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Original scientific paper

BENEFITS AND CHALLENGES IN CONDUCTING LONG-TERM GROWTH HORMONE THERAPY IN PATIENTS WITH PRADER-WILLI SYNDROME

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The purpose of this report is to comment the results from long-term growth hormone (GH) treatment of Bulgarian patients suffering from rare genetic disease - Prader-Willi syndrome (PWS) with reference to the age, body composition, complications and genetic etiology. Statistical analysis was performed by ANOVA with post hoc Kruskal-Wallis test and Dunn's multiple comparison tests. In 90% of the patients maternal uniparental disomy (mUPD) was found to be the cause of the disease. No cases due to imprinting defects are found. The BMI data shows no statistically significant difference between BMI at diagnosis (21.850), at the beginning of the GH therapy (21.852) and current BMI (24.09) - measured under the GH background. Early GH treatment allows to overcome arising obstacles in time and to improve the quality of life for PWS children and their families. During the fourteen years study period only ten patients were diagnosed with the disease. Ninety percent (n=9) of the children were found to be with maternal UPD (mUPD) and only one case was due to deletion in 15q11-13. These results are in agreement with other studies in the field which shows the need for reassessment and new robust statistical analysis of the frequency of genetic mechanisms for PWS.

Keywords: PWS, growth hormone, treatment, mUPD.

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INTRODUCTION

Prader-Willi syndrome (PWS) is a rare genetic disorder, originally described by Pradder, Labhart and Willi (PRADER *et al.*, 1956) as a dysmorphic syndrome. Now it is known that PWS results from the absence of paternally expressed genes in the 15q11-13 chromosomal region, which can be due to different genetic mechanisms: *de novo* paternally inherited deletion of the chromosome 15q11.2-q13 region (70% of cases), unbalanced chromosomal abberations in the paternal chromosome 15 with missing 15q11.2-q13 region (1-2% of cases), balanced chromosomal translocation with cleavage site in the 15q11.2-q13 region and physical destruction of PWSCR (Prader-Willi Syndrome Critical Region) (1-2% of cases), maternal disomy 15 or defects in the genomic imprinting centre (25% of cases) (CASSIDY *et al.*, 2012; HADJIDEKOVA *et al.*, 2014).

PWS is a complex genetic disease with distinctive facial dysmorphism and significant cognitive, neurologic, endocrine and behavioral abnormalities. In infancy, it is characterized by weak muscle tone, feeding difficulties and poor growth due to growth hormone (GH) deficiency. Later in the childhood uncontrollable appetite occurs, which is prerequisite for chronic overeating and obesity. Decreased secretion of growth hormone, lack of puberty leap, increased food intake and reduced physical activity, leads to short stature with final average height 155 cm for men and 148 cm for women, body mass index (BMI) above 30 and abnormal body composition with increased fat mass and relative reduction in the muscle mass (CASSIDY, 1997; DONALDSON *et al.*, 1994; HOLM *et al.*, 1993).

The current treatment approaches of PWS are dedicated to the prevention of behavioral problems and uncontrolled obesity, the most serious complications of the syndrome (LAURANCE *et al.*, 1981). Strategies for managing the obesity include constant supervision by parents, restriction of access to food and adjustment of the energy intake to cause weight reduction. However, these actions are without a satisfactory weight control. The most effective strategy in the management of morbid obesity is reported to be the surgical management with gastric bypass - used in the extreme cases only, but it does not provide the improveness in the growth and body composition. Another approach is the pharmacotherapy of the Prader-Willi syndrome (SOPER *et al.*, 1975). Various medicinal products have been tried but the most beneficial effect shows the growth hormone therapy, which leads to an increase in the muscle mass, height, stamina, bone mineral density; improvement in weight distribution and decreasing of body fats (DEAL *et al.*, 2013; GOLDSTONE *et al.*, 2008; SELIKOWITZ *et al.*, 1990; ZLOTKIN *et al.*, 1986).

In this paper, we report our results from GH treatment of ten Bulgarian PWS patients with special reference to the relationships between GH, height, BMI and mUPD. We hope that our experience will contribute to the better monitoring of the PWS, improvement in the current therapeutic approach and revision of genetic subtype proportions.

METHODS

We provide the retrospective study of the long-term treatment of the patients, suffering from PWS. For the statistical analysis one-way ANOVA with post hoc Kruskal-Wallis test and Dunn's multiple comparison tests were used. $P<0.05$ was considered to indicate a statistically significant difference, where the '*' denotes $P<0.05$ and '***' - $P<0.001$. All the data are presented as means with standard deviation (SD) and standard error of the mean (SEM).

The subjects in the survey were 10 Bulgarian patients with PWS, four males and six females, aged between 1 and 17 years. The legal guardians of all hospitalized children have filled and signed Informed consent upon admittance. All procedures used are part of the standard protocol for treatment of PWS in Bulgaria. The risks and benefits of GH treatment were thoroughly discussed with the child's parents before taking the decision for GH pharmacotherapy.

The diagnosis of Prader-Willi syndrome was made by a clinical geneticist, based on dysmorphic features and clinical symptoms and then confirmed by appropriate genetic tests (Fig 1). For optimal treatment results, appropriate nutritional intake and physical activity was recommended. The GH therapy started at a low dose and was gradually titrated to obtain optimal efficacy while minimizing side effects (CARREL *et al.*, 1999). The patients in our study were treated with recombinant GH with the dose of 0.035 mg/kg body weight per day as recommended in the summary of product characteristics. Daily doses of 2.7 mg were not exceeded. GH was administered on a daily basis by subcutaneous injection, since this was considered to impact positively upon patient compliance and reduce the problems with adherence (DUMAS *et al.*, 2006; SMITH *et al.*, 1993).

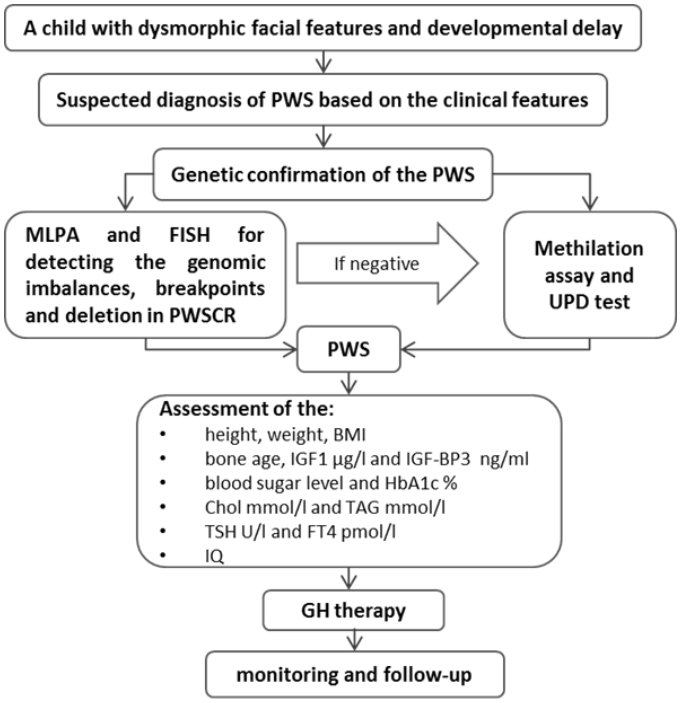

Fig.1. An algorithm applied for the selection and follow up of patients with PWS and assessment of the effect of GH therapy.

The effect of the GH treatment was evaluated in comparison to the normal human parameters for Bulgarian population, Length-for-age and Weight-for-age Charts. The patients were monitored for height, weight, BMI, bone age, IGF1, IGF-BP3, blood sugar level, HbA1c, cholesterol, TAG, TSH, FT4 and IQ (BAKKER *et al.*, 2015; GORANSON, 2011).

RESULTS

The cytogenetic analyses found no chromosomal rearrangements. Surprisingly in 90% of the patients (9 cases) maternal uniparental disomy (UPD) was found to be the cause for the development of PWS. Only one (10%) has developed PWS due to deletion in 15q11-13 chromosomal region. No cases due to imprinting defects were found.

Overall, the results presented below show the data from the mean age at diagnosis of the PWS, the mean age of the beginning the growth hormone (GH) therapy and the mean threatment period (Fig.2A, Table1); the mean data of BMI at diagnosis, BMI at the beginning of the GH therapy and current BMI (Fig.2B, Table 1). The ranges, mean and median values for the parameters used to follow-up the effect of GH treatment are demonstrated in Table 1. The obtained data show that treatment, started before facing of obesity symptoms, gave satisfactory results in terms of keeping normal BMI and the parameters used for physical monitoring.

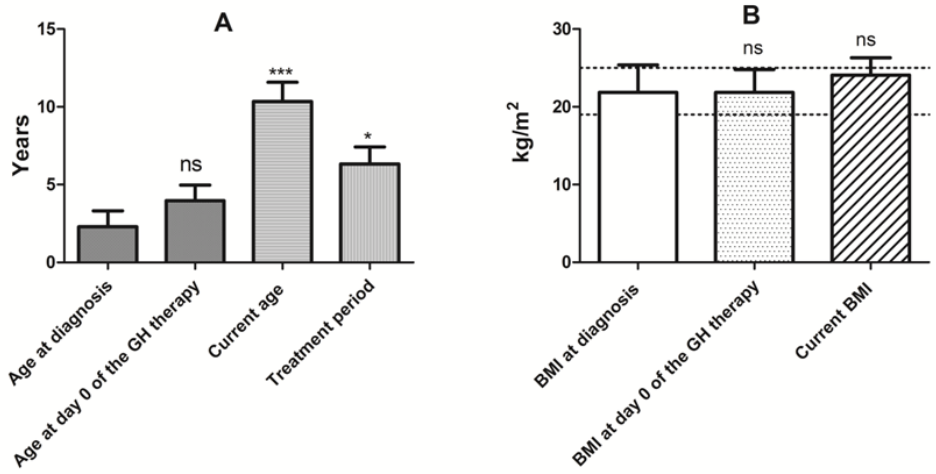

Fig.2. (A) Data of the mean value of age of: diagnosis for PWS, start of GH therapy, current age and treatment period. Significance testing was performed in comparison to the mean age at diagnosis. P<0.05 was considered to indicate a statistically significant difference, where the '*' denotes P<0.05, '***' - P<0.001 and ns – no statistical significance; (B) Data of the mean value of BMI at diagnosis, at the start of GH therapy and current BMI. Significance testing was performed in comparison to the mean value of BMI at diagnosis. ns denotes no statistical significance.

Table 1. Statistical Analysis of the PWS Patients' Data.

	Minimum	25% Percentile	Median	75% Percentile	Maximum	Mean	Std. Deviation	Std. Error	Lower 95% CI	Upper 95% CI
Age at diagnosis (years)	0.3	0.6875	1.5	2.19	11.3	2.293	3.241	1.025	-0.0255	4.612
Age at day 0 of the GH therapy	0.75	1.75	3.455	5.063	11.58	3.974	3.138	0.9923	1.729	6.219
Current age (years)	5.08	7.163	9.915	14.17	16.75	10.34	3.941	1.246	7.521	13.16
Treatment period (years)	2.3	4.413	5.335	7.313	14	6.329	3.427	1.084	3.878	8.78
BMI at diagnosis kg/m2	14.32	16.48	18.74	22.12	49.36	21.85	10.65	3.549	13.67	30.03
BMI at day 0 of the GH therapy	14.32	17.32	18.9	23.34	46.66	21.85	9.276	2.933	15.22	28.49
Current BMI kg/m2	14.79	20.19	22.47	27.65	39.4	24.09	7.045	2.228	19.05	29.13
IQ	25.4	61.23	76.99	86.98	97.4	73.43	21.22	6.712	58.25	88.61
IGF1 µg/l	110.8	148.9	240	310.6	471.2	248.3	110.8	35.02	169.1	327.6
IGF-BP3 ng/ml	2607	3831	5099	5900	7541	4951	1492	471.8	3884	6018
Chol mmol/l	4.09	4.367	4.718	5.481	6.645	4.999	0.8841	0.2796	4.367	5.632
TAG mmol/l	0.575	0.75	1.111	1.434	4.725	1.419	1.228	0.3885	0.54	2.298
Blood sugar mmol/l	4.194	4.539	4.727	5.095	5.463	4.793	0.4069	0.1287	4.502	5.084
TSH U/l	0.8923	1.329	1.788	2.288	3.181	1.883	0.6932	0.2192	1.387	2.379
FT4 pmol/l	12.02	13.1	13.9	15.36	18.77	14.34	1.909	0.6037	12.98	15.71

The table shows the results of statistical analysis of the evaluated parameters during the treatment. The one-way analysis of variance (ANOVA) with subsequent non-parametric Kruskal-Wallis test were used.

The median age at diagnosis of the PWS appeared to be 1 years and 6 months, with range 4 m - 11y 4 m. The median age, at which the children begun the growth hormone (GH) therapy, is about 3 years and a half, with range 9 m – 11y 7 m. The median current age of the children cohort is 9 years and 11 months and the mean treatment period is 5 y 4 m (range 2 y 4 m – 14 y) (Table 1, Fig.2.A). There was only one case of complication for the GH usage - upper airway obstruction and sleep apnea for a period of 2 months. After stopping treatment, breathing improved. Further treatment (six months later) continued without any problem (Patient 5, male Fig.3).

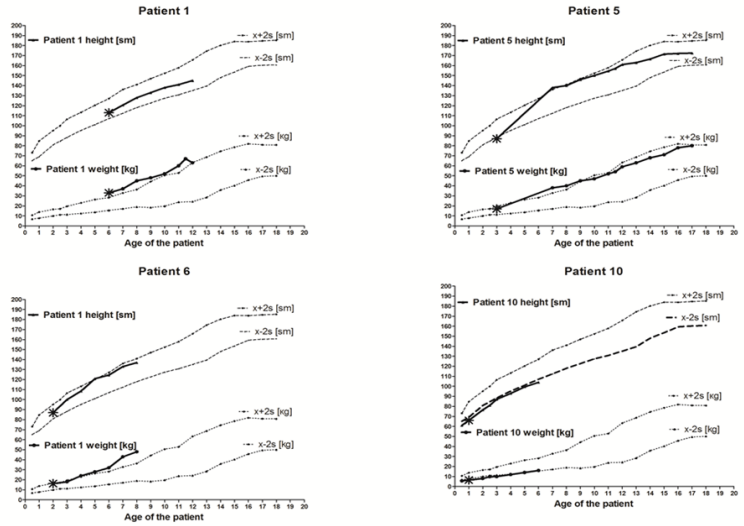

Fig.3. Individual development of boys with PWS demonstrated through height and weight chart. With the star symbol (*) is noted the start of the GH therapy. Dotted lines denoted the normal range [x-2S-x+2S] of length-for-age (upper) and weight-for-age (lower) for male in Bulgarian population.

The data analysis shows no statistically significant difference between the mean age of diagnosis of the PWS and the mean age of the start the GH therapy – which correspond with the fast treatment initiation (Fig 2A), because the general therapeutic approach is to start the GH therapy before the beginning of the symptoms of hyperphagia, obesity and growth retardation. This was not performed only in one patient - Patient 9, due to delayed diagnosis (11y 7m), when the BMI was significantly increased (46.65). The statistically significant difference ($P<0.0001$) between the mean age at diagnosis and current age of the PWS children (Fig.2A) represents a considerably long period of GC therapy. The BMI data also show that there is no statistically significant difference between BMI at diagnosis, BMI at the beginning of the GH therapy and current BMI, measured under the GH background. Moreover, the BMI is within the normal range [19-25]. BMI at diagnosis was 21.85; BMI at the beginning of the GH therapy – 21.85 and the current BMI is – 24.09 (Table 1, Fig.2B).

The Figure 3 and Figure 4 present the individual parameters of growth (height and weight) of the studied children with PWS – boys and girls respectively. The most of the collected data are since the first visit of the child to our hospital. In the majority of cases the therapy with GH starts within a year after the diagnosis of the disease, so generally there was no GH therapy delay. Such a delay was observed only for Patient 4, where the diagnosis was set up at 2y 6m and the treatment starts at 4 y 9m due to low body weight at 2y 6m (14 kg, SDS 0.84) and parental factor.

For the patient No 5 – a 17-year-old boy the treatment with the GH was interrupted twice. Firstly, for the period of four months due to elevated blood sugar level – 6.8 mmol/l (13 years of age) and secondly for 6 months because of elevated level of HbA1c – 6.02% [4.8÷5.9]

(16 years of age). There was progressive scoliosis, which was surgically corrected at 14 years of age. In Case No 8 the GH treatment was interrupted only once for 3 months, again due to elevated blood sugar level and scoliosis. In this patient dislocation of the right hip is also observed.

All of the patients excluding patient 9 have height and weight within the normal range for Bulgarian population. The rates for Bulgarian populations are equal to the rates for the other European populations.

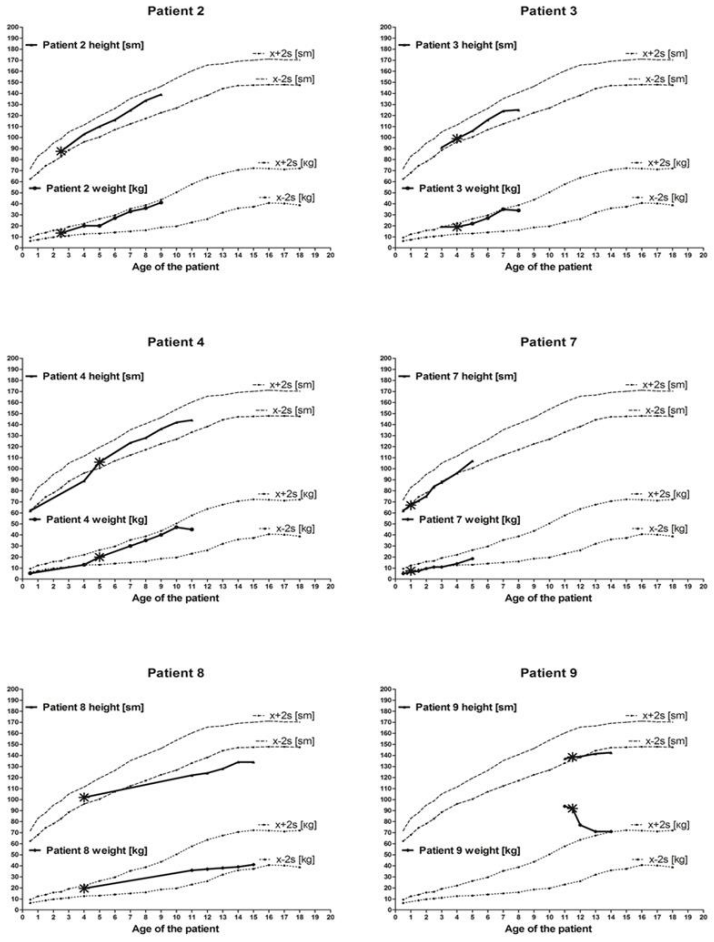

Fig.4. Individual development of girls with PWS demonstrated through height and weight chart. With the star symbol (*) is noted the start of the GH therapy. Dotted lines denoted the normal range [x-2S-x+2S] of length-for-age (upper) and weight-for-age (lower) for male in Bulgarian population

DISCUSSION

To the best of our knowledge there are only 35 children diagnosed with PWS in Bulgaria - data taken from the registries of the two national centers, working with PWS children. There are no other studies from Bulgaria that discuss PWS epidemiology. Although the small number of our cohort (10 patients), 90% from the children were found to be with maternal UPD (mUPD) and only one case was due to deletion in 15q11-13. To the best of our knowledge, there are only few studies that discuss the difference in the genetic background in PWS patients. For example in the studies from MASCARI *et al.,* (1992) and CASSIDY *et al.,* (1997) the frequency of the PWS due to mUPD were found to be 60% (18 out of 30 patients) and 31% (17 out of 54 patients) respectively. WHITTINGTON *et al.* (2007) shows that 50% of studied PWS children are with mUPD (17 out of 34 children). These data is not in accordance with the proportion of mUPD PWS cases in the medical literature, which is thought to be around 25% of the all PWS cases. The higher incidence of UPD is usually attributed to the increasing maternal age, low diagnostic yield for mUPD cases or the increasing share of babies born after assisted reproductive technologies (ART) (CASSIDY *et al.*, 2012; GOLD *et al.*, 2014; HADJIDEKOVA *et al.*, 2014). In our study the mean maternal age at term of mUPD cases was 32.7 (26-41) and no child was born after ART. So these factors do not have an impact on the increased incidence of mUPD in our cohort. Nevertheless, our results, together with the results of the previously mentioned studies, support the need for a review of the proportions of PWS genetic subtypes. While not all of the results were statistically significant, the overall direction of growing trends of mUPD is clearly visible. This shows the need for the set-up of a single register, which will include all diagnosed cases, so to make an accurate statistical analysis.

Our data show that the diagnosis of the PWS in Bulgaria is determined at relatively early age - 1 years and 6 months, followed by the adequate growth hormone (GH) therapy - before the hyperphagia, obesity and growth retardation occur. The median age of GH treatment was initiated at 3y 11m, which is comparably lower than the mean age of 7 y as reported by Takeda *et al.*(2010). Our results are in agreement with the results from the other studies about the improvement of the height and body composition in the PWS patients, if the therapy begun during infancy (AYCAN and BAS, 2014; CARREL *et al.*, 2010). Inadequate diagnosis and monitoring due to untypical clinical picture during infancy, symptoms of growth retardation in the first two years or lack of funding can lead to GH therapy delay (AYCAN and BAS, 2014; DEAL *et al.*, 2013). In our cohort such a delay can be found solely in Case No 9, since the child was addressed late by the general practitioner for diagnosis. Her therapy with GH starts out comparatively late in the life – 11y7m, when the BMI was significantly increased (46.65). Notwithstanding, after 2y 4m treatment, the BMI reduces to 39.4.

The general therapeutic approach to our PWS patients with early treatment, before facing of obesity symptoms, and regular follow-up, gave satisfactory results in terms of keeping normal BMI and the parameters used for the monitoring (Table 1). Moreover, the rates of the BMI at diagnosis, at day 0 of the GH therapy and current BMI are close, within the normal range and the differences between them showed no statistical significance (Figure 2B).

Now it is known about the short term improvements in body composition with growth hormone therapy (PATERSON and DONALDSON, 2003). However, it is still unclear whether these can be sustained in the longer term and unlikely that growth hormone treatment alone will

normalise body composition (MYERS *et al.*, 2000). The positive aspect of the GH therapy for PWS patients in terms of longitudinal growth increase as well as the long-term efficacy of the GH treatment are observed in the review from BURMAN *et al.* (2001). In our cohort the effects of long-term GH therapy can be traced within Case No 5 and Case No 8 with more than 14 and 11 years of therapy respectively. Despite the alleged negative effects of growth hormone treatment described in some cases– increasing the degree of scoliosis and insulin resistance, the beneficial effect from the GH therapy is obvious (CARREL *et al.*, 2010; MYERS *et al.*, 2007). The patients have no obesity; BMI is 26.8 in the first case and 23.2 in the second; the height in the Patient 5 is within the normal range (0.15 SDS), the height in Patient 8 is below the norms for the age (-4.54 SDS), but with the clear growing tendency (Fig.3 and Fig.4).

The average intelligence quotient (IQ) in our PWS patients is determined as 73.43 in a range of 25.4 – 97.4. Indeed in the majority of them the IQ was 10 to 15 points lower in the GH therapy initiation day than the current IQ, which corresponds to the data from MYERS *et al.* (2007) and FESTEN *et al.* (2008). In one girl the current IQ score was decreased and one girl shows the same level of intiligence. Furthermore, we cannot comment if there is the relationship between the GH treatment and the IQ level, because of the difficulties of mental deficiency assessment due to the hypotonia in the infancy and generally the children with higher muscle tone are manifested with higher IQ. However, we think that the mobile and good physically developed children with PWS have cognitive benefits according to the severely obese, immobile children.

Based on our study we can make an inference that early diagnosis, early GH treatment and long lasting GH therapy improve the quality of life for children with Prader-Willy syndrome and their families, regardless the side effects of GH therapy. But in conclusion we can say that reassessment of the frequency of genetic mechanisms for PWS is critical because it changes the approach to diagnosis and therapeutic response. For this purpose, it is advisable to create a unified database where all diagnosed cases should be reported and a new robust statistical analysis should be performed.

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PREDNOSTI I IZAZOVI U PRIMENI DUGOROČNE TERAPIJE HORMONOM RASTA KOD BOLESNIKA SA PRADER-WILLI SINDROMOM

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Izvod

Svrha ovog rada je da komentariše rezultate dugoročnog lečenja hormonom rasta (GH) bugarskih pacijenata koji pate od retke genetske bolesti - Prader-Willi sindroma (PVS) u odnosu na starost, sastav tela, komplikacije i genetsku etiologiju. Statistička analiza je izvršena ANOVA post-hoc Kruskal-Valis-ovim testom i Dunn-ovim višestrukim uporednim testovima. Kod 90% bolesnika otkriveno je da je uzrokovana bolest uniparentalnom disomijom (mUPD) majke. Podaci BMI ne pokazuju statistički značajnu razliku između BMI u dijagnozi (21.850), na početku GH terapije (21.852) i trenutnog BMI (24.09) - mereno pod GH pozadinom. Rani GH tretman omogućava prevazilaženje nastalih prepreka u vremenu i poboljšanje kvaliteta života dece sa invaliditetom, ali i njihovih porodica. Tokom četrnaestogodišnjeg perioda ispitivanja samo je kod deset pacijenata dijagnostikovana bolest. Otkriveno je da je devedeset procenata (n = 9) dece s UPD-om majke (mUPD), a samo jedan slučaj je nastao zbog delecije 15q11-13. Ovi rezultati su u saglasnosti sa drugim studijama u toj oblasti koje pokazuju potrebu za ponovnom procenom i novom robusnom statističkom analizom učestalosti genetskih mehanizama za PVS.

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