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A Case Series Study on Growth Hormone Therapy in Children with Prader-Willi Syndrome in Portugal

Estudo de Série de Casos sobre Terapia com Hormona de Crescimento em Crianças com Síndrome de Prader-Willi em Portugal

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ABSTRACT

Introduction: Prader-Willi syndrome is a multisystemic genetic disorder associated with shorter adult height. Nowadays, all paediatric Prader-Willi syndrome patients are considered for growth hormone treatment. We present the experience of this treatment at a Portuguese paediatric endocrinology unit and intend to emphasise the importance of creating a follow-up national network of these patients.

Material and Methods: Longitudinal, retrospective, analytical study of Prader-Willis syndrome patients using data between 1989 and 2021. Growth hormone therapy was offered to eligible patients. The analysis included all Prader-Willis syndrome patients, with a comparison between treated and untreated patients; a longitudinal analysis of patients receiving growth hormone therapy (baseline, 12 and 36 months of follow-up) was also carried out. The statistical analysis was carried out using STATA® v13.0.

Results: Out of 38 patients with Prader-William syndrome, 61% were male. The median age at diagnosis was four months and 61% received growth hormone therapy. The patients who reached adulthood, or 18 years old, had a median near-adult height, Z-score of −2.71, and their median body mass index indicated class 2 obesity, regardless of growth hormone therapy. Patients had a lower body mass index in the growth hormone group (35 *vs* 51 kg/m^2, $p < 0.042$) near-adult height.

Conclusion: This case series represents the first national study that included patients on growth hormone therapy after the National Health Service started supporting the treatment for Prader-Willi syndrome patients and supports its use, reinforcing the positive effects on growth and body mass index. Longer follow-up studies are needed to analyse the effect of growth hormone on patient metabolic profiling, body composition and cognitive level.

Keywords: Child; Human Growth Hormone/therapeutic use; Portugal; Prader-Willi Syndrome/drug therapy

RESUMO

Introdução: A síndrome de Prader-Willi é uma doença genética multissistémica associada a baixa estatura. Atualmente, todos os doentes pediátricos com síndrome de Prader-Willi são candidatos a terapia com hormona do crescimento. Apresentamos a experiência desta terapêutica numa unidade de Endocrinologia Pediátrica portuguesa e realçamos a importância de criar uma base de dados nacional de seguimento destes doentes.

Material e Métodos: Estudo longitudinal, retrospetivo e analítico de doentes com síndrome de Prader-Willi utilizando dados entre 1989 e 2021. A terapia com hormona de crescimento foi administrada aos doentes elegíveis. Foi realizada análise de todos os doentes com síndrome de Prader-Willi, com comparação doentes tratados/não tratados; foi também realizada uma análise longitudinal dos doentes sob hormona de crescimento (início/12/36 meses de seguimento). O tratamento estatístico foi realizado com recurso ao STATA® v13.0.

Resultados: De um total de 38 doentes com síndrome de Prader-Willi, 61% eram do sexo masculino. Idade média de diagnóstico quatro meses e 61% sob hormona de crescimento. Os doentes que atingiram a idade adulta apresentaram um *Z-score* de mediana de estatura alvo de -2,71, e índice de massa corporal obesidade nível 2, independentemente da terapêutica com hormona de crescimento. Os doentes apresentaram um índice de massa corporal menor no grupo tratado com hormona de crescimento (35 *vs* 51 kg/m^2, $p < 0,042$).

Conclusão: Este estudo de série de casos de doentes com síndrome de Prader-Willi tratados com hormona de crescimento é pioneiro a nível nacional desde a comparticipação deste tratamento pelo Sistema Nacional de Saúde português e apoia esta terapêutica, reforçando os seus efeitos positivos no crescimento e índice de massa corporal. Serão necessários estudos com seguimento mais prolongado para analisar o seu efeito no perfil metabólico, composição corporal e cognição.

Palavras-chave: Criança; Hormona do Crescimento Humano/uso terapêutico; Portugal; Síndrome de Prader-Willi/tratamento farmacológico

INTRODUCTION

Prader-Willi syndrome (PWS) is a multisystemic genetic disorder that occurs in approximately 1/10 000 – 30 000 live births.[1] The prevalence of the disorder is similar in both males and females.[2] PWS is associated with a loss of expression of paternal alleles in the PWS region of chromosome 15.[3] In 70% of cases, PWS is caused by a non-inherited paternal deletion in the region 15q11-q13. Twenty-five per cent occur by maternal uniparental disomy of the chromosome (two chromosome 15 inherited from mother and none chromosome 15 inherited from father), 15.3% by genomic imprinting defects, and the last 2% of cases are caused by rare translocations.[3] In the past, the diagnosis

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was usually made only after the onset of hyperphagia and obesity – the most common features of this syndrome – but currently it is frequently diagnosed during the neonatal period with confirmation by a genetic test.[4]

The clinical signs and symptoms of PWS vary by age group. During pregnancy, it is not uncommon to detect some abnormalities such as decreased foetal activity, polyhydramnios and abnormal position of the extremities (elbows in flexion and feet in dorsal extension).[2] During the neonatal period and the first months of life, the most common features are severe hypotonia, feeding difficulties, weak crying, growth retardation, genital hypoplasia (cryptorchidism, scrotal and clitoral hypoplasia), among many other signs and symptoms.[2] Hyperphagia and subsequent obesity (unless a restrictive diet is implemented) are the main characteristics of these patients during childhood. Other common findings are decreased muscular mass, increased body fat, developmental delay, temperature instability, decreased pain sensitivity, respiratory problems such as central or obstructive apnoea, scoliosis and behavioural problems such as hiding or stealing food, as well as taking food out of the trash.[1,2] Adolescence is a period characterised by compulsive eating and an increase in weight with a high prevalence of morbid obesity and related complications such as obstructive sleep apnoea syndrome, *cor pulmonale*, diabetes *mellitus*, atherosclerosis, hypertension and hepatic steatosis.[1,2] Neurodevelopmental and psychiatric features such as cognitive impairment, skin picking, maladaptive behaviour including a high propensity to psychosis and self-injury may be seen.[1,2] All these characteristics plus the delayed onset of puberty seem to be related with a complex hypothalamic dysfunction.[1] A typical pattern of growth may be noted, with approximately half of the newborns being small for gestational age, with a later decline in growth velocity culminating in a shorter adult height.[1]

In the early 1990s, a treatment for PWS patients was recommended for those with confirmed growth-hormone (GH) deficiency.[2] Human recombinant GH was introduced with the aim of improving linear growth, body composition, and bone density in children with PWS. Treatment not only improved the lipid profile and measures of physical performance but also benefitted cognitive and motor development. Currently, children with PWS should all be considered for treatment with GH without a prior need to test for GH deficiency, provided they meet the clinical criteria for growth failure. Situations that preclude starting therapy are related to comorbidities such as severe obesity, uncontrolled diabetes *mellitus*, untreated severe obstructive sleep apnoea (OSA), active cancer, non-alcoholic hepatitis, psychosis and severe scoliosis.[2,4] With the purpose of excluding these conditions, PWS patients are required to have normal findings upon otorhinolaryngology and orthopaedic examination and a polysomnography test prior to starting therapy.

Until 2010, due to a lack of coverage from the National Health Service (NHS) in Portugal, GH treatment for PWS children would only be given to those with confirmed GH deficiency. Since then, the Portuguese NHS has fully sponsored GH treatment for all eligible PWS patients after the approval of an expert committee.

Regarding the start of GH therapy, evidence suggests that greater effects are seen in the first years of life, thus recommending the introduction of therapy as early as four to six months of age and before age of two.[5] Consensus guidelines recommend starting GH at a dose of 0.35 to 0.5 mg/m^2/day for infants and children based on their body surface area. Subsequent increments in dosage should be made up to approximately 1 mg/m^2/day, titrating dosage to achieve an optimal IGF-1 target in the upper part of the normal range for age.[5]

Once treatment has been started, a close follow-up of comorbidities should be kept, particularly if patients develop intercurrent upper respiratory tract infections or increased obstructive symptoms. Suspension of treatment should be considered if marked worsening of obesity, OSA, metabolic profile or scoliosis occurs.[6]

Given the confirmed benefits of GH therapy in children with PWS, we present a case-series study on the experience of GH treatment in PWS patients at a Portuguese paediatric endocrinology unit of a tertiary hospital. Furthermore, we intend to emphasise the importance of creating a network for the follow-up of PWS patients at the national level.

MATERIAL AND METHODS

Study design and sample

A longitudinal, retrospective, analytical study was performed at a paediatric endocrinology unit of a tertiary hospital in Lisbon. This study included 38 patients with the diagnosis of PWS. GH therapy was offered to eligible patients. Clinical data were collected by reviewing patient medical records from 1989 to 2021.

The study was divided into two sections. The first addressed clinical data at the point of PW diagnosis, comorbidities, growth patterns at birth and inclusion criteria for the start of GH therapy. Growth pattern standards at birth were obtained by using the Fenton growth charts.[7] A comparison between the subgroups of treated and untreated patients was also performed.

The second section comprised a longitudinal analysis of growth patterns and laboratory markers on lipid profiling in patients receiving GH therapy. Clinical and laboratory data were collected at the beginning of GH therapy (baseline) and then at 12 and 36 months of follow-up. Intention-to-treat was applied. Whenever significant comorbidities were seen during GH treatment, patients were

discontinued from therapy. Growth standards in this section were obtained using the World Health Organization growth reference charts.[8] The predicted child's near-adult height based on mid-parental height was calculated using Tanner's standards of growth. Laboratory reference values for lipid profiling were applied according to the NCEP/NHANES III study,[9] in which borderline values of total cholesterol levels range from 170 - 190 mg/dL, triglycerides 75 - 129 mg/dL, LDL cholesterol 110 - 129 and HDL cholesterol 40 - 45 mg/dL.

Data analysis

A descriptive analysis was initially performed and followed by a bivariate analysis comparing patients on or off GH therapy. Continuous data with a normal distribution were presented as mean ± standard deviation, and group comparisons were performed using a Student's *t*-test. Continuous data with non-normal distribution were presented as median with interquartile ranges and compared across groups using the Wilcoxon rank-sum test. Categorical variables were presented as percentages and compared across groups using a Pearson chi-square test.

We next proceeded to use descriptive longitudinal analysis to compare growth patterns and the lipid profiling work-up from the baseline up to 36 months after the beginning of GH therapy. Two-sided *p*-values < 0.05 were used for statistical significance. Statistical analysis was conducted using STATA® v13.0.

RESULTS

Baseline characteristics

Of the 38 patients with PWS, 61% were male. The median age at diagnosis was four months (IQR 1 - 18), and the most commonly described genetic anomalies were maternal uniparental disomy (50%) followed by paternal deletion of chromosome 15 (32%). The most common clinical findings in these patients were hypotonia (37/38), feeding disturbances (23/38), undescended testis (15/38) and neurodevelopmental impairment (10/38); [see Appendix 1, Table 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/17559/Appendix_01.pdf)]. At birth, the mean gestational age was 37 ± 3 weeks and both weight and height averages were within normal standards (Table 1). Patients' comorbidities varied widely but the most frequently assessed were OSA (13/38), cognitive impairment (13/38), aggressiveness/impulsiveness disorders (10/38) and undescended testis (8/38); [see Appendix 1, Table 2 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/17559/Appendix_01.pdf)]. From all the PWS children, 23 (61%) were deemed eligible to receive GH therapy. The average age when beginning therapy was 9.8 ± 4.9 years. The patients who reached adulthood, that is, 18 years old, within the time of the study had a median near-adult height, Z-score of −2.71 (IQR −3.34; −2.00), and their median body mass index (BMI) indicated class 2 obesity (37.6 kg/m^2) regardless of GH therapy (Table 2).

Table 1 – Clinical characteristics of PWS patients (n = 38)/PWS patients on GH therapy (n = 23)

Sex, %	
Female	39.5
Male	60.5
Gestational age, weeks	37 ± 3
Birth weight, Z-score	−1.25 ± 0.64
Birth height, Z-score	−0.64 ± 0.93
Age at diagnosis, months	4 (1;18)
Genetic abnormalities, %	
Maternal uniparental disomy	50.0
Paternal deletion of Chr. 15	32.3
Unknown	17.7
Age at beginning of therapy, years	9.8 ± 4.9
Dose of GH, mg/m^2	
Baseline	0.28 ± 0.18
12-months	0.56 ± 0.25
36-months	0.52 ± 0.24
BMI at beginning of adulthood (18 years-old), kg/m^2	37.60 (31.70; 43.20)
Near-adult height, Z-score	−2.71 (−3.34; −1.99)

Data are reported with mean +/-standard deviation, or median and interquartile range (IQR). Categorical variables were presented as percentages.

Table 2 – Bivariate analysis comparing Prader–Willi patients according to GH therapy

	Patients w/o GH therapy (n = 15)	Patients with GH therapy (n = 23)	*p*
Age at diagnosis (months)	3.5 (1; 26)	4 (1 – 18)	ns
Sex (male, %)	46.7	69.6	ns
Gestational age (weeks)	39 (35; 40)	36 (34 – 39)	0.047
Birth weight, Z-score	−1.53 (−1.93; −1.20)	−1.07 (−1.44, −0.70)	0.031
Birth length, Z-score	−1 (−2.10; −0.50)	−0.15 (−0.80; 0)	0.007
Body mass index at adult age (kg/m^2)	50.7 (38; 58)	35 (30; 41)	0.042
Difference between mid-parental height and near-adult height (cm)	19.12 ± 11.59	13.97 ± 8.27	ns

Data are reported with median + interquartile range (IQR) and mean ± standard deviation. Group comparisons in non-normal data were performed using Wilcoxon Rank sum test, while in normal data Student *t*-test was used. Categorical variables were presented as percentages and compared across groups using a Pearson chi-square test.
ns: non-significant

Bivariate analysis

At the bivariate level, although there were no significant differences between groups regarding gender, a higher trend towards male patients was noted in the GH therapy group (70% *vs* 40%). Conversely, significant findings were found in the GH therapy group, with these patients being more premature (36 weeks *versus* 39 weeks, $p < 0.047$) and having better Z-scores in weight and height at birth (although still within normal standards). We also found that patients who had reached their final height had a significantly lower BMI in the GH group (35 *vs* 51 kg/m^2, $p < 0.042$). In the group of patients who reached the final height, those who had been on GH therapy differed less from their mid-parental near-adult height (13.90 *vs* 19.10 cm), though the results were not statistically significant (Table 2). In our sample, 14 of 23 patients treated with GH reached their final height, whereas five of 15 untreated patients reached their final height.

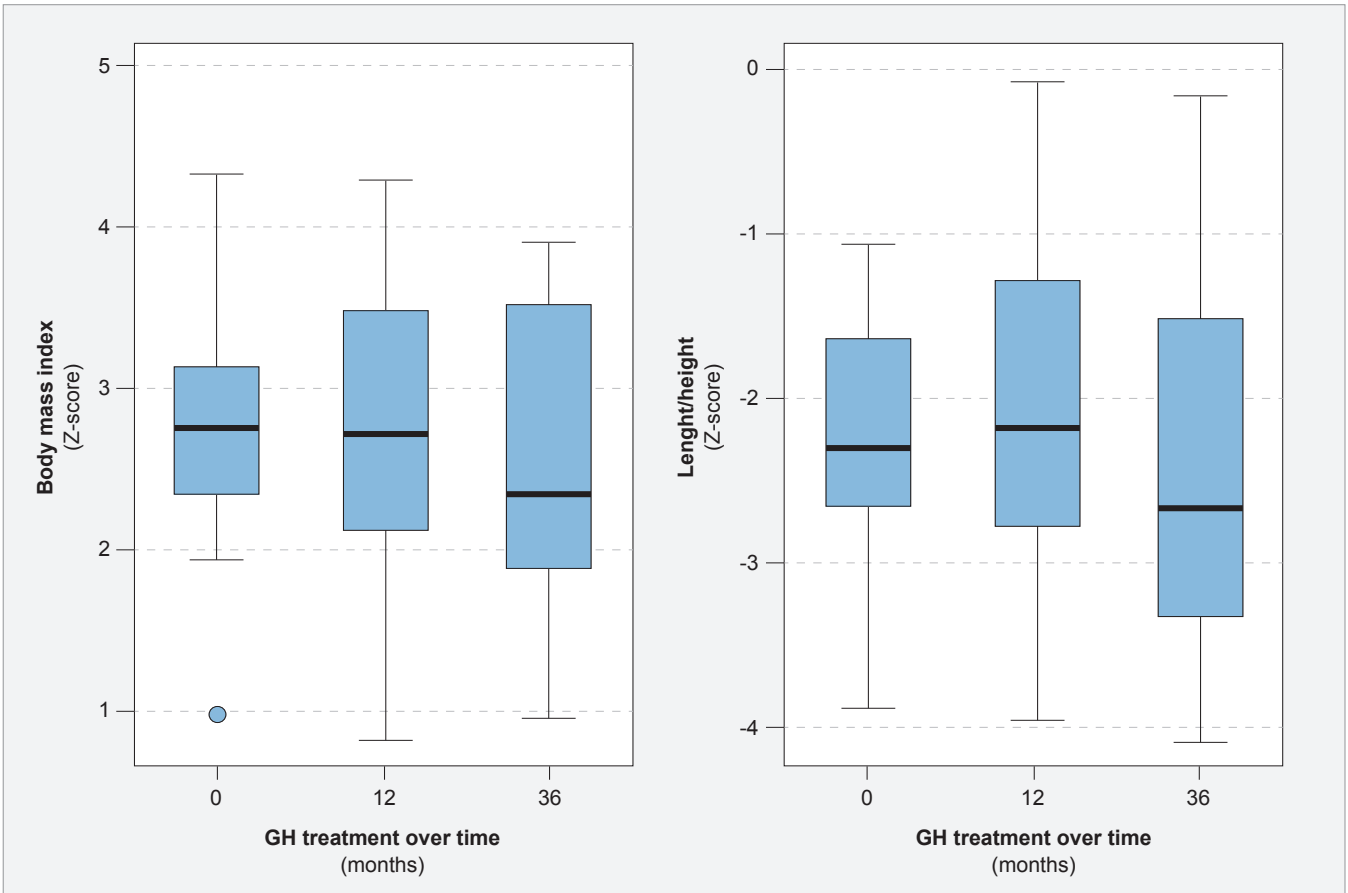

Figure 1 – Body mass index and length/height variations in PWS patients treated with GH

Longitudinal descriptive analysis: GH therapy group

In those who were treated with GH, the average age at the beginning of therapy was 9.8 ± 5 years. As per the protocol, GH was incrementally increased over time with a starting mean dosage of 0.28 ± 0.20 mg/m²/day, increasing to 0.52 ± 0.24 mg/m²/day at 36 months. Although the variables examined did not yield significant differences at the different time points of consultation, some considerations were noteworthy. In particular, BMI Z-scores seemed to follow a downward trend over time (2.76 to 2.35), whereas the trend in height leaned towards a worsening short stature (−2.30 to −2.76), as seen in Fig. 1. Regarding the lipid profile workup, changes over time in total cholesterol, LDL-cholesterol and triglycerides appeared to follow an upward trend (see Table 3), although values were still within the reference range, as seen in Figs. 2 and 3. In contrast, median HDL cholesterol values seemed to be falling over time.

Of the 23 patients who underwent GH therapy, eight

Table 3 – Longitudinal analysis of growth characteristics and lipid workup of PWS patients that were started on GH therapy

	Baseline (n = 23)	12-month follow-up (n = 18)	36-month follow-up (n = 15)	*p*
BMI Z-score	2.76 (2.34; 3.14)	2.72 (2.13; 3.49)	2.35 (1.88; 3.51)	ns
Height Z-score	−2.30 (−2.67; −1.64)	−2.18 (−2,79; −1.29)	−2.67 (−3.33; −1.52)	ns
Total cholesterol, mg/dL	167 (144; 180)	173 (149; 195)	180 (165; 191)	ns
Triglycerides, mg/dL	64 (52; 78)	73 (43; 56)	94 (52; 107)	ns
HDL-cholesterol, mg/dL	48 (42; 57)	51 (43; 56)	47 (43; 52)	ns
LDL-cholesterol, mg/dL	102 (84; 118)	115 (85; 125)	118 (90; 121)	ns

Data are reported with median and inter-quartile range (IQR); group comparisons were performed using Wilcoxon rank sum test.
ns: non-significant

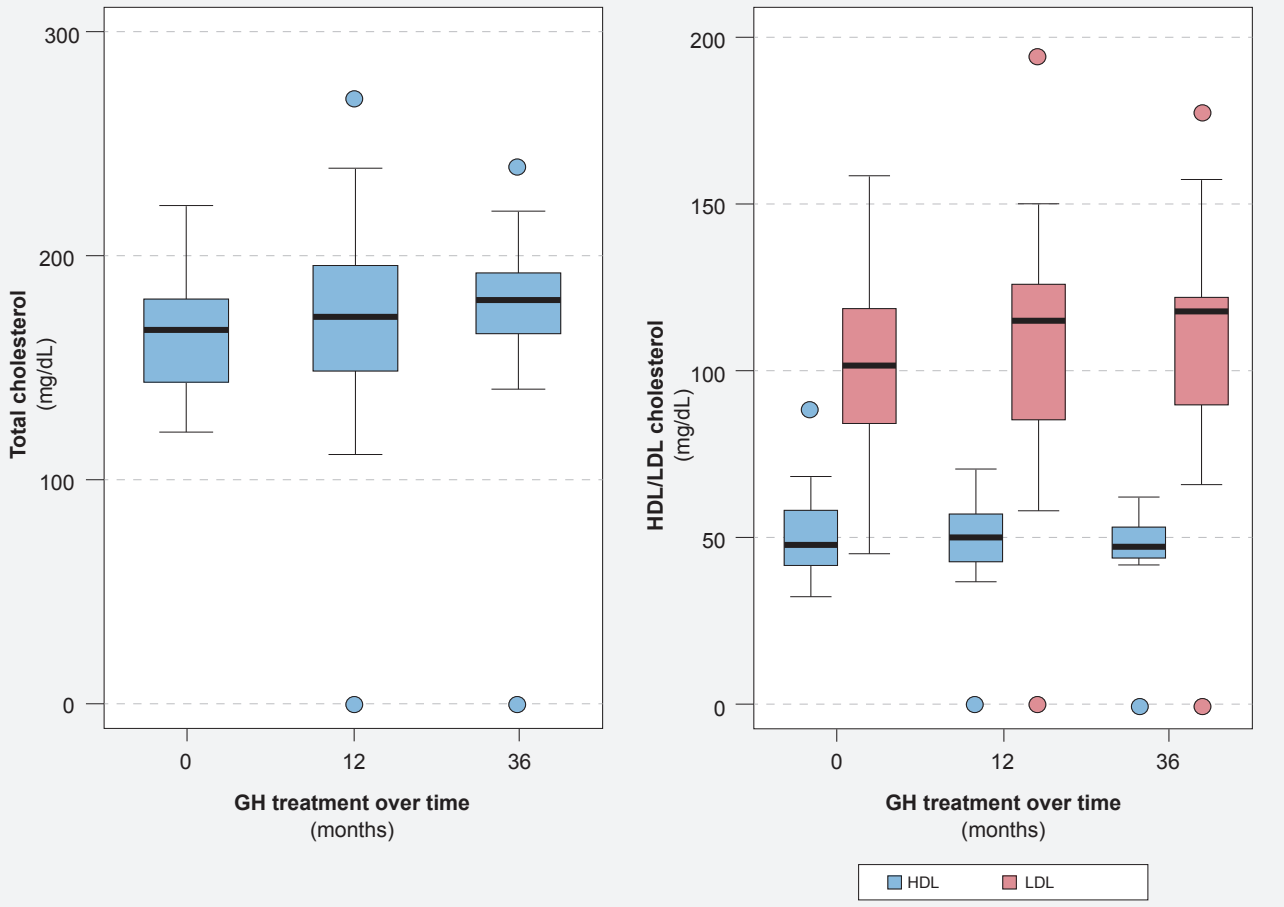

Figure 2 – Cholesterol level variations in PWS patients treated with GH

discontinued treatment due to various reasons such as sleep apnoea, development of type 2 diabetes *mellitus*, retinopathy, parental choice or having reached final height.

DISCUSSION

The findings in this study regarding PWS patients are in agreement with previous studies in the literature, namely, there was no gender predominance,[2] average age at diagnosis was similar[4] and predominant genetic abnormalities were the same.[3] An association of PWS with late prematurity may be related with complications that can occur during pregnancy such as decreased foetal activity, polyhydramnios, intrauterine growth restriction, breech presentation and abnormal position of the hands and feet (flexed elbows and feet in plantar flexion) during third-trimester ultrasonography.[2,10,11] These features may contribute to deliveries at an earlier gestational age. Nonetheless, in our case series, most deliveries occurred at gestation term, and birth weight and length agreed with reference values for the general population.

The early infancy period in PWS patients is dominated by muscular hypotonia with feeding difficulties and failure to thrive, followed in later infancy or early childhood by excessive appetite, leading to obesity.[1] As the condition is associated with changes in body composition such as decreased muscular mass, increased body fat and short stature,[12] it was unsurprising to find that all our patients had an increased BMI, indicating obesity. Those who reached final height were all also well below the reference values for the general population. Related to obesity, PWS patients are at a high risk of sleep-related disturbances, including OSA. These morbidities can manifest in up to 70% of PWS patients and may be associated with daytime sleepiness and behavioural disturbances.[13] About two-thirds of boys with PWS will display undescended testis, most likely related with hypogonadism – a universal feature of PWS. The majority of PWS patients are infertile.[14]

Neurodevelopmental delay and behavioural problems are also common findings of PWS.[2] Mental and motor retardation are almost always present and the intelligence quotient is generally 40 points below the mean values of the population.[2] PWS is also associated with a hypothalamic-hypophyseal function disorder and the patients should be investigated for central hypothyroidism and hypophyseal adrenal insufficiency at the time of diagnosis.[2] The vast majority of the clinical findings present in our patients are in agreement with the description above, particularly in regard to hypotonia, feeding disturbances, undescended testis and neurodevelopmental impairment. The most frequently assessed comorbidities were OSA, cognitive impairment, aggressiveness/impulsiveness disorders and undescended testis, which is also in line with the literature described above.

In our case series, 15 (39%) patients did not undergo treatment with GH due to a few specific situations, namely, treatment not being covered by the Portuguese National Health Service before 2010 and the presence of severe comorbidities.

Concerning body composition, we noticed a significant decrease in BMI in the GH-treated patient group, which was also described in previous studies. For instance, Aycan *et al*[2] showed an improvement of body composition, basal energy consumption, muscle strength, exercise tolerance and decreased fat mass in PWS children following therapy with GH. Additionally, although not statistically significant, the difference between mid-parental near-adult height and final height in those who reached final height by the end of our study was lower in the GH-treated group, meaning these patients were closer to their mid-parental near-adult height than the untreated patients. These findings also support the likely beneficial effect of this therapy on final stature.[12] The therapeutic dose increment was performed according to current guidelines (final dose of 1 mg/m²/day to be reached in the first weeks to months after a progressive

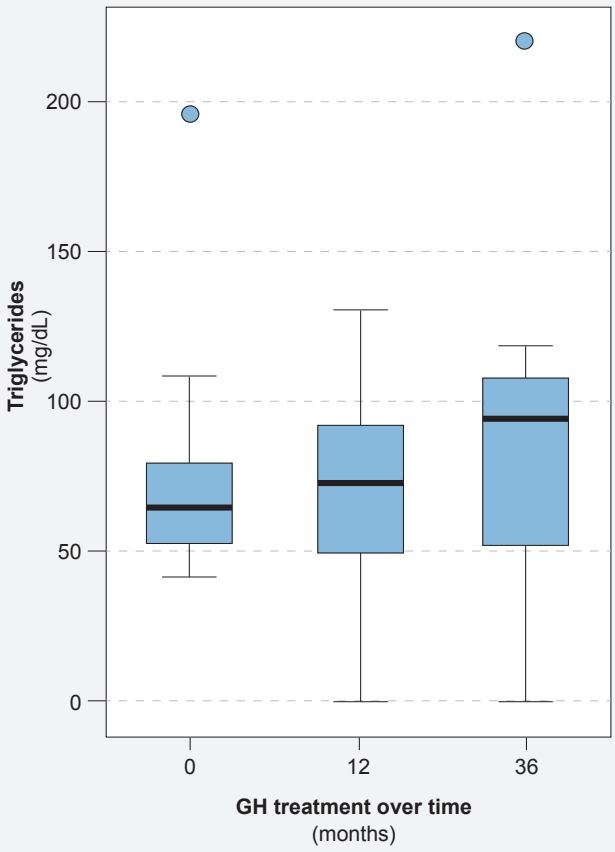

Figure 3 – Triglyceride level variations in PWS patients treated with GH

dose escalation).[3]

As expected, a downward trend in BMI was seen for GH-treated patients over the period of 36 months of treatment. However, this was not seen for stature, which seemed to worsen over the same period. This fact was contrary to what has been described in the literature.[3] A possible explanation may be that the average age at the beginning of GH therapy, which is later than the current guidelines that recommend an early introduction before two years of age, was decisive for therapeutic efficacy.[3] Moreover, the treatment follow-up time in our study (maximum 36 months) may not have been enough to show positive results for stature.

Regarding lipid profile, a slight increase in cholesterol and triglyceride levels was noticed over time, though not exceeding normal reference values. This trend was contrary to what has been described in previous studies.[2,15] A few confounders may contribute to these results, such as worsening of the compulsive eating behaviours that are characteristic of this condition,[12] and a lack of comparison with untreated patients who might have followed a different trend.

To the best of our knowledge, this case series represents the first national study that included patients on GH after the National Health Service started supporting the treatment for all eligible PWS patients. One of the strengths of this study is the detailed demographic and clinical characterisation of patients with PWS followed at one of the largest national referral centres. Despite these results demonstrating an overall benefit of GH on BMI in PWS children, other studies are needed to observe the effect of GH on patients' metabolic profiling, other aspects of body composition (body fat and muscle mass) and cognitive level.

The limitations of our study include the use of retrospective data, a higher chance of information bias, limited access to PWS patients probably due to the rarity of the disease or to undiagnosed or misdiagnosed cases, and the short time of follow-up of treated patients (maximum 36 months).

Future studies should examine prospective comparisons between treated and untreated PWS patients and include other factors such as biometric (serial impedance assessment), clinical (cognitive impairment severity) and laboratory (fasting glucose, haemoglobin A1c) parameters that were not addressed in this study.

On a final note, the present study helped advance the creation of a Portuguese nationwide database of PWS patients with the aim of expanding clinical knowledge and including the experience of other clinical centres.

CONCLUSION

This study supports GH therapy in patients with PWS, reinforcing the positive effects on growth and BMI. Other prospective studies with a longer follow-up period should be performed to evaluate other benefits of GH therapy. Based on this study, a nationwide database is being created to effectively monitor the follow-up data of patients with PWS.

AUTHOR CONTRIBUTIONS

All authors contributed to the literature research, study conception and design, data collection, analysis and interpretation, drafting of the article, version review, critical review of the article's content and approval of the final version.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

COMPETING INTERESTS

All authors report no conflicts of interest.

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