

Isolated hypogonadotropic hypogonadism in adolescence: Do we need to measure the pituitary, stalk or other imaging markers? A retrospective magnetic resonance imaging study

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ABSTRACT

Background. Rapid changes in the size of the pituitary gland occur during the pubertal period. Therefore, measuring and reporting magnetic resonance imaging (MRI) in adolescents with pituitary disorders can cause unease among radiologists. Our aim was to compare the size of the pituitary gland, stalk and other previously described imaging tools in patients with isolated hypogonadotropic hypogonadism (HH) versus adolescents with a normal pituitary gland.

Methods. Forty-one patients (22 female, 19 male, mean age 16.3 ±2.0 years) with HH who underwent MRI prior to starting hormone treatment were enrolled. Age, sex, and genetic mutations were noted. Pituitary height, width on the coronal plane, anteroposterior (AP) diameter on the sagittal plane, stalk thickness, pons ratio (PR), clivus canal angle (CCA) and Klaus index (KI) were measured by two radiologists twice with a one-month interval blinded to each other and patient information. Measurements were compared with the control group, including 83 subjects with normal hypothalamic-pituitary-gonadal axis and normal pituitary gland on MRI. Inter-rater and intra-rater agreements were also evaluated.

Results. No significant differences were found between the two groups regarding height, width or AP diameter ($p = 0.437, 0.836, 0.681$ respectively). No significant differences were found between the two groups regarding CCA and PR ($p = 0.890, 0.412$ respectively). The KI of the male patients was significantly higher than that of the female patients and the control group ($p < 0.001$). The interrater agreement was moderate for pituitary height and width, poor for pituitary AP diameter and stalk thickness, good for PR and KI, and excellent for CCA.

Conclusions. The measurements of the pituitary gland, stalk and posterior fossa structures were similar in adolescents with or without isolated HH. Consequently, pituitary gland, stalk or other posterior fossa measurements are unnecessary when evaluating a normal appearing pituitary gland on MRI.

Key words: hypogonadotropic hypogonadism, magnetic resonance imaging, delayed puberty, pons ratio, clivus canal angle.

Hypogonadotropic hypogonadism (HH), also known as secondary or central hypogonadism, reflects gonadal dysfunction resulting from hypothalamic-pituitary insufficiency.¹ It can

be either congenital (called idiopathic) or due to an acquired cause. Isolated HH is more common in males, with prevalence rates of approximately 1:4000 to 1:10000 among males and 1:50000 among females.² Since the most common known genetic cause is Kallmann syndrome, isolated HH can be divided into three categories: Kallmann syndrome, isolated HH with normosmia, and complex non-Kallmann syndromes.³ Although many tests are available to assess HH, most of them have limited accuracy in differentiating HH from

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constitutional delay of growth and puberty in adolescents.^{4,5} Since treatment can be considered at a younger age (up to 12 years old) for children with HH to maintain physiologic and psychosocial health, a definitive diagnosis is very important.⁶

Magnetic resonance imaging (MRI) of the pituitary gland is generally preferred before starting treatment for HH to exclude tumoral, infiltrative lesions, or malformative midline abnormalities affecting the hypothalamic-pituitary region that could damage GnRH neurons, the pituitary stalk, or pituitary gonadotrope cells and thereby prevent pubertal development.⁷ MRI is also quite useful for evaluating the olfactory bulbs, tracts and sulci to differentiate Kallman syndrome from other causes of HH.⁸ The pituitary size varies according to age, sex, and puberty, and the measures in patients with pituitary disorders can sometimes cause clinical and radiological confusion. There have been many studies defining the normal size and volume of the pituitary gland and stalk in children and adolescents.⁹⁻¹¹ However, there have been no comparative studies of the pituitary gland and stalk size between isolated HH patients and healthy adolescents in the literature.

In previous studies evaluating disorders of the hypothalamic-pituitary region, particularly for growth hormone deficiency, the pons ratio (PR) was described and suggested as an imaging biomarker. The PR was found to be significantly higher in patients with pituitary insufficiency than in healthy children.^{12,13} The clivus canal angle (CCA) and Klaus index (KI) were also significantly different between those patients and the control group.¹² The first objective of our study was to assess the pituitary and stalk diameters of adolescents with isolated HH and compare them with those of healthy peers located in a similar region. Our second aim was to measure previously described imaging parameters (PR, CCA and KI) in our patients and compare them between the sexes and with healthy adolescents.

Material and Methods

Patients and Control Group

Ethics approval for this retrospective study was obtained from Diyarbakir Gazi Yaşargil Training and Research Hospital Non-Interventional Clinical Research Ethics Committee (approval number: 2021/947, date of approval: 03/12/2021). We evaluated the patients diagnosed with HH in our pediatric endocrinology department between January 2017 and June 2022. Clinical and laboratory data of the patients were obtained from their files in the archive of pediatric endocrinology. The diagnostic criteria for HH were absent or incomplete pubertal development (menarche and secondary sexual characters) for age, low gonadal volume of bilateral gonads without any organic gonadal lesion, low estradiol concentrations for female, low total testosterone for males and low or inappropriately normal serum gonadotropin concentrations, and normal results for prolactin, thyroid-stimulating hormone, growth hormone, cortisol and adrenocorticotropic hormone to exclude complete pituitary insufficiency.

We identified 46 patients (26 females and 20 males) with a clinical diagnosis of isolated HH, and 41 (22 females and 19 males) of those had available MRI examinations in our radiology archive. Age, sex, genetic mutations, age at MRI examination, and clinical findings were noted. We also formed a healthy control group for comparison with the patients instead of using normal reference values from the literature to prevent age, sex, and ethnicity discrepancies. We attempted to maintain an approximately 1:2 case/control ratio to increase the statistical power of the analysis. Subjects in the control group were selected for each patient of a similar age (\pm 12 months) at MRI examination. The control group consisted of patients who presented with various complaints, but laboratory data regarding the hypothalamic-pituitary axis were normal. We retrieved 100 pituitary MRI studies from our radiology archive to form the control group. We excluded seventeen patients who

had abnormal findings on pituitary MRI (six Rathke cleft cysts, five partial empty sella, three nonfunctioning adenomas, two suprasellar arachnoid cysts and one generalized atrophy of the brain and cerebellum). The remaining 83 patients constituted our control group. A flow chart of the sample selection for the study and control groups is presented in Fig. 1.

Imaging Evaluations

Pituitary MRI examinations in both groups were performed on a 1.5-T Signa HDxt scanner (General Electric Healthcare; Milwaukee, WI, USA) with an 8-channel, 8-element phased array head coil. The standard pituitary imaging protocol comprised coronal T1-weighted and T2-weighted images (slice thickness, 2 mm), mid-sagittal pre- and postcontrast T1-weighted images covering the area between the lateral wall of each cavernous sinus (slice thickness, 3 mm), and dynamic coronal T1-weighted images including 5 phases (1 precontrast and 4 postcontrast studies, 40-second interval between the phases and slice thickness, 2 mm).

For parametric data, pituitary height was measured from the postcontrast sagittal or coronal image for each patient, which revealed that the borders of the pituitary gland were more conspicuous than in the other sequences.

Width was measured from the coronal images; anteroposterior (AP) diameter and pituitary stalk thickness were measured from the sagittal images (Fig. 2A,2B). The PR, CCA and KI were measured from mid-sagittal images. To measure the PR, a line from the tip of the dorsum sella to the fastigium of the fourth ventricle was drawn. The ratio of the height of the pons above this line to the total height of the pons on mid-sagittal images was defined as the PR (Fig. 2C). The CCA was the angle between the line coursing through the dorsal surface of the clivus and the posterior margin of the odontoid process of the C2 vertebra (Fig. 2D). The KI was the shortest distance between the tip of the odontoid process and Twining's line (the line between the tuberculum sella and torcula) (Fig. 2E).¹²

Images were reviewed by two radiologists with 7 (E.A.) and 5 (C.C.) years of experience in neuroimaging. Measurements were performed twice by the two radiologists independently, without knowledge of the patient's information, with a one-month interval between measurements. Measurements were performed on the best quality series, and these series were recorded. All of the measurements were performed utilizing RadiAnt DICOM Viewer software, version 2022.1.1 (Medixant, Poznan, Poland, <https://www.radiantviewer.com>).

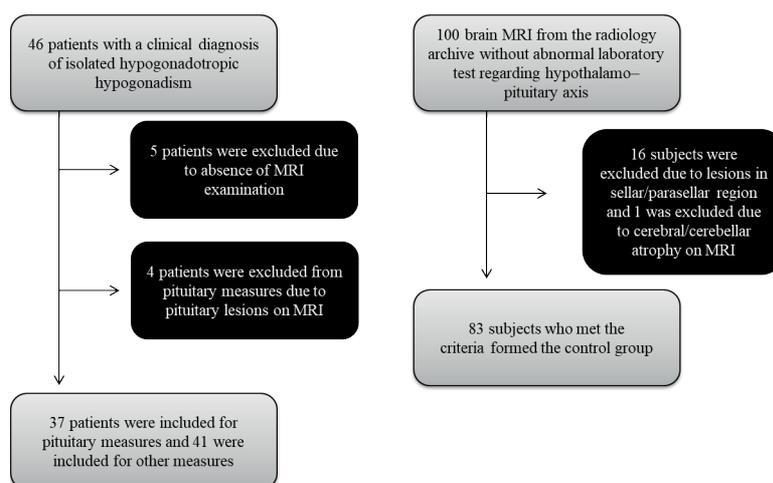


Fig. 1. Flow chart of the sample selection for the study and control groups.

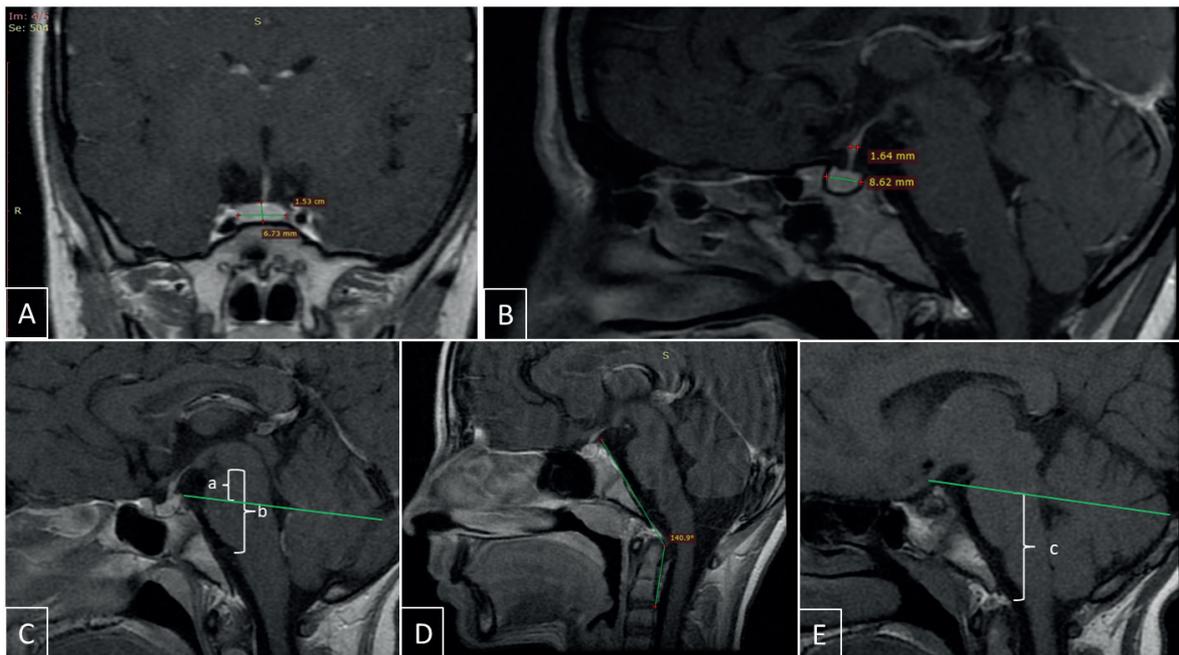


Fig. 2. Measurement methods used in the study. (A) Pituitary height and width measurements from coronal postcontrast T1-weighted images at the widest points of the pituitary gland. (B) Mid-sagittal T1-weighted image presents the anteroposterior diameter of the pituitary gland and the thickness of the stalk. (C) Mid-sagittal T1-weighted image demonstrates the pons ratio (a/b). (D) Mid-sagittal T1-weighted image represents measurement of the clivus canal angle, the angle between the dorsal surface of the clivus and the posterior margin of the odontoid process of the C2 vertebra. (E) Mid-sagittal T1-weighted image demonstrates the Klaus index (c) between the tip of the odontoid process and the line connecting the tuberculum sella and internal occipital protuberance.

Statistical analysis

Descriptive statistics were expressed as the mean \pm standard deviation (SD) for continuous variables and as numbers and percentages for categorical variables. The median values of four measurements of distances, ratios and angles of the control and patient groups were used to prevent the effects of outliers. For continuous variables, the Kolmogorov-Smirnov test was used to test for the normal distribution of data. Pearson's chi-square test was used to compare categorical variables among groups. Student's t test was used for the comparison of two parametric variables that showed a normal distribution, and the Mann-Whitney U test was used for the comparison of two parametric variables that showed a nonnormal distribution.

To evaluate the reliability of inter-rater and intra-rater measurements, the intraclass

correlation coefficient (ICC) was used with two-way random and two-way mixed effects models, respectively. When evaluating intra-rater reliability, average values of two measurements from each reviewer were used. The 95% confidence interval (CI) of the ICC estimate was used to evaluate the level of reliability, which was classified as excellent for values greater than 0.85, good for values between 0.70 and 0.85, moderate for values between 0.5 and 0.75, and poor for values less than 0.5.¹⁴

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) for Windows, version 23.0 (SPSS Inc., Chicago, IL, USA). The level of significance was set at $p < 0.05$, and the significance level was adjusted according to Bonferroni's correction for multiple comparisons.

Results

The study group included 41 patients with isolated HH (22 female and 19 male, mean age at MRI = 16.3 ± 2 years old (range between 12.8 and 21.1 years)), and the control group included 83 healthy subjects (57 female and 26 male, mean age at MRI = 15.4 ± 3.6 years old (range between 12.1 and 22 years)). The demographic data of the patient and healthy control groups are presented in Table I. No significant difference was found between the two groups regarding age and sex (p = 0.166 and 0.122). Four patients (9.76%) had an organic lesion on pituitary MRI; three of those were Rathke cleft cysts (pars intermedia cysts), and one lesion was a partial empty sella. We excluded these patients from pituitary and stalk measures but included them in the CCA, PR, and KI measures. Therefore, 37 patients were included in the study group for pituitary height, width and AP diameter and for stalk thickness measurements, whereas 41 patients were included for PR, CCA and KI. Sixteen of the 41 (39%) patients were evaluated with next-generation sequencing of 38 targeted

genes responsible for HH. Seven patients (43.8%) had a mutation in a particular gene (three had a mutation in *TACR3*, one had a mutation in *PROK2*, one had a mutation in *GNRHR*, one had a mutation in *WDR11* and one had a mutation in *SOX10*). No genetic mutations were identified in the remaining nine patients.

Pituitary gland, stalk and other measurements

In the comparison of the pituitary gland measurements, no significant differences were found between the two groups regarding height, width and AP diameter (p = 0.437, 0.836 and 0.681, respectively). Pituitary stalk thickness was significantly higher in patients than in the control group (p < 0.001). Additionally, no significant difference was found between the two groups regarding CCA and PR (p = 0.890, and 0.412). The KI was significantly higher in patients than in healthy controls (p = 0.027). The mean values and comparison of the measurements of the study group and the control group are presented in Table II and Fig. 3.

Table I. Demographic data of the study group, control group and their comparison.

	Central hypogonadism	Healthy subjects	P value
Number of cases	41	83	
Mean age ± SD (min/max) (years)	16.3±2.0 (12.8/21.1)	15.4±3.6 (12.1/22.0)	0.121
Gender (F/M)	22/19	57/26	0.122
Mean age ± SD of females (years)	16.5 ±2.1	15.9 ±3.8	0.386
Mean age ± SD of males (years)	16.1 ±1.9	14.2 ±2.7	0.033

F: female, M: male, max: maximum, min: minimum, SD: standard deviation

Table II. Mean distance and angle measurement parameters of the study group and the control group and comparison.

Measurement Parameters	Central hypogonadism (n=41) mean ± SD	Healthy subjects (n=83) mean ± SD	P value
Pituitary Height (mm)*	5.4 ± 1.01	5.6 ± 0.93	0.346**
Pituitary Width (mm)*	13.7 ± 2.18	13.9 ± 2.13	0.745**
Pituitary AP diameter (mm)*	9.5 ± 1.10	9.4 ± 1.22	0.781***
Pituitary stalk thickness*	1.9 ± 0.34	1.6 ± 0.25	<0.001***
Pons Ratio	0.32 ± 0.04	0.32 ± 0.04	0.827***
Clivus canal angle	149.8 ± 6.91	148.7 ± 8.68	0.406**
Klaus index (mm)	39.0 ± 3.66	37.7 ± 3.33	0.032**

AP: anteroposterior, n: number of subjects, SD: standard deviation . *Calculated in 37/41 patients with central hypogonadism
t test *Mann-Whitney U test

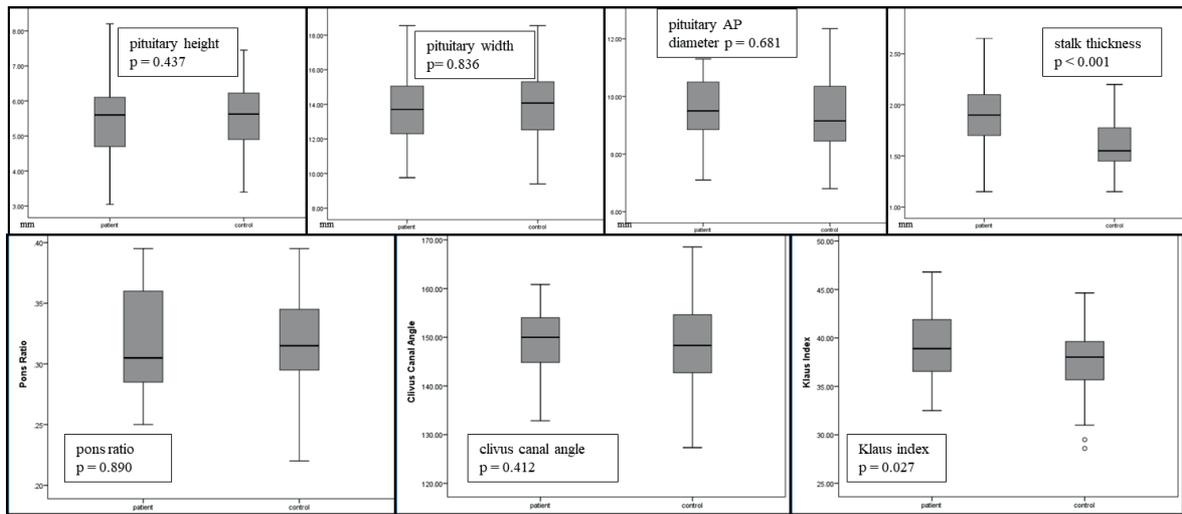


Fig. 3. Boxplot graphs showing the comparison of the diameter, index and angle measurements with p values between the adolescents with hypogonadotropic hypogonadism and the healthy subjects.

We also compared the measurements of the study group and the control group separately according to sex. In isolated HH patients, KI was significantly higher in males than in females ($p = 0.001$). No significant differences were found among the other measurements of the study group ($p > 0.05$). There were no significant differences between males and females in the control group among any of the measurement parameters ($p > 0.05$) (Table III).

The reliability analysis between the radiologists and the agreement between the two measurements of each individual radiologist

are shown in Table IV. According to the 95% CIs of the ICC values, inter-rater agreement was moderate for pituitary height and width, poor for pituitary AP diameter and stalk thickness, good for PR and KI, and excellent for CCA. For reviewer 1 (E.A.), the inter-rater agreement was moderate for pituitary height and width, poor for pituitary AP diameter and stalk thickness, moderate for PR and excellent for CCA and KI. For reviewer 2 (C.Ç.), the inter-rater agreement was good for pituitary height, moderate for pituitary width, poor for pituitary AP diameter and stalk thickness, moderate for PR, excellent for CCA and good for KI.

Table III. Mean values of the study parameters according to sex in each group and comparison.

Measurement parameters	Central hypogonadism			Healthy subjects		
	Females mean \pm SD (n = 22)	Males mean \pm SD (n = 19)	P value	Females mean \pm SD (n = 57)	Males mean \pm SD (n = 26)	P value
Pituitary height (mm)	5.5 \pm 1.1	5.3 \pm 0.9	0.450*	5.7 \pm 1.0	5.4 \pm 0.8	0.175*
Pituitary width (mm)	13.6 \pm 2.2	13.9 \pm 2.2	0.652*	14.2 \pm 2.2	13.2 \pm 1.8	0.066*
Pituitary AP diameter (mm)	9.4 \pm 1.2	9.5 \pm 1.0	0.649*	9.5 \pm 1.3	9.2 \pm 1.0	0.271**
Pituitary stalk thickness	1.9 \pm 0.3	1.9 \pm 0.4	0.726*	1.6 \pm 0.3	1.6 \pm 0.2	0.246**
Pons ratio	0.31 \pm 0.05	0.32 \pm 0.04	0.791*	0.32 \pm 0.04	0.32 \pm 0.04	0.908*
Clivus canal angle	150.7 \pm 6.2	149.7 \pm 7.7	0.647*	149.8 \pm 9.3	147.2 \pm 6.6	0.203*
Klaus index (mm)	37.5 \pm 2.9	41.1 \pm 3.5	0.001*	37.3 \pm 3.4	38.7 \pm 3.1	0.078*

AP: anteroposterior, n: number of subjects, SD: standard deviation *t test **Mann-Whitney U test

Table IV. Inter-rater and intra-rater agreement intraclass coefficient (ICC) values with 95% confidence intervals.

	Pituitary height ICC (95% CI)	Pituitary width ICC (95% CI)	Pituitary AP length ICC (95% CI)	Stalk thickness ICC (95% CI)	Pons ratio ICC (95% CI)	Clivus canal angle ICC (95% CI)	Klaus index ICC (95% CI)
Inter-rater Agreement	0.790 (0.593–0.892)	0.831 (0.671–0.913)	0.648 (0.317–0.819)	0.584 (0.324–0.762)	0.884 (0.780–0.939)	0.948 (0.901–0.972)	0.914 (0.838–0.955)
Intra-rater Rater 1	0.801 (0.613–0.897)	0.837 (0.683–0.916)	0.728 (0.471–0.860)	0.609 (0.358–0.777)	0.836 (0.689–0.913)	0.946 (0.898–0.972)	0.929 (0.867–0.963)
Agreement Rater 2	0.891 (0.791–0.943)	0.824 (0.659–0.909)	0.737 (0.498–0.862)	0.652 (0.324–0.821)	0.785 (0.593–0.886)	0.931 (0.869–0.963)	0.916 (0.841–0.956)

* ICC: intraclass correlation coefficient, CI: confidence interval, AP: antero-posterior; all measurements had p values of < 0.005

Discussion

Based on the results of our study, there were no significant differences between the adolescents with isolated HH and healthy adolescents regarding the pituitary diameters, PR and CCA. Although the stalk thickness of the patient group was significantly higher than that of the control group, the reliability of this measurement was the lowest among all parameters of the study. The KI was found to be significantly higher than that of healthy subjects, and it was mainly based on the higher KI of males in the patient group. The KI is the craniocaudal distance of a particular part of the cranium, which might be affected by height differences among the subjects. Since we did not have the height information from both groups during the MRI examination, we were not able to correlate the height and KI values.

Pituitary MRI is generally included in the diagnostic investigation of pituitary endocrinopathies since it has the highest diagnostic accuracy among radiological modalities.^{15,16} The gradual increase in normal pituitary gland volume during the pubertal period is a well-known phenomenon.¹⁷ This increase in pituitary height begins at the age of 11 years old in females and 13 years old in males, reaches the maximum volume in the third decade of life and then gradually decreases.^{9,17} Due to changing size in the pubertal period, the interpretation of pituitary MRI in adolescents can cause uncertainty among radiologists. Therefore, many articles have been published providing normative data for pituitary and stalk size and volume in the literature.^{9,10,17,18} The abovementioned increase in pituitary volume during puberty has generally been attributed to the increase in gonadotropins (LH and FSH). However, our study showed that no significant difference was seen between hypogonadotropic and normogonadotropic adolescents in a similar age group regarding pituitary size. Although our study was based on a small number of subjects with a particular disorder, the findings can encourage researchers to revise this generally accepted hypothesis.

As a general opinion, the height and volume of the pituitary gland are larger in females than males during the pubertal period.^{9,17} In the present study, although females had slightly larger height in both groups, there were no significant differences between males and females according to pituitary height, width and AP diameter in either the isolated HH group or the healthy subjects. Similar to our results, no significant difference was found between female and male subjects in the study by Naik et al.¹⁸ performed on an Indian population between 10 and 19 years old according to pituitary height, length and width.

Pituitary stalk thickness also shows a correlation with pituitary gland enlargement during the pubertal period in healthy adolescents. Sari et al.⁹ suggested using the pituitary stalk to basilar artery ratio on the same axial plane for evaluating stalk thickening. The maximum ratios were 0.73 and 0.70 for females and males, respectively, in adolescents, without significant differences between genders. However, the diameter of the arteries of the vertebrobasilar system is very variable, and the normal basilar artery diameter ranges from 3 to 7 mm.¹⁹ Therefore, we believed that the aforementioned ratio was an unreliable tool, and we directly measured the stalk thickness on the sagittal plane. In our study, HH patients (mean 1.9 mm \pm 0.34) had significantly thicker stalks than the control group (mean 1.6 mm \pm 0.25). The most frequent cause of stalk thickening in adolescents is inflammatory and infectious etiologies such as lymphocytic hypophysitis, tuberculosis, or neurosarcoidosis. Also, the most common functional disorder is central diabetes insipidus, which is a posterior pituitary disorder.²⁰ However, recent studies showed that stalk thickening also indicates an anterior pituitary disorder or the combination of an anterior and posterior pituitary disorder.^{20,21} Ling et al.²¹ evaluated the etiology of stalk thickening in 325 patients with a median age of 30.5 years, and 277

of those had an anterior pituitary disorder. The most common cause of the anterior pituitary disorder was hypogonadism (31%), followed by growth hormone deficiency (25.3%) and hypothyroidism (6.8%), which is concordant with our study.²¹ Nevertheless, poor interrater and intrarater ICC of the pituitary stalk and nonnormal distributions of the values of both groups decreased the reliability of our stalk measurements.

Four of 41 patients (9.76%) in our study group and 16 of 100 (16%) subjects with a normal hypothalamic-pituitary-gonadal axis forming the control group had non-adenomatous pituitary lesions on MRI. The most common lesion was a Rathke cleft cyst, followed by a partially empty sella. Accordingly, a partially empty sella is found in 20% of the population, and Rathke cleft cysts are found in 11-33% of autopsy series.^{22,23} In the study by Tang et al.², empty sella were found in 7.1% of isolated HHs. These results suggest that organic lesions of the pituitary gland can be seen in isolated HH but not more frequently than in the normal population.

The low pituitary gland height in adolescents with isolated or multiple pituitary hormone deficiencies was reported to be between 25% and 62%.^{13,24,25} This broad variation renders height measurement unreliable; therefore, other imaging tools have been described, such as PR, CCA and KI.^{12,13} Although pituitary diameter measurements vary greatly during puberty, these imaging methods are not affected by pubertal status. In patients with growth hormone deficiency, endochondral ossification and the development of sphenoid-occipital synchondrosis and the skull base cause delays due to reduced production of insulin-like growth factor 1, also called somatomedin C.²⁶ Underdevelopment of the skull base, particularly the posterior fossa, can cause a superior shift of the brain stem along with the hypothalamus, leading to traction in

the pituitary stalk.¹³ In previous studies, PR was significantly higher in children with growth hormone deficiency, likely due to upward displacement of the pons.^{12,13} Additionally, CCA and KI were significantly lower in those patients, probably due to underdevelopment of the posterior fossa skull base.¹² Other pituitary hormones, such as gonadotropin, TSH and ACTH, have been suggested to potentiate this effect together with growth hormone deficiency, thereby leading to a higher PR.¹³ However, we did not find a significant difference between the isolated HH patients and the control group according to PR or CCA. In contrast to previous studies, KI was significantly higher in males with isolated HH than in females and healthy controls. However, we had only 19 males with isolated HH, and we were not able to correlate with the height of the subjects, which might have led to bias in our data.

This study has several limitations. First, due to the retrospective nature of the study, we were not able to arrange the imaging protocol according to our parameters, but we had to use the available examinations instead. 3D T1 or axial thin section steady-state free precession (SSFP) with a higher magnetic field would be more accurate for evaluating tiny anatomical structures, particularly the pituitary stalk. We were not able to control the positions of the patients during MRI scanning, which might have affected the CCA measurements. Second, we could not compare the different types of isolated HH, such as Kallmann syndrome, which is diagnosed with the detection of genetic mutations or objective smell identification tests.²⁷ Finally, the number of included patients might not be sufficient to attain a definitive conclusion. Further multicenter, prospective studies and comparisons with other types of central hypogonadism are required to validate our results. Since the time of examination could

not be organized, no correlation between the hormonal levels and MRI measurements was established.

In conclusion, this study revealed that pituitary measurements on pituitary MRI did not contribute any additional value when evaluating isolated HH in adolescents other than entailing a loss of time. Therefore, only evaluating structural abnormalities and lesions seems to be sufficient in these patients. Further studies of similar parameters in other pituitary disorders in the same age group would be beneficial to expand on our results.

Ethical approval

Ethics approval for the retrospective study was obtained from Diyarbakir Gazi Yasargil Training and Research Hospital Non-Interventional Clinical Research Ethics Committee (approval number: 2021/947, date of approval: 03/12/2021).

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: EA, RY; data collection: RY, ŞÖ; analysis and interpretation of results: EA, CÇ; draft manuscript preparation: EA. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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