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Comparison of the clinical picture and hormonal test results in children with growth hormone deficiency and idiopathic short stature – diagnostic difficulties and brief overview

Porównanie obrazu klinicznego i wyników badań hormonalnych u dzieci z niedoborem hormonu wzrostu oraz idiopatycznym niedoborem wzrostu – trudności diagnostyczne i omówienie tematu

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Abstract

Introduction and objective: Short stature is a common paediatric problem. Some children with short stature present growth hormone (GH) deficiency (GHD), whereas others have no hormonal disturbances (idiopathic short stature, ISS). Distinguishing between these two conditions is the task of the paediatric endocrinology centres. The aim of this study was to compare the clinical picture and hormonal tests results in patients with short stature caused by GHD and ISS. **Materials and methods:** The study included 100 short stature children. In all the children, medical history was obtained and a physical examination was performed. Next, bone age, insulin-like growth factor type 1 (IGF-1) levels, and GH secretion in two stimulation tests were assessed. With respect to the GH results, the children were divided into two groups: GHD (n = 38) and ISS (n = 62). **Results:** There were no significant differences between the groups with respect to age, sex, puberty stage, bone age, birth length and birth weight. Growth retardation was observed in both groups with a similar frequency, but in the ISS group it occurred significantly earlier. The mother's height was lower in the ISS group. Body mass was significantly higher, but IGF-1 significantly lower in the GHD group. In both groups, the maximum GH secretion in the stimulation tests was higher after clonidine than after glucagon, which indicates that this test is more reliable. **Conclusions:** A similar degree of growth deficiency, growth rate deceleration and bone age delay are observed in ISS and GHD children, though ISS children are thinner and have higher IGF-1 levels. Despite some differences in clinical presentation, all short stature patients with growth rate deceleration should undergo thorough diagnostic testing along with GH stimulation tests.

Keywords: children, growth, growth hormone, IGF-1, short stature

Streszczenie

Wprowadzenie i cel: Niskorosłość jest częstym problemem pediatrycznym. U niektórych dzieci z niskorosłością występuje niedobór hormonu wzrostu (*growth hormone deficiency*, GHD), podczas gdy u innych nie stwierdza się żadnych zaburzeń hormonalnych (niskorosłość idiopatyczna – *idiopathic short stature*, ISS). Rozróżnienie tych dwóch jednostek chorobowych jest wyzwaniem dla ośrodków endokrynologii dziecięcej. Celem pracy było porównanie obrazu klinicznego i wyników badań hormonalnych u pacjentów z niskorosłością spowodowaną GHD i ISS. **Materiał i metody:** Badaniem objęto 100 dzieci z niskorosłością. U wszystkich dzieci przeprowadzono wywiad lekarski i badanie przedmiotowe. Następnie oceniano wiek kostny, stężenie insulinopodobnego czynnika wzrostu typu 1 (*insulin-like growth factor type 1*, IGF-1) oraz wydzielanie hormonu wzrostu w dwóch testach stymulacyjnych. Na podstawie uzyskanych wyników wydzielania hormonu wzrostu dzieci podzielono na dwie grupy: GHD (n = 38) i ISS (n = 62). **Wyniki:** Nie stwierdzono istotnych różnic między grupami pod względem: wieku, płci, stadium dojrzewania płciowego, wieku kostnego, urodzeniowej długości ciała i urodzeniowej masy ciała. Zahamowanie wzrastania obserwowano w obu grupach z podobną częstością, ale w ISS wystąpiło ono istotnie wcześniej. Wzrost matki był niższy

w grupie ISS. Masa ciała była istotnie wyższa, natomiast stężenie IGF-1 istotnie niższe w grupie GHD niż w grupie ISS. W obu grupach maksymalne wydzielanie hormonu wzrostu w testach stymulacyjnych było wyższe po podaniu klonidyny niż po podaniu glukagonu, co wskazuje na większą wiarygodność pierwszego z wymienionych testów. **Wnioski:** U dzieci z ISS i GHD obserwuje się podobny stopień niedoboru wzrostu, spowolnienia tempa wzrastania i opóźnienia wieku kostnego, natomiast dzieci z ISS są szczuplejsze i mają wyższe stężenie IGF-1 niż dzieci z GHD. Pomimo pewnych różnic w obrazie klinicznym wszyscy pacjenci z niskorosłością i zwolnieniem tempa wzrastania powinni zostać poddani dokładnym badaniom diagnostycznym wraz z testami oceniającymi wydzielanie hormonu wzrostu.

Słowa kluczowe: dzieci, wzrost, hormon wzrostu, IGF-1, niski wzrost

INTRODUCTION

Short stature is a frequent diagnostic concern in paediatrics, and it ranks among the most common reasons children are referred to paediatric endocrinologists. Short stature is defined as height less than two standard deviation scores (SDS) below the mean for sex and age of the reference data calculated for a given population (−2.0 SDS), which is an equivalent of 2.3 centiles on the centile charts. For simplicity, it is often considered as less than the 3rd centile for sex and age for a given population. Thus, about 2% of children are diagnosed as short stature[1]. In some cases, it is possible to link short stature to a specific disease entity. The assessment of a child with short stature should include a clinical evaluation by a paediatrician to look for systemic causes of the condition (e.g. coeliac disease, inflammatory bowel disease, chronic respiratory, cardiovascular or oncohaematological disorders), as well as a thorough endocrine assessment, including medical and family history, physical examination with auxological measurements, laboratory tests, and selected radiological imaging assessments. Genetic testing should also be performed, particularly when dysmorphic features are present. Special attention should be paid to weight disturbances (both undernutrition and obesity) and other abnormalities on physical examination. Furthermore, it is important to collect data on medications taken by the examined child (e.g. glucocorticosteroid therapy). The diagnostic process should also take into account diseases directly related to the growth process. It is widely acknowledged that growth hormone (GH) stimulates the production of insulin-like growth factor type 1 (IGF-1) and, in this way, plays a key role in promoting longitudinal growth in children, while growth hormone deficiency (GHD) is one of main endocrine cause of short stature. Physiologically, GH is secreted by the somatotropic cells of the anterior pituitary gland; therefore, GHD is a condition in which the production and secretion of GH by these cells is impaired. GHD may be idiopathic or associated with the presence of congenital or acquired organic lesions of the pituitary region. It is estimated that 3–30% of GHD cases may have a genetic basis[1].

In contrast, in a significant proportion of assessed children, the cause of short stature cannot be found on the basis of medical history, physical examination, and tests results. This group of patients is diagnosed with so-called idiopathic short stature (ISS)[2]. The birth weight and length of children with ISS is within the normal range, and their short stature is not caused by any systemic diseases, hormonal causes, bone and cartilage abnormalities or genetic defects[2]. Unfortunately, most of these children do not reach normal target height (TH). The aim of this study was to compare the clinical picture and hormonal test results in patients with short stature caused by GHD and in patients diagnosed with ISS.

METHODS

The study included 100 children with short stature who were admitted consecutively to the Department of Endocrinology and Metabolic Diseases of the Polish Mother's Memorial Hospital – Research Institute in Łódź from April 2021 to April 2023, and whose parents gave a written consent to participate in the study.

Inclusion criteria:

- age ≥2.0 and ≤17.0 years;
- patient's height less than −2.0 SDS with respect to age and sex;
- no identifiable organic or genetic causes of short stature;
- born at term (≥37 weeks of pregnancy) and with normal body length and weight (appropriate for gestational age, AGA);
- written consent of the legal representative to participate in the study.

Exclusion criteria:

- health problems that may cause growth failure (e.g. chronic diseases of the gastrointestinal tract, respiratory system, cardiovascular system, endocrine conditions – such as decompensated hypothyroidism, genetic disorders);
- children with prematurity (<37 week of pregnancy) or small for gestational age (less than −2.0 SDS as regards to birth weight or birth length – SGA).

In all the children the medical history was gathered, an auxological assessment of the child was performed, basic laboratory tests were done and the serum IGF-1 level was measured, and two stimulation tests for GH secretion were carried out.

Auxological evaluation

In all the children, a paediatric examination was conducted with a focus on anthropometric measurements.

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Height measurements were taken in the morning using a Harpenden-type stadiometer. The child's body height in relation to the range of reference values for age and sex was expressed by the height SDS[3]. The height age (HA) was determined for each patient by checking on a centile chart the age at which a child growing along the 50th centile had the height of the assessed patient. The patient's TH was calculated from the measured or reported heights of the parents[3]. The body mass index (BMI) was calculated and adjusted with respect to the reference values for sex and calendar age (CA), and for HA for the Polish population, and expressed as SDS[4,5]. Pubertal development was assessed by the Tanner scale[6,7]. Bone age (BA) was estimated according to Greulich–Pyle (G&P) evaluation standards based on radiographs of the wrist and hand of the non-dominant hand.

Laboratory methods

IGF-1 concentration was assessed using IMMULITE, DPC assays. For IGF-1, the World Health Organization (WHO)/National Institute for Biological Standards and Control (NIBSC) 1st IRR (international reference reagent) 87/518 standard was used, with an analytical sensitivity of 20 ng/mL, a calibration range up to 1,600 ng/mL, an intra-assay coefficient of variation: 3.1–4.3%, and an inter-assay coefficient of variation – CV: 5.8–8.4%. IGF-1 levels were expressed in terms of standard deviation score for sex and age (IGF-1 SDS), according to reference data. GH concentrations were determined using a two-site chemiluminescent enzyme immunometric assay (hGH IMMULITE, DPC) for the quantitative measurement of human GH, calibrated to the WHO IRP (international reference preparation) 80/505 standard. The analytical sensitivity of the assay was up to 0.01 ng/mL, the calibration range was up to 40 ng/mL, the intra-assay coefficient of variation was 5.3–6.5%, and the inter-assay coefficient of variation was 5.5–6.2%.

Two stimulation tests for GH secretion were performed. In one test, clonidine administered orally was used as a stimulator, at a dose of 0.15 mg/m^2 body surface area. The test lasted 120 minutes. Blood was drawn at 0, 30, 60, 90, and 120 minutes. In the other test, glucagon was administered intramuscularly at a dose of 30 μg/kg (maximum dose – 1 mg). The test lasted 180 minutes. Subsequent blood samples were taken at 0, 90, 120, 150, and 180 minutes of the test. In addition, blood glucose measurements were taken every 30 minutes throughout the test.

GHD was diagnosed when maximum GH secretion in both stimulation tests was found to be below 10 ng/mL. ISS was diagnosed when maximal GH secretion in at least one stimulation test was equal or above 10 ng/mL (exclusion of GHD) and after other causes of short stature were excluded (e.g. chronic diseases, endocrine diseases such as hypothyroidism or Cushing's syndrome as well as genetic disorders).

Auxological characteristics	ISS ($n = 62$)	GHD ($n = 38$)	p
CA [years]	10.4 ± 2.8	10.8 ± 2.9	0.48
Sex: male, *n* (%)	34 (54.84%)	25 (65.7%)	0.28
Height [cm]	127.9 ± 14.2	131.0 ± 15.4	0.22
Height SDS	−2.6 ± 0.5	−2.4 ± 0.3	0.16
BMI [kg/m^2]	15.8 ± 2.1	17.6 ± 3.2	**0.01***
BMI SDS for CA	−0.9 ± 1,1	0.0 ± 1.6	**0.01***
HA [years]	7.8 ± 2.4	8.3 ± 2.5	0.21
BMI SDS for HA	−0.3 ± 1.4	0.7 ± 1.8	**0.01***

* $p < 0.05$.
ISS – idiopathic short stature; **GHD** – growth hormone deficiency; **CA** – calendar age; **SDS** – standard deviation score; **BMI** – body mass index; **HA** – height age.

Tab. 1. Age, sex, and auxological parameters of short stature children in the two analysed groups

Statistical analysis

Statistical analysis of the collected data was performed using STATISTICA ver. 13.3 software (StatSoft, Poland). The Shapiro–Wilk test was used to evaluate normality of distribution and the Levene's test was applied to assess equality of variance. Comparative analysis of continuous independent variables was carried out by parametric (Student's *t*-test) and non-parametric tests (Mann–Whitney *U* test). Intergroup comparisons of nominal/qualitative variables were performed using the chi-square test. Continuous variables were presented by mean and standard deviation (mean ± *SD*), and categorical variables by *N* (%). Statistically significant differences were taken as *p*-values below 0.05.

Institutional review board statement

Approval to conduct the study was obtained from the Bioethics Committee at the Polish Mother's Memorial Hospital – Research Institute in Łódź (Opinion No. 47/2020).

Informed consent statement

The legal representatives of all patients gave their informed written consent to participate in the study prior to their inclusion.

RESULTS

Study group characteristics

One hundred (100) short stature children (59 boys and 41 girls) aged from 2.0 to 16.0 years were divided into groups with respect to the results of GH stimulation tests: 38 children were diagnosed with GHD and 62 children with ISS. There were no statistically significant differences between the groups regarding sex or age. Study group characteristics by diagnosis are presented in Tab. 1.

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Sex/birth weight and length		ISS ($n = 62$) (34 males, 28 females)	GHD ($n = 38$) (25 males, 13 females)	p
Female	Weight [g]	3,257.7 ± 343.6	3,115.5 ± 371.6	0.29
	Length [cm]	52.6 ± 3.5	53.9 ± 2.2	0.32
Male	Weight [g]	3,323.3 ± 334.9	3,427.4 ± 565.4	0.54
	Length [cm]	54.0 ± 3.3	54.6 ± 2.9	0.69

ISS – idiopatic short stature; **GHD** – growth hormone deficiency

Tab. 2. Birth weight and birth length of short stature children in the two analysed groups

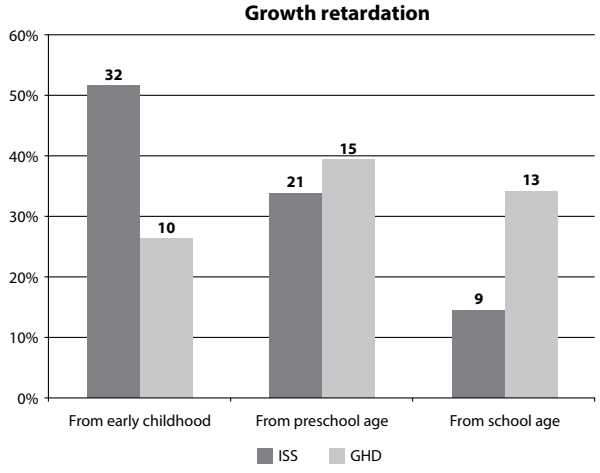
Perinatal period

All the patients were born between 37 and 42 gestational weeks, median ±39 weeks (mean 39.21 ± 1.0 for the ISS group, 38.94 ± 1.1 for the GHD group; $p = 0.27$). 51% patients were born by spontaneous labour, 48% by cesarean section, 1% by forceps delivery. 51% ISS and 42% GHD children were born from the first delivery, and 39% and 48% from the second delivery, respectively. Also, 10% of the analysed short stature children from each group was born from the third delivery. There was a history of miscarriage in 16% mothers of children with ISS and 6% mothers of children with GHD.

Mean ± *SD* for birth weight was 3,297.1 ± 333.6 g for ISS patients and 3,326.6 ± 518.4 g for GHD; $p < 0.73$. Mean ± *SD* for birth length was 53.3 ± 3.4 cm for patients in the ISS group and 54.4 ± 2.7 cm for patients in the GHD group; $p = 0.13$. There were no significant differences between the groups, or in the subgroups, when divided by sex (Tab. 2).

Growth retardation

Growth retardation was assessed based on data available from 65 patients (39 with ISS, 26 with GHD). Deceleration of growth rate was observed from early childhood (from birth to 3 years of age) in 51.6% of children with ISS and 26.3% of children with GHD; from the preschool period (3–6 years of age) in 33.9% of patients with ISS and 39.5% of patients with GHD; and from the school period (7–13 years of age) in 14.5% of patients with ISS and 34.2% of patients with GHD (Fig. 1). Growth retardation was observed significantly earlier in the patients with ISS ($p = 0.02$).



GHD – growth hormone deficiency; **ISS** – idiopathic short stature.

Fig. 1. Percentage of children with ISS and GHD with observed growth retardation from a given age range

Height	ISS	GHD	p
Mother's height [cm]	160.1 ± 5.3	162.7 ± 5.6	**0.02***
Mother's height SDS	−0.9 ± 1.0	−0.4 ± 1.0	**0.02***
Father's height [cm]	174.6 ± 6.0	175.4 ± 6.6	0.49
Father's height SDS	−0.7 ± 1.0	−0.5 ± 1.1	0.49
TH [cm]	168.1 ± 7.5	170.8 ± 7.7	0.13
TH SDS	−0.8 ± 0.7	−0.5 ± 0.9	0.13

* $p < 0.05$.
ISS – idiopathic short stature; **GHD** – growth hormone deficiency;
SDS – standard deviation score; **TH** – target height.

Tab. 3. Parental height and TH of short stature children in the two analysed groups

Parental height and target height

Mother's height and SDS of maternal height were significantly lower in the ISS group than in the GHD group, while no significant differences were detected with respect to father's height and SDS of paternal height (Tab. 3). The TH and TH SDS tended to be lower in the ISS group than in the GHD group (Tab. 3). Among patients with ISS, we identified a subgroup of patients with familial short stature (FSS), that is, patients with an only slight height deficiency compared to their parental height[8]. FSS patients were identified based on the formula proposed by Ranke (height SDS > TH SDS −1.28)[8], with 28% of patients with ISS meeting the criteria for FSS.

Assessment of height age

As mentioned above, HA was determined by checking on a centile chart the age at which a child growing along the 50th percentile had the height of the assessed patient. Calculation of HA was necessary to draw reliable conclusions about body weight for children who were short or tall. The mean HA was 7.77 ± 2.4 years for ISS patients and 8.33 ± 2.5 years for GHD patients; the differences were not statistically significant ($p = 0.21$).

Comparison of body weight and nutritional status (BMI)

Patients in the ISS group had significantly lower BMI compared to those in the GHD group. Mean standard deviation score of BMI for both CA (−0.88 ± 1.1 vs. −0.01 ± 1.6; $p = 0.01$) and HA were significantly lower than in the GHD group (−0.34 ± 1.4 vs. 0.69 ± 1.8; $p = 0.01$) (Fig. 2).

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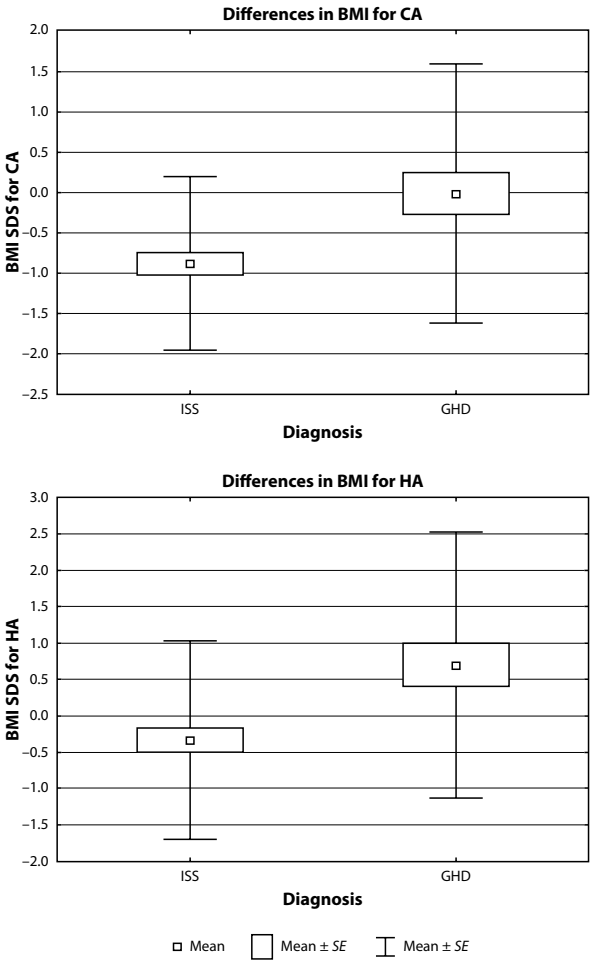

BMI – body mass index; **CA** – calendar age; **GHD** – growth hormone deficiency; **HA** – height age; **ISS** – idiopathic short stature; **SDS** – standard deviation score; **SE** – standard error.

Fig. 2. Comparison of body weight and BMI SDS for CA and BMI SDS for HA in children with ISS and with GHD

Puberty

The stage of pubertal development assessed by the Tanner scale did not differ between the groups. Most patients were prepubertal (Tanner 1): 71% ISS and 73% GHD. The age of entering puberty (Tanner 2) was similar for patients from the ISS and GHD groups with respect to sex. The mean age of puberty onset was 11.82 ± 1.5 for girls and 13.41 ± 0.9 years for boys. Delayed puberty was found in two boys from the ISS group. The stage of puberty of patients in both groups is presented in Tab. 4.

Assessment of bone age

BA was delayed in relation to CA in 75 patients (75%), and consistent with CA in 24 patients (24%); in one patient the BA result was unavailable. Delayed BA was found in 80% of ISS patients and 68% of GHD patients ($p = 0.9$). In particular, 68% of patients had their BA delayed by more than one year, while a further 22% – by only about six months. There were no significant differences in BA delay (mean ± *SD* was −1.75 ± 1.3 years in the ISS group and −1.60 ± 1.6 years in the GHD group; $p = 0.37$).

Puberty (Tanner scale)	ISS; *n* (%)	GHD; *n* (%)
1	44 (71%)	29 (73%)
2	13 (21%)	9 (23%)
3	4 (6%)	2 (5%)
4	1 (2%)	0 (0%)

ISS – idiopathic short stature; **GHD** – growth hormone deficiency.

Tab. 4. Distribution of stages of puberty (according to the Tanner scale) among short stature children in the two analysed groups

Comparison of IGF-1 concentrations

The IGF-1 serum levels did not differ between the groups (155.48 ± 86.9 ng/mL for ISS vs. 137.17 ± 59.5 ng/mL for GHD; $p = 0.46$). In contrast, by objectifying the results by expressing them as SDS values, the standard deviation score of IGF-1 was significantly lower in the GHD group than in the ISS group (−1.67 ± 1.0 vs. −1.3 ± 0.84; $p = 0.04$).

Evaluation of growth hormone secretion in stimulation tests

Decreased GH secretion (GH peak <10 ng/mL) in both stimulation tests was observed in 38 patients (these children formed the GHD group). In turn, in the ISS group – GH peak ≥10 ng/mL in only one stimulation test was found in 41 patients: 33 patients after clonidine and eight after glucagon administration ($p = 0.0001$), while GH peak secretion ≥10 ng/mL in both tests was found in 21 cases. This data indicated that the results of clonidine stimulation test in eight children (12.9%) and glucagon stimulation test in 33 children (53.2%) were false negative. On the other hand, in each individual group (ISS and GHD), maximum GH secretion was significantly higher after clonidine stimulation than after glucagon administration (Tab. 5).

DISCUSSION

In our study, patients with ISS had significantly lower BMI than patients with GHD. The mean BMI SDS in the ISS group was about −1.0. Accordingly, children with ISS were assessed as leaner than healthy individuals[9]. Inadequate nutrient intake by some patients diagnosed with ISS may contribute to short stature. Therefore, patients with ISS, especially those with a low BMI, should be evaluated for food intake and possible nutritional deficiencies, and preferably referred to a nutritionist. If there are doubts about whether all relevant diagnostic tests have been performed, the patient should be re-evaluated by a paediatrician, since

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Diagnosis	GH secretion <10 ng/mL		Number of patients	Mean GH peak for clonidine [ng/mL]	Mean GH peak for glucagon [ng/mL]	*p*
	Clonidine	Glucagon				
GHD	Yes	Yes	38	6.1 + 2.6	4.9 ± 2.7	**0.03***
ISS	Yes	No	8	14.0 ± 4.4	10.1 ± 5.5	**0.0001***
ISS	No	Yes	33			
ISS	No	No	21			
Total	46	71	62	8.1 ± 5.3	11.0 ± 5.5	**0.0001***

* $p < 0.05$.
GH – growth hormone; **GHD** – growth hormone deficiency; **ISS** – idiopathic short stature.

Tab. 5. GH concentrations obtained in the stimulation tests in short stature children in the two analysed groups

numerous paediatric conditions can manifest with short stature and malnutrition. On the other hand, children diagnosed with GHD more often exhibit an increased amount of subcutaneous truncal fat. In fact, GH has beneficial effects not only on growth, but also on improving lipid metabolism and normalising body composition (reducing body fat, increasing muscle tissue), enhancing basal metabolism, as well as improving muscle tone and bone mineralisation[10]. Thus, GH deficiency (besides short stature) leads to negative metabolic consequences which can be improved with recombinant human growth hormone (rhGH) treatment. It is well known that adult patients with GHD, in comparison with the healthy population, have abnormal body composition (increased body fat, decreased lean body mass), as well as certain metabolic disturbances[10,11]. These abnormalities begin in childhood, although not all children with GHD are affected in the same way[12]. In our previous study comparing the metabolic test results of children with GHD (aged 5.7–15.3 years) with a group of healthy peers, we found that children with GHD showed significantly higher levels of triglycerides, with comparable cholesterol levels and similar glucose and insulin concentrations analysed during oral glucose tolerance test (OGTT)[13]. We observed that it depended on additional factors, including ghrelin, adiponectin and IGF-1 bioavailability[13]. Therefore, for children with GHD, implementation of proper eating habits and support of a dietician are also important.

While the children with ISS and GHD from our study differed in BMI, it appeared that there were no significant differences in their birth weight and birth length. This seems to be an interesting observation, because low birth weight and/or length are known to predispose to the development of obesity and metabolic complications later in life[14]. Moreover, comparing to the mean birth weight and length of children born in the Łódź region (the 50th percentile depending on the gestational week varied: 3,072–3,614 g and 53.2–56.1 cm for boys, and 2,876–3,346 g and 51.9–55.6 cm for girls, respectively), the birth length and weight of children in our study did not stand out considerably from the healthy population[15].

It is worth emphasising that GH has a very limited effect on foetal growth; it changes only after birth, i.e. it becomes visible in infancy and later[14]. Therefore, children who are diagnosed as GHD later in life may be born with normal birth weight and length (besides some children with severe congenital GHD)[16]. Thus, growth deficit is unlikely to be evident in the neonatal period, but other symptoms may be present including hypoglycaemia, prolonged hyperbilirubinemia, and microgenitalism[17].

While in numerous short stature patients impaired growth is observed from early childhood, this is especially visible among children with ISS[18]. According to our analysis, growth retardation during early childhood was also observed significantly more often in the ISS than in the GHD group. Precisely, growth retardation was found in more than half of ISS patients before the age of three years and in a total of 85% no later than from the preschool period.

To evaluate a child's height, it is necessary to relate it to the reference values for age and sex in a given population and calculate the height SDS or assess height on a centile chart. It is also extremely important to estimate the height velocity (HV), which is assessed by two measurements taken at least six months apart. Calculation of HV facilitates the identification of a child's growth trajectory over time and the assessment of potential disturbances. Child's height should also be related to the height of the parents, by determining the TH as well as calculating the standard deviation of TH (TH SDS) which is relevant for assessing how much the patient's current height differs from the TH[2]. In our study, the values of mother's height *SD* were significantly lower in the ISS group than in the GHD group. This finding can be explained by the fact that some children with ISS may be diagnosed with FSS. FSS is a normal variation of growth that can be attributed to the inheritance of various genes associated with growth. Short stature is usually observed from early childhood, and the HV is usually normal and harmonious throughout the child's life. In our cohort, 28% of patients with ISS were found to meet the criteria for FSS.

Apart from FSS, growth retardation during childhood often occurs in children with delayed puberty (i.e. constitutional delay of puberty and growth, CDPG). Thus, it also is important to take a family history regarding the course of growth and puberty, as it is possible that children mimic slow growth and puberty trajectory that occurred in their parents. The height velocity of those children usually decreases significantly in early childhood, but – in the

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subsequent years – the growth curve follows a linear course below the 3rd–5th centile[19]. Sex hormones have a stimulating effect on the synthesis and secretion of GH; therefore, a growth spurt is observed during puberty. That is why the growth of children with delayed puberty begins to diverge visibly from their peers. Such children grow at a slower rate but for a longer period of time. Finally, during late puberty they experience an associated growth spurt, which in most cases results in a normal TH[19]. In Poland, the first signs of puberty generally appear in girls between 10 and 11, and in boys between 11.5 and 12.5 years of age[20]. In our study, girls and boys began puberty at an older age than the mean age in the population. Delayed puberty was found only in two boys from the ISS group. However, it was impossible to assess whether short stature had been caused by CDPG in the majority of children. Delayed puberty can be established if the first pubertal signs (Tanner stage 2) are not present in girls from the age of 13 and in boys from the age of 14, whereas most of our patients (69) were younger.

In children with GHD, there may be decreased growth velocity from the first years of life depending on the severity of growth hormone deficiency. In some cases of GHD, an abrupt impairment of growth velocity is observed (progressive decrease in height SDS corrected for TH). This may suggest an acquired cause of GHD, e.g. related to cancer or its treatment. GHD can also be associated with genetic factors that cause structural abnormalities of the pituitary gland region or impaired synthesis and secretion of GH. Nevertheless, in most patients, as in the children in our study, the cause of GHD remains undetermined (the so-called idiopathic GHD). In ISS and GHD patients (and including FSS, CDPG), growth deceleration may be the only observation, making the process of differential diagnosis challenging. Nevertheless, BA assessment through wrist and hand radiographs may be helpful.

Bone age delay results from insufficient effects of growth hormone on the maturation of growth cartilage. It usually occurs in children with GHD and CDPG. In contrast, in children with FSS, BA is relevant to the calendar age. In our study, delayed BA was found in 80% of ISS patients and 68% of GHD patients When commenting on this finding, it is worth highlighting two facts. Firstly, the assessment of BA is stepwise, based on G&P atlas standards (i.e. characteristic time points at which significant changes occur in the number and shape of the ossification centre of the individual bones of the wrist and non-dominant hand in a growing child). The assessment is quite subjective and impacted by the experience of the assessor. Secondly, BA is related to IGF-1 concentrations and the duration of GHD, so it is less delayed in children who develop GHD later in life and in those who have partial GH deficiency (with preserved IGF-1 secretion). Furthermore, in pubertal children BA starts to advance due to sex hormones (mainly oestrogens), with any previous delay considerably reduced. So, it is worth emphasising that delayed BA is not an absolute requirement for the diagnosis of GHD. It may also occur in short stature resulting from other causes (i.e. hypothyroidism, malabsorption syndromes). IGF-1 is a major mediator of GH action in bones and other peripheral tissues. Therefore, IGF-1 blood levels should be measured during the diagnostic process[21]. In children with short stature, IGF-1 serum concentrations are often reduced. In our study, the mean SDS of IGF-1 was decreased compared to the standard values specified by the kit manufacturer. Moreover, it tended to be lower in the GHD group than in the ISS group, which may result from various causes of growth impairment and a wide spectrum of GH resistance among diverse groups of ISS patients.

The reason for the difficulties in diagnosing GHD and ISS is that there is a *continuum* between GH deficiency and normal GH secretion. In order to evaluate GH secretion, stimulation tests (with two different GH stimulants) are performed. In the present study, clonidine and glucagon tests were used. In the analysed group, decreased GH secretion in both tests was found in 38 patients (GHD group), with significant differences observed with respect to the results of each test. In both groups, the maximum GH secretion in the stimulation tests was higher after clonidine than after glucagon, which indicates that this test is more reliable. Actually, there are many doubts about the repeatability and reliability of these tests. Unfortunately, many healthy children with normal growth get abnormal results of these tests (suggesting reduced GH secretion)[22]. Because natural GH secretion is usually lower before puberty, some experts suggest using sex hormones just before conducting GH stimulation tests in adolescents to prevent false-positive results[10]. In Poland, according to the consensus guideline published by the Growth Hormone Research Society, the maximum GH secretion in two different stimulation tests below 10 ng/mL is arbitrarily considered as reduced GH secretion. Patients who do not meet the criteria for GHD after other causes of short stature have been excluded are diagnosed with ISS[2].

CONCLUSIONS

In conclusion, every short stature child, after excluding other common causes of short stature, should be referred for evaluation by a paediatric endocrinologist. In our study, growth retardation was observed significantly earlier in patients with ISS. Moreover, the maternal height and standard deviation of maternal height were notably lower in the ISS group. Patients with ISS also had lower BMI and higher IGF-1 levels than patients with GHD. Since it is not possible to determine the cause of short stature based on the clinical picture of short stature children (particularly those with slow HV, low IGF-1, and normal body weight and maternal height) should undergo detailed diagnostic testing. Despite some drawbacks of GH stimulation tests, there are currently no better means of GHD diagnostics, with the clonidine

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test appearing to be more reliable. Short stature patients, particularly underweight ones, should be carefully assessed in terms of nutrition and dietary deficiencies, and evaluated for the presence of chronic diseases that may contribute to malnutrition and short stature.

Conflict of interest

The authors declare no conflict of interest.

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Author contribution

Original concept of study: AF, RS. Collection, recording and/or compilation of data: AF. Analysis and interpretation of data: AF, RS. Writing of manuscript: AF. Critical review of manuscript: AL, RS. Final approval of manuscript: AL, RS.

References

1. Mullis PE: Genetics of isolated growth hormone deficiency. J Clin Res Pediatr Endocrinol 2010; 2: 52–62.
2. Cohen LE: Idiopathic short stature: a clinical review. JAMA 2014; 311: 1787–1796.
3. Smyczyńska J, Lewiński A, Hilczer M: [Indices of auxological development in diagnosing children with short stature and monitoring the therapy effectiveness]. Pediatr Endocrinol 2013; 12: 51–56.
4. Kułaga Z, Grajda A, Gurzkowska B et al.: Polish 2012 growth references for preschool children. Eur J Pediatr 2013; 172: 753–761.
5. Kułaga Z, Litwin M, Tkaczyk M et al.: Polish 2010 growth references for school-aged children and adolescents. Eur J Pediatr 2011; 170: 599–609.
6. Marshall WA, Tanner JM: Variations in pattern of pubertal changes in girls. Arch Dis Child 1969; 44: 291–303.
7. Marshall WA, Tanner JM: Variations in the pattern of pubertal changes in boys. Arch Dis Child 1970; 45: 13–23.
8. Ranke MB, Lindberg A: Growth hormone treatment of idiopathic short stature: analysis of the database from KIGS, the Kabi Pharmacia International Growth Study. Acta Paediatr Suppl 1994; 406: 18–23; discussion 24.
9. Thibault H, Souberbielle JC, Taieb C et al.: Idiopathic prepubertal short stature is associated with low body mass index. Horm Res 1993; 40: 136–140.
10. Ranke MB, Wit JM: Growth hormone – past, present and future. Nat Rev Endocrinol 2018; 14: 285–300.
11. Lewiński A, Smyczyńska J, Stawerska R et al.: National program of severe growth hormone deficiency treatment in adults and adolescents after completion of growth promoting therapy. Endokrynol Pol 2018; 69: 468–524.
12. Meazza C, Elsedfy HH, Pagani S et al.: Metabolic parameters and adipokine profile in growth hormone deficient (GHD) children before and after 12-month GH treatment. Horm Metab Res 2014; 46: 219–223.
13. Stawerska R, Smyczyńska J, Hilczer M et al.: Relationship between IGF-I concentration and metabolic profile in children with growth hormone deficiency: the influence of children's nutritional state as well as the ghrelin, leptin, adiponectin, and resistin serum concentrations. Int J Endocrinol 2017; 2017: 5713249.
14. Barker DJ, Hales CN, Fall CH et al.: Type 2 (non-insulin-dependent) diabetes mellitus, hypertension and hyperlipidaemia (syndrome X): relation to reduced fetal growth. Diabetologia 1993; 36: 62–67.
15. Rosset I: Rozkłady centylowe wielkości urodzeniowych noworodków łódzkich urodzonych w terminie. Pediatr Pol 2009; 84: 151–158.
16. Boguszewski MCS: Growth hormone deficiency and replacement in children. Rev Endocr Metab Disord 2021; 22: 101–108.
17. Chinoy A, Murray PG: Diagnosis of growth hormone deficiency in the paediatric and transitional age. Best Pract Res Clin Endocrinol Metab 2016; 30: 737–747.
18. Albertsson-Wikland K: Characteristics of children with idiopathic short stature in the Kabi Pharmacia International Growth Study, and their response to growth hormone treatment. International Board of the Kabi Pharmacia International Growth Study. Acta Paediatr Suppl 1993; 82 Suppl 391: 75–78.
19. Rogol AD, Hayden GF: Etiologies and early diagnosis of short stature and growth failure in children and adolescents. J Pediatr 2014; 164 (5 Suppl): S1–S14.e6.
20. Małecka-Tendera E: Rozwój fizyczny i prawidłowe dojrzewanie płciowe. Available from: http://www.mp.pl/social/article/68312 [cited: 13 October 2023].
21. Savage MO, Burren CP, Rosenfeld RG: The continuum of growth hormone–IGF-I axis defects causing short stature: diagnostic and therapeutic challenges. Clin Endocrinol (Oxf) 2010; 72: 721–728.
22. Smyczyńska J, Stawerska R, Lewiński A et al.: Do IGF-I concentrations better reflect growth hormone (GH) action in children with short stature than the results of GH stimulating tests? Evidence from the simultaneous assessment of thyroid function. Thyroid Res 2011; 4: 6.