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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].

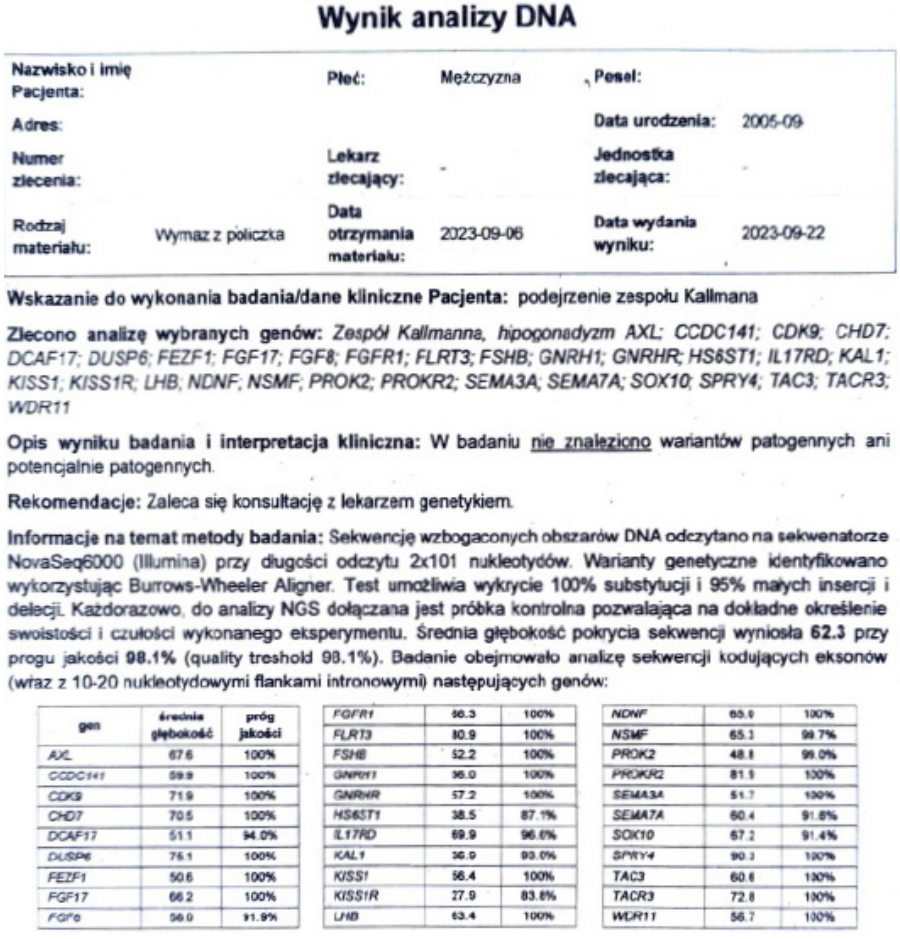
Despite the availability of extensive diagnostic tools, including genetic evaluation, the exact aetiology of the disorder remains undetermined in more than half of cases[4].

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

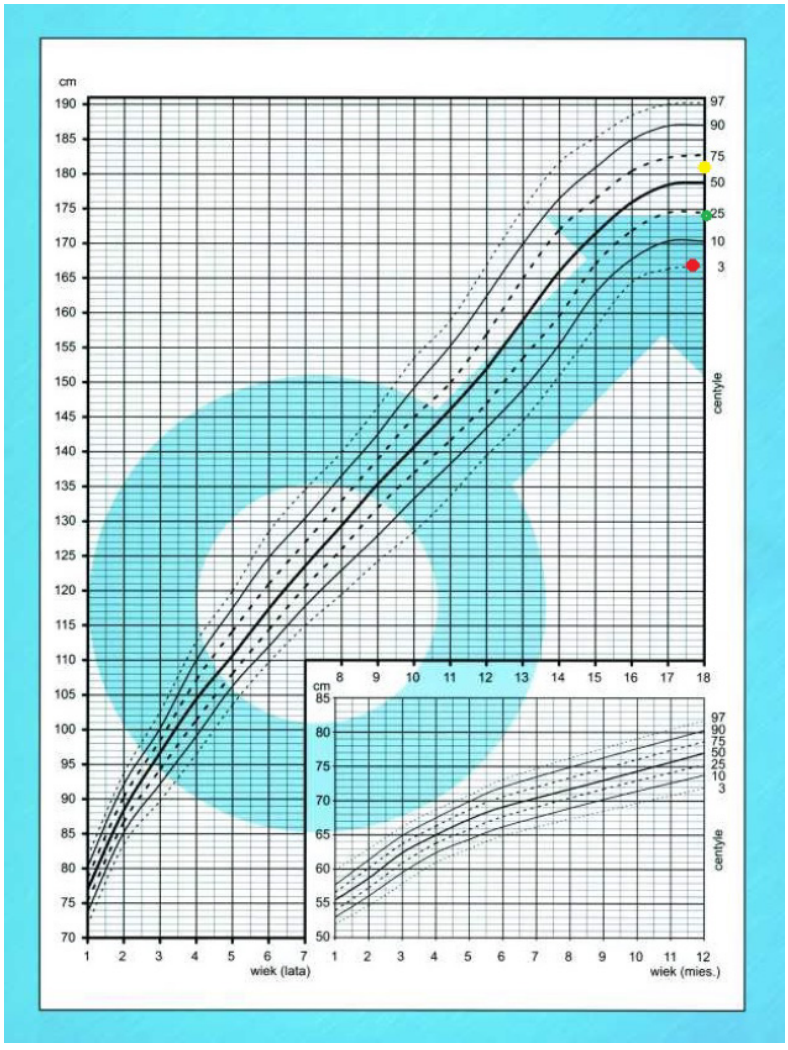

Fig. 2. Percentile grid of the patient. Red – initial height, green – final height, yellow – estimated/target height (based on the height of the parents)

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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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