Original Article

GROWTH HORMONE TREATMENT: FIRST RESULTS OF THE PARTNERSHIP PROGRAM FOR THE ESTABLISHMENT OF A GROWTH CENTER AT THE UNIVERSITY CLINIC OF PEDIATRICS – PLEVEN

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Summary

In March 2018, in the Clinic of Pediatrics of the University Hospital "G. Stranski "- Pleven, we have created a Center for diagnosing and treating children with growth disorders, in active collaboration with an established expert center. During the study, 53 children with height <-2 SDS were referred to the newly established Growth Center. The diagnoses of children receiving treatment with growth hormone (GH) were made in clinical settings based on the history, physical status, auxological assessment, imaging studies, basal and stimulated hormone tests, genetic tests. The children's mean age was 9.7 ± 4.5 years, with a significant gender difference (p>0.05), living mainly in cities. For 18 months, we treated a total of 11 children (54.5% male) with an average age at the start of GH therapy of 8.1 ± 4.4 years and an average growth velocity of 10.3 ± 7.7 cm/year. Treatment with GH was introduced in Pleven after successfully establishing the Growth Center in the Clinic of Pediatrics. The first results showed a significant increase in the number of diagnosed and treated children whose follow-up we found an acceleration in growth and bone maturation, positive body composition changes, and lack of side effects from the treatment.

Keywords: short stature, GH deficiency, GH therapy, childhood, a partnership program

Introduction

Short stature is defined as a height < 3th percentile; height standard deviation score (SDS) < -2 SDS or height < -1.5 SD below the midparental height [1]**.** Growth hormone deficiency (GHD) is a rare but important cause of short stature in children, and its diagnosis is not easy to make. Early diagnosis gives a chance to shorten the time until an appropriate diagnosis and growth hormone (GH) treatment is introduced. The use of GH (extracted from human pituitary) in a patient with GHD was first reported in 1958 [2]. In 1985, after many established Jacobs-Creutzfeldt disease cases in patients treated with pituitary GH, its use [3] was replaced by recombinant human GH (rhGH). In Bulgaria, treatment of children with pituitary GH was introduced in the first specialized center in Sofia by Prof. L. Peneva in the 1980s. [4] Since 1993, Bulgarian children have been treated with rhGH as a pilot treatment in several university centers of the country, including that in

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Pleven for a short period (N. Stanimirova) [5]. A second diagnostic and treatment center was established in 2011 at the St. Marina University Hospital in Varna. During the last nine years, the National Health Insurance Fund (NHIF) has fully reimbursed the diagnosis and treatment of pathological short stature. The number of pediatric endocrinologists is increasing, and the hospital diagnostics in specialized medical establishments are well organized and reimbursed by the NHIF. Based on the nature of the diagnosis, the distribution of children treated with GH should be even in the country. However, few patients from Central North Bulgaria and in Pleven have been treated with GH until 2018. The children from our region had limited access to health services related to such a fundamental issue for their development as growing tall, which created inequality compared to other Bulgarian children.

The diagnoses for which the NHIF in Bulgaria reimburses GH treatment are GHD (hypopituitarism), Turner syndrome (TS), Prader-Willi syndrome (PWS), and children with chronic renal failure and growth retardation. With the help of donated funds in Bulgaria, children born small for gestational age (SGA) are also treated with GH, without postnatal catch-up in growth, and children with Silver-Russell syndrome (SRS) and children with Noonan syndrome. These are rare diseases with an established frequency and difficult diagnosis [6]. Until establishing the Growth Center, single patients with growth disorders were admitted to the Pediatric Clinic, but no diagnostic tests or treatment with GH were performed.

The diagnosis of GHD is based on data from auxological examination and clinical phenotype, hormonal status, and specific tests for stimulated GH secretion [7]. Most often, children with GHD present with growth retardation after three years of age. Treatment with GH leads to catching up in growth and reaching their target height. In addition to accelerating growth, GH positively affects lipid, protein, and carbohydrate metabolism and bone mineralization [8].

A Specialized Commission issues the protocol for treatment with GH in a medical institution for hospital care, which has concluded a contract with the NHIF. Thanks to the Partnership Program from 01.06.2019, such a commission has been established at the Clinic of Pediatrics in G. Stranski University Hospital - Pleven.

Patients and Methods

The center for diagnosis and treatment of children with growth disorders (Growth Center for short) was started in March 2018 in the Clinic of Pediatrics, and active collaboration with a recognized expert Center for Rare Endocrine Diseases in Varna (VECRED) at St. Marina University Hospital, with experience in the diagnosis and treatment of GH. We were also supported by the project of the Bulgarian Pediatric Association “Partners4Growth”.

During the study, 53 children with a short stature <-2 SDS, selected in an outpatient setting were referred to the newly established Growth Center. All patients underwent a physical examination to diagnose hitherto undiagnosed chronic diseases and syndromes. Information was collected about short relatives, and the growth process of the parents was assessed.

The rules for measuring height and body weight were followed with certified instruments - height was measured with an accuracy of 0.5 cm, and body weight with an accuracy of 100 g [9]. According to Tanner’s formulas, target height (TH) was calculated for each of the studied children compared to their midparental height. Pubertal development was assessed and staged on the Tanner scale (1970). The standard deviation score (SDS) for height and weight was calculated using the application of the Centers for Disease Control at the US National Institutes of Health from 2000 (peditools.org/growthpedi), as well as according to the local standard of N. Stanimirova 2007 [10]. Body mass index (BMI) is calculated by the standard formula: BMI = body weight (kg) / height (m^2) [11].

The diagnoses of isolated GHD (IGHD), multiple pituitary hormone deficiencies (MPHD), Turner syndrome (TS), Prader-Willi syndrome (PWS), Noonan syndrome were made in clinical conditions based on a combination of history, physical status, axiological assessment, imaging studies, basal and stimulated hormone tests, and genetic research. Patients with IGHD and MPHD were followed for six months before performing diagnostic tests. X-ray of the left wrist to determine bone maturation was assessed according to Greulich and Pyle atlas. In some of the patients, a genetic examination and

imaging of the pituitary area were performed. Two different stimulation tests for maximal GH secretion were performed on each child on two consecutive days according to the methodology described by Ranke (2011) [7]. Insulin-induced hypoglycemia (IIH) test, glucagon test (GT), and clonidine test were used.

Patients with proven IGHD, MPHD, TS, and PWS who initiated rhGH treatment were followed at 3-6 month intervals following the NHIF algorithm. A detailed conversation was held about the children's condition at each visit, aiming to identify side effects from treatment and compliance. A thorough physical examination was performed to assess height and weight, growth rate, and weight gain. All children underwent biochemical, hormonal, and imaging studies following the requirements of the NHIF.

Results

The mean age of the 53 young children referred to the Growth Center was 9.7 ± 4.5 years (0.9-17.8 years, median 10.3 years), without significant gender difference (p> 0.05), residing mainly in cities.

During the study period, a total of 11 children (20.8%) started treatment with rhGH - 10 children diagnosed with IGHD (n=5), MPHD (n=2), TS (n=1), and PWS (n=2), as well as and one patient with Noonan syndrome, whose therapy is provided by the Bulgarian Christmas charity initiative. In terms of gender, there is no significant difference (6 boys and five girls) (p> 0.05). However, in the group of children with IGHD and MPHD, in contrast to the total number of treated children (n=11), male dominance was observed (n=5, 71.4%), with only two girls (1 with congenital MPHD and 1 with organic MPHD after surgical treatment of craniopharyngioma) were treated with rhGH. All children were in the prepubertal stage.

GH treatment was initiated immediately after diagnosis, at a mean age of 8.1 ± 4.4 years. The youngest patient was 11 months old, and the oldest - 12 years and three months. (Figure 1)

Bone age (BA) before starting treatment with rhGH was 5.3 ± 3.5 years, lagging behind the chronological average of 2.6 ± 0.7 SDS years.

The diagnosis was made later than the age at which growth retardation had been observed in the family, averaging 5.5 ± 3.6 years. This delay was more significant in children with a history of familial short stature and rural residence. Stimulation tests for maximal GH secretion were performed in 6 of the patients with suspected GHD and in 1 patient tested for GHD without confirmation of the diagnosis. The side effects

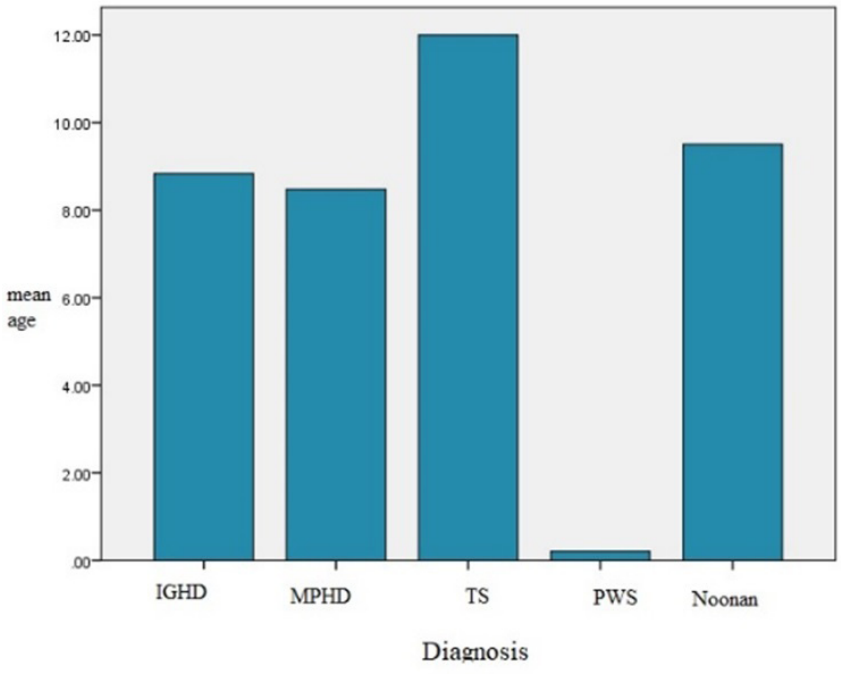

Figure 1. Average age at diagnosis

of pharmacological stimuli in our patients were nausea and abdominal pain during GT (n=4), drowsiness in the clonidine test (n=1), and drowsiness, pallor, and hunger during IIH (n=3).

MRI demonstrated pathology of the hypothalamic-pituitary area (ectopia of the pituitary gland and thinned infundibulum) in one patient in the group of children with IGHD and MPHD. One patient with TS was diagnosed by cytogenetic examination.

Follow-up of GH therapy

The follow-up was 18 months (March 2018 - September 2019). During this period, ascending growth curves were seen in all the children treated at the center, with an average growth rate for the first year of treatment of 10.3 ± 7.7 cm. The most pronounced acceleration in growth (catch-up growth) was observed in a patient with congenital MPHD and the two patients with PWS who started treatment before one year. The average growth rate for the whole group of children with GHD was 10.18 cm, and for those with PWS, TS, and Noonan syndrome - 15.7 cm.

We found a decreasing degree of lag in linear growth (from - 7.1 SDS to +0.4 SDS). Figure 2 presents the SDS graph of growth after initiation of GH treatment in 10 children. Patient 11 was

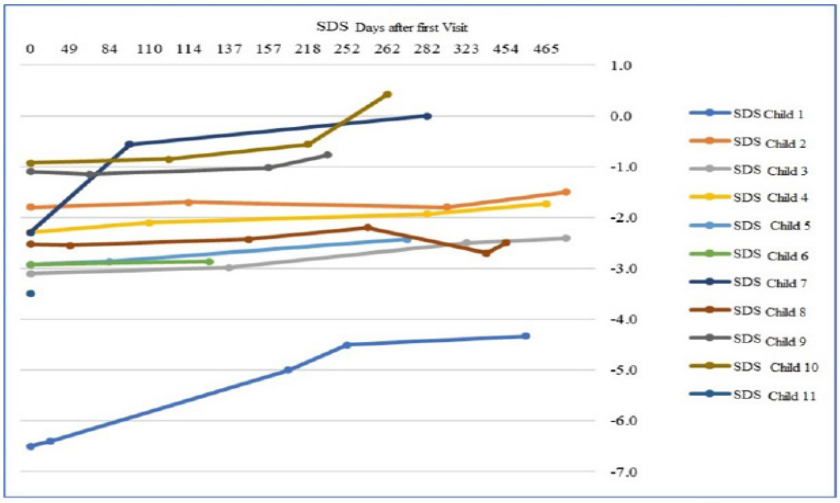

Figure 2. Changes in SDS for height after initiation of GH treatment

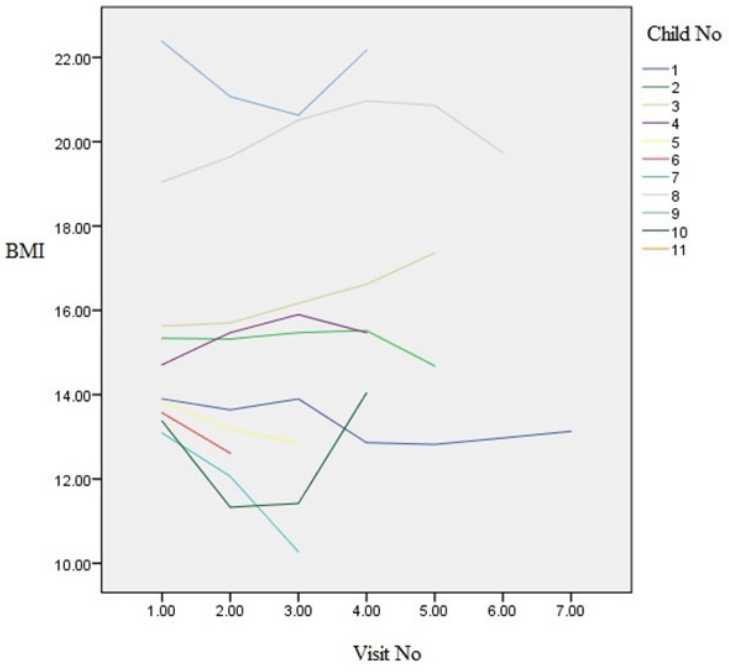

Figure 3. Change in BMI after initiation of GH treatment

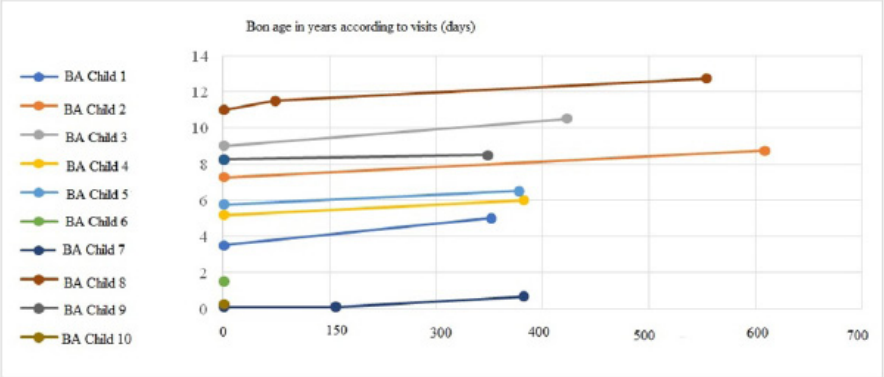

Figure 4. Dynamics in BA in children treated with GH

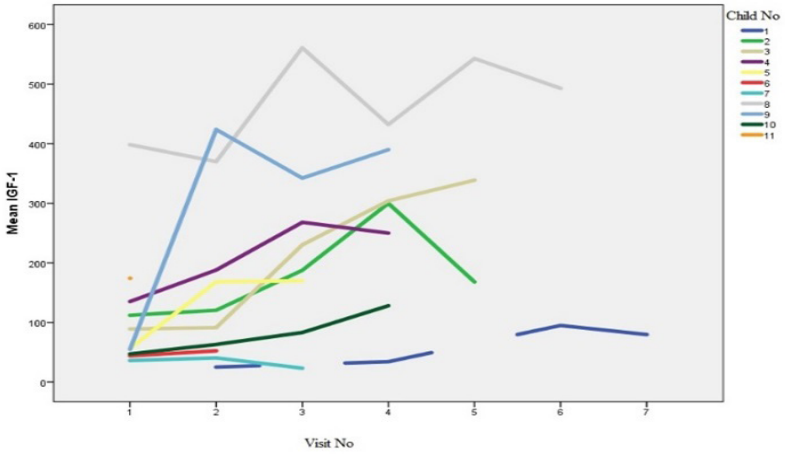

Figure 5. Dynamic monitoring of IGF-1 levels in GH-treated patients

enrolled shortly before the end of the study, and no growth rate was observed.

Changes in body weight and BMI were also observed in patients starting GH therapy. Except for two children, all the others (80%) had a decreased BMI, with a change in mean BMI of 15.5 kg/m^2±2.8 SDS at the start of therapy to 15.0 kg/m^2±3.2 SDS and 15.2 kg/m^2±3.6 SDS, respectively, after six months and 12 months of treatment. (Figure 3)

In all children treated with GH, the BA was assessed about a year after treatment initiation. The results presented in Figure 4 showed a slight to moderate acceleration in bone maturation in all of them.

GH therapy monitoring included both auxological parameters (height and body weight, BMI) and IGF-1 levels. Figure 5 shows the change in IGF-1 levels in the monitored patients after initiation of GH treatment. An increase in the absolute value of IGF-1 was reported in all, without exceeding the age reference limits.

During the study period, no severe side effects from GH were observed in the treated children, except for a short-term edematous syndrome in one patient during the first month of therapy.

Discussion

For the first time, this study presents the results from the treatment of children with GH in a newly established Growth Center in Pleven, in active partnership with a recognized expert center. The purpose of this collaboration was the faster and better introduction of diagnosis and treatment of children with various forms of short stature, which had not been performed before at the University Clinic of Pediatrics, despite the available resources of specialists in pediatric endocrinology and infrastructure. The improved diagnostic and treatment process at the Growth Center created an opportunity for easy and timely access to treatment for children with rare diseases and growth disorders from the region, whose group includes GHD, TS, PWS, Noonan's syndrome.

The mean age of our patients diagnosed with IGHD and MPHD was 8.8 ± 4.3 years and 9.5 ± 0.1 years, close to that reported in the literature [12]. However, in numerous publications, it has been shown that earlier diagnosis of GHD and, respectively, early treatment with GH determine the achievement of a more significant improvement in the patient's final height [13-15]. These data support our goal of achieving timely diagnosis in children with growth retardation from the Pleven region and lowering the age at the beginning of treatment with GH.

We did not find significant gender differences in all diagnoses, except for congenital forms of IGHD or MPHD, where males dominated, and there was only one girl (16.6%). These data are in agreement with those reported by Thomas et al.[16], where boys diagnosed with IGHD and MTD were 2 to 4 times more than girls. Similar results have been reported by Lindsay et al. [17].

In almost all the children monitored at the Center, the diagnoses and treatment were delayed compared to the observed growth retardation time. Only the children with PWS were diagnosed soon after birth, but GH treatment was started at 11 months. Early initiation of therapy (before six months of age) is widely disclosed in available consensus and authorized by the NHIF. [18]. The reason for this delay is the lack of access to specific medical care offered before the establishment of the Growth Center in Pleven.

A patient with TS was diagnosed by cytogenetic examination, whose diagnosis, though nine years later from the observed lag in growth, could have still been missing without screening tests at the newly established center. The late diagnosis of the patient with TS did not differ from the literature data. It shows the broad scope of future actions to raise awareness of the problem among physicians and other health professionals and parents, and society. Such awareness is the only way to achieve an earlier and timely diagnosis and, consequently, better treatment [19]. Our data corresponds to the published world statistics for relatively late diagnosis in girls with TS, at 15 years on average [20]. Also, the delay in diagnosing diseases with pathological short stature is more significant in children with a history of familial short stature and children from rural areas. Providing quality pediatric care in villages and small towns remains an unresolved issue.

The way we used MRI imaging in children with short stature coincided with the world recommendations for MRI of the hypothalamic-pituitary area [21]. This study allowed us to detect an anatomical defect of the pituitary gland in one of the treated children with GHD, which focused our attention on implementing periodic screening for concomitant hormonal deficiencies and the development of MPHD.

After diagnosing at the Center for Growth of children with IGHD, MPHD, and syndrome diagnoses with growth retardation, GH treatment was started on time. The dosage of GH used was according to the recommendations in the most recently published world guideline [8,22]. We aimed at using the lowest effective dose, leading to an appropriate response, expressed in growth acceleration. The initial doses (0.027 - 0.034 mg/kg/d) used in children with GHD were close to those summarized in recent publications and most commonly used in European countries [23]. In all patients, GH treatment resulted in accelerated growth and bone maturation. Follow-up showed good compliance, regular application of GH, al contributing to good results.

In addition to its effect on growth, GH also has an essential metabolic effect. The first reports of significant body composition changes in children with GHD were reported more than 40 years ago[24]. In our patients, the published data were confirmed, and in almost all children treated with GH, weight loss or retention and BMI decreased after initiation of treatment. According to literature data, treatment with GH leads to a reduction and normalization of the percentage of body fat within the first six months from the start of treatment, which has a beneficial effect on lipid metabolism [25]. Patients with PWS who started early treatment with GH (before two years of age) have been shown with improved body composition, motor function, height, and lipid profile, compared to untreated ones [26].

Many studies in children with prepubertal short stature have shown an increase in IGF-1 from baseline after GH initiation. Monitoring of IGF-1 levels is a good indicator of growth in response to GH treatment [27]. The Growth Hormone Research / IGF Society's recommendations are to measure circulating

IGF-1 as part of continuous monitoring and adaptation in GH treatment to avoid above-normal IGF-1 levels [28]. As recommended, IGF-1 was monitored at each visit in patients treated at the Growth Center, with ascending IGF-1 levels within the reference range.

Although short stature in children is less common, the psychological aspect is essential due to the possible stigmatization of a short child. The observed improvement in self-esteem and psychological status, although without the possibility of objectification, agrees with the published data on better self-esteem after treatment with GH [29,30]. We also report less stressful conditions in the parents and their strict control of the therapy.

The Partnership Program proved extremely useful in diagnosing and treating patients with rare diseases and syndromes from the Pleven region. The foundations of referral and collaboration with VECRED were laid. The children were observed and treated in Pleven. Once a year, they visited VECRED for assessment and guidelines for further therapy according to the recommendations for monitoring children with rare endocrine diseases in specialized expert centers. This sustains the team's qualification, saves money and time for families, and ensures the highest follow-up quality.

Conclusion

With the help of a Partnership program at the Clinic of Pediatrics - Pleven, a Growth Center was established. GH treatment was initiated for the children diagnosed with growth problems. So far, there is a significant increase in the number of diagnosed and treated children. Follow-up has demonstrated an acceleration in growth and bone maturation and positive body composition changes without side effects, and all patients have complied with treatment. There is improved psychosocial performance, which guarantees even better achievements in the future.

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