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Pituitary imaging findings in pediatric patients with idiopathic hypogonadotropic hypogonadism

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Objective. Idiopathic hypogonadotropic hypogonadism in children is a disease leading to a puberty absence. Some hypothalamic and pituitary defects cause hypogonadotropic hypogonadism. Pituitary magnetic resonance imaging is routinely performed in these patients. In our study, we provide an information about pituitary pathologies associated with an idiopathic hypogonadotropic hypogonadism in childhood.

Methods. Twenty-two patients, who were admitted to the pediatric endocrine outpatient clinic of our hospital because of their undeveloped secondary sex characteristics during adolescence, were included in our study. Age, gender, history, physical examination findings, and laboratory tests were recorded in patients. Pituitary magnetic resonance imaging results were examined. The criteria for the diagnosis of hypogonadism were: absence of puberty or delayed puberty, clinical signs or symptoms of hypogonadism, and presence of low or normal gonadotropin levels.

Results. In the present study, 22 patients were diagnosed with hypogonadotropic hypogonadism. The mean age of the patients was 15.90±1.09 years. Basal and stimulated luteinizing hormone and follicular stimulating hormone levels of the patients were found to be low. Prolactin, cortisol, adrenocorticotropic hormone, free thyroxine, and thyroid stimulating hormone levels were within normal limits in all patients. The pituitary magnetic resonance imaging revealed six patients with pituitary adenoma, one with empty sella turcica, and five with pituitary hypoplasia.

Conclusions. The present data showed that in the presence of hypogonadotropic hypogonadism, the hypothalamic-pituitary abnormalities are more likely to be present in the children compared to the adult population. Thus, it can be strongly emphasized the importance of the pituitary imaging examination, especially in the idiopathic hypogonadotropic hypogonadism cases.

Key words: hypogonadotropic hypogonadism, pituitary hypoplasia, pituitary imaging examination

Normal functioning of the hypothalamic-pituitary-gonadal axis is required for the normal human puberty progression initiation and maintenance (Wang et al. 2017). Hypogonadotropic hypogonadism can be congenital or acquired. The congenital hypogonadotropic hypogonadism is the most common cause of permanent hypogonadotropic hypogonadism in both genders (Laitinen et al. 2011). Congenital hypogonadotropic hypogonadism is divided into two types depending on the presence of the sense of smell: anosmic or hypoosmic hypogonadotropic hypogonadism (Kallmann syndrome) and congenital normosmic isolated hypogonadotropic hypogonadism (idiopathic hypogonadotropic hypogonadism). The incidence of congenital hypogonadotropic hypogonadism is approximately 1–10,100,000

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live births. Approximately two-third of the cases are Kallmann syndrome and one-third are idiopathic hypogonadotropic hypogonadism (Fraietta et al. 2013). Idiopathic hypogonadotropic hypogonadism is characterized by low levels of gonadotropin and sex steroids due to anatomical or functional abnormalities in the hypothalamic-pituitary-gonadal axis (Fraietta et al. 2013). Pulsatile secretion of the hypothalamic gonadotropin-releasing hormone (GnRH) is the most important factor in the puberty initiation (Young et al. 2019). The pathogenetic mechanism of idiopathic hypogonadotropic hypogonadism involves developing or differentiating failure of GnRH neurons in the hypothalamus resulting in a lack of GnRH secretion or its pulsatile release (Fraietta et al. 2013). In these patients, pituitary magnetic resonance imaging (MRI) has been performed to reveal anatomical defects (Dugeroglu and Karakas 2018).

In the present study, we provide information about the demographic characteristics and pituitary pathologies of patients diagnosed with idiopathic hypogonadotropic hypogonadism in childhood. In addition, we aimed to reveal the importance of pituitary imaging in patients with hypogonadotropic hypogonadism and thus to identify the pituitary pathologies that can be simultaneously seen with hypogonadotropic hypogonadism.

Materials and Methods

Subjects and parameters. Our study included 22 adolescent patients with hypogonadotropic hypogonadism who were admitted to our hospital's pediatric endocrinology outpatient clinic between October 2018 and May 2020 because their secondary sex characteristics have not been developed. Approval of this study was obtained from the Local Ethical Committee (approval number: 2020/08-08). Written consent was obtained from the patients and/or their parents.

The criteria for the diagnosis of idiopathic hypogonadotropic hypogonadism included: 1) absence of puberty or delayed puberty with testicular volume <4 mL in boys older than 14 years and no thelarche in girls older than 13 years; 2) clinical signs or symptoms of hypogonadism (micropenis, cryptorchidism, absence of breast development, etc.); 3) in the presence of low or normal gonadotropin, a serum testosterone level in boys below 1 ng/mL or a serum estradiol level in girls below 20 pg/mL (Dugeroglu and Karakas 2018). Age, gender, history, family history, and physical examination findings (anthropometric measurements and secondary sex characteristics) of the patients were recorded. Anthropometric measurements included weight and height measurements. Testicular volume was measured using a prader orchideometer. The presence of breast development and menstrual bleeding were evaluated in girls. The Tanner scale was used to evaluate the sexual maturity stage of patients.

Laboratory tests for basal luteinizing hormone (LH) (limit of quantification, LOQ: 0.5 mlU/mL; cross-reactivity: 0.001%), follicular stimulating hormone (FSH) (limit of detection, LOD: 0.05 mlU/mL; cross-reactivity: 0.0%), estradiol (E2) (LOQ: ≤10 pg/mL; cross-reactivity: 0.0%), prolactin (PRL) (LOD: 0.06 ng/mL; cross-reactivity: 0.0%), free thyroxine (fT4) (LOQ: 0.4 ng/dL; LOD: 0.28 ng/dL; cross-reactivity: ≤0.003%), thyroid stimulating hormone (TSH) (LOQ: ≤0.0025 μIU/mL; cross-reactivity: 0.0%), cortisol (LOQ: 0.25 ng/dL; cross-reactivity: 1.9%), and adrenocorticotropic hormone (ACTH) (LOQ: 3.13 pg/mL; cross-reactivity: <0.1%) were conducted. All hormones were measured using the chemiluminescent immunoassay (Abbott, ci16200, USA) method. All patients underwent a GnRH stimulation test. Before GnRH injection, the basal hormone levels of LH, FSH, and testosterone (male) or E2 (female) were measured. LH and FSH levels were measured 15, 30, 60, and 90 min after LH-releasing hormone (LHRH) injection (2.5 μg/kg, gonadorelin acetate).

To rule out delayed puberty, all patients were re-evaluated for endogenous production after six months of induction therapy with estradiol (2 mg/day) or testosterone (50 mg/month). Patients accepted as experiencing delayed puberty were excluded from the study. All patients were evaluated with karyotype. Pelvic ultrasound was performed in female patients to determine the size and the shape of the uterus.

Pituitary magnetic resonance imaging (MRI) results were retrospectively reviewed by a single experienced radiologist. MRI were performed using a 1.5 Tesla MRI machine. A 0.5 molar contrast agent containing gadolinium was used. After unenhanced T2 and T1 weighted coronal sequence, contrast-enhanced T1 weighted dynamic sequences, and contrast-enhanced sagittal T1 weighted sequence were obtained. MRI findings were evaluated according to the morphological appearance (normal, partial or completely empty sella turcica, macroadenoma, and microadenoma).

Statistical analysis. Numerical data are shown as mean and standard deviation (SD). Categorical variables were expressed as frequency and percentage. Calculations were performed with Excel Programme (Microsoft Office 2007).

Results

Twenty-two patients diagnosed with idiopathic hypogonadotropic hypogonadism participated in this study. The mean age of the patients was 15.9±1.09 years and 20 (90.9%) of them were girls. No patients had anosmia. When the patients reported that they can smell their own odor, the smell test was omitted. There were 2 patients with a parental relationship in their histories and 9 (40.9%) patients had a family history of hypogonadism. There was no history suggesting hypothalamic amenorrhea. Demographic data, physical examination, and laboratory results of the patients are shown in Table 1.

Testicular size in 2 male patients was prepubertal and pubic hair was Tanner stage 1 on physical examination. Eighteen female patients were at breast Tanner stage 1 and two female patients were at breast Tanner stage 2. The patients with the mean height standard deviation scores (SDS) –0.84±0.71, the body weight SDS –0.04±1.19, and BMI <15th percentile were excluded from the study. None of the patients had dysmorphic findings. The karyotype results of all patients were normal. In all female patients, the uterine size was small for their age.

Table 1
Demographic, physical, laboratory, and MRI characteristics of patients

Parameter	n=22
Patient demographic data	
Age (years)	15.9±1.09
Gender (F/M)	20/2
Family history [n, (%)]	9 (40.9%)
Anthropometric measurements	
Height (SDS)	–0.84±0.71
Weight (SDS)	–0.04±1.19
BMI (SDS)	0.06±0.99
Laboratory findings	
Basal LH (mIU/mL)	0.07±0.07
Basal FSH (mIU/mL)	0.31±0.26
Stimulated LH (mIU/mL)	1.46±1.01
Stimulated FSH (mIU/mL)	2.78±1.31
Pituitary MRI findings	
Pituitary microadenoma [n (%)]	6 (27.2%)
Empty sella turcica [n (%]	1 (4.5%)
Pituitary hypoplasia [n (%)]	5 (22.7%)

Data are presented as mean ± standard deviation (SD).
Abbreviations: BMI – body mass index; FSH – follicle-stimulating hormone; LH – luteinizing hormone; MRI – magnetic resonance imaging; SDS – standard deviation scores.

The mean basal LH and FSH values of the patients were 0.07±0.07 mIU/mL and 0.31±0.26 mIU/mL, respectively. The mean stimulated LH and FSH values of the patients were 1.46±1.01 mIU/mL and 2.78±1.31 mIU/mL, respectively. The levels of prolactin, cortisol, ACTH, fT4, and TSH were within normal limits in each patient.

Pituitary MRI revealed that 6 patients (27.2%) had pituitary microadenoma (pituitary adenoma size <10mm), 1 patient (4.5%) had empty sella turcica, and 5 patients (22.7%) had pituitary hypoplasia (Figures 1, 2).

Discussion

This study evaluated the clinical and endocrinological features and pituitary imaging findings of idiopathic hypogonadotropic hypogonadism in a pediatric population. Generally, the studies conducted on patients with idiopathic hypogonadotropic hypogonadism have a high male predominance (Shin et al. 2015). However, in our study in eastern Turkey, females dominated in the idiopathic hypogonadotropic hypogonadism-diagnosed patient group.

In a study examining pituitary pathologies and MRI imaging in children and adolescents, the pituitary MRI has been found to be normal in patients with hypogonadotropic hypogonadism (three Kallmann syndrome, one Prader-Willi syndrome, and two idiopathic hypogonadism) (Cacciari et al. 1990). Pituitary lesions were not detected in 84% of the pituitary MRI scans performed on the diagnosis of hypogonadism in a large group of patients (Famini et al. 2011). However, in the same study, positive pituitary MRI findings were typically present in patients with hypogonadotropic hypogonadism who also had very low testosterone and/or E2 levels (Famini et al. 2011). In our pediatric patient group, the hormone levels of the patients were very low and we obtained more pathological results in pituitary MRI scans compared to the literature.

Most pituitary adenomas are diagnosed when they cause clinical symptoms associated with hormonal hypo/hypersecretion or sellar compression (Freda et al. 2011; Hirsch et al. 2015). Pituitary adenoma may also be found incidentally in a pituitary MRI, which is usually performed for another reason. According to autopsy data, the mean frequency of pituitary adenomas in individuals with suspected pituitary disease is 10.6% and ranges between 1.5% and 27%.

In a study conducted in adult patients with hypogonadotropic hypogonadism, pituitary microadenoma has been found in 10.7% of patients and no macroadenoma was found (Molitch 2008; Hirsch et al. 2015). In our study, pituitary adenoma was found at a higher rate (27.2%) than the mean frequency of nonfunctional pituitary adenomas seen in the general population. All of these were microadenomas. In contrast to the high prevalence of pituitary microincidentalomas, macroadenomas are found in only 0.2% and 0.16% of patients examined with CT and MRI scans, respectively (Nammour et al. 1997; Hirsch et al. 2015). In our study, similar to the literature, none of the patients had macroadenoma or pituitary adenoma compression symptoms. In addition, none of the patients had pituitary hormonal abnormalities except hypogonadotropic hypogonadism. Therefore, the clinical significance of the pituitary lesions detection was probably negligible.

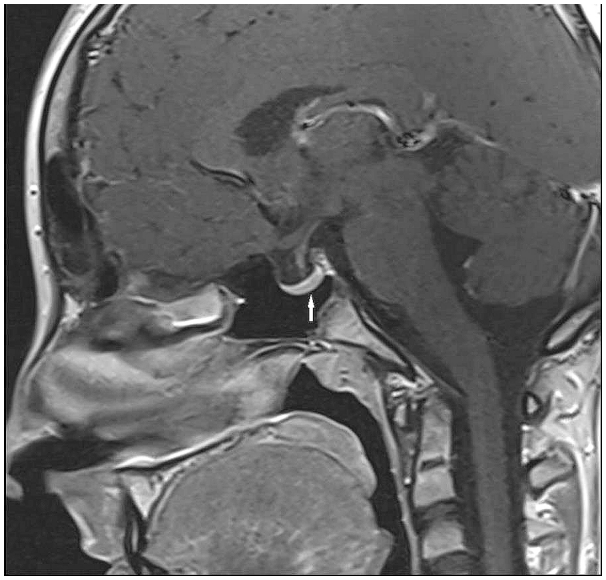


Figure 1. Seventeen-year-old female patient. The pituitary gland (upper white arrow) measured 2 mm thick on contrast-enhanced sagittal T1W pituitary magnetic resonance imaging.

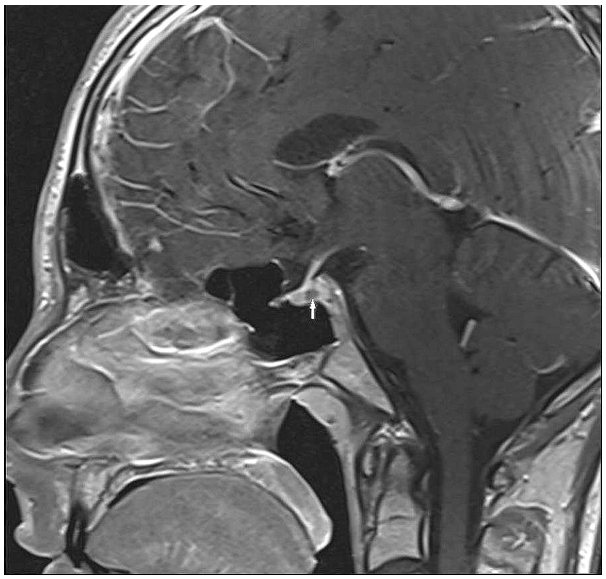


Figure 2. Fifteen-year-old female patient. Hypointense nodular appearance (white arrow) with a 3.5 mm diameter localized to the posterior of the pituitary gland, compatible with a microadenoma with less contrast than the pituitary gland in contrast-enhanced, sagittal T1W pituitary magnetic resonance imaging.

In one study, empty sella turcica in children was associated with a hypothalamic-pituitary dysfunction; 10.9% of patients with possible hypothalamic-pituitary disorders showed empty sella turcica. However, the incidence of empty sella turcica in children is estimated to be 1.2%, which is significantly lower than in adults (Takanashi et al. 2001). In pituitary MRI examinations performed on patients with hypogonadotropic hypogonadism in adults, pituitary hypoplasia has been found in 5.3% and empty sella turcica in 1.3% (Famini et al. 2011). In another study, it has been reported that the hypothalamo-pituitary axis was morphologically normal in patients with idiopathic hypogonadotropic hypogonadism, but pituitary hypoplasia may occur in the same conditions (Argyropoulou and Kiortsis 2005). In a study conducted on children, empty sella turcica has been found in 5.9% of patients with hypogonadotropic hypogonadism (Cacciari et al. 1994). In our study, the rate of pituitary hypoplasia was 22.7% and empty sella turcica was found in 4.5% of patients, which is higher than the incidence of empty sella turcica in children, in general. In addition, we found that the incidence of pituitary hypoplasia in patients with idiopathic hypogonadotropic hypogonadism was higher than in adult patients with hypogonadotropic hypogonadism. This suggests that the rate of detection of pituitary pathology may be higher in pediatric patients with idiopathic hypogonadotropic hypogonadism.

The limitations of the present study relate to its retrospective and non-randomized design and the low number of cases.

Conclusion

We presented the pituitary imaging findings in pediatric patients with idiopathic hypogonadotropic hypogonadism, which is rare. In our study, we found

that the probability of pituitary pathology increased in our patients with very low gonadotropin and sex steroid levels, similar to the literature. We think that pituitary imaging is important in clinical practice in this rare patient group, and that the detected pituitary pathologies will contribute to the etiology of patients with idiopathic hypogonadotropic hypogonadism.

Conflict of interests: *The authors declare no conflict of interest.*

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