Case Report

Van Wyk-Grumbach Syndrome: case report and review of the literature

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Abstract

Van Wyk-Grumbach syndrome (VWGS) is a rare cause of precocious puberty due to long-standing hypothyroidism. We report an 8-year-old girl presenting with vaginal bleeding. She had short stature and normal bone age. Pelvic ultrasound showed enlarged multicystic ovaries and cranial imaging revealed pituitary hyperplasia. Laboratory results showed elevated follicle-stimulating hormone with suppressed luteinizing hormone, hyperestrogenism, and hyperprolactinemia. Subsequent evaluation revealed severe autoimmune hypothyroidism. Based on the clinical findings and imaging VWGS was diagnosed and showed excellent response to thyroid replacement therapy. Hypothyroidism should be considered in prepubertal females with incomplete precocious puberty even in patients with a normal bone age.

Introduction

First described in 1960, Van Wyk-Grumbach syndrome (VWGS) is characterized by long-standing primary hypothyroidism, isosexual precocious puberty, delayed bone age, multicystic ovaries and pituitary enlargement, in varying combinations (1,2). In isosexual precocity, children develop early phenotypically appropriate secondary sexual characteristics. This rare syndrome is a clinical diagnostic challenge as untreated juvenile hypothyroidism classically leads to delayed puberty. The reversion of the pubertal development after thyroid hormone replacement was an essential finding in this syndrome (1).

Here, we report an 8-year-old patient presenting with vaginal bleeding who was subsequently diagnosed as VWGS, highlighting the importance of careful clinical evaluation of patients with precocious puberty for concurrent signs of hypothyroidism. We provide a brief review of the literature.

Case presentation

An 8-year-old girl presented to the emergency department of our institution with vaginal bleeding. There was no history of local trauma or other bleeding manifestations. Her past medical history was unremarkable. On physical examination, her height was 122,5 cm (-1.5 standard deviation score (SDS)), her weight was at the mean at 27,9 kg and her body mass index was 18,6 kg/m² (+2 SDS). Her breast and pubic hair development were staged as Tanner 2 and she had no axillary hair. The external genitalia showed signs of estrogenization including increased size and color of the labia majora. There were no traumatic lesions.

On investigation, bone age was in accordance with the chronological age using the Greulich and Pyle atlas. Pelvic ultrasound revealed a pubertal size uterus with a body to cervix ratio > 1.2, a thickened endometrium and enlarged cystic ovaries (Figure 1). Hematologic investigations revealed mild normocytic anemia and a normal coagulation profile. Hormonal laboratory results showed low prepubertal luteinizing hormone (LH) levels but elevated follicle-stimulating hormone (FSH) levels,

Figure 1: Pelvic ultrasonographic findings. (a) Sagittal image showing a pubertal size uterus measuring 50 x 21 mm with a thickened endometrium (1.6 cm). (b, c) Multicystic enlarged right and left ovaries measuring 42 x 18 x 14 mm and 60 x 27 x 24 mm respectively.

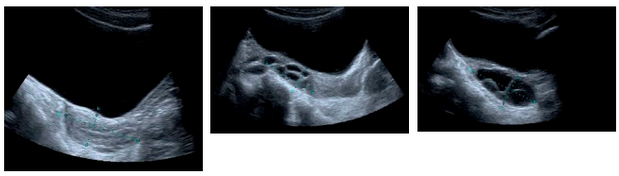
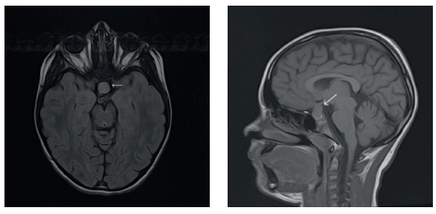


Figure 2: Cranial magnetic resonance imaging. (a, b) Sagittal and transverse scan showing enlargement of the pituitary gland (arrow) measuring 18.5 x 17.5 x 11.5 mm with homogeneous enhancement, suprasellar extension and compression of the optic chiasm.



hyperestrogenism, and hyperprolactinemia (Table 1). The luteinizing hormone-releasing hormone stimulation test showed a predominant FSH response with suppressed LH. Cranial magnetic resonance imaging revealed pituitary gland hyperplasia with suprasellar extension and invasion of the cavernous sinus (Figure 2).

At follow-up, physical examination revealed features suggestive of hypothyroidism: increasing weight gain, dry scaly skin, constipation, and dull behavior. There was no goiter. Workup revealed severe primary hypothyroidism, with highly elevated levels of thyroid-stimulating

Table 1: Laboratory results at diagnosis and at follow-up.

Laboratory test (SI unit)	At diagnosis	After 2 months of treatment	After 12 months of treatment	Normal range
FSH (IU/l)	8.4		4.7	Prepubertal : 0,3-3
LH (IU/l)	< 0,1		0.8	Prepubertal : 0.3-2
Estradiol (pg/ml)	32			< 10
Prolactin (ng/ml)	61		5.5	< 20
TSH (mUI/l)	920	0.9	0.53	0.66-4.14
FT4 (ng/l)	0.3	18.6	13.4	9-16.5
FT3 (pg/ml)	< 0.26			2.7-5.2
Anti-TG (UI/ml)	5370		340	<40
Anti-TPO (UI/ml)	> 3000		59	< 25
Anti-TPO (UI/ml)	1 (3%)	1 (6%)	0 (0%)	
Anti-TPO (UI/ml)	1 (3%)	1 (6%)	0 (0%)	

(FSH: follicle-stimulating hormone; LH: luteinizing hormone; TSH: thyroid-stimulating hormone; FT4: free thyroxine; FT3: free triiodothyronine; Anti-TG: Anti-thyroglobulin antibody; Anti-TPO: Anti-thyroid peroxidase antibody).

hormone (TSH), extremely low levels of free thyroxine (FT4) and free triiodothyronine (FT3). Autoimmune hypothyroidism was diagnosed with significant elevations of antithyroid antibodies (Table 1). Thyroid doppler ultrasonography showed a normal volume for age, heterogeneous echogenicity and normal parenchymal vascularity.

Thyroid hormone replacement was initiated at 100 mcg/day and resulted in significant clinical improvement after 2 months: prompt cessation of vaginal bleeding, weight loss, resolution of constipation and improvement in mood and school performance. Her height had increased by 1 cm, and her weight decreased by 2.9 kg. There was no regression, nor progression of pubertal development. Her TSH level normalized and her free thyroxine level increased. There was a normalization of the FSH, LH, estradiol and prolactin (Table 1). She developed normal puberty with menarche at 12.5 years of age. At her last examination at the age of 16 years, her weight was 55 kg (mean) and her height was 162 cm (-0.5 SDS). Her adult height fell within her mid parental height range.

Discussion

Precocious puberty may be a rare complication of untreated juvenile hypothyroidism which is usually associated with delayed puberty. A 10-year retrospective study reported a 24% incidence of precocious puberty among 33 children with severe hypothyroidism (3). The classic features of this isosexual precocity include breast development with or without galactorrhea, menstrual bleeding and large multicystic ovaries (2,4). Although less commonly described in boys, affected males present with premature testicular enlargement without virilization (5). Other unique pubertal features include delayed pubic and axillary hair growth and paradoxically short stature with delayed bone maturation. Biochemical evaluation reveals high FSH concentrations with low non-stimulable LH (2,4,5). These discordant features should draw the clinicians' attention and help to point towards the diagnosis of VWGS.

We present a case of VWGS in an 8-year-old patient with severe long-term untreated autoimmune hypothyroidism, peripheral precocious puberty including early menarche and thelarche, along with enlarged multicystic ovaries and pituitary hyperplasia. She had a short stature without delayed bone maturation which is usually a distinguishing feature to differentiate VWGS from the classic causes of precocious puberty (1). A review of the literature revealed 3 cases of VWGS with normal bone age (6–8). Durbin et al reported an 11-year-old girl whose precocious pubertal changes were not obvious and whose bone age was normal. They explained that their patient already experienced pubertal changes prior to the development of hypothyroidism. They concluded that VWGS can occur at different stages of pubertal development and lead to different clinical presentations (6). The delay in bone age presumably also depends on the duration and severity of hypothyroidism. Moreover, high serum estradiol levels, which promote growth, could decrease the degree of bone age delay.

Although all patients present with a clinical phenotype of hypothyroidism, this is often not the primary reason for referral (5). the insidious onset of vague symptoms such as short stature, weight gain, dry skin, constipation, fatigue and poor school performance may delay diagnosis (9). In addition, the other associated symptoms of VWGS may distract clinicians from the underlying causal hypothyroidism. This is illustrated in our case report as several suggestive features of hypothyroidism were discovered only at follow-up. Careful clinical examination and thyroid function should therefore be performed in patients with precocious puberty and short stature, especially when bone maturation is not advanced. VWGS is predominantly associated with long-standing acquired hypothyroidism such as autoimmune thyroiditis, but cases have been reported secondary to unrecognized congenital hypothyroidism (5).

Although discussed by many authors, the pathophysiologic mechanisms of VWGS remain unclear. In primary hypothyroidism, the reduction of thyroid hormones leads to a lack of negative feedback on the hypothalamus resulting in elevated thyrotropin-releasing hormone (TRH) (2,9). Elevated TRH induces thyrotrophic hyperplasia, which is responsible for pituitary enlargement and increased TSH production. It can also lead to lactotrophic hyperplasia resulting in hyperprolactinemia as seen in our case (2,5,9). Although early studies hypothesized that high levels of TRH also induced excessive production of gonadotropins through the pituitary-hypothalamic axis, later studies demonstrated molecular similarities between TSH and FSH receptors, which share a common alpha subunit leading to cross-reactivity (1,10). The most accepted theory is that high levels of TSH stimulate the FSH receptor, resulting in increased estrogen secretion, cystic ovarian enlargement and precocious puberty with breast development and vaginal bleeding (10). Axillary and pubic hair are absent as there is no adrenarche. Another theory explaining the discordance of FSH and LH postulates that hyperprolactinemia increases ovarian sensitivity to gonadotrophins and in turn inhibits LH secretion while producing FSH (2–4). However, prolactin levels are not always elevated (2).

VWGS has good prognosis after thyroid hormone replacement therapy. In the present case, stabilization of pubertal development and normalization of biochemical parameters were achieved after substitution therapy with L-thyroxine. Although no imaging follow-up was performed in our patient, regression of ovarian cyst size and pituitary gland hyperplasia have been described in the literature (2,5,6). Moreover, our patient entered physiologic puberty at an appropriate age, resumed a normal growth velocity and eventually reached her target height. Although most case reports describe remarkably rapid catch-up growth after thyroid hormone replacement, some report a reduced final height compared to mid-parental height (5). Niedziela et al. report that even in the setting of long-term acquired hypothyroidism, the predicted

final height may be within the normal range (8). In contrast, Cabrera et al. report that more than half of their prepubertal patients with severe hypothyroidism were smaller than 2 SDS beneath their target height (3). Indeed, growth recovery may be incomplete, depending on the severity of hypothyroidism prior to treatment and the catch-up period before true puberty occurs (2,5). Longer-term studies are needed to better characterize growth outcomes in these pediatric patients with severe, long-standing hypothyroidism.

Conclusion

This rare syndrome represents a diagnostic challenge. Although delayed bone age is a distinctive feature, VWGS can occur in individuals with normal bone maturation. Thyroid function tests should therefore be performed in patients with precocious puberty without advanced growth and bone maturation. Thyroid hormone replacement provides rapid clinical improvement although adult height should be documented in long-term and multicenter studies.

Conflicts of interest

There are no conflicts of interest.

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