Clinical Case Report

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Primary hypothyroidism in a child leads to pituitary hyperplasia

A case report and literature review

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Abstract

Rationale: A sellar mass in children is most often seen in craniopharyngeal tumors, intracranial germ cell tumors, or pituitary adenomas. However, pituitary hyperplasia secondary to primary hypothyroidism (PHPH) is not commonly seen in children.

Patient concerns: A 10-year-old girl was admitted due to growth retardation and obesity for 4 years. On physical examination, the patient had a height of 118 cm, body weight of 46 kg, body mass index (BMI) of 33.0 kg/m^2.

Diagnoses: After magnetic resonance imaging (MRI) and laboratory tests, her initial diagnosis was Hashimoto's thyroiditis, primary hypothyroidism, and reactive pituitary hyperplasia.

Interventions: She was treated with oral L-thyroxine tablets.

Outcomes: After 6 months, physical examination showed a height of 125 cm, weight of 36 kg, BMI of 23.0 kg/m^2. She developed well, with 12 cm of yearly growth thereafter.

Lessons: The diagnosis of PHPH in a child is very important and sometimes difficult. Based on the summary and analysis of previous cases, we can learn that the main manifestations of PHPH include growth arrest and obesity, perhaps accompanied by symptoms caused by a decreased thyroid hormone concentration and elevated prolactin (PRL) concentration. Intracranial MRI shows diffuse enlargement of the anterior lobe of the pituitary gland, with a dome-shaped blunt edge change. Thyroid hormone levels may decrease, whereas the thyroid stimulating hormone (TSH) level increases, commonly accompanied by an elevated PRL, reduced growth hormone (GH) levels, and positive findings of TPOAb and TGAb. Improvement of symptoms and the normalization of hormone levels as well as restoration of pituitary size can be achieved after treated with thyroid hormone replacement therapy. And a hasty decision on surgical resection should be avoided when the diagnosis is uncertain.

Abbreviation: MRI = magnetic resonance imaging, CT = computed tomography, BMI = body mass index, PRL = prolactin, TSH = thyroid stimulating hormone, LH = luteinizing hormone, PHPH = pituitary hyperplasia secondary to primary hypothyroidism, ACTH = adrenocorticotrophin hormone, FSH = follicle-stimulating hormone, GH = growth hormone, TRH = thyrotropin-releasing hormone.

Keywords: pituitary adenoma, pituitary hyperplasia, primary hypothyroidism

1. Introduction

Primary hypothyroidism occurs when the thyroid gland does not make sufficient amounts of thyroid hormone. Low thyroid hormone levels result in loss of inhibition of the release of thyroid stimulating hormone (TSH) and proliferation of TSH-releasing cells, leading to reactive hyperplasia of the anterior pituitary, known as pituitary hyperplasia secondary to primary hypothyroidism (PHPH).[1] Adult PHPH was first recognized by Niepce in 1851, and similar cases were subsequently reported.[2–4] PHPH in children is rare though.[5] Here, we report a case of pediatric PHPH and then review 17 published cases of pediatric PHPH with summaries of the clinical manifestations, laboratory test results, and differential diagnosis of PHPH.

2. Case report

This study was approved by the Ethics Committee and Institutional Review Board of the First Hospital of Jilin University.

Medical history: A 10-year-old girl was admitted due to growth retardation and obesity for 4 years. She had been affected by intermittent urinary tract infection for 5 years along with no menstruation, and computed tomography (CT) scanning showed horseshoe kidneys. All family members had a height greater than 160 cm and denied a family history of thyroid disease and autoimmune disease. On physical examination, the patient had a height of 118 cm, bodyweight of 46 kg, body mass index (BMI) of 33.0 kg/m^2, nonpalpable thyroid glands, underdeveloped breasts, and no armpit hair, and was prepubertal (Tanner's stage 1). The child had normal speech and limb activity. The neurological examination was normal.

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Laboratory and radiological examination: Intracranial magnetic resonance imaging (MRI) showed that the sella was of normal size and the sellar floor was slightly downward. Also, the pituitary was enlarged with superior convexity and suprasellar extension to form a gourd-shape appearance, 13.4 mm in length. The pituitary was enhanced uniformly after injection of contrast agent. The pituitary stalk was thickened and centered, tilting slightly backward. There were no abnormalities in the morphology or signal-intensity of bilateral cavernous sinus (Fig. 1). The thyroid ultrasound examination showed irregular and uneven echo-density. Laboratory tests showed a remarkable increase in TSH (75 μIU/mL, normal 0.4–4.0 μIU/mL) and a decrease in thyroid hormones (T3 60.00 ng/dL, normal 81.00–178.00 ng/dL; T4 3.00 ng/dL, normal 5.20–12.50 ng/dL), thyroglobulin

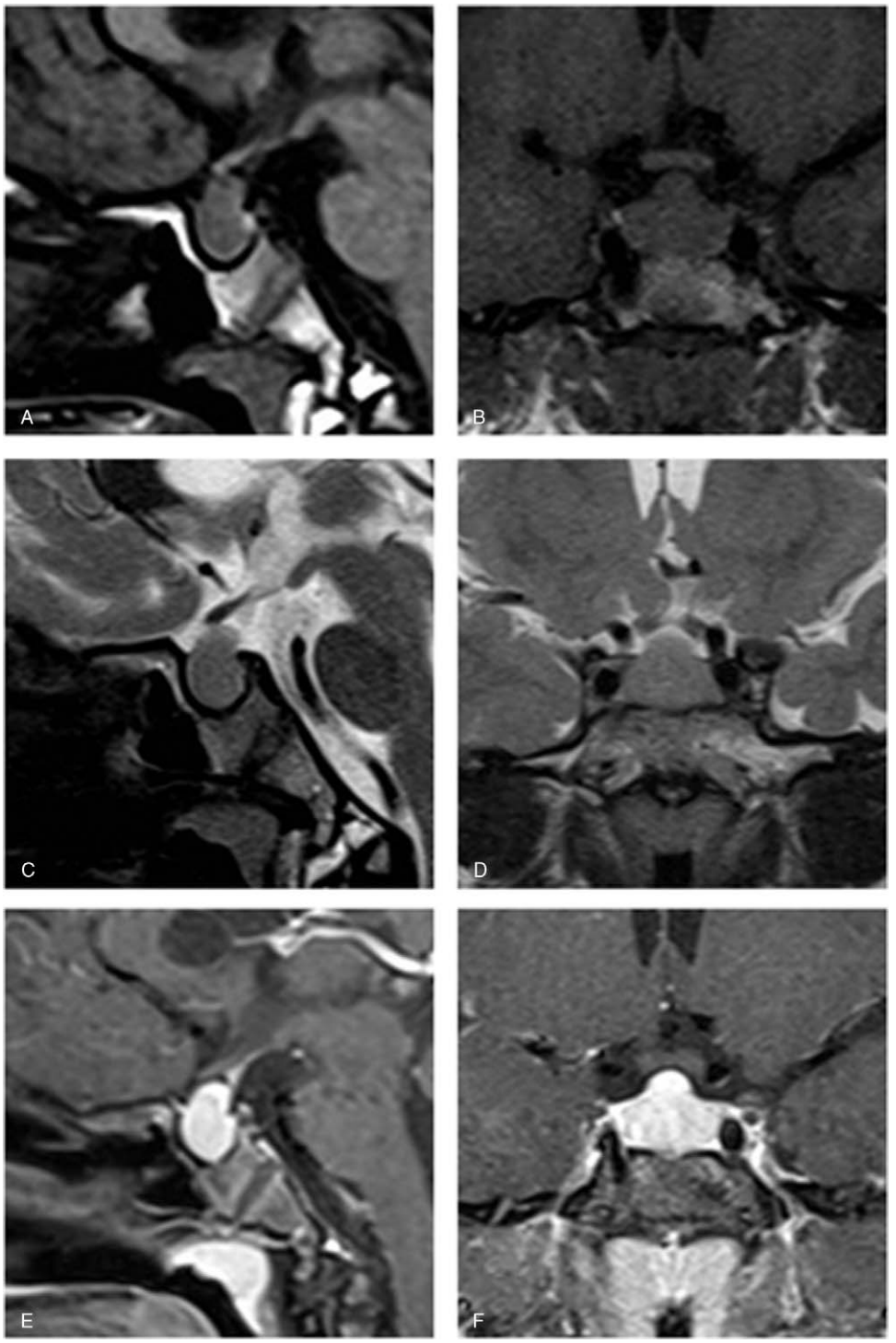

Figure 1. Intracranial MRI of the patient before treatment. A: Sagittal T1WI, uniform signal intensity; B: Coronal T1WI; C: Sagittal T2WI, uniform signal intensity; D: Coronal T2WI; E, Contrast-enhanced, sagittal T1WI, pituitary enlargement with suprasellar extension, significantly uniform enhancement, length 13.4 mm, without oppression of optic chiasm; F: Contrast-enhanced, coronal T1WI, normal signal intensity of cavernous sinus. MRI = magnetic resonance imaging.

Table 1

Growth hormone stimulation test.

	Time after clonidine intake (min)				
	0	30	60	90	120
GH (ng/ml)	0.250	0.15	0.93	1.61	0.39

antibody (TGAb; 4000.00 IU/mL, normal <115 IU/mL) and antithyroid peroxidase antibody (TPOAb; 491.00 UI/mL, normal <35.00 IU/mL). The growth hormone (GH) level was slightly decreased (initial 0.25 ng/mL, peak 1.61 ng/mL) (Table 1). The levels of serum cortisol, GH, adrenocorticotrophin hormone (ACTH), follicle-stimulating hormone (FSH), prolactin (PRL), estradiol, and testosterone were within normal range.

Diagnosis and treatment: According to the clinical manifestations, imaging findings, and laboratory results, the initial diagnosis was Hashimoto's thyroiditis, primary hypothyroidism, and reactive pituitary hyperplasia. The patient was treated with oral L-thyroxine tablets, 35 μg/day. One month later, the hormone levels were re-tested, and the dose of L-thyroxine was adjusted to 75 μg/day. After 6 months, physical examination showed a height of 125 cm, weight of 36 kg, BMI of 23.0 kg/m^2 and normal mental development. The nervous system examination also was normal. MRI examination showed that the sella was of normal size. The volume of the pituitary was significantly reduced, with length of 3.8 mm. The signal intensity in the pituitary was uniform, and no abnormal signals were observed. The pituitary stalk was centered, and no abnormalities were found in the optic chiasma and bilateral internal carotid arteries

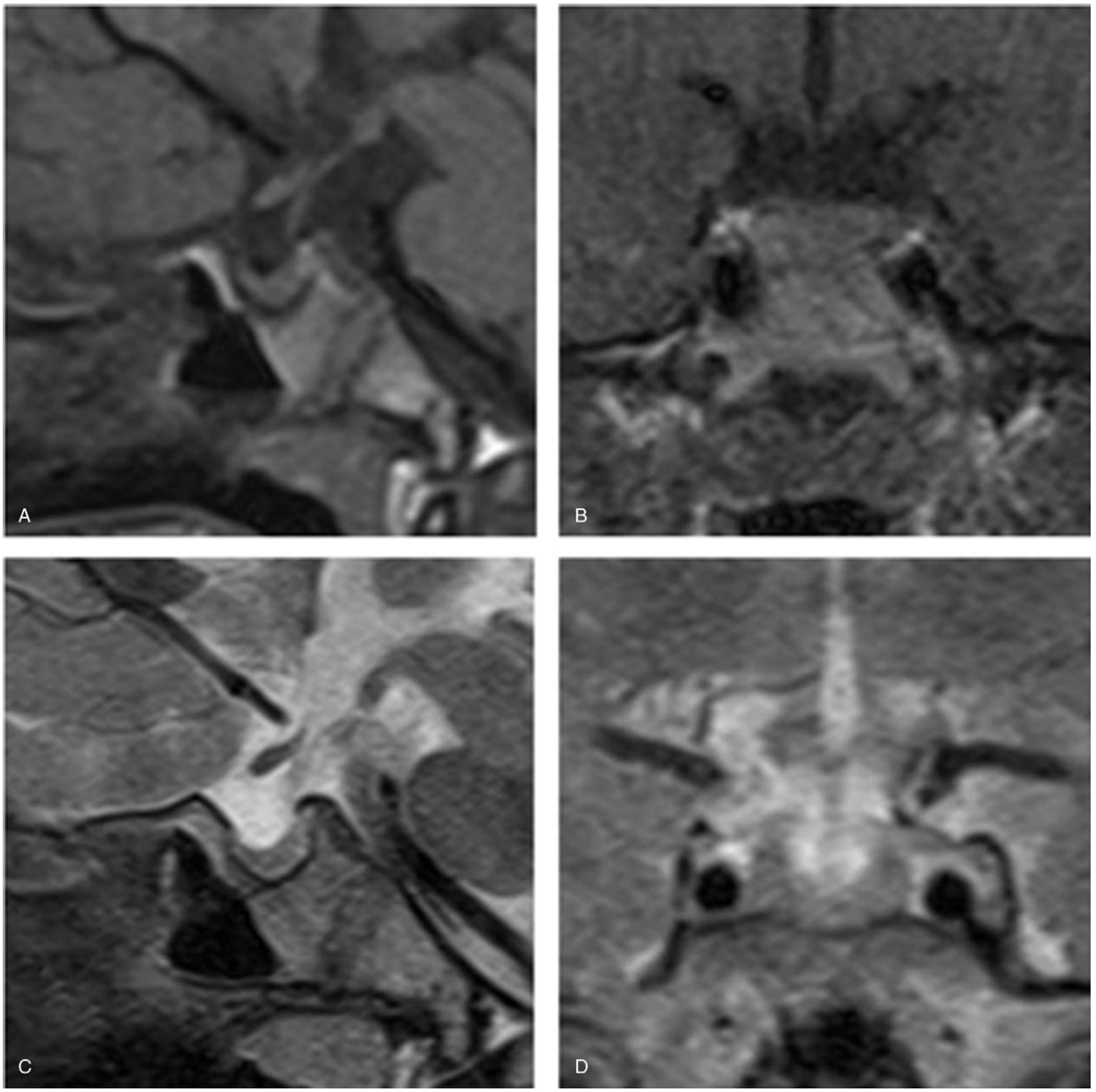

Figure 2. Intracranial MRI of the patient after treatment. A: Sagittal T1WI, uniform signal intensity; B: Coronal T1WI; C: Sagittal T2WI, uniform signal intensity. The mass was reduced in size after treatment, length 3.8 mm; D: Coronal T2WI. MRI = magnetic resonance imaging.

Table 2

Blood hormone levels before and after treatment.

	Before treatment	After treatment Normal range
T3, ng/dL	60	NA 81-178
T4, μg/dL	3.0	NA 5.2–12.5
fT3, pmol/L	4.93	7.99 1.50–4.10
fT4, pmol/L	1.62	12.23 0.89–1.76
TSH, μIU/mL	75.00	0.19 0.40–4.00
TGAb, IU/mL	4000.0	NA <115.0
TPOAb, IU/mL	491.0	NA <35.0

fT = free thyroid, NA = not available, T = thyroid, TGAb = thyroglobulin antibody, TPOAb = anti-thyroid peroxidase antibody, TSH = thyroid stimulating hormone.

(Fig. 2). Laboratory tests showed that TSH and thyroid hormone levels were largely within normal ranges (Table 2). The child continued to take oral L-thyroxine and was followed up regularly. She developed well, with 12 cm of yearly growth thereafter.

3. Literature review

General information: A total of 17 case reports published from 1980 to 2017 and including 17 cases of pediatric PHPH were retrieved from Pubmed (Table 3). These patients included 5 boys and 12 girls, with a male to female ratio of 1:2.4. The mean patient age was 12.3 ± 3.3 years old (range, 5–18 years). Eleven cases exhibited height retardation, of which 8 cases were obese. Six cases had symptoms of fatigue and drowsiness; 5 cases had dry, rough skin; 4 cases had headache, nausea and vomiting; and 3 cases presented inattention and poor concentration. Clinical manifestations, including polyuria, polydipsia, amenorrhea, vaginal bleeding, anemia, mental retardation, muscle pain, myositis, convulsions, muscle weakness, cold, and myxedema were observed in a minority of children.

Imaging findings: Intracranial MRI or CT showed the pituitary was enlarged with suprasellar extension in all children. Oppression of the suprasellar cistern was observed in 5 cases, invasion of the optic chiasm in 8 cases, and pituitary stalk dislocation backward in 1 case, without invasion of the cavernous sinus. Among 8 cases for which contrast enhancement was applied, 7 cases showed homogeneous enhancement and 1 case showed rim enhancement.

Laboratory tests: All patients presented a decreased level of T3 or T4 and elevated level of TSH. PRL was found to be increased in 13 cases, along with a decreased peak value of GH in 3 cases, positive expression of TGAb and/or TPOAb in 5 cases, and decreased levels of sex hormones in 1 case.

Treatment outcomes: The patients' symptoms were relieved after treatment for an average duration of 5.5 ± 4.9 months (range, 1–18 months). MRI or CT examination showed that the pituitary gland was partially diminished or completely restored to normal. In 4 cases, the pituitary gland was partially diminished within an average time interval of 3.3 ± 1.7 months (range, 2 weeks–18 months). In 13 cases, the pituitary gland was completely restored to normal within an average time interval of 7.7 ± 5.2 months (range, 1–18 months). In 8 cases, blood hormone levels gradually recovered to the normal range within an average time interval of 7.79 ± 5.4 months (range, 1–18 months).

4. Discussion

In 1996, Desai et al reported for the first time that hypothyroidism is associated with pituitary enlargement in children.[6] PHPH is caused by low thyroid hormone levels in primary hypothyroidism, which diminishes the negative feedback of the thyroid hormone to the hypothalamus, leading to over-secretion of thyrotropin-releasing hormone (TRH) and proliferation of TSH-secreting cells[1].[1] Hashimoto's thyroiditis is the most common cause of hypothyroidism in children and adolescents. The differential diagnosis of PHPH from pituitary adenoma is a challenge based on laboratory tests, imaging findings and clinical manifestations. However, because the treatments for PHPH and pituitary adenoma are completely different, accurate identification is extremely important. Pituitary adenoma is usually treated with surgical resection, whereas patients with pituitary hyperplasia achieve satisfactory outcomes with thyroid hormone replacement therapy. If a misdiagnosis is made, surgical removal in the case of pituitary hyperplasia will cause irreversible pituitary dysfunction and resultant growth and mental retardation in children.

For children with pituitary hyperplasia, physiological versus pathological hyperplasia should be determined first. Physiological pituitary growth stimulation is observed during puberty and pregnancy/lactation and results in enlargement of the pituitary gland.[7] It has been reported that the gland increases in size markedly and may reach up to approximately 8 mm in length in males and 10 mm in length in females at puberty.[8,9] The mean length of the normal gland increases to up to 10 mm during pregnancy and up to 12 mm in the initial postpartum period before rapidly returning to its normal size at 1 week after delivery.[7] A pathological pituitary disorder may develop in response to low thyroid function, which leads to compensatory pituitary hyperplasia through negative feedback effects, commonly observed in hypothyroidism, adrenal insufficiency, hypogonadism, and with long-term use of exogenous estrogen,[10] as well as in pituitary hyperemia due to traumatic, iatrogenic and spontaneous cerebrospinal fluid leakage.[9] This case and all 17 cases reviewed in this article presented pituitary enlargement accompanied by abnormal laboratory test results and obvious clinical manifestations, which were attributed to pathological pituitary hyperplasia.

Clinical manifestations: The clinical manifestations of PHPH include a series of symptoms of hypothyroidism (fatigue, cold feeling, myxedema, etc.), menstrual disorders, galactorrhea, infertility, and other symptoms caused by a high PRL level. Vision impairment or loss is not commonly observed. Of the 17 cases reviewed, 11 showed a delayed growth spurt, including 8 cases with obesity, and the two most common symptoms also appear in the present case. Symptoms of fatigue and drowsiness were reported in 6 cases; 5 cases presented with dry and rough skin. Therefore, PHPH is mainly characterized by growth retardation and obesity and occasionally associated with hypothyroidism, precocious puberty, and hyperprolactinemia, but rarely affects a child's intelligence. In contrast, patients with pituitary adenoma exhibit symptoms of endocrine disorders such as menolipsis, lactation, infertility, gigantism, acromegaly, and Cushing syndrome in the initial stage; and visual impairment or loss may develop in the advanced stage.

Imaging findings: Intracranial MRI images show diffuse enlargement of the anterior lobe of the pituitary gland, with uniform T1 and T2 signals, but no obvious signs of bleeding, necrosis, or cystic fibrosis. Sellar extension may be observed, as manifested by a dome-shaped blunt edge change.[11] The extension shows uniform enhancement, with the peak enhancement being similar to that of the normal pituitary gland. The posterior lobe of the pituitary gland shows normally a high signal

Table 3

Literature review of PHPH in children.

No	Author/Year	Age	Gender	Symptoms and signs	Imaging findings	Laboratory tests	Treatment	Therapeutic effect
1	Yamamoto, 1987[21]	13	Female	Short stature, anemia	CT showed a round isodense mass with homogeneous enhancement in the midline of the pituitary region	T3, T4↓; TSH↑	Oral thyroxine, 40 μg daily	After 5 months, the mass decreased and the symptoms subsided
2	Takahashi, 1991[22]	5	Female	Short stature, anemia, dry and rough skin, abdominal distension	CT revealed a round mass in the sella and suprasellar region, with homogeneous enhancement.	T3, T4↓; TSH↑; PRL↑	Oral thyroxine	After 3 months, the symptoms improved; MRI showed that the pituitary gland restored to normal
3	Adams, 1992[23]	12	Female	Polyuria, polydipsia; headache; anorexia, vomiting	Cranial CT revealed a low-density mass in the sella with suprasellar extension, edge enhancement.	T3, T4↓; TSH↑; PRL↑	Oral L-thyroxine tablets, 100ug daily	After 2 weeks, the headache was relieved, the mass was reduced with edge enhancement disappeared; After 16 weeks, the hormone levels returned to normal with disappearance of diabetes insipidus
4	Riedl, 1997[24]	16	Female	Growth retardation, obesity, low intelligence	MRI of the pituitary region showed a suprasellar mass (12 × 15 mm)	T3, T4↓; TSH↑; GH↓	Oral L-thyroxine tablets, 75ug daily; growth hormone, 4 U daily, subcutaneous injection	After 6 months later, the growth rate of 6 cm/year; 9 months later, MRI showed basically normal pituitary gland size.
5	Ehirim, 1998[25]	13	Male	Nausea, vomiting for 10 months; dry skin	MRI: pituitary enlargement with suprasellar extension, approaching the optic chiasm, homogeneous enhancement.	T3, T4↓; TSH↑	Oral thyroxine	After 1 year, the symptoms were relieved and the hormone levels restored to normal; MRI showed normal size of pituitary gland
6	Kocova, 2001[14]	11	Female	Vaginal bleeding, poor learning ability, drowsiness, height retardation, obesity for 3 years, dry skin, cold feeling	MRI: A large intrasellar mass expanding beyond the suprasella turcica, with homogeneous enhancement.	T3, T4↓; TSH↑; GH↓	Oral thyroxine	After 1 month, the symptoms were relieved and the normalization of hormone levels as well as the pituitary structure were observed.
7	Weiss, 2003[26]	16	Female	Drowsiness, myalgia, fatigue for 1 year; dry skin, cold extremities, leg cramps for 1 year; menarche at 12 years old and irregular menstruation for 2 years, decreased menstruation for 5 months, then amenorrhea	CT: pituitary enlargement, 13 × 11 mm, involvement of optic chiasm and right optic nerve	T3, T4↓; TSH↑; PRL↑; antithyroid microsomal antibodies (+)	Oral thyroxine; tempertory cortisol supplements	After 2 weeks MRI showed that the length of the pituitary gland decreased by 2mm; 8 months later, thyroid hormone level returned to normal; 10 months later, weight loss and regular menstruation was achieved, and MRI showed a normal pituitary size
8	Hopper, 2005[27]	11	Female	Headache, dizziness, drowsiness for 2 months, myxedema, slow heart rate	CT revealed a pituitary mass; MRI showed ituitary enlargement with invasion to the optic chiasm	T3, T4↓; TSH↑; PRL↑; Microsomal thyroid antibodies (+)	Oral thyroxine	After 5 months, the symptoms disappeared, and hormone levels were normal; MRI showed normal pituitary size
9	William, 2005[18]	12	Female	Headache, vomiting, maxillary pain, fatigue, low learning ability, short stature	MRI revealed a sellar mass with a suprasellar cistern extension compressing the optic chiasm.	T3, T4↓; TSH↑; PRL↑	Oral thyroxine	After 1 month, the symptoms were partially relieved and MRI showed that the pituitary gland restored to normal
10	Chingyi, 2008[5]	10	Female	Height retardation, hypertrophy	MRI revealed a mass in the sella and suprasellar region, measuring 3.8 × 9.6 × 12.1 mm	T3, T4↓; TSH↑; PRL↑	Oral thyroxine, 100ug daily	After 2 months, the symptoms improved; 3 months later, MRI showed restoration of normal pituitary size
11	Eom, 2009[28]	9	Female	Height retardation, obesity, myxedema	MRI revealed a large sellar mass (length 20 mm) with suprasellar cistern extension, slightly compressing the optic chiasm, homogeneous enhancement.	T3, T4↓; TSH ↑; PRL↑	Oral L-thyroxine tablets	After 4 months, the pituitary mass regressed, and her symptoms resolved and the height increased
12	Roberto, 2011[19]	11	Male	Persistent headache, height retardation, obesity	MRI showed an intrasellar and suprasellar pituitary mass with homogeneously enhancement, extending on the suprasellar cistern with mild compression of the optic chiasm; the pituitary stalk and posterior pituitary were dislocated backwards.	T3, T4↓; TSH ↑; PRL↑	Oral thyroxine, 50 μg daily	After 3 months, headache was relieved, height growth velocity increased (7 cm/year), bodyweight decreased; 5 months later, MRI revealed regression of the mass to normal level
13	Nicholas, 2013[29]	9	Female	Spasm without fever, height retardation, obesity	MRI revealed a mass in the sella and suprasellar region, length14 mm	T3, T4↓; TSH ↑; PRL↑; TGAb, TPOAb (+)	Oral thyroxine	After 9 months, blood hormone levels recovered; MRI showed the length of the mass had decreased to 6.7 mm; spasm was relieved
14	Noelle, 2013[30]	13	Female	Short stature, obesity for 6 years, cold feeling, dry skin, fatigue, delayed puberty	MRI revealed a sellar mass with suprasellar cistern extension, length 14 mm.	T3, T4↓; TSH ↑; PRL↑	Oral thyroxine, 25 μg daily at initial, then 100 μg daily	After 18 months, the symptoms were relieved and MRI showed that the pituitary gland restored to normal

(*continued*)

Table 3
(continued).

No	Author/Year	Age	Gender	Symptoms and signs	Imaging findings	Laboratory tests	Treatment	Therapeutic effect
15	Rajendra, 2013[31]	12	Male	Intermittent headache for 1 year, fatigue, hoarseness, cold feeling, dry and rough skin,short stature, obesity	MRI revealed a mass in the sella and suprasellar region, size 20 × 16 × 14 mm	T3, T4↓; TSH ↑; PRL↑; TPOAb (+)	Oral thyroxine, 100 μg daily	After 6 months, the symptoms were relieved and blood hormone levels returned to normal; MRI showed normal pituitary gland size
16	Siddiqi, 2015[32]	18	Male	Impaired vision, fatigue, drowsiness, lack of concentration, memory decline for 2 years	CT revealed a sellar mass; MRI showed sellar mass with suprasellar cistern extension, slightly compressing the optic chiasm.	T3, T4↓; TSH ↑; PRL↑	Oral thyroxine	After 3 months, blood hormone levels returned to normal, and MRI showed an decrease in pituitary size; 12 months later, the symptoms were completely relieved
17	Ammar, 2017[33]	18	Male	Height retardation, obesity	MRI showed sellar and suprasellar mass with homogeneous enhancement, compressing the optic chiasm, size 16 × 13 × 12 mm	T3, T4↓; TSH ↑; PRL↑; TPOAb (+)	Oral thyroxine	After 3 months, the symptoms improved; 1 year later, blood hormone levels were basically decreased to normal range; MRI showed pituitary mass resolution.

CT = computed tomography, MRI = magnetic resonance imaging, PRL = prolactin, TPOAb = anti-thyroid peroxidase antibody, TSH = thyroid stimulating hormone.

intensity. With the progression of disease, the pituitary stalk may be normal or thickened but not distorted, with a suprasellar extension to form a gourd-shaped appearance, probably extending on the suprasellar cistern or occasionally compressing the optic chiasm, but rarely invading the cavernous sinus or skull bone. In the 17 cases reviewed, pituitary enlargement with suprasellar extension was observed in all cases, compression of the suprasellar cistern was observed in 5 cases, the optic chiasm was reported in 8 cases, and pituitary stalk dislocation occurred in 1 case, without evidence of invasion to the cavernous sinus. The present case showed the pituitary was enlarged with superior convexity and suprasellar extension to form a gourd-shape appearance. For pituitary adenoma, MR images show mixed signals of high and low intensities.[12] With tumor progression, the pituitary stalk may be distorted or dislocated, and the mass grows towards the suprasellar region, invading the cavernous sinus or sphenoid sinus, oppressing the optic chiasm, and even surrounding the internal carotid artery.

Laboratory tests: Patients with PHPH usually have decreased plasma levels of FT3, FT4, T3, and T4 and reactively increased TSH (TSH >100 μIU/mL). Long-term stimulation to release endogenous PRH can also promote proliferation of PRL-releasing cells, leading to over-secretion of PRL.[13] Thyroid hormone binding to nuclear receptors is known to stimulate GH synthesis. Thereby, children with PHPH exhibit low or absent secretion of GH from the pituitary gland.[14] TPOAb and/or TGAb have been found to be positive in the majority of patients with hyperthyroidism due to Hashimoto's thyroiditis, whereas elevated concentrations of serum FSH and luteinizing hormone (LH) are occasionally observed in PHPH patients. This case and all 17 cases reviewed in this article had declined T3 or T4 therapy and had elevated TSH levels. Among the 17 cases, elevated PRL was found in 13 cases, a decrease in the GH peak in 3 cases, positive TPOAb and/or TGAb expression in 5 cases, and a decline in sex hormone levels in 1 case. And the present case also showed a decrease in the GH peak and positive TPOAb and/or TGAb expression.

Patients with TSH-secreting pituitary adenoma may have an elevated TSH level (but typically less than 50 μIU/mL) and increased FT3, FT4, T3, and T4 levels. These patients do not respond to TRH stimulation test and have an elevated α-subunit/TSH ratio. The sensitivities of the unresponsive TRH test and elevated α-subunit/TSH ratio for identifying pituitary adenomas are 71% and 83%, respectively.[15] The level of TSH (typically less than 50 μIU/mL) is also commonly elevated in patients harboring nonfunctional pituitary adenoma. Other hormones, such as plasma PRL, GH, or FSH and LH, may be elevated in patients with pituitary prolactinoma, GH-secreting pituitary adenoma or gonadotropin-secreting adenoma, respectively. As a space occupying lesion, a pituitary mass leads to declined pituitary function, impaired pituitary TSH secretion, and subsequently decreased plasma levels of FT3, FT4, T3, and T4.

Diagnostic therapy: The diagnosis of PHPH is often difficult but can be confirmed by diagnostic therapy. The diagnosis can be made if the patient's symptoms are improved by appropriate treatment, with a reduced pituitary mass or restored blood hormone levels.[16] The proportions of TSH normalization and mass regression are up to 95% and 62%, respectively.[17] PHTH is mainly treated with L-thyroxine replacement therapy, starting with a low dose. Based on the literature, the regression of the pituitary mass to a normal size occurred over 2 to 4 months,[16] ranging between 1 and 18 months.[18,19] With thyroxine

supplementation, the enlarged size of the pituitary gland is gradually restored to normal. However, PHPH complicated with pituitary TSH-secreting adenoma should be considered,[20] if the TSH level as well as the pituitary gland continuously increase after diagnostic treatment, and the mass requires surgical resection.

Sellar masses in children are most often seen in cases of craniopharyngeal tumors, intracranial germ cell tumors, pituitary adenomas, or pituitary hyperplasia. The former 2 conditions are easy to identify, but clinically and biochemically, it may be difficult to distinguish pituitary hyperplasia from pituitary adenoma. Herein, based on the summary and analysis of previous cases, we put forward some personal opinions on the diagnostic criteria for PHPH in children as follows:

the main manifestations of PHPH include growth arrest and obesity, perhaps accompanied by symptoms caused by a decreased thyroid hormone concentration and elevated PRL concentration.

Intracranial MRI shows diffuse enlargement of the anterior lobe of the pituitary gland, with a dome-shaped blunt edge change. Homogeneous enhancement of the mass can be observed. With the progression of disease, the pituitary stalk may be normal or thickened but not distorted, with a suprasellar extension to form a gourd-shaped appearance, probably extending on the suprasellar cistern or occasionally compressing the optic chiasm, but rarely invading the cavernous sinus.

Thyroid hormone levels may decrease, whereas the TSH level increases (TSH $>$ 100 μIU/ml), commonly accompanied by an elevated PRL, reduced GH levels, and positive findings of TPOAb and TGAb. 4) Improvement of symptoms and the normalization of hormone levels as well as restoration of pituitary size can be achieved after treated with thyroid hormone replacement therapy. The preliminary diagnosis can be made based on the aforementioned 3 criteria; a definitive diagnosis requires at least the presence of the fourth criterion. However, diagnosis of PHPH can be excluded if the fourth criterion is not met. Surgical resection should be considered, and a hasty decision on surgical resection should be avoided when the diagnosis is uncertain. Although the present case eventually diagnosed correctly and the symptoms were relieved partly after treatment, it was difficult to return to normal.

In conclusion, we reviewed 17 cases of pediatric PHPH and summarized the clinical manifestations, laboratory test results, and differential diagnosis of PHPH in children, which may help to identify PHPH and guide treatment decisions, in order to avoid to the greatest extent, the adverse consequences caused by misdiagnosis. Given that PHPH is not common in children, further reliable evidence is needed for an accurate understanding of disease progression and to establish scientific criteria for diagnosis. Although these symptoms are reversible after thyroid hormone replacement therapy, some children with severe dysplasia or short stature still find it difficult to develop normally. Thus, further research is urgently needed to improve early diagnosis of PHPH in children.

Author contributions

Conceptualization: Junguo Cao.
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