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Growth hormone treatment in pediatrics: What can we improve?

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Abstract
Objectives: To analyze the age at which treatment with growth hormone (GH) is started in the different indications approved in our country, as well as to assess the response to it and detect points of improvement.
Material and methods: A descriptive, observational and retrospective study of pediatric patients receiving GH treatment in December 2020 and monitored in the pediatric Endocrinology Unit of a tertiary care hospital.
Results: A total of 111 patients (52 females) were included in the study. The mean age at the start of treatment was 6.6 years old, being delayed in all diagnostic groups with respect to what is approved for each indication. The indication for which they most frequently received treatment was GH deficiency (n = 60, 54%). In this diagnostic group, there is a predominance of males (39 boys vs 21 girls, and a significantly greater increase in height z score (greater height SDS) is observed in those with early start of treatment compared to those who start late (greaterheight SDS 0.93 vs 0.6; $P < .05$).

All diagnostic groups presented a greater height SDS and height velocity. No adverse effects were observed in any patient.
Conclusion: GH treatment is effective and safe for the approved indications. The age of initiation of treatment is a point to improve in all indications, especially in SGA patients. For this, good coordination between primary care pediatricians and pediatric endocrinologists is essential, as well as specific training to identify early signs of different pathologies.

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PALABRAS CLAVE
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Pequeño para edad gestacional (PEG);
Retraso diagnóstico

Tratamiento con hormona de crecimiento en pediatría, ¿qué podemos mejorar?

Resumen
Objetivos: Analizar la edad de inicio de tratamiento con hormona de crecimiento (GH) en las distintas indicaciones aprobadas en nuestro país, valorar la respuesta y detectar puntos de mejora.
Material y métodos: Estudio descriptivo, observacional y retrospectivo de pacientes pediátricos que recibían tratamiento con GH en diciembre de 2020 y se controlaban en la Unidad de Endocrinología Pediátrica de un hospital de tercer nivel.
Resultados: Se incluyeron 111 pacientes (52 mujeres). La edad media al inicio del tratamiento fue 6,6 años, estando en todos los grupos diagnósticos retrasada con respecto a lo que está aprobado para cada indicación. La indicación por la que más frecuentemente recibían el tratamiento fue el déficit de GH (54%). En este grupo diagnóstico, hay un predominio de varones (39 niños vs 21 niñas) y se observa un incremento de z-score de talla (Δ SDS talla) significativamente mayor en aquellos con inicio precoz del tratamiento frente a los que comienzan de forma tardía (Δ SDS talla 0,93 vs 0,6; $P < ,05$).

Todos los grupos diagnósticos presentan un Δ SDS talla y de velocidad de crecimiento (VC). Ningún paciente presentó efectos adversos.
Conclusión: El tratamiento con GH es eficaz y seguro para las indicaciones aprobadas. La edad de inicio del tratamiento es un punto a mejorar en todas las indicaciones, especialmente en los PEG. Para ello, es fundamental una buena coordinación entre los pediatras de atención primaria y los endocrinólogos pediátricos, así como formación específica para identificar signos precoces de las distintas patologías.

Introduction

Growth hormone (GH) or somatotropin treatment is approved in Spain for the following indications: GH deficiency; impaired growth in chronic kidney disease (CKD); Turner's syndrome; Prader-Willi syndrome; Noonan syndrome; patients diagnosed as small for gestational age (SGA); and patients with abnormalities of the SHOX gene.[1]

The aim of the treatment is to increase growth rate (GR) and reach an adequate adult height within the growth potential of each patient[2] and its effectiveness depends on both the indication and the age at which the treatment is started. For optimal efficacy, the treatment should be started as early as possible.[3]

The aims of this study were to analyse the age treatment is started in the different indications, assess the response and identify points for improvement.

Material and methods

We carried out a retrospective, descriptive, observational study, which included all patients receiving GH treatment in December 2020 under follow-up by the paediatric endocrinology unit of a tertiary hospital.

We analysed the age when treatment started and the indication for which it was received. The age of treatment onset in each diagnostic group was then compared with the recommended age for that specific indication.

To study patient progress once GH treatment had started, we collected the GR expressed in cm/year and in z-score (standard deviation [SD]), and the height z-score (height SD). To calculate the GR SD, we used the tables from the Estudio longitudinal español de crecimiento 1978–2000 [Spanish 1978–2000 longitudinal study of growth], adjusted depending on whether they were in the early, normal or late maturing group according to the Fernández et al. tables.[4] All variables were analysed both at the start of treatment and one year later. Subsequently, patients with GH deficiency who had started treatment early (males < 9 years of age and females < 8 years) were compared with those who started treatment late.

We also recorded any adverse effects of the medication patients may have experienced up to the time of the study.

For the statistical analysis, the SPSS program was used. Means, medians and ranges were calculated. Student's *t*-test was performed for statistical significance.

The study was approved by the Independent Ethics Committee of the Principality of Asturias (IECm). Patient confidentiality was maintained throughout.

Results

We included 111 patients (59 male) who received treatment with GH in December 2020.

Table 1 shows the characteristics of the patients receiving GH treatment based on diagnosis. The most common indication, with 60 patients (54%), was GH deficiency. Of these 60 patients, 57 had isolated GH deficiency, while three, all female, had combined pituitary hormone deficiency. In these

Table 1 Age at diagnosis, SD (z-score) for height and growth rate (GR) at start of treatment and one year later, according to indication.

Diagnosis	Number of patient (%)	Mean age at start of treatment (range)	Height SD at start of treatment	Height SD one year later	Height SD increase in the first year	GR SD at start of treatment	GR SD one year later	Increase in GR SD in the first year
GH deficiency	60 (54)	7.6 (0–16)	−2.9	−2.1	+0.8	−1.4	+3.6	+5
SGA	34 (30.6)	5.4 (4–10)	−3.3	−2.6	+0.7	−1.5	+2.1	+3.6
Abnormality of the SHOX gene	9 (8.1)	7.8 (2–13)	−2.5	−1.7	+0.8	−1.9	+4.9	+6.8
Turner's Synd.	4 (3.6)	5.0 (2–8)	−2.6	−1.9	+0.7	−1.7	+2.8	+4.5
Prader-Willi Synd.	4 (3.6)	2.7 (2–4)	−2.0	−0.9	+1.1	−1.0	+2.7	+3.7

SGA: small for gestational age; SHOX: Short Stature Homeobox; Synd.: syndrome.

three patients, the diagnosis was made before the age of one month.

The mean age at the start of treatment was 6.6 years, with a median of 5 years. Patients with Prader-Willi syndrome were younger at the start of treatment (2.7 years of age).

Table 1 shows the GR SD according to age and gender at the start of treatment and one year later. At the start of treatment, patients with abnormalities in the SHOX gene were those with the lowest SD (−1.9), although a greater increase can be seen during the first year of treatment in these patients (4.9 SD at first follow-up).

Patients in the SGA group had the lowest height SD at the start of treatment (−3.31). Patients with Prader-Willi syndrome were those with the largest increase in (ΔSDS talla) height SD in the first year of treatment.

Patients with GH deficiency (39 males, 21 females) were subdivided into two groups based on whether they had started treatment early or late. The results are shown in Table 2.

The differences in the ΔSDS talla height SD between those who started treatment early versus those who started late were significant ($P < .05$), but not the differences in the increase in GR SD (ΔSDS VC).

None of the patients had adverse effects during the study period.

None of them abandoned the treatment or were withdrawn due to lack of efficacy.

Discussion

We studied the characteristics of paediatric patients receiving GH treatment at a tertiary hospital and the differences in progress according to diagnosis and age when treatment was started. We did not include patients with Noonan syndrome, as at the time the study was carried out the indication was not yet approved.

In our study, no gender differences were identified in the overall number of patients treated with GH. However, in those diagnosed with GH deficiency, in line with other studies, there were almost twice as many males as females.[5,6] This may be explained by the greater frequency of delayed puberty in males, which leads to the diagnosis of isolated GH deficiency. However, given the large difference observed, we cannot ignore the fact that height may still be given more importance in males, with males and their families being more insistent about referral to the paediatric endocrinology clinic than for females and therefore being more likely to be diagnosed.

As in other studies,[7,8] the most common reason for patients receiving GH treatment was growth hormone deficiency.

Evidence points to GH treatment being more effective the sooner it is started.[3] In our patients, the age at which treatment began was quite late in all groups, well above the age at which its use would be authorised.[9]

In our study, the patients with GH deficiency started receiving treatment at a mean age of 7.2 years, data comparable to the study by Ranke and Lindberg,[10] whose patients had a mean age of 6.9–8.4 years. Although other studies, such as those by Luzuriaga et al.[7] and Ariza Jiménez et al.,[11]

Table 2 Changes in height and growth rate (GR) in patients treated for GH deficiency.

	Height SD at start of treatment	Height SD first year	Height SD increase	GR SD at start of treatment	GR SD first year	GR SD increase
Early start (n = 32) (males < 9 years of age, females < 8 years)	−3.31	−2.3	+0.93	−1.55	+3.15	+4.8
Late start (n = 28)	−2.55	−1.9	+0.6	−1.2	+4.3	+5.6

SD: z-score.

recorded even older ages for starting treatment (mean of 9.8 years and 9.9 years, respectively), we believe that our figures should still be improved.

Comparison of the age when treatment in children with GH deficiency is started in different countries[9] shows that, although they are all late in starting treatment, in Germany they start the earliest. There, the CrescNet screening programme, which ran from 2000 to 2005, led to a reduction in the age at diagnosis of GH deficiency and to treatment being started at a younger age, and this has continued to decrease since the implementation of the programme.[3,12]

To analyse the patient group with GH deficiency, we used the same criteria as in the Nordinet® International Outcome Study (IOS),[13] considering the start of treatment before eight years of age in girls and nine years of age in boys as early. We found that the ΔSDS VC GR SD was higher in patients who started late, which may be explained by the fact that many had already started the puberty growth spurt, so the GR was higher than in the younger children. However, the ΔSDS talla height SD was significantly higher in subjects starting early, probably for the same reason, as older patients usually have a delay in bone age and are artificially compared with patients who are in full puberty growth spurt.

In the case of SGA patients, most of them go through a catch-up growth spurt before three years of age.[14] For that reason, one of the inclusion criteria for treatment is not having had adequate catch-up growth at four years of age.[1] In our study, SGA patients started treatment with a mean age of 5.4 years, better than that reported by the Spanish SGA study carried out by the Sociedad Española de Endocrinología Pediátrica (SEEP) [Spanish Society of Paediatric Endocrinology],[15] where the mean age was 7.2 ± 2.8 years. However, our patients are delayed compared to the age indicated in the inclusion criteria (4 years).

One interesting point is that, considering the prevalence of SGA and the number of births in our healthcare area, the number of SGA treated is much lower than would be expected. According to data from our hospital, there was an estimated average of 2289 births per year between 2011 and 2016, from which we would expect about 230 SGA children per year, approximately 10% of whom would not go through catch-up. However, at our centre, at the time of the study, only 34 patients were receiving GH treatment for this indication. These data reflect the need to improve the follow-up of these children and for close collaboration between paediatric endocrinologists and primary care paediatricians for the referral of these patients, thereby guaranteeing that they develop properly, and optimising their adult height.

Various studies show that the longer the GH treatment lasts in SGA patients, the more effective it is, so the sooner it is started, the longer they will be able to keep taking the treatment and the better the outcome. In addition, the greatest increase in GR occurs during the first years, so the smaller the child, the more growth potential they will have and, consequently, the taller they will become.[16]

Patients with abnormalities in the SHOX gene were the ones with the longest delay in starting treatment, with a mean of 7.8 years, two years below the 9.8 ± 1.6 years in the Font et al. study.[17] This may be due to the fact that the characteristic deformities of this syndrome begin to be visible at school age, which is why diagnosis is often delayed, unless it is suspected as a result of family history.[18]

Girls with Turner's syndrome can start GH treatment from the age of two years[1] and it should not be delayed beyond the age of four years.[18] In our study, the mean age was five years, which is better than other studies, such as that conducted by Sánchez Marco et al.[19] (mean 7.9 ± 4.1) or Stocholm et al.[20] (median of 15 years), but still far from ideal.

The patients who started treatment youngest, at a mean of 2.75 years of age, were those with Prader-Willi syndrome, although they were still delayed compared to the indicated age (2 years).[1] This group of patients also had a higher ΔSDS talla height SD during the first year of treatment, although these differences are not significant, probably due to the small number of patients with this diagnosis. Starting treatment at an early age brings additional benefits to these patients; it decreases fat mass, improves cognitive function, normalises head circumference and improves the sitting height to standing height ratio.[21–23] Ayet-Roger et al.[24] found that children with Prader-Willi syndrome who started GH treatment before two years of age had better cognitive development than those who began treatment after the age of two, leading us to conclude that perhaps treatment should be started earlier in these patients.

None of the diagnostic groups in our sample met the criteria for inadequate response to GH used in their study by Collett-Solberg et al[25,26] (increase in GR < 2 cm/year, Δ GR SD < 0 or Δ height SD < 0.3/year in the first 6–12 months of treatment).

No adverse effects were recorded in any of the patients studied, proving the safety of this drug when adhering to the approved doses and indications.[27]

Our study has limitations typical of a retrospective study, such as incomplete information for some patients. In addition, the small number of patients did not allow separation of the sample by diagnosis, gender, puberty stage and sever-

ity of GH deficiency. Moreover, the difference in the number of patients in each diagnostic group makes it difficult to compare the data between them, and the small sample of subjects in some of the disorders means that their results are not representative. It should also be noted that we do not know if there was adequate adherence, which is a very important factor in determining the treatment response.[28]

Conclusions

GH deficiency is the most common indication for which patients receive GH treatment in our population. There are still gender-based differences, which should be corrected. We found significant differences in treatment response in patients with GH deficiency who received treatment early compared to those who started at a later age.

Treatment with GH in the approved indications is effective and safe, but some aspects such as the age at which treatment begins need to be improved. The different specialists therefore need specific training to identify early signs, and screening programmes should be set up to enable early diagnosis. It is also essential to have highly effective coordination between primary care paediatricians and paediatric endocrinologists, in order to start treatment as soon as possible and thus optimise the height of these patients.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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