Van Wyk-Grumbach Syndrome with Kocher-Debré-Sémélaigne Syndrome: Case Report of a Rare Association

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What Is Known about This Topic?

- Van Wyk-Grumbach and Kocher-Debré-Sémélaigne syndromes are two rare presentations of primary hypothyroidism in pediatric patients. Only a single case of the simultaneous occurrence of these two syndromes has been described in the medical literature.

What Does This Case Report Add?

- This is the second description of the simultaneous occurrence of these rare syndromes, and we have shown that their manifestations fully resolve by thyroxine treatment without any sequelae.

Key Words

Van Wyk-Grumbach syndrome · Juvenile hypothyroidism · Isosexual pseudoprecocious puberty · Multicystic ovaries · Kocher-Debré-Sémélaigne syndrome

Abstract

Background: Van Wyk-Grumbach syndrome (VWGS) is a rare presentation of juvenile hypothyroidism which manifests in females as chronic autoimmune hypothyroidism, isosexual pseudoprecocious puberty, and multicystic ovaries. It uniquely presents with short stature and delayed bone age unlike other causes of precocious puberty. Kocher-Debré-Sémélaigne (KDSS) is a rare presentation of juvenile hypothyroidism manifesting as calf muscle pseudohypertrophy,

delayed contraction and relaxation of reflexes, and percussion myxedema. **Objectives:** To diagnose the rare association of VWGS and KDSS and to conduct a follow-up of the patient on replacement therapy. **Methods:** We present a case of a 9-year-old female child who presented to the endocrine department with complaints of intermittent vaginal bleeding, short stature, and difficulty in walking. On evaluation she was found to be having autoimmune hypothyroidism, FSH-dominated isosexual pseudoprecocious puberty, delayed bone age, secondary pituitary macroadenoma, delayed relaxation of deep tendon reflexes, and pseudohypertrophy of calf muscles. The diagnosis of VWGS associated with KDSS was made. The patient was initially put on 25 µg thyroxine replacement, which was titrated accordingly, and was followed up after 6 months and 1 year. **Results:** All the

features of the syndrome improved after 12 months of adequate thyroxine replacement. **Conclusions:** VWGS and KDSS are rare presentations of juvenile hypothyroidism, and their association is even rarer. Early diagnosis and prompt replacement therapy can avoid unnecessary investigations and surgical interventions.

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Introduction

Primary hypothyroidism usually presents with subtle signs and symptoms [1]. However, it can present rare syndromes like Van Wyk-Grumbach syndrome (VWGS) and Kocher-Debré-Sémélaigne syndrome (KDSS).

VWGS presents as precocious menarche, breast development, galactorrhea, delayed bone age, and multicystic ovaries in combination with long-standing primary hypothyroidism [2]. Affected girls usually present with a hypothyroid appearance, short stature, isosexual pseudoprecocious puberty with breast development, uterine bleeding, and multicystic ovaries, but in the absence of axillary and pubic hair [3]. Most cases of hypothyroidism result from autoimmune thyroid destruction, and usually all manifestations regress after the initiation of adequate thyroid hormone replacement. The probable mechanism of this unusual presentation is structural homology between the different glycoprotein hormones acting through G-protein-coupled receptors [2].

KDSS is a rare presentation of juvenile hypothyroidism which manifests as a combination of hypothyroidism, calf muscle pseudohypertrophy, delayed contraction and relaxation of reflexes, and percussion myxedema [4]. The pathogenesis of the syndrome is still unclear, but the

accumulation of glycogen and glucosaminoglycans is thought to play an important role [4].

We describe the case of a girl who presented with the combination of manifestations of VWGS with KDSS and improved after 1 year of adequate thyroxine replacement therapy.

Case Report

An Asian Indian female child aged 9 years and 3 months presented to the endocrinology outpatient clinic with complaints of intermittent vaginal bleeding, short stature, and difficulty in walking. The girl was born at 36 weeks of gestation out of a nonconsanguineous marriage. Delivery was vaginal with cephalic presentation. The patient had no pre- or postnatal complications, and development progressed normally until the age of 4 years. The patient complained of intermittent vaginal bleeding since the age of 4 years, which was associated with cramping abdominal pain, and each episode lasted for about 4–5 days. There was no history of birth trauma, cranial irradiation, visual disturbances, headache, sexual abuse, foreign body, or genital tract infection. Paradoxical to the other causes of sexual precocity, the patient also suffered from growth retardation for the same duration, which was associated with lethargy, dry skin, and constipation.

On examination, the patient showed a typical hypothyroid facies with coarse features and puffiness along with dry brittle hair (fig. 1a, b). On anthropometry, the patient's height was 91.5 cm (<3rd percentile, standard deviation score: –6.32), and the upper/lower segment ratio was 1.32. Her Tanner stage was prepubertal (no thelarche and no axillary or pubic hair). The patient had bradycardia and nonpalpable thyroid gland. Fundus examination and visual acuity were normal. The patient's systemic examination was unremarkable except for delayed relaxation of deep tendon reflexes, pseudohypertrophy of bilateral calf muscles, and pseudomyotonia.

Laboratory testing showed very high thyrotropin (TSH) and anti-thrombopoietin (TPO) antibody concentrations, along with a very low thyroxine (T_4) concentration (TSH: 520 μ IU/ml, T_4 : 12.87 nmol/l, anti-thyroid peroxidase antibodies: 1,300 IU/ml),

Table 1. Hormonal and serological profile

Serial No.	Parameter	Baseline value	After 6 months	After 12 months	Reference range
1	TSH	520.0000 mU/l	8.3456 mU/l	2.3345 mU/l	0.5–4.3 mU/l
2	T_4	12.87 nmol/l	56.88 nmol/l	102.96 nmol/l	60.5–133.8 nmol/l
3	Anti-thyroid peroxidase antibodies	1,300 IU/ml	–	–	<35 IU/ml
4	FSH	21.89 IU/l	4.74 IU/l	1.4 IU/l	0.4–6.5 IU/l (9–13 years)
5	LH	0.05 IU/l	0.04 IU/l	0.07 IU/l	<3.36 IU/l (prepubertal)
6	Prolactin	4.626 nmol/l	0.607 nmol/l	0.29 nmol/l	0.03–0.54 nmol/l
7	Estradiol	73.4 pmol/l	23.78 pmol/l	16.99 pmol/l	<59 pmol/l (1–9 years)
8	Cortisol	262.1 nmol/l	286.9 nmol/l	303.4 nmol/l	55–469 nmol/l
9	CPK	2,246 IU/l	123 IU/l	83 IU/l	35–145 IU/l

confirming the diagnosis of autoimmune primary hypothyroidism. Basal FSH, prolactin, and estradiol concentrations were significantly raised and were in the pubertal range, while LH was still prepubertal (FSH: 21.89 IU/l, LH: 0.05 IU/l, prolactin: 4.62 nmol/l, estradiol: 73.4 pmol/l), pointing towards the diagnosis of VWGS. Basal fasting cortisol was normal (cortisol: 262.1 nmol/l) (table 1). The patient's creatine phosphokinase (CPK) level was exceptionally high (CPK: 2,246 IU/l, normal level: 35–145 IU/l), confirming the diagnosis of KDSS (table 1). All hormonal investigations were done by chemiluminescence immunoassay using Abbott ARCHITECT i1000sr immunoassay analyzer (USA).

On X-ray, of the patient's left hand showed a significantly delayed bone age (Tanner-Whitehouse 2, TW2, method) (fig. 2). Ultrasonography showed a uterus with a pubertal size (65 × 25 mm). The right ovary showed single large cyst (51 × 24 mm), and the left ovary showed multiple cysts (fig. 3). A contrast-enhanced MRI of the brain revealed expansion of the sella turcica with a large, well-defined lobulated dumbbell-shaped mass lesion (measuring 12 × 11.5 × 16 mm) within the pituitary with suprasellar extension and infiltration of both the cavernous sinus and the abutting bilateral internal carotid artery (fig. 4).

On the basis of clinical history, physical examination, and additional investigations the patient was diagnosed with a combination of VWGS and KDSS. The patient was started on thyroxine replacement 25 µg per day, which was titrated guided by periodic laboratory investigations. After 12 months of follow-up all the clinical and biochemical parameters (table 1) improved, including the disappearance of secondary pituitary macroadenoma and pseudohypertrophy of the calf muscles.

Discussion

Primary hypothyroidism usually presents with subtle manifestations such as weight gain, poor concentration, depression, fatigue, muscular weakness, menstrual irregularities, short stature, etc. [1]. Rarely, it can present with unusual syndromes like VWGS and KDSS. VWGS was firstly described in the medical literature by Van Wyk and Grumbach [2] in 1960 in 3 girls who presented with hypothyroidism, precocious menarche, galactorrhea, and delayed bone age. There was precocious thelarche but an absence of pubic and axillary hair. The isosexual precocious puberty in VWGS is always incomplete [5]. The patient described in the present case report also had incomplete isosexual precocious puberty manifesting with menarche. The pathophysiology is probably related to the complex interaction between the hypothalamic-pituitary thyroid

Fig. 1. The patient's features. **a** Coarse facial features, puffiness of face, dry brittle hair, dry skin, and depressed nasal bridge. **b** Short and chubby fingers, and pale and dry skin. **c** Pseudohypertrophy of the calf muscles.

Fig. 2. X-ray of the patient's left hand, showing a significant delay of bone age of 3 years (TW2 method).

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Fig. 3. Uterus of pubertal size (65 × 25 mm), with the right ovary showing a single large cyst (51 × 24 mm) and the left ovary showing multiple cysts.

Fig. 4. Expansion of the sella with large-sized secondary macroadenoma (12 × 11.5 × 16 mm); a well-defined lobulated dumbbell-shaped enhancing mass lesion within the pituitary with suprasellar extension and infiltration of both the cavernous sinus and the abutting bilateral internal carotid artery.

and gonadal axes [3, 6]. In their original work, Van Wyk and Grumbach [2] hypothesized the pathophysiology as a 'hormonal overlap in pituitary feedback' causing increased production of not only TSH but also prolactin, gonadotropins, and estradiol [2, 6]. TRH-mediated excess prolactin production leads to the slowing of GnRH pulse frequency [3]. This slowing of GnRH pulse frequency causes an increase in FSH production and LH suppression [3], as is seen in the present case. A remote explanation for the raised FSH could be cross-reactivity of exceptionally high TSH with standard FSH assays [3]. Prolactin also causes ovarian sensitization to gonadotropins and accelerates follicular maturation [7]. One proposed novel mechanism is cross-reactivity of excessively high TSH acting as a competitive inhibitor of FSH on ovarian FSH receptors due to 'specificity spillover', leading to follicular maturation and multicystic changes, especially in the vulnerable peripubertal period [3, 6, 8]. Both are also seen in the present case. This occurs because of structural similarities between the pituitary glycoprotein hormones [3].

Paradoxical to other causes of precocious puberty, one of the unique features of isosexual precocious puberty caused by hypothyroidism is delayed bone age with growth retardation, despite the pubertal range of estradiol concentrations. This can be attributed to the extremely low thyroxine concentrations, and signs and symptoms are successfully reverted by adequate thyroxine replacement, as in the case of our patient [3].

Our patient's other features of pseudohypertrophy of calf muscles, delayed relaxation of deep tendon reflexes, and percussion myxedema, along with raised serum CPK, point towards KDSS – another rare presentation of juvenile hypothyroidism. This syndrome was initially firstly reported by Emil Theodore Kocher in 1892, while in 1935 Robert Debré and Georges Sémélaigne emphasized the occurrence of muscular pseudohypertrophy [9]. KDSS is a hypothyroid myopathy presenting as pseudohypertrophy of the affected muscles, delayed contraction and relaxation of deep tendon reflexes, pseudomyotonia, and myokymia [4]. The syndrome mainly affects children be-

tween the ages of 18 months and 10 years. Its adult version is known as ‘Hoffman’s syndrome’. The distribution of involvement is muscles of the extremities, limb girdle, trunk, hands, and feet, but it is more prominent in the muscles of limbs [10]. The male/female ratio is 1:2. The pathogenesis is incompletely understood, but increased glycogen and mucopolysaccharide deposits are being held responsible for the pseudohypertrophy of the involved muscles.

A shift of fast-twitch fibers to slow-twitch fibers in the involved muscles is considered to be the cause of delayed contraction and relaxation [4]. Biochemically, it is marked by high levels of CPK in a hypothyroid patient, while histochemical and ultrastructural changes on muscle biopsy are nonspecific. All of these findings normalize on adequate thyroxine replacement [4].

The association between VWGS and KDSS was reported previously by Akman et al. [11] in 2015, who described a 17-year-old patient with congenital hypothyroidism presenting with menstrual irregularities, multicystic ovaries, and muscle pain. High levels of CPK along with pseudohypertrophy of the muscles were present. All

the features were relieved after a short duration of thyroxine therapy. Similarly, the patient described in the present case had a resolution of all manifestations after 1 year of thyroxine replacement.

Conclusion

Hypothyroidism is a common endocrine disorder that usually presents with subtle signs and symptoms but rarely presents as VWGS or KDSS, or even both. Both syndromes are easily reversible by early diagnosis and adequate thyroxine therapy. High clinical suspicion, early diagnosis, and timely treatment can avoid unnecessary imaging and surgical intervention.

Disclosure Statement

There is no conflict of interest. None of the authors has received any kind of financial assistance from any commercial organizations in preparing the manuscript.

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