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Characteristics of paediatric hypopituitarism patients in Latvia: a single-centre 25-year retrospective study

Charakterystyka pacjentów pediatrycznych z niedoczynnością przysadki na Łotwie: jednoośrodkowe 25-letnie badanie retrospektywne

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Abstract

Introduction: Hypopituitarism is a chronic disease characterized by partial or complete absence of secretion of one or more pituitary hormones. Delayed diagnosis can have serious consequences during the neonatal period and adulthood.

Material and methods: A retrospective study was conducted on patients who had started treatment in the Children's Clinical University Hospital from 1 January 1995 to 31 December 2020. In total 243 patients were included; they were divided into 3 subgroups: isolated growth hormone deficiency, multiple pituitary hormone deficiency, and panhypopituitarism.

Results: The prevalence of hypopituitarism in Latvia is about 45 cases per 100,000 live births. The average detection age of abnormal growth in Latvia is 8 years and 3 months. Most cases had isolated growth hormone deficiency, at 67.1% (n = 163), followed by cases of multiple pituitary hormone deficiency, at 26.3% (n = 64), and cases of panhypopituitarism, at 6.6% (n = 16). Abnormalities in MRI were found in 44.7% (n = 101) of patients. The most best therapeutic effect was achieved in the first year of treatment: with growth of an average of 9.3 cm (+0.1 SD) for isolated growth hormone deficiency, 9.0 cm (+0.6 SD) for multiple pituitary hormone deficiency, and 11.7 cm (+1SD) for patients with panhypopituitarism.

Conclusions: It is important to increase awareness and promote early diagnosis for hypopituitarism patients in Latvia and in Europe. More attention should be paid to education about growth restriction problems to parents, caregivers, and other specialists. The treatment should be adjusted individually with the focus not only on physical and mental health but also on safety and treatment costs.

Key words:
pediatrics, endocrinology, pituitary insufficiency, panhypopituitarism.

Introduction

Hypopituitarism is a chronic endocrine disorder characterized by impaired, partial or complete, secretion of one or more pituitary hormone/s [1–3]. Isolated growth hormone deficiency (IGHD) is the most common pituitary hormone deficiency in children [2, 4]. The incidence of IGHD is one in 4000 to one in 10,000 live births [5]. The incidence of multiple pituitary hormone deficiency (MPHD) in the paediatric population is less than 3 cases per 1,000,000 population per year [6].

Hypopituitarism has congenital and acquired forms; therefore, it can manifest itself in different periods of life: neonatal, infancy, childhood, adolescence, and adulthood [6, 7]. According to the literature, 52% of newborns with congenital hypopituitarism have their first signs of disease in the neonatal period, but less than 50% of patients are diagnosed at this age [8]. Delayed diagnosis of the disease can lead to serious short- and long-term complications [9], but optimal and approved diagnostic guidelines for children are still in being developed [7]. Timely initiation of adequate treatment in children at an early age can significantly improve their quality of life [2, 9, 10].

Aim of the study

The aim of this study is to analyse the epidemiological data, clinical manifestations, anthropometric data, changes in imaging findings, and results of treatment in Latvian patients with hypopituitarism in a 25-year period. Also to compare these data with existing scientific literature and evaluate diagnostic and treatment efficiency, with the aim of promoting public understanding of growth disorders and facilitating both parents and caregivers with understandable and accessible information. No similar studies have been conducted in Latvia before 2020 for paediatric patients.

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Material and methods

The retrospective cross-sectional study included all patients with a primary diagnosis of hypopituitarism, who started growth hormone (GH) therapy at the Children's Clinical University Hospital in Riga, Latvia from 1 January 1995 to 31 December 2020 (every child in Latvia with this diagnosis is referred to this hospital). Patient medical records and hospital information systems were used for the data collection. Microsoft Excel software was used for data gathering, and IBM SPSS Statistics 23 program was used to convey statistical analysis.

In descriptive statistics, Shapiro-Wilk tests and visual histogram evaluation were used to analyse the consistency of the quantitative data and normal distribution. Data that did not correspond to the normal distribution were expressed as median, interquartile norm (Q1–Q3), minimum and maximum values, and analysed by non-parametric Kruskal-Wallis test. The permission of the Ethics Committee of Riga Stradins University was obtained for this research.

Results

General and birth data of the patients included in the study

The study included 243 patients with a diagnosis of hypopituitarism, of whom 78.2% (n = 190) were male and 21.8% (n = 53) were female. All patients were divided into 3 subgroups: isolated growth hormone deficiency (IGHD) 67.1% (n = 163), multiple pituitary hormone deficiency (MPHD) 26.3% (n = 64), and panhypopituitarism (PH) 6.6% (n = 16).

The median birth weight (Q1–Q3) for all patients was 3275 g (2952–3600), and the median birth height was 51 cm (50–53 cm). The median gestational age was 39 weeks (36–40 weeks). The median birth weight of men was 3280 g (2982–3650 g) (–0.18 SD), the median height was 52 cm (50–53 cm) (+0.77 SD), and the median gestational age was 39 weeks (37–40). The median birth weight of women was 3230 g (2800–3500) (+0.37 SD), the median height was 51 cm (50–52 cm) (+1 SD), and the median gestational age was 38 weeks (36–39 weeks).

First signs and complaints of the disease

First signs and complaints of hypopituitarism predominantly were observed by the patients themselves or the parents; as a result, they went to an endocrinologist or were hospitalized. The first signs and complaints were divided into the 12 most common categories, and the frequency of them in each of the three subgroups are described in Table I. The median age of the first signs and complaints for patients was 7 years and 6 months (4.3–11.8), with a range from 1 month to 17.5 years.

Age of diagnosis of the disease

The median age of the patients for the final diagnosis was 8 years and 3 months. The median age at the time of diagnosis in the IGHD group was 7 years and 11 months, in the MPHD group it was 11 years and 6 months, and in the PH group it was 3 years and 4 months. At the time of diagnosis, anthropometric parameters of patients were determined: height (cm), weight (kg), and how these readings deviate from paediatric standard deviations (SD), and body mass index (kg/m^2). These data are listed in Table II.

Bone age

Bone age (BA) was determined using X-ray (according to the standardized RUS method) in 83.5% (n = 203) of all study patients. The median BA was 8 years and 5 months (4.5–11.8). In patients who underwent X-ray BA analysis, for 3% of patients (n = 6) the BA was equal to the chronological age (CA) at the moment of diagnosis, and for 81.8% (n = 166) of patients the BA was less than the CA. In these patients, the median difference between CA and BA was 16 months. The age difference between the 3 subgroups was 14 (7–22) months in the IGHD group, 19 (12–26.5) months in the MPHD group, and 25.5 (22.5–27.5) months in the PH group.

Growth hormone stimulation tests and other laboratory evaluations

Two GH stimulation tests (with clonidine and insulin) were performed in 48.6% (n = 118) of patients. Only one test with either clonidine or insulin was performed in 32.9% (n = 80) and 14.4% (n=35) of patients, respectively. None of the tests were performed in 4.1% (n = 10) of the patients. Less than a half (44.4%) of the patients with idiopathic GHD, i.e. without pathological changes in the pituitary gland in MRI, had only one GH stimulation test performed.

During the clonidine test, severe (a peak GH level < 3 ng/ml) growth hormone deficiency (GHD) was observed in 21.7% (n = 43), moderate (3.01–7 ng/ml) in 42.9% (n = 85), and mild (mild > 7.01 ng/ml) in 35.4% (n = 70) of patients.

Insulin-like growth factor 1 (IGF-1) was tested for 87.3% (213) of patients.

Imaging of the brain

Brain-imaging was performed in 93% (n = 226) of patients, of whom 96% (n = 217) underwent MRI and 4% (n = 9) CT. Abnormalities were found in 44.7% (n = 101) of patients. Abnormalities in MRI findings were detected in 38.7% (n = 58) of patients in the IGHD group, in 46.7% (n = 28) in the MPHD group, and in 93.8% (n = 15) in the PH group. Hypoplastic adenohypophysis with ectopic neurohypophysis and structural changes in the pituitary stalk were found in 6.6% (n = 16) of patients, 3 in the IGHD, 4 in the MPHD, and 9 in the PH group. More detailed changes in the MRI finding and frequency of them in each of the 3 subgroups are described in Table III.

Characteristics of the underlying disease

Patients in the MPHD group were diagnosed with GHD and deficiency of various other pituitary hormones in 4 different combinations. 51.6% (n = 33) were diagnosed with GHD and secondary hypothyroidism, 32.9% (n = 21) with GHD and secondary hypogonadism, 10.9% (n = 7) with GHD, secondary hypothyroidism, and secondary hypogonadism, and 4.7% (n = 3) with GHD and secondary hypocorticism.

Table I. First signs and complaints of the disease

	All patients (%)	IGHD (%)	MPHD (%)	PH (%)
Slow growth from birth	23	25.2	17.2	25
Slow growth in recent years	49.4	45.4	59.4	50
Reduced appetite	24.3	26.4	20.3	18.8
Short stature	36.2	39.9	34.4	6.3
Constipation	5.3	6.7	3.1	0
Headache, weakness, fatigue, dizziness	9.9	9.2	12.5	6.3
Stomach-ache	3.7	3.7	4.7	0
Excessive weight gain, increased appetite	6.2	4.3	12.5	0
Hypoglycaemia, prolonged conjugated hyperbilirubinaemia	3.7	0.6	3.1	37.5
Difficulty to concentrate at school	4.5	12.9	14.1	18.8
Abnormalities of external genitalia	10.7	6.7	12.5	43.8

Table II. Patients' anthropometric measurements at final diagnosis

Parameter	IGHD	MPHD	PH
Height, cm (min-max)	116.5 (97–134) (–2.5 SDS)	132 (104.7–145) (–2.4 SDS)	87 (66.3–101.8) (–2.7 SDS)
Weight, kg (min-max)	20 (14–30) (–1.9 SDS)	30 (17.5–39) (–1.6 SDS)	12.9 (7.3–17.9) (–1.2 SDS)
BMI, kg/m^2 (min-max)	15.7 (14.4–17.3) (–0,71 SDS)	17 (15.6–19.5) (–0,18 SDS)	16.4 (15.8–17.2) (1,01 SDS)

Table III. MRI findings of the brain

MRI findings	All patients (%)	IGHD (%)	MPHD (%)	PH (%)
Without abnormalities	58.4	61.3	53.3	6.3
Hypoplastic anterior pituitary	29.6	24.7	35	87.5
Ectopic posterior pituitary	11.1	5.3	10	81.3
Abnormal pituitary infundibulum	8.6	3.3	11.7	56.3
Chiari I malformation	2.9	4	1.7	0
Optic nerve hypoplasia	0.8	0.7	0	6.3
Septo-optic dysplasia	0.8	0	0	12.5
Other structure anomalies in the pituitary gland (not specified)	7.8	7.3	11.7	6.3
Other brain structure anomalies (not specified)	6.6	5.3	6.7	25

In the PH group secondary hypothyroidism and secondary hypocorticism were diagnosed in all cases (n = 16), and secondary hypogonadism was diagnosed in 50% of cases (n = 8). One patient in this group also had diabetes mellitus.

Growth hormone therapy

The median age at initiation of growth hormone therapy was 9 years and 2 months, ranging from 3 months to 18 years and 3 months. In the IGHD group, the median age of onset of treatment was 8 years and 4 months, in the MPHD group it was 11 years and 11 months, and in the PH group it was 3 years and 6 months.

At the beginning of treatment with growth hormone (GH), patients' height (cm) and weight (kg), compliance with standard deviation appropriate for the child's age (SD), and body mass index (kg/m^2) were determined. These data are listed in Table IV. Patient anthropometric measurements were assessed 12 months after initiation of GH therapy. These data are listed in Table V.

The median growth rate and weight difference in the first year of treatment were determined: 9.2 cm (7.8–11.5) and 4.0 kg (2.7–6.0) for men, for women – 9.5 cm (7.4–11.8) and 4.6 kg (2.9–5.8), IGHD patients – 9.3 cm (8–11.4) and 4.0 kg (2.8–6.0), MPHD patients – 9.0 cm (7.4–11.4) and 4.8 kg (2.9–6.3), and PH patients – 11.7 cm (6.6–16.2) and 2.95 kg (2.4–4.32).

By 31 December 2020, 30.5% (n = 74) of the study participants had completed treatment, 8.6% (n = 21) had promptly interrupted or discontinued treatment, and 44.4% (n = 108) were still receiving treatment. There are no data available for 16.5% (n = 40) of the patients. Of the patients who continued treatment (n = 108), the numerical distribution was as follows: 82.4% (n = 89) of men and 17.6% (n = 19) of women, 60.2% (n = 65) in the IGHD group, 25.9% (n = 28) in the MPHD group, and 3.9% (n = 15) in the PH group. Of the patients who completed GH therapy, the median duration of treatment was 7 years and 1 month for men, for women 5 years and 8 months, in the IGHD group it was 5 years and 9 months, and in the MPHD group it was 5 years.

Discussion

This research is in line with previous results – the most common hormone deficiency in the paediatric population is IGHD [2, 4, 9]; the majority of patients in this study (67.1%) were diagnosed with IGHD. This research also confirms previous findings that pituitary hormone deficiency most frequently begins with impaired GH secretion, followed by other pituitary hormone deficiencies [11].

Evaluation of anthropometric measurements from the participants' birth shows that GHD does not affect intrauterine growth, but there is a significant effect to the postnatal period, when a delay in the children's physical development is observed [3, 12–14].

It is stated that early representation of the disease corresponds to severity of symptoms and the increased likelihood of inherited hypopituitarism, which was also confirmed by the results of this study [4, 15]. Although growth failure or other initial signs and complaints in patients were registered around 7 years and 6 months, the average age of final diagnosis was 8 years and 3 months. It is plausible that the first signs and symptoms were missed or underestimated due to insufficient knowledge and/or understanding of growth restriction disorders and their incidence. The median age of diagnosis is the lowest in the PH group compared to the other groups (3 years and 4 months), which could be explained by the fact that these children suffer from severe congenital hypopituitarism, and

Table IV. Patients' anthropometric measurements at the beginning of treatment with GH therapy

Parameter	IGHD	MPHD	PH
Height, cm (min-max)	118.2 (98.8–135) (–2.3 SDS)	133.6 (112.5–146.2) (–3 SDS)	88 (71.7–102.6) (–2.8 SDS)
Weight, kg (min-max)	20.75 (14.9–31) (–2.1 SDS)	31.3 (20–40.7) (–1.5 SDS)	13.6 (7.9–17.9) (–1.0 SDS)

Table V. Patients' anthropometric measurements 12 months after initiation of GH therapy

Parameter	IGHD	MPHD	PH
Height, cm (min-max)	124.2 (106.5–140.6) (–2.2 SDS)	135 (106.6–150.7) (–2.4 SDS)	99.2 (83.1–108.7) (–1.8 SDS)
Weight, kg (min-max)	23.6 (17–34.4) (–1.9 SDS)	30.2 (20.1–44.8) (–1.3 SDS)	15.2 (11.7–20.7) (–1.2 SDS)

therefore symptoms are more severe in nature and present themselves early [7].

The median age at the diagnosis in the IGHD patient group was 7 years and 11 months. Child *et al*. in 2019 reported that the median age of diagnosis of IGHD patients in their study was 11 years and 1 month [16]. Boros *et al*. in 2019 proposed that patients diagnosed with the disease after the age of 10 years should considered as very late for the diagnosis of the disease; therefore, 40% of our study population could be classified as very late for final diagnosis [17]. Nevertheless, current available scientific literature regarding the average age of diagnosis is heterogenous, but the key fact about diagnostic process is clear: the sooner the diagnosis is made, the sooner effective treatment can be started and a positive outcome achieved.

In our study, 81.8% ($n = 166$) of patients were found to have negative deviance from the patients' CA when compared to BA, which is also described in the literature as one of the major diagnostic methods for hypopituitarism [14, 18]. The median BA and CA differences for all patients were 16 months. In the PH group the difference was the greatest (25.5 months) compared to the other 2 subgroups of the disease, which can be explained by the consequences of complete hormone deficiency in PH patients [9].

The discussion on what constitutes an optimal diagnostic process for GHD continues. Because of the issues with pulsatile GH secretion and complicated GH stimulation test procedures, the diagnosis of GHD is made including other assessments and tests, e.g. IGF-1, IGFBP-3, and others. Testing IGF-1 has some advantages (IGF-system peptides are stable during the day, and it is used as a long-term biomarker during GH replacement therapy), but its level in blood is also dependent on many other factors, for instance, nutritional status, other diseases (diabetes, hypothyroidism, renal failure), and other conditions could be the reason for low IGF-1. We emphasize that interpretation of all diagnostic methods is valuable for a correct final diagnosis, as well as IGF-1 [7, 14–19].

Two independent GH stimulation tests are recommended to confirm GHD [9, 20], but in our study, we observed that less than half of all patients (48.6%) had 2 GH stimulation tests done. A possible explanation for this is that diagnostic tactics have changed and have improved for the last 25 years in Latvia. It could be argued that the possible reasoning for doing only one test is that if the first test result showed persuasively insufficient levels of GH, then the second test was not done. Moreover, we cannot deny the fact that a single GH stimulation test could have led to some misdiagnosis or delayed treatment.

In our study 44.7% of the patients had established changes in their MRI findings, which corresponds with the previously reported incidence in the literature, in which 40–60% GHD patients were diagnosed with abnormalities in the hypothalamic-pituitary axis [2]. The results of MRI in our study correspond to the literature, i.e. in IGHD patients the abnormalities were observed the least, and the most abnormalities were detected in the PH group [9, 21, 22]. Adenohypophyseal hypoplasia was the most common finding in all 3 patient subgroups. It has been reported that adenohypophyseal hypoplasia with ectopic neurohypophysis and structural changes in the pituitary stalk is more common in patients with MPHD than in IGHD [22, 23]. This is also confirmed in our study: out of 16 patients with this MRI finding, 13 of them were in the MPHD and PH groups. The diameter and volume of the pituitary gland vary in children of different ages and genders. Therefore, pituitary radiological examinations are often subjective due to the lack of united assessment criteria in Latvia. Moreover, it is hard to compare the results of our study with previously published studies [24]. Even though normal MRI findings were found in several patients (55.3%), it is necessary to also exclude genetic mutations that can cause hormone insufficiency while leaving the MRI findings within the norm. It is unlikely that MRI is the best method of analysis for every patient.

In contrast with previously published findings that 50% of patients with IGHD have another pituitary hormone deficiency [21], we confirmed that only 26.3% of patients had MPHD and 6.6% had PH. Deficiency of various hormones develops gradually, and perhaps some patients at the time of this study were not yet diagnosed but could be diagnosed later in life. Differences between geographical regions and ethnicities have not been compared before, and this could be an interesting new field of research in the future.

According to the National Institute for Health and Care Excellence, patients with IGHD who received growth hormone therapy grew by an average of 8–11 cm in the first year of treatment [25]. As we described in the results section, the data from this study are similar. Based on the data obtained in this study, it can be concluded that the effectiveness of treatment after the first year does not differ significantly between the sexes, but there is a difference between the 3 subgroups of the disease. The more severe the pituitary hormone deficiency, the earlier the final diagnosis is made and the earlier the treatment is initiated, consequently the better the efficacy of GH on the patients' height during the first year of treatment, which corresponds with the research results of Ranke *et al.* [10]

Ranke *et al*. (2015) reported that patients with idiopathic IGHD, who have started growth hormone replacement therapy between the ages of 0 and 3 years (mean 1.9 years), had an increase of height +1.7 SD (8.2 cm/year) in the first year of treatment, and patients who started treatment from 7 to 8 years (mean 7.5 years) had a height increase of +0.6 SD (4.6 cm/year) [10]. Huet *et al*. reported that the mean age of diagnosis of hypopituitarism (both IGHD and MPHD) in patients is 5.7 years, and height increased by +1.7 SD in the first year of treatment. Both studies uphold the importance of initiating treatment as early as possible [26]. These values correlate with the results of this study because in all 3 subgroups the median growth rate in the first year of treatment was from 9 cm to 11.7 cm.

We are aware that our research may have limitations. Firstly, it is possible that some patients' records were not preserved or were lost in the hospital's physical and electronic systems. The second limitation to fully evaluate the effectiveness of therapy is that almost 10% of patients interrupted or discontinued treatment and 44.4% of patients were still undergoing treatment. Finally, regardless of the increase in the number of hypopituita-

rism patients in recent years, a considerable number of cases in Latvia are diagnosed late, if at all. This could be related to difficult access to paediatric endocrinology specialists in previous decades and the lack of awareness of the need to monitor children's physical development on a regular basis not only the first year of life but also until adulthood. In future research the correlation between patients' socioeconomic status or parents' education level and the age of diagnosis could be analysed; therefore, more targeted awareness campaigns could be designed for the risk groups.

Currently, the main focus of researchers is to improve the administration of medication and its regimen in order to achieve the best physiological daily rhythm of hormones and to improve patients' quality of life while at the same time improving patients' compliance [3, 27]. In the meantime, several studies are exploring the potential genetic alterations that may be predisposing factors for the development of hypopituitarism; there are currently more than 60 different gene mutations described that are associated with the development of hypopituitarism. Further advancements in genetic analysis could prevent unnecessary invasive diagnostic testing [28].

Conclusions

Our work has led us to conclude that it is very important to increase awareness and promote early diagnosis of hypopituitarism patients. More attention should be paid to raising awareness about growth restriction problems to parents, caregivers, teachers, and general practitioners. A widely targeted awareness campaign would be indicated in Latvia to improve the diagnostic age of hypopituitarism. The tools for appropriately adjusting treatment need to be further individualized and optimized with a focus on physical and mental health, and likewise in terms of safety and costs.

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