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Multisystem Endocrine Disorders

Van Wyk-Grumbach Syndrome in an Egyptian Female Pediatric Patient: a Rare Presentation of a Common Disease

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Abstract

Van Wyk-Grumbach syndrome is a rare presentation of long standing pre-pubertal hypothyroidism characterized by bilateral multicystic ovaries, vaginal bleeding and delayed skeletal growth in case of female. Case Presentation: we present a clinical course, diagnosis and management of a case of Van Wyk-Grumbach syndrome in a 10-years old Egyptian counselled for recurrent vaginal bleeding and pubertal advancement for age. She was noted to have Tanner 4 breasts with no pubic hairs. Laboratory investigation revealed very high levels of thyroid stimulating hormone along with very low free thyroxine, suggesting long-standing untreated hypothyroidism. A pelvic ultrasound was done, which showed multiple simple cysts in both ovaries. Bone age was delayed. The diagnosis of Van Wyk-Grumbach syndrome was made based on the clinical and laboratory criteria. L-T4 therapy was initiated and successfully reversed the symptoms in 3 months duration. Conclusion: This case showed the importance of early identification of precocious puberty in association with delayed bone age and ovarian cyst as manifestations of hypothyroidism to prevent serious complications like Van Wyk-Grumbach syndrome. Precocious puberty associated with delayed bone age should attract attention to the diagnosis of this unique condition. The rapid initiation of L-T4 replacement therapy totally reversed this condition; stopped the rapid progression of precocious puberty and ovarian cystic enlargement allowing for adequate final adult height achievement.

Introduction

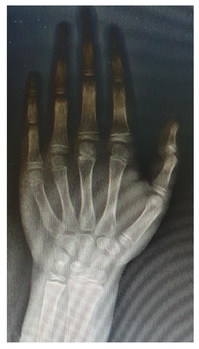
Van Wyk-Grumbach described a rare syndrome in 1960 with the following features; long standing untreated prepubertal hypothyroidism resulting in the development of isosexual precocious pseudo-puberty in the presence of large multicystic ovaries and delayed bone age in a female child (1). This syndrome differs from other causes of precocious puberty in that the girls are usually short with delayed bone age and no pubic hair development, unlike other known causes of precocious puberty in which bone age advancement is a prominent feature. Laboratory investigations shows very high elevation of Thyroid Stimulating Syndrome (TSH), elevated Follicle Stimulating Hormone (FSH), Prolactin and 17-β estradiol with low level of Luteinizing Hormone (LH). FSH and LH share the common β-subunit of TSH thus increased TSH act at the FSH receptor as TSH, therefore, high TSH stimulates the ovarian FSH because of this unique molecular mimicry producing elevated level of estrogen which causes enlargement of ovary of both ovaries associated with cystic changes and hence, the onset of menarche (2).

Case Presentation

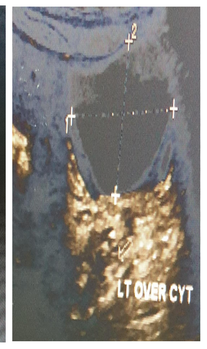
10.23-year-old Egyptian girl who presented with a 3-month history of vaginal bleeding (relatively precious menarche), progressive weight gain. Reviewing her history no remarkable finding was detected. Her mother noticed lack of interest in going to school, cold intolerance, easy fatiguability. There was no family history of autoimmune disorders, precocious puberty or any consanguineous marriage. She had normal stature (well below −1.1 standard deviations). This girl breast development of Tanner stage 4 with no pubic hairs (P1). She was diagnosed to have acquired hypothyroidism and gonadotropin-releasing hormone-independent precocious puberty with sonographic evidence of pubertal changes in the uterus and multicystic ovaries. Interestingly, she wasn't short as described. The diagnosis of Van Wyk-Grumbach syndrome was made based on the clinical and laboratory features. Her symptoms were successfully managed with L-thyroxine therapy. Physical examination; she had dull face, cold dry skin, her height was 133 cm (-1.1 SDS) with weight of 44 kg (+1.35 SDS), BMI 24.9 (+2.41 SDS), body temperature 36.6˚C, pulse rate 83/min, respiratory rate 20/min and blood pressure of 115/60 mm Hg. The thyroid gland was slightly enlarged. The girl had thelarche (Tanner stage 4), well developed labia, clitoris and absent pubic hair or axillary hair. Laboratory results are summarized in table 1.

Investigations

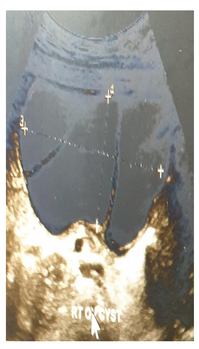
Her laboratory results together with the ultrasonographic characteristics of the thyroid gland suggests autoimmune hypothyroidism; thyroid peroxidase antibody titer: 1430 IU/l and thyroglobulin antibody titer: 820 IU/l , thyroid US showed mild thyroid enlargement with heterogenous echo-pattern and high vascularity suggestive of thyroiditis. Parents refused to do thyroid scan.



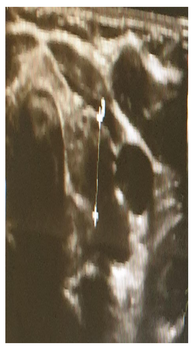
Bone age by G-P is 8y and 10 month



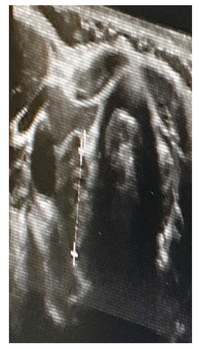
Left ovarian cyst



Right ovarian cyst



Right thyroid lobe



Left thyroid lobe

Table (1): Laboratory Investigations and imaging.

Investigations	Before treatment	3 months after treatment
Free T4 (Pmol/l)	<5.1	12
TSH (mIU/l)	>100	2.5
Estradiol (Pg/ml)	52	15
LH (U/l)	0.01	0.03
FSH (mIU/ml)	5.7	4.9
Thyroid Ultrasound	Right lobe 1.1x1.2 x2.3 cm Left lobe 1.1x1.2x3.2 cm	Right lobe 0.9x1.2x1.3 cm Left lobe 1x0.8x1.9 cm
Ovarian Ultrasound	Right ovarian cyst 4.5x3.6x8.6 cm Left ovarian cyst 7x2.5x7.9 cm	Cysts disappeared Right ovarian size 2.1x1.3x1.5 vol (2.5 ml) Left ovarian size 3.6x3.3x3.8 vol (24.4 ml)

Treatment

The patient was started on oral tablet of L-T4 at a dose of 50 mic/day and gradually increased to 100 mic/day.

Outcome and Follow up

The patient received only T4 therapy in our clinic. Review ultrasound scan of the pelvis region was done 3 months later, and it revealed complete resolution of the cystic lesions observed in both ovaries. Vaginal bleeding stopped within 2 months of therapy. Thyroid profile was normalized.

Discussion and Conclusions

- The combination of precocious puberty and delayed growth is characteristic of Van Wyk-Grumbach syndrome.
- Delayed bone age and short stature in the absence of pubic or axillary hair (no adrenarche stimulation) differentiate this unique condition from other causes of precocious puberty.
- Sexual precocity evident by isolated breast development and occurring in an obese short-statured girl associated with delayed bone age would be the alarming signs of this rare diagnosis.
- Increased levels of TSH acting on FSH receptors and induce FSH-like effects on the ovaries, resulting in multicystic ovaries, uterine enlargement with bleeding and breast enlargement in girls.
- Untreated prolonged hypothyroidism can progress to serious complications including van Wyk-Grumbach syndrome and even pituitary adenoma.
- Hypothyroid children have delayed growth and increased weight; although obesity is common but decreased growth velocity is the most prominent feature.

References

1. Van Wyk JJ, Grumbach MM. Syndrome of precocious menstruation and galactorrhea in juvenile hypothyroidism: an example of hormonal overlap in pituitary feedback. J Pediatr 1960 Sep 1;57(3):416–35.
2. Ryan GL, Feng X, d'Alva CB, Zhang M, Van Voorhis BJ, Pinto EM, Kubias AE, Antonini SR, Latronico AC, Segaloff DL. Evaluating the roles of follicle-stimulating hormone receptor polymorphisms in gonadal hyperstimulation associated with severe juvenile primary hypothyroidism. J Clin Endocrinol Metab 2007 Jun 1;92(6):2312–7.

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