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Adherence to Growth Hormone Treatment in Children During the COVID-19 Pandemic

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What is already known on this topic?

Treatment adherence is crucial for successful treatment with growth hormone (GH) therapy. Non-adherence affects linear growth. Non-adherence rates vary widely, from 5% to 80%. Older age and prolonged duration of treatment with growth hormone increase non-adherence.

What this study adds?

The median age at diagnosis was lower than KIGS data. Poor adherence was 15% of patients. Poor adherence rate was higher when compared to previous Turkish studies. The Coronavirus disease-2019 pandemic may have affected the non-adherence rate.

Abstract

Objective: Treatment adherence is crucial for the success of growth hormone (GH) therapy. Reported non-adherence rates in GH treatment have varied widely. Several factors may have an impact on adherence. Apart from these factors, the global impact of the Coronavirus disease-2019 (COVID-19) pandemic, including problems with hospital admission and routine follow-up of patients using GH treatment, may have additionally affected the adherence rate. The primary objective of this study was to investigate adherence to treatment in patients receiving GH. In addition, potential problems with GH treatment during the pandemic were investigated.

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Methods: This was a multicenter survey study that was sent to pediatric endocrinologists during the pandemic period (June-December 2021). Patient data, diagnosis, history of pituitary surgery, current GH doses, duration of GH therapy, the person administering therapy (either parent/patient), duration of missed doses, reasons for missed doses, as well as problems associated with GH therapy, missed dose data and the causes in the recent year (after the onset of the pandemic) were questioned. Treatment adherence was categorized based on missed dose rates over the past month (0 to 5%, full adherence; 5.1 to 10% moderate adherence; >10% non-adherence).
Results: The study cohort consisted of 427 cases (56.2% male) from thirteen centers. Median age of diagnosis was 8.13 (0.13-16) years. Treatment indications were isolated GH deficiency (61.4%), multiple pituitary hormone deficiency (14%), Turner syndrome (7.5%), idiopathic GH deficiency (7.5%), small for gestational age (2.8%), and "others" (6.8%). GH therapy was administered by parents in 70% and by patients in 30%. Mean daily dose was 32.3 µg/kg, the annual growth rate was 1.15 standard deviation score (minimum -2.74, maximum 9.3). Overall GH adherence rate was good in 70.3%, moderate in 14.7%, and poor in 15% of the patients. The reasons for non-adherence were mainly due to forgetfulness, being tired, inability to access medication, and/or pen problems. It was noteworthy that there was a negative effect on adherence during the COVID-19 pandemic reported by 22% of patients and the main reasons given were problems obtaining an appointment, taking the medication, and anxiety about going to hospital. There was no difference between genders in the adherence rate. Non-adherence to GH treatment decreased significantly when the patient: administered the treatment; was older; had longer duration of treatment; and during the pandemic. There was a non-significant decrease in annual growth rate as non-adherence rate increased.
Conclusion: During the COVID-19 pandemic, the poor adherence rate was 15%, and duration of GH therapy and older age were important factors. There was a negative effect on adherence during the pandemic period.
Keywords: Children, growth hormone, adherence, COVID-19, pandemic

Introduction

Treatment adherence is crucial for successful treatment with growth hormone (GH) therapy. Patient motivation and adherence to treatment may decrease over time because of several factors, including daily injections and prolonged duration of the therapy (1). Non-adherence is the leading cause of insufficient height gain in patients on GH therapy (2,3). Reported medication non-adherence rates vary widely, from 5% to 80% depending on the method (4). A more recent systematic review reported that medication non-adherence rates varied from 7 to 71% across the included studies (1). Treatment adherence may be influenced by many factors including patient unwillingness (fear, reasons associated with injections), forgetfulness, treatment duration, low socioeconomic status, type of injector, lack of satisfaction with treatment effect, and inability to perceive the consequences of missing a dose (3,4). There is no standardized method to ensure adherence to GH therapy. Medication adherence has been investigated through GH prescription reviews, GH patient family questionnaires, serum insulin-like growth factor 1 (IGF-1) monitoring and urinary GH measurements. Despite having lower sensitivity, questionnaires are the simplest method for these types of investigations.

There was widespread disruption of routine hospital visits and monitoring of patients on GH therapy, dating from the start of the Coronavirus disease-2019 (COVID-19) pandemic, with the first case reported in Turkey on March 11, 2020. The global effect of the pandemic included widespread disruption of routine health services and interruption to patients' treatments.

The objective of this study was to investigate treatment adherence in patients on GH therapy during pandemic period through a questionnaire. This study was also designed to investigate potential therapeutic problems that might be experienced during the pandemic.

Methods

The survey was conducted by the Turkish Society for Pediatric Endocrinology and Diabetes. The authors prepared the questionnaire via online meetings. The centers tested the draft questionnaire before sending it. The study questionnaire included separate items for physicians and families (Supplementary Questionnaire 1). An email was sent to each member, asking them to provide the study questionnaire to all their patients on GH.

Patient data, date of diagnosis, age at diagnosis, age at the onset of treatment, age at last examination, parental educational attainment, monthly household income, diagnosis [isolated GH deficiency, multiple pituitary hormone deficiencies, Turner syndrome, skeletal dysplasia, small for gestational age (SGA), chronic kidney insufficiency, Prader-Willi syndrome], history of pituitary surgery, current GH doses, duration of GH therapy, person administering GH therapy (mother and/or father or patient), duration of missed doses, reasons for missed doses, problems associated with GH therapy, and missed dose data in the preceding year (during the pandemic) and effects of the COVID-19 pandemic were queried. Treatment adherence was categorized based on reported missed dose rates over the month preceding questionnaire completion, as follows: 0 to 5% (0-1 missed doses per month) was designated full

adherence; 5.1 to 10% (2 missed doses per month) was moderate adherence; and >10% (≥3 missed doses per month) was non-adherence. The growth velocity standard deviation (SD) score (SDS) calculation was made using the Baumgartner method (5).

This study was approved on June 2, 2021 (approval no. 2021-7/22) by the Ethics Committee of the Medical School of Bursa Uludağ University.

Statistical Analysis

The IBM Statistical Package for the Social Sciences, version 23 (IBM Inc., Armonk, NY, USA) were used to analyze study data. Descriptive statistics are presented as numbers and percentages for categorical variables and mean ± SD or median (range or interquartile range) for numerical data. Visual analytics (histograms and probability graphs and analytic methods (Kolmogorov-Smirnov or Shapiro-Wilk tests) were used to investigate normality of data set distribution. The chi-square test was used for two- or multiple-group comparison of categorical variables, as appropriate. For non-parametric data the Mann-Whitney U test was used for two-group comparisons and the Kruskal-Wallis test was used for multiple-group comparison. Spearman's correlation coefficient test was used for analysis of correlation between non-normally distributed numerical data. A p-value less than 0.05 was considered statistically significant.

Results

This study included questionnaire responses about 427 patients (56.2% males) from 13 sites. The median age at diagnosis, at the onset of the GH therapy and at study entry were 8.13 (0.13-16 years), 8.71 (0.3-16.1 years) and 12.03 (1.08-18 years) years, respectively. Treatment duration was 0 to 6 months in 8.2% (n=35), 6 to 12 months in 12.6% (n=54), 1 to 3 years in 39.6% (n=169) and more than 3 years in 39.6% (n=169) of patients. More than three quarters (77.8%) of patients were on daily GH replacement therapy and 22.7% (n=97) reported that they returned empty vials for the purpose of adherence monitoring. The monthly family income was less than the minimum wage in 22.2%, up to minimum wage x2 in 44%, from minimum wage x2 to minimum wage x4 in 23% and more than minimum wage x4 in 10.3% of the families. The training for GH injections was provided by a company nurse (70.3%; n=300), a hospital nurse (25.1%; n=107), or a physician (4.7%; n=20). GH replacement therapy was administered by parents (299 patients; 70%), or by the patients themselves (128 patients; 30%).

Indications for GH replacement therapy included isolated GH deficiency (61.4%), congenital or acquired multiple pituitary hormone deficiency (14%), Turner syndrome (7.5%), idiopathic GH deficiency (7.5%), SGA (2.8%), and others (6.8%), the latter grouping including Noonan syndrome, skeletal dysplasia, Prader-Willi syndrome, chronic kidney insufficiency, congenital adrenal hyperplasia, Silver Russell syndrome, cystic fibrosis, distal renal tubular acidosis and hypophosphatemic rickets (Table 1). The mean daily GH dose was 32.69 (13.8-67) µg/kg. GH dose by diagnosis is also shown in Table 1. Overall annual growth rate was 1.15±1.37 SDS on treatment during the pandemic. The growth rate increase by diagnosis is shown in Table 1.

The analysis of the adherence to GH therapy indicated full adherence in 70.3%, moderate adherence in 14.7%, and poor adherence in 15% of patients. The reasons for missing a dose (n=193) included forgetfulness (51.8%), treatment fatigue (13.5%), running out of medication (13.5%), overnight stays (3.5%), pen cartridge problems (2.8%), infections (1.6%) and "others" (1.6%). When asked if the COVID-19 pandemic had a negative effect on adherence, 22% (n=94) of the patients/families responded that it had. In those who responded positively, inability to get an appointment, inability to access the medication, hospital visit anxiety, having COVID infection, and treatment discontinuation were the specific mechanisms by which the COVID-19 pandemic impacted their adherence (Table 2).

When the data were analyzed by good, moderate, and poor adherence grouping, there was no significant intergroup differences in terms of sex, age at diagnosis, parental educational attainment, daily dose or annual growth rate. However, prolonged treatment duration, older age, and self-injection had a significant impact on the number of missed doses during the COVID-19 pandemic. Although patients who missed more doses tended to have a poorer annual growth rate, this association was not significant and there was no correlation. However, there was a significant negative correlation between the decrease in the annual growth rate SDS and longer treatment duration ($r=-0.202$, $p<0.01$). Furthermore, higher rates of missing doses correlated with duration of GH treatment duration ($r=0.129$, $p<0.01$, Figure 1).

Missed dose rate was higher in the groups with acquired multiple pituitary hormone deficiency and chronic kidney insufficiency (Figure 2).

When the present study compared to a previous Turkish study (19), it was noted that non-adherence rate was higher (15% vs. 7.4%, Figure 3).

Table 1. The diagnosis age, growth hormone dose and annual growth rate by growth hormone treatment indication

Growth hormone treatment indication	n	Diagnosis age (median) (min-max)	Age of onset of the treatment (median) (min-max)	Growth hormone doses (μg/kg/day) (mean ± SD)	Annual growth rate SDS (median) (min-max)
Isolated GH deficiency	262	9.4 (0.5-16)	10.15 (0.6-16)	31.65 ± 6.75	1.16 (-2.55-9.4)
Multiple pituitary hormone deficiencies (congenital)	50	4.75 (0.16-15)	6.35 (0.3-15.2)	30.65 ± 6.77	1.19 (-2.74-5.8)
Multiple pituitary hormone deficiencies (acquired)	10	8.7 (3-15.9)	10.95 (3.7-16.1)	28.5 ± 4.17	0.92 (-0.11-3.24)
Turner syndrome	32	7.05 (0.13-13.8)	7.35 (1.2-14.1)	44.75 ± 6.52	0.91 (-1.43-3.4)
Idiopathic GH deficiency	32	8.7 (0.58-12.9)	9.35 (0.83-14)	32.83 ± 5.23	0.65 (-1.41-4.33)
SGA	12	7.2 (3-12.8)	7.2 (3-13)	42.5 ± 13.12	1.04 (-1.22-5.22)
Noonan syndrome	9	7.7 (3.5-14.5)	7.7 (4.8-14.5)	35.74 ± 5.88	0.84 (-0.81-2.03)
Skeletal dysplasia	7	6 (3.7-9.5)	7 (3.7-10)	32.19 ± 9.17	0.17 (-0.65-2.81)
Prader-Willi syndrome	4	0.92 (0.3-3)	1.05 (0.3-3.3)	22.25 ± 8.96	-0.14 (-2.08-2.7)
Chronic kidney insufficiency	3	7.1 (2.2-9.5)	8.08 (7-9.5)	25 ± 8.66	0.22 (-0.63-0.64)
Congenital adrenal hyperplasia	2	7.85 (5-10.7)	7.85 (5-10.7)	23.4 ± 2.26	0.63 (0.57-0.69)
Silver Russel syndrome	1	1	1.3	28	2.1
Cystic fibrosis	1	11	11	37	0.68
Distal renal tubular acidosis	1	7.08	7.08	22	1.89
Hypophosphatemic rickets	1	9	9	25	-0.04

SGA: small for gestational age, GH: growth hormone, SDS: standard deviation (SD) score, min-max: minimum-maximum

Table 2. Adherence rate, non-adherence reason, and pandemic effect on adherence

Adherence rate	Good (70.3%), moderate (14.7%), poor (15%)
Reason of non-adherence (n = 193)	Forgetfulness (51.8%) Treatment fatigue (13.5%) Inability to access medication (13.8%) Pen problems (2.8%) Infection (1.6%) Others (1.6%)
Pandemic effect on adherence (n = 94)	Appointment problems (58.5%) Taking medication problems (17%) Anxiety about going to the hospital (11.7%) COVID-19 infection in patient or relatives (8.5%) Cessation of GH treatment by patient (4.3%)

COVID-19: Coronavirus disease-2019, GH: growth hormone

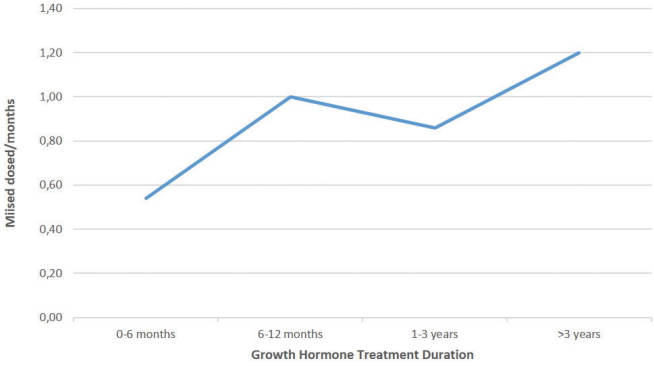

Figure 1. The missed dose rate by duration of growth hormone treatment

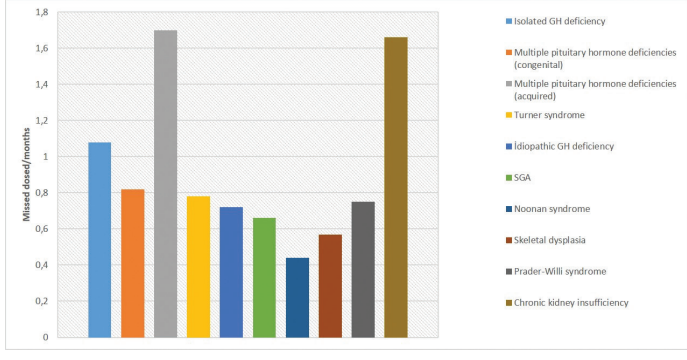

Figure 2. Missed dose per month rate according to the etiology of growth hormone treatment indication

SGA: small for gestational age, GH: growth hormone

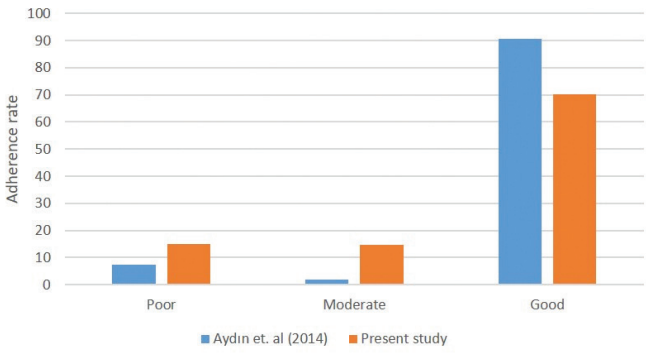

Figure 3. Comparison of GH adherence rate by category (good, moderate, poor) in the present study and in a previous Turkish study which was performed before the COVID-19 pandemic (17)

COVID-19: Coronavirus disease-2019, GH: growth hormone

Discussion

This multi-center, retrospective, questionnaire-based study provided data about adherence to GH replacement therapy in a Turkish pediatric population. However, as this study was conducted during the pandemic, study data may also be interpreted in the light of the effect of the Pandemic on GH treatment adherence.

The median age at diagnosis was lower than KIGS data. At the onset of GH therapy, the mean age in KIGS data was 10.7 years versus 8.7 years in the present study. The same trend was seen in GH indication subgroupings with KIGS reporting diagnosis ages of 9.1 years in IGHD, 6.2 years in congenital MPHD, 9.7 years in acquired MPHD, 9.7 years in ISS, 6.9 years in SGA, and 9.7 years in Turner syndrome (6,7,8). Lower median values in all subgroups might indicate earlier diagnosis in our cohort but the data from KIGS comes from many countries and settings and is therefore extremely heterogeneous. GH replacement doses were in line with those reported in the literature (9).

Results from adherence studies show wide variations due to methodological differences. Treatment adherence may be evaluated based on the number of missed injections since the last visit, or the number of missed injections per week or per month. In the present study poor treatment adherence was defined as ≥3 missed doses per month. Treatment adherence is a major factor in the efficacy of GH replacement therapy and poor adherence will also impact treatment costs. Previous studies indicated that non-adherence might result in medication waste of up to 15% (10). Early discontinuation rates have been reported in as much as 52% of patients on GH therapy (11) but an improvement of 10% in the adherence to GH therapy has been shown to result in an increase of 1.1 cm in the annual growth rate (1). The national survey of adherence to GH therapy in New Zealand concluded that a missed dose rate of more than one per week may lead to a significant decrease in linear growth. The height velocity (HV) SDS significantly decreased in 66% of children who missed more than one dose per week (12).

In a trial conducted in Israel between 2004 and 2015, adherence to GH treatment was evaluated based on proportion of days covered (PDC) defined as the days covered by filled medication/GH therapy days prescribed by physician, in 2,379 patients monitored through the healthcare system. A PDC of ≥80% was defined as good adherence. The rates of good adherence gradually decreased, being 78.2% in the first year, 75.6% in the second year and 68.1% in the third year (13). In a study using data from Easypod in 1,190 patients, treatment adherence was 93.7% in the first year and 70.2% in the fifth year (14). In keeping with these earlier reports, in the present study adherence rates decreased as the duration of GH therapy increased.

In a systematic review of 11 eligible studies conducted in 2022, reported 12-month adherence rates varied between 73.3% and 95.3% with a mean of 79.3% (15). In an earlier study from Turkey, Aycan et al. (16) reported an adherence rate of 92% in a series of 689 patients. A Turkish multicenter study evaluated 1-year adherence rate in a series of 216 patients (17). A missed dose rate higher than 10% was classified as poor adherence. The rate of poor adherence was reported to be 2.8% in the third month, 5.1% in the sixth month and 7.4% in the twelfth month. HV SDS was found to be increased with adherence and IGF-1 levels correlated with HV and HV SDS. Adherence rates were better in male patients. No differences were found in adherence rates between the subgroups when categorized by age, socioeconomic level and conditions underlying GH treatment requirement. Treatment adherence correlated with IGF-1. In the present study, the rate of poor adherence to GH therapy was 15%, and in keeping with earlier reports, increased non-adherence rates were associated with decreased growth SDS with statistical insignificance.

The missed dose rate was higher in the groups with acquired multiple pituitary hormone deficiency and chronic kidney insufficiency in the present study. This may be related to the characteristics of the diagnosis. There are many factors that will affect the GH response in both acquired multiple pituitary hormone deficiency and kidney insufficiency, such as excessive medication use, repeated surgery, interventions, and frequent hospitalizations.

Access to medication, patient and family motivation, and receipt of training may influence adherence rates (2). The response to GH therapy is influenced by several factors, mainly individual differences in response, age at diagnosis, current age, and medication dose (18). A study in 110 patients evaluated treatment adherence in the first two years. The rate of treatment adherence was 90% and there was a negative correlation between adherence and age, pretreatment growth rate and treatment duration, whereas a positive correlation was identified between the parental educational attainment and treatment adherence (19). Another factor that has been shown to negatively impact treatment adherence was a reluctance to undergo injections in adolescents, as these are largely self-administered. Treatment adherence rates were low and family support was shown to be important for adolescents requiring GH injections (20). Treatment fatigue is another reason for treatment discontinuation among patients or may lead to reductions in doses and dose frequency. Treatment fatigue is more likely to occur in older patients and patients who have longer durations of therapy (21).

Children may refuse to do the injections themselves while other factors that may influence treatment adherence include being in adolescence, treatment duration, low socioeconomic status, type of the injector used, reluctance to undergo injections, unsatisfactory treatment effect, and inability to perceive the consequences of missing a dose (22). Furthermore, needle visibility and painful injections (due to ingredients) have been reported as other issues associated with GH therapy (23). In the present study, adherence to GH therapy decreased as patient age and treatment duration increased. These findings are in keeping with earlier reports and suggest that there is still a need for novel strategies to counter these negative influences on GH treatment adherence.

Regional differences may also impact treatment adherence. A study conducted in Iran evaluated 169 patients and reported that high costs, inability to access medication, being anxious about long-term complications, treatment fatigue, unsatisfactory treatment outcome, and painful injections were the most prominent reasons for non-adherence (24). Problems associated with treatment adherence were reported in highly religious communities, based on data from a study of 2,263 patients assessed through the health system records in Israel. Thus report showed ultra-religious population had higher risk for non-adherence. Besides, a low adherence rate in the subgroup of patients starting GH replacement therapy before the age of eight years was found. Furthermore, treatment adherence got worse with increasing treatment duration (25).

In the present study, the reasons for missing a dose were mainly forgetfulness, treatment fatigue, running out of medication, overnight stays, pen cartridge problems, and infections. The last three reasons may have had a greater effect during the pandemic. The announcement of the Turkish Medicines and Medical Devices Agency of the Ministry of Health on "Access to Chronic Disease Medication without Prescription" on March 16, 2020 allowed access to medicines in our country. In studies conducted before the pandemic, the rate of non-adherence was found to be between 8% and 10%, considering methodological differences between these studies (16,17). The COVID-19 pandemic may have played a role in the increased rate of non-adherence in the present study. Non-adherence rates were higher during the COVID-19 pandemic, with 15% being classified as poor adherence and a further 14.7% being classified as moderate adherence.

There are limited studies on the impact of COVID-19 on adherence to GH therapy. In a study conducted in Italy, the mean good, moderate and low adherence rates were found to be 82.2%, 13.1% and 4.7% based on Morisky Medication Adherence Scale scores from 107 patients with a mean age of 11.3 years. The low adherence rate in adolescents was 5-fold higher than the rest of patients but this was consistent with pre-pandemic data (26). Another study conducted in Italy reported that treatment adherence was not negatively affected by changes in behavior mandated because of the pandemic (27). Treatment adherence was evaluated before and after the pandemic in a larger series from 18 countries using data recorded by the Easypod system. Adherence was evaluated by restrictions, school closures, and stay at home orders during the pandemic in 9,562 patients before the pandemic and 7,782 patients after the pandemic in a population of patients aged 6 to 18 years. Surprisingly, treatment adherence increased by 3% compared to the rates before the pandemic (28). Moreover, a study conducted in Saudi Arabia reported an adherence rate of 92%, in 130 patients with a mean age of 12.5 years (29).

Study Limitations

The strengths of the study include multicenter design, standardized questionnaire and forms for physicians. Limitations include survey design with self-reporting of some data, differences between the centers in terms of diagnostic and therapeutic approaches to GH deficiency and a lack of standardization in completing the forms. Serum IGF-1 levels were requested in the questionnaire. However, as the IGF-1 norms and measurement methods of each center were not standardized, they were not evaluated in the results section.

Conclusion

The results of this study showed the age at diagnosis to be lower than previously reported. GH replacement therapy was administered to patients at appropriate doses. However, the rate of non-adherence to GH therapy was higher than previously reported in Turkish studies. In keeping with earlier reports, older age and prolonged duration of treatment with GH contributed to increased non-adherence rates while the effects of the pandemic may have contributed to overall worse adherence in this study.

Ethics

Ethics Committee Approval: This study was approved on June 2, 2021 (approval no. 2021-7/22) by the Ethics Committee of the Medical School of Bursa Uludağ University.

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices - Concept - Design - Data Collection or Processing - Analysis or Interpretation - Literature Search - Writing: Erdal Eren, Semra Çetinkaya, Yasemin Denkboy Öngen, Ummahan Tercan, Şükran Darcan, Hande Turan, Murat Aydın, Fatma Yavuzyılmaz, Fatih Kilci, Beray Selver Eklioğlu, Nihal Hatipoğlu, Kübra Yüksek Acinikli, Zerrin Orbak, Emine Çamtosun, Şenay Savaş Erdeve, Emrullah Arslan, Oya Ercan, Feyza Darendeliler.

Conflict of Interest: One author of this article, Feyza Darendeliler, is a member of the Editorial Board of the Journal of Clinical Research in Pediatric Endocrinology. However, she did not take part in any stage of the editorial decision of the manuscript. The editors who evaluated this manuscript are from different institutions. The other authors declared no conflict of interest.

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