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Van Wyk and Grumbach Syndrome: An Unusual Presentation of Acquired Hypothyroidism

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1 Abstract

The association in young females of isosexual precocious puberty and/or polycystic ovaries, delayed bone age and hypothyroidism is known as the Van Wyk and Grumbach syndrome (VWGS). A 9-year-old girl presented with breast development, premature menarch and growth delay. An X-ray of the wrist showed a delayed bone age and laboratory data revealed high circulating levels of TSH with prepubertal LH level. The VWGS was diagnosed and thyroid hormone replacement was started with resolution of the symptoms. Clinically this syndrome is a diagnostic challenge because hypothyroidism usually leads to pubertal and growth delay, whereas in case of VWGS hypothyroidism leads to growth delay and precocious puberty. The pathophysiology of VWGS is not yet clear, but the most accepted theory states that the high concentrations of TSH act directly on FSH receptors and produce gonadal enlargement. Thyroid hormone replacement therapy results in a resolution of all signs and symptoms. Our case is unique as this girl did not have multi cystic ovaries.

2 Keywords

Hypothyroidism; precocious puberty; Van Wyk and Grumbach syndrome

3 Introduction

In 1960, Van Wyk and Grumbach first described a syndrome characterised by precocious breast development, uterine bleeding and multicystic ovaries in the presence of longstanding primary hypothyroidism [1]. Clinically, girls show the classical 'hypothyroid' appearance, delayed growth, isosexual precocious pseudopuberty with breast development with or without galactorrhoea, uterine bleeding but absence of significant pubic or axillary hair

development. Imaging studies typically reveal enlarged multicystic ovaries, a pubertal uterus, enlarged pituitary gland, and unique to this cause of sexual precocity, delayed bone age [2]. Biochemically, low FT4 is combined with raised levels of TSH exceeding 100 mIU/l. Most cases also describe the presence of autoantibodies against Thyroid Peroxidase (TPO Ab) or Thyroglobulin (Tg Ab). However, the syndrome can also appear in cases of congenital hypothyroidism, ectopic thyroid tissue or tumors that cause hypothyroidism. It is important to recognize this syndrome as all clinical and biochemical findings undergo complete remission when patients are started on an adequate thyroid replacement therapy and they spontaneously enter true puberty at an appropriate time [2].

4 CaseReport

A girl aged 9 years was referred to the endocrinology department with a suspicion of precocious puberty after having had progressive breast enlargement since 7 years of age and two episodes, 4 months apart, of per-vaginal bleeding lasting 3–4 days with associated cramp-like abdominal pain. She had no family history of thyroid disease, autoimmunity or precocious puberty. She was born at 37 weeks gestation with a birth weight of 2.800 kg and no antenatal or postnatal difficulties. Routine neonatal blood spot screening was normal. She had no history of headache, vomiting or visual symptoms. However, she had experienced some recent weight gain and poor growth.

Upon physical examination, her height was 91.5 cm (< -4 SDS), with weight of 24 kg (-1 SDS), BMI of 29 kg/m², blood pressure of 100/60 mmHg, and pulse rate of 59 beats/min. She had a puffy face with yellowish discoloration and very dry skin, and her thyroid gland was normal on palpation. She did not have edema of her extremities. On pubertal assessment, her breasts were Tanner stage 3 and pubic hair was Tanner stage 1.

She had normocytic normochromic anemia with a hemoglobin level of 8.5 g/dl (normal: 12–14 g/dl). Hormonal investigations revealed TSH > 150 μ IU/ml (normal: 0.35– 5.5 μ IU/ml), FT4 0.5 ng/ml (normal: 4.5–12.6 ng/ml), FSH 7.5 mIU/ml (0.3–2.8), LH < 0.07 mIU/ml (0.1–6.0) and prolactin 11.6 ng/ml (2.8–29.2). Tg Ab 1335 IU/ml (normal range <150

IU/ml) and TPO Ab 1000 IU/ml (normal range <75 IU/ml) were elevated. Abdominal ultrasound was normal with normal appearance of the uterus, ovaries and no visible endometrial line. X-ray of the wrist revealed a delayed bone age. Her chronological age at presentation was 8 years and 10 months. Her bone age was estimated at 2 years using Greulich and Pyle's atlas. Ultra sonography of the thyroid showed a heterogeneous and strongly vasculated thyroid gland, a finding highly suggestive for thyroiditis. Brain magnetic resonance imaging (MRI) showed an enlarged adenohypophysis, measuring 19x15 mm with homogeneous enhancement (Figure 1).

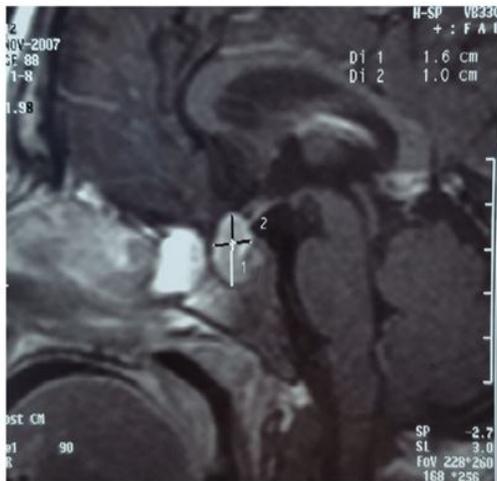


Figure 1: Initial MRI of the pituitary gland. Post enhanced T1 weighted sagittal MRI shows marked enlargement of the pituitary gland that extends slightly into the suprasellar region, with homogeneous enhancement.

With these results, the diagnosis of ovarian hyper stimulation secondary to severe hypothyroidism was made. The patient was started on levothyroxine 25 μg daily, and then the dose was increased gradually to 175 μg (7 $\mu\text{g}/\text{Kg}/\text{day}$). Upon follow-up, 2 months after starting on treatment, she reported significant improvement of her energy level, and she grew 3 cm and had a significant change in her physical appearance with the improvement of her facial puffiness, normalization of her skin color, and dryness. There was also a significant involution of her breast tissue. Repeat laboratory tests 6 months later showed improvement in thyroid function tests (TSH 0.84 $\mu\text{IU}/\text{ml}$). Brain MRI 10 months after thyroid replacement therapy, showed a reduction in the size of the anterior pituitary gland, which was essentially normal (Figure 2).

5 Discussion

Precocious puberty is a known, but rare complication of severe acquired juvenile hypothyroidism, and was first described by Kendle in 1905. It was not until 1960 when the term “Van Wyk and Grumbach syndrome” was coined [1]. Van Wyk and Grumbach described a syndrome of precocious menstruation in juvenile hypothyroidism, with reversion to a pre-pubertal state after thy-

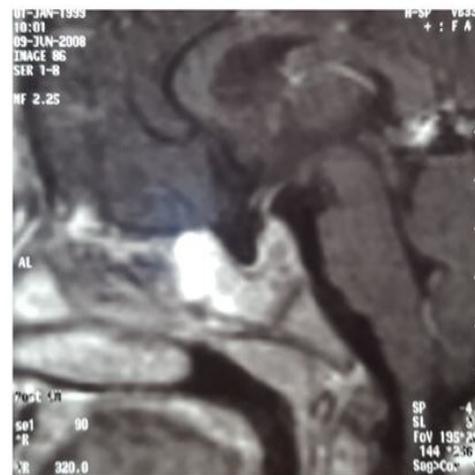


Figure 2: Follow up MRI of the sella 10 months after treatment. The pituitary gland is normal in size and configuration, remains confined to the sella, and shows homogeneous enhancement.

roid replacement therapy. A clue to the diagnosis is the delayed bone age, because VWGS is the only form of precocious puberty in which the bone age is delayed [1].

Most cases of VWGS concern pre-pubertal children, but it has also been described in young women. The predominance in pre-pubertal children can be explained by the assumption that the pre-pubertal gonads are more susceptible to stimulation by TSH, because they are primed to be activated by very low levels of FSH, as at the onset of puberty.

In girls, the condition usually presents with vaginal bleeding, and uncommonly with breast development and/or galactorrhea. Despite the precocious puberty, there is lack of pubic hair. In boys we find macroorchidism without significant signs of virilization. The salient diagnostic features include long-standing hypothyroidism [1,3], high levels of TSH, isosexual precocity with lack of pubic and axillary hair growth, and delayed bone age [4].

The most common cause of hypothyroidism in these patients is autoimmune thyroiditis [5]. Pituitary hyperplasia, a common finding in VWGS, has been blamed on long standing thyrotrope hyperplasia in response to the decreased thyroid hormone. Hyperprolactinemia, usually found in laboratory data has two etiologies. Some postulate that the thyrotrope hyperplasia in the pituitary compresses the pituitary stalk disrupting hypothalamic inhibition of prolactin. TRH is also known to stimulate prolactin. When thyroid hormone is low, TRH increases lead to increased levels of prolactin [6].

The exact mechanism of the development of precocious puberty in VWGS remains speculative. Mandl hypothesized in 1980 that continuous high TRH concentrations would stimulate not only TSH, but FSH secretion as well. This had already been put forward by Van Wyk and Grumbach in 1960 and was later named the “overlap theory” [7]. Various studies, however, demonstrate that gonadotropins are not routinely elevated in the VWGS [7]. Thus, elevated gonadotropins alone cannot completely explain the gonadal stimulation seen in severe juvenile hypothyroidism.

TSH levels are consistently elevated in such patients and the tendency to manifest sexual precocity may be directly related to the severity of TSH elevation. This is probably due to a “spill-over effect” of glycoprotein hormones. TSH, which is markedly increased in the VWGS, has a small FSH and LH-like effect [7]. Using recombinant tools, it has been shown that human TSH can interact with the human FSH receptor to stimulate the adenylyl cyclase activity. Human recombinant TSH at a dose about 1000-fold greater than human FSH evoked a dose-dependent cyclic AMP response in Chinese hamster ovary cells transfected with the human FSH receptor suggesting that relatively low FSH-like activity of TSH can be clinically significant at very high concentrations of TSH present in severe hypothyroidism [7].

In males a direct effect of severe hypothyroidism on the prepubertal testis leads to over proliferation of Sertoli cells and macroorchidism [8]. In females, the multi cystic ovaries may result from elevated levels of circulating gonadotropins. It is also possible that high levels of PRL enhance the sensitivity of the ovaries to circulating gonadotrophins by increasing ovarian LH receptors [9]. However, ovarian enlargement may be secondary to a myxedematous infiltration [10].

Anemia is not so uncommon in hypothyroidism and has been noted in several case reports of the Van Wyk–Grumbach syndrome. The proposed mechanism involves decreased red cell production in response to the reduced metabolic requirements for oxygen in tissues in hypothyroidism. In addition, the anemia may also be exaggerated by menorrhagia, dietary deficiency or pernicious anemia [11].

6 Conclusion

The association of isosexual precocious puberty, delayed bone age and hypothyroidism is known as the VWGS. This case demonstrates that VWGS should be kept in mind even in cases without clear ovarian involvement (no multi cystic ovaries). Early recognition and initiation of thyroid hormone replacement can avoid further diagnostic procedure and unnecessary surgery, resolve symptoms and improve final height achieved. The pathophysiology of VWGS is not yet clear, but the most accepted theory states that the high concentrations of TSH act directly on FSH receptors. Further studies are necessary to confirm this theory.

7 References

1. Van Wyk JJ and Grumbach MM. Syndrome of precocious menstruation and galactorrhoea in juvenile hypothyroidism: an example of hormonal overlap in pituitary feedback. *Journal of Pediatrics*. 1960;57(3):416–435. Doi: 10.1016/S0022-3476(60)80250-8

2. E Baranowski and W Hogler. An unusual presentation of acquired hypothyroidism: the Van Wyk–Grumbach syndrome. *European Journal of Endocrinology*. 2012;166:537–542.

3. Kubota K, Itho M, Kishi H, Igarashi S and Minegishi T. Primary hypothyroidism presenting as multiple ovarian cysts in an adult woman: a case report. *Gynecological Endocrinology*. 2008;24:586–589. Doi:10.1080/09513590802288192

4. Ryan GL, Feng X, d’Alva CB, Zhang M, Van Voorhis BJ, Pinto EM, et al. Evaluating the roles of follicle-stimulating hormone receptor polymorphisms in gonadal hyperstimulation associated with severe juvenile primary hypothyroidism. *Journal of Clinical Endocrinology and Metabolism*. 2007;92(6):2312–2317.

5. Gordon CM, Austin DJ, Radovick S and Lufer MR. Primary hypothyroidism presenting as severe vaginal bleeding in a prepubertal girl. *J Pediatr Adolesc Gynecol*. 1997;10(1):35–38.

6. Browne LP, Boswell HB, Crotty EJ, O’Hara SM, Birkemeier KL and Guillerman RP. Van Wyk and Grumbach syndrome revisited: Imaging and clinical findings in pre- and postpubertal girls. *Pediatr Radiol*. 2008;38(5):538–542. Doi: 10.1007/s00247-008-0777-1

7. Anasti JN, Flack MR, Froehlich J, Nelson LM & Nisula BC. A potential novel mechanism for precocious puberty in juvenile hypothyroidism. *Journal of Clinical Endocrinology and Metabolism*. 1995;80(1):276–279. Doi: 10.1210/jcem.80.1.7829625

8. Jannini EA, Ulisse S and D’Armiento M. Thyroid hormone and male gonadal function. *Endocr Rev*. 1995;16(4):443–459.

9. Chattopadhyay A, Kumar V & Marulaiah M. Polycystic ovaries, precocious puberty and acquired hypothyroidism: the Van Wyk and Grumbach syndrome. *Journal of Pediatric Surgery*. 2003;38(9):1390–1392. |

10. Hansen KA, Tho SP, Hanly M, Moretuzzo RW & McDonough PG. Massive ovarian enlargement in primary hypothyroidism. *Fertility and Sterility*. 1997;67(1):169–171. Doi: 10.1016/S0015-0282(97)81876-6

11. Chu JY, Monteleone JA, Peden VH, Graviss ER and Vernava BS. Anaemia in children and adolescents with hypothyroidism. *Clinical Paediatrics*. 1981;20(11):696–699.