Case Report

Van Wyk Grumbach Syndrome in a 7-year-old girl: a case report

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ABSTRACT

Van Wyk Grumbach syndrome (VWGS) is a rare syndrome, characterized by hypothyroidism, delayed bone age, isosexual precocious puberty and ovarian cysts. The symptoms completely reverse back to pre-pubertal state after treatment with thyroxine. This case report illustrates a seven-year-old girl who was referred with vaginal bleeding, ovarian cysts and had the features suggestive of VWGS. We explore risk factors for VWGS, and discuss the clinical presentation, pathophysiological mechanisms, and management of this patient.

Keywords: hypothyroidism, precocious puberty, ovarian cysts

Van Wyk Grumbach syndrome is a result of prolonged untreated primary hypothyroidism.[1–3] Primary hypothyroidism is a common endocrine abnormality leading to multiple system impairments, one of which is reproductive disorders.[4] Primary hypothyroidism in childhood often presents with a delayed puberty, but long standing hypothyroidism can rarely manifest as precocious puberty.[2,5,6] Precocious puberty in VWGS can present breast enlargement and uterine bleeding without axillary or pubic hair.[1,3,7] The development of isosexual precocious pseudo-puberty in VWGS is characterized by extra-pituitary secretion of gonadotropins (GnRH independent).[2,8] Bone age is accelerated in precocious puberty, but is delayed in the VWGS.[1]

Ovarian cyst is a common cause of gynecologic surgery.[4,9] The etiology varies from complex composition of the ovary or result from endocrine abnormality.[4] Ovarian cysts concomitant with precocious puberty, pituitary hyperplasia and prolonged untreated hypothyroidism was first described by Van Wyk and Grumbach.[6] The exact mechanism is still not clear. In 1960, Van Wyk and Grumbach were treated three girls with precocious menstruation, hypothyroidism, delayed bone age, and enlarged ovarian cysts with thyroxine, then the symptoms regressed over 6 months to 1 year with medical therapy alone without any surgical intervention.[6,8]

CASE REPORT

A 7-year-old girl was referred to the pediatric endocrine specialty clinic from gynecologist with vaginal bleeding for 3 days and bilateral ovarian cysts, concerning for precocious puberty. She has never menarche before, also her axillary and pubic hair have not grown. She has no abdominal pain or mass, weight loss, cold intolerance,

constipation, vomiting, headache, or visual symptoms. She was the first child of non-consanguineous marriage, full-term baby by caesarean delivery, birth weight 3800 grams, no history of feeding difficulties, hypotonia, prolonged jaundice, seizure, constipation or umbilical hernia. There was a history of thyroglossal duct cyst surgery 3 years ago due to neck cyst from birth that enlarges 3 cm. No history of routine drug use or radiation exposure. She had normal Denver II of development. There was history of short stature in the family and her grandmother has a goiter. No family history of ovarian cyst, precocious or delayed puberty, infertility, genital abnormalities or malignancy.

She has short stature and obesity. Her body has been fat since few years, even though she only ate 1-2 times a day. Her height was 110 cm (<3rd percentile), weight was 28,3 kg (75-90th percentile), body mass index was 25 (BMI for age percentile >97th), mid upper arm circumference was 21 cm, and upper segment was 59,5 cm (upper/lower ratio 1,1). Her height below mid parental height range prediction (158,5 ± 8,5 cm) and height percentiles decreased crossing multiple curves during 3 years from 97 cm (50th percentile) to 110 cm (<3rd percentile). Her pulse rate was 84 bpm, respiratory rate 18 x/min, temperature 36,5^{o}C and blood pressure 96/65 mmHg. Tanner's staging for sexual maturation was A1M2P1. There was postoperative scars in the middle of the neck, but thyroid gland not enlarged and no thyroid nodules palpable. There was no dysmorphic features, clitoromegaly, hyperpigmentation, ambiguous genitalia or other abnormalities.

From laboratory examination, she had a normal hemoglobin level of 12,5 g/dL. Hormonal profile revealed hypothyroidism with low free thyroxine (FT4) 8.43 pmol/L (normal 9-20), high thyroid-stimulating hormone (TSH) >1000 uIU/ml (0.4-6), also hypergonadotropic hypogonadism with high FSH 6,11 mIU/ml (Tanner 1 = 0,38-3,6), low estradiol 11 pg/ml (<18) and LH 0,24 mIU/ml (0,7 - 2). Thyroglobulin antibody (TgAb) <0,9 IU/L (≤1,75) and anti-thyroid peroxidase antibody (TPO) <0,5 U/mL (<5,61). Prolactin and insulin-like growth factor-1 (IGF-1) were not done due to financial constraints. Pelvic ultrasonography showed bilateral cysts with left ovarian cyst size 3.14 x 2.5 x 1.8 cm, and right adnexal cyst 5.2 x 4.08 x 4.9 cm (Figure 1). Tumor marker was normal with HCG <2 mIU/ml (<2), AFP 1.53 ng/ml (0.89 - 8.78), CA-125 12.54 U/mL (<35). Thyroid ultrasonography did not reveal any residual thyroglossal duct cyst, thyroid nodule or other abnormality. Her bone age revealed delayed bone age 2 years based on Greulich and Pyle's atlas (Figure 2). Head CT scan did not reveal any mass or abnormality (Figure 3).

The diagnosis VWGS based on the findings of precocious puberty, hypothyroidism, delayed bone age, and bilateral ovarian cysts. She received L-thyroxine therapy daily dose of 100 μg (3,5 μg/kg/day) and evaluated thyroid functions every month. During follow-up, her compliance was good and the L-thyroxine dose was titrated based on thyroid laboratory results from a daily dose of 100 μg to 75 μg. After 4 months of L-thyroxine therapy, she had clinical improvement with weight 24,1 kg (25-50th percentile), height 116 cm (3rd percentile), BMI for age 75-90th percentile, normal thyroid functions with FT4 17.42 pmol/L (9-20) and TSH 1.482 uIU/ml (0.4-6) and the repeat pelvic USG revealed complete regression of bilateral ovarian cysts (Figure 4).

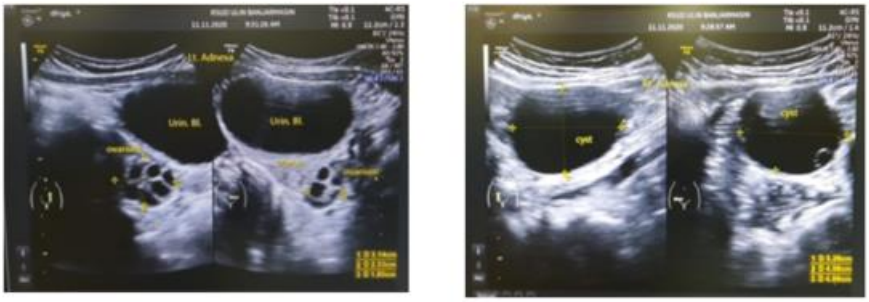

Figure 1 Pelvic USG before thyroxin treatment
Note: Left ovarian cyst size 3.14 x 2.5 x 1.8 cm, right adnexal cyst 5.2 x 4.08 x 4.9 cm

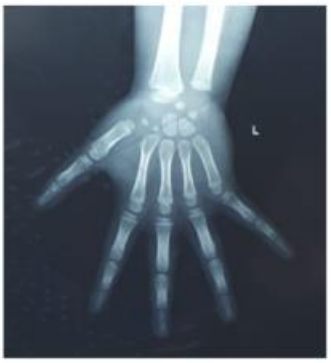

Figure 2 Bone Age
Note: delayed bone age 2 years

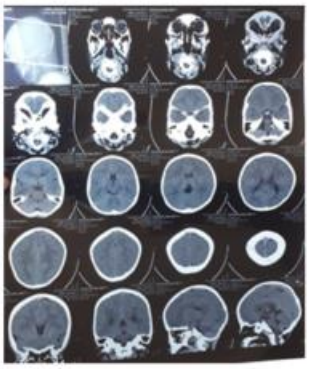

Figure 3 Normal Head CT scan

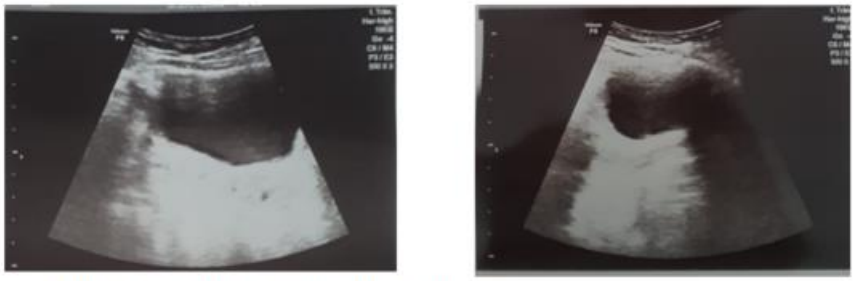

Figure 4 Pelvic USG after thyroxin treatment
Note: No cysts were found

DISCUSSION

Our patient presented with features of vaginal bleeding, precocious puberty, bilateral ovarian cysts, hypothyroidism and delayed bone age. Normally, puberty begins with activation of hypothalamic-pituitary-gonadal (HPG) axis, and estradiol will cause breast enlargement, pubertal growth spurt, and rapid bone maturation, then menarche usually occurs at least 2 years after onset of breast enlargement.[10] Precocious puberty in girls defined as signs of puberty before 8 years of age, referring to breast enlargement (confirmed by palpation).[10,11] The etiology divided into central (GnRH dependent) and peripheral (GnRH independent).[10,11] In our case, precocious puberty with bilateral ovarian cysts may suggested an estrogen-secreting ovarian tumor, but there was discrepancy because of delayed bone age and severe hypothyroidism, which is typical to VWGS.[8] The etiology precocious puberty in VWGS is due to TSH-mediated activation of gonadal FSH receptors (GnRH independent).[8]

Childhood ovarian cysts more common in adolescent periods. Mostly asymptomatic or mild, and usually discovered incidentally by ultrasonography.[12] The etiology includes functional cysts, neoplastic/ malignancy,

endocrine abnormality, etc.[4,12,13] Functional cysts occur during normal menstrual cycle when follicles fail to rupture during ovulation or when corpus luteum not dissolution, then continue to grow because of hormonal stimulation. While the neoplastic cysts arise from the inappropriate overgrowth of cells within the ovary.[12] One of endocrine causes of ovarian cyst formation is hypothyroidism.[12,13] Pathophysiology is still not clear, but the hypothesis because of structural resemblance between TSH and FSH (interaction between high TSH and ovarian FSH receptor).[4] Surgery intervention for ovarian cysts performed if adnexal torsion, acute rupture with hemorrhage, or suspected malignancy.[12,13] Hypothyroidism and other endocrine abnormalities (McCune-Albright syndrome, ectopic gonadotrophin adenoma secreting FSH) should be ruled out in childhood ovarian cysts to avoid unnecessary surgical intervention.[4,9]

Hypothyroidism is a deficiency in thyroid hormone. The etiology includes congenital or childhood (acquired); primary (thyroid gland), secondary (pituitary) or tertiary (hypothalamus); permanent or transient.[14,15] The most common cause of acquired childhood hypothyroidism is Hashimoto (autoimmune) thyroiditis.[6,7,14] The other cause are post-ablation (surgical, irradiation to neck), medication effects, iodine deficiency, late-onset congenital hypothyroidism, etc.[14] Several case studies report VWGS due to autoimmune thyroiditis,[2,16,17] suprasellar mass (pituitary hyperplasia),[3,18–20] post resection thyroglossal duct cyst,[21] genetic disorders (Alport syndrome).[22] In our case, it is still possible caused by post-surgical, or late-onset congenital.

Untreated hypothyroidism can cause complications including short stature, obesity, hyperlipidemia, delayed puberty, or in rare case, precocious puberty, such as VWGS.[7,21,22] VWGS can be diagnosed by clinical profile and laboratory examinations without doing surgery. Clinical profile is characterized by severe hypothyroidism, isosexual precocious puberty, delayed bone age, ovarian cysts.[3,8,23] Girls can have breast enlargement, vaginal bleeding, galactorrhea and ovarian cysts, whereas boys only have testicular enlargement without virilization. [2,17] Hormonal profile in VWGS is characterized by elevated TSH, prolactin, estradiol, pre-pubertal LH and decreased free thyroxine.[2,20]

Mechanisms of VWGS refer to high TSH levels stimulate FSH receptors, inducing FSH-like effects on gonads (gonad hyperstimulation, increased ovary size and cysts, myxedematous infiltration of the ovary, increased estrogen with uterine bleeding, breast enlargement), without increased androgens (absence of axillary and pubic hair).[1,3,8] High TSH also increasing prolactin, then effects of high prolactin are selective suppression of LH with an increased FSH production that cause increased follicular maturation.[8,19] Beside cysts and precocious puberty, the effect of high TSH causes slow chondrocyte differentiation resulting delayed bone age, also decreased metabolism/oxygen requirement resulting decreased red blood cell production (anemia).[8]

The raised tumor markers (CA-125, AFP, LDH) can be found in VWGS, which adding confusion to ovarian germ cell tumor.[8,16,17,24] An elevated tumor marker can cause significant anxiety for both patients and clinicians. CA-125 is secreted by mesothelial cells in response to stress-mechanical (fluid overload) or inflammatory mediators (TNF, interleukins). The elevated CA-125 and alpha fetoprotein (AFP) in VWGS due to increased secretion by ovarian cyst, peritoneal inflammation, long standing hypothyroidism or delayed clearance.[16,17]

Hypothyroidism causes myopathy and elevation of muscle enzymes such as lactate dehydrogenase (LDH).[8] In our case, there was no increase in tumor markers.

Therapy of VWGS is aimed at the management of hypothyroidism. Thyroid hormone replacement results in complete regression of symptoms to pre-pubertal state without surgery (oophorectomy or cystectomy).[7,8] The duration of thyroxine therapy was different in some case studies, range from 1 months to several years.[2–4,8,9,17,24,25] Follow-up include clinical examination (weight, height), thyroid functions, tumor markers and pelvic USG can be done 3 monthly.[8] In our case, vanishing ovarian cysts and normal thyroid function achieved within 4 months of thyroxine therapy.

CONCLUSION

VWGS is a rare case. It is characterized by juvenile hypothyroidism, isosexual precocious puberty and delayed bone age. Severe hypothyroidism can cause ovarian cysts, breast enlargement and vaginal bleeding. Thyroid hormone replacement is the key management of patients with VWGS. Ovarian cysts and other symptoms completely regress with medical therapy alone. Early recognition and initiation of hypothyroidism treatment avoids unnecessary surgery intervention in girl with VWGS.

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Nil.

CONFLICTS OF INTEREST

There are no conflicts of interest.

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