Original article

Arch Argent Pediatr. 2026;e202611133

Longitudinal changes in nonfunctioning pituitary neuroendocrine tumors in children receiving growth hormone therapy: A comparison with untreated patients

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ABSTRACT

Background: Growth hormone deficiency (GHD) may result from structural abnormalities or space-occupying lesions of the pituitary gland; therefore, pituitary magnetic resonance imaging (MRI) is routinely performed as part of the etiological assessment. The reported prevalence of incidentally detected pituitary neuroendocrine tumors (PitNETs) in pediatric patients with GHD ranges from 0.5% to 20.3% across studies. PitNETs are rare in childhood and account for approximately 2.7% of supratentorial pediatric tumors and 3.6–6% of surgically treated PitNETs. Insulin-like growth factor-1 (IGF-I), a mitogenic agent elevated during recombinant human growth hormone (rhGH) therapy, has raised theoretical concerns regarding tumor growth stimulation.

Objective: To evaluate longitudinal changes in tumor size of nonfunctional PiNETs, in patients with pre-existing PitNETs receiving rhGH therapy compared with untreated controls.

Methods: This single-center retrospective cohort study included 15 GHD patients with PitNETs detected before rhGH initiation and 30 control patients with nonfunctional incidental PitNETs who did not receive rhGH therapy. Radiological follow-up was performed at baseline and at 6, 12, 18, 24, and 36 months.

Results: No significant longitudinal changes in PitNETs width or length were observed in either group. One rhGH-treated patient underwent PitNET excision. Indications for pituitary imaging in the control group were predominantly central precocious puberty, headache, central hypothyroidism, and short stature.

Conclusion: RhGH therapy was not associated with significant progression of nonfunctional PitNETs during a 36-month follow-up, supporting its safety when accompanied by regular radiological surveillance.

Keywords: *pituitary neoplasms; neuroendrocrine tumors; growth hormone, deficiency; growth hormone, analogs and derivatives; insulin-like growth factor I.*

doi: http://dx.doi.org/10.5546/aap.2026-11133.eng

To cite: Bahar YF, Çetin K, Donbaloğlu Z, Parlak M, Tuhan HÜ. Longitudinal changes in nonfunctioning pituitary neuroendocrine tumors in children receiving growth hormone therapy: A comparison with untreated patients. *Arch Argent Pediatr.* 2026;e202611133. Online ahead of print 30-JUL-2026.

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Funding: *None.*

Conflict of Interest: *None.*

Received: *4-28-2026*
Accepted: *6-11-2026*

INTRODUCTION

Growth hormone deficiency (GHD) is a rare endocrine disorder that affects approximately 1 in 4000 children.[1] The etiology of GHD may be idiopathic or associated with identifiable causes such as brain tumors, structural abnormalities of the hypothalamic-pituitary axis, or genetic mutations affecting the synthesis or secretion of growth hormone (GH). The diagnosis of GHD is established in children who present with short stature (height standard deviation score [SDS] <-2), reduced growth velocity (growth velocity SDS <-1), and an inadequate GH response (peak GH < 10 ng/mL) to at least two different stimulation tests (e.g., L-dopa, clonidine, insulin tolerance test [ITT], or glucagon).[2]

Following diagnosis, recombinant human growth hormone (rhGH) therapy is initiated to improve growth velocity and achieve target adult height.[3,4] It is widely used in pediatric patients with growth hormone deficiency (GHD) and other causes of short stature.[5] Pituitary MRI is routinely performed in children with growth failure, leading to increased detection of incidental pituitary lesions, now classified as pituitary neuroendocrine tumors (PitNETs).[6,7] The reported prevalence of PitNETs in pediatric GHD ranges from 0.5% to 20.3%.[6,7]

PitNETs are less common in children than in adults, representing approximately 2.7% of supratentorial tumors in the pediatric population and accounting for 3.6–6% of all surgically treated PitNETs.[8-11] These tumors are generally small (≤10 mm) and are frequently non-functional, meaning they are not associated with clinical or biochemical evidence or hormone hypersecretion. However, functioning PitNETs most commonly prolactin-secreting tumors may present with endocrine symptoms. Overall, pediatric pituitary tumors are more frequently observed in females than in males.[2,4,9,10] The mitogenic properties of growth hormone, which elevate insulin-like growth factor I (IGF-I) levels, have raised concerns regarding its potential role in tumor development and progression.[12] Limited data exist on the effects of rhGH therapy on nonfunctioning PitNET in children.[13]

Therefore, the aim of this study was to evaluate the longitudinal changes in tumor size in pediatric patients with GHD and incidentally detected nonfunctional PitNET receiving rhGH therapy, and to compare these findings with a control group of patients with PitNETs who did not receive rhGH therapy. Clarifying the potential impact of rhGH therapy on PitNET growth is essential for informed clinical decision making and long term follow-up strategies.

MATERIALS AND METHODS

Study design and participant selection

This single-center, retrospective cohort study included 15 pediatric patients diagnosed with GHD and PitNETs, all of whom received rhGH therapy. A control group of 30 patients with PitNET but without GHD, and who did not receive rhGH therapy, was also included for comparison. All participants were followed at the Department of Pediatric Endocrinology, Akdeniz University Hospital, between January 2022 and January 2025. The control group consisted of patients who underwent evaluation for various clinical indications, including central precocious puberty, headache, central hypothyroidism, and short stature, and were subsequently found to have PitNETs on central nervous system (CNS) imaging. A flowchart illustrating patient selection, exclusion criteria, and final cohort allocation is presented in *Figure 1*.

Diagnostic and treatment procedures of participants

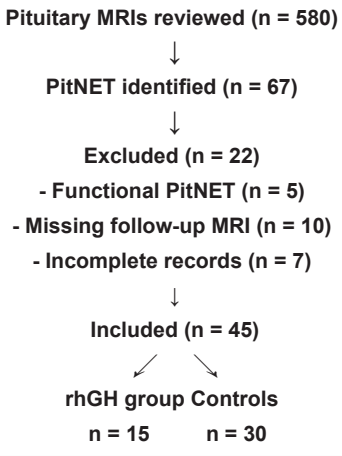
GHD was diagnosed based on auxological criteria (height SDS <-2 and growth velocity SDS <-1) and in insufficient response to at least two growth hormone stimulation tests, specifically L-dopa and clonidine, demonstrated by a peak GH level below 10 ng/mL.[2,14]

Except for one patient, rhGH treatment was administered as daily subcutaneous injections at a dose ranging from 20 to 35 µg/kg per day. The weekly rhGH therapy dose was administered as 0.66 mg/kg per week. During the treatment periods, IGF-I levels ranged between +1 SDS and +2 SDS.

All patients underwent pituitary MRI before rhGH initiation. MRI examinations were performed using a 1.5-T scanner with a dedicated contrast-enhanced pituitary protocol. Tumor dimensions were assessed by measuring maximal lesion length and width on serial MRI examinations, which were reviewed by experienced neuroradiologists as part of routine clinical practice. Follow-up MRI studies were evaluated at baseline and at 6, 12, 18, 24, and 36 months when available, and longitudinal changes in tumor dimensions were analyzed.

All patients except one, were found to have PitNETs measuring less than 10 mm in diameter.

Figure 1. Flowchart of patient selection and study cohort formation



In all cases, IGF-I, prolactin, ACTH, cortisol, free thyroxine (fT4), and thyroid stimulating hormone (TSH) levels were measured and other anterior pituitary functions were evaluated. Patients with biochemical or clinical evidence of hormone hypersecretion were excluded from the study.

Statistical analysis

Categorical variables are presented as frequencies (n) and percentages. Continuous variables are summarized as mean ± standard deviation (SD), standard deviation score (SDS), or median (IQR), as appropriate. Normality was assessed using the Shapiro–Wilk test. Because tumor size data were not normally distributed, they are presented as median (IQR). Between-group comparisons were performed using the Mann–Whitney U test and within-group comparisons using the Wilcoxon signed-rank test. Longitudinal effects of rhGH therapy and time on PitNET width and length were evaluated using linear mixed-effects models, with treatment group and time as fixed effects and subject-specific random intercepts as random effects. A diagonal covariance structure was specified for residual variance. Results from mixed-effects models are reported as β coefficients with 95% confidence intervals (CIs). Statistical analyses were performed using IBM SPSS Statistics version 23.0 (IBM Corp., Armonk, NY, USA), and $p < 0.05$ was considered statistically significant.

Ethics

This study protocol was reviewed and approved by the Akdeniz University Ethics Committee (Approval No: TBAEK-5/ 02.01.2025). The study was conducted in accordance with the Declaration of Helsinki and the ethical guidelines for medical and health research involving human subjects.

RESULTS

The mean age at diagnosis was 12.46 ± 4.17 years in the rhGH treated GHD group and 13.06 ± 3.07 years in the control group, with no statistically significant difference between the two ($p = 0.802$) (*Table 1*). There were significant differences in body weight (BW), height, and body mass index (BMI) SDS values between patients who received rhGH therapy and those who did not (*Table 1*). No significant differences were observed between the groups in terms of other laboratory parameters (*Table 1*). Of the 15 patients in this group, 9 were female and 6 were male. Among the patients receiving rhGH therapy, one had a diagnosis of mixed gonadal dysgenesis and another had Turner syndrome. Among patients receiving rhGH therapy, three individuals had multiple pituitary hormone deficiencies: one with combined GH and TSH deficiency, one with GH, TSH, and gonadotropin deficiencies, and one with GH and gonadotropin deficiency. The remaining 12 patients were diagnosed with isolated GHD.

No significant changes in PitNET dimensions were observed during follow-up in the rhGH-treated group (*Table 2*). One patient underwent surgical excision of the PitNET as a result of progressive growth detected on follow- up imaging. A 13-year-old patient with a three-year history of short stature was initiated on daily rhGH therapy. PitNET had been identified

Table 1. Baseline laboratory and clinical characteristics of patients with pituitary neuroendocrine tumors receiving recombinant human growth hormone therapy and untreated controls

Variables	rhGH receiving group n = 15	Control group n = 30	*P* value
Sex (F/M)	9/6	25/5	0.37
Age (year)	12.46 ± 4.17	13.06 ± 3.07	0.802
Weight (kg)	-1.72 ± 1.18	0.40 ± 1.20	<0.01
Height (cm)	-1.51 ± 1.60	0.45 ± 1.26	<0.01
BMI (kg/m^2)	-0.63 ± 1.22	0.37 ± 1.11	0.03
ACTH (7,2-63,3 ng/L)	26.49 ± 18.5	19.14 ± 9.55	0.052
Cortisol (4,82-19,5 ug/dL)	10.74 ± 4.07	9.30 ± 3.08	0.511
Prolactin (4,04-15,2 µg/L)	5.85 ± 3.46	14.97 ± 23.45	0.270
TSH (0,7-5,97 mIU/L)	2.13 ± 1.44	1.91 ± 0.81	0.133
fT_4 (0,96-1,77 ng/dL)	1.20 ± 0.16	1.30 ± 0.16	0.868
LH (IU/L)	7.48 ± 9.84	5.88 ± 14.75	0.977
FSH (IU/L)	4.53 ± 3.8	4.38 ± 3.66	**0.837**

Data are presented as mean ± standard deviation (SD). Between-group comparisons were performed using the Mann–Whitney U test. F, female; M, male; BMI, body mass index; ACTH, adrenocorticotropic hormone; TSH, thyroid-stimulating hormone; fT4, free thyroxine; LH, luteinizing hormone; FSH, follicle-stimulating hormone.

Table 2. Longitudinal comparison of pituitary neuroendocrine tumors size in patients receiving rhGH therapy relative to baseline (time of diagnosis)

Time point	PitNET's width median IQR, mm	*P* value	PitNET's length median (IQR), mm	*P* value
Baseline	1.0 (1.0-2.8)	-	3.5(2.5-4.5)	-
6 months	3.0 (2.0-3.5)	0. 109	4.5(3.5-5.5)	0.285
12 months	1.0 (1.0-3.5)	0. 180	3.5(2.0-4.5)	497
18 months	1.0 (1.0-2.0)	0. 100	3.0(1.0-3.5)	0.288
24 months	1.0 (1.0-2.0)	0. 273	3.0(1.5-3.5)	0.148
36 months	1.0 (1.0-2.0)	0. 180	2.0(1.0-3.5)	0.070

Data are presented as median (IQR) values. Comparisons between baseline and each follow-up time point (6, 12, 18, 24, and 36 months) were performed separately for PitNET width and PitNET length using the Wilcoxon signed-rank test.

prior to treatment, and serial pituitary imaging was performed throughout the follow-up period. During follow-up, the lesion was surgically excised after the tumor size increased beyond 10 mm. Growth hormone therapy was discontinued after the patient achieved a final height of 167 cm. Following the age of 18 years, the patient continued follow-up under adult endocrinology care.

In the control group, pituitary imaging was performed for various clinical indications: central precocious puberty (n = 18), headache (n = 6), central hypothyroidism (n = 3), and short stature (n = 3). This group included 25 females and 5 males. Similarly, no significant changes in PitNET dimensions were observed in the control group throughout follow-up (*Table 3*). No PitNET enlargement was observed in any of the patients in the control group during follow-up.

The effects of rhGH therapy and time on PitNET dimensions were evaluated using a linear mixed-effects model. No significant effects of rhGH therapy (β = −0.307, 95% CI: −1.350 to 0.736, p = 0.562) or time (F(5,196) = 0.897, p = 0.484) were observed on PitNET width. For PitNET length, the overall model was significant (F[6,196) = 3.857, p = 0.001), with a significant effect of time (F[5,196) = 4.481, p = 0.001), whereas rhGH therapy was not associated with changes in length (β = −0.542, 95% CI: −1.747 to 0.664, p = 0.377). Although modest time-related variations in length were observed, these were unrelated to rhGH therapy and were not indicative of clinically meaningful tumor progression.

DISCUSSION

We evaluated longitudinal changes in incidental nonfunctional PitNETs in pediatric GHD patients receiving rhGH and compared them with untreated controls. No significant differences in tumor progression were observed between groups. Although PitNET length showed time-

Table 3. Longitudinal comparison of pituitary neuroendocrine tumors size in untreated control patients relative to baseline (time of diagnosis)

Time point	PitNET's width median(IQR), mm	*P* value	PitNET's length median(IQR), mm	*P* value
Baseline	1.0 (1.0-3.0)	-	2.0 (2.0-6.0)	-
6 months	1.0 (1.0-3.0)	0. 068	3.0 (2.0-6.0)	0.228
12 months	1.0 (1.0-3.0)	0. 715	3.25 (2.0-6.0)	0.082
18 months	1.5 (1.0-3.0)	0. 838	3.5 (2.0-4.0)	0. 500
24 months	1.0 (1.0-3.0)	0. 207	3.75 (2.0-5.0)	0. 1
36 months	1.0 (1.0-3.0)	0. 476	3.0 (2.0-4.0)	0. 12

Data are presented as median (IQR) values. Comparisons between baseline and each follow-up time point (6, 12, 18, 24, and 36 months) were performed separately for PitNET width and PitNET length using the Wilcoxon signed-rank test.

related variation, these changes were unrelated to rhGH exposure and were not clinically meaningful. Overall, rhGH therapy did not appear to adversely affect the radiological course of incidental nonfunctional PitNETs during childhood.

The potential impact of rhGH therapy on PitNET growth has long been a concern due to the mitogenic and anti-apoptotic properties of GH and its downstream mediator, IGF-I. However, most data addressing this issue originate from adult populations, and evidence in pediatric patients remains limited. Our findings add to the limited pediatric evidence and suggest that rhGH therapy does not appear to be associated with clinically meaningful PitNET progression.

Derrick et al. showed that PitNET's are common in childhood GHD cases. In the study; the fact that most of the PitNET were micro (<1 cm), their typical localization and the absence of any visual changes suggest that these lesions may not represent a clear etiological factor for GHD.[7]

A meta-analysis combining data from epidemiological, postmortem, and radiologic studies estimated the prevalence of pituitary PitNET's to be approximately 16.7% in the general population.[15] In adult populations, the reported prevalence of PitNET ranges from 10% to 33.3%, whereas Hirsch et al. identified PitNET's in 29% of pediatric cases.[16,17] The frequency of PitNET in individuals diagnosed with GHD varies considerably among studies. Derrick et al. reported a prevalence of 20.3% in a cohort of 261 GHD patients.[7] In contrast, data from the Pfizer International Growth Database (KIGS), which encompasses over 15 000 GHD patients, demonstrated a markedly lower prevalence of 0.5%.[6] Supporting the findings of Derrick et al., a single-center study conducted in Türkiye identified PitNETs in 18.3% of 87 pediatric GHD patients, indicating a relatively high prevalence rate in this subgroup.[7,18] Upon detection of a PitNET, it is imperative to evaluate the functional status of the lesion, as this has direct implications for clinical management. Hormonal evaluation (IGF-I, prolactin, ACTH, cortisol, fT4, TSH) is essential in PitNET cases.

GH exerts its effects directly by binding to its specific receptor and indirectly by stimulating IGF-I production. Increased IGF-I levels promote cell proliferation and inhibit apoptosis, contributing to tissue growth and regeneration. These mitogenic and anti-apoptotic properties have been implicated in the potential modulation of tumor progression. The dual action of GH enhancing IGF-I-mediated cell proliferation and suppressing apoptosis has raised legitimate concerns regarding its potential role in promoting tumor growth and progression.[19-22]

Due to the potential mitogenic and anti-apoptotic effects of GH, studies assessing its long-term safety have been limited, with the majority conducted in adult populations. Studies specifically evaluating the effect of rhGH treatment in patients with PitNET have not shown a significant increase in tumor growth or recurrence rates.[20-23]

Derrick and colleagues evaluated CNS imaging in a cohort of 346 patients with short stature and 195 patients diagnosed with precocious puberty. The prevalence of pituitary PitNETs was found to be similarly high in both groups; no significant difference was observed based on gender (p = 0.46).[7] Notably, none of the PitNETs demonstrated growth, even among patients who received rhGH therapy. However, the study did not include a control group of patients who did not undergo rhGH therapy, limiting the ability to assess causal relationships.[7] Consistent with these findings, rhGH-treated patients and untreated controls

showed similar longitudinal radiological outcomes, with no evidence of increased PitNET progression associated with rhGH therapy.

In a separate single-center study conducted in Turkey, PitNET was detected in 18.3% of children with GH deficiency. No significant difference in PitNET size was observed between patients who received and those who did not receive treatment.[18] Consistent with these findings, our own study also found no statistically significant difference in PitNET size between patients who received and did not receive rhGH treatment during the 36-month follow-up period (6th, 12th, 18th, 24th, and 36th months).

Research evaluating the association between rhGH treatment and the risk of malignant tumor recurrence or the development of secondary neoplasms has focused largely on childhood cancer survivors who received rhGH treatment.[24-26] While some studies report a slight increase in the risk of developing secondary tumors, the majority of the available literature indicates no significant association between rhGH treatment and an increased risk of malignancy or tumor recurrence.[27-30] In our study, secondary malignancies were not detected in the patients.

Buchfelder et al., in a retrospective case-control study of surgically treated PitNET patients, found no significant difference in tumor growth between those who received and did not receive GH treatment.[31] Similarly, Arnold et al., analyzed 130 surgically treated PitNET patients, 23 of whom received GH therapy, and tumor progression was observed in 35% of treated patients and 36% of untreated patients, concluding that GH therapy did not contribute to tumor progression.[32] Furthermore, a meta-analysis in adult individuals reported that approximately 10% of PitNET's may grow spontaneously regardless of treatment.[17]

An important finding was the significant time-related variation in PitNET length detected by the mixed-effects model, despite the absence of any rhGH treatment effect. This suggests that minor longitudinal fluctuations in lesion size may occur independently of rhGH exposure and do not necessarily indicate clinically meaningful tumor progression. No significant differences in these changes were observed between groups.

Several limitations should be acknowledged. The retrospective single-center design and relatively small sample size may have limited statistical power. In addition, differences in baseline characteristics and the heterogeneous nature of the control group may have introduced residual confounding. Given the small size of most lesions, minor longitudinal variations in lesion dimensions should be interpreted cautiously, as they may partly reflect measurement variability rather than true biological tumor growth. Despite these limitations, no evidence of increased PitNET progression was observed in rhGH-treated patients during the 36-month follow-up. Larger prospective multicenter studies are needed to confirm these findings.

CONCLUSION

PitNETs are rare in childhood. In this cohort of children with incidental nonfunctional PitNETs, rhGH therapy was not associated with clinically meaningful tumor progression during 36 months of radiological follow-up. Radiological outcomes were comparable between treated and untreated patients. Larger prospective studies are needed to confirm these findings and further clarify the long-term safety of rhGH therapy in this population. ■

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