eat and drink normally(see for example: 45, see polemically: 43: 122).

Patients in a VS, however, are not "ill" in the common sense of the word, yet they can be kept alive for many years without feeling anything. It may be argued that the symbolism of nutrition loses its meaning when a person permanently ceases to feel such needs, for this means – as Daniel Callahan puts it – that the body gradually shuts down its functions. Artificial nutrition and hydration are supposed to meet the individual needs of patients, not just maintain normal physiological parameters(46). The symbolism of care is not an argument in itself: it can only be considered valid if the care benefits the patient. When the clinical condition is not promising to improve, such external supply only sustains a purely biological continuance, and, for this reason, its futility can legitimately be considered(4: 178–185).

As rightly noted in the famous House of Lords' judgment of 4 February 1993, in the *Anthony Bland* case[26], medical treatment and care are provided for the benefit of the patient. If a patient has suffered irreversible brain damage, is permanently unconscious, and, in the unanimous opinion of the experts, has no prospect of recovery, then continued life support must be considered pointless. Continuing the invasive treatment would be justified only if it brought any benefit. However, neither continued vegetation thanks to artificial nutrition nor death caused by its discontinuation are associated with any feelings on the part of the patient. Artificial preservation of biological life is a futile and useless activity that serves only itself, but not the person of the patient. However, the judges stipulated, among other things, that if the patient showed even the slightest glimmer of consciousness, this would create a "non-zero" interest in continuing the treatment. The guardian *at litem* of Anthony Bland submitted that artificial feeding was an ordinary caring action, such as the duty to feed a baby or an incapable person, that is an elementary duty which existed independently of all questions of treatment and which the person in charge could not omit to perform. Judges did not accept this argument. In their opinion, feeding a person in a vegetative state is not the same as feeding a baby, for such a person is not capable of obtaining food and swallowing, that is of eating and drinking in the literal meaning of these words. Tube feeding is a highly invasive procedure and is inevitably associated with the continuous use of catheters and enemas, and as a consequence, constant fighting with urinary tract infections. In this context, ordinary humanitarian care is not an issue. In the Court's opinion, there is an analogy to the ventilator, which artificially breathes air in and out of the lungs of a patient incapable of breathing normally. Judges did not accept analogies submitted by the guardian *at litem* that discontinuance of artificial feeding in the present case was equivalent to cutting a mountaineer's rope or severing the air pipe of a deep sea diver. Discontinuance of life support should properly be categorised as an omission. The use of the word "omission" may seem inadequate where discontinuance of life support requires some active step to press the button. However, in the context of life sustenance, discontinuing the procedure is not different from failure to initiate it(See more: 47).

The dispute is irresolvable because the position regarding all nutrition as compulsory primary care has been influenced by the Catholic doctrine and is the result of a top-down assumption, so it does not lend itself to rational persuasion. The adoption of one of the two views depends essentially on social convention: whether such invasive nutrition should be treated on par with medical treatment and judged according to therapeutic expediency or treated as an unshakeable principle of care.

Assessing the appropriateness of maintaining CANH requires an answer to the question whether it provides a real and perceived benefit to the patient at a given stage of treatment. If, on the other hand, nutrition and hydration are only implementing a top-down rule, it is unnecessary from the point of view of the patient's well-being, and this is the main argument in favour of lawful discontinuation. When the continuation of care is of no benefit to the recipient, its value becomes purely abstract. Caring for a person who

24. See also: Beauchamp TL, Childress JF: Principles of Biomedical Ethics. 6th ed., Oxford University Press, Oxford 2009.
25. Koop CE: Ethical and surgical considerations in the care of the newborn with congenital abnormalities. In: Horan DJ, Delahoyde M (eds.): Infanticide and the Handicapped Newborn. Brigham Young University Press, Provo: 89–106, esp. 105; follow: Beauchamp TL, Childress JF: Zasady etyki medycznej. 4th ed., Książka i Wiedza, Warszawa 1996: 216.
26. *Airedale NHS Trust v. Bland* [1993] IM ER 821 Hls.

does not need to be fed is detached from the interests of the person being fed, ceases to serve them, and becomes an empty phrase. It serves the benefit of third parties only: it provides the caregiver with positive reinforcement and the moral satisfaction that they are "doing their bit". In this, I think, one must look for the reasons for the absolute insistence on maintaining CANH even for decades in patients in a state of permanent loss or initial lack of consciousness. This balance does not consider the individual interest of the patient, but the emotional needs of those close to them who take comfort from their continued life. It could be argued, perversely, that if the patient does not care anymore, then at least others should be allowed to enjoy it. In this case, however, the unconscious patient becomes a 'toy' in the hands of others, serving others' needs and interests, which is clearly unacceptable.

The implicit assumption that people always need food and water does not stand up to the fact that such needs are not felt by patients in an irreversible VS and, consequently, there is no perceived benefit in satisfying them and no positive effect on the quality of life in this state. Although withdrawal of CANH leads to death from starvation and thirst, this effect is a normal consequence of illness or injury. Assisted feeding does stop it, but only temporarily, as it offers no hope of lasting improvement and is therefore pointless from this point of view. The inability to eat independently due to the loss of the swallowing reflex abrogates the duty to feed on the part of caregivers who are not qualified to use methods requiring medical knowledge. However, the possession of adequate knowledge, skills, and means does not always automatically prejudge the existence of such a duty on the part of physicians. The decisive factor should be the considerations of purposefulness understood in two ways: as therapeutic – that is, for the improvement or preservation of health, or as the satisfaction of individual needs with the benefit felt by the patient. The fact of staying alive but in a VS does not in itself constitute a subjective advantage. The futility of applying CANH to such patients should be understood as sustaining a purely biological duration without any perceived benefit. Feeding is not purposeful in itself. It is not unusual to see the desirability of feeding in terms of individual benefit, just as the desirability of treatment. Unnecessary nutrition must be considered futile regardless of whether it is assigned the status of a medical procedure or a symbol of caring and humanity in a particular case. Withdrawal of CANH which brings no perceptible benefit to the patient, should, therefore, be considered morally and legally permissible. It cannot be included in the category of "passive euthanasia" because, in such circumstances, the continuation cannot be a duty.

CASES

In the previous part of the article, the theoretical aspects of the cessation of futile treatment were analysed in the context of a possible breach of medical duties, a violation of professional ethics, the criteria for qualifying certain behaviours as passive euthanasia, and the potential commission of a crime. This section of the article will cite several well-known and representative medical cases, decided abroad by court rulings, as a source of arguments for withholding or continuing a treatment with highly questionable chances of success, or treatment deemed futile at some stage. I will juxtapose these with domestic cases, reported by parents and commented on mainly by bioethicists. Although these cases are few in number due to limited access to such knowledge for non-physicians, some of the constatations made in the course of foreign litigation may nevertheless prove useful for applying to such cases. It is desirable that there are as few such disputes as possible, but on the other hand, resolving them under the solemnity of the court allows the public to become familiar with the reasoning, thereby promoting a mature and substantive discussion of such problems. It is unfortunate that, so far, this discussion has not developed in Poland, and individual cases of children, usually known second-hand, only trigger emotions that drown out rational thought.

Newborns born in extreme prematurity

The difficulty in assessing cases of premature birth arises from the fact that if the infants are born "beyond" healthy, i.e. unaffected by birth defects, their condition cannot be described as end-of-life. The hope that they will be able to survive and improve their health is, in principle, justified. However, the lack of clear boundaries between the concepts of "prolongation of life" and "prolongation of death" creates problems with the unequivocal qualification of corresponding clinical situations. The most intense discussion in the global literature concerns the limit from which one may speak of the medically assisted possibility of premature newborn survival: determining the parameters of gestational age and/or body weight at which, after applying the latest achievements of medicine, it is possible to keep the newborn alive. This threshold was set by World Health Organization (WHO) for birth statistics at 22 weeks of gestation or 500 g body weight. However, epidemiological studies show that survival at such low neonatal maturity is negligible[48]. Currently, WHO assumes that viability can be considered when a child has a 50% chance of survival with or without intensive neonatal care intervention[49]. Despite enormous technological progress, that threshold remains at 24 weeks' gestation. Moreover, WHO itself recognises that, at present, in most high-income countries, premature babies born around 24 weeks of gestation have a 50% chance of survival[49]. The use of baseline data for statistical purposes should not be confused with actual survival, which is assessed mainly on the basis of the degree of development of internal organs, for which the arithmetic of pregnancy is only indicative. Many countries have introduced the concept of a "border zone" in their recommendations, referring to a period of gestational maturity during which there

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is great uncertainty about the survival and assessment of the development of the newborn. This zone is defined differently in various countries and ranges between the 22nd and 25th weeks of pregnancy. Below this interval, only palliative care is proposed to protect the newborn from suffering during the transition to natural death. In addition, it is now pointed out that the criteria of gestational age and body weight are insufficient. Decisions are further complicated by the fact that the organs of extremely immature newborns continue to develop, which may result in remedial processes[49]. When this fails, death occurs due to multi-organ failure, most often circulatory and respiratory failure[50]. A separate issue is, therefore, rescuing the neonate immediately after birth in order to correctly diagnose and determine the chances of survival and potential treatment options. Another problem is maintaining life in the event of a sharp deterioration of the condition after some time. The so-called "waiting resuscitation" gives time to observe, gather information, obtain test results, and discuss possible reductions in procedures in the event of a very poor prognosis[50]. No medical decision is ever certain, so in the case of newborn babies, it is only possible to make a prognosis. This is as normal as any statistical risk of complications, although in this category of cases it is characterised by the greatest uncertainty, because the gradual progression of development is moving in the opposite direction of organ failure. Withdrawal of treatment with slim chances of success does not amount to euthanasia in any adequate sense of the word, but acquiescence to death by ceasing futile and vicious treatment. The balance of benefits and discomforts also needs to take into account the suffering inflicted on a pain-stricken being by sustaining vital functions with the use of a ventilator, feeding probes, and intravenous infusions. Invasive surgeries, although feasible, are sometimes disproportionate to the possibility of survival and the anticipated quality of the existence preserved at such cost. Some decisions can be painful, and if the problem overwhelms the parents, the guardianship court must step in to make them[see more: 51].

However, without reference to a specific case, these criteria are presented as a set of dry generalities. A vivid example of decision-making doubts is provided by the British case of Charlotte Wyatt, illustrating the dynamic development of the clinical situation of a premature baby.

Charlotte Wyatt was born prematurely (2003) at 26 weeks' gestation and weighed 458 grams – as a newborn on the verge of viability. She was brain damaged and had severe problems with her organs – pulmonary hypertension resulting from damage to her lungs with recurrent urinary tract infections and worsening kidney function. In the first year of her life, Charlotte had to be resuscitated three times. She had severe respiratory failure requiring ventilation and needed to have her head constantly enclosed in a transparent plastic box and receive almost the maximum oxygenation possible. Doctors established that Charlotte had no sense of sight or hearing and would remain effectively without volition. Their prognosis was that she would not develop neurologically or respond to stimuli – except distress and pain – including future treatment, and were unanimous in describing her quality of life as terrible and the endurance of further aggressive treatment as intolerable. The hospital that provided her care asked the court for a declaration that it would be lawful to withhold artificial ventilation should Charlotte suffer a fourth crisis. The parents were hoping for "a miracle born of divine intervention" and contested the application. While it was not illegal to use a ventilator, the doctors believed that with such a dire prognosis, it was not in the best interests of the child. They were particularly reluctant to perform surgical tracheostomy. This sparked a year-and-a-half dispute, during which six rulings were issued. In the first[27], Mark Hedley J, privately chair of The Lawyers' Christian Fellowship[28], repeatedly stressed the adoption of a strong presumption in favour of the preservation of life. He stated that, to respect Charlotte's sanctity of life and her right to dignity, recourse should be made to the principle of best interests. As one of the important factors to be taken into account, he highlighted the concept of "intolerable to that child", according to which the court may consider the cessation of maintenance of life to be lawful if it determines that the continuation of treatment so reduces the quality of life of the child that it becomes intolerable. The phrase "to that child" emphasises that the test refers to the child and not to the party making the decision. Hedley J emphasised that "the issue in all probability is not whether this baby should live or die but how and when she should die". In his view, any consideration of best interests for a person at risk of imminent death should involve securing a "good" death – not under anaesthetic or during painful and futile treatment, but peacefully, in the arms of those who love her most. As a result, the judge authorised the doctors, in the event of disagreement with the parents, not to submit the child to artificial ventilation or similar aggressive treatment. This relief was "only permissive, not mandatory declaration". The key was to assess Charlotte's actual condition at the time of making the decision. The girl's condition was slowly improving. The need for administered oxygen decreased, and her responses to the environment and stimuli became better and better. At the third sitting in April 2005, the judge concluded that Charlotte's improved state of health no longer allowed her life to be described as intolerable. The child began to respond to loud noises, looked behind large coloured objects, and usually no longer needed sedatives. However, experts continued to argue that Charlotte would not be able to withstand the invasive efforts to manage another respiratory crisis, given her severe chronic lung disease and

27. *Portsmouth NHS Trust v. Wyatt & Ors* [2004] EWHC 2247 (Fam) 7 Oct. 2004 (called Wyatt No 1).
28. http://www.lawcf.org/index.asp?page=Mr+Justice+Mark+Hedley, follow Szewczyk K: Kazus Charlotte Wyatt – opis; Interdyscyplinarne Centrum Bioetyki UJ, http://bazy.incet.uj.edu.pl/dzialy.php?l=pl&p=31&i=3&m=27&n=1&z=&kk=126&k=187.

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malnutrition resulting from food intolerance. The prognosis that such "futile aggressive treatment" would restore her to her current condition seemed slim and would most likely either threaten her chance of a peaceful death or return her to an "intolerable" existence[29]. The judge again ruled ahead of time not to implement ventilation, although he stipulated that his verdict needed ongoing review, and the Court of Appeal upheld this ruling[30]. The hospital asked for a ruling that, in the event of a further dispute with the Wyatts, the final decision would rest with the doctors. However, Hedley J considered that a "novel" declaration of this sort was not required[31]. A doctor is obliged to act in the best interests of the patient, working "in partnership with the parents". However, clinical judgment can comprise an intellectual dimension and a "professional conscience, intuition or hunch and the clinician cannot be compelled to act contrary to his or her conscience"[32]. This, according to the judge, provided the doctors with sufficient protection. Further improvements in Charlotte's health justified the prognosis of leaving the hospital, but after trial visits at home, she developed a cough and a viral infection. In the event of deterioration, only the use of a ventilator would be viable, but doctors still considered this to be futile and contrary to her best interests, given Charlotte's lung condition. At the end of the dispute, the judge again issued a "permissive, not mandatory" order leaving the decision to the doctors[33]. Charlotte's body self-controlled the infection. She remained dependent on oxygen, required increased round-the-clock care and feeding by tube, with the mental development of a 12-week-old child. At the end of 2006, she was permanently discharged from hospital(based on: 52).

Charlotte Wyatt's case is a model example of a detailed and conscientious consideration by the court of the slowly changing pros and cons of the girl's situation, taking into account the extreme suffering involved. Media coverage also reached Poland, my homeland: an article was published with the sensational headline "Parents fight the hospital for the life of their child"[34], as if the doctors wanted the patient dead. On the other hand, the axis of judgements was a life without pleasure and the amount of suffering paid for by a treatment that had not worked in the first place.

One day in the hospital, Charlotte was found to have a fractured femur. This had nothing to do with abuse or mishandling but was due to her extremely brittle bones. The doctors decided to administer diamorphine, although the parents refused, fearing that it would affect her breathing[35]. The fact that Charlotte recovered enough not to spend her life in the hospital is not thanks to her parents or the public, but to the doctors. Clearly, allowing them to stop invasive medical techniques in the event of another acute crisis and granting the freedom to make decisions based on clinical chances did not result in hasty consent to death. The doctors only wanted to preserve their professional freedom to decide not to take disproportionate medical measures(2: 140–145, see also: 53). Judge Hedley said that parents' wishes should be taken into account to the extent that a doctor's professional judgment and conscience allows, but no further.

Children affected by lethal malformations

Children with lethal malformations usually do not live long after birth, but each case is different, and therefore both the length and quality of life may vary. The lethal nature of some defects may be determined by their severity – examples include Down syndrome or spina bifida. It is understood that improvement is, in principle, excluded; however, in some cases, it is possible to live a tolerable quality of life for a certain period of time. Surgical corrections will not remove the cause of the disease, but they can improve functioning. Still, the invasiveness of the intervention, its likelihood of success, and its potential to improve overall health are not insignificant considerations.

Numerous cases of ruling on the withdrawal of over-invasive and futile treatment with reference to the best interests of the child, understood as protecting it from excessive suffering, are referred to in Richard Huxtable's extensive study(based on: 52: 40–44). According to him, the British standard of resolution in all similar cases is essentially the same: the decision depends on the best interests of the patient(based on: 52: 37), starting with the *Re B* case of 1981[36]. B, named Alexandra, was a newborn with Down syndrome and bowel obstruction. Corrective surgery could relatively easily remove the obstruction and prevent death. However, doctors disagreed on whether the child's health situation was "worthy" of surgery, and Alexandra's parents were strongly opposed to the procedure. The decision of the court of first instance, which was made in favour of the parents, was subsequently overturned by the Court of Appeal, with the critical remark that the judge had been too concerned about the wishes of the parents, while his duty was to consider the best interests of the child. Alexandra may have been severely physically and mentally disabled, but not to the point where the operation made no sense. In authorising the procedure, Lord Templeman J pointed out that the outcome might have been different if "severe proven damage" had been demonstrated, which would have condemned the child to a life full of pain and suffering, and "awful that in effect the child

29. *Re Wyatt (a child) (medical treatment: continuation of order)* [2005] EWHC 693 (Wyatt No 3). Based on: Huxtable R: Law at the limits of life: children, welfare and best interests. In: Huxtable R (ed.): Law, Ethics and Compromise at the Limits of Life: To Treat or not to Treat? Routlege, London 2013: 34–36.
30. *Wyatt & Anor v. Portsmouth Hospital NHS Trust* [2005] EWCA Civ 1181 (*Wyatt No 4*).
31. *Portsmouth NHS Trust v. W* [2005] EWHC 2293 (*Wyatt No 5*).
32. Ibidem § 40.
33. *Re Wyatt* [2006] EWHC 319 (*Wyatt No 6*).
34. Pszczółkowska D: Rodzice walczą ze szpitalem o życie dziecka. Gazeta Wyborcza 22.04.2005. Available from: http://wiadomosci.gazeta.pl/wiadomosci/1,60085,2667836.html.
35. *Re Wyatt (a child) (medical treatment: continuation of order)* [2005] EWHC 693 (*Wyatt No 3*).
36. *Re B (a minor) (wardship: medical treatment)* (1981) 1 WLR: 1421.

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must be condemned to die". However, in the event of an unknown prognosis, it would have been inappropriate to refrain from the operation[37]. In connection with this ruling, the well-known criminal law scholar Glanville Williams put forward the argument that failure to perform a life-saving operation on a severely defective newborn could always expose the parties to a murder charge unless the facts of the case meet the criteria for a "Templeman exception"[38].

A different assessment was made by a US court in an earlier case known as the *Baby Houle Case* (1974). Robert Houle was born with many injuries. His entire left side was malformed; he had no left eye, was practically without a left ear, had a deformed left hand; some of his vertebrae were not fused(54) (the spine image may correspond to open meningomyelocele symptoms). Suffering from a tracheoesophageal fistula, he could not be fed orally. Inhaled air entered the stomach, and stomach contents entered the lungs. The condition of the child deteriorated significantly after the first day of life. Circulatory failure caused hypoxia, and extensive brain damage was suspected (later it turned out that the child had a hidden heart defect and lung hypoplasia). Reflexes deteriorated, and pneumonia developed. However, the tracheoesophageal fistula, the main and immediate threat to life, could be operated on relatively easily. The parents refused to give their consent due to the accompanying complications and profound deformities. The case was brought to court because several doctors from the hospital had a different opinion. After passing the case through successive instances, the Supreme Court ruled that, from the moment of birth, a human being is entitled to full legal protection, and the most fundamental right of every human being is the right to life. He ordered an urgent operation[39], as a result of which the child died in hospital. The doctors and the court focused, as can be seen, on the immediate cause of the threat to life, and not on the presumed defect of the neural tube and the generally unsuccessful prognosis. However, in the overall assessment of the case, it would be necessary to take into account the sum of all damage and subsequent complications, which, *prima facie,* could indicate a condition so severe that even a successful operation would merely prolong the agony.

Carrying out an invasive procedure with poor prognosis or its abandonment and limitation to palliative care can pose a serious dilemma. In Poland, a case of this type occurred in 2012. Madzia Słabiak was born with hypoplastic left heart syndrome (HLHS), a lethal defect caused by aortic stenosis. With this defect, palliative surgery immediately after birth and three or four highly invasive cardiac surgeries in the first years of life do not eliminate the cause of the disease but, if successful, may prolong life. The procedures are associated with a significant risk of death or serious complications, and the heart remains abnormal, with an active single ventricle, resulting in severe disability and major limitations. Madzia's poor prognosis was further aggravated by a narrowing of the foramen ovale. The girl's parents decided to refuse treatment. They declared that they wanted their daughter to be able to pass away in peace, surrounded by their love, without condemning her to pain and suffering. They also declined resuscitation. Among the doctors in the maternity ward, disapproval prevailed, but unexpected support came from the ethics committee of the paediatric hospital, where Madzia was planned to be transported. The committee issued an opinion stating that doctors are not obliged to apply for a court permit that opposes the will of the parents because, with such a prognosis, the parents "have the right" to refuse treatment. The statistical mortality in such cases is about 50%, and Madzia would have faced an even greater risk. The committee found no reason to believe that the parents acted to the detriment of the child, driven by excessive fear or misguided pity. Finally, the parents were able to take the child home and give her palliative care. Madzia survived for 38 days. She passed away peacefully and without suffering, with her parents and under the care of a home hospice(55).

Kazimierz Szewczyk observed that an important factor inducing many doctors to undertake aggressive treatment is an attitude that is seemingly ethically principled, or serves as a kind of moral refuge. Repeated declarations such as "it is my duty to save lives in all circumstance", intended to put an end to any discussion, stem both from a misunderstanding of the aims of medicine and from a reluctance to engage in deeper moral reflection(1).

From other sources, it is known that in the US, some medical units offer palliative care for such cases, referred to as "comfort care", which consists of not introducing Prostin (a drug that allows the child to survive until surgery) and focusing on relieving unpleasant symptoms. This path is described by the mother of a boy with HLHS diagnosed in the 20th week of pregnancy – Amy Kuebelbeck – in the book titled "Waiting with Gabriel: A Story of Cherishing a Baby's Brief Life". The path that Amy took in deciding not to treat her son is similar to that of Madzia's parents. However, Amy failed to obtain permission to take Gabriel home(55).

Some lethal defects are diagnosed only at a certain stage of life, when the child begins to show more and more disturbing symptoms that herald imminent death. It may also happen that a progressive disease, before it develops its terminal form, leaves some time for a good life. Then it is important to be able to recognise the moment when medical intervention should cease, since death is certain.

In 2006, a British court ruled on the case of 18-month-old M, who had been diagnosed with the most severe form of spinal muscular atrophy (SMA), a genetic condition that gradually removes the ability to move muscles voluntarily. The condition is degenerative and progressive, meaning it can only deteriorate towards an inevitable death. By the time of the hearing, M could only move his eyebrows to indicate

37. *Re B (a minor):* 1424.
38. Williams G: Letter: Life of a Child. The Times, 13.08.1981: 9; follow: Huxtable R: Law, Ethics and Compromise, at 38.
39. *Maine Medical Center v. Houle*, Maine Supreme Judicial Court No. 74–145 (Super Ct, Cumberland City, ME February 14, 1974).

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pleasure or pain. However, it was accepted that he may have normal cognitive function and that he could hear and occasionally see. M could survive for a few more years or might die suddenly and soon. He required positive-pressure ventilation via an invasive endotracheal tube. He could not swallow and was fed through a gastrostomy tube. The treating doctors considered that M's quality of life was so poor and that the burdens of living were so great that it was unethical (the word "cruel" was used) to continue keeping him alive artificially, and that his endotracheal tube should be withdrawn[40]. The hospital sought permission to withdraw M's life-sustaining ventilation, but the parents objected. M was conscious. It was probable that he continued to see, hear and feel, and have a close relationship with his family. He may well have been aware of his surroundings, and of his family and the people close to him, and have the normal thoughts and mental processes of an 18-month-old child. There was no objective evidence to suggest that his cognition was normal – but none to indicate that it was abnormal, either. M also seemed to gain pleasure from TV and DVDs as well as music played to him on CDs. However, it was not possible to give an opinion about his cognitive function, as it was impossible to assess. It was also very difficult to determine how much discomfort or distress M experienced. In Holman J's opinion, the positives felt by M, although not subject to "mathematical" quantification, outweighed the discomfort, anxiety, and pain described by the doctors. This proportion would certainly change as M approached the inevitable end of his life. Therefore, the judge refused to allow the withdrawal of pressure ventilation but agreed not to implement other life-saving measures (like cardiopulmonary resuscitation – CPR). "There are, however, procedures which go beyond maintaining ventilation, which require the positive infliction of pain and which, if required, will mean that M has moved naturally towards his death despite the ventilation. If that point is reached, it would be in his best interests then to withhold those procedures even though he would then probably die"[41].

The court ruled differently in the case of K – a five-and-a-half-month-old girl[42]. She was born prematurely with congenital myotonic dystrophy (CMD), a neuromuscular disorder causing chronic muscle weakness. K was a severe case. She had major issues with gut motility, leaving her unable to tolerate milk feeds. She required mechanical ventilation by CPAP (oxygen delivered under pressure through small tubes into the nostrils) and was dependent on artificial nutrition given intravenously via the central line (total parenteral nutrition – TPN). Progressive muscle dystrophy was accompanied by numerous complications. Infections led to septicaemia. This caused thrombocytopaenia (low platelets), which in turn led to a large right-sided intraventricular haemorrhage (bleeding into the fluid cavity on the right side of her brain). Following her second episode of septicaemia, K was afflicted by a left-sided focal seizure involving rhythmic twitching of her left arm and left leg. The consultant neonatologist situated her clinical state somewhere between "no chance" and "no purpose", with a prognosis that she was unlikely to survive one year. Treatment could be considered futile and burdensome, as the dysfunctions had deteriorated irreversibly and she was experiencing increasing discomfort. In this state, it was considered unreasonable to expect K to endure such a degree of irreversible impairment. The ruling allowed for the removal of the central line and the initiation of palliative care. Potter J concluded "that it would not only be a mercy, but it is in her best interests, to cease to provide TPN while she is still clinically stable, so that she may die in peace and over a comparatively short space of time"[43]. Nobody opposed.

On the other hand, the Polish case known as "Chazan's newborn" provides a negative example of an approach to caring for a suffering child. After the prenatal diagnosis of numerous and severe foetal defects, the future parents asked for a termination of the pregnancy on embryopathological reasons. They were prevented from exercising this right by the then director of the Holy Family Hospital in Warsaw, Bogdan Chazan[44]. The boy was born in June 2014 and lived for nine days. He had a cerebral hernia accompanied by anencephalia. The bone loss of the skull cover was so significant that the right hemisphere of the brain was covered only by membranous tissues and fused with them, forming the wall of a vast fluid reservoir, with parts of the brain preserved only fragmentarily. The examination showed, among others, massive hydrocephalus with reduced brain mantle, left ventricular distortion, a left frontal cyst, and dramatic craniofacial deformities[45]. The size of the defects and the extremely poor prognosis meant transition to palliative care in a hospital setting, including analgesic administration of morphine. In addition to the incubator and intravenous irrigation, enteral feeding was provided through a probe, and the site of bone loss was secured with a sterile dressing. Initially, the child's condition was stable. On the sixth day of life, progressive respiratory and circulatory failure occurred, while by the ninth day, the child intolerance to nutrition, cardiac arrest, and death. The cause was extensive purulent leptomeningitis, softening of the neuroglial tissue, and features of cortical and white matter atrophy. The child died in agony, which, according to the parents' accounts, was not suppressed by morphine. The pain was prolonged by artificial nutrition. Without it, the patient would have died faster

40. An *NHS Trust v. MB* [2006] EWHC 507 § 10.
41. Ibidem par. 91.
42. *Re K (a child) (withdrawal of treatment)* [2006] EWHC 1007, Follow: Huxtable R: Law at the limits of life: at 48.
43. Ibidem par. 57.
44. See: MAW: Śledztwo w sprawie odmowy aborcji przez prof. Chazana umorzone. Newsweek Polska 4.05.2015. Available from: https://www.newsweek.pl/polska/sledztwo-w-sprawie-odmowy-aborcji-przez-prof-chazana-umorzone/mx589bh.
45. Case description according to the autopsy report made available with the permission of the prosecutor's office. Parents' report: https://serwisy.gazetaprawna.pl/zdrowie/artykuly/878315,rodzice-dziecka-ktorym-prof-chazan-odmowil-aborcji-po-urodzeniu-lekarze-bali-nam-sie-je-pokazac.html.

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and would not have lived to experience the moment when the suppuration and putrefaction process caused unbearable pain. The parents were probably too devastated by the situation to question the doctors' decisions.

Polish legal practice also involves the case of a child with Krabbe disease who was born in 2008. The case emerged during a compensation claim for negligent prenatal testing (the parents' claim was dismissed due to the non-fault nature of the diagnostic error)[46]. A boy named D was born with a cleft upper lip, maxillary alveolar process, and hard and soft palate. He was also soon diagnosed with bilateral hearing loss. After six months, the boy was hospitalised for loss of appetite, increased muscle tone, contracture of his upper extremities and spasticity in his lower extremities. During another hospital stay, at the age of seven months, he was diagnosed with Krabbe disease, spastic quadriparesis, regression of psychomotor development, symptomatic epilepsy, bilateral otitis media, and gastroesophageal reflux. Probe feeding and hospice care, and consultation with the Metabolic Disorders Clinic were recommended. Two and a half months later, D was hospitalised again and treated surgically for reflux. Krabbe disease is associated with great suffering, which is relieved with strong medications. The child died four months after surgery. Until his death, he required constant care and feeding through an enteral probe. Both parents lived with the knowledge that, after a few months of suffering, their son would die, as the same thing had happened to their first child. They seem to have relied on doctors' decisions on how to provide care. The case is particularly difficult to evaluate, as the symptoms of the disease did not occur immediately. However, it had been known for some time that D was dying, and the reflux prevented him from taking food by the usual route. Yet the patient was operated on and fed by probe until the end. The question remains: why, when he had no chance of survival anyway and required painkillers. Pain relief is, of course, justified, but feeding only prolonged dying[(23)].

By way of an addendum, another recent case of a child with Krabbe disease must be cited here. It illustrates, at the same time, the possible attitude of parents to a properly drawn up protocol for discontinuing the child's futile treatment. Noah was the son of a well-known travel reporter and photographer. He was diagnosed with the disease at the age of six months and died before he was two years old[47]. Symptomatic treatment with bone marrow transplantation is now possible, and this fact changes the perspective somewhat. Experimental gene therapies are also underway. Noah's diagnosis, however, came too late for him to be eligible for treatment. His mother perceived the late diagnosis and the omission of treatment as an injustice and has called for the introduction of newborn screening for Krabbe disease (which is very rare and mainly affects individuals of Scandinavian origin). In desperation, she even subjected her baby to intravenous stem cell injections in Slovakia and spinal cord injections in Thailand. "We wanted so much to save him that we did too much" – she admitted. In the end, the parents were allowed to take Noah home from the hospital in Krakow to die there, after the futile treatment protocol was drawn up and entered into the system. The mother described the procedure as a "verdict" and regretted that the decision was made by a medical consortium without even asking the parents for their opinion. The dying boy's parents tried to prolong his life using an artificial respiration mask they had received in Thailand. This brief description shows that medical communication with the parents of a child suffering from a fatal and rare disease was failing, leading them to misunderstand the critical situation and make desperate attempts to save what cannot be saved. Such parents become easy targets for charlatans. For the comfort of the child's short life, it would have been worthwhile to put more effort into properly informing the parents. According to the mother's report, they could not accept the painful truth until the very end. This carries the risk of medically unwarranted subjecting the child abroad to experimental therapies of dubious and unproven efficacy, as well as forcible and undermining already fragile health travel around the world in search of the impossible.

Difficult diagnoses

More decision-making problems arise with diagnoses of poorly understood diseases, even when the child enters the end-stage state and doctors plan to withdraw intensive care. The last line of resistance for desperate parents is to request experimental treatment. Here, arguments are put forward about the duty of doctors to seek all possible methods of treatment, even those of unproven effectiveness, or about their duty to maintain the vital functions of the patient until effective treatment is invented. This phenomenon is illustrated by the recent high-profile cases of Charlie Gard and Alfie Evans and, more recently, Indi Gregory. The first two have already been discussed in other studies[(33,56)], so they will be cited here only briefly. The court rulings have been widely commented on, but only specialists have the patience to analyse them legally and medically. Other recipients are generally content with press reports, which inevitably take shortcuts. Hence, it is easy to fall into a schematic superficiality that gives an incomplete picture and opens the door to interpretation abuse[48]. A verdict does not create reality, but rather documents important legal events and medical evidence. The epilogues can be read about in the press. Charlie Gard was diagnosed at the age of 8 months with mitochondrial DNA depletion syndrome (MDDS), which soon caused severe and permanent damage. Charlie

46. Sąd Apelacyjny w Białymstoku, wyrok z 24.04.2013 r. I ACa 787/12 (Portal Orzeczeń Sądów Powszechnych).
47. Demianowicz A: Trzeciego cudu nie było. Wysokie Obcasy 1.03.2025: 6–9.
48. E.g. Roszkiewicz J: Czy można uśmiercić pacjenta z powodu niskiej jakości życia? Uwagi na tle orzecznictwa Europejskiego Trybunału Praw Człowieka. Forum Prawnicze 2023; 1.

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suffered from the *RRM2B* mutation of MDDS. He could not move his limbs or breathe on his own, had frequent epileptic seizures, and remained without cognitive or sensual contact with his surroundings, except for his supposed ability to feel pain. His life expectancy was estimated at 6–9 months. Parents insisted on the use of "pioneering" nucleoside treatment. In fact, this type of treatment had not even reached the experimental stage in mice, let alone been tried on humans with this strain of MDDS. Despite this, a doctor in the U.S. initially agreed to carry out the treatment (for adequate remuneration), although there was no evidence that nucleoside treatment could cross the blood–brain barrier, which it must do to treat *RRM2B*. The doctor also confirmed during this telephone conversation that he had never treated with nucleoside treatment anyone who had encephalopathy. Therefore, he was unable to indicate on any scientific basis whether a patient with encephalopathy would respond positively[49]. Domestic and foreign specialists agreed that at such an advanced stage of the disease, treatment would be futile – it would not reverse brain damage or significantly improve health or quality of life, and it would expose the patient to additional suffering. Domestic courts considered that there was therefore a risk of significant harm and, based on the criterion of the best interests of the child, refused to allow Charlie to leave the country and decided to lawfully withdraw all treatment, save for palliative care, to permit Charlie to die with dignity. The court put its role in deciding the family's private case as follows: "Some people may ask why the court has any function in this process, why can the parents not just make the decision for themselves? The answer is that, although the parents have parental responsibility, overriding control is by law vested in the court exercising its independent and objective judgment in the child's best interests"[50]. The parents lodged a complaint with the ECHR. The court found no infringement and declared the application inadmissible, giving priority to the best interests of the child, including in particular his physical integrity[51]. It accepted as a starting point that when the fair balance that must exist between the competing interests and means of protecting the child, the parents and public order is upset, within the margin of discretion of national law, priority can and should be given to the best interests of the child (par. 107), taking into account the child's well-being in terms of bodily integrity. Such a solution is also supported by a broad international consensus based on the best interests criterion. The Court went on to note that the domestic courts found that there was a risk of significant harm to Charlie if the treatment requested by his parents was implemented in his case, because, according to experts, experimental treatment with no chance of success would not benefit the patient, but would only prolong his suffering. The findings of the national courts were considered by the Court to be thorough and meticulous, and in conclusion, the Court found no violation of the Convention and declared the complaint inadmissible. Finally, the doctors managed to convince the parents and the maintenance of the child's life was withdrawn with their approval. Charlie died on 28 July 2017[(57)].

American law provides for the possibility of using experimental treatment under compassionate use. However, its hypothetical efficacy in the case of Charlie Gard was questioned by experts and therefore the parents' insistence was not considered[(58)]. As has rightly been commented, even the granting of such consent by a domestic court would not guarantee access to treatment in the USA. It is under the strict control of the Food and Drug Administration, and pharmaceutical companies are not allowed to make untested products available to doctors[(59)], especially when the method is at such an early stage of development that it is doubtful that it will bring the benefits that the patient expects[(60)]. On the other hand, pioneers of novel therapies often face resistance from the medical community, and there would be no progress in medicine if they did not break the rules by means that are not always legal. Individual patients can benefit from this. However, formalised authorisation procedures aim to provide a civilised framework for experimentation and to protect dependent and vulnerable patients.

These remarks also apply, but only in theory, to Alfie Evans, who suffered from a progressive neurodegenerative disorder of unknown origin that had already destroyed almost his entire brain. Eventually, Alfie found himself in a deep coma, unable to receive stimuli. He lost the ability to swallow and required CANH and ventilator support, with no hope of any improvement. Doctors decided that treatment options had been exhausted and further intensive care would be futile and inhumane, so they recommended withdrawing it. His parents objected and wanted to transport Alfie by air to Italy, where the Vatican's Bambino Gesu clinic in Rome volunteered to keep him alive indefinitely (it had also previously made a similar promise to Charlie Gard). After hearing numerous opinions from specialists, Hayden J ruled that mechanical ventilation was no longer in the child's best interests and would not be legal at this stage, so he decided to gradually disconnect Alfie from the ventilator[52]. To justify his position, he cited, among other things, the Royal College of Paediatrics and Child Health's March 2015 recommendations, Making Decisions to Limit in Life-limiting and Life-threatening Conditions in Children: Framework for Practice. In its second order, dated 11/04/2018, it approved Alfie's inclusion in palliative care. The appeal of the parents was unanimously dismissed[53]. The Court of Appeal found that Alfie's best interests were served by neither the

49. *Great Ormond Street Hospital v. Yates and others* [2017], 11.04.2017 EWHC 972 (Fam) No. FD17P00103.
50. *Great Ormond Street Hospital v. Yates and others*: 11.
51. ECHR 27.06.2017. *Charles Gard and Others v. The United Kingdom*, No 39793/17.
52. *Alder Hey Hospital v. Evans* [2018] EWHC 308 (Fam), 20.02.2018.
53. Court of Appeal, Civil Division, 2018/PL/10809 [2018] EWCA 984 (Civ).

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continuation of on-site treatment nor the arduous travel for the same purpose to Italy, as it gave no hope of improvement and could cause additional suffering during transit[54]. The parents' complaint to the ECHR was rejected without examination, and their application for a life-sustaining security order was denied[55]. Mechanical ventilation was disconnected. Three days later, Alfie's father announced that the child was breathing on his own[56], and two days later, on 28 April 2018, Alfie died.

Both cases concerned treatment that was considered futile by national medical consultants. In the case of Charlie Gard, it was a denial of experimental treatment, completely untested on humans, offering very doubtful chances of alleviating symptoms, and only slightly delaying the moment of death, but at the expense of additional suffering, and the cessation of mechanical ventilation(61). Alfie Evans's case concerned artificial life support.

In the Alfie case, the position of the Expert Team of the Polish Bishops' Conference on Bioethics was issued. It claimed that the disconnection from the ventilator was an act of murder, and not a withdrawal of "persistent" treatment, because hydration, nutrition and ventilation fall within the scope of minimal care, as long as the body is capable of living, that is, as long as the processes proper to it "are not exclusively the result of forcing through medical procedures": in the event of brain death or when the organism reaches its "natural" end (terminal states as a result of old age, illness, the effects of an accident). Concern for the boy's welfare requires a search for the causes of his illness and methods of treatment, including alternative therapeutic solutions, even experimental ones. Abandoning persistent treatment when it is technically possible to sustain organ function that does not benefit the patient by improving his health is legally permissible only if it involves excessive or disproportionate discomfort or if it could not be evaluated as a life-saving activity in view of the fact that it merely prolongs the agonal state. "The legality of deciding whether it is in a particular patient's best interest to continue his or her treatment because of his or her ability to experience the world in a particular way is highly morally questionable and stems from a strictly arbitrary ruling on the norms governing social life. Deprivation of life under such circumstances should properly be understood as euthanasia or homicide" (par. 10). "A legal system that genuinely takes into account the principle of protecting the dignity of the human person requires life-saving measures to be taken until clearly opposed by the properly understood good of the human person, that is, only when the measures are glaringly disproportionate to their effects, prolong the patient's suffering and when they are not the cause of his death" (par. 11).

What we have here is a proliferation of fallacies and the imposition of impossible obligations on medical personnel, in particular the requirement to continue seeking treatment even after it has been ruled that the possibilities of medicine have been exhausted and the patient's health has steadily deteriorated. In doing so, the KEP proclaims that the criterion of quality of life is arbitrary. In doing so, it disavows the strenuous efforts of weighing multiple goods and factors in determining the best interests of a particular patient through numerous court rulings, which in light of the court decisions cited earlier amounts to mere principled lip service. Instead, the KEP operates on the notion of "properly understood good of the human person", and this only serves as a stark example of arbitrariness. This good supposedly allows the withdrawal of only such measures that both prolong suffering, are glaringly disproportionate to the effects and when they are not (?) the cause of death. It constructs the judgment that only in the circumstances it has specified is withdrawal of a patient's treatment "legally permissible". Meanwhile, nothing of the sort emerges from the common law. Therefore, it is all the more worth emphasising the usefulness of the concept of futile treatment, recognised by medical professionals, when resolving critical issues in medical care(2: 148–149).

Charlie's parents, along Alfie's, have called for a reform of the law that would shift the boundary of judicial interference in medical decisions regarding critically ill children from a best interest test to a concern of significant or serious harm. According to Allison Howells, there is another reason why allowing parents the freedom to make final decisions in cases involving a critically ill child is not appropriate. Their judgment is often impaired, and what they do in an effort to protect their children "makes them vulnerable to the factors of time, emotional energy and money spent", which should be taken into account in the course of litigation(62). It is done by the Best Interests Test, giving weight to the parents' views, but not overriding power(33).

An American case cited by Anna Alchniewicz can be offered in support of this argument. It involved a 13-year-old girl, Jahi McMath, diagnosed with brain death after complications from tonsil and soft palate surgery. According to California's version of the Uniform Determination of Death Act, death was pronounced, but the patient was not immediately disconnected from the ventilator, as state regulations mandate that the family be given a short time to say goodbye. This family, however, not only objected to disconnecting the ventilator, but demanded the implementation of artificial nutrition. The hospital refused, considering it unethical and incompatible with medical professionalism to perform treatment on a corpse. The case went to court, where a peculiar settlement was reached. The hospital agreed to release Jahi McMath's body to the coroner, who issued a death certificate on 3 January 2014, and listed the cause of death as "under investigation". Two days later, the girl was and transported to New Jersey, one of the two states, alongside New York, where it is possible to express

54. *In the matter of Alfie Evans No 2*, 20.04.2018 [2018] EWHC 308 (Fam): 13.
55. *Evans v. the United Kingdom*, ECHR 23.04.2018, No 18770/18.
56. Who was Alfie Evans and what was the row over his treatment? BBC News 28.04.2018. Available from: https://www.bbc.com/news/uk-england-merseyside-43754949.

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disagreement with the diagnosis of death according to neurological criteria. Jahi McMath was admitted to the Catholic University Hospital in New Brunswick. One of the surgeons performed a tracheotomy, and a feeding tube was connected. Much of the hospital staff was opposed to carrying out these measures on a corpse, but nevertheless Jahi spent the next eight months in the hospital's intensive care unit[63].

Similar to Alfie Evans was the clinical condition of less than eight-month-old Indi Gregory. Soon after birth, she developed symptoms of numerous ailments and went on to develop seizures. In summary, Indi had profound and devastating cardiological, neurological, and metabolic disorders, which caused progressive damage to the brain, characterised by epileptic encephalopathy, respiratory insufficiency, abnormalities in the brain, developmental arrest, and early death. She was also diagnosed with intestinal malrotation where the gut is not positioned correctly, for which she underwent a corrective surgical procedure. Indi was on full life support for about a month, intubated, ventilated, with multi-organ support, and sedated. She was receiving the highest level of intensive care support but showed no sign of recovery. Her conditions were untreatable. The hospital asked the court for permission to withdraw treatment in the event that she deteriorated to a point where such treatment would be required to sustain life. Because there was no prospect of recovery, Indi's life expectancy was very short. The multiple treatments she was receiving were causing her tremendous pain and suffering. Indi's parents opposed the application.

A consultant stated that currently Indi showed minimal awareness of the world around her and she had very poor neurological functioning. She was one of the most severely ill children Dr E had ever dealt with. A second opinion by Dr S, from a different hospital, concluded: "Very sadly, further ventilation, painful procedures, or resuscitation is not appropriate. This is on the basis that physiological deterioration is occurring regardless of treatment, and that the severity of her progressive neurological condition is such that she can no longer benefit from continued life". A High Court judge, Peel J, took the view that the parents did not recognise the pain Indi was suffering, perhaps because they saw her through their own lens, which was "completely understandable. They were hoping against hope for something positive to emerge"[57]. However, the evidence clearly established that Indi was experiencing significant pain and distress several times a day, each episode lasting up to ten minutes. This pain was caused by her multiple treatment interventions. With a heavy heart, Peel J came to the conclusion that the burdens of invasive treatment outweighed the benefits. The significant pain was not justified when set against the incurable set of conditions, very short life expectancy, no prospect of recovery and, at best, minimal engagement with the world around her. Having weighed up all the competing considerations, the girl's best interests would be served by permitting the hospital to withdraw invasive treatment in accordance with the care plan presented – weaning Indi off intubation within one week and facilitating the use of a bag mask for up to a week after extubation, providing her with treatment to alleviate pain, and making her as comfortable as possible. That might take place at home or in a hospice, according to the parents' choice. At a later sitting, Peel J ruled that he could not consent to Indi being taken home because of the medical requirement to always keep her in a state of sedation – a 24/7 care package (with two nurses in attendance) – which would be very problematic to arrange. He also denied the parents permission to take Indi to a hospital in Italy for treatment there[58]. In Britain, as in Poland, it is possible to provide care through a home hospice, but there are many indications that the court did not trust Indi's parents and decided to prevent them from taking the child abroad. All the more so, since in the meantime Indi was granted emergency Italian citizenship by the country's prime minister, Giorgia Meloni, as part of an extraordinary last-minute attempt to have her flown to the Bambino Gesu clinic in Rome for treatment. However, the judges referred to the intervention by Italian consular officials as "wholly misconceived". Indi died in a hospice on 13 November 2023, four days after three appeal court judges ruled that life support treatment could be withdrawn only in a hospital or hospice, and not at the family home[59].

The point is that at some stage of medical care for a patient with irreversible brain damage, after the withdrawal of other forms of treatment, it is possible to maintain vital functions using invasive techniques. As long as mechanical ventilation and parenteral nutrition are in place, the patient is considered "alive". The child receives only pain stimuli from the environment, but the pain can be relieved by sedation. This is the case, for example, in Poland. Individuals might spend years in a vegetative state in nursing homes[60]. Among them are children admitted shortly after birth with congenital defects, with no prognosis that they might ever gain consciousness. Their bodies gradually grow pubic hair, breasts, genitalia, but they are not even aware of their own existence[61]. "They lie for several – over a dozen years, without awareness, e.g. after cardiac arrest, or not breathing as a result of muscular dystrophy", says Elżbieta Rękorajska MD. "You don't just die in a hospital. If resuscitation has been waived, please explain why. No one wants to know why

57. In the matter of Indi Gregory, The High Court of Justice, Fam., 13 Oct. 2023, Case No: FD23P00452: 43.

58. In the matter of Indi Gregory, The High Court of Justice, 8 Nov. 2023 [2023] EWHC 2798 (Fam.).

59. Halliday J: Indi Gregory, baby girl at the centre of a legal battle, dies after life support removed. The Guardian 13.11. 2023. Available from: https://www.theguardian.com/uk-news/2023/nov/13/indi-gregory-baby-girl-at-centre-of-legal-battle-dies-after-life-support-removed.

60. See: Nie rozmawiamy o tym, stoimy obok – rozmowa z Barbarą Kaczmarską, dyrektorką Zakładu Opiekuńczo-Leczniczego im. Sue Ryder w Warszawie. Wysokie Obcasy, 9.07.2011 r.

61. See: Siedlecka E: Kiedy można umrzeć. Polityka 2021; 11: 17–20. Dr. E. Rękorajska: za: ibidem: 18.

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they were resuscitated. The doctor invokes the conscience clause, unwarranted medical procedures escalate. Vegetative states persist for years"[62]. Such biological persistence does not benefit patients in the slightest. So, the question is what value it presents and whom it really serves.

The child says they've had enough

Despite the widely accepted view that futile treatment is inappropriate and even constitutes medical misconduct, on the basis of a review of cases it seems that it is maintained more often in relation to children than in relation to adults. Disputes about this also show that it is not always easy to determine which medical activities should be classified as futile. To consciously demand the cessation of futile treatment, the child must understand that it is indeed futile. This does not mean that there is always a duty to make him or her aware of it. Sometimes, we protect terminally ill children from the painful truth in the hope that they will not realise it and will pass away unexpectedly by themselves, preferably in their sleep. This attitude narrows the number of situations when a child manages to recognise that treatment has no sense. However, deceiving a dying child with "white lies" can have a moral justification only if it remains undetectable – for example, so that it is not exposed by an internet search on a smartphone, or so that it does not insult the intelligence of the patient. When the dynamics of the disease are at an end stage that can be readily identified, it is impossible to pretend that it is not getting worse. This applies especially to the experience of chronic diseases, when the patient spends a large part of their life in hospitals. The starting point for respect for the autonomy of a dying child is the set of criteria from the classic informed consent canon developed by Beauchamp and Childress: disclosure of material information, ability to cope with the decision task (factual competence), awareness and understanding of the situation (competence to understand and decide), understanding of information and recommendation, voluntariness with intention and without controlling influences (intentionality and freedom from pressure)[27: 120–121]. However, this set of criteria should be adjusted to account for specific factors: 1) the case concerns a child; therefore, a negligible factor should be included for the adult patient – the authenticity of the decision – i.e. one expressed in a well-recognised self-interest and without regard to others; 2) the decision is a manifestation of negative autonomy; 3) the treatment in question is futile, but its cessation will accelerate imminent death. It is therefore not a question of considering the pros, cons, and risks of improvement-prospecting treatment, but one of the personal experiences of an intolerable end-stage situation. It is obvious that one should not take seriously a six-year-old running around the haematology ward shouting "I want to die!" while suffering side effects of chemotherapy with a successful prognosis. The focus here is solely on states without hope and without any prospects, and at the same time causing suffering or at least a sense of utter futility of further efforts. This is illustrated by the genuine example of a 15-year-old with Duchenne muscular dystrophy who cried out: "Let me finally fucking die!"[63] after hearing about the planned implementation of parenteral feeding (the dynamics of muscle atrophic diseases is that they gradually deprive the patient of all the pleasures of life, and one of the last is enjoying the taste of food). In the literature, it is pointed out that the child's mental agility, which determines competence, should be seen as a spectrum. According to the scale developed by Priscilla Alderson, four levels of child involvement in decision-making can be distinguished: 1) being informed; 2) being consulted; 3) having views taken into account in decision-making; 4) being respected as the main decision-maker. Achieving the first level of fitness only entitles children to receive appropriate information. Entering the second allows them to express their own opinion on the treatment. The third level allows co-decision on treatment, but only the fourth gives the paediatric patient a decisive vote[64]. The fact that the patient can understand the content of the information provided does not mean that they will be able to use this information effectively. "Children progress through varying degrees of competence as they grow, develop and acquire life experience. Their involvement in decision-making is subject to their level of competence and this must be judged on an individual basis". Although the age criterion is adopted for legal purposes, in practice age is not necessarily a good measure of capacity. As Carol Kendrick's research has shown, nine-year-old children suffering from cancer already understand that a certain type of treatment can cause side effects (such as falling hair or swollen cheeks) and can accept this for its therapeutic purpose. They also understand disease-induced changes in the body, recognise their causes, and quickly learn the right medical terminology[65]. These findings provide strong support for the proposed partnership treatment of child patients, whenever they are able to at least understand the information provided. Achieving this first level of ability should be a clear signal that the child's competence should be viewed as high. It goes without saying that the message should be adapted to the child's cognitive abilities.

However, this does not provide an unambiguous answer to the question whether a decision to refuse treatment at the end of life requires more or less competence. Initially, it can only be assumed that this competence is very different from positive autonomy. For example, the ethical guidelines adopted at the Royal Children's Hospital Melbourne provide that decision-making during palliative care requires: 1) the ability to understand one's illness in physiological terms and to conceptualise death as an irreversible

62. From care and treatment facility with mechanical ventilation in Konstancin-Jeziorna.

63. This example was given by a doctor during a discussion at a legal-medical conference in Białystok, Poland, in March 2023.

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phenomenon; 2) the capacity to reason and consider future implications (formal operations stage of cognitive development); 3) the ability to act autonomously and not acquiesce to the authority of doctors and parents[66].

This results in increased requirements for the actual ability to cope with the decision-making task. On the other hand, the end-stage condition and futility of further treatment of the child require, in my opinion, greater than usual trust and respect for the child's individual feelings, as long as they are fixed and internalised feelings, rather than merely impulsive reactions. Consequently, the decision to discontinue futile treatment does not fall within the scope of all the criteria for the precise determination of competence set out in the literature. In particular, the assessment of rationality, in the sense of logical-cognitive competence, should not be a decisive criterion. To a greater extent than usual, it is worth taking into account so-called emotional intelligence. If it is possible to feel the suffering of a completely incompetent child and decide to withhold intensive care, it is all the more necessary to respect the will of a child suffering in the same way, but who is able to consciously express their needs. This is especially true for chronically ill children. Priscilla Alderson saw a high probability that children who have experienced chronic illness and hospital more clearly felt the limitations of treatment or its failure, and this enabled them to make a more realistic assessment of their situation[64: 15–16]. In turn, Anna Tyborowska's team has shown that under conditions of severe stress – perhaps caused by poor health – children's intellectual performance increases significantly thanks to the accelerated development of certain brain structures observed at such moments[67].

For this reason, it is possible, in my opinion, to relax some of the criteria for the effectiveness of opposition to futile treatment and to reduce them to an informed understanding of the health situation – including its inevitability and the implications of a faster death, the intentionality of the decision, and assurance that it is authentic and free – that is, only taken for one's own sake. The demand to stop futile treatment declared as intolerable may just as well result from the conviction of being a burden for parents or siblings or from the desire to meet someone's expectations. I reiterate that this is not a question of abandoning mandatory activities dictated by positive medical indications, but of suspending procedures that prolong agony and *de facto* interfere with dying – such as, in particular, mechanical ventilation and CANH in the terminal phase of the disease.

CONCLUSIONS

In the analysed cases, doctors often emphasised the suffering of small patients under medical care and used it as a crowning argument for stopping intensive care, although they sometimes exaggerated this argument due to their lack of perception of simple pleasures that prevailed over the ailments. The nurses' accounts cited in several judgments were more nuanced and provided information about the daily feelings of young patients, including their enjoyment of life. Day-to-day observation at the bedside were also reported by parents, but their objectivity was sometimes undermined by wishful thinking. Many times, they saw what they wanted to see, and they supplanted unfavourable knowledge. In a child, the individual benefits of life predominantly take the form of simple pleasures: warmth, respite from convulsions, closeness and contact with loved ones, positive sensory sensations from the environment, lack of pain, shortness of breath or anxiety, the ability to breathe without difficulty, eat well, digest and excrete well without painful interference, absence of persistent vomiting, no hunger or thirst. In older and more self-aware children, it may also be important to look forward to a promised pleasure or a new experience. With the prospect of improving or maintaining health, suffering and pain can be considered explicable, but suffering and pain before death have no justification. In the Judeo-Christian cultural circle, suffering is of extreme importance, and this hinders the rational weighing of pros and cons: to sustain a dwindling life in suffering for as long as possible – or to end suffering at the expense of shortening life in the face of imminent death. It is rightly repeated that the decision-making criteria for further treatment and intensive care must be adapted to the individual condition of the child concerned. The starting point, however, is at least the hypothesis of a successful prognosis, or a reasonably stable clinical condition that is bearable. Charlotte Wyatt spent a long time balancing on the verge of death, mentally disabled and malnourished, but gradually achieving improvement. Due to persistent respiratory problems, the moment of cessation of efforts was considered a respiratory crisis requiring the use of a ventilator because, according to doctors, Charlotte's weak body would not be able to survive it anyway. The court-approved attitude of waiting in readiness for rescue was adopted, but without using the most invasive method – in this case, considered ineffective. Medically justified consent to death was therefore by refraining from connecting the ventilator. Alexandra, who had Down syndrome, received surgical clearing of the intestines, her condition otherwise justified a positive prognosis. Robert Houle was in a much worse situation, but the surgery to close the fistula was ordered by a court in the name of "everyone's right to life" rather than based on a comprehensive consideration of the prognosis. Madzia Słabiak passed away in peace, as the prognosis for two coexisting heart defects was so poor that the parents were "allowed' to make this decision. However, if they had insisted on treatment, operations would have been carried out. In the case of M, the court ordered the temporary maintenance of mechanical ventilation and medical nutrition because the patient, although completely inert, still enjoyed life in his own modest way. The court decided, in opposition to the doctors, that the benefits of life outweighed the ailments, although the moment would come when the ailments would prevail and resuscitation should not be performed. The critical moment would therefore be cardiac arrest in the course of SMA.

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In the case of K, the court found that this moment had already occurred. The disease was fatal as in M's case, but K suffered such severe ailments with virtually no life benefit that withholding TPN nutrition was considered an act of mercy. In the Chazan case, such a severe form of anencephalia condemns the patient to inevitable death immediately after birth, so any intervention would only prolong dying. In my opinion, the most humane way to treat this boy would have been to use appetite suppressants and not connect him to feeding tubes. The moment when life-sustaining care should have been abandoned was the moment of birth. Charlie Gard, Alfie Evans, and Indi Gregory suffered from terminal mitochondrial diseases. Each of them was in a state of deep collapse and at the stage when medicine had nothing to offer but palliative care, so the decisions taken to stop mechanical ventilation were justified. Indi received life-saving intestinal surgery at an early stage, before she developed all the dysfunctions and when the prognosis of her condition was not yet known, so it was justifiable to carry out the procedure. The 15-year-old with Duchenne dystrophy, who understood his situation, should have had the right to refuse invasive care when in a terminal state – provided he was not acting on a momentary impulse, but was refusing intentionally, freely, and solely for his own sake. The same should apply to all children who meet the material criteria of "mature minors".

A child patient is at the beginning of the path of life, which, as a rule, should not be closed. However, this path can be blind, short, and so thorny that no one should be condemned to walk it. In states of imminent death, it may, in my opinion, be considered inhumane to allow a child to feel the full extent of their suffering, so it is better to put an end to it before it truly begins. It may even be necessary to comprehensively consider the desirability of palliative surgery as well as discharge from the hospital – so that the actual decision does not fall exclusively into the hands of parents. Such children should only live for themselves and not for others, and the quality of life should be assessed solely from their point of view: the pleasures of living in such a state. From this perspective, it should make no difference whether the intervention involves treatment in the strict sense, medical nutrition, or mechanical ventilation. The assessment is hindered only by a rigid attachment to the principles of so-called primary care and instinctive opposition to allowing death from starvation and dehydration. The argument is used that feeding the hungry is one of the simplest gestures of concern and a symbol of the fact that human life is always embedded in the life of the whole society and community(65). The caring symbolism of nutrition, however, is not an argument in itself: it can be considered justified only if nutrition brings benefits to the patient. In my opinion, therefore, it is reasonable to consider its futility. The position of any nutrition as part of mandatory primary care results from a top-down assumption, so as an unshakable care principle, it does not yield to rational persuasion. However, if, at a given stage of medical care, nutrition and hydration do not bring the patient any real or perceived benefit from life but only follow an arbitrarily adopted principle – then, from the point of view of the patient's good, it is superfluous, and this is the main argument in favour of legal cessation because its value is purely abstract. Feeding a person for whom it is not necessary undermines their interests, ceases to serve them, and becomes an empty act. In fact, it works for the benefit of third parties instead. It provides carers with positive reinforcement and moral satisfaction that they are "doing their job". The insistence of parents to continue such care more satisfies their own emotional need and can be judged as a violation of the child's privacy – the right to pass away in peace and dignity. Maintaining life at all costs through medical intervention reduces the patient to the role of a doll in a game of feeding and changing.

Sustaining life in the end-stage of a terminal illness can be considered harmful if it brings nothing but prolongation of suffering. Based on the review of cases, it is therefore worth summarising when interventions including medical nutrition and hydration can be considered futile.

1. When there is no benefit in remaining in a certain state without any hope of improvement – e.g. with severe and lethal Edwards or Patau syndromes in the very short term[64], or in an irreversible vegetative state resulting from birth defects.
2. When there is an established inability to live and the prospect of imminent death. The inability to live can also be the sum of many defects – as suggested by the Baby Houle Case.
3. When it causes or prolongs torment in the absence of any chance of improvement, delaying the inevitable death – as was the case with the incranial newborn in the Chazan case. In other words, "in circumstances where the end is postponed only for a short time"[65].
4. When it only brings additional suffering before inevitable death. This might include pressurised air pumping by a ventilator or pain caused by numerous injections, drips, and catheters, the meticulous description of which occupied a lot of space in the Indi Gregory judgement.
5. In the terminal state of a terminal disease with a longer course, when the only sensation felt is pain.
6. When the possibility of survival depends on mechanical surgical correction – such as clearing the intestines, ballooning critically narrowed blood vessels, or implanting a valve reducing hydrocephalus – the appropriateness of the procedure should be weighed against the general condition of the child so as not to unnecessarily prolong suffering. Let us remember that this applies only to the context of a clearly lethal defect, with no prospects for the future, where the treatment itself brings additional ailments and may not even provide relief.

64. See: *Re L* (a child) *(medical treatment: benefit)* [2004] EWHC 2713; follow: Huxtable R: Law at the limits of life: children, welfare and best interests. In: Huxtable R: Law, Ethics and Compromise at the Limits of Life: To Treat or not to Treat? Routlege, London 2013: 46.
65. *Re B (a child) (medical treatment)* [2008] EWHC 1996 § 18.

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7. When death by starvation through appetite suppression means such as dihydrocodeine is more tolerable (i.e. causes less suffering) than dying in agony caused by incurable defects or fatal deformities. In the case of baby girl K with congenital myotonic dystrophy, the court's authorisation stated that medical personnel could remove the intravenous line providing parenteral nutrition and begin palliative care, since the expert neonatologist placed K's condition somewhere between "no chance" and "no purpose" situations. In turn, the judge concluded that it would not only be merciful, but also in K's best interest to stop administering TPN while she was still clinically stable, so she could die peacefully and in a relatively short period of time.

Under such circumstances, further treatment should be considered futile, because it neither achieves the therapeutic goal nor benefits the patient. Not only is it permissible to be discontinued through a collegial decision of a team of medical specialists, without the need to appeal to the court, but the Code of Medical Ethics, in its updated version, states categorically that a doctor is not allowed to administer futile treatment. Professional guidelines, on the other hand, recognise futile treatment as a medical malpractice. In this way, the laws of medical knowledge and medical ethics form a model for the proper handling of clinical situations "without purpose and without exit". These documents mark an effort to somehow flesh out the criteria that justify the cessation of treatment in accordance with medical knowledge, and to create reasonably clear ethical principles. In the absence of specific legal regulations, ethics and professional guidelines supplement the overly laconic law, and are mandated by the reference in Article 4 of the UZL. The same directives should guide the courts, once they have undertaken the moral effort of issuing rulings authorising the withdrawal of treatment. It has been shown that a substantive legal basis exists, as does a legal interest on the part of the doctors or the treatment entity. The status of the applicant in such a proceeding allows them to take an active part in it as the "host" of the proceeding, provided they take the trouble to specify this interest in the application and are not deterred by a refusal.

In adjudicating, the court's task will first be to determine whether the medical opinion is consistent, complete, and free of inaccuracies. As a review of British rulings shows, courts there make extensive use of independent expert opinions to make sure that all the advantages and disadvantages of continuing treatment have been thoroughly analysed, and no important factor has been overlooked. They also give careful consideration to parental opinions, emphasising great respect for the devotion of the parents standing by the child's bedside and declaring sympathy for their suffering. One can see a certain diplomacy in this, but at the same time one can sense sincere empathy on the part of the judges, evident in the stylistic layer of the justifications. Regardless, the court's verdict is guided by the criterion of the child's best interests, including the individual benefits of medical care and their relation to burdens and ailments. This balance is made in each recognised case and with the indication that the court does not make a subjective and top-down valuation of the patient's quality of life, but rather tries to empathise with the patient's condition and assess how THAT child perceives his condition.

The best interest test finds a statutory basis in British law; nevertheless, it is simultaneously explained that it is an expression equivalent to the criterion of child welfare. The British use the terms "child welfare" and "best interests" interchangeably, with equal effect of assessing the multi-factor balance. The concept of child well-being is capacious enough to include such an expansion. The evaluation thus breaks away from any principlism in favour of the interests of that child taken personally: it requires empathy with the patient's position and enjoyment of life. While there is a strong presumption in favour of life, this can be rebutted if continued treatment or a new intervention is deemed futile. The best interest test is both comprehensive and pragmatic. It provides a well-established analytical framework that has evolved over decades in the British judiciary and allows for the consideration of a broad context of various factors, including possible harm[68], and at the same time has been practiced and passed the test also in very unusual cases. If the case goes to court, there should be a balancing act, taking into account all the factors that count for and against, not just medical ones[based on: 52]. Whatever name you give it, in determining the welfare of a child, it is always necessary to collate all those interests of the child that can be established and then balance them. This is an obvious course of action from a pragmatic point of view. It is also obvious that in this balancing act there is no room for the parents' own views on what they personally consider "good" for the child. As Beauchamp and Childress point out, "quality of life estimation" does not refer to the social value of individuals (in particular, it does not promote the opposition "useful" – "not useful"), but rather to their individual lives[27: 193]. One assesses the value that life represents for a particular person, not for the general public or from the point of view of third parties. In other words, one balances what benefits that particular person derives from staying alive. Rather, it is a matter of determining all the benefits and inconveniences, and then comparing what prevails, or at least whether the inconveniences are worth enduring for the sake of the pleasures experienced. Under ordinary circumstances, the drastic nature and invasiveness of medical measures used are outweighed by the prognosis for improvement of the condition. However, when the prognosis is inauspicious – nothing justifies the drastic measures and invasiveness anymore, especially when the pain is felt until the very end. The argument raised in the British verdicts that human dignity is being violated by sustaining the body's vital functions by force is based on the conviction that remaining in such a condition without any chance of improvement makes such continuance unworthy of a human being in light of the image it presents. The argument relating to respect for the "dignity

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of the human being" serves both supporters and opponents of life support by means of advanced technology. The former argue that dignity will be violated by disconnecting mechanical ventilation and feeding by probe, because it condemns a person to suffocation and death by starvation, while so-called primary care is one of the chief humanitarian duties. The other group argues that most people would not want to be kept in a condition that not only serves them in no way, but also exposes them to a deplorable view as an entirely externally powered facility. Very young children are indifferent to this, while it will be important to feel any pleasure from living in such a state.

In the *Bland* case, the House of Lords ruled in favour of discontinuing life support when the balance of value of less than or equal to zero. The best interests criterion is objectified and thus well suited for use in cases of patients who are incapable of making decisions and, at the same time, unable to express their preferences in any way. However, deciding according to the quality of life criterion is sometimes seen as an "undoubted flaw" in the objective test[66]. It is significant that the objectification of references was considered an unquestionable flaw merely because of the reference to the criterion of quality of life. This suggests some kind of misunderstanding or a programmatic closure to a particular message. Therefore, it should be emphasised once again that the quality of life is evaluated in the subjective perception of it by the patient in question. The well-being of the child as a patient undergoing intensive and highly invasive life support requires a positive outcome of all factors signifying a benefit, that is, a satisfactory quality of life for the child. Of crucial importance is the quality of life as perceived by that child, particularly when it turns out to be "unbearable". The suffering factor should be one of the more relevant indications.

Quality of life assessment is a criterion commonly considered in the application of various treatment methods. For example, it often favours a sparing method over a radical one and opposes a disproportionately invasive one. Foreign judgments present the argument that an incompetent patient should not be exposed to a futile treatment that an informed patient would most likely reject for the sake of quality of life in that condition. An alternate decision requires adopting the same criteria(3: 635–636). An individual's life is of good quality when an analysis of interests – benefits, burdens, and hardships – allows one to conclude that the person (and not someone else) derives a tangible benefit from this life. This is how the best interests should be understood, taking into account individual factors. The criterion of quality of life according to best interests is not universal for everyone. It is useful only when the preservation of life requires medical maintenance or highly invasive procedures, while the individual concerned is not competent enough to decide for themselves(69).

The second major issue is how to choose the right moment to stop intensive care. No human being, let alone an unintelligent child with profound injuries, has an obligation to endure suffering, and adults should not avoid decisions that shorten it in declining states. On the child's side, it is possible to note at most a survival instinct that causes another aggressive resuscitation to have a positive effect for a short time. The right to die in peace and dignity is, of course, also held by newborns and infants, because they too feel pain, cold, or loneliness. Pain is a primitive response, so in the cases of Charlie Gard and Alfie Evans it was implicitly assumed that it was felt by them, and this was taken into account when refusing to transport patients pointlessly from place to place. Before there was an unexpected improvement in Charlotte Wyatt's condition, doctors testified that "she only feels pain". When the perceived stimuli are limited to unpleasant ones with no chance of any improvement, one may argue that keeping the patient in pain is undignified. When suffering is not relieved by medication – one can ask the rhetorical question whether it is better for a person to remain in this state longer or shorter. The desirability of palliative care is not disputed by anyone, but one should also consider its limits. This is because some of the medical activities carried out under its banner – including feasible but not always necessary corrective surgery, artificial ventilation, and continued nutrition until the very ned – are still questionable. The gastric probe feeding of the "Chazan newborn" made him suffer longer than he had to, because as the parents observed – the morphine did not work, presumably because he had developed purulent inflammation. In my opinion, we should not have waited for this to happen, because the child's death was inevitable and imminent anyway. This case in particular makes one wonder whether the recommendation included in the 2011 Paediatric Guidelines to continue feeding for neurological conditions with dysphagia is appropriate to the clinical condition of a child born without a skull. Such a severe lethal defect means that the baby is born only to die imminently. Artificial nutrition delays "natural" death. When death arrives with unbearable agony, the problem arises as to what purpose is served by delaying it. One principled prohibition blocks individual and comprehensive evaluation of such cases, and this is presumably what it was formulated for. Thus, any "but" will be equated with a violation of the order. This is wrong because it is arbitrary and unreflective. Such a generally formulated recommendation has nothing to do with current medical knowledge. It is harmful and leads to the multiplication of suffering. The argument that "because they will starve" rises to the status of a taboo halting all further thought. Meanwhile, force-feeding interferes with the usual course and decline of an incurable disease. If nothing else, the conscience clause should deter fierce treatment and life support at all costs, especially at the expense of prolonging agony. It is sufficient not to insert a feeding probe, but to administer drugs to relieve and abolish the feeling of hunger. The patient's interest in

66. Śliwka M: Prawa pacjenta w prawie polskim na tle prawnoporównawczym. 2nd ed., TNOiK, Toruń 2010: 367.

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abandoning nutrition is to shorten unmeasurable torment if it accompanies a congenital lethal defect or in the hopeless condition of an incurable disease. Appetite suppressants then make starvation death come gently and shorten other forms of suffering. One can find examples when this is, in my opinion, morally justified. I aim to distinguish whether the dying process is of "bearable" quality (as in the case of Madzia Słabiak), or whether it takes place in agony.

Death-inducing discontinuance of care may be the subject of an objection only if it is possible to establish duty of action on the part of doctors. Positive indications for treatment depend on what it improves and for how long. Treatments are advisable if they improve the comfort of life, or at least alleviate the process of dying. They are not advisable if they only serve to "do something" that is technically possible but will not bring the patient any benefit. This principle applies equally to feeding and hydration – although here we touch on the global taboo of so-called "primary care". The mechanism of judicial review of decisions in such cases is valid, but as long as the body actually remains independent and unaffected by external ideological pressures.

Conflict of interest

The author does not report any financial or personal connections with other persons or organisations which might negatively affect the content of this publication and/or claim authorship rights to this publication.

Author contribution

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Opieka lekarza rodzinnego i pediatry nad pacjentem z rdzeniowym zanikiem mięśni

Family doctor and paediatrician care for a patient with spinal muscular atrophy

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Streszczenie

Rdzeniowy zanik mięśni (*spinal muscular atrophy*, SMA) w swoim naturalnym przebiegu jest chorobą neurodegeneracyjną, prowadzącą do niepełnosprawności ruchowej, postępującej niewydolności oddechowej i ostatecznie zgonu. Szacuje się, że częstość występowania tej choroby w populacji polskiej wynosi około 1/7600 urodzeń. Obecnie skuteczne, nowoczesne metody leczenia pozwalają traktować SMA jako chorobę przewlekłą. Wczesna i efektywna diagnostyka prowadzona w oparciu o noworodkowy przesiew populacyjny, a następnie wdrożenie jednej z trzech dostępnych terapii umożliwia spowolnienie procesu chorobowego i nabywanie przez pacjentów kolejnych umiejętności rozwoju ruchowego. Kompleksowa opieka dotycząca odżywienia, diagnozowania zaburzeń układu oddechowego, pokarmowego i mięśniowo-szkieletowego oraz rehabilitacji pozostaje wyzwaniem dla systemu ochrony zdrowia. W artykule omówiono podstawowe zagadnienia dotyczące etiologii i dziedziczenia SMA, typowego obrazu klinicznego choroby, zasad funkcjonowania w Polsce badań przesiewowych noworodków, terapii dostępnych w ramach programu lekowego (nusinersen, rysdyplam, onasemnogen abeparwowek), a także codziennej opieki nad pacjentami z rozpoznaniem SMA i stosowanej u nich profilaktyki zdrowotnej. Ważnym zadaniem lekarzy podstawowej opieki zdrowotnej jest aktywne poszukiwanie możliwych powikłań choroby i działań niepożądanych stosowanych leków oraz realizowanie programu szczepień. Pacjenci z SMA będą stanowić coraz większy odsetek chorych w gabinetach lekarzy rodzinnych, dlatego wyjątkowo istotna jest ścisła współpraca pomiędzy lekarzami rodzinnymi, pediatrami i neurologami w kwestii pełnej i skoordynowanej opieki.

Słowa kluczowe: rdzeniowy zanik mięśni, rehabilitacja, terapia genowa, badania przesiewowe noworodków

Abstract

Spinal muscular atrophy (SMA) is a neurodegenerative disease leading to motor disability, progressive respiratory failure and ultimately death. Its incidence is estimated at approximately 1/7,600 births in the Polish population. Owing to effective, modern treatment methods, SMA may be nowadays considered a chronic disease. Early and effective diagnosis based on newborn screening, followed by the implementation of one of the three available therapies, makes it possible to slow down the disease progress and to acquire further motor development skills by patients. Comprehensive care including nutrition, diagnosis of respiratory, gastrointestinal, and musculoskeletal disorders, and rehabilitation remain a challenge for the health care system. In the paper we discuss basic issues on the aetiology, inheritance patterns and typical clinical picture of SMA, the principles of neonatal screening in Poland, the treatments available as part of the drug therapy program (nusinersen, risdiplam, onasemnogene abeparvovec), as well as everyday care and health prevention in patients diagnosed with SMA. Special attention was paid to physiotherapy and motor improvement. An important task of primary care physicians is to actively search for possible complications of the disease and adverse effects of treatment methods, and to implement the vaccination programme. Individuals with SMA will constitute an increasing percentage of patients in general practice offices,

which is why close cooperation between general practitioners, paediatricians and neurologists is extremely important to ensure comprehensive and coordinated care.

Keywords: spinal muscular atrophy, rehabilitation, gene therapy, newborn screening

WSTĘP

Rdzeniowy zanik mięśni (*spinal muscular atrophy*, SMA) jest neurodegeneracyjną, genetycznie uwarunkowaną chorobą, w której dochodzi do postępującego osłabienia siły mięśniowej na skutek uszkodzenia motoneuronów alfa rogów przednich rdzenia kręgowego[1]. Zanik tkanki mięśniowej obejmuje początkowo dosiebne grupy mięśni kończyn górnych i dolnych, a następnie mięśnie oddechowe, w naturalnym przebiegu choroby doprowadzając ostatecznie do zgonu. W ciągu ostatniej dekady dokonał się ogromny postęp w zakresie leczenia SMA, zmieniając charakter choroby z potencjalnie śmiertelnej na przewlekłą.

Szacowana częstość występowania SMA na świecie wynosi 1 na 11 000 urodzeń. Choroba dziedziczy się w sposób autosomalny recesywny, a nosicielem zmutowanej kopii genu *SMN1* (*surviving motor neuron 1*) jest jedna osoba na 40–67 w populacji[2]. Dzięki wprowadzeniu powszechnych badań przesiewowych noworodków znana jest częstość występowania choroby w Polsce, która wynosi około 1 na 7000 urodzeń, co pokrywa się z danymi dotyczącymi populacji niemieckiej (1:6910)[3,4].

Molekularne podłoże SMA polega w zdecydowanej większości przypadków (około 96%) na biallelicznej delecji eksonu 7 genu *SMN1* zlokalizowanego na długim ramieniu chromosomu 5 (5q11.2–q13.3). Mutacja powoduje brak produkcji funkcjonalnego białka SMN, niezbędnego do prawidłowego działania motoneuronów. W okolicy centromeru tego samego chromosomu jest zlokalizowany gen *SMN2*, paralog genu *SMN1*, dzięki któremu produkowana jest niewielka ilość stabilnego białka SMN[5]. Liczba kopii genu *SMN2* u pacjentów z SMA jest różna, a przy jej zwielokrotnieniu (np. w mechanizmie duplikacji) objawy choroby pojawiają się zazwyczaj później i postępują wolniej[6]. W niewielkim odsetku przypadków za wystąpienie SMA odpowiadają mutacje punktowe.

Klasyfikacji SMA na pięć typów dokonano na podstawie przebiegu klinicznego i wieku, w którym występują pierwsze objawy choroby. Wyróżnia się w niej typ 0, rzadko występującą postać o najostrzejszym przebiegu i najwcześniejszej prezentacji. Matki dzieci z SMA tego typu zazwyczaj słabo czują ruchy płodu podczas ciąży, a dzieci po urodzeniu są zupełnie wiotkie oraz niewydolne oddechowo i wymagają wentylacji mechanicznej. W przypadku typu 1 (najczęstszego) objawy choroby pojawiają się w pierwszym półroczu życia dziecka. Na skutek szybko narastającego osłabienia siły mięśniowej chorzy nie osiągają kamienia milowego samodzielnego siedzenia, a w przypadku braku leczenia wymagają wentylacji inwazyjnej zazwyczaj w drugim półroczu życia[7]. Ten typ był do niedawna uznawany za najczęstszą uwarunkowaną genetycznie przyczynę zgonu u niemowląt. Dzieci z SMA typu 2 w rozwoju osiągają kamień milowy samodzielnego siedzenia, ale same nie chodzą, a początek objawów zazwyczaj przypada na 7.–18. miesiąc życia. W typie 3 pierwsze objawy pojawiają się po rozpoczęciu chodzenia, a w rzadko występującym typie 4 do osłabienia siły mięśniowej dochodzi u pacjentów dorosłych[8].

Obecnie dzięki badaniom przesiewowym i możliwości wdrożenia leczenia przed pojawieniem się ewidentnych objawów klinicznych opisana klasyfikacja zyskuje znaczenie historyczne. Pacjenci z SMA żyją znacznie dłużej i poprawia się ich jakość życia. Wyzwaniem staje się konieczność zorganizowania opieki wielodyscyplinarnej i zmierzenia się z problemami typowymi dla pacjentów z chorobą nerwowo-mięśniową o przebiegu przewlekłym. Celem pracy jest wprowadzenie lekarzy rodzinnych i pediatrów w zagadnienia związane z opieką nad chorym z SMA.

POWSZECHNE BADANIA PRZESIEWOWE NOWORODKÓW

Zgodnie z Rządowym Programem Badań Przesiewowych Noworodków badania w kierunku SMA rozpoczęły się w kwietniu 2021 roku. Stopniowo włączano do badań kolejne województwa, a od kwietnia 2022 roku badaniami objęte są wszystkie noworodki urodzone w Polsce. Podobnie jak w innych badaniach przesiewowych (np. w kierunku mukowiscydozy czy fenyloketonurii), w 3. dobie życia jest pobierana krew włośniczkowa na bibułę. W pierwszym kroku stosuje się metodę amplifikacji DNA za pomocą łańcuchowej reakcji polimerazy (*polymerase chain reaction*, PCR) uzupełnioną analizą krzywej topnienia produktów amplifikacji (*high-resolution melting analysis*, HRM) umożliwiającą wykrycie w badanej krwi homozygotycznej delecji eksonu 7 genu *SMN1*. Ze względu na możliwość uzyskania wyników fałszywie dodatnich w przypadku próbek dających wynik nieprawidłowy lub wątpliwy przeprowadza się weryfikację metodą MLPA (*multiplex-ligation dependent probe amplification*)[9]. Ograniczeniem badania przesiewowego jest niemożność rozpoznania delecji heterozygotycznej z mutacją punktową drugiego allelu. W związku z tym szacuje się, że rocznie w Polsce u 1–2 dzieci z SMA choroba nie zostanie wykryta w screeningu. Placówką odpowiedzialną za wykonywanie analiz jest Zakład Badań Przesiewowych i Diagnostyki Metabolicznej oraz Zakład Genetyki Medycznej Instytutu Matki i Dziecka w Warszawie.

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Do 7 czerwca 2024 roku badaniem objęto łącznie niespełna 106 tysięcy noworodków, uzyskując 103 wyniki dodatnie, co pozwala oszacować częstość występowania choroby na 1 na 7602 (dane dotychczas niepublikowane, uzyskane dzięki uprzejmości prof. Moniki Gos). O nieprawidłowym wyniku badania informowany jest ośrodek zajmujący się diagnostyką i leczeniem w województwie odpowiadającym miejscu zamieszkania pacjenta lub najbliższym ościennym, który niezwłocznie powiadamia rodziców i wzywa ich z dzieckiem do szpitala w celu omówienia wyniku, oceny klinicznej i pobrania próbki krwi żylnej na badanie weryfikujące. Wykaz jednostek jest dostępny na stronach internetowych Narodowego Funduszu Zdrowia (NFZ) i Fundacji SMA[10]. Wyniki badania przesiewowego są dostępne około 8. dnia życia dziecka (mediana; *SD* 3,65), badanie potwierdzające – w 14. dniu (mediana; *SD* 4,94; dane dzięki uprzejmości prof. Moniki Gos). Zgodnie z polskim prawem do przeprowadzenia wszystkich opisywanych analiz (badań genetycznych) niezbędna jest pisemna zgoda rodzica lub opiekuna prawnego. Należy pamiętać, że w przypadku porodów domowych krew pobiera położna przyjmująca poród lub położna/pielęgniarka środowiskowa, a proces poprawnego przeprowadzenia badania przesiewowego poza szpitalem powinien nadzorować lekarz podstawowej opieki zdrowotnej (POZ). Zgodnie z założeniem Europejskiego Sojuszu na rzecz Badań Przesiewowych w SMA (European Alliance for Newborn Screening in Spinal Muscular Atrophy) wszystkie państwa europejskie powinny zostać objęte badaniami przesiewowymi do końca 2025 roku[11].

MOŻLIWOŚCI TERAPEUTYCZNE U PACJENTÓW Z SMA

Na początku 2019 roku uruchomiono pierwszy polski program lekowy dla chorych na SMA umożliwiający wdrożenie leczenia nusinersenem. Od 1 września 2022 roku program rozszerzono i obecnie refundowane przez NFZ są trzy terapie – poza wymienionym nusinersenem można stosować rysdyplam i onasemnogen abeparwowek (tab. 1)[12]. Działanie każdego z tych leków polega na zwiększeniu ilości produkowanego białka SMN.

Nazwa leku	Nusinersen	Rysdyplam	Onasemnogen abeparwowek
Typ leku	Antysensowny oligonukleotyd	Mała cząsteczka	Terapia genowa oparta na AAV9
Sposób działania	Zwiększa produkcję białka SMN poprzez wpływ na splicing genu *SMN2*		Dostarcza funkcjonalny transgen *SMN*
Droga podania	Intratekalna	Doustna	Dożylna
Dawkowanie	4 dawki wysycające, następnie co 4 miesiące	Codziennie	Jednorazowo
Konieczność stosowania glikokortykosteroidów	Nie	Nie	Tak

Tab. 1. Dostępne metody leczenia pacjentów z SMA

Nusinersen jest lekiem stosowanym w praktyce klinicznej najdłużej. Mechanizm działania tego antysensownego oligonukleotydu (*antisense oligonucleotide*, ASO) polega na zwiększeniu proporcji włączania eksonu 7 do mRNA kodującego białko SMN. Lek, wiążąc się z miejscem intronowego wyciszacza splicingu w pre-mRNA, wypiera czynniki splicingowe, co ostatecznie prowadzi do utrzymania eksonu 7 w mRNA dla genu *SMN2* i umożliwia produkcję funkcjonalnego białka SMN. Cząstka nusinersenu nie przekracza bariery krew–mózg, dlatego lek podaje się intratekalnie, drogą nakłucia lędźwiowego[13]. Początkowe dawki, tzw. wysycające, podaje się w dniach 0., 14., 28. i 63., a kolejne co 4 miesiące. Zalecana dawka jest niezależna od masy ciała pacjenta i wynosi 12 mg (5 ml). Pacjenci zazwyczaj są przyjmowani na jednodniowy pobyt szpitalny w celu wykonania podstawowych badań wykluczających ewentualne przeciwwskazania do procedury nakłucia lędźwiowego, a po podaniu leku i obserwacji są wypisywani do domu. Podanie nusinersenu bywa trudne technicznie – zwłaszcza u pacjentów z nasiloną skoliozą lub otyłych – i zazwyczaj wiąże się z koniecznością zastosowania płytkiej sedacji. Najczęstsze działania niepożądane są związane z procedurą podania leku i obejmują popunkcyjne bóle głowy, wymioty oraz ból grzbietu. Przy kwalifikacji pacjenta do leczenia nusinersenem należy ocenić morfologię krwi obwodowej, aktywność aminotransferaz i parametry układu krzepnięcia oraz wykonać badanie ogólne moczu.

Lekiem o podobnym mechanizmie działania jest rysdyplam, który koryguje proces składania pre-mRNA genu *SMN2*. Jest dostępny w postaci zawiesiny doustnej podawanej raz dziennie po posiłku, a dawkowanie zależy od masy ciała (0,15 mg/kg m.c. u dzieci poniżej 2. miesiąca życia, 0,20 mg/kg m.c. – do 2 lat, 0,25 mg/kg m.c. – starszych i 5 mg – po osiągnięciu 20 kg). Do często występujących działań niepożądanych zalicza się biegunkę, wysypkę, ból głowy i gorączkę. Przed rozpoczęciem leczenia u chorych rutynowo wykonuje się podstawowe oznaczenia laboratoryjne: morfologię krwi z rozmazem, aktywność aminotransferaz i stężenie bilirubiny.

W odróżnieniu od opisanych dwóch leków onasemnogen abeparwowek jest preparatem podawanym jednorazowo, dożylnie i w dawce zależnej od masy ciała. Ludzki transgen SMN jest dostarczany w kapsydzie adenowirusa AAV9 (*adeno-associated virus 9*) i ostatecznie – funkcjonując w postaci episomalnej DNA w jądrze komórkowym neuronów ruchowych – zapewnia alternatywne źródło długotrwałej ekspresji białka SMN[13]. Wirus AAV9 cechuje się zdolnością przekraczania bariery krew–mózg i nie jest chorobotwórczy dla człowieka. Przed podaniem onasemnogenu abeparwowek wykonuje się oznaczenie miana przeciwciał anty-AAV9 (miano >1:50 uniemożliwia podanie preparatu), aktywności aminotransferaz i bilirubiny, liczby płytek krwi i stężenia troponiny I. Do najczęściej

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zgłaszanych działań niepożądanych należą przemijające zwiększenie aktywności aminotransferaz wątrobowych, wymioty, małopłytkowość, gorączka i podwyższone stężenie troponiny I. W celu zmniejszenia ryzyka hepatotoksyczności, począwszy od doby poprzedzającej podanie leku, stosuje się glikokortykosteroidy w dawce odpowiadającej 1 mg/kg m.c. prednizolonu przez miesiąc, następnie stopniowo zmniejszanej.

Jednym z elementów decydujących o wyborze terapii jest liczba kopii genu *SMN2*. Pacjenci z nie więcej niż trzema kopiami mogą otrzymać każdy z trzech wymienionych leków. Pacjenci z czterema kopiami, po spełnieniu pozostałych kryteriów kwalifikacji, mogą otrzymać nusinersen lub rysdyplam[14]. Szczegółowe kryteria kwalifikacji do każdej z tych terapii są dostępne w aktualnym załączniku do programu lekowego leczenia chorych na SMA (B.102.FM).

Wszystkie wymienione terapie cechuje wysoka skuteczność potwierdzona w kilkunastu badaniach klinicznych oraz tzw. danych rzeczywistych (*real-world evidence*, RWE) [15,16]. Niezależnie od rodzaju stosowanego leczenia wyjątkowo ważny jest czas jego wdrożenia, zgodnie z pojawiającym się w piśmiennictwie określeniem „czas to motoneuron" ilustrującym także neurodegeneracyjne podłoże choroby[17].

Stosunkowo nową grupę leków stosowanych jako terapia dodana stanowią inhibitory miostatyny (m.in. apitegromab i taldefgrobep). Miostatyna to białko z rodziny różnicujących czynników wzrostu (*growth differentiation factor*, GDF) odpowiedzialne za ograniczenie wzrostu tkanki mięśniowej. Zastosowanie inhibitora powoduje zatem zwiększenie masy mięśniowej. Wstępne wyniki toczących się badań klinicznych są obiecujące[18].

ROLA LEKARZA RODZINNEGO I PEDIATRY W OPIECE NAD DZIECKIEM Z SMA

Znajomość objawów SMA jest szczególnie ważna dla lekarzy pierwszego kontaktu. W najbliższych latach pod opiekę lekarzy rodzinnych i pediatrów wciąż trafiać będą dzieci nieobjęte przesiewem noworodkowym ze względu na wiek, celową rezygnację z badania lub jego wynik fałszywie ujemny (w związku z obecnością m.in. mutacji punktowych). Obecność następujących objawów powinna skłonić lekarza do poszerzenia diagnostyki, skierowania do neurologa dziecięcego lub – w przypadku znacznie nasilonych nieprawidłowości – do szpitala:

- opóźnienie lub brak osiągania kamieni milowych rozwoju motoryki dużej i małej;
- utrata wcześniej zdobytych kamieni milowych;
- osłabienie siły mięśniowej kończyn o dystrybucji proksymalnej;
- wiotkość, słabe poruszanie kończynami, pozycja „żabki", brak dźwigania głowy;
- męczenie się przy karmieniu;
- cichy płacz;
- brak odruchów ścięgnisto-okostnowych;
- drżenia palców rąk i fascykulacje języka.

Pacjenci z rozpoznaniem SMA, objęci programem leczenia, są regularnie kontrolowani przez lekarzy z ośrodków prowadzących terapię. Należy jednak pamiętać, że to lekarz POZ jest specjalistą, do którego w pierwszej kolejności trafiają pacjenci z bieżącymi problemami dotyczącymi kontroli rozwoju, leczenia infekcji czy wdrożenia profilaktyki czynnej zakażeń. W celu opracowania praktycznych standardów postępowania pacjentów z SMA podzielono na chodzących (*walkers*), siedzących (*sitters*) oraz niechodzących, leżących (*non-sitters*)[19].

W kwestii żywienia rola lekarza rodzinnego polega przede wszystkim na regularnej kontroli przyrostów masy ciała i wzrostu. U dzieci z nasilonymi objawami, chorujących wiele lat, można rozważyć zastosowanie siatek centylowych przeznaczonych dla pacjentów z SMA[20]. Porada dietetyczna dla dzieci chodzących nie różni się znacząco od wskazówek stosowanych w populacji zdrowej, chociaż szczególną uwagę należy zwrócić na profilaktykę otyłości i suplementację witaminy D. W odróżnieniu od tej grupy dzieci niechodzące często cechują się zaburzeniami połykania i wymagają opieki poradni żywieniowej, gastroenterologicznej oraz dietetycznej, a także żywienia za pomocą sondy dożołądkowej lub przezskórnej gastrostomii odżywczej. Częstym problemem są zaparcia, w przypadku których postępowanie farmakologiczne obejmuje zastosowanie makrogoli, wlewki doodbytniczej z mieszanki fosforanowej, ewentualnie laktulozy.

Wpływ objawów SMA na układ oddechowy staje się szczególnie widoczny w trakcie infekcji. Nawracające objawy zakażenia dróg oddechowych powinny nasunąć podejrzenie aspiracji pokarmu[19]. Przesiewowa ocena układu oddechowego u pacjentów niesiedzących obejmuje przede wszystkim badanie fizykalne i nieinwazyjny pomiar zawartości tlenu we krwi za pomocą pulsoksymetru. Przy podejrzeniu hipowentylacji w ramach szczegółowej diagnostyki stosuje się kapnometrię i polisomnografię. Część pacjentów wymaga zastosowania nieinwazyjnej wentylacji dodatnimi ciśnieniami (*non-invasive ventilation*) – zazwyczaj początkowo w godzinach nocnych oraz w trakcie infekcji – lub stałej wentylacji przez rurkę tracheostomijną. W ramach fizjoterapii, poza terapią manualną, są stosowane asystory kaszlu (tzw. koflatory). U dzieci siedzących i chodzących zwraca się uwagę na ocenę efektywności kaszlu, a w ramach kontroli specjalistycznych zaleca się wykonanie spirometrii.

Kwestie ortopedyczne dotyczą głównie deformacji kręgosłupa i klatki piersiowej, przykurczy stawowych oraz niestabilności stawów biodrowych[21,22]. Skolioza występuje przede wszystkim u pacjentów z SMA typu 1 i 2, a jej częstość u dzieci nieleczonych szacuje się na 60–90%[23]. Ocena postawy powinna być rutynowym elementem badania chorych z SMA w gabinecie lekarza rodzinnego. W ramach diagnostyki rozszerzonej wskazana jest densytometryczna ocena gęstości kości.

W przypadku wątpliwości lekarz rodzinny powinien dysponować danymi kontaktowymi ośrodka zajmującego się leczeniem danego pacjenta. Dobrą praktyką jest umieszczenie

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w książeczce zdrowia dziecka informacji o rozpoznaniu i stosowanej terapii oraz danych kontaktowych do ośrodka leczącego.

PROFILAKTYKA CZYNNA CHORÓB U DZIECI Z SMA

Chociaż SMA jest postępującą chorobą układu nerwowego, realizacja obowiązującego Programu Szczepień Ochronnych w tej grupie chorych jest szczególnie istotna[24]. Zaleca się podaż bezkomórkowego preparatu przeciwko krztuścowi (DTPa), stosowanie szczepionek poliwalentnych („5 w 1" lub „6 w 1"), a także dodatkowo szczepienia przeciwko meningokokom (grupy B i grup A, C, W-135, Y), ospie wietrznej oraz coroczne przeciwko grypie.
Pacjentów leczonych nusinersenem i rysdyplamem należy szczepić według zasad ogólnych. U pacjentów leczonych onasemnogenem abeparwowek zgodnie ze stanowiskiem Polskiego Towarzystwa Wakcynologii należy zachować co najmniej dwutygodniowy odstęp między szczepionką BCG a terapią genową z uwagi na konieczność jej łączenia ze stosowaniem glikokortykosteroidów[25]. W czasie steroidoterpii nie zaleca się także innych szczepień preparatami zawierającymi atenuowane drobnoustroje (tzw. żywymi). Należy zatem rozważyć zasadność szczepienia przeciwko rotawirusom. Po zakończeniu leczenia glikokortykosteroidami nie ma przeciwwskazań do immunizacji czynnej szczepionkami żywymi.
Od początku kwietnia 2024 roku rozszerzono grupę pacjentów kwalifikujących się do programu profilaktyki zakażeń wirusem RS przy użyciu paliwizumabu o dzieci z rozpoznanym SMA do 2. roku życia – niezależnie od stosowanego leczenia.

REHABILITACJA PACJENTÓW Z RDZENIOWYM ZANIKIEM MIĘŚNI

Od czasu wprowadzenia leczenia farmakologicznego chorych na SMA pojawiło się wiele dowodów na to, że odpowiednio dostosowana i regularnie stosowana fizjoterapia może korzystnie wpływać na spowolnienie progresji choroby. Uznaje się, że przyczyny utraty czynności funkcjonalnych u chorych na SMA mogą być związane z narastaniem przykurczów stawowych, znacznym i dynamicznym zwiększeniem się skoliozy lub nadmiernym przyrostem masy ciała[26]. Wobec tego fizjoterapia pacjentów z SMA powinna być dostosowana do indywidualnych potrzeb oraz stanu funkcjonalnego pacjenta z uwzględnieniem korzyści wynikających ze stosowania aparatów ortopedycznych, ortez i ćwiczeń indywidualnych[27,28].
W grupie dzieci bez objawów klinicznych SMA celem fizjoterapii jest utrzymanie bezobjawowego stanu funkcjonalnego dziecka i zindywidualizowana neurostymulacja rozwoju. W tym celu podczas terapii wskazane są metody fizjoterapeutyczne z obszaru wczesnego wspomagania rozwoju: utrzymanie prawidłowej symetrii ciała, ćwiczenia ukierunkowane na budowanie prawidłowego napięcia mięśniowego i wydolności oddechowej oraz wspomaganie pionizacji i umiejętności prawidłowego chodu. W przypadku znacznych deformacji w obrębie stóp i kręgosłupa wskazane jest stosowanie gorsetów i ortez[29].
Chorzy niesiedzący wymagają fizjoterapii służącej treningowi pozycji siedzącej, z wykorzystaniem indywidualnie dostosowanych siedzisk i zaopatrzenia ortopedycznego w postaci gorsetów, a ponadto terapii oddechowej, ćwiczeń rozciągających minimalizujących przykurcze w stawach, pionizacji oraz terapii chodu z wykorzystaniem technologii wspomaganych robotycznie. Dodatkowo w profilaktyce przykurczów mięśniowych ważne jest stosowanie ortez kończyn dolnych (np. nocnych przez co najmniej 60 minut) oraz profilaktyka zwichnięć stawów biodrowych i skoliozy (za pomocą gorsetów), jak również fizjoterapia klatki piersiowej[19,27,30].
Szczególnym celem fizjoterapii pacjentów siedzących powinno być budowanie wydolności w tej pozycji, profilaktyka skoliozy i zapobieganie deformacjom w obrębie kończyn dolnych. Jest to możliwe dzięki regularnemu stosowaniu gorsetów i ortez AFO (*ankle foot orthosis*) lub KAFO (*knee ankle foot orthosis*). Zaleca się także trening pionizacji z wykorzystaniem pionizatorów przez przynajmniej 60 minut dziennie, a silne rekomendacje obejmują terapię oddechową, pozycjonowanie pacjenta w indywidualnie dobranych siedziskach oraz ćwiczenia rozciągające i zwiększające ruchomość w stawach. Zastosowanie znajdują również ćwiczenia zwiększające wydolność i siłę mięśniową. W celu poprawy lub umożliwienia przemieszczania się należy rozważyć stosowanie wózków aktywnych lub elektrycznych. Ponadto istotną rolę terapeutyczną może odgrywać terapia chodu z wykorzystaniem np. technologii wspomaganych robotycznie[30].
W grupie pacjentów chodzących wskazany jest model fizjoterapii ukierunkowany na wzmacnianie wydolności tlenowej oraz siły mięśniowej kończyn górnych i dolnych, a także trening i doskonalenie samodzielnego lub wspomaganego chodu. Zaleca się fizjoterapię w wodzie, z wykorzystaniem cykloergometrów lub bieżni, jak również hipoterapię, jogę i fizjoterapię wspomaganą technologiczne. Nie należy pomijać terapii oddechowej ani ćwiczeń rozciągających i zwiększających ruchomość w stawach. W przypadku wystąpienia deformacji w stawach lub skoliozy wskazane jest zaopatrzenie ortopedyczne w postaci ortez i gorsetów[27,30].
W celu profilaktyki zwichnięć stawów biodrowych i skolioz rekomenduje się regularne kontrole ortopedyczne z wykonaniem zdjęć rentgenowskich oraz stosowanie pionizacji z wykorzystaniem ortez typu AFO lub KAFO. U pacjentów ze skoliozą (kąt Cobba: 15–20°) wskazane jest stosowanie gorsetów i regularne kontrole ortopedyczne. Optymalna częstotliwość fizjoterapii u pacjentów z SMA to 3–5 dni w tygodniu.

OPIEKA NAD RODZINĄ PACJENTA Z SMA

Chorzy na SMA potrzebują wielospecjalistycznej, długotrwałej opieki, regularnych wizyt w gabinetach lekarskich i szpitalach oraz intensywnej rehabilitacji, co często wymaga zaangażowania całej rodziny i przeorganizowania jej życia codziennego.

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Mając na uwadze autosomalne recesywne dziedziczenie choroby, konieczne jest zapewnienie konsultacji genetycznej członkom rodziny, zwłaszcza rodzeństwu chorego. Porada genetyka klinicznego może być przesłanką do prowadzenia diagnostyki prenatalnej u matki dziecka z SMA w celu ewentualnego szybkiego wdrożenia leczenia w przypadku urodzenia kolejnych chorych dzieci.

Rola lekarza rodzinnego i pediatry w opiece nad pacjentem z SMA jest niezmiernie ważna. Czas przeżycia chorych ulega istotnemu wydłużeniu, a wraz z wiekiem pojawiają się nowe trudności do pokonania. Powodzenie leczenia i satysfakcja z nim związana wymagają stałej i efektywnej współpracy pacjenta, lekarza POZ i pozostałych specjalistów.

Konflikt interesów

Autorzy nie zgłaszają żadnych finansowych ani osobistych powiązań z innymi osobami lub organizacjami, które mogłyby negatywnie wpłynąć na treść publikacji oraz rościć sobie prawo do tej publikacji.

Wkład autorów

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Aktualne zasady postępowania u dzieci w przypadkach połknięcia baterii guzikowych

Current guidelines for treatment after button battery ingestion

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Streszczenie

Wprowadzenie i cel: Połknięcie baterii guzikowej jest jedną z najniebezpieczniejszych form połknięcia ciała obcego w populacji pediatrycznej. Stanowi poważne zagrożenie dla zdrowia i życia dziecka. Rozległość uszkodzeń zależy od czasu kontaktu baterii z błoną śluzową przełyku, ucisku ciała obcego na ścianę przełyku, lokalnego przepływu prądu i ewentualnego wycieku substancji z baterii. Na skutek działania baterii na ściany przełyku mogą wystąpić groźne dla życia powikłania, takie jak perforacja przełyku i zapalenie śródpiersia, a długotrwała ekspozycja może wytworzyć przetoki w kierunku tchawicy, dużych naczyń i kręgosłupa. Odległe następstwa połknięcia baterii to przede wszystkim zwężenia przełyku, a do rzadkich powikłań zalicza się porażenia fałdów głosowych i uszkodzenie kręgosłupa. Celem badania było opracowanie aktualnych zasad postępowania w przypadku połknięcia baterii guzikowych przez dziecko. **Materiał i metody:** Korzystając z baz danych PubMed i Cochrane Library, przeprowadzono przegląd piśmiennictwa obejmującego lata 2018–2023. **Wyniki:** Znaleziono 11 artykułów, w których oceniono 1057 dzieci. U 309 z nich bateria guzikowa była zaklinowana w przełyku, a u pozostałych 748 stwierdzono jej obecność w żołądku bądź w jelicie cienkim lub grubym. Analizie poddano dane epidemiologiczne pacjentów, główne dolegliwości, wyniki badań obrazowych, leczenie oraz powikłania wczesne i odległe. Przedstawiono sposób postępowania w oparciu o zalecenia National Capital Poison Center oraz dane z piśmiennictwa z ostatnich 5 lat. **Wnioski:** Połknięcie baterii guzikowej jest najniebezpieczniejszą formą połknięcia ciała obcego, powszechnie spotykaną w populacji pediatrycznej. Ryzyko powikłań rośnie wraz z czasem zalegania ciała obcego w przełyku. Po usunięciu baterii z przełyku uraz może rozwijać się nawet tygodniami, powodując odległe powikłania. Ważne są działania prewencyjne polegające na zapobieganiu incydentom połknięcia baterii.

Słowa kluczowe: połknięcie baterii guzikowej, ciało obce przełyku, oparzenie przełyku

Abstract

Aim: Button battery ingestion is one of the most dangerous forms of foreign body ingestion commonly seen in paediatrics. It poses a serious threat to both the health and life of children. The extent of the damage depends on the duration of contact between the battery and the oesophageal mucosa, the pressure exerted by the foreign body on the oesophageal wall, the local electric current flow, and the potential leakage of toxic substances. Complications following battery exposure include oesophageal burns and perforation, oesophageal-tracheal fistula, oesophageal-aortic fistula, mediastinitis, gastric perforation, intestinal perforation, and peritonitis. Long-term complications are oesophageal strictures, while rare complications include vocal fold paralysis and spinal injury. The aim of this study is to establish updated guidelines for the management of children in cases of button battery ingestion. **Materials and methods:** A comprehensive literature search was performed for the years 2018–2023. **Results:** A total of 1,057 children treated after for button battery ingestion were included in the study. Among the patients, 309 were found to have a button battery lodged in the oesophagus, while in the remaining 748 children, the foreign body was located in the stomach, duodenum, or small intestine. The patients' epidemiological data, clinical manifestations, radiological findings, treatment, complications, and long-term outcomes were analysed. Current management guidelines based on National Capital Poison Center recommendations and literature data from recent years were presented. **Conclusions:** Button battery ingestion is one of the most dangerous forms of foreign body ingestion commonly seen in the paediatric population. The longer the foreign body is lodged in the oesophagus, the higher the risk of complications. Once

the battery is removed from the oesophagus, the injury may continue to develop for up to several weeks, causing distant complications. Preventive measures to reduce the risk of battery ingestion incidents are essential.

Keywords: button battery ingestion, oesophageal foreign body, oesophageal burn

WPROWADZENIE

Przypadkowe połknięcia baterii dotyczą najczęściej małych dzieci. W ciągu ostatniej dekady częstość tych zdarzeń systematycznie rosła ze względu na powszechne stosowanie baterii w wielu urządzeniach i zabawkach. Współcześnie używa się coraz częściej większych rozmiarów baterii litowo-jonowych, zwanych guzikowymi (średnica: 20–22 mm). Takie baterie ze względu na większą średnicę cechują się większym ryzykiem zaklinowania się w przełyku[1–3]. Ciała obce w przełyku zatrzymują się na wysokości jednego z trzech fizjologicznych zwężeń: na poziomie górnego zwieracza przełyku (najczęściej, w 60–70% przypadków), w środkowym odcinku przełyku w miejscu skrzyżowania z łukiem aorty (10–20%) lub powyżej dolnego zwieracza przełyku (20%)(2). Większość przypadków (80%) połknięcia ciał obcych dotyczy dzieci od 6. miesiąca do 3. roku życia. Małe dzieci często wkładają do ust znalezione przedmioty, a niewielka średnica ich przełyku sprzyja utknięciu ciała obcego w jego świetle[3,4].
Główne objawy ciała obcego w przełyku obejmują zaburzenia połykania, ból podczas połykania, ślinotok i wymioty, z objawami towarzyszącymi w postaci ogólnego niepokoju i drażliwości, krztuszenia się, kaszlu, zaburzeń oddychania oraz gorączki. U małych dzieci ciało obce w przełyku początkowo może nie powodować objawów[5–10]. W przypadku baterii zalegających w przełyku dolegliwości występują u 57% dzieci, a w dolnym odcinku przewodu pokarmowego – u 24%[3].
Ze względu na stan bezpośredniego zagrożenia życia każdy przypadek podejrzenia połknięcia baterii wymaga szybkiej diagnostyki i leczenia. Rozpoznanie ustala się na podstawie zdjęcia rentgenowskiego (RTG) z projekcją przednio-tylną i boczną obejmującego szyję i klatkę piersiową, a w razie potrzeby także jamę brzuszną. Baterie guzikowe są okrągłe i wyglądem przypominają monety, dlatego w obrazie radiologicznym należy zwrócić uwagę na charakterystyczny dla baterii „podwójny pierścień" („halo"), a na zdjęciu bocznym „stopień" na baterii[4,11,12]. Biegun ujemny baterii znajduje się na węższym pierścieniu, co ma istotne znaczenie, ponieważ od strony tego bieguna następuje największe uszkodzenie tkanek. Określenie jego położenia jest więc ważne dla oceny najbardziej zagrożonych struktur[11,12]. W baterii, która składa się z anody (bieguna ujemnego), katody (bieguna dodatniego) i przedziałów zawierających elektrolit, zachodzi reakcja chemiczna, w której jest wytwarzana energia elektryczna. Do uszkodzenia ścian przewodu pokarmowego dochodzi w wyniku czterech różnych mechanizmów. Pierwszy polega na ucisku wywieranym przez ciało obce na ścianę przełyku. Ucisk ten powoduje jej niedokrwienie i powstawanie początkowo odleżyny, a następnie martwicy i perforacji. Kolejny i najistotniejszy mechanizm opiera się na powstaniu martwicy rozpływnej wskutek aktywności elektrycznej baterii. Jej szczelne przyleganie do ścian przełyku powoduje zamknięcie obwodu pomiędzy dwoma biegunami baterii i przepływ prądu. Bardziej narażona na uszkodzenia jest ściana stykająca się z ujemnym biegunem baterii – dochodzi tu do wytwarzania jonów wodorotlenkowych, elektrolizy tkanek, podwyższenia pH do 12–13, rozmiękania i martwicy rozpływnej ściany przewodu pokarmowego[10,14–16]. Elektrochemiczny skład baterii odpowiada za rozległe uszkodzenie tkanek w razie ich kontaktu z baterią. W zależności od rodzaju baterie zawierają mangan, kobalt, nikiel, jony litu oraz związki glinu, kadmu, chromu, żelaza, rtęci, ołowiu i baru[14]. Wyciekowi elektrolitów z baterii sprzyja wilgotne środowisko. Ostatni mechanizm opiera się na zatruciu organizmu poprzez wchłanianie toksycznych substancji (głównie związków rtęci) przez ścianę jelita do krwiobiegu[14,16].
Najistotniejszym czynnikiem wpływającym na rozległość urazu jest czas kontaktu baterii ze ścianą przełyku[7,8,16]. Już po 15 minutach ekspozycji błony śluzowej przełyku na baterię pojawiają się widoczne obrażenia błony śluzowej, a martwica ściany przełyku stwierdzana jest zwykle po 12 godzinach od połknięcia baterii[7,8]. Ciężkie powikłania rozwijają się u 12% dzieci <6. roku życia[8].
Uszkodzenie ściany przełyku stwarza ryzyko wytworzenia się przetoki pomiędzy przełykiem a otaczającymi tkankami (tchawicą, aortą i innymi dużymi naczyniami), prowadząc do wielu potencjalnych stanów zagrażających życiu. Do takich groźnych powikłań zalicza się perforację przełyku, zapalenie śródpiersia, krwotok z dużych naczyń, przetokę przełykowo-tchawiczą, porażenie fałdów głosowych i uszkodzenie kręgosłupa[5,7,10,17–20]. Opisywano także przypadki śmiertelne, w tym zgon po połknięciu baterii z aparatu fotograficznego spowodowany gwałtownym krwotokiem z żył tarczowych dolnych na skutek głębokiej martwicy ściany przełyku[17]. W literaturze opisywano także powikłania odległe, takie jak obustronne porażenie fałdów głosowych, które wystąpiło po miesiącu od usunięcia baterii guzikowej z przełyku u dziecka[21]. Ciekawym przypadkiem była pacjentka z zaburzeniami rytmu serca i zmianami w EKG (uniesienie odcinka ST, wyższa amplituda odprowadzeń, dwufazowy załamek T, wydłużenie odstępu QT) spowodowanymi aktywnymi elektrycznie połkniętymi bateriami w przebiegu próby samobójczej[22]. Rozległy uraz ściany przełyku powinien zawsze nasuwać podejrzenie przetoki do dróg oddechowych, dlatego w takich przypadkach należy wykonać endoskopię tchawicy i oskrzeli[7]. Najczęstszym powikłaniem odległym jest zwężenie przełyku, które występuje

u 5–41% dzieci[1,3,16,18,23,24]. Jego częstość wydaje się jednak niedoszacowana, ponieważ nie wykonuje się rutynowych kontrolnych endoskopii po kilku tygodniach od zdarzenia[23]. Głównym czynnikiem zwiększającym ryzyko zwężenia przełyku jest czas zalegania w nim baterii[1,18,24]. Częstość wystąpienia zwężeń po oparzeniu kaustycznym przełyku zależy od stopnia oparzenia – najwięcej z nich rozwija się w przypadku oparzeń II i III stopnia śluzówki. Natomiast do powikłań po ekspozycji dolnego odcinka przewodu pokarmowego na baterię zaliczamy martwicę i perforację żołądka, dwunastnicy, jelita cienkiego, krwotoki i zapalenia otrzewnej[1,5,6].
W niniejszej pracy przeprowadzono analizę piśmiennictwa w celu przedstawienia aktualnych zasad postępowania u dzieci w przypadkach połknięcia baterii guzikowych.

MATERIAŁ I METODY

Przeprowadzono przegląd piśmiennictwa przy użyciu baz danych PubMed i Cochrane Library, z wykorzystaniem terminów: "button battery" AND "battery ingestion" AND "esophageal foreign body" AND "child(ren)" AND "English (language)". Analizie poddano prace z lat 2018–2023. Kryteria włączenia publikacji do analizy obejmowały dane na temat rodzaju baterii, przebiegu klinicznego, czasu zalegania ciała obcego w przełyku, rodzaju wykonanych badań diagnostycznych, sposobów leczenia, stwierdzonych powikłań oraz trwałych następstw. Wyszukane artykuły poddano przeglądowi pełnotekstowemu. Do analizy zakwalifikowano prace retrospektywne; jedna z nich miała charakter kohortowy. Przedstawiono aktualne wytyczne postępowania w oparciu o zalecenia National Capital Poison Center i dane z piśmiennictwa z ostatnich lat.

WYNIKI

Do analizy zakwalifikowano 11 publikacji z lat 2018–2023. W 11 pracach[1,3,5,6,10,15,18–20,24,25] oceniono 1057 pacjentów, stosunek płci męskiej do żeńskiej wynosił 51% do 49%, a średni wiek w momencie rozpoznania – 2,6 roku (przedział: 0,1 roku – 17 lat). Spośród opisanych dzieci u 309 stwierdzono baterię guzikową zaklinowaną w przełyku, u pozostałych 748 – w żołądku bądź jelicie cienkim lub grubym. Głównymi dolegliwościami były ślinotok (30%), zaburzenia połykania (28%), nudności i wymioty (28%), niechęć do jedzenia (25%), ból gardła (18%), ból w klatce piersiowej (18%), gorączka (11%), ból brzucha, chrypka, zaburzenia oddychania do stridoru włącznie, zaburzenia hemodynamiczne oraz bladość powłok. U 42% pacjentów przebieg był bezobjawowy. Powikłania po połknięciu baterii guzikowej obejmowały perforację przełyku, przetoki przełykowo-tchawicze, jedno- i obustronne porażenia fałdów głosowych, zapalenie śródpiersia, perforację żołądka lub dwunastnicy, przetoki przełykowo-aortalne, zapalenie otrzewnej, wytworzenia się ropnia tylnogardłowego oraz zapalenie stawów kręgosłupa w odcinku C7–T2. U 5% dzieci wystąpiło zwężenie światła przełyku. Antybiotykoterapię zaordynowano u 7% dzieci, u których w przebiegu choroby wystąpiła gorączka lub perforacja przewodu pokarmowego. Tylko w dwóch ośrodkach zastosowano leczenie przeciwrefluksowe inhibitorami pompy protonowej[1,3]. Pięciu pacjentów zmarło (0,5%).
Lokalizację baterii w przewodzie pokarmowym, zestawienie głównych objawów klinicznych i wczesnych oraz odległych powikłań w poszczególnych publikacjach przedstawiono w tab. 1.
Opracowanie schematu postępowania oparto na doniesieniach z ostatnich lat i na zaleceniach National Capital Poison Center[26].

OMÓWIENIE

Obecność baterii w przewodzie pokarmowym podejrzewa się w dwóch sytuacjach – bez względu na obecność objawów, gdy jej połknięcie było zauważone przez rodzica lub opiekuna, lub gdy u dziecka występują niepokojące objawy, takie jak ślinienie się, niechęć do jedzenia, krztuszenie się, wymioty, a także świst oddechowy, kaszel lub duszność. W obu sytuacjach nie wolno prowokować wymiotów; zaleca się wykonanie w szpitalnym oddziale ratunkowym zdjęcia RTG szyi, klatki piersiowej i jamy brzusznej w projekcji AP i bocznej (ryc. 1). Dalsze postępowanie zależy od wyniku badania obrazowego i lokalizacji baterii[26].

POSTĘPOWANIE W PRZYPADKU BATERII W PRZEŁYKU

Gdy opiekun zauważył połknięcie baterii przez dziecko >1. roku życia, National Capital Poison Center zaleca podawanie miodu w ilości 10 ml (2 łyżeczki) co 10 minut (do 6 dawek). Alternatywnie można podać doustnie sukralfat (zawiesinę 1 g/10 ml) w ilości 10 ml (2 łyżeczki) co 10 minut (do 6 dawek). Wymienionych substancji nie podaje się przy zaleganiu baterii w przełyku >12 godzin. Spożycie miodu lub przyjęcie sukralfatu nie wpływa na pozostanie pacjenta na czczo w związku z planowanym znieczuleniem ogólnym[27,28].
Po stwierdzeniu baterii zaklinowanej w przełyku należy ją jak najszybciej usunąć, bez względu na to, czy pacjent jest na czczo, czy po posiłku. Ryzyko powikłań rośnie wraz z czasem bezpośredniego kontaktu baterii z błoną śluzową przełyku. Należy pamiętać, że w początkowym okresie taki stan może być bezobjawowy i nie powinno to opóźniać zabiegu. W przypadku zalegania baterii w przełyku >12 godzin mówi się o tzw. opóźnionej diagnozie. Pierwsze uwidocznienie baterii na zdjęciu RTG lub jej usunięcie >12 godzin od połknięcia jest wskazaniem do wykonania tomografii komputerowej w celu oceny uszkodzenia naczyń i struktur sąsiadujących[4].
Zalecana jest metoda sztywnej endoskopii – poza usunięciem ciała obcego należy ocenić błonę śluzową po kontakcie z baterią, rozległość i głębokość oparzenia oraz opisać lokalizację ściany kontaktującej się z ujemnym biegunem baterii. Po wykluczeniu widocznych cech oparzenia ściany przełyku zaleca się profilaktyczne przepłukanie narażonych na kontakt z baterią tkanek 50–150 ml 0,25-procentowego roztworu

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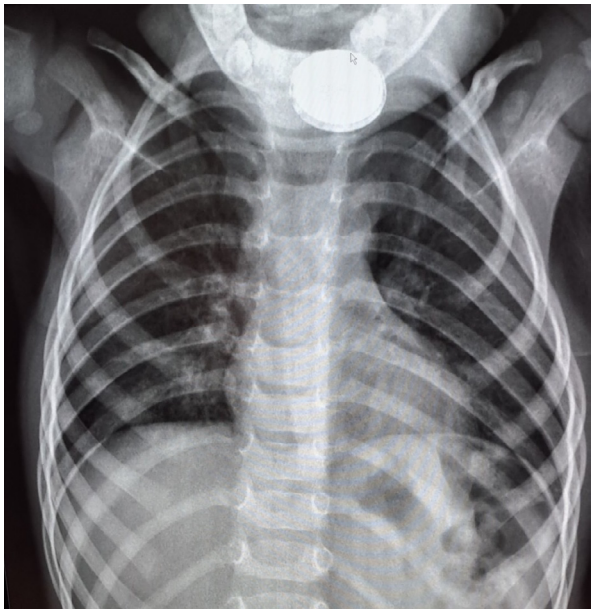
	Liczba pacjentów (*N*)	Liczba chorych z baterią w przełyku	Liczba chorych z baterią poza przełykiem	Główne objawy	Powikłania wczesne	Liczba chorych ze zwężeniem przełyku
Krom i wsp., 2018[10]	16	16	0	Wymioty, dysfagia, gorączka	Przetoka przełykowo-tchawicza, porażenie fałdów głosowych	5
Dörterler, 2019[24]	17	17	0	Ślinotok, wymioty	Porażenie fałdów głosowych, przetoka przełykowo-tchawicza	7
Duan i wsp., 2020[25]	34	34	0	Ból gardła, dysfagia, wymioty, ślinotok, chrypka, stridor	Przetoka przełykowo-tchawicza, porażenie fałdów głosowych	0
Akilov i wsp., 2021[20]	122	26	96	Ślinotok, nudności, wymioty, kaszel, gorączka	Perforacja przełyku, zapalenie śródpiersia, owrzodzenie przełyku	1
Shafiq i wsp., 2021[6]	56	18	38	Dysfagia, kaszel, wymioty, ból brzucha	Perforacja żołądka, zapalenie otrzewnej	2
Bettadahalli i wsp., 2022[15]	100	100	0	Wymioty, dysfagia, gorączka, kaszel, ból gardła, stridor	Przetoka przełykowo-tchawicza, perforacja przełyku, ropień tylnogardłowy	0
Quitadamo i wsp., 2022[5]	118	12	106	Ból w klatce piersiowej, nudności	Perforacja jelita	3
Lorenzo i wsp., 2022[3]	35	14	21	Wymioty, ślinotok, gorączka, niechęć do jedzenia, ból brzucha, smoliste stolce, kaszel	Infekcja, zapalenie śródpiersia, posocznica, zwężenie podgłośniowe, zespół ostrej niewydolności oddechowej	6
Scalise i wsp., 2023[18]	143	36	107	Wymioty, kaszel, ból brzucha, gorączka, ślinotok, duszność,	Perforacja przełyku, zapalenie śródpiersia, przetoka przełykowo-tchawicza, przetoka przełykowo-naczyniowa	9
Afshari i wsp., 2023[19]	1	1	0	Krwawe wymioty, spadek masy ciała	Zapalenie stawów kręgosłupa C7–T2	0

Tab. 1. Liczba analizowanych pacjentów, lokalizacja baterii w przewodzie pokarmowym, główne objawy kliniczne oraz powikłania wczesne i późne po połknięciu baterii

kwasu octowego w celu zneutralizowania pozostałych wodorotlenków i zahamowania postępującego procesu oparzenia zasadami[8,26,29]. Po przepłukaniu przełyku nadmiar płynu należy odessać. Pacjenci z widocznymi cechami uszkodzenia przełyku powinni zostać hospitalizowani i poddani obserwacji ze względu na wysokie ryzyko miejscowego obrzęku oraz upośledzenia drożności dróg oddechowych. Zdjęcie RTG przełyku z kontrastem (z zastosowaniem rozpuszczalnego w wodzie środka kontrastowego) wykonuje się 1–2 dni po usunięciu baterii. Bardzo ważne jest leczenie przeciwbólowe. Antybiotykoterapia o szerokim spektrum jest zalecana w przypadku widocznego poważnego uszkodzenia ściany przewodu pokarmowego (oparzenia II i III stopnia) lub potwierdzonej perforacji oraz u pacjentów z towarzyszącą gorączką[13,30]. Nie ma ustalonego schematu w zakresie stosowania antybiotykoterapii. W ośrodku autorów artykułu stosuje się amoksycylinę z kwasem klawulanowym (przez 7 dni). Chociaż skuteczność leków przeciwrefluksowych w minimalizowaniu uszkodzenia ściany przełyku nie została potwierdzona w badaniach, to terapia inhibitorami pompy protonowej wydaje się zasadna[1,13]. W ośrodku autorów artykułu chorym podaje się dożylnie omeprazol przez cały okres hospitalizacji. Konieczna jest obserwacja dziecka w kierunku potencjalnych powikłań (perforacji przełyku, zapalenia śródpiersia, przetoki przełykowo-tchawiczej, krwotoku, zapalenia płuc i zapalenia stawów kręgosłupa). Należy pamiętać, że 98% przetok i zwężeń przełyku rozpoznaje się nawet po wielu tygodniach od usunięcia baterii[16,23]. Pacjenci,



Ryc. 1. Zalegająca w przełyku bateria widoczna w badaniu RTG klatki piersiowej

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u których usunięto baterię z górnego odcinka przełyku, powinni być uważnie monitorowani pod względem zmiany barwy głosu, zaburzeń oddychania lub stridoru – wystąpienie tych objawów stanowi wskazanie do wykonania endoskopii krtani. Potencjalnym powikłaniem połknięcia baterii jest jedno- lub obustronny niedowład/porażenie fałdów głosowych z powodu uszkodzenia nerwu krtaniowego wstecznego lub chrząstek nalewkowatych. Zaklinowanie baterii (zwłaszcza z kontaktem z jej biegunem ujemnym) na wysokości skrzyżowania przełyku z aortą lub innych dużych naczyń krwionośnych wiąże się z ryzykiem zagrażającego życiu krwotoku. Zaleca się wykonanie tomografii komputerowej z kontrastem lub rezonansu magnetycznego w celu potwierdzenia, czy między obszarem uszkodzenia przełyku a sąsiednimi naczyniami znajduje się co najmniej 3 mm zdrowej tkanki. Możliwe są też niewielkie krwawienia bezobjawowe. W razie podejrzenia tworzenia się przetoki przełykowo-naczyniowej dziecko należy obserwować w ośrodku z oddziałem kardiochirurgii. Wprowadzenie żywienia doustnego zależy od stanu miejscowego i towarzyszących objawów. U dzieci bez objawów klinicznych, u których nie stwierdzono zmian na błonie śluzowej przełyku, zaleca się płynną dietę po 24 godzinach od zabiegu. W przypadku prawidłowego przyjmowania pokarmów dziecko wypisuje się do domu. Po kilku dniach dieta może zostać zamieniona na papkowatą, ale u wszystkich dzieci po usunięciu baterii z przełyku stosuje się miękkie pokarmy przez 28 dni, aby uniknąć mechanicznego uszkodzenia gojącego się przełyku. W przypadkach głębszych uszkodzeń, obejmujących warstwę mięśniową przełyku (II i III stopnia), karmienie prowadzi się przez sondę żołądkową, którą należy założyć podczas endoskopii bezpośrednio po usunięciu baterii. U dzieci, które usunęły sondę, stosuje się dietę „0" i wykonuje kontrolne zdjęcie RTG przełyku z zastosowaniem środka kontrastowego rozpuszczalnego w wodzie. W przypadkach głębokich uszkodzeń ścian przełyku kontrolną ezofagoskopię z powodu potencjalnych zwężeń wykonuje się najwcześniej po 4 tygodniach od urazu[7,13]. Wcześniejsze wykonanie endoskopii zwiększa ryzyko jatrogennej perforacji[16].

POSTĘPOWANIE W PRZYPADKACH BATERII PONIŻEJ PRZEŁYKU, W DOLNYCH ODCINKACH PRZEWODU POKARMOWEGO

Jeśli pojedyncza bateria o średnicy <12 mm przedostała się poza przełyk (do żołądka i dalej), w przypadku dzieci >12. roku życia, bez objawów i chorób układu pokarmowego w wywiadzie dopuszczalna jest obserwacja w warunkach domowych z normalną dietą i aktywnością fizyczną do czasu wydalenia baterii w stolcu[26]. Baterie przechodzą przez jelita w ciągu 24–48 godzin i interwencja rzadko jest wymagana. W razie nieznalezienia ciała obcego w stolcu przez 7–14 dni i bezobjawowego przebiegu wskazane jest ponowne badanie RTG przewodu pokarmowego i endoskopowe usunięcie baterii[26]. Wytyczne NASPGHAN (North American Society for Pediatric Gastroenterology, Hepatology and Nutrition) zalecają jej endoskopowe usunięcie, jeśli zalega w żołądku przez 2–4 dni. Gdy bateria utknęła w jelicie cienkim i powoduje objawy, konieczne jest jej usunięcie chirurgiczne. Jeżeli bateria przedostanie się do okrężnicy, to prawie zawsze jest wydalana bez interwencji zabiegowej[3,4]. Powikłania w przypadkach obecności baterii poza przełykiem są rzadkie i występują w 7% przypadków przy lokalizacji w żołądku i 1,3% – w jelicie[4]. Należy pamiętać, że obecność baterii guzikowej w żołądku lub w dalszych odcinkach przewodu pokarmowego nie wyklucza współistniejącego uszkodzenia przełyku[4].

W zmniejszaniu liczby przypadków połknięcia baterii guzikowych bardzo ważną rolę odgrywają działania prewencyjne. Strategie zapobiegania obejmują podnoszenie świadomości społecznej i współpracę z przemysłem w celu powszechnego wprowadzenia zabezpieczeń na bateriach dostępnych w sprzedaży. Obecnie stosuje się takie zabezpieczenia, jak naklejki ochronne na bateriach, podwójne plastikowe opakowania, które można otworzyć jedynie przy użyciu nożyczek, lub pokrywanie baterii guzikowych warstwą bardzo gorzkiej, nietoksycznej i nieszkodliwej po spożyciu substancji. Bardzo ważne działania profilaktyczne obejmują powszechną edukację rodziców oraz opiekunów małych dzieci w zakresie bezpiecznego użytkowania, przechowywania i wyrzucania baterii. Ważne jest również szkolenie lekarzy pierwszego kontaktu na temat wczesnej diagnostyki i właściwego szybkiego postępowania w przypadku połknięcia baterii przez dziecko. Na przykład w Stanach Zjednoczonych działa infolinia National Battery Ingestion Hotline, dostarczająca informacji i wskazówek dotyczących postępowania po połknięciu baterii skierowana zarówno do społeczeństwa, jak i lekarzy, a w Australii w poczekalniach gabinetów lekarskich są prezentowane plakaty edukacyjne.

WNIOSKI

Połknięcie baterii guzikowej jest najniebezpieczniejszą formą połknięcia ciała obcego powszechnie spotykaną w populacji pediatrycznej, szczególnie u małych dzieci do 3. roku życia. Ryzyko powikłań rośnie wraz z czasem zalegania ciała obcego w przełyku. Po usunięciu baterii z przełyku uraz może rozwijać się nawet przez kilka tygodni, powodując odległe powikłania zagrażające życiu dziecka. Ważne są działania prewencyjne polegające na zapobieganiu incydentom połknięcia baterii.

Konflikt interesów

Autorzy nie zgłaszają żadnych finansowych ani osobistych powiązań z innymi osobami lub organizacjami, które mogłyby negatywnie wpłynąć na treść publikacji oraz rościć sobie prawo do tej publikacji.

Wkład autorów

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Endometriosis and diet – can anti-inflammatory foods alleviate symptoms?

Endometrioza i dieta – czy produkty przeciwzapalne mogą łagodzić objawy?

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Abstract

Endometriosis is a chronic, oestrogen-dependent inflammatory disease characterised by the implantation of endometrial tissue outside the uterine cavity. Pathogenetic factors include immune system dysfunction, angiogenesis disturbances, hormonal imbalance, and genetic predisposition. Key roles are played by activated macrophages and pro-inflammatory cytokines (IL-1, IL-6, TNF-α), as well as an altered Th1/Th2 lymphocyte balance and reduced NK cell activity. Endometriosis significantly reduces the quality of life for patients, affecting their physical, mental, and social well-being. According to the European Society of Human Reproduction and Embryology recommendations, endometriosis treatment should be multi-faceted, incorporating hormonal therapy and non-pharmacological methods such as dietary adjustments. Increasing research confirms the positive impact of an anti-inflammatory diet on reducing inflammation and alleviating endometriosis symptoms. Such a diet focuses on consuming foods rich in omega-3 polyunsaturated fatty acids, polyphenols, and terpenes, which have anti-inflammatory and antioxidant properties. The mechanisms of its action include modulating gut microbiota, reducing inflammatory markers (C-reactive protein, IL-6, TNF-α), and regulating oxidative stress. Studies show that women following an anti-inflammatory diet for at least three months experience reduced levels of inflammatory markers and relief from pain symptoms. Key dietary components, such as eicosapentaenoic and docosahexaenoic acids, work by inhibiting arachidonic acid metabolism and synthesising pro-resolving mediators, thereby reducing the production of pro-inflammatory cytokines. Polyphenols and terpenes affect cell signalling pathways and reduce the expression of pro-inflammatory genes. In conclusion, an anti-inflammatory diet is a promising adjunct to endometriosis therapy, helping to reduce inflammation and improving patients' quality of life. However, further research is needed to determine optimal dietary components and their dosages.

Keywords: endometriosis, anti-inflammatory diet, pain, endometriosis treatment

Streszczenie

Endometrioza to przewlekła, estrogenozależna choroba zapalna charakteryzująca się implantacją tkanki endometrium poza jamą macicy. Do czynników patogenetycznych zalicza się dysfunkcję układu odpornościowego, zaburzenia angiogenezy i równowagi hormonalnej oraz predyspozycje genetyczne. Główną rolę odgrywają tu m.in. aktywowane makrofagi i cytokiny prozapalne (IL-1, IL-6, TNF-α), a także zaburzona równowaga limfocytów Th1/Th2 i obniżona aktywność komórek NK. Endometrioza znacząco obniża jakość życia, wpływając na zdrowie fizyczne, psychiczne i społeczne pacjentek. Zgodnie z zaleceniami European Society of Human Reproduction and Embryology leczenie endometriozy powinno być wielotorowe i obejmować terapię hormonalną oraz metody niefarmakologiczne, takie jak zmiana nawyków żywieniowych. Coraz więcej badań potwierdza korzystny wpływ diety przeciwzapalnej na zmniejszenie stanu zapalnego i łagodzenie objawów endometriozy. Dieta ta bazuje na spożywaniu produktów bogatych w wielonienasycone kwasy tłuszczowe omega-3, polifenole i terpeny, które wykazują właściwości przeciwzapalne i antyoksydacyjne. Mechanizmy jej działania obejmują m.in. modulację mikrobioty jelitowej, zmniejszenie stężenia markerów zapalnych (białka C-reaktywnego, IL-6, TNF-α) i regulację stresu

oksydacyjnego. Badania wskazują, że u kobiet stosujących dietę przeciwzapalną przez co najmniej 3 miesiące obserwuje się zmniejszenie stężenia markerów zapalnych i złagodzenie dolegliwości bólowych. Główne składniki diety, takie jak kwas eikozapentaenowy i dokozaheksaenowy, działają poprzez hamowanie metabolizmu kwasu arachidonowego i syntezę mediatorów proresolucyjnych, co przyczynia się do zmniejszenia produkcji cytokin prozapalnych. Z kolei polifenole i terpeny wpływają na szlaki sygnalizacyjne komórek i zmniejszają ekspresję genów prozapalnych. Podsumowując, dieta przeciwzapalna stanowi obiecujące uzupełnienie terapii endometriozy, wspierając redukcję stanu zapalnego i poprawiając jakość życia pacjentek. Wymaga jednak dalszych badań, aby ustalić optymalne składniki i dawki.

Słowa kluczowe: endometrioza, dieta przeciwzapalna, ból, leczenie endometriozy

Endometriosis is an oestrogen-dependent, progressive chronic disease with an inflammatory basis, in which endometrial cells implant outside the uterine cavity. According to World Health Organization data, endometriosis affects approximately 190 million women of reproductive age. However, due to still imperfect diagnostic methods, it is estimated that the actual prevalence may be significantly higher[1]. The disease was first described in 1690 by Daniel Shroen, while Karl von Rokitansky authored the first reports on the pathogenesis of endometriosis in 1860[2]. Despite over 150 years of knowledge about the disease, its aetiology remains unclear. Furthermore, it is still not understood why some women experience the classic symptoms of endometriosis, while others, despite significant pelvic changes, experience neither pain nor issues with conceiving. Moreover, the time from the onset of symptoms to diagnosis remains lengthy, averaging 5–12 years[3].

Endometriosis significantly affects women's physical health. The National Health Service lists it among the 20 most painful diseases globally[4]. It often leads to prolonged absences from work or school, creating an economic burden. The disease profoundly impacts women's mental and emotional well-being, social activity, and sexual relationships. Research has shown that endometriosis can reduce the quality of life to a degree similar to cancer[5].

One of the pathomechanisms of endometriosis is a chronic inflammatory process linked to immune system dysfunction, which varies in severity depending on the disease stage[6]. Macrophages play a crucial role in identifying foreign cells and presenting them to T lymphocytes. Women with endometriosis exhibit an increased number of activated macrophages in the peritoneal cavity, which have reduced phagocytic capabilities. Proinflammatory cytokines, such as interleukin (IL) 1, IL-6, IL-8, and tumour necrosis factor-alpha (TNF-α), are also produced in higher concentrations. Additionally, macrophages in the peritoneal cavity of women with endometriosis show increased expression of cyclooxygenase-2 (COX-2), leading to elevated prostaglandin secretion. Increased cytokine release and decreased anti-inflammatory factor production contribute to both the de novo development and progression of endometriosis[6,7].

Another critical mechanism in the pathogenesis of endometriosis is the disrupted balance between helper T lymphocytes type 1 (Th1) and type 2 (Th2). Th1 lymphocytes are responsible for cytokine production and promoting cellular immune responses, while Th2 lymphocytes regulate cytokine secretion to support B cell differentiation and humoral responses. Studies indicate that Th2 lymphocyte activity predominates in women with endometriosis[8].

Women with endometriosis also exhibit reduced activity of natural killer (NK) cells, which are crucial for natural cytotoxicity. NK cell dysfunction limits their ability to eliminate endometrial elements from the peritoneal cavity, which enter through retrograde menstrual flow, allowing endometrial cell implantation outside the uterus[9].

Angiogenesis plays a vital role in the development of ectopic endometrium, especially in the microenvironment of the peritoneal cavity. This process is accompanied by the formation of nerve fibres, which contribute to pain in patients. Vascular endothelial growth factor (VEGF) is responsible for the formation and growth of new blood vessels. Elevated VEGF levels have been found in the peritoneal fluid of women with endometriosis, with levels correlating positively with disease severity[10].

Treatment for endometriosis depends on the symptoms and a woman's reproductive plans. Hormonal therapy is the cornerstone of treatment, aiming to alleviate pain and slow disease progression. According to the European Society of Human Reproduction and Embryology (ESHRE) guidelines, endometriosis treatment should be multi-faceted, encompassing hormonal therapy alongside non-pharmacological methods. These methods include dietary adjustments, regular physical activity, physiotherapy, and psychotherapy. Surgical intervention, once considered the gold standard for diagnosing endometriosis, is no longer viewed as a first-line approach. Surgery should be undertaken only after a careful assessment of the benefits and risks, and when conservative treatment is ineffective[11].

Emerging evidence highlights the positive role of dietary changes in managing endometriosis. An anti-inflammatory diet helps reduce systemic chronic inflammation. Studies show that 76% of women adopt non-pharmacological methods to manage symptoms after being diagnosed with endometriosis, with almost half (44%) modifying their dietary habits[12]. Another study found that 55.5% of women experienced reduced pain due to conscious food choices. Dietary factors can influence the development and progression of endometriosis by regulating steroid hormone

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metabolism, the menstrual cycle, inflammation, oxidative stress, and muscle contractions[13]. This article aims to discuss the principles of an anti-inflammatory diet and review research findings on its impact on the disease.

Dietary interventions in chronic pain patients have been shown to reduce intestinal barrier permeability by lowering the production of pro-inflammatory mediators, preventing harmful metabolites from entering the bloodstream. Moreover, consuming anti-inflammatory foods appears to improve the quality of life[14].

Dietary habits depend, among other factors, on geographical location. The typical Western diet is characterised by high consumption of saturated fats, refined carbohydrates, red meat, salt, and sugary beverages. This diet promotes excessive production of pro-inflammatory mediators while reducing anti-inflammatory mediators, including antioxidants. The Western diet has been shown to negatively impact chronic diseases, such as cardiovascular diseases, diabetes, gastrointestinal disorders, immune system dysfunction, and endometriosis[14,15]. Geographical and sociodemographic factors also influence the prevalence of endometriosis [16].

The principles of the anti-inflammatory diet were first introduced in 1995 by Barry Sears in "The Zone Diet", with a revised version appearing in 2015. The diet's concept is based on macronutrient proportions and their effect on insulin and cortisol levels. Various types of anti-inflammatory diets exist, such as the Nordic diet, the Okinawa diet, and the Mediterranean diet[17].

Two studies analysed the relationship between green vegetable and fruit consumption, measured in servings per week or day, and the risk of endometriosis[18,19]. An inverse relationship was observed between the consumption of green vegetables and fruits and the risk of endometriosis. Data were analysed based on the number of servings per week. Significant risk reduction was noted with high consumption of green vegetables (odds ratio, OR 0.3; 95% confidence interval, 95% CI 0.2–0.5; $p = 0.0001$) and fresh fruits (OR 0.6; 95% CI 0.4–0.8; $p = 0.002$). These relationships remained consistent even after adjusting for confounding factors[18].

In a case-control study by Trabert et al., the role of a diet rich in green vegetables and fruits was analysed similarly to the Italian study, considering daily servings. Increased daily fruit servings were associated with a higher disease risk (two or more servings per day compared to one or fewer: OR 1.5; 95% CI 1.2–2.3; $p = 0.04$), while no association with vegetable consumption was found[19].

Interestingly, vegetables (particularly green ones) contain folic acid, methionine, and vitamin B_6, which are associated with "nutritional genomics". A group of nutrients known as lipotropic, including methionine, choline, folic acid, and vitamin B_6, plays a key role in this context. These nutrients can influence the human genome by altering gene expression or their products and affecting DNA methylation[20].

The primary components of an anti-inflammatory diet are polyunsaturated fatty acids, phenolic compounds, and terpenes/terpenoids. Omega-3 PUFAs exhibit immunomodulatory and anti-inflammatory effects. Their mechanism of action is complex. Prostaglandins and leukotrienes, produced from arachidonic acid (AA), a member of the omega-6 fatty acids, have pro-inflammatory effects. Omega-3 fatty acids – eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) – demonstrate a range of anti-inflammatory actions. Increasing EPA and DHA levels in the membranes of cells involved in the inflammatory process impacts the physical properties of these membranes and the formation of signalling platforms called lipid rafts. EPA and DHA disrupt arachidonic acid metabolism. EPA generates weaker (less pro-inflammatory) analogues, and both EPA and DHA are substrates for the synthesis of resolvins, protectins, neuroprotectins, and maresins, which are specialised pro-resolving mediators. By affecting early membrane signals and the profile of lipid mediators produced, EPA and DHA alter intra- and intercellular signalling. This leads to modified patterns of gene expression and protein production within cells, resulting in reduced production of inflammatory cytokines, chemokines, adhesion molecules, proteases, and enzymes. The anti-inflammatory effects of EPA and DHA are significant for both the prevention and treatment of inflammatory conditions. It has been shown that increasing EPA and DHA intake inhibits arachidonic acid metabolism and reduces the expression of COX-2 genes and proteins[21]. Studies have observed decreased production of series-2 prostaglandins (e.g. PGE_2) and series-4 leukotrienes by inflammatory cells following EPA and DHA supplementation for several weeks to months. In these studies, a dose-dependent effect on PGE_2 production was observed, with an EPA intake of 1.35 g/day for three months being insufficient to inhibit PGE_2, while 2.7 g/day significantly reduced PGE_2 production. This suggests that the threshold for EPA's anti-inflammatory effect lies between 1.35 and 2.7 g/day[22].

Phenolic compounds are a large, heterogeneous group of molecules widely distributed in nature. Polyphenols are found in many plants, fruits (particularly berries), tea, and cocoa, and possess anti-inflammatory and antioxidant properties. They have been shown to influence cellular signalling pathways, such as NF-κB, thereby reducing the expression of pro-inflammatory cytokines. Additionally, some polyphenols, such as resveratrol and quercetin, act as AMPK activators, promoting anti-inflammatory responses and improving metabolism. Research indicates that consuming polyphenol-rich foods is associated with a reduced risk of cardiovascular diseases, type 2 diabetes, and overall inflammation. However, due to limited clear scientific evidence, establishing reference intake norms for polyphenols is challenging. Some studies suggest that total flavonoid intake above 500 mg/day offers health benefits[23].

Terpenes and terpenoids, a large group of compounds primarily derived from the secondary metabolism of plants, have demonstrated anti-inflammatory properties both *in vitro* and *in vivo* by regulating pro-inflammatory mediators

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and transcription factors, disrupting signalling pathways, and reducing oxidative stress[24].

Current literature suggests that following an anti-inflammatory diet for at least three months can significantly reduce inflammatory marker levels, thereby alleviating pain symptoms in women with endometriosis[14]. This phenomenon is complex and involves several mechanisms.

One such mechanism is the modulation of gut microbiota by an anti-inflammatory diet. The human gut contains trillions of microorganisms that play crucial roles in digestion, immune function, and neurotransmitter production. Dietary components, especially polyphenols and fibre, can significantly influence the composition and function of gut microbiota. A plant-rich diet promotes microbiota diversity, which is highly beneficial for health. Through the production of short-chain fatty acids, gut microbiota positively affects nervous system function by reducing symptoms such as fatigue, low mood, stress sensitivity, and cognitive dysfunction. Enriching the diet with prebiotics (e.g. fermentable fibre) and probiotics can further help reduce inflammation and improve intestinal barrier integrity. Dysbiosis, or microbial imbalance, is associated with chronic inflammatory diseases[25].

Another mechanism of action for an anti-inflammatory diet involves the modulation of inflammatory pathways. Dietary components can either exacerbate or reduce inflammation by lowering levels of inflammatory markers, including C-reactive protein (CRP), IL-6, and TNF-α[26].

A third key mechanism is the regulation of oxidative stress, defined as an imbalance between free radicals and antioxidants. Antioxidants are compounds that help neutralise harmful free radicals in the body, preventing cellular damage. They are categorised into two main types: exogenous and endogenous antioxidants. Exogenous antioxidants, such as vitamins, minerals, and polyphenols, cannot be synthesised by the body in sufficient quantities and must be supplied through diet. Endogenous antioxidants, such as superoxide dismutase (SOD), glutathione, and ubiquinol, are produced within the body. Many components of an anti-inflammatory diet, including vitamins C and E, carotenoids, and polyphenols, act as antioxidants, directly neutralising harmful free radicals[27].

The effectiveness of an anti-inflammatory diet can be assessed by monitoring three key markers:

1. lipid stress – a TG/HDL ratio (in mg/dL) <1 indicates good insulin sensitivity;
2. inflammatory stress – an AA/EPA ratio in the range of 1.5–3 maintains inflammatory balance;
3. glycaemic stress – HbA_{1c} levels between 4.9–5.1% reflect proper carbohydrate metabolism regulation[28].

Not all dietary patterns are strictly pro- or anti-inflammatory. Classifying a specific dietary pattern can be facilitated using the empirical Dietary Inflammatory Index (DII). The DII was created to analyse the overall dietary pattern in relation to plasma markers of inflammation and to determine the inflammatory potential of diets. Developed based on global literature from 1950 to 2010, the DII incorporates 1,943 articles and 45 selected dietary components. The authors of the DII assessed the relationship between dietary products/components and inflammatory markers (IL-1β, IL-4, IL-6, IL-10, TNF-α, and CRP). They determined whether the 45 individual dietary components increased (+1), decreased (−1), or had no effect (0) on these inflammatory markers. The DII can be used for initial assessment of the inflammatory contribution of a patient's current diet and to monitor dietary changes over time[29].

DISCUSSION

Various biological mechanisms have been proposed to explain the influence of dietary factors on the risk of developing endometriosis. However, available epidemiological data and observational studies do not always consistently support these hypotheses. Due to the limited number of scientific studies, this report provides a detailed overview of the results from several available studies to highlight even minor effects that could serve as a foundation for further research, emphasising the need for additional analyses.

Hormonal therapy remains the cornerstone of endometriosis treatment. Implementing non-pharmacological treatment methods, including an anti-inflammatory diet, significantly improves the effectiveness of therapy. However, there is a group of patients for whom hormonal therapy cannot be applied – for example, women trying to conceive, those with contraindications to hormonal treatment, or those who refuse hormonal therapy. For these women, the cornerstone of care will be the implementation of non-pharmacological methods of pain reduction, with the anti-inflammatory diet playing a key role.

It is important to note that endometriosis is a multi-stage condition, beginning with the initial development of the disease, followed by proliferation, vascularisation, and peritoneal invasion of endometrial lesions, all accompanied by an inflammatory response. Various dietary components may have varying effects at specific stages of disease progression. Future research should aim to separately analyse the impact of diet on both the development of endometriosis and its clinical consequences.

CONCLUSIONS

In summary, endometriosis is an oestrogen-dependent, chronic, and progressive disease. Its pathomechanism involves chronic inflammation and immune system dysfunction. Treatment is primarily based on hormonal therapy, but non-pharmacological methods, including an anti-inflammatory diet, are playing an increasingly important role. The key components of an anti-inflammatory diet include PUFAs, phenolic compounds, and terpenes/terpenoids. A diet rich in these substances helps regulate oxidative stress and inflammation, positively affecting gut microbiota and immune system function as early as three months

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after implementation. Further research is needed to explore the effects of diet on the different stages of endometriosis development and the need for personalised therapy.

Conflict of interest

The authors do not report any financial or personal connections with other persons or organisations which might negatively affect the content of this publication and/or claim authorship rights to this publication.

Author contribution

Original concept of study; collection, recording and/or compilation of data; analysis and interpretation of data: MMR. Writing of manuscript; critical review of manuscript; final approval of manuscript: MMR, DW.

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Chrononutrition and the role of melatonin in neonates

Chronobiologiczna rola melatoniny i jej znaczenie w żywieniu noworodków

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Abstract

Melatonin plays a pivotal role in the regulation of biological rhythms, beginning during prenatal development through maternal signalling and continuing postnatally via breast milk. In neonates, whose circadian systems are functionally immature, maternal melatonin serves as a critical entraining agent, facilitating the synchronisation of the sleep–wake cycle, supporting neurodevelopmental processes, and enhancing immune system maturation. Breast milk demonstrates distinct diurnal variations in melatonin concentration, alongside other bioactive components, establishing it as a vital chrononutritional medium. This rhythmic delivery is particularly significant for preterm infants, who lack sufficient endogenous melatonin production and are especially reliant on exogenous sources for circadian entrainment. Several factors, including the mode of delivery, maternal health, circadian alignment, and the handling or processing of expressed breast milk, may influence melatonin content and its bioavailability. Disruption of circadian rhythms, whether due to environmental factors such as continuous light exposure in neonatal intensive care units or desynchronised feeding schedules – can interfere with optimal physiological development. Recognising the chronobiological significance of melatonin opens new perspectives in neonatal care. Promoting feeding practices aligned with circadian principles, including time-of-day-sensitive milk administration, may support more favourable neurodevelopmental and immunological outcomes, particularly in vulnerable preterm populations. This knowledge has the potential to inform future evidence-based strategies in perinatal and neonatal clinical care.

Keywords: melatonin, breast milk, chrononutrition, circadian rhythm

Streszczenie

Melatonina odgrywa kluczową rolę w regulacji rytmów biologicznych. U noworodków, u których zegar biologiczny nie jest jeszcze w pełni dojrzały, melatonina pochodzenia matczynego wspomaga synchronizację rytmów okołodobowych, wpływając korzystnie na cykl snu i czuwania, rozwój ośrodkowego układu nerwowego oraz funkcjonowanie układu odpornościowego. Wykazano, że mleko matki charakteryzuje się dobową zmiennością stężenia melatoniny oraz innych związków bioaktywnych. Zjawisko to ma szczególne znaczenie w przypadku noworodków przedwcześnie urodzonych, u których endogenna produkcja melatoniny jest jeszcze niewystarczająca. Na zawartość melatoniny w mleku mogą wpływać takie czynniki, jak sposób porodu, stan zdrowia matki czy metody przetwarzania mleka. Zakłócenia w rytmie okołodobowym – spowodowane np. ciągłą ekspozycją na światło lub brakiem synchronizacji czasowej podawania mleka – mogą niekorzystnie oddziaływać na rozwój dziecka. Zrozumienie chronobiologicznej roli melatoniny oraz promowanie praktyk karmienia piersią z uwzględnieniem rytmów dobowych może przyczynić się do poprawy wyników zdrowotnych noworodków i stanowić punkt wyjścia do opracowania skutecznych strategii opieki klinicznej.

Słowa kluczowe: melatonina, mleko kobiece, chronożywienie, rytm dobowy

BIOLOGICAL RHYTHMS AND MELATONIN

Life on Earth is governed by a complex interplay of biological rhythms that regulate physiological processes, behaviour, and overall health. At the core of these rhythms lies the biological clock, an intrinsic timekeeping system that regulates various biological functions in response to environmental cues, particularly the light-dark cycle[1]. These rhythms, known as circadian rhythms, are primarily regulated by the suprachiasmatic nucleus (SCN) in the hypothalamus, which synchronises peripheral clocks throughout the body[2].

The detection of ambient light is initially mediated by the retina, which perceives variations in light intensity, duration, and photoperiodicity over the 24-hour circadian cycle. This photic input is subsequently transduced into a neurochemical signal through the synthesis and secretion of melatonin by the pineal gland. Melatonin, derived from the essential amino acid tryptophan, is primarily synthesised during the dark phase of the photoperiodic cycle. Following its synthesis, melatonin is rapidly released into the circulatory system, where it exerts systemic chronobiotic effects. The amplitude and duration of nocturnal melatonin secretion are directly modulated by the length of the dark phase, while melatonin production during the light phase remains minimal. Owing to its strict dark-dependent secretion pattern, melatonin is often referred to as the "hormone of darkness". Additionally, its seasonal fluctuations in nocturnal secretion duration allow it to function as both a circadian "clock" and an annual "calendar", playing a pivotal role in the entrainment of biological rhythms and physiological processes[3].

The regulation of melatonin synthesis follows a well-defined pathway that begins in the retina and ends in the pineal gland. Light is detected by a specialised group of retinal ganglion cells (intrinsically photosensitive retinal ganglion cells, ipRGCs), which contain the photopigment melanopsin. This enables them to sense ambient light levels independently of vision. These cells send signals to the suprachiasmatic nucleus of the hypothalamus, the body's master circadian clock. The SCN transmits circadian signals to the pineal gland via a multi-synaptic pathway that culminates in the sympathetic nerve terminals of the superior cervical ganglia (SCG). In humans, this pathway governs the release of noradrenaline, which is elevated during the dark phase and suppressed during daylight. Pinealocytes express α- and β1-adrenergic receptors, and their activation triggers an intracellular cascade, leading to an increase in cyclic adenosine monophosphate (cAMP) levels. This, in turn, upregulates the expression and enzymatic activity of arylalkylamine N-acetyltransferase (AA-NAT), a key enzyme in melatonin biosynthesis[4].

Melatonin is synthesised through a multi-step biochemical pathway, beginning with tryptophan, which is converted to serotonin and subsequently into melatonin. AA-NAT has traditionally been considered the rate-limiting enzyme in this pathway. However, studies in freely moving rats have shown that nocturnal increases in AA-NAT protein levels and enzymatic activity do not directly correlate with melatonin release, challenging its role as the primary rate-limiting factor. The final step in melatonin biosynthesis involves the methylation of N-acetylserotonin by acetylserotonin O-methyltransferase (ASMT). This enzymatic process plays a critical role in establishing the nocturnal peak in circulating melatonin levels. The circadian synthesis and secretion of melatonin by the pineal gland are key to regulating the sleep–wake cycle and overall chronobiological functions[5,6].

DEVELOPMENT OF BIOLOGICAL RHYTHMS IN NEONATES

The establishment of biological rhythms in humans begins before birth but remains immature at delivery. By approximately 30 weeks of gestation, preliminary foetal circadian rhythms begin to emerge; however, at birth, the pineal gland and SCN, though structurally present, remain functionally immature. As a result, newborns exhibit fragmented sleep–wake cycles and irregular physiological rhythms. During foetal life, the developing biological clock is influenced by maternal circadian signals, including fluctuations in melatonin and body temperature. The transfer of maternal melatonin to the foetus *in utero* plays a crucial role in regulating foetal circadian rhythms and supporting neurodevelopment. Since the foetal pineal gland is not yet capable of synthesising melatonin independently, maternal melatonin crosses the placenta and influences the developing SCN. This transfer helps entrain the foetal biological clock to the maternal light-dark cycle, thereby preparing the newborn for postnatal circadian regulation. The presence of melatonin receptors in the foetal brain as early as the second trimester suggests that maternal melatonin plays a significant role in neuroprotection, antioxidative defence, and sleep–wake cycle organisation[7,8].

The infant pineal gland is initially incapable of producing pulsatile melatonin secretion, despite the presence of noradrenaline, the neurotransmitter required for melatonin synthesis. As a result, newborns rely on maternal breast milk as an external melatonin source. Studies have shown that breast milk melatonin follows a circadian rhythm, with higher concentrations at night and undetectable levels during the day, aiding in the regulation of the infant's sleep–wake cycle[8–10].

Over the first few months of life, circadian rhythms progressively consolidate. By two to three months of age, infants begin to develop more structured sleep-wake patterns that align with external light-dark cycles, and the production of melatonin and cortisol starts to follow a rhythmic pattern, signalling the maturation of the biological clock. By four to six months, many infants establish a stable day-night sleep cycle, influenced by light exposure, feeding schedules, and parental interactions. By three to six months, most full-term infants exhibit a stable endogenous melatonin rhythm, coinciding with longer nocturnal sleep episodes. During this critical period, external zeitgebers – such as light exposure, feeding schedules, and parental care – play an essential role in entraining the infant's circadian system[8].

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Preterm infants exhibit delayed maturation of melatonin secretion compared to full-term neonates. Studies indicate that melatonin concentrations in preterm infants are significantly lower in the early postnatal period. Unlike full-term infants, preterm neonates may experience a prolonged phase of melatonin deficiency due to the immaturity of their SCN and pineal gland. Additionally, the transition from maternal melatonin supply *in utero* to autonomous production postnatally is further delayed in preterm neonates, potentially impacting their sleep–wake cycles and neurodevelopment. Consequently, breast milk, which contains higher melatonin levels at night, plays a crucial role in providing exogenous melatonin to preterm infants, supporting the development of their circadian rhythms. This suggests that interventions such as breastfeeding, nonpooled donor milk, or chrononutrition strategies could help support the circadian maturation of preterm infants. This consolidation of biological rhythms highlights the essential role of maternal chrononutritional support, particularly via breast milk, in shaping the infant's developing sleep–wake cycle and hormonal regulation[8].

BREAST MILK

During gestation, the foetus is continuously entrained to the maternal circadian, physiological, metabolic, and behavioural rhythms for approximately nine months. This intricate temporal synchronisation is abruptly interrupted at birth, necessitating an adaptive mechanism to support postnatal circadian entrainment. Maternal milk serves as a biologically optimised substitute, exhibiting circadian fluctuations in composition that align with the maternal rhythm[11].

In humans, neonates feed both day and night, with dynamic variations in the nutritive and bioactive components facilitating the infant's metabolic and developmental adaptation to the external environment. Recognising the critical role of breastfeeding, the World Health Organization (WHO) recommends exclusive breastfeeding for at least the first six months to enhance infant survival, healthy growth, and neurodevelopment. Despite this, global breastfeeding rates remain suboptimal, highlighting the need for greater public health efforts to promote and support breastfeeding practices[12].

Breast milk composition exhibits diurnal oscillations, effectively acting as a chrononutritional agent. This is particularly relevant in cases where expressed or donor milk is used, as potential temporal mismatches between milk expression and feeding times may disrupt the infant's natural circadian entrainment. Empirical studies have identified circadian rhythmicity in several human milk constituents, including melatonin and cortisol, both of which exhibit distinct peak concentrations corresponding to nighttime and morning hours, respectively. A deeper understanding of the chronobiology of lactation could inform neonatal care strategies by emphasising the optimal timing of breastfeeding and milk expression. Additionally, incorporating circadian variables into human milk research may help refine experimental methodologies by controlling for potential confounders.

Growing evidence highlights the presence of chronobiotic compounds in milk, which play a crucial role in shaping the infant's sleep–wake cycle. A recent study has demonstrated that breastfed infants establish a circadian rest–activity rhythm by six weeks of age, whereas this rhythm emerges around 12 weeks in infants receiving mixed feeding (breast milk and formula) or in exclusively formula-fed babies. Furthermore, exclusively breastfed infants exhibit superior sleep patterns compared to their formula-fed counterparts[11,13,14].

According to Oliveira et al., the rhythmic concentration of melatonin in breast milk helps regulate the infant's sleep–wake cycle, promoting longer and more restful sleep at night[10]. Several factors influence the melatonin content in breast milk, including maternal age, health, and mode of delivery. Studies have shown that melatonin concentrations are generally higher in mothers who deliver vaginally compared to those who undergo caesarean sections, possibly due to differences in stress hormone levels and circadian regulation during labour and delivery. Moreover, melatonin in breast milk is believed to contribute to gastrointestinal comfort in infants by relaxing smooth intestinal muscles, which may help alleviate colic and enhance digestion. Given its antioxidative and immunomodulatory properties, melatonin in breast milk also plays a protective role in infant health.

Qin et al. demonstrated a distinct circadian rhythm of melatonin in both preterm and term breast milk across various lactation stages, underscoring its potential clinical importance in neonatal care[15]. The highest melatonin levels were observed in colostrum, followed by transitional and mature milk, with a significant decline over the first month postpartum. Notably, preterm milk exhibited a higher peak melatonin concentration than term milk, particularly in colostrum, suggesting a mechanism supporting the underdeveloped circadian systems of premature infants. Given their heightened vulnerability, these findings reinforce the importance of breast milk – especially early lactation milk – as a natural source of neuroprotective and sleep-regulating factors in neonatal and paediatric care.

Systematic reviews by Italianer et al.[16] and Oliveira et al.[10] address crucial knowledge gaps and explore the physiological and clinical implications of chronobiological patterns in maternal milk, particularly in neonatal and paediatric care.

CHRONONUTRITION AND CONSEQUENCES OF MELATONIN RHYTHM DISRUPTION

Chrononutrition is a field that seeks to optimise nutrient intake and dietary composition in alignment with an individual's biological clock, ensuring that the timing of food consumption maximises physiological and metabolic benefits[17]. While most existing research has focused on adults, the implications of chrononutrition during early development remain insufficiently explored. Given that rest–activity cycles and nutritional requirements undergo significant changes throughout the lifespan, a better understanding of

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temporal variations in nutrient delivery during infancy is of particular clinical importance.

Neonates, unlike adults, exhibit round-the-clock feeding patterns, a phenomenon with distinct biological significance. Breast milk composition is not static; rather, it fluctuates according to maternal circadian rhythms, delivering time-dependent bioactive compounds, nutrients, and hormones that may contribute to the entrainment of the infant's developing circadian system. Furthermore, neonates exhibit sensitivity to both breast milk-derived and environmental circadian cues, which are critical for the proper maturation of their internal biological rhythms.

Beyond sleep regulation, the nocturnal transfer of melatonin via breast milk appears to contribute to reduced discomfort in infants. At two months of age, breastfed infants have been shown to experience fewer colic episodes and less severe irritability than formula-fed infants, suggesting a protective effect of milk-derived chronobiotics in promoting infant well-being[18].

Circadian rhythms play a vital role in the well-being of preterm infants. Studies have shown that premature babies in neonatal intensive care units (NICUs), who are separated from their mothers and exposed to continuous lighting experience negative health outcomes. These infants, who are unable to produce their own melatonin, exhibit lower weight gain, prolonged need for ventilatory support and phototherapy, poor motor coordination, and delayed oral feeding responses. In contrast, infants exposed to a cycled light–dark environment and fed with their mother's milk show improved weight gain, better oxygen saturation, faster melatonin rhythm development, and shorter hospital stays. Given these benefits, neonatal care societies are now recommending light–dark cycle exposure for premature infants in clinical settings[11].

Recent findings suggest a significant interplay between melatonin levels in human breast milk and maternal obesity, with potential implications for the infant's immune programming and metabolic health. In pregnancies complicated by maternal obesity, colostrum – naturally rich in immunomodulatory components – exhibits both altered immune cell function and elevated melatonin levels. This increase in melatonin may represent a compensatory mechanism aimed at restoring immune balance, as studies have shown that melatonin can enhance phagocyte function and lymphocyte proliferation, while reducing apoptosis in colostral immune cells of obese mothers[19,20]. Furthermore, melatonin's anti-inflammatory and anti-obesogenic properties have been noted to influence energy homeostasis and metabolic programming, potentially protecting the infant against the development of obesity and metabolic syndrome later in life[21]. While elevated melatonin levels in the colostrum of obese mothers may confer protective benefits, further research is needed to determine whether a threshold effect exists and how this hormonal modulation interacts with other bioactive milk components to influence childhood obesity risk.

Melatonin plays a crucial role in immune system regulation. Human lymphocytes possess melatonin receptors, allowing them to respond to fluctuations in this hormone. Studies have shown that melatonin enhances the phagocytic and bactericidal activity of colostrum-derived lymphocytes exposed to *Escherichia coli* by stimulating cellular oxidative metabolism. Additionally, tumour necrosis factor alpha (TNF-α), an inflammatory regulator found in human milk, can inhibit melatonin synthesis in the pineal gland. Caesarean deliveries increase TNF-α levels in colostrum, potentially suppressing nocturnal melatonin production, leading to inflammation and disrupting melatonin's protective effects in newborns[11,20,22,23].

Emerging evidence highlights the role of breast milk melatonin as a key modulator of the gut–brain axis during early neonatal development. Beyond its well-established role in circadian entrainment, melatonin in breast milk exhibits direct regulatory effects on the gut microbiota, influencing the maturation of the intestinal barrier and local immune responses. This interaction is particularly significant given the increasing recognition of how gut microbial composition impacts brain homeostasis and neurodevelopment via immunological and neurochemical pathways. In animal models, melatonin supplementation has been found to mitigate gut dysbiosis and neuroinflammation caused by sleep deprivation, reducing microglial overactivation and neuronal apoptosis in the central nervous system[24]. Through its antioxidant and anti-inflammatory actions, breast milk melatonin may contribute to healthy neurodevelopment by supporting a balanced gut microbiome, thereby reinforcing the bidirectional communication between the gut and brain. These findings position melatonin as a potential chrononutrient with a lasting impact on the infant's neurological and immunological trajectory.

EFFECT OF BREAST MILK PASTEURISATION ON ITS MELATONIN CONTENT

Pasteurisation, while essential for ensuring the microbiological safety of donor human milk, appears to significantly reduce the melatonin content in breast milk, potentially diminishing its chronobiological and immunological benefits. The most widely used method, Holder pasteurisation (heating at 62.5°C for 30 minutes), has been shown to cause a notable decline in melatonin levels, irrespective of whether rapid or slow cooling is employed post-treatment. One study cited in the review reported a reduction in melatonin concentrations from a mean of 51.92 pg/mL to 39.66 pg/mL after Holder pasteurisation of night-expressed milk. Given melatonin's critical roles in circadian entrainment, antioxidant defence, and immune modulation – especially in preterm infants who are highly reliant on exogenous melatonin sources – this reduction may have clinical implications. These findings underscore the need for further research into alternative pasteurisation methods or melatonin-preserving techniques to maintain the bioactivity of breast milk

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provided through milk banks[23]. In contrast, Chrustek et al. demonstrated that Holder pasteurisation preserves melatonin levels in human milk, supporting its continued use in human milk banks without diminishing this functional component[25]. As human milk banks are essential in providing safe donor breast milk to infants, particularly preterm and medically vulnerable neonates, when maternal milk is unavailable, the effects of Holder pasteurisation on melatonin content needs further investigation.

CONCLUSIONS

The findings summarised in this review highlight the critical role of melatonin as a chronobiotic hormone essential for the development and synchronisation of biological rhythms in neonates. Beginning *in utero* and continuing through early infancy, melatonin – primarily sourced from maternal circulation and breast milk – serves as a fundamental entraining signal for the immature circadian system of newborns. Its influence extends beyond sleep regulation, encompassing neurodevelopment, immune modulation, metabolic programming, and the maturation of the gut–brain axis.

Chrononutrition, particularly the temporal patterning of breast milk composition, emerges as a key physiological mechanism supporting postnatal circadian alignment. The presence of melatonin and other bioactive compounds in night-expressed milk reinforces the importance of preserving diurnal feeding rhythms, especially in preterm infants, who exhibit delayed melatonin production and rely more heavily on exogenous sources.

Despite its promising benefits, factors such as pasteurisation and maternal health status may modulate melatonin levels in milk, highlighting the need for further research into strategies that preserve its chronobiological function in clinical settings. Advancing our understanding of chrononutrition and its translational potential could lead to innovative neonatal care practices that optimise early-life health outcomes through personalised and time-sensitive nutritional support.

Conflict of interest

The author does not report any financial or personal connections with other persons or organisations which might negatively affect the content of this publication and/or claim authorship rights to this publication.

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Interplay between EDA-EDAR and WNT signalling pathways in the development of skin appendages in hypohidrotic ectodermal dysplasia

Współzależność między ścieżkami sygnałowymi EDA-EDAR oraz WNT w rozwoju przydatków skóry w hipohydrotycznej dysplazji ektodermalnej

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Abstract

Ectodermal dysplasia comprises a group of hereditary disorders affecting the development of the skin and its appendages. Among the more than 150 characterised forms of ectodermal dysplasia, hypohidrotic ectodermal dysplasia is the most prevalent in children. Hypohidrotic ectodermal dysplasia is marked by reduced sweating, sparse hair, a limited number of conical-shaped teeth, and brittle nails. The condition results from mutations in genes involved in the EDA-EDAR-EDARADD-NF-κB signalling pathway, which is crucial for early epithelial-mesenchymal communication during the formation of skin appendages. The Wnt/β-catenin pathway also plays a vital role in the development of hair follicles, teeth, and other ectodermal structures. In this article, publicly available single-cell gene expression data from a mouse model were re-analysed to investigate the expression profiles of genes from both the EDA-EDAR and WNT pathways. *Wnt10b*, *Dkk4* and *Edar* were confirmed to be expressed in epidermal keratinocytes, particularly in Fgf20-positive early placode-forming cells. Furthermore, correlated expression of *Edaradd* and *NF-κB* was observed during early appendage formation, while Eda ligand expression was detected in Dkk1-positive mesenchymal progenitor cells, transiently amplifying to become the first dermal condensate and subsequently dermal papilla cells. These findings further support previous observations that EDA-A1 signalling through EDAR-EDARADD and NF-κB enhances WNT pathway activity, creating a mutually reinforcing network. Disruption of this feedback loop between the EDA-EDAR and WNT pathways give rise to the characteristic phenotypes of hypohidrotic ectodermal dysplasia observed in children. Early restoration of the EDA-EDAR and WNT signalling pathways may offer a promising therapeutic strategy for rescuing skin appendage development and thus reducing the effects of ectodermal dysplasias in the future.

Keywords: hypohidrotic ectodermal dysplasia, EDA-EDAR signalling, WNT pathway, skin appendages, hair follicle development

Streszczenie

Dysplazja ektodermalna to grupa dziedzicznych zaburzeń rozwoju skóry i jej przydatków. Spośród ponad 150 scharakteryzowanych postaci dysplazji ektodermalnej najpowszechniej występującą u dzieci jest hipohydrotyczna dysplazja ektodermalna, manifestująca się ograniczoną potliwością, rzadkim owłosieniem, obecnością zaledwie kilku stożkowatych zębów oraz łamliwymi paznokciami. Ten fenotyp jest wynikiem mutacji w genach należących do szlaku sygnałowego EDA-EDAR-

EDARADD-NF-κB, który jest kluczowy dla wczesnej komunikacji naskórkowo-mezenchymalnej podczas formowania się przydatków skóry. Podczas rozwoju zębów, włosów i innych struktur ektodermalnych niezbędne jest także uczestnictwo szlaku WNT z β-kateniną. W artykule ponownie przeanalizowano publicznie dostępne dane z transkryptomiki pojedynczych komórek w modelu mysim i zbadano profile ekspresji genów należących do szlaków sygnałowych EDA-EDAR oraz WNT. Na tej podstawie potwierdzono ekspresję genów *Wnt10b*, *Dkk4* oraz *Edar* w keratynocytach naskórka, szczególnie wśród tych Fgf20-dodatnich, tworzących wczesne plakody. Ponadto zaobserwowano, że korelowało to z ekspresją genów *Edaradd* i *NF-κB*. Ekspresja ligandu Eda była natomiast obecna w Dkk1-dodatnich, mezenchymalnych komórkach progenitorowych, przejściowo aktywowanych w celu stworzenia początkowego skupiska komórek dermalnych dla przyszłej brodawki włosa. Wymienione odkrycia potwierdzają zaobserwowany wcześniej wpływ sygnalizacji EDA-A1 przez EDAR-EDARADD i NF-κB na wzmocnienie aktywności szlaku WNT, tworzący wzajemnie wspierający się system regulacyjny. Zaburzenia w sprzężeniu zwrotnym pomiędzy tymi ścieżkami manifestują się typowym fenotypem dla dzieci z hipohydrotyczną dysplazją ektodermalną. W związku z tym wczesne przywrócenie działania szlaków EDA i WNT może wyznaczyć drogę do skutecznych terapii przywracających rozwój przydatków skóry i redukujących objawy dysplazji ektodermalnej w przyszłości.

Słowa kluczowe: hipohydrotyczna dysplazja ektodermalna, sygnalizacja EDA-EDAR, szlak WNT, przydatki skóry, rozwój mieszków włosowych

INTRODUCTION

Ectodermal dysplasias (ED) comprise a group of inherited disorders that affect the development and maintenance of two or more structures derived from the ectoderm, including hair, nail, skin, and sweat glands. Hypohidrotic (or anhidrotic) ectodermal dysplasia (HED), also known as Christ–Siemens–Touraine syndrome, is the most common form of ED. It may be inherited in an X-linked (XL), autosomal recessive (AR), or autosomal dominant (AD) manner[1–3]. HED is characterised by sparse hair, abnormal or missing teeth (hypodontia or anodontia), reduced sweating, and slow-growing or absent nails. The condition affects approximately 1/15,000 to 1/100,000 individuals worldwide[4–6]. The clinical manifestations of HED are diverse and can significantly impact the quality of life, as shown in Fig. 1.

Skin abnormalities

Sweat gland deficiency is one of the hallmark features of HED, manifesting as a reduced ability to sweat

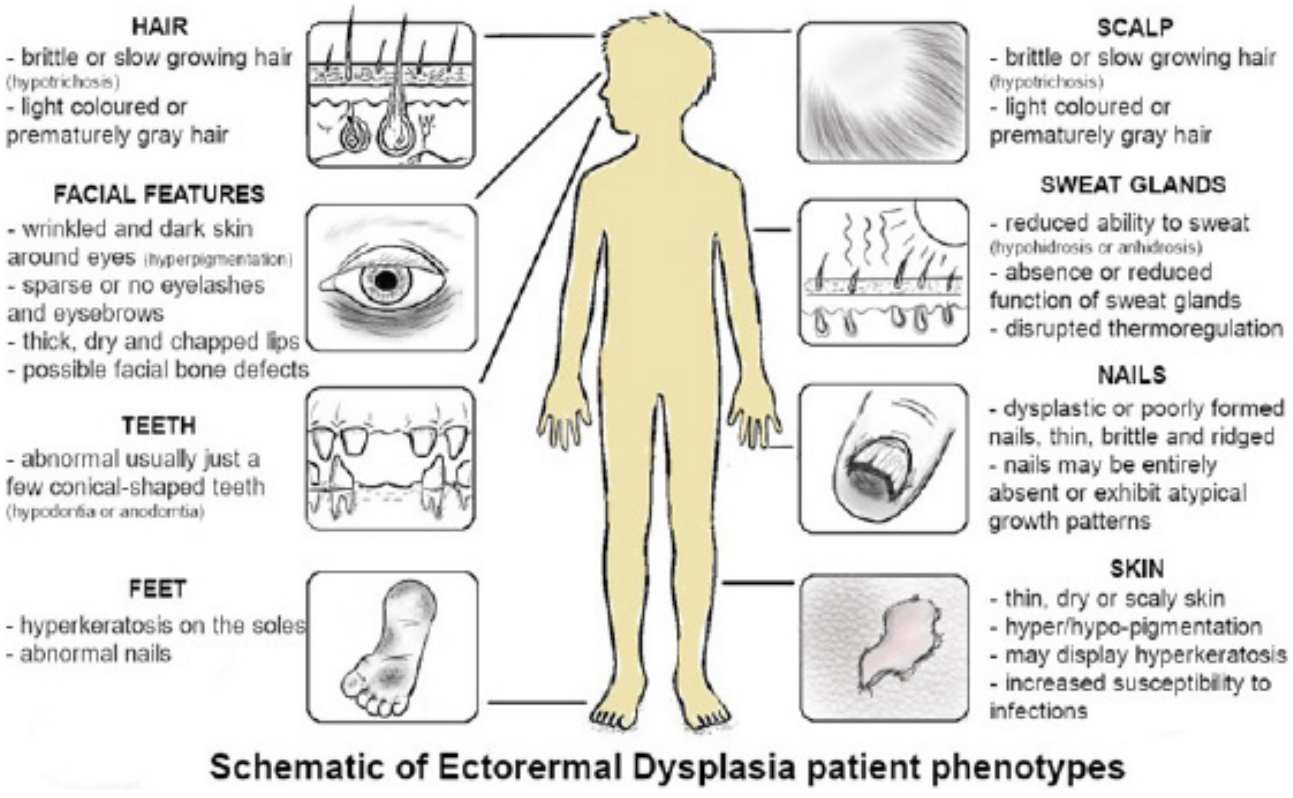

Fig. 1. Schematic of ED patient phenotypes. The clinical manifestations of ED vary depending on the specific type, but they generally affect structures derived from the ectoderm, including the skin, hair, nails, teeth, and sweat glands

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(hypohidrosis or anhidrosis) due to underdeveloped or absent eccrine glands. This leads to heat intolerance and recurrent episodes of hyperthermia. The skin is typically thin, dry, and eczematous, with regional hyperkeratosis. Characteristic periorbital hyperpigmentation and fine wrinkles around the eyes give an appearance of premature aging[4] (Fig. 1).

Hair abnormalities

Affected individuals have sparse scalp hair (hypotrichosis), which is often light-coloured, brittle, and slow-growing. Eyebrows and eyelashes are also sparse or absent[5] (Fig. 1).

Dental abnormalities

Tooth development abnormalities, including hypodontia (missing teeth) or malformed teeth, are common. Usually, just a few conical-shaped teeth are present, often smaller and pointed in appearance[4,7]. Other clinical manifestations include dysmorphic facial features, respiratory issues, and immune system implications (Fig. 1).

Nail abnormalities

Nails, derived from the ectodermal layer, can be affected by ED, though not all individuals with the condition experience nail abnormalities. Common manifestations include small, brittle, discoloured, or misshapen nails, which may grow slowly or shed periodically, and are prone to splitting and breaking[8–10].

At the cellular and molecular levels, the development of the skin and its appendages is a complex process. However, EDA-EDAR and WNT are the two major pathways playing a critical role in this process. Mutations or impairment in any of the components of these two pathways lead to abnormalities in the development of ectodermal derivatives[4,5].

EDA-EDAR-EDARADD PATHWAY AND ITS FUNCTION IN DEVELOPMENT OF SKIN APPENDAGES

The *EDA* (ectodysplasin A) gene encodes the ligand EDA, which belongs to the tumour necrosis factor (TNF) ligand superfamily. EDA has 8 isoforms due to alternative splicing, of which only EDA-A1 (a 391-amino acid protein) and EDA-A2 (a 389-amino acid protein) have receptor-binding domains. EDA-A1 is a type II transmembrane protein with 4 functional domains; an N-terminal intracellular domain, a furin protease recognition sequence, a collagen-like repeat domain, and a C-terminal TNF homology domain (THD). EDA-A1 contains a unique 2-amino acid motif (Val-Glu) in comparison to EDA-A2 in THD, required for EDAR (ectodysplasin A receptor) selective binding. In EDA-A1, the C-terminal portion comprising the collagen and TNF homology domains is cleaved at the furin consensus site, releasing homotrimers that can bind to its receptor EDAR, which is encoded on chromosome 2. While EDA-A2 shares much of its structure with EDA-A1, it lacks the Val-Glu motif in the TNF homology domain, which defines its binding to XEDAR (X-linked EDA receptor), also known as EDA2R (ectodysplasin A2 receptor) instead of EDAR[11,12] (Fig. 2). In general, the EDA protein plays a crucial role in the development of ectodermal tissues.

It is involved in epithelial-mesenchymal signalling during the morphogenesis of ectodermal organs[13]. It promotes cell adhesion to the extracellular matrix, which is consistent with its role in regulating epithelial-mesenchymal interaction during the development of ectodermal appendages[13,14]. EDA also participates in multiple signalling pathways, such as Wnt/β-catenin, JNK, BMP/Smad, and FGF signalling[15]. In relation to the skin and its appendages, EDA defines structure in several ways. In hair follicles (HF), it enables the development of HF types prior to birth and then modulates hair thickness and influences hair fibre shape in adults[16,17]. A mouse model study suggests that transgenic expression of the EDA-A1 isoform can rescue the development of several skin appendages[18,19]. In teeth, EDA deficiency can reduce the size of the region where Sonic hedgehog (*Shh*) is expressed in the primary enamel knot, leading to the formation of an abnormal enamel organ and a hypoplastic function incisor[14,20]. Mutant mice lacking EDA exhibit taurodontism, characterised by enlarged pulp chambers with absent or delayed tooth root bifurcation (tooth root branching)[13,21].

EDAR encodes the receptor EDAR, which belongs to the TNF receptor family. EDAR is a type I transmembrane protein containing 448 amino acids. It is a receptor for the soluble ligand EDA isoform A1, but not for the EDA isoform A2[11,12]. It has 3 cysteine-rich domains (CRDs) in the extracellular region, a transmembrane region, and an intracellular signalling domain known as the death domain.

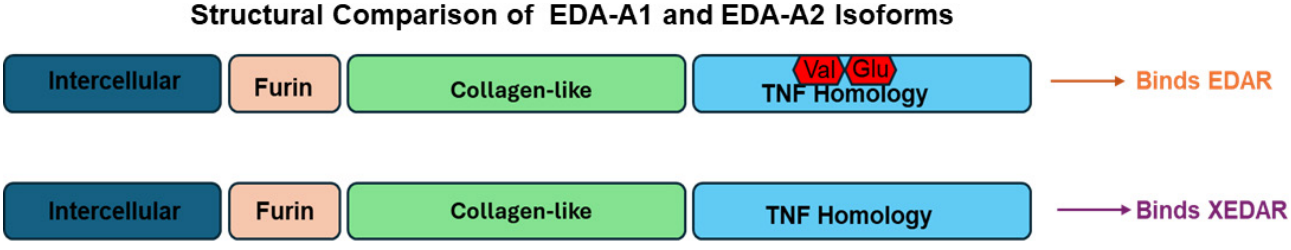

Fig. 2. Structural comparison of EDA-A1 and EDA-A2 isoforms and their selective binding to specific receptors: EDAR and XEDAR

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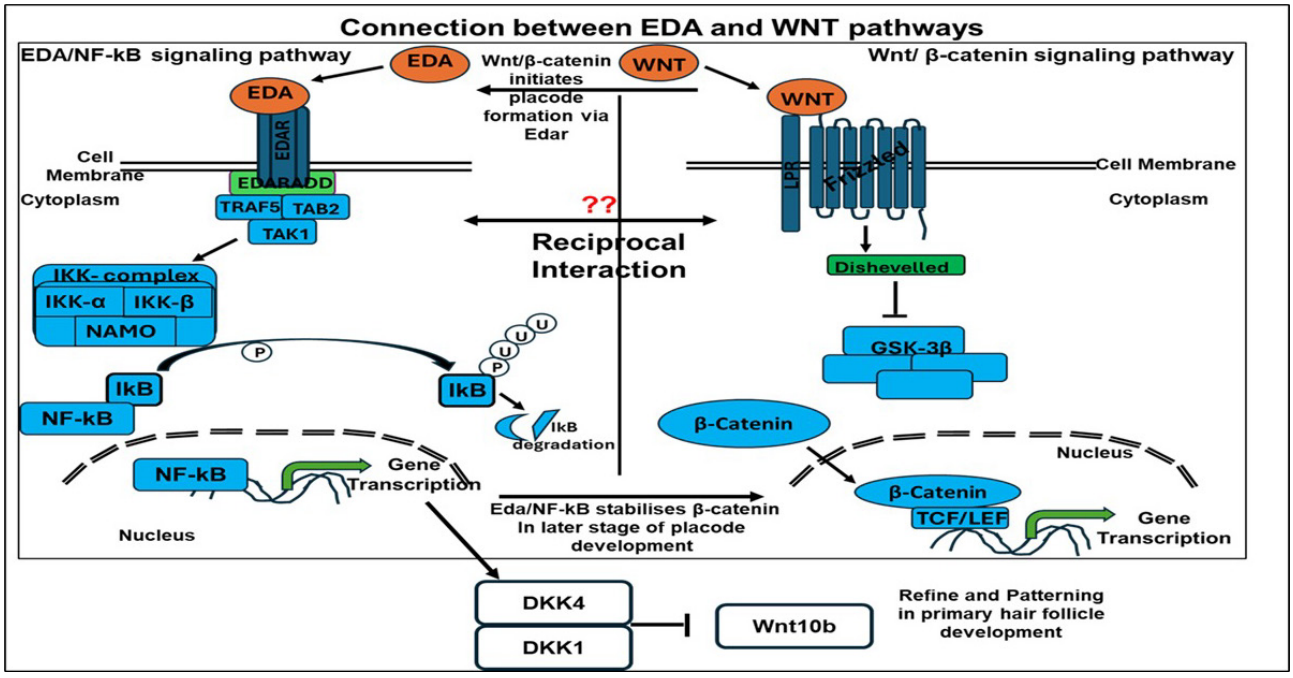

Fig. 3. Summary schematic presentation of the EDA and WNT pathways and their connections in skin appendage development. The mutual coordination of the EDA and WNT pathways is necessary for refining and patterning primary hair follicle development, where Wnt/β-catenin initiates placode formation via the activation of Edar, and the Eda-Edar-NF-κB pathway reinforces the stabilisation of β-catenin in the later stage of placode development. Further reciprocal interactions between these two pathways remain to be discovered

The CRDs in EDAR are characteristic of the TNF receptor superfamily and are essential for ligand binding – in this case, to EDA-A1, and are therefore also referred to as the ligand-binding domain (LBD).

The homotrimers released from EDA-A1 binds specifically to the LBD region of EDAR, which then recruits to its intracellular death domain the adaptor protein EDARADD (EDAR-associated death domain), a 208-amino acid protein. EDARADD consists of a C-terminal death domain and a Traf-binding consensus sequence[11,12]. The death domain interacts with EDAR, and the Traf-binding consensus sequence combines with the TRAF6/TAK1/TAB2 complex. TRAF6 acts as a scaffold molecule to recruit the IKK complex, and activated IKK then phosphorylates IkB proteins, leading to their degradation[11,13]. The degradation of IkB releases NF-κB (nuclear factor-kappaB), which then translocates to the nucleus to initiate the transcription of downstream genes[22]. Thus, the death domain of EDARADD interacts with the death domain of EDAR, forming the EDA-EDAR-EDARADD complex, which initiates a signalling cascade leading to the activation of NF-κB[23]. NF-κB translocates to the nucleus (Fig. 3) and activates the transcription of target genes required for epidermal patterning and appendage formation. The EDA-A1-EDAR signalling pathway is required for the development of ectodermal derivatives such as hair, teeth, nails, and sweat glands[24].

Thus, impairment in any of these components can disrupt the signalling cascade, leading to the manifestation of HED, characterised by defects in the structure of the appendages mentioned previously. On the other hand, EDA-A2/XEDAR signalling pathways is more specific to mammary gland development and less critical in the development of appendages. It may possess a redundant or compensatory role and is rarely linked to human disease[24].

EDA-EDAR IN HAIR MORPHOGENESIS

HF morphogenesis is a complex biological process mediated by communication between epithelial and mesenchymal cells. HF induction begins with a signal from the mesenchyme, known as the "first dermal message", promoting the formation of thickenings in the epithelium called HF placodes[25]. The identity of this signal is still unclear, though its transduction has been associated with the Wnt signalling pathway. Impairment of this pathway, whether through ablation of the Wnt transducer, i.e. β-catenin, in the dermis, or through abrogation of epidermal Wnt secretion, prevents the formation of placodes[26,27]. The formed placode acts as a signalling centre. Reanalysis of single-cell gene expression data in mice revealed activation of EDA-EDAR signalling in the formed placodes (Fig. 4), alongside the expression of many downstream genes, including *Fgf20*[28], *Shh*[29], *Wnt10b*, and *Dkk4*[17]. *Fgf20* is necessary for the clustering of underlying dermal fibroblasts, leading to the formation of the dermal condensate (DC), which subsequently matures into hair follicle dermal papillae[17,28]. Shh is essential for the formation of proper DC and, consequently, for HF development; its absence results in arrest of this process[29–31]. Similarly, *Wnt10b*, among other Wnt ligands constituting the placode signal, is crucial for hair development

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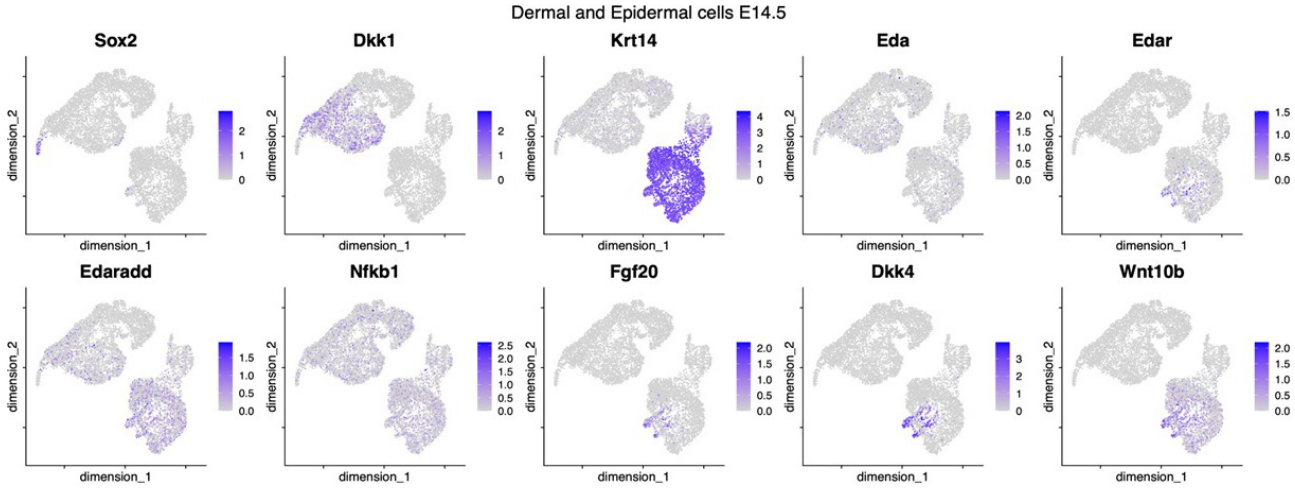

Fig. 4. UMAP plots depicting the expression of EDA/EDAR-related genes in dermal (left) and epidermal (right) cells during hair morphogenesis on day E14.5. Sox2 is a marker of dermal condensate (DC), Dkk1 marks DC progenitors, and Eda, Edar, Edaradd and Nfkb1 belong to the Eda-Edar pathway. Krt14, Fgf20, Dkk4, Wnt10b are epidermal placode markers

and growth[27], while *Dkk4* expression can potentially control placode size and spacing[32].

WNT PATHWAY AND ITS FUNCTION IN DEVELOPMENT OF SKIN APPENDAGES

WNTs (Wingless and Int-1) are typically 350–400 amino-acid long, and are secreted, lipid-modified signalling glycoprotein[33]. They have a two-domain structure: the amino-terminal is composed of a cluster of alpha-helices with 10 conserved cysteine residues forming 5 disulphide bridges, while the carboxy-terminal domain is dominated by two beta-sheets and maintained by 6 disulphide bridges. These disulphide bridges are thought to maintain a globular secondary structure. WNTs undergo lipid modification and glycosylation to ensure proper secretion and binding to their receptors[34]. They act as ligands to activate different Wnt pathways via paracrine and autocrine routes, binding to frizzled receptors on the cell membrane. Sequences of WNT proteins are conserved across species, and the orthologs are easy to identify[35]. WNT proteins control a wide range of processes, such as cell fate, embryonic development, stem cell proliferation, maintenance and differentiation, tissue homeostasis, and regulation of gene expression[36]. They play pivotal roles in the development of skin and its appendages, such as placode formation, epithelial cell fate decisions, and inductive signalling to dermal condensation. Some of the Wnt genes, such as *Wnt3*, *Wnt7b*, *Wnt7a*, *Wnt10a* and *Wnt10b*, play well-known roles in hair follicle development. For example, overexpression of *Wnt3a* activates β-catenin and promotes hair growth. Macrophage-derived extracellular vesicles containing Wnt3a enhance hair follicle regeneration[37]. *Wnt10b* promotes hair growth by enhancing the switch from telogen to anagen. In *in-vitro* culture, *Wnt10b* enhances the differentiation of cultured skin epithelial cells into the hair shaft and inner root sheath by stabilising β-catenin. *Wnt7a* and *Wnt7b* are important regulators of hair follicle stem cell (HFSC) homeostasis and the hair follicle cycle[38,39]. *Wnt5a*, a non-canonical Wnt, is expressed in bulge and secondary hair germ cells during the telogen stage, antagonises the function of canonical Wnts, and inhibits dermal cell proliferation[40] Meanwhile, Wnt1a-enriched conditioned media accelerates hair follicle progression from telogen to anagen[41]. Wnt modulators, such as R-spondins, which enhance Wnt signalling during development, regulate hair follicle development and HFSC homeostasis, affecting hair regeneration[42]. *Wls* (also known as Wntless, Evi, and GPR177) encodes a multipass transmembrane protein that transports lipid-modified Wnts to the cell surface. Genetic ablation of epithelial *Wls* inhibits hair placode formation and diminishes the expression of placode markers[41]. At the cell surface, WNT protein binds to the N-terminal extracellular cysteine-rich domain of a frizzled family receptor (FZD). To facilitate Wnt signalling, the co-receptor LRP5/6 may be required alongside the interaction between the WNT and FZD proteins. Upon activation of the receptor, a signal is sent to the cytoplasm through the phosphoprotein Dishevelled (DSH), which, along with other components, inactivates GSK-3 β and induces β-catenin stability[33,36]. Epithelial deletion of β-catenin results in the absence of hair and mammary placode formation[43]. Stabilised β-catenin binds to the T-cell factor (TCF)/lymphoid enhancer factor (LEF) complex and translocates to the nucleus (Fig. 3). DKK1 (Dickkopf) inhibits Wnt action by binding with the LRP co-receptor, and skin-specific overexpression of Dkk1-leads to a complete block in the development of skin appendages. Overexpression of Dkk1 also halts tooth development at the placode stage[41]. In the nucleus, β-catenin facilitates the expression of genes involved in epithelial tissue development. Activation of the Wnt/β-catenin pathway directs epithelial cells towards appendage formation, and overexpression of stabilised β-catenin in mouse skin results in more hair formation and faster hair regeneration[44]. The Wnt/ β-catenin signalling pathway is considered the central signalling pathway for the transformation of hair follicles

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from the resting phase to the growth phase. It participates in all stages of hair follicle development and determines the differentiation fate of cells during development[45].

CONNECTION BETWEEN EDA AND WNT PATHWAYS

The Wnt signalling pathway and the EDA-EDAR-NF-κB pathway are deeply interconnected in the development of ectodermal appendages – such as hair follicles, teeth, and sweat glands – and their dysregulation contributes to the phenotypes observed in EDA pathway-deficient patients, such as in HED. These pathways interact in complex ways to ensure proper patterning and maintenance of these structures[17]. However, their reciprocal recruitment at different stages of skin appendage development is still unexplored (Fig. 3). Both pathways regulate the expression of overlapping target genes involved in ectoderm development. For instance, genes like *Shh* and *Dkk4* are regulated by both pathways and play roles in hair follicle and tooth development[46]. The EDA-EDAR pathway influences Wnt signalling by modulating the activity of β-catenin. EDAR signalling has been shown to stabilise β-catenin, enhancing Wnt-mediated gene transcription. In the same way, activated Wnt/β-catenin can upregulate the expression of EDAR, creating a positive feedback loop during hair follicle formation[15,17]. Studies have shown that elevated EDAR signalling can lead to increased expression of Wnt10b and Dkk4, demonstrating amplified signal transduction through these pathways[47]. Dkk4, a Wnt inhibitor, is regulated by EDAR signalling and can modulate Wnt activity to fine-tune it during developmental processes such as tooth development. EDA-EDAR-NF-κB signalling is required to refine and maintain the pattern of Wnt/β-catenin activity in the later stage of placode development[48]. Specifically, Wnt10b has been identified as a direct NF-κB target gene, necessary for maintaining the localised expression pattern critical for appendages[17]. Thus, in conclusion, several studies have shown that activation of the EDA-EDAR-NF-κB pathway influences Wnt signalling genes and vice versa during the earlier embryonic development of skin and its appendages, shaping and refining their structure[17,49].

In EDA-deficient patients with EDA mutations, this upregulation fails, leading to reduced or absent Wnt expression and impaired or delayed initiation of appendage formation. Wnt and EDA cooperate in positive feedback loops. Canonical Wnt/β-catenin signalling initiates placode formation, which triggers EDA expression and then reinforces Wnt signalling via NF-κB activation. This loop is essential for amplifying and stabilising epithelial patterning signals. Indeed, without EDA, this loop is disrupted, resulting in abortive placode development and sparse or absent hair, conical or missing teeth, and hypoplastic glands. During development, Wnt10a/b and EDA are co-expressed in epidermal placodes, hair germs, and dental lamina. This spatial co-localisation suggests they act in coordinated modules during morphogenesis. In Eda-null (Tabby) mice, expression of Wnt10a is dramatically reduced in placodes during budding morphogenesis[50].

Rescue of EDA signalling restores Wnt expression and partially rescues hair and tooth development. WNT10A mutations in humans also cause syndromes with overlapping phenotypes, such as odontohypophosphatasia and HED.

CONCLUDING REMARKS

The most prevalent form of ED in children is HED, in which impaired development of skin appendages results from mutations in genes related to the EDA-EDAR-EDARADD signalling pathway. Independently, the canonical WNT signalling pathway was previously identified as a key regulator in the development of hair and teeth. In this study, mouse single-cell gene expression data were re-analysed, confirming the expression of *Edaradd* and *NF*-κB alongside canonical WNT pathway genes in epidermal placodes. Expression of the Eda ligand was found in Dkk1+ dermal cells, thus providing additional convergent evidence supporting previous findings that EDA-A1 signalling enhances WNT pathway activity, forming a mutually reinforcing regulatory network during the early stages of skin appendage primordial formation. These findings highlight the potential for early therapeutic restoration of EDA and WNT pathway activity, offering a promising avenue for treating patients with ED and restoring proper development of skin appendages in the future.

MATERIALS AND METHODS

- Raw 10X sequencing data from control E14.5 mouse skin samples were processed using the standard 10X CellRanger pipeline. The resulting nUMI count matrices were deposited at GEO: GSE198487 by Qu et al.[30]. They were filtered, centred, and normalised in Seurat[51,52].
- Image analysis scRNA-seq data was visualised using the ggplot2 and cowplot R libraries.
- Software R (https://www.r-project.org/) and Seurat (http://satijalab.org/seurat/).

Conflict of interest

The authors do not report any financial or personal connections with other persons or organisations which might negatively affect the content of this publication and/or claim authorship rights to this publication.

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Author contribution

Original concept of study; final approval of manuscript: KK. Collection, recording and/or compilation of data; writing of manuscript: AJ, KŁ, APC, KK. Analysis and interpretation of data; critical review of manuscript: AJ, KŁ, KK.

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Ocena stężenia witaminy K_2 u dzieci i nastolatków ze złamaniami kości – badanie pilotażowe

Vitamin K_2 levels in children and adolescents with bone fractures – a pilot study

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Streszczenie

Wprowadzenie i cel: Poza układem krzepnięcia witamina K_2 wpływa na procesy kalcyfikacji ścian naczyń krwionośnych i gospodarkę mineralną szkieletu. Oznaczanie jej stężenia i wyznaczanie norm referencyjnych dotyczy przede wszystkich populacji zagrożonych osteoporozą, a niewiele badań przeprowadzono z udziałem populacji wieku rozwojowego. Celem pracy była ocena stężenia witaminy K_2 u dzieci i nastolatków ze złamaniami kości. **Materiał i metody:** Grupę badaną stanowiło 145 dzieci w wieku 5–17 lat hospitalizowanych z powodu podejrzenia zaburzeń mineralizacji kośćca. Pacjentów podzielono na trzy grupy: dzieci z wrodzoną łamliwością kości (n = 29), dzieci z co najmniej dwoma złamaniami pourazowymi (n = 48) i dzieci zdrowe (n = 68). U wszystkich badanych przeprowadzono ocenę rozwoju fizycznego zgodnie z przyjętymi metodami i oceniono stężenie witaminy K_2 metodą immunoenzymatyczną (ELISA) z użyciem zestawu firmy SunRedBio (Chiny). **Wyniki:** Rozwój somatyczny ocenianej grupy dzieci był prawidłowy, u dzieci z wrodzoną łamliwością kości wykazano niższy wzrost i mniejszą masę ciała w porównaniu z pozostałymi grupami. Stężenie witaminy K_2 u 80% dzieci zdrowych wynosiło 0,90–12,46 ng/ml. Stężenia witaminy K_2 w grupach II i III były niskie – w grupie z łamliwością kości 2,7 ng/ml, a w grupie ze złamaniami 2,05 ng/ml – i nie różniły się istotnie statystycznie między dziećmi uznanymi za zdrowe a pacjentami ze złamaniami kości, w tym z wrodzoną łamliwością kości. **Wnioski:** Stężenie witaminy K_2 w badanej populacji dzieci i nastolatków ze złamaniami kości w wywiadzie mieściło się w granicach uznanych za referencyjne dla tej grupy wiekowej, co sugeruje, że u badanych złamania nie były związane z niedoborem tej witaminy.

Słowa kluczowe: witamina K_2, dzieci, złamania kości

Abstract

Introduction and objective: In addition to coagulation, vitamin K_2 influences vascular calcification and skeletal mineral balance. Evaluation of its levels and setting reference ranges are mainly relevant for all populations at risk of osteoporosis. However, only few reports have focused on the developmental age population. The aim of this study was to assess vitamin K_2 levels in children with bone fractures. **Materials and methods:** The study group consisted of 145 children aged 5–17 years, hospitalised for suspected metabolic bone diseases. Patients were divided into three groups: healthy children (n = 68), children with osteogenesis imperfecta (n = 29), and children with traumatic fractures (n = 48). All children were assessed for physical development using established methods, and had their vitamin K_2 levels measured with immunoenzymatic assay (ELISA), using a SunRedBio kit (China). **Results:** The evaluated group of children showed normal somatic development. Children with osteogenesis imperfecta showed lower height and body weight compared to the other groups. Vitamin K_2 ranged from 0.90 to 12.46 ng/mL in 80% of healthy children. Low vitamin K_2 levels (2.7 ng/mL for osteogenesis imperfecta and 2.05 ng/mL for fractures) were found in groups 2 and 3, and did not differ statistically significantly between children considered healthy and patients with bone fractures, including those with osteogenesis imperfecta. **Conclusions:** Children with a history of bone fractures have vitamin K_2 levels within the reference ranges for this age group, suggesting that bone fractures in this group are not associated with vitamin K_2 deficiency.

Keywords: vitamin K_2, children, bone fracture

WSTĘP

Udział witamin K w procesach gospodarki mineralnej organizmu sprawia, że zwiększa się zainteresowanie oznaczeniami różnych jej form w licznych jednostkach chorobowych. Poza układem krzepnięcia witamina K_2 wpływa na procesy kalcyfikacji ścian naczyń krwionośnych i gospodarkę mineralną szkieletu. Oznaczanie jej stężenia i wyznaczanie norm referencyjnych dotyczy przede wszystkich populacji zagrożonych osteoporozą, a niewiele badań przeprowadzono z udziałem populacji wieku rozwojowego.

Istnieje wiele metod oceny stężenia witaminy K w organizmie, zarówno pośrednich, jak i bezpośrednich. Brakuje jednak jednolitych standardów, co utrudnia dokładne określenie jej optymalnego stężenia i porównywanie wyników różnych badań, w których ponadto stosowano różne jednostki miary[1].

Według Mager i wsp. pomiary pośrednie mogą zawierać błędy, dlatego należy je stosować ostrożnie[2,3]. Do metod pośrednich zalicza się oznaczanie z krwi czasu protrombinowego oraz stężeń osteokalcyny niekarboksylowanej, białka Gla macierzy i PIVKA II, czyli protein indukowanych niedoborem witaminy K, oraz z moczu stężeń metabolitów witaminy K (7C-aglikonu i 5C-aglikonu). Za preferowaną metodę oceny stężeń witaminy K i jej metabolitów uznaje się ich pomiar bezpośredni[4]. Metodami bezpośrednimi oznaczania witaminy K u ludzi są m.in. wysokosprawna chromatografia cieczowa (*high-performance liquid chromatography*, HPLC) z detekcją ultrafioletową (UV), HPLC z detekcją fluorescencji, HPLC z detekcją elektrochemiczną (*electrochemical detectors*, ECD) i tandemowa spektrometria mas chromatografii cieczowej (*liquid chromatography atmospheric pressure chemical ionization tandem mass spectrometry*, LC-APCI-MS/MS), która cechuje się najwyższą czułością[1].

Chociaż stężenie witaminy K metodami bezpośrednimi oceniało wielu autorów, to większość prac dotyczyła osób dorosłych. Tsugawa i wsp., badając za pomocą LC-APCI-MS/MS grupę kobiet po 30. roku życia, określili średnie wartości MK-4 i MK-7 (menachinon z 4 i 7 jednostkami prenylowymi) na poziomie odpowiednio 0,07–0,1 ng/ml i 4,21–8,42 ng/ml[5]. W 2018 roku Klapkova i wsp. za pomocą HPLC z detekcją fluorescencji u kobiet po menopauzie wyznaczyli średnie stężenie MK-4 na poziomie 0,433 ± 0,394 ng/ml, a MK-7 – 1,002 ± 1,020 ng/ml[6]. Próbę oznaczenia stężenia witaminy K_2 w grupie dzieci w wieku 8–14 lat (chorych na celiakię lub zdrowych) podjęli w 2018 roku Volkan i wsp., którzy używając zestawu immunologicznego Human Vitamin K_2 Elis, stwierdzili, że wynosiło ono 2,64 ± 2,1 nmol/l[7]. W 2022 roku Du i Li u dzieci wieku 1–14 lat za pomocą tandemowej spektrometrii mas wysokosprawnej chromatografii cieczowej wykazali, że mediana stężenia witaminy K_2 wynosiła 0,1 (przedział międzykwartylowy P25, P75 – 0,1, 0,2) ng/ml[8].

Celem niniejszej pracy była ocena stężenia witaminy K_2 u dzieci i nastolatków ze złamaniami kości.

MATERIAŁ I METODY

Badania przeprowadzono z udziałem 145 dzieci w wieku 5–17 lat, które były hospitalizowane w Klinice Pediatrii, Patologii Noworodka i Chorób Metabolicznych Kości z powodu podejrzenia zaburzeń mineralizacji kośćca po przebytych złamaniach lub były uznane za zdrowe, bez chorób przewlekłych. Uczestników podzielono na trzy grupy: I (n = 29) stanowiły dzieci ze złamaniami w przebiegu wrodzonej łamliwości kości, II (n = 48) – dzieci ze złamaniami bez choroby metabolicznej kości, a III (kontrolną; n = 68) – dzieci uznane za zdrowe. Żadne dziecko przed włączeniem do badania nie suplementowało witaminy K.

U wszystkich pacjentów wykonano badanie podmiotowe i pomiary antropometryczne (wysokość i masa ciała, wskaźnik masy ciała – *body mass index*, BMI). Oznaczono u nich także stężenie witaminy K_2 w surowicy metodą immunoenzymatyczną (*enzyme-linked immunosorbent assay*, ELISA) z użyciem zestawu firmy SunRedBio (Chiny). Czułość zestawu wynosiła 2,225 ng/ml.

Analizę statystyczną wykonano w programie statystycznym R w wersji 4.0.1.

Na przeprowadzenie badań uzyskano zgodę Komisji Bioetycznej przy Uniwersytecie Medycznym w Łodzi (nr RNN/116/17/KE).

WYNIKI

Nie potwierdzono istotnych statystycznie różnic między trzema badanymi grupami pod względem wieku, BMI, Z-score BMI ani masy ciała. W przypadku wysokości ciała wykazano, że grupy różniły się w sposób istotny zarówno w ujęciu absolutnym, jak i Z-score. Z kolei dla masy ciała różnica między grupami była istotna statystycznie wyłącznie dla ujęcia Z-score. Analiza *post-hoc* wykazała, że grupa I cechowała się istotnie niższą średnią wysokością i masą ciała niż grupy II i III (tab. 1).

Analizę stężenia witaminy K_2 w poszczególnych grupach przedstawiono w tab. 2.

Na podstawie indywidualnych wartości średnich i *SD* stężeń witaminy K_2 u dzieci z grupy III wykreślono krzywą rozkładu tych stężeń i uzyskano wykres asymetryczny, prawostronny (ryc. 1). W tej grupie nie obserwowano bardzo niskich stężeń tej witaminy. Potwierdzeniem tego spostrzeżenia jest przeprowadzony test Shapiro–Wilka dla stężenia witaminy K_2 w tej grupie (p < 0,001) (ryc. 1).

Dla danych o dystrybucji odbiegającej od rozkładu normalnego można zaprezentować rozkład za pomocą decyli, stanowiących punkt odniesienia dla danego wyniku na tle całej grupy. W tym celu w tab. 3 przedstawiono podział decylowy dla witaminy K_2 w grupie III i na jego podstawie stwierdzono, że po wyłączeniu z niej 20% dzieci cechujących się skrajnymi wartościami stężeń witaminy K_2 u pozostałych 80% jej stężenie wynosiło 0,90–12,46 ng/ml.

Następnie oceniono stężenie witaminy K_2 w analizowanych grupach pacjentów. U dzieci z grupy II mediana

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Zmienna	Wszyscy badani	Grupa I	Grupa II	Grupa III	*p*
Wiek [lata]	9,98 ± 2,70	9,90 ± 3,72	10,48 ± 2,20	9,66 ± 2,50	0,488
Wysokość ciała [cm]	143,00 (127,25; 157,00)	127,00[a,b] (109,00; 146,00)	144,50[a] (132,38; 160,00)	144,75[b] (129,63; 157,00)	0,006
Z-score wysokość ciała	0,29 (−0,74; 1,01)	−1,14[c,d] (−3,92; −0,27)	0,35[c,e] (−0,41; 0,86)	0,65[d,e] (−0,11; 1,64)	<0,001
Masa ciała [kg]	36,00 (25,50; 43,50)	29,00 (17,00; 43,50)	37,50 (30,30; 45,75)	35,75 (26,33; 40,75)	0,155
Z-score masa ciała	−0,03 (−0,97; 0,66)	−1,07[f,g] (−2,07; 0,27)	0,20[f] (−0,58; 0,86)	−0,07[g] (−0,69; 0,88)	0,021
BMI	17,23 (14,86; 20,14)	18,11 (14,72; 21,97)	17,89 (15,47; 20,13)	16,38 (14,54; 18,44)	0,072
Z-score BMI	−0,13 (−1,17; 0,78)	0,12 (−1,38; 1,23)	0,14 (−0,81; 0,93)	−0,41 (−1,19; 0,23)	0,157

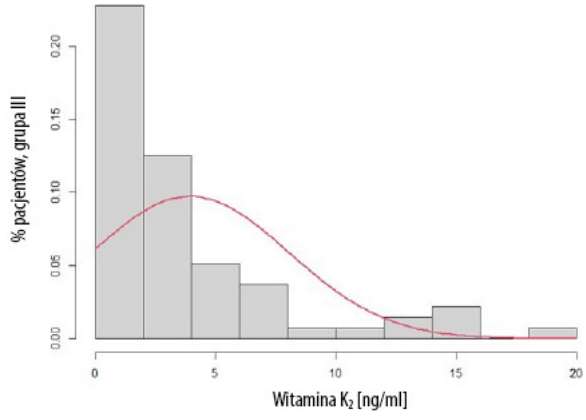
Dane przedstawione jako średnia arytmetyczna ± *SD* lub jako mediana (Q1; Q3), zależnie od normalności rozkładu. Grupy porównano za pomocą analizy wariancji ANOVA lub testu Kruskala–Wallisa z testem *post-hoc* Dunna. a–h – istotne statystycznie różnice dla testu *post-hoc* Dunna (a: $p = 0{,}001$, b: $p = 0{,}002$, c, d: $p < 0{,}001$, e: $p = 0{,}048$, f: $p = 0{,}004$, g: $p = 0{,}011$).
BMI – *body mass index*, wskaźnik masy ciała.

Tab. 1. Ocena rozwoju biologicznego (antropometryczna) badanej populacji z podziałem na grupy

Witamina K_2 [ng/ml]	*N*	*M*	*SD*	*MD*	Q1	Q3	Min.	Maks.
Wszyscy badani	145	3,85	3,88	2,40	1,30	4,80	0,40	18,10
Grupa I	29	4,22	3,86	2,70	1,70	4,90	0,80	15,30
Grupa II	48	3,48	3,55	2,05	1,10	4,80	0,60	16,00
Grupy I + II	77	3,76	3,66	2,40	1,30	4,80	0,60	16,00
Grupa III	68	3,94	4,13	2,30	1,28	5,23	0,40	18,10

N – liczba obserwacji; ***M*** – średnia arytmetyczna; ***SD*** – odchylenie standardowe; ***MD*** – mediana; **Q1** – kwartyl pierwszy; **Q3** – kwartyl trzeci; **Min.** – minimum; **Maks.** – maksimum.

Tab. 2. Stężenie witaminy K_2 w badanej populacji z podziałem na grupy



Ryc. 1. Histogram stężenia witaminy K_2 u dzieci z grupy III

Decyl	Witamina K_2 [ng/ml]
1.	0,90
2.	1,00
3.	1,37
4.	1,70
5.	2,30
6.	3,10
7.	4,08
8.	6,06
9.	10,75

Tab. 3. Podział decylowy stężenia witaminy K_2 u dzieci z grupy III

	Grupa II	Grupa III	*MD* (95% CI)	*p*
n	48	68		
Witamina K_2 [ng/ml]	2,05 (1,10; 4,80)	2,30 (1,28; 5,23)	−0,25 (−0,80; 0,40)	0,575

Dane przedstawione jako mediana (Q1; Q3). ***MD*** – różnica w medianach pomiędzy obiema grupami z 95-procentowym poziomem ufności.
Test *U* Manna–Whitneya.

Tab. 4. Porównanie średniego stężenia witaminy K_2 pomiędzy pacjentami ze złamaniami a pacjentami bez złamań kości

	Grupa I	Grupa III	*MD* (95% CI)	*p*
n	29	68		
Witamina K_2 [ng/ml]	2,70 (1,70; 4,90)	2,30 (1,28; 5,23)	0,40 (−0,50; 1,30)	0,424

Dane przedstawione jako mediana (Q1; Q3). ***MD*** – różnica w medianach pomiędzy obiema grupami z 95-procentowym poziomem ufności.
Test *U* Manna–Whitneya.

Tab. 5. Porównanie średniego stężenia witaminy K_2 pomiędzy grupami I i III

	Grupy I + II	Grupa III	*MD* (95% CI)	*p*
n	77	68		
Witamina K_2 [ng/ml]	2,40 (1,30; 4,80)	2,30 (1,28; 5,23)	0,10 (−0,60; 0,60)	0,997

Dane przedstawione jako mediana (Q1; Q3). ***MD*** – różnica w medianach pomiędzy obiema grupami z 95-procentowym poziomem ufności.
Test *U* Manna–Whitneya.

Tab. 6. Porównanie średniego stężenia witaminy K_2 pomiędzy pacjentami ze złamaniami kości (grupy I i II łącznie) a pacjentami z grupy III

stężenia witaminy K_2 wynosiła 2,05 ng/ml, a u dzieci z grupy III – 2,30 ng/ml. Nie potwierdzono istotnej statystycznie różnicy w stężeniu witaminy K_2 pomiędzy obiema grupami (mediana – *MD* = −0,25; 95% CI: −0,80, 0,40; $p = 0{,}575$) (tab. 4).

U dzieci z grupy I mediana stężenia witaminy K_2 wynosiła 2,70 ng/ml, a u dzieci z grupy III – 2,30 ng/ml. Nie potwierdzono istotnej statystycznie różnicy w stężeniu witaminy K_2 pomiędzy obiema grupami (*MD* = 0,40; 95% CI: −0,50, 1,30, $p = 0{,}424$) (tab. 5).

Po połączeniu grup *I* i *II* w jedną grupę i porównaniu dla niej stężenia witaminy K_2 z grupą III również nie potwierdzono istotnej statystycznie różnicy w stężeniu witaminy K_2

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pomiędzy obiema grupami (*MD* = 0,10; 95% CI: –0,60, 0,60; *p* = 0,997) (tab. 6).
Oznacza to, że w badanej grupie dzieci i nastolatków nie wykazano związku pomiędzy stężeniem witaminy K_2 a występowaniem złamań kości (tab. 6).

OMÓWIENIE

Witaminy K odgrywają główną rolę w procesach krzepnięcia, metabolizmu kostnego i zwapnień w układzie krążenia. Opracowano liczne metody oceny stężenia witaminy K w organizmie. Za wskaźnik jego zaopatrzenia w witaminę K uznaje się witaminę K_1, a jej niedobór określa się jako stężenie <0,15 μg/l. Ryzyko niedoboru zwiększają takie czynniki, jak zaburzenia wchłaniania lipidów, niedożywienie, zaburzenia czynności nerek i nowotwory oraz okresy noworodkowy i inwolucyjny[9].
Do oceny stężenia witaminy K_2 w populacji wieku rozwojowego włączono dzieci uznane za zdrowe i dzieci ze złamaniami kości bez istotnych zaburzeń mineralizacji kośćca. U wszystkich pacjentów wykonano pomiary antropometryczne w celu wykluczenia niedożywienia, ponieważ nie analizowano nawyków żywieniowych ani diety. W ten sposób potwierdzono, że u włączonych do badania dzieci nie występowały czynniki ryzyka niedoboru tej witaminy.
Na podstawie badań van Summeren i wsp., którzy jako jedni z pierwszych ocenili witaminę K u dzieci i uznali, że witamina K_2 (menachinony) jest bardziej efektywna niż K_1 w kontekście zdrowia kości[10,11], zdecydowano się w niniejszym badaniu oznaczać stężenia witaminy K_2.
Wykorzystano do tego metodę immunoenzymatyczną ELISA. W piśmiennictwie zarówno polskim, jak i zagranicznym nie znaleziono dla tej metody wartości referencyjnych dla populacji wieku rozwojowego. W związku z tym stworzono własną grupę odniesienia, w której za stężenie prawidłowe uznano 0,90–12,46 ng/ml.
W literaturze opisano różne metody oznaczania stężenia witamin K, zarówno pośrednie, jak i bezpośrednie. Ich różnorodność utrudnia uzyskanie jednorodnych norm i wartości referencyjnych[5–9,13–16], co wynika z wielu ról witaminy K w patofizjologii ocenianych zaburzeń. W niniejszej pracy podjęto próbę oznaczenia stężeń witaminy K_2 u dzieci i młodzieży ze złamaniami kości, ponieważ zdecydowana większość dostępnego piśmiennictwa dotyczy osób dorosłych z osteoporozą. Ponieważ w profilaktyce złamań osteoporotycznych wieku dojrzałego stosowane są preparaty witaminy D i wybrane postacie witaminy K, zasadne było pytanie, czy u dzieci także powinna być stosowana witamina K, aby zmniejszyć ryzyko złamania kości.
Próby oznaczenia stężenia witaminy K w surowicy u dorosłych podjęli m.in. Fusaro i wsp., którzy przeanalizowali dane 387 dializowanych pacjentów leczonych sewelamerem lub nieprzyjmujących tego leku. Okazało się, że średnie stężenia MK-4 i MK-7 wyniosły odpowiednio 0,45 (przedział międzykwartylowy 0,15, 0,67) ng/ml i 1,15 (przedział międzykwartylowy 0,53, 1,22) ng/ml[17]. Z kolei Klapkova i wsp. oznaczyli stężenie witaminy K_2 u 350 kobiet po menopauzie (z osteoporozą lub bez niej) i stwierdzili, że średnie stężenia u kobiet z osteoporozą wynosiły 0,890 ± 0,291 ng/ml dla MK-4 oraz 1,002 ± 1,020 ng/ml dla MK-7, a u pacjentek bez osteoporozy odpowiednio 0,825 ± 0,266 ng/ml i 1,186 ± 1,076 ng/ml[5]. Witamina K_2 (menachinon) występuje w różnych postaciach. Menachinony zawierają nienasycony łańcuch boczny ze zmienną liczbą jednostek prenylu, który wskazuje na rodzaj menachinonu, np. MK-4 zawiera cztery jednostki prenylowe, a MK-7 – siedem[23]. Te dwie formy są najczęściej stosowane w leczeniu osteoporozy wieku dojrzałego.
Zdecydowanie wyższe stężenia witaminy K wykazali badacze z Japonii, co jest konsekwencją diety bogatej w natto w tym regionie. Suhara i wsp., badając dorosłych chorych na osteoporozę lub zdrowych, stwierdzili, że stężenie MK-7 wynosiło 6,37±7,45 ng/ml[18]. Podobnie wysokie wartości – 3,82 ± 3,11 ng/ml i 16,27 ± 20,58 ng/ml – wykazali także inni badacze[19,20]. Rozbieżności te, które mogą wynikać z różnych nawyków żywieniowych, zamieszkiwania w różnych strefach geograficznych lub z odrębności kulturowych, stwarzają olbrzymie trudności w wyznaczeniu jednolitych wartości referencyjnych.
Badań dotyczących oznaczania witaminy K za pomocą metod bezpośrednich w populacji wieku rozwojowego przeprowadzono niewiele.
Kürşat i wsp. przeanalizowali stężenia witaminy K_2 u zdrowych tureckich dzieci w wieku od 0,5 roku do 6 lat, u których występowały drgawki gorączkowe. Badacze zastosowali tę samą metodę oznaczenia stężenia witaminy K_2 co autorzy niniejszej pracy (ELISA), ale uzyskali jednak zdecydowanie wyższe wartości średnie, które wynosiły 675,6 ng/ml[14]. Może to wynikać z różnicy wiekowej pomiędzy badanymi grupami, bowiem w niniejszym badaniu większy udział stanowiły dzieci do 17. roku życia.
Największą grupę, bo aż 1732 pacjentów w wieku 1–14 lat, ocenili Du i Li, którzy oznaczali stężenie witaminy K_2 metodą HPLC (mediana stężenia wynosiła 0,1 i malała wraz z wiekiem od 0,11 w grupie 1–3 lata do 0,08 w wieku 6–14 lat). Ponadto badacze ci wykazali niewielką ujemną korelację pomiędzy wiekiem a stężeniem witaminy K_2 (p = 0,031, r = –0,18)[8], czego nie stwierdzono w niniejszym badaniu.
W jednym z najnowszych doniesień z 2024 roku Chen i wsp. analizowali dane 807 zdrowych dzieci w wieku 0–14 lat, u których oznaczyli stężenie witaminy K metodą HPLC. Badacze określili wartości referencyjne stężenia witaminy K_1 dla grup wiekowych 0–3 lata (0,10–1,73 μg/l) i 4–14 lat (0,09–4,54 μg/l). Przedział dla wartości referencyjnych MK-4 dla wszystkich dzieci wyniósł natomiast 0–0,42 μg/l[21].
Popko i wsp. przeprowadzili badania z udziałem populacji podobnej do opisywanej w niniejszej pracy, tzn. dzieci z terenu północno-wschodniej Polski, u których doszło do złamań kości. Opisali jednak pośrednio witaminę K i jej rolę w patofizjologii złamań kości poprzez ocenę metodą ELISA dwóch form osteokalcyny[22].

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Z cytowanych rezultatów badań wynika, że ocena stężenia witaminy K jest trudnym i złożonym procesem, który zależy od wielu czynników, w tym wyboru metody oznaczeń, grupy badanej i celu badania. Dodatkowo w pracy Fusaro i wsp. podkreślono, że ocena stężenia witaminy K może być utrudniona z powodu interferencji lipidów i jego niskich wartości we krwi, a także jej niepolarnych właściwości, szczególnie w przypadku niektórych form MK[1].

WNIOSKI

Stężenia witaminy K_2 w badanej populacji dzieci i nastolatków ze złamaniami kości w wywiadzie mieściły się w granicach uznanych za referencyjne dla tej grupy wiekowej, co sugeruje, że złamania kości u badanych nie były związane z niedoborem tej witaminy.

Konflikt interesów

Autorzy nie zgłaszają żadnych finansowych ani osobistych powiązań z innymi osobami lub organizacjami, które mogłyby negatywnie wpłynąć na treść publikacji oraz rościć sobie prawo do tej publikacji.

Wkład autorów

Koncepcja i projekt badania: MP, EJP. Gromadzenie i/lub zestawianie danych: MP, EW. Analiza i interpretacja danych; napisanie artykułu: MP. Krytyczne zrecenzowanie artykułu; zatwierdzenie ostatecznej wersji artykułu: EJP.

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The relationship between body weight and self-perception among young individuals in the Silesian Voivodeship

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Abstract

Introduction and objective: The perception of one's own body is determined by many factors, including gender, media, societal expectations, and the quality of life. The aim of this study was to assess how young people from the Silesian Voivodeship perceive their own bodies in relation to weight and gender. **Materials and methods:** The study involved 560 (100%) female and male secondary school students in the Silesian Voivodeship. The subjects were aged 16 to 18 ($\bar{x}$ = 17.19 ± 0.8). The study used a proprietary questionnaire consisting of questions regarding the basic data of the surveyed adolescents and their body weight and height, as well as the Polish version of the Body Esteem Scale (BES). **Results:** Spearman's rank correlation test showed a statistically significant negative relationship between body mass index (BMI) and scores on the "Physical Condition" subscale ($p < 0.012$) in the subgroup of boys and a statistically significant negative relationship between BMI and scores on the "Sexual Attractiveness" ($p = 0.021$) and "Weight Control" ($p < 0.0001$) subscales in the subgroup of girls. **Conclusions:** An increase in BMI negatively affects body perception among young people in the Silesian Voivodeship, causing a decrease in self-esteem. Girls with increased BMI focus on the negative perception of body parts that can be changed through physical exercise or diet. Boys, on the other hand, base their self-esteem on parameters related to endurance, agility, strength and functionality, and efficiency, and not necessarily on appearance.

Keywords: obesity, children, perception, body

Streszczenie

Wprowadzenie i cel: Postrzeganie własnego ciała jest determinowane wieloma czynnikami, m.in. płcią, wpływem mediów, oczekiwaniami innych ludzi, a także jakością życia. Celem badania była ocena postrzegania własnego ciała przez młodzież województwa śląskiego w zależności od masy ciała i płci. **Materiał i metody:** W badaniu wzięło udział 560 (100%) uczennic i uczniów szkół średnich z województwa śląskiego. Badani byli w wieku od 16 do 18 lat ($\bar{x}$ = 17,19 ± 0,8). Do jego przeprowadzenia wykorzystano autorski kwestionariusz ankiety zawierający pytania dotyczące podstawowych danych badanej młodzieży oraz jej masy i wzrostu, a także polską wersję Body Esteem Scale (BES). **Wyniki:** Test korelacji rang Spearmana wykazał w podgrupie chłopców istotną statystycznie ujemną zależność między wartością wskaźnika masy ciała a punktami uzyskanymi w podskali „Kondycja fizyczna" (p <0,012), natomiast w podgrupie dziewcząt – istotną statystycznie ujemną zależność wartości wskaźnika masy ciała od punktów uzyskanych w podskali „Atrakcyjność seksualna" (p = 0,021) i „Kontrola masy ciała" (p < 0,0001). **Wnioski:** Wzrost wartości wskaźnika masy ciała wpływał na postrzeganie własnego

ciała przez młodzież województwa śląskiego, powodując spadek ich samooceny. Dziewczęta ze zwiększoną masą ciała skupiały się na negatywnym postrzeganiu tych części ciała, które można zmienić dzięki ćwiczeniom fizycznym lub diecie. Poczucie własnej wartości chłopców koncentrowało się na parametrach związanych z wytrzymałością, zwinnością, siłą oraz funkcjonalnością i wydajnością, a niekoniecznie z wyglądem.

Słowa kluczowe: otyłość, dzieci, postrzeganie, ciało

INTRODUCTION

Body image is one of the components of personal identity and can be defined as the mental image formed on the basis of anthropometric measurements, shapes, and contours, along with the emotions associated with them, affecting satisfaction with it in its entirety or its specific parts[1]. The perception of one's own body is determined by many factors. These include, among others, gender, media influence, societal expectations, the level of self-esteem, cultural factors, and the quality of life[2]. Dissatisfaction with one's own appearance often focuses on the physical aspect and develops already in adolescence under the influence of these factors. It is also associated with negative consequences, often leading to risky behaviours (e.g. the use of anabolic steroids, drugs allegedly accelerating fat burning, or calorie restriction) and the development of mental health disorders such as depression or anxiety[3]. Mentioning these disorders additionally deepens the negative effects of dissatisfaction with one's appearance.

One of the main determinants of body perception is its mass and related disorders. Overweight and obesity are defined as an abnormal excess of adipose tissue that negatively affects both mental and physical health. These conditions are becoming a global issue with serious health implications, the most severe of which are related to cardiovascular diseases and cancer[4]. Determining the presence of overweight or obesity is based on calculating the body mass index (BMI), which, despite its limitations, has remained the main method of diagnosis for many years[5].

The opposite of increased body weight is being underweight. In 2016, approximately 75 million girls and 117 million boys worldwide were below a normal body weight. Studies have shown that reduced body weight is often underestimated and constitutes a serious health concern, especially among children and adolescents[6]. It may also contribute to the development of disorders of the nervous and musculoskeletal systems, as well as increase the risk of cancer and infertility[7].

Young people, especially those in the process of forming their body image, often struggle with the perception of their own bodies. A particularly challenging period is early adolescence and secondary school years, when changes taking place in the body become more pronounced. Millions of students struggle with emotional and behavioural problems related not only to peer pressure, but also to the demands placed on them, also have a problem with the correct image of their own body. The aim of the study was to assess body image perception among young people from the Silesian Voivodeship depending on their weight and gender.

MATERIALS AND METHODS

The study involved 560 (100%) female and male secondary school students from the Silesian Voivodeship. The subjects were aged 16 to 18 ($\bar{x} = 17.19 \pm 0.8$). The results presented were obtained as part of a project submitted for evaluation to the Bioethics Committee of the Medical University of Silesia in Katowice, which consented to its implementation in accordance with the principles of Good Clinical Practice (PCN/0022/KB1/36/21). Taking the above into account, before the commencement of the study, written informed consent was obtained from all participants and their legal guardians. The study was conducted while maintaining full anonymity both at the stage of collecting and analysing the obtained data. The inclusion criteria were: current attendance at a secondary school, written parental consent for the child's participation in the study, and the ability to understand the questions and complete the questionnaire.

The study used a proprietary questionnaire consisting of questions regarding the basic data of the participants and their body weight and height. Additionally, the Polish version of the Body Esteem Scale (BES), prepared by Lipowska et al., was used to assess the attitude of the subjects towards their own body[8]. The Polish version of the BES questionnaire consists of 35 items and evaluates body perception across three subscales, taking into account gender.

The subscales for girls include:

- "Sexual Attractiveness" – associated with the perception of body parts whose appearance cannot typically be changed through physical exercise (e.g. assessment of satisfaction with the appearance of the lips);
- "Weight Control" – related to satisfaction with parts of the body whose appearance can be modified through exercise or diet;

and

- "Physical Condition" – pertains to self-assessment of parameters such as endurance, strength, and agility.

The subscales for boys include:

- "Physical Attractiveness" – based on the evaluation of features that, in combination, largely determine the perception of a man as handsome;
- "Upper Body Strength" – based on the assessment of both individual body parts (e.g. chest or arms) and their

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function and fitness, which together form the basis for assessing a man as strong and physically capable;

and

- "Physical Condition" – pertains, as in the corresponding subscale for girls, to the assessment of endurance, strength, and agility.

In individual questions regarding body-related self-esteem, the respondents provided answers on a 5-point Likert scale, where 1 indicated strongly negative feelings, 5 – strongly positive feelings, and 3 – a neutral attitude. Then, according to the available key, the numerical values marked in individual questions were added up, and on their basis, each respondent was classified into a self-assessment category in all assessed subclasses. The numerical values of the summed points and the grades of self-assessment assigned to them are presented in Tab. S1 (Supplementary Material).

Body mass index (BMI) was calculated based on the height and weight values provided by the respondents according to the standard formula: BMI = body weight [kg] / height^2 [m^2]. On the basis of the obtained BMI values, the subjects were classified into one of three categories: reduced body weight (RBW) relative to normal (BMI < 18.5 kg/m^2), correct body weight (CBW) (BMI = 18.50–24.99 kg/m^2), or increased body weight (IBW) in relation to normal (BMI ≥ 25.00 kg/m^2).

Statistical analyses were performed using Statistica 12.1 software. The Shapiro–Wilk test showed that the analysed data did not follow a normal distribution; hence, non-parametric tests were applied in the calculations.

The figures in the Results section include only those analyses that demonstrated statistical significance between the number of points obtained in individual subscales, taking into account the sex and body weight of the respondents. Detailed numerical values are presented in the Supplementary Material to this article.

RESULTS

General characteristics of the study group are presented in Tab. 1.

The majority of the study group were girls (329; 58.75%) and respondents living in cities (510; 91.07%). Over 13% (74; 13.21%) of the respondents were individuals with increased body weight.

Tab. 2 presents the characteristics of the study group with respect to body weight and gender.

Approximately 14% (44; 13.37%) of girls had reduced body weight, while just over 10% (34; 10.33%) had increased body weight. In the group of boys, over 17% (40; 17.32%) were overweight or obese.

Tab. 3 presents the characteristics of boys and girls, taking into account the results of Spearman's rank correlation test, BMI values, and scores on the individual BES subscales.

Spearman's rank correlation test showed a statistically significant negative relationship between BMI and scores obtained on the "Physical Condition" subscale ($p < 0.012$) in the subgroup of boys, while in the subgroup of girls, a statistically significant negative relationship between BMI

Study group (560; 100%)							
Variables						**Data**	
						n	**%**
Sex				**Girls**		329	58.75
				Boys		231	41.25
Place of residence				**City**		510	91.07
				Village		50	8.93
Age [years]				**16**		137	24.46
				17		178	31.79
				18		245	43.75
Body mass index (BMI)				**Reduced body weight (RBW)**	M_{BMI}	69	12.32
					15.26		
					SD		
					0.57		
				Correct body weight (CBW)	M_{BMI}	417	74.46
					21.23		
					SD		
					1.7		
				Increased body weight (IBW)	M_{BMI}	74	13.21
					27.82		
M_{BMI}	***SD***	**Min.**	**Max.**		***SD***		
21.64	3.24	14.93	39.06		2.59		
n – sample size; **BMI** – body mass index; M_{BMI} – average BMI value; ***SD*** – standard deviation.							

Tab. 1. General characteristics of the study group

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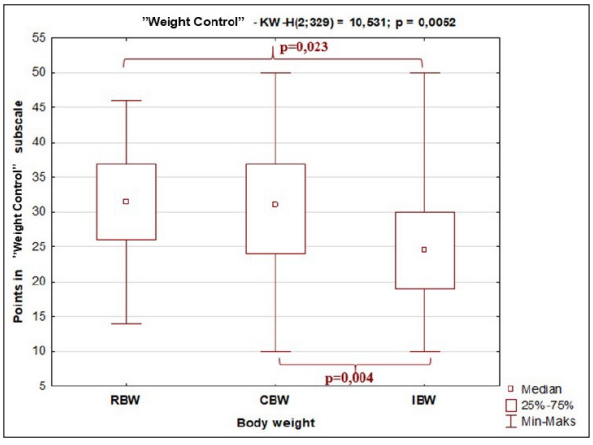
Study group (560; 100%)			
Sex	**Body mass index (BMI)**	***n***	**%**
Girls (329; 100%)	Reduced body weight (RBW)	44	13.37
	Correct body weight (CBW)	251	76.29
	Increased body weight (IBW)	34	10.33
Boys (231; 100%)	Reduced body weight (RBW)	25	10.82
	Correct body weight (CBW)	166	71.86
	Increased body weight (IBW)	40	17.32
n – sample size.			

Tab. 2. Characteristics of the study group with regard to sex and body weight

Variables	R_G	p_G	R_B	p_B
BMI & "Sexual Attractiveness"/"Physical Attractiveness"	–0.127	0.021*	–0.034	0.602
BMI & "Weight Control"/"Upper Body Strength"	–0.267	<0.0001*	0.034	0.609
BMI & "Physical Condition"	–0.092	0.095	–0.166	0.012*

BMI – body mass index; ***R*** – Spearman's rank correlation coefficient; **G** – girls; **B** – boys; ***p*** – test probability.
* Statistically significant at $p < 0.05$.

Tab. 3. Spearman's rank correlation test results

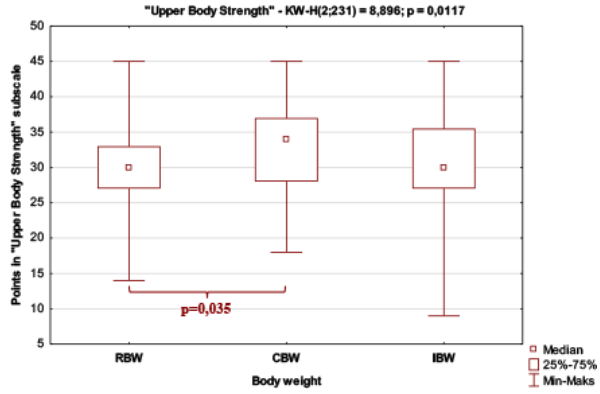


KW–H – Kruskal–Wallis test result; ***p*** – statistical significance; **RBW** – reduced body weight; **CBW** – correct body weight; **IBW** – increased body weight.

Fig. 1. Characteristics of the surveyed group of girls, taking into account the scores on the "Weight Control" subscale

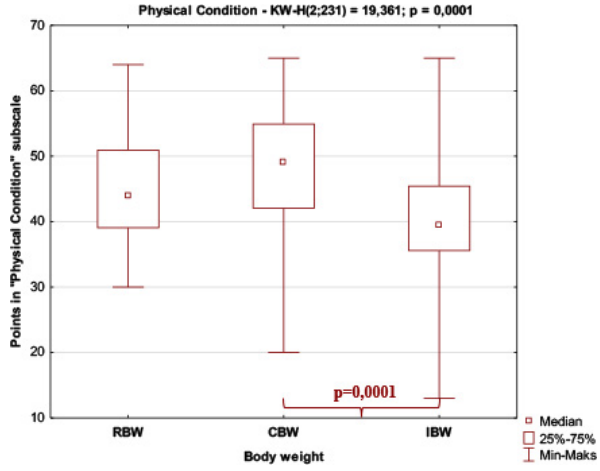
and scores on the "Sexual Attractiveness" ($p = 0.021$) and "Weight Control" ($p < 0.0001$) subscales.

Tab. S2 (Supplementary Material) presents the characteristics of the study group, taking into account BMI and the level of self-esteem obtained in the BES questionnaire, depending on the gender of the respondents. Among the girls with reduced body weight, the highest levels of self-esteem were found in all analysed subscales ("Sexual Attractiveness" – 20; 45.45%, "Weight Control" – 29; 65.91%, "Physical Condition" – 26; 59.09%). Conversely, among girls with increased body mass (34; 100%), most (11; 32.35%) had a low level of self-esteem in the "Sexual Attractiveness" subscale. Identical quantitative and percentage distributions in



KW–H – Kruskal–Walli's test result; ***p*** – statistical significance; **RBW** – reduced body weight; **CBW** – correct body weight; **IBW**– increased body weight.

Fig. 2. Characteristics of the surveyed group of girls, taking into account the scores on the "Upper Body Strength" subscale depending on body weight



KW–H – Kruskal–Wallis test result; ***p*** – statistical significance; **RBW** – reduced body weight; **CBW** – correct body weight; **IBW** – increased body weight.

Fig. 3. Characteristics of the group of boys, taking into account the scores on the "Physical Condition" BES subscale, depending on body weight

this subgroup were observed in the "Weight Control" and "Physical Condition" subscales (low – 4; 11.76%, moderate – 25; 73.53%, high level of self-esteem – 5; 14.71%).

Among the boys with reduced body weight, the majority had a moderate level of self-esteem across all analysed subscales ("Physical Attractiveness" – 12; 54.55%, "Upper Body Strength" – 15; 68.18%, "Physical Condition" – 17; 77.27%). Among boys with increased body weight, the majority also had a moderate degree of self-esteem across all analysed subscales ("Physical Attractiveness" – 20; 50.00%, "Upper Body Strength" – 30; 75.00%, "Physical Condition – 21; 52.50%). However, compared to boys with normal weight, these boys had slightly lower self-esteem in the "Physical Attractiveness" (90; 54.22% vs. 20; 50.00%) and "Physical Condition" (96; 57.83% vs. 21; 52.50%) subscales.

Tab. S3 (Supplementary Material) presents the characteristics of the study group of girls, taking into account the scores obtained in individual subscales depending on

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body weight. Fig. 1 illustrates statistically significant differences in scores obtained in the "Weight Control" subscale. Tab. S4 (Supplementary Material) presents the results of the Kruskall–Wallis test post-hoc analysis of scores obtained by girls on the "Weight Control" subscale in relation to body weight.

Among the examined girls, the Kruskal–Wallis test showed a statistically significant difference between the groups (RBW, CBW, IBW) in terms of points scored on the "Weight Control" subscale ($H = 10.531$, $p = 0.0052$). Post-hoc analysis performed for the aforementioned subscale showed statistically significant differences ($p = 0.023$) between the points scored by girls with reduced versus increased body weight, as well as between girls with normal versus increased body weight ($p = 0.004$).

Tab. S5 (Supplementary Material) presents the characteristics of the group of boys, taking into account their score on individual scales depending on body weight.

Figs. 2 and 3 show the characteristics of the study group of boys, highlighting statistically significant differences in points scored on the "Upper Body Strength" and "Physical Condition" subscales depending on body weight. Tab. S6 (Supplementary Material) provides the post-hoc analysis of points scored by boys in these subscales, as determined by the Kruskal–Wallis test.

In the subgroup of boys, the Kruskal–Wallis test showed a statistically significant difference between the compared groups (RBW, CBW, IBW) in terms of points scored on the "Upper Body Strength" subscale ($H = 8.896$, $p = 0.0117$) and the "Physical Condition" subscale ($H = 19.361$, $p = 0.0001$). Post-hoc analyses performed for the above-mentioned subscale showed a statistically significant difference between the number of points obtained by individuals with reduced and normal body weight on the "Upper Body Strength" subscale ($p = 0.035$) and between those with normal and increased body weight ($p = 0.023$) on the Physical Condition subscale ($p = 0.0001$).

DISCUSSION

The study aimed to assess body self-perception in young people from the Silesian Voivodeship depending on their body weight.

In the standardised questionnaire used, the "Weight Control" subscale assesses satisfaction with body parts whose appearance can be changed through physical exercise or dieting, while the "Sexual Attractiveness" subscale is related to the perception of body parts whose appearance cannot be altered through physical exercise, but only through treatments such as cosmetic procedures. The Kruskal–Wallis test showed a statistically significant difference between the compared groups of girls in terms of points scored on the "Weight Control" subscale. Post-hoc analysis showed a statistically significant difference between the points obtained by girls with reduced and increased body weight, as well as between those with normal and increased body weight. This may indicate that the self-esteem of girls with increased body weight is focused on body parts that can be improved through physical exercise or dieting. Moreover, a statistically significant relationship was found between BMI values and points scored on the "Sexual Attractiveness" and "Weight Control" subscales. Research has shown that an increase in body weight has a negative impact on body self-perception in girls, both in relation to features that can and cannot be changed through physical exercise.

Spearman's rank correlation test showed in the subgroup of boys a negative relationship between BMI and points scored on the "Physical Condition" subscale examining the self-perception of endurance, strength, and agility. However, the above test did not show any correlations in the remaining subscales of the BES questionnaire regarding "Physical Attractiveness", which evaluates the combination of features which largely determine the definition of a man as handsome, as well as "Upper Body Strength", which assesses not only the appearance of individual body parts but also their function and fitness, forming the basis for evaluating a man as strong and physically capable. The Kruskal–Wallis test showed a statistically significant difference between the groups in terms of points scored on the "Upper Body Strength" and "Physical Condition" subscales. Post-hoc analyses performed for the "Upper Body Strength" subscale showed a statistically significant difference between the number of points scored by boys with reduced body weight, and for the "Physical Condition" subscale, between boys with normal and increased body weight. Interpreting the results, it can be concluded that among boys, self-esteem related to physical condition decreased as BMI increased. Boys with reduced body weight had lower self-esteem compared to those with normal body weight, but also function and fitness, particularly regarding body parts that serve as the basis for evaluating a man as strong and physically able. Overweight and obese boys, when compared to their peers with normal body weight, also showed lower self-esteem in terms of physical condition.

As already mentioned, the appearance of individual body parts affects a person's self-esteem, with obesity having a particularly pronounced impact. Over the last 10 years, the number of obesity patients has increased dramatically, both among children, adolescents, and adults[9]. The World Health Organization reported that, in 2022, approximately 650 million adults and 350 million children were overweight or obese[10]. Research conducted by Dale et al. showed that obesity had a negative impact on self-esteem[11], which was also confirmed by studies conducted by Moradi et al., who showed a positive relationship between obesity and the risk of body dissatisfaction and low self-esteem among children and youth. They also demonstrated a significantly positive relationship between overweight status and the risk of developing low self-esteem[12]. A study by Gong et al. involving a group of 48,558 children revealed that late-onset or chronic weight gain was a predictor of

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low overall, social, and learning/school-related self-esteem. According to the researchers, children who managed to lose weight could achieve a level of social self-esteem equal to or even higher than that of children with constantly low or normal body weight[13]. However, the meta-analysis by Wang et al. showed that the incidence of symptoms of depression and anxiety in overweight/obese children/adolescents in China was higher compared to those without these pathologies[14], while the study by Sánchez-Rojas et al., conducted with a group of 295 children, including 116 with abnormally increased body weight and 179 with normal body weight, showed that body image and satisfaction with it differed between the groups, with a relationship between self-esteem and depressive symptoms, which can emerge as early as school age[15]. A meta-analysis conducted by Barnes et al. showed a link between body dissatisfaction in men and the possibility of developing depression[16]. The above relationship was also demonstrated in women[17].

Another factor influencing body perception is the media. They are used by young people almost constantly, and changing trends have a strong impact on how young people shape their self-image. The media encourages young people to adopt the models of physical beauty they propose, which often results in body dissatisfaction. The inability to meet these standards becomes burdensome and demotivating, and the constant pursuit of the "perfect body" may turn into risky behaviours, including the development of eating disorders which, in the most severe cases, pose a threat to health and life[18]. Both restrictive eating and overeating do not provide significant benefits, and research also suggests that long-term media exposure is associated with an increased tendency to develop unhealthy eating habits[19].

The limitations of the present study include a relatively small number of respondents and disparities in the size of the compared groups. Additionally, there is the issue of the accuracy of the information provided by the respondents concerning, for example, body weight. Despite the use of all possible measures to prevent any outside interference during the completion of the questionnaires, it cannot be unequivocally stated that the data provided by the respondents was 100% true. Nevertheless, the study proves that body weight affects the perception and self-esteem of secondary school students in the Silesian Voivodeship. It also outlines the problems faced by individuals with both reduced and excessive body weight, and confirms the need to conduct systematic education in this area, focusing on healthy eating habits and striving to maintain a CBW. Ultimately, this is essential for achieving a good quality of life and overall health.

CONCLUSIONS

1. An increase in BMI affects the body perception among young people in the Silesian Voivodeship, causing a decrease in self-esteem in terms of "Physical Attractiveness" and "Weight Control" in girls, and "Physical Condition" in boys.
2. The observed difference between BMI category and scores on the "Weight Control" subscale suggests that girls with increased body mass focus on the negative perception of body parts that can be changed through physical exercise or diet.
3. The differences in scores between boys with normal and reduced body weight on the "Upper Body Strength" subscale and boys with normal and increased body weight on the "Physical Condition" subscale may indicate that their self-esteem is focused on parameters related to endurance, agility, strength, functionality and efficiency, and not necessarily appearance.

Conflict of interest

The authors do not report any financial or personal connections with other persons or organisations which might negatively affect the content of this publication and/or claim authorship rights to this publication.

Author contribution

Original concept of study; collection, recording and/or compilation of data; writing of manuscript: JD, OS, KS. Analysis and interpretation of data: JD, OS, KS, HM, LP, ZG. Critical review of manuscript: JD, HM, LP, ZG. Final approval of manuscript: JD, OS, KS, HM, LP, ZG.

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Nephrocalcinosis in hyperphosphataemic familial tumoural calcinosis in a 36-year-old woman

Nefrokalcynoza w przebiegu rodzinnej kalcynozy guzowatej u 36-letniej kobiety

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Abstract

Nephrocalcinosis is characterised by the deposition of calcium oxalate or calcium phosphate in the tubulointerstitial regions of the kidney. Rarely, disturbances in phosphate homeostasis in the course of hyperphosphataemic familial tumoural calcinosis can be the cause of nephrocalcinosis. The main symptoms of this condition include ectopic calcifications, hyperostosis, and dental abnormalities. In this article, we present the clinical and genetic description of a case involving a 36-year-old woman in whom nephrocalcinosis was incidentally discovered and subsequently led to the diagnosis of hyperphosphataemic familial tumoural calcinosis. In the course of the molecular diagnostic process, whole-exome short-read sequencing detected a heterozygous in-frame deletion (c.1093_1095del; p.Gly365del) in the *GALNT3* gene, while long-read single-molecule real-time sequencing identified a complex indel (c.1382_1388delins814) in *GALNT3* exon 7. To the authors' knowledge, this is the first described case of a patient with this specific mutation.

Keywords: nephrocalcinosis, hyperphosphataemic familial tumoural calcinosis, hyperphosphataemia, fibroblast growth factor 23

Streszczenie

Nefrokalcynoza, inaczej wapnica nerek, polega na osadzaniu się złogów wapniowo-szczawianowych lub wapniowo-fosforanowych w obszarach cewkowo-śródmiąższowych nerek. Bardzo rzadką przyczyną nefrokalcynozy mogą być zaburzenia homeostazy fosforanowej w przebiegu rodzinnej kalcynozy guzowatej. Głównymi objawami tej choroby są zwapnienia w tkankach miękkich i naczyniach krwionośnych, hiperostoza oraz zaburzenia uzębienia. W artykule przedstawiono kliniczny i genetyczny opis przypadku 36-letniej kobiety, u której objawem klinicznym, który nakierował na diagnostykę rodzinnej kalcynozy guzowatej, była przypadkowo stwierdzona nefrokalcynoza. W toku diagnostyki molekularnej wykonano sekwencjonowanie krótkich fragmentów eksonów i sekwencjonowanie całego genomu metodą pojedynczej molekuły w czasie rzeczywistym, wykrywając odpowiednio heterozygotyczną delecję w ramce odczytu (c.1093_1095del; p.Gly365del) w genie *GALNT3* i złożony polimorfizm insercyjno-delecyjny (indel) (c.1382_1388delins814) w eksonie 7 *GALNT3*. Zgodnie z wiedzą autorów jest to pierwszy opisany przypadek pacjenta z tą mutacją.

Słowa kluczowe: nefrokalcynoza, rodzinna kalcynoza guzowata, hiperfosfatemia, czynnik wzrostu fibroblastów 23

INTRODUCTION

Nephrocalcinosis (NC) is associated with calcium oxalate or calcium phosphate deposits in the tubulointerstitial regions of the kidney. Currently, the term NC is used to describe radiological changes in the kidneys. In 1991, Al-Murrani et al. introduced an ultrasound classification that distinguishes three types: I – slight increase in echogenicity at the pyramid edges, II – slight increase in echogenicity involving the entire pyramids, III – significant increase in echogenicity involving the entire pyramids[1]. In the differential diagnosis of the causes of NC, acquired factors should be considered, including primary hyperparathyroidism, sarcoidosis, hypervitaminosis D_3, and congenital genetically determined disorders (distal tubular acidosis, hypophosphataemic rickets, familial hypomagnesaemia with hypercalciuria and nephrocalcinosis, Bartter's syndrome, Dent's disease, primary hyperoxaluria, and renal-enamel syndrome)[2,3].

Deficiency or resistance to the most potent phosphate-regulating hormone, called fibroblast growth factor 23 (FGF23), leads to a rare disorder which usually presents with a clinical picture opposite to that of phosphopaenic rickets – named hyperphosphataemic familial tumoural calcinosis (HFTC). The main symptoms of this condition include calcifications in soft tissues and blood vessels, hyperostosis, and dental disorders[4,5]. This article presents a case report of a woman whose initial diagnosis of accidentally discovered nephrocalcinosis ultimately led to the diagnosis of HFTC.

CLINICAL CASE DESCRIPTION

A 36-year-old Caucasian woman was consulted by a nephrologist due to NC grade I and a 5 mm hyperechoic area in the kidney cortex, incidentally identified during a routine ultrasonography (US) review. The radiologist's report described this area as an angiomyolipoma (AML). In addition, the patient's medical history revealed recurrent osteoarticular symptoms, including pain and limited mobility in large joints. Bone densitometry showed bone mineral density verging on osteopaenia.

Moreover, radiological examinations revealed periarticular calcifications in the right shoulder joint, left knee joint, and metatarsal joints. Prior to this, the patient had undergone two surgical orthopaedic surgical procedures, 17 and 2 years before her first nephrology consultation, and was at that time consulted by an orthopaedist about periarticular calcifications in her bilateral hip joints to determine eligibility for further surgery. She had also undergone surgery for carpal tunnel syndrome in her right wrist. Additionally, her ophthalmological examination revealed the presence of fine angioid streaks.

In a 24-hour urine collection, calcium excretion ranged from 3.9 mg/kg at the beginning of the disease to 6.4 mg/kg in subsequent analyses. Excretion levels of other ions, oxalates, and citrates remained within normal limits. Laboratory test results from the past decade are summarised in Tab. 1. It should be emphasised that each blood test sample exhibited hyperphosphataemia, while estimated glomerular filtration rate (eGFR) levels were confirmed to be either normal or slightly decreased. The mean eGFR, calculated according to the 2021 CKD-EPI definition using creatinine and cystatin C, indicated chronic kidney disease (CKD) stage II (84 mL/min/1.73 m^2, range: 64–102 mL/min/1.73 m^2), although the most recent eGFR level was 80 mL/min/1.73 m^2. Nonetheless, cystatin C concentrations remained within normal laboratory reference ranges throughout the observation period.

Slightly decreased eGFR levels did not account for the consistently elevated phosphate concentrations. Therefore, given the low 25-hydroxyvitamin D_3 levels, normal PTH activity, and absence of mutations in the *CYP24A1* gene, FGF23 measurement was conducted, with low levels of this phosphatonin anticipated. Nevertheless, the results exceeded more than 12 times the upper limit of the normal range. Based on these findings, HFTC was suspected, likely caused by a mutation in the FGF23 receptor.

As the next step in diagnostics, whole-exome short-read sequencing (WES) was performed, detecting a heterozygous in-frame deletion (c.1093_1095del; p.Gly365del) in the *GALNT3* gene. Short-read sequence alignment suggested an additional structural genomic variant in this gene but was unable to characterise the alteration. To resolve this, whole-genome long-read single-molecule real-time (SMRT) sequencing was conducted, which detected a second complex indel (c.1382_1388delins814) in *GALNT3* exon 7, confirming the clinical diagnosis of HFTC type 1 (Fig. 1).

Since the diagnosis of NC, the patient remained on continuous pharmacological treatment, including magnesium citrate and potassium citrate. Additionally, the water intake exceeds 2.5 litres per day. Initially, due to the diagnosis of NC, vitamin D_3 supplementation was withheld until the completion of full diagnostic evaluation, resulting in persistently suboptimal levels. Currently, the patient receives 1,000 IU of vitamin D_3 daily, with periodic monitoring of 25-hydroxyvitamin D_3 levels to maintain concentrations at the lower limit of the reference range. Due to gastrointestinal adverse effects, the patient does not tolerate calcium phosphate binders such as calcium carbonate and acetate. Owing to the lack of reimbursement of non-calcium

	Mean value	Range	Reference values
Ca serum	2.4	2.27–2.5	2.15–2.5 mmol/L
P serum	1.8	1.51–2.19	0.81–1.45 mmol/L
PTH	34.2	26.6–42.75	15–65 pg/mL
Cr serum	78.3	67–99	44–80 µmol/L
Cystatin C	0.82	0.76–0.89	0.53–0.95 mg/L
25(OH)D_3	25	17.5–28.7	31–50 ng/mL
1,25(OH)$_2D_3$	77	64.4–89.6	25–86.5 pg/mL
FGF23	1,304.5	1,085–1,524	26–110 kRU/L
Ca urine (24 h)	5.4	3.9–6.4	<4 mg/kg/day
FGF23 – fibroblast growth factor 23; **PTH** – parathormone.			

Tab. 1. Laboratory results of the patient

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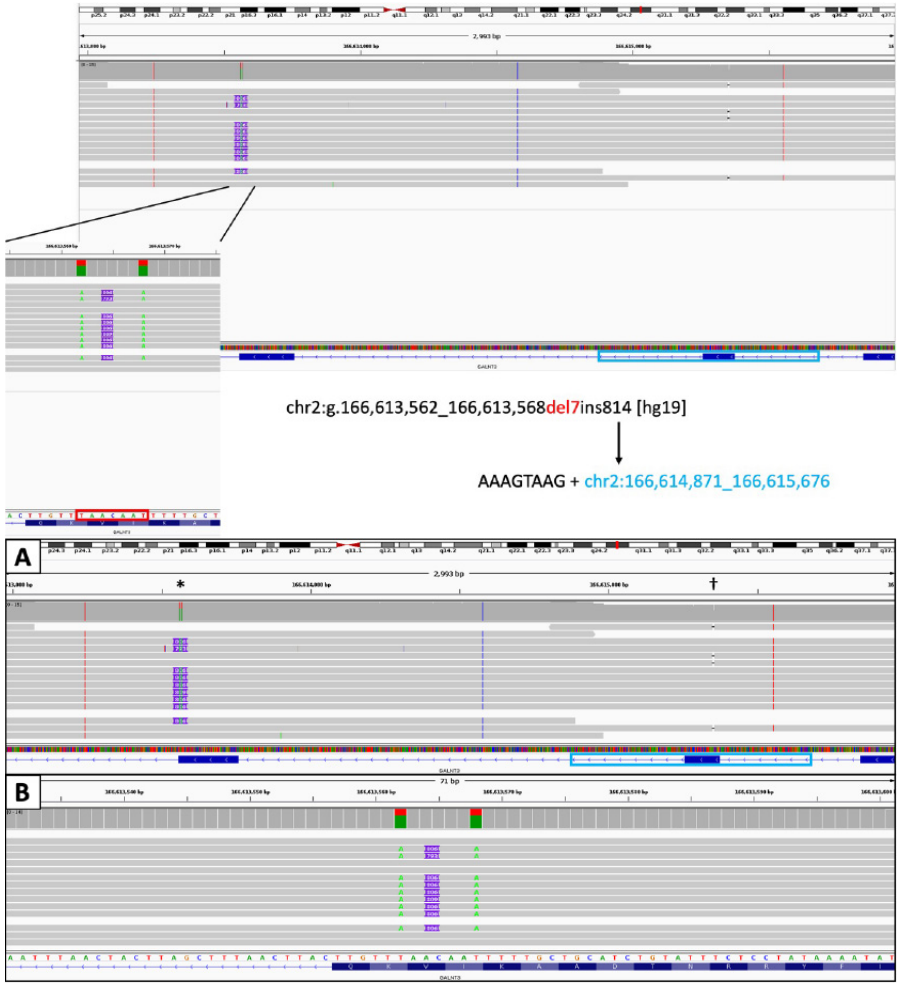

Fig. 1. Alignment representation of the GALNT3 *variants.* **A.** *Long-read alignment detects two variants: the inframe deletion c.1093_1095del (marked with †) and the complex indel c.1382_1388delins814 (marked with *). From reads spanning both variants, compound-heterozygosity is clearly demonstrated. The light blue box in the gene view corresponds to the sequence inserted at * (chr2:166,614,871_166,615,676[hg19]), which was identified using BLAST alignment search.* **B.** *Closeup of the complex indel shows two adjacent apparent single nucleotide variants. Manual sequence realignment resolves the indel as c.1382_1388delins814*

phosphate binders (which are recommended in the literature[4]) in Poland, the patient is unable to take them. She remains under ongoing supervision by a dietician and adheres to a low-phosphate diet.

DISCUSSION

HFTC is a condition characterised by elevated phosphate levels in the blood (hyperphosphataemia) and abnormal deposits of phosphate and calcium (calcinosis) in body tissues. HFTC typically develops in early childhood to early adulthood, although in some cases, including the present one, deposits first appear in infancy or later in adulthood[5,6].

HFTC results from a relative deficiency or resistance to FGF23. The clinical diagnosis is established based on the presence of tumoural calcinosis, whose symptoms may include periarticular calcinosis (around the hips, shoulders, and elbows) and in the soft tissues of the extremities, as well as in blood vessels and, in some cases, brain tissue. Other features of HFTC include corneal calcification, angioid streaks, inflammation of long bones (diaphysis), excessive bone growth (hyperostosis), and, in some individuals, dental abnormalities (enamel hypoplasia, obliteration of pulp canals and chambers, pulp stones, and bulbous roots)[4–6].

The characteristic laboratory findings include hyperphosphataemia due to inappropriately increased renal tubular reabsorption of phosphorus (TRP), elevated or inappropriately normal 1,25-dihydroxyvitamin D_3 levels, and elevated C-terminal FGF23 fragments[4,7].

HFTC is an autosomal recessive and genetically heterogeneous disorder associated with biallelic pathogenic variants in: (1) the gene encoding *FGF23*; (2) *GALNT3*, which encodes the protein (ppGalNacT3) responsible for FGF23 glycosylation; and potentially (3) *KL*, the gene encoding KLOTHO, a critical co-receptor for FGF23 signalling[8–11]. The proteins encoded by these genes are involved in general phosphate homeostasis. Identification of biallelic pathogenic variants in *FGF23*, *GALNT3*, or *KL* by molecular genetic

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testing confirms the diagnosis, although an acquired autoimmune form of hyperphosphataemic tumoural calcinosis has also been reported[5,6].

The ppGalNacT3 protein, encoded by the *GALNT3* gene, attaches sugar molecules to FGF23 through a process called O-glycosylation, which enables FGF23 to move out of the cell and protects the protein from degradation[6]. Biallelic pathogenic variants in the *GALNT3* gene result in the production of a ppGalNacT3 protein that is presumed to be unable to O-glycosylate FGF23[8]. Consequently, the FGF23 protein undergoes rapid cleavage into biologically inactive N- and C-terminal fragments, leading to reduced circulating levels of intact (active) FGF23. This reduction is due to FGF23 being trapped inside the cell and degraded, rather than being secreted[4,6,9].

In patients with HFTC caused by a *GALNT3* mutation, serum FGF23 levels are elevated when measured with an assay that detects both the carboxy (C)-terminal fragments (cFGF23) and the intact/active molecule (iFGF23). However, when measured using an assay that detects only iFGF23, concentrations are low. This finding suggests that the biological activity of FGF23 depends on the presence of an intact molecule, which is not secreted in patients with the mutation. In these patients, the intact (active) protein is retained within the Golgi complex[12].

These disruptions to FGF23 function lead to increased phosphate absorption by the kidneys. Calcinosis occurs when excess phosphate combines with calcium to form deposits that build up in soft tissues. Although phosphate levels are increased, calcium levels typically remain within the normal range[4,7,9]. Since no causal treatment for HFTC is currently available, management focuses on lowering serum phosphate levels, mainly by limiting their absorption from the gastrointestinal tract. The efficacy of treatment with drugs that increase renal phosphate excretion, such as acetazolamide and probenecid, remains unconfirmed[4]. Additionally, symptomatic pharmacological treatment includes the use of non-steroidal anti-inflammatory drugs, as well as surgical removal of calcifications from soft tissues and joints, with variable clinical outcomes[4].

According to current literature, a mutation in the *GALNT3* gene (2p24.3) leads to low iFGF23 levels, while increasing cFGF23 concentrations[5]. Initially, this imbalance may hinder the diagnostic process of hyperphosphataemia.

The prevalence of HFTC is unknown, but it is considered a rare condition, predominantly diagnosed in individuals of Middle Eastern and African origin[7,8]. An interesting point is that NC (the first abnormality in this patient's diagnostic work-up) may play a role both in the course of hypophosphataemic rickets and HFTC. However, according to the literature, it is an extremely rare finding in the latter condition[5,13].

CONCLUSIONS

1. The identification of NC with persistently (even if only mildly) elevated phosphate concentrations, normal 25-hydroxyvitamin D_3 and PTH levels, and normal or marginally decreased eGFR levels should prompt the measurement of iFGF23 concentration and genetic testing for HFTC.
2. When conducting- laboratory diagnostics, it is important to acknowledge the limitations of the assays used when measuring serum FGF23 concentrations, as some do not detect intact/active molecules (iFGF23), which may disrupt and delay the patient's diagnostic process.

Conflict of interest

The authors do not report any financial or personal connections with other persons or organisations which might negatively affect the content of this publication and/or claim authorship rights to this publication.

Author contribution

Original concept of study: MM, MB. Collection, recording and/or compilation of data: MM, MB, FE, BBB. Analysis and interpretation of data: MM, MB, FE, EJW, BBB. Writing of manuscript: MM, MB, EJW. Critical review of manuscript: MM, MB, DD, BBB. Final approval of manuscript: MM, MB, FE, EJW, DD, BBB.

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Ventricular arrhythmia detected by an Apple Watch – a case report

Arytmia komorowa udokumentowana przez Apple Watch – opis przypadku

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Abstract

The impact of digital health innovations on healthcare is rapidly accelerating. In particular, wearable devices for ambulatory cardiac monitoring are gaining increasing popularity among the general population. A 45-year-old physically active male presented to a cardiology clinic following an episode of palpitations and dizziness, which occurred after a 24-hour work shift. Shortly after symptom onset, he used his Apple Watch to perform an electrocardiogram, which detected monomorphic ventricular tachycardia, followed by sinus rhythm and a premature atrial extrasystole. Despite further extensive testing, no clear cause of ventricular tachycardia was identified. This case highlights the growing role of wearable devices, such as smartwatches, in cardiac monitoring and their ability to detect significant arrhythmias in asymptomatic individuals. However, it also raises questions regarding the extent of diagnostic testing required for such findings, particularly in cases of self-limiting arrhythmias.

Keywords: monitoring, case report, wearable technology, ventricular arrythmia, Apple Watch, m-health

Streszczenie

Wpływ innowacji w zakresie cyfrowego zdrowia na opiekę zdrowotną wciąż się zwiększa. W szczególności coraz większą popularność zyskują urządzenia służące do ambulatoryjnego monitorowania czynności serca. Różne typy przenośnych urządzeń do elektrokardiografii są dostępne zarówno dla osób zdrowych, jak i dla pacjentów cierpiących na choroby układu sercowo-naczyniowego. Czterdziestopięcioletni, aktywny fizycznie mężczyzna zgłosił się do poradni kardiologicznej z powodu epizodów kołatania serca z towarzyszącymi zawrotami głowy, które wystąpiły rano po 24-godzinnym dyżurze. Kilka sekund po wystąpieniu objawów pacjent wykonał elektrokardiogram za pomocą zegarka Apple Watch, który wykazał monomorficzną tachykardię komorową. Mimo przeprowadzenia szerokiej diagnostyki nie zidentyfikowano przyczyny złożonej arytmii komorowej. Przypadek ten podkreśla rosnącą rolę urządzeń, takich jak smartwatche, w monitorowaniu pracy serca oraz ich zdolność do wykrywania istotnych arytmii u osób bezobjawowych. Zwraca także uwagę na dylematy dotyczące zakresu diagnostyki w takich przypadkach oraz podkreśla znaczenie indywidualnego podejścia do pacjenta i potrzebę opracowania wytycznych dotyczących klinicznej oceny arytmii wykrywanych przez urządzenia noszone.

Słowa kluczowe: monitorowanie, opis przypadku, urządzenia/technologia noszalna, arytmia komorowa, Apple Watch, m-zdrowie

INTRODUCTION

The impact of digital health innovations on healthcare is rapidly accelerating. In particular, wearable devices for ambulatory cardiac monitoring are gaining increasing popularity among the general population. Different types of portable devices for electrocardiography (ECG) are available, both for healthy individuals and patients afflicted with cardiovascular diseases[1,2]. The use of mobile devices in health services is referred to as mobile health (m-health)[3,4]. M-health technologies provide health services anytime and anywhere, overcoming temporal and geographic barriers[3]. Highlighting m-health technologies, the demand for wearable devices continues to grow[3]. The wearables market is expected to see an annual growth rate of 20% in the coming years, reaching approximately 150 billion euros by 2028[5].

Smartwatches are especially popular for their 24-hour monitoring of heart rate and ECG, including during periods of exercise or intense physical activity. These devices enable the detection of serious ECG abnormalities in otherwise asymptomatic individuals[6]. Some smartwatches, such as the Apple Watch (AW), have been approved by the Food and Drug Administration for the diagnosis of atrial fibrillation (AF)[7–9]. Moreover, the usefulness of smartwatches in diagnosing other ECG abnormalities, such as ventricular tachycardia (VT), recurrent nocturnal ST-T deviation, sinus bradycardia, second- and third-degree atrioventricular block, and atrioventricular reentry tachycardia, has also been previously reported[10–18]. What is worth underlining is that these medical situations fall outside the designed detection parameters of the AW and other smartwatches.

The widespread availability of wearable devices and the increasing health awareness, especially among young and physically active individuals, may pose challenges for cardiologists. Many people may seek professional advice after receiving a supposed "diagnosis" from their smartwatch. Here, we present one example of such a patient.

A 45-year-old healthy, physically active man presented to the cardiology clinic because of palpitation episodes with accompanying dizziness, which occurred in the morning after a 24-hour work shift. A few seconds after the onset of symptoms, he decided to perform an ECG using an AW (Fig. 1). In the past, he had experienced palpitations, but of a different type. He denied loss of consciousness, chest pain, or exercise intolerance. A single-lead AW ECG recorded monomorphic VT (Fig. 1), followed by sinus rhythm and a single premature atrial extrasystole. This finding prompted further diagnostic tests. The resting 12-lead ECG revealed sinus bradycardia (53 bpm), incomplete right bundle branch block, and heart axis deviation to the left (Fig. 2). An extended 7-day Holter ECG recorded 607 instances of single premature ventricular extrasystole without any complex ventricular arrhythmia. Transthoracic echocardiography showed a normal left ventricle size and left ventricular ejection fraction. To exclude coronary artery disease, computed tomography was performed, revealing only early-stage atherosclerosis – non-calcified, high-risk atherosclerotic plaques resulting in 15–20% stenosis in the left anterior descending artery; there were no other stenoses. Gadolinium-enhanced cardiac magnetic resonance imaging showed normal sizes of both ventricles, normal regional contractility, and normal global left ventricular systolic function (70%). In late post-contrast enhancement sequences, a discrete intramuscular area of enhancement within the basal segments of the anteroseptal and inferoseptal walls was noted, but without any areas of myocardial fibrosis or necrosis. Laboratory tests (conducted a few days after arrhythmia) revealed normal complete blood count, electrolytes, and renal parameters. Because of hyperlipidaemia (a low-density lipoprotein cholesterol concentration of 169 mg/dL) and early-stage coronary atherosclerosis, rosuvastatin was recommended at a daily dose of 40 mg. As the cause of VT remained unidentified, an electrophysiology study was conducted, during which no ventricular arrhythmia was detected. At the follow-up, the patient did not report any further palpitations or dizziness.

DISCUSSION

It is a significant advancement in self-care to be able to monitor health status, including ECG, heart rate, blood pressure, and oxygen saturation, using a simple and comfortable wearable device like a smartwatch. The widespread use of smartwatches enables the detection of previously undiagnosed heart rhythm disturbances and can reassure

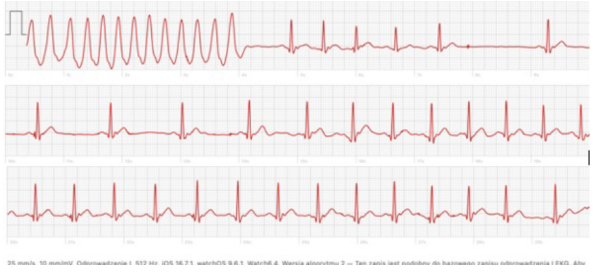

Fig. 1. Apple Watch single-lead ECG showing monomorphic ventricular tachycardia and sinus rhythm (25 mm/s, 10 mm/mV)

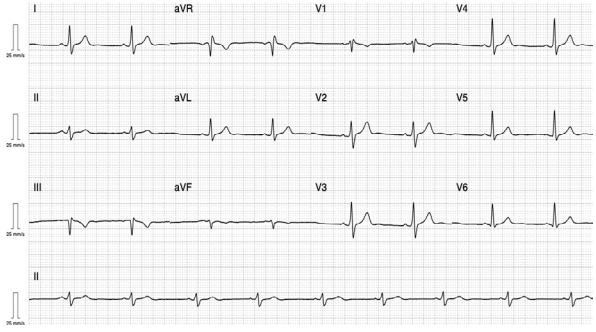

Fig. 2. Rest ECG

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patients who experience palpitations but have a normal ECG. Smartwatches can passively measure pulse rate from the wrist using photoplethysmography with an optical sensor[19] and hence detect pulse irregularity and variability in real time, which may indicate irregular heart rhythms, such as AF. However, for other types of arrhythmias, ECG recording must generally be initiated by the patient themselves by touching the electrode on the device with the opposite hand. This is why the detection of most abnormalities remains symptom-driven. Some case reports describe clinically relevant diagnoses, such as ischaemia and ventricular arrhythmia treated by percutaneous coronary intervention (PCI)[15] or arrhythmia managed with catheter ablation and insertion of an implantable defibrillator[11–18]. The recognition of these abnormalities by wearable devices has significantly influenced the course of diagnostics and therapy. However, a major limitation is that such devices only record a single-lead ECG[19]. Additionally, in cases of symptom-driven initiation, it is not possible to record the preceding ECG (as shown in Fig. 1).

AF is the most common sustained arrythmia worldwide, with its incidence doubling every few decades[20]. According to the European Society of Cardiology guidelines for AF management, AF can be recognised by a standard ECG (6 or more leads) or by a 1- or 2-lead ECG (for example recorded by a smartwatch, wearable patches, or biotextiles); however, photoplethysmography (PPG) may be indicative for AF, though diagnostic[20].

The deployment smart devices, including smart watches, may differ between cases of primary and secondary prevention in patients after a thromboembolic event. In the latter group, prolonged monitoring has a class I recommendation, whereas in patients with risk factors, it carries a class IIa recommendation[20]. Future research should focus on monitoring with the AW in patients after thromboembolic events or those with more than one point on the CHA2DS2-VA scale.

Interventions utilising smartphones have been considered effective tools for the self-management of chronic diseases, such as diabetes and hypertension[21]. Mobile health interventions also hold potential for reaching a substantial proportion of the global population, given their popularity. Users of m-health benefit from having information, self-monitoring, and continuous ongoing support. The World Health Organization (WHO) has also emphasised critical recommendations for using m-health to maximise its benefits, including the importance of perceived utility, ease of use, and addressing technical concerns such as privacy, security, and cost. Additionally, WHO highlights the need for familiarity with technology, careful evaluation of risk-benefit profiles, and seamless integration with existing health systems. By addressing these factors, m-health interventions can be effectively optimised to improve healthcare delivery, especially in resource-limited settings[22].

The question remains whether each detected abnormality should lead to extended diagnostics, especially given that worldwide sales of smartwatches have exceeded 1 billion in 2022[23]. This case report highlights the future of cardiology with smartwatch diagnoses which, in some cases, will result in further clinical evaluations. This underscores the need for studies and guidelines to address this issue. Even in cases of AF detection through various screening methods, the balance between benefit and harm is debatable[24]. Data from the STROKESTOP study[25] showed that to prevent one stroke among individuals aged 75 to 76 years, 10,000 people would need to be screened. This is associated not only with high costs, but also with the potentially harmful consequences of anticoagulation treatment. Therefore, it is crucial to learn how to react to different types of abnormalities detected by smartwatches and to search for markers that can improve risk evaluation. The plan of action is obvious in cases of second- and third-degree atrioventricular block or atrioventricular reentry tachycardia, but how far should testing go in cases of oligosymptomatic and self-limiting VT?

In this presented case, after a detailed discussion with the patient, the decision was made to extend diagnostic testing to include an invasive electrophysiology study. However, this report shows that such cases require an individualised approach.

CONCLUSIONS

The integration of wearable technology into healthcare, particularly for the monitoring of cardiac conditions, marks a significant advancement in patient self-care and health management. This case report underscores the importance of utilising data from wearable devices, such as smartwatches. As the popularity of these devices continues to rise, it is essential that healthcare professionals make informed decisions regarding the expansion of diagnostic procedures based on the data provided by wearables. While these devices offer the potential for enhanced detection of heart rhythm disturbances, the reliance on patient-driven symptom reporting calls for a cautious and judicious approach to further diagnostic testing. Individualised assessment and clear guidelines are crucial to balance the benefits of wearable technology with the potential risks and costs associated with excessive diagnostic procedures. Ultimately, as the capabilities of wearable devices in cardiac care continue to be explored, it will be essential to refine strategies for managing abnormal findings and optimising patient outcomes within this evolving landscape of digital health innovation.

Conflict of interest

The authors do not report any financial or personal connections with other persons or organisations which might negatively affect the content of this publication and/or claim authorship rights to this publication.

Author contribution

Original concept of study; collection, recording and/or compilation of data; analysis and interpretation of data: AG. Writing of manuscript: AG, PK. Critical review of manuscript: PK. Final approval of manuscript: AG, PK.

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Idiopathic hypogonadotropic hypogonadism as a cause of delayed puberty

Idiopatyczny hipogonadyzm hipogonadotropowy jako przyczyna opóźnionego dojrzewania

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Abstract

Hypogonadotropic hypogonadism is a condition resulting from dysfunction of the hypothalamic-pituitary-gonadal axis, leading to impaired production of sex hormones and disrupted development. In many cases, an accurate diagnosis is unobtainable. This report presents the case of a 17-year-old patient with an incidental diagnosis of delayed puberty who underwent a full diagnostic procedure, which did not reveal a clear cause of hypogonadism. Following treatment with gonadotropins, proper testosterone levels, full masculinisation, and psychical well-being were achieved. This case highlights that accurate examinations during standard paediatric visits are crucial for the diagnosis of delayed puberty and other development abnormalities. Diagnosing hypogonadotropic hypogonadism is challenging, and determining a definitive diagnosis is often difficult. Individualised treatment with gonadotropins or testosterone is necessary for achieving sexual development and proper social functioning.

Keywords: gonadotropins, hypogonadotropic hypogonadism, delayed puberty

Streszczenie

Hipogonadyzm hipogonadotropowy to stan wynikający z dysfunkcji osi podwzgórze–przysadka–gonady, prowadzący do upośledzenia wytwarzania hormonów płciowych i prawidłowego rozwoju. W wielu przypadkach dokładna diagnoza przyczyny hipogonadyzmu jest niemożliwa. W pracy opisano przypadek 17-letniego pacjenta, u którego przypadkowo rozpoznano opóźnione dojrzewanie płciowe. W toku przeprowadzonej diagnostyki nie ujawniono jednoznacznej przyczyny hipogonadyzmu. Dzięki wprowadzonemu leczeniu gonadotropinami pacjent uzyskał odpowiednie stężenie testosteronu, pełną maskulinizację i rozwój psychospołeczny zgodny z płcią. Przypadek dowodzi, że dokładne badanie przedmiotowe podczas standardowych wizyt pediatrycznych jest kluczowe w diagnostyce opóźnionego dojrzewania i innych nieprawidłowości rozwojowych. Diagnostyka hipogonadyzmu hipogonadotropowego jest trudna, a ostateczne rozpoznanie często nieosiągalne. W przypadkach rozpoznanego hipogonadyzmu osiągnięcie prawidłowego rozwoju płciowego i funkcjonowania społecznego możliwe jest przy zastosowaniu zindywidualizowanej terapii gonadotropinami lub testosteronem.

Słowa kluczowe: gonadotropiny, hipogonadyzm hipogonadotropowy, opóźnienie dojrzewania

INTRODUCTION

Hypogonadotropic hypogonadism is a condition resulting from dysfunction of the hypothalamic-pituitary-gonadal axis, leading to impaired production of sex hormones[1].

It may arise from secondary causes, most commonly neoplastic changes in the hypothalamus and pituitary (e.g. craniopharyngioma, pituitary adenoma), or from mutations in genes responsible for the proper differentiation or function of gonadotropic cells[2,3].

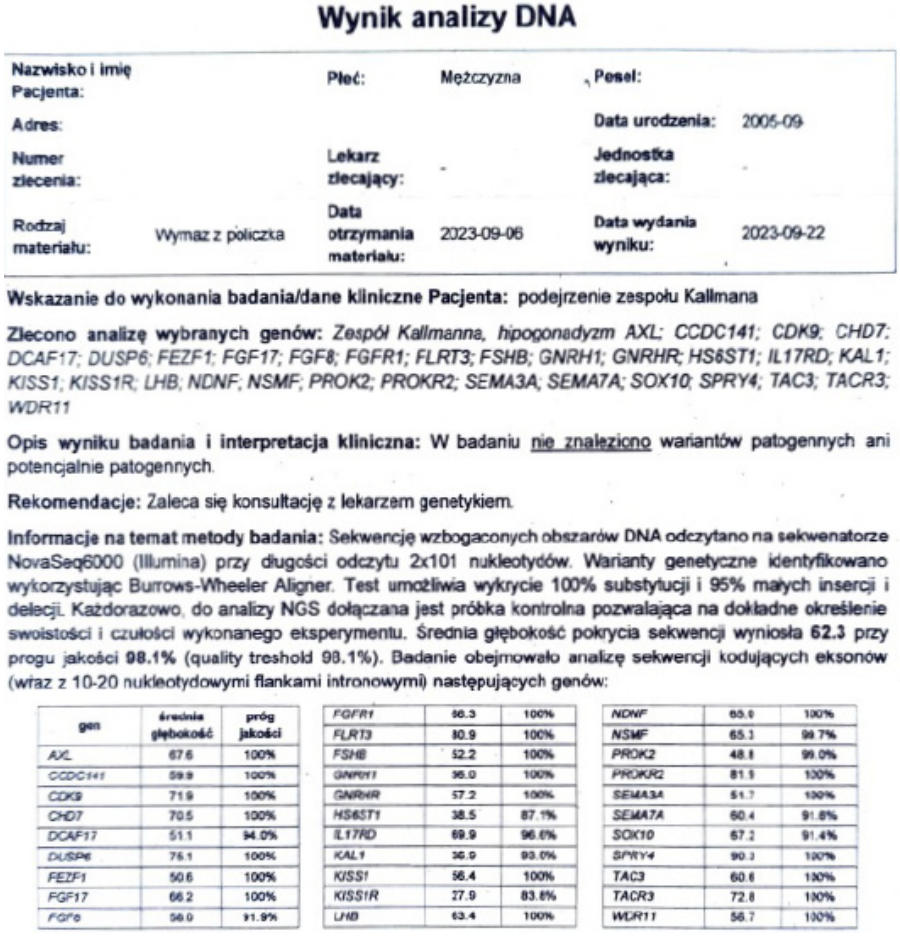
Despite the availability of extensive diagnostic tools, including genetic evaluation, the exact aetiology of the disorder remains undetermined in more than half of cases[4].

CASE REPORT

A 17-year-old (+11 months) patient diagnosed with delayed puberty was referred to the Department of Endocrinology for hormonal evaluation. In June 2023, the patient presented to the Emergency Department with fever of unknown origin. During the consultation, a paediatrician noted the absence of pubertal development and recommended further diagnostic evaluation. Subsequently, the patient was hospitalised in the Department of Endocrinology in August 2023.

On physical examination, the absence of clinical signs of puberty was confirmed (Tanner stage: Testis 1, Pubarche 1, Axillarche 4). Notably, a review of the patient's medical documentation showed a lack of prior assessment of sexual characteristics or percentile grids. Laboratory tests revealed a prepubertal total testosterone (TTE) concentration of 0.102 ng/mL, with no other laboratory abnormalities. No pathological lesions were diagnosed in magnetic resonance imaging (MRI) of the pituitary region. A gonadotropin-releasing hormone (GnRH) stimulation test demonstrated a normal pituitary response, with an increase in follicle-stimulating hormone (FSH) and luteinising hormone (LH) levels >5× the baseline. Karyotype analysis and genetic testing did not identify any genetic causes of hypogonadism (Fig. 1).

Treatment with human chorionic gonadotropin (hCG) at a dose of 2,500 IU twice weekly was initiated. During a follow-up hospitalisation in April 2024, secondary sexual characteristics were observed, with Tanner staging as follows: Testis 2, Pubarche 4, Axillarche 5. Increased testicular and penile volume, a reduction in gynaecomastia, and further growth were observed. Repeat GnRH stimulation



Wynik analizy DNA

Nazwisko i imię Pacjenta:		**Płeć:**	Mężczyzna	**Pesel:**	
Adres:				**Data urodzenia:**	2005-09
Numer zlecenia:		**Lekarz zlecający:**	-	**Jednostka zlecająca:**	-
Rodzaj materiału:	Wymaz z policzka	**Data otrzymania materiału:**	2023-09-06	**Data wydania wyniku:**	2023-09-22

Wskazanie do wykonania badania/dane kliniczne Pacjenta: podejrzenie zespołu Kallmana

Zlecono analizę wybranych genów: *Zespół Kallmanna, hipogonadyzm AXL; CCDC141; CDK9; CHD7; DCAF17; DUSP6; FEZF1; FGF17; FGF8; FGFR1; FLRT3; FSHB; GNRH1; GNRHR; HS6ST1; IL17RD; KAL1; KISS1; KISS1R; LHB; NDNF; NSMF; PROK2; PROKR2; SEMA3A; SEMA7A; SOX10; SPRY4; TAC3; TACR3; WDR11*

Opis wyniku badania i interpretacja kliniczna: W badaniu nie znaleziono wariantów patogennych ani potencjalnie patogennych.

Rekomendacje: Zaleca się konsultację z lekarzem genetykiem.

Informacje na temat metody badania: Sekwencję wzbogaconych obszarów DNA odczytano na sekwenatorze NovaSeq6000 (Illumina) przy długości odczytu 2x101 nukleotydów. Warianty genetyczne identyfikowano wykorzystując Burrows-Wheeler Aligner. Test umożliwia wykrycie 100% substytucji i 95% małych insercji i delecji. Każdorazowo, do analizy NGS dołączana jest próbka kontrolna pozwalająca na dokładne określenie swoistości i czułości wykonanego eksperymentu. Średnia głębokość pokrycia sekwencji wyniosła **62.3** przy progu jakości **98.1%** (quality treshold 98.1%). Badanie obejmowało analizę sekwencji kodujących eksonów (wraz z 10-20 nukleotydowymi flankami intronowymi) następujących genów:

gen	średnia głębokość	próg jakości
AXL	67.6	100%
CCDC141	59.9	100%
CDK9	71.9	100%
CHD7	70.5	100%
DCAF17	51.1	94.0%
DUSP6	75.1	100%
FEZF1	50.6	100%
FGF17	66.2	100%
FGF8	56.0	91.9%
FGFR1	66.3	100%
FLRT3	80.9	100%
FSHB	52.2	100%
GNRH1	36.0	100%
GNRHR	57.2	100%
HS6ST1	38.5	87.1%
IL17RD	69.9	96.6%
KAL1	36.9	93.0%
KISS1	56.4	100%
KISS1R	27.9	83.8%
LHB	63.4	100%
NDNF	65.0	100%
NSMF	65.3	99.7%
PROK2	48.8	99.0%
PROKR2	81.3	100%
SEMA3A	51.7	100%
SEMA7A	60.4	91.8%
SOX10	67.2	91.4%
SPRY4	90.3	100%
TAC3	60.8	100%
TACR3	72.8	100%
WDR11	56.7	100%

Fig. 1. Result of genetic assessment

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Parameter	Units	Reference range	08.2023	04.2024	08.2024	01.2025
Age	Years old	NO	17	18	18	19
Testicular volume	mL	>12	5.2	7.7	9	10.4
TTE	ng/mL	2.8–8.2	0.102	0.114	0.129	2.07
E2	pg/mL	11.2–43.2	<5	<5	<5	15.7
LH	IU/L	1.0–8.0	1.74	2.3	1.28	5.77
FSH	IU/L	1.0–8.0	1.71	2.6	1.1	3.49
SHBG	µg/mL	1.37–4.59	2.15	1.93	1.73	1.48
Bone age	NA	NA	14	15	16	17
Height	cm	*	166	168	173	174
Testies	NA	1–5	1	2	2	2
Pubache	NA	1–5	1	3	4	5
Axillarche	NA	1–5	4	5	5	5
Inhibin B	pg/mL	120–400	NA	55	60	61
DHEAS	µg/dL	70–492	197	196	158	199
PRL	ng/mL	1.0–16.0	3.4	2.2	2.2	3.7
TSH	mIU/L	0.27–4.20	1.63	1.72	1.92	1.78

TTE – total testosterone; **E2** – oestradiol; **LH** – luteinising hormone; **FSH** – follicle-stimulating hormone; **SHBG** – sex-hormone binding globulin; **DHEAS** – dehydroepiandrosterone sulphate; **PRL** – prolactin; **TSH** – thyrotropin; **NA** – not applicable.
* Estimated/target height.

Tab. 1. Results of laboratory tests, testicular volume, bone age, and Tanner scale during the treatment

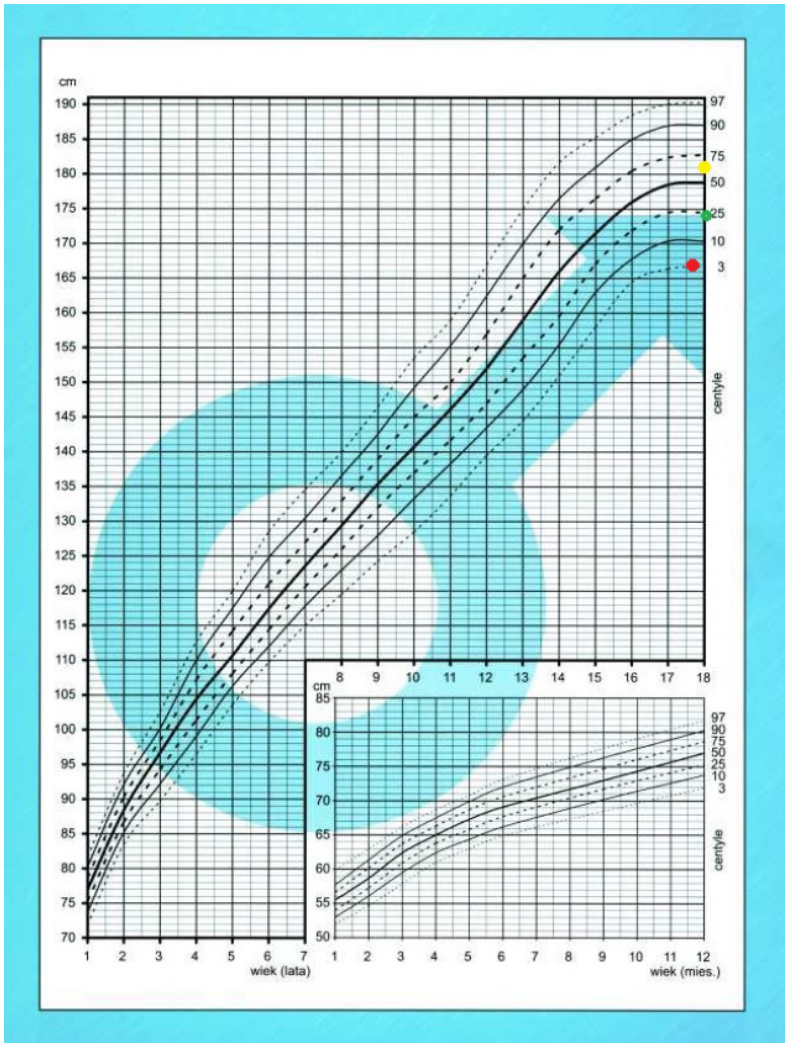

Fig. 2. Percentile grid of the patient. Red – initial height, green – final height, yellow – estimated/target height (based on the height of the parents)

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testing showed normal FSH and LH levels. However, after a two-week cessation of gonadotropin therapy, biochemical and clinical hypogonadism re-emerged.

A brief trial of human menopausal gonadotropin (hMG) therapy was undertaken; however, due to the absence of increased inhibin B levels, lack of significant testicular growth at the subsequent follow-up, and the high cost of therapy, treatment was reverted to hCG monotherapy.

During a follow-up hospitalisation in January 2025, further increases in penile and testicular size (both measuring 5.2 mL) were observed. Mild gynaecomastia was detected on ultrasound, measuring 13 × 4 mm on the right and 19 × 7 mm on the left, likely physiological. TTE concentration three days post-hCG injection remained within the reference range; however, after hCG cessation, TTE concentration decreased again. Given the patient's satisfaction with the observed testicular and penile growth, and his preference to continue gonadotropin therapy, hCG treatment was maintained despite the recommendation to transition to testosterone therapy.

Detailed laboratory results, testicular volumes (measured by ultrasound), bone age, and Tanner staging throughout treatment are summarised in Tab. 1 and Fig. 2.

DISCUSSION

The presented case highlights the challenges in diagnosing patients with hypogonadotropic hypogonadism. Moreover, it underscores how the process of standard paediatric care should not be conducted. A diagnosis of delayed puberty at nearly 18 years of age should not happen if the patient had been properly examined at least once. The absence of percentile grids in the medical records also makes assessment difficult. Paediatricians and general practitioners should recognise the crucial role of physical examination in early detection. Fortunately, the patient underwent treatment which helped with the development of tertiary sexual characteristics. This case is also interesting due to potential irregularities not only in GnRH production, but also in testicular response. Two GnRH stimulation tests proved proper pituitary response, thus suggesting that cyclic secretion of endogenous GnRH might be impaired. Moreover, there was no Sertoli cells response to hMG, as evidenced by the lack of inhibin B increase and minimal testicular volume change during treatment. Due to the high cost and lack of reimbursement of the drug in Poland the treatment was withdrawn. Nevertheless, the patient achieved his personalised treatment goals – masculinisation and genital growth. The issue of fertility is questionable but still undetermined, as the patient refused semen analysis.

Hypogonadotropic hypogonadism is always challenging both for the diagnosis and treatment, as the number of genes responsible for sexual development remains an open question[5,6]. The most recent meta-analysis of 103 studies including 5328 patients from 21 countries demonstrated that hCG, hMG, FSH, and GnRH can be effective treatments. Moreover, gonadotropins induced significant increases in testicular volume, penile size, and testosterone levels in over 98% of cases. Spermatogenesis was obtainable with the use of hCG + FSH in 86% cases, while hCG alone gave only 40% efficacy. Thus, patients with hypogonadotropic hypogonadism are not necessarily deprived of the possibility of biological parenthood.

SUMMARY

Every paediatric patient should be thoroughly examined during visits to exclude delayed puberty or other development abnormalities.

Hypogonadotropic hypogonadism is diagnostically challenging, and a definitive diagnosis is often difficult to establish.

The most important aspect for both the physical and mental health of the patient is initiating an individualised therapy tailored to their needs and expectations, as well as those of their family.

Treatment with gonadotropins, although conducted "off-label", most closely mimics the physiological processes of sex hormone production, enabling normal sexual development and induction of testicular volume growth.

Conflict of interest

The authors do not report any financial or personal connections with other persons or organisations which might negatively affect the content of this publication and/or claim authorship rights to this publication.

Author contribution

Original concept of study; collection, recording and/or compilation of data; analysis and interpretation of data: ADD, DABK. Writing of manuscript: ADD, MS. Critical review of manuscript; final approval of manuscript: MS, GWK.

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