Van Wyk Grumbach Syndrome: A Rare Cause of Precocity in a Common Condition

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A nine-year old myxedematous girl with short stature, isosexual pseudoprecocious puberty and bilateral multicystic ovaries underwent pelvic laparotomy due to an acute abdomen because of adnexal torsion. She also had delayed bone age, severe hypothyroidism, hyperprolactinemia, hyperestrogenism and pituitary adenoma. All of these findings led to the diagnosis of Van Wyk Grumbach Syndrome, which is a rare condition characterized by long standing untreated hypothyroidism, pseudoprecocious puberty and multicystic ovaries. Administration of levothyroxine effected gradual regression and reversal of symptoms. This case highlights the significance of recognizing the clinical features of this syndrome in order to medically treat the child and thus, prevent its undesirable effects in the physical and mental growth and possible surgical complications that may affect her future reproductive capacity.

Keywords: Van Wyk Grumbach Syndrome, hypothyroidism, precocious puberty, multicystic ovaries

Introduction

Van Wyk Grumbach Syndrome was first described by Judson Van Wyk and Melvin Grumbach in 1960.[1] It is characterized by severe hypothyroidism, pseudoprecocious puberty and multicystic ovaries. Although the pathophysiology is still uncertain, it is believed to be caused by a "hormonal overlap" in the pituitary feedback mechanism, wherein the elevated thyroid stimulating hormone mimics the action of gonadotropins on the ovaries.[2] The features that distinguishes this syndrome from other causes of precocious puberty are short stature, delayed bone age and the absence of pubic hair. This paper presents a surgical complication that could have been prevented with early recognition and treatment of this syndrome.

The Case

A 9-year old girl was admitted by the Pediatrics department due to severe abdominal pain associated with nausea and vomiting. Her physical and mental development was incompatible for age (Figure 1A). She was 93 cm tall, which is less than the 3rd percentile of the World Health Organization height-for-age growth chart and with a BMI of 23.7 kg/m^2. She was lethargic, pale with myxedematous features. On physical examination, breast budding was present (Tanner stage 2) (Figure 1B) but there was no growth of axillary or pubic hair (Tanner stage 1) (Figure 1C). The abdomen was globular and distended with protruding umbilicus (Figure 1C). It was soft but with direct tenderness on all quadrants. No rebound tenderness was elicited. Her external genitalia was normal for age with intact hymen. Rectal examination showed short cervix but uterus and adnexae could not be assessed due to abdominal distension. Her past history revealed she had her menarche at the age of 6, and subsequent menstruation was irregular every 1-3 months amounting to 1-3 moderately soaked panty liners per day. A delay in her physical and mental development was first observed at age 4.

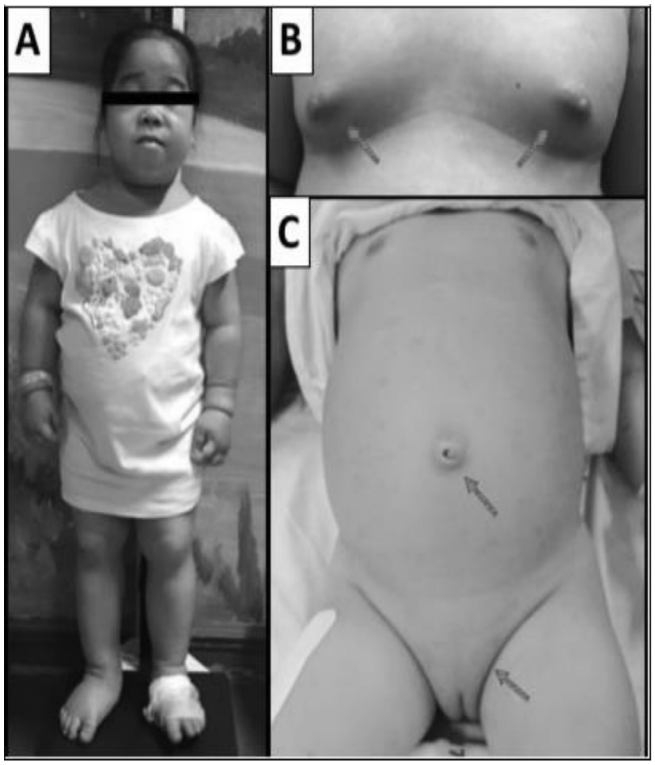

Figure 1. (A) Index patient; (B) Breast budding; (C) Globular abdomen, protruding umbilicus, no pubic hair

On imaging, whole abdominal ultrasound revealed a complex pelvoabdominal mass superior to the uterus measuring 11.1cm x 11.3cm x 5.7cm, possibly of left ovarian origin, with no distinct vascularity on color Doppler. The uterus was enlarged for age measuring 4.7cm x 3.7cm x 2.9cm and the right ovary had multiple follicles measuring 4.9cm x 3.4cm. She was subsequently referred to the gynecology department. Complete blood count revealed severe anemia with low hemoglobin at 3.9mg/dL, in which a total of 500cc packed red blood cell was transfused, thus increasing her hemoglobin to 12.2 g/dL.

A repeat transabdominal ultrasound revealed hemoperitoneum and probable ruptured left multiloculated ovarian cyst (8.78cm x 7.36cm x 9.3cm) with solid area and no color flow. The patient underwent emergency exploratory laparotomy. About 200 mL of hemoperitoneum was evacuated. The left ovary was enlarged to 10cm x 8cm x 4.5 cm (Figure 2A), necrotic and twisted 2x in its pedicle (Figure 2B) with 5-cm area of rupture (Figure 2A). The right ovary had smooth yellowish capsule and was enlarged to 6cm x 5cm x 4cm (Figure 2C). Left salpingooophorectomy was done. The patient tolerated the procedure well. The final histopathology report of the left ovary disclosed serous cystadenoma.

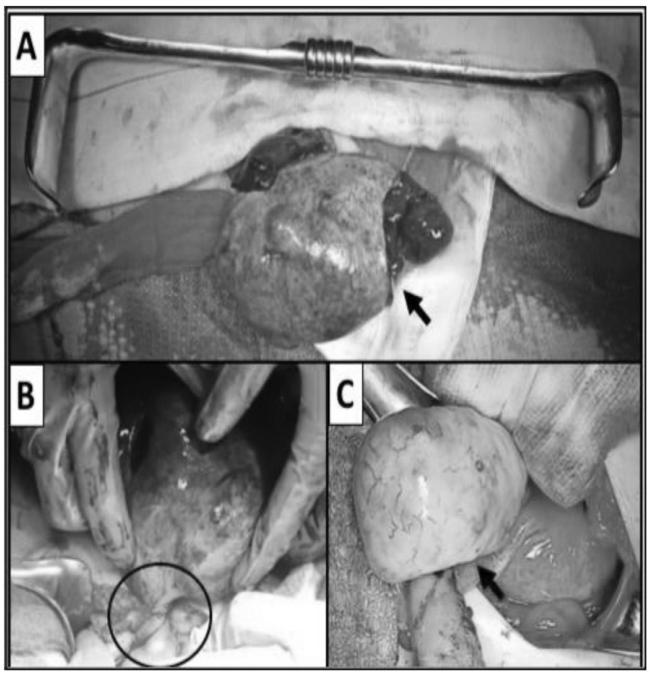

Figure 2. Intraoperative findings: (a) Ruptured left ovarian cyst; (B) Left ovarian cyst twisted 2x; (C) Enlarged right ovary

Post-operatively, other hormonal investigations revealed normal growth hormone, severe hypothyroidism with markedly elevated thyroid stimulating hormone (576.051 mIU/L – reference value: 0.64-6.27 mIU/L), hyperprolactinemia and hyperestrogenism (Table 1). X-ray of left hand revealed incompatible bone age of 1 year and 6 month based on Greulich and Pyle chart. Cranial CT scan revealed an enhancing nodule within the sella turcica measuring 1.1cm x 1.3cm x 1cm, likely a pituitary adenoma. With the diagnosis of pseudoprecocious puberty secondary to hypothyroidism, bromocriptine and levothyroxine replacement were initiated. The rest of the hospital stay was unremarkable. She was discharged on the 8th hospital day with a final diagnosis of Van Wyk Grumbach Syndrome.

On follow-up with the pediatric endocrinologist, thyroid ultrasound revealed normal sized thyroid gland with signs of parenchymal disease. Both anti-microsomal antibody and anti-thyroglobulin

Table 1. Hormonal investigation.

	Patient	Reference Range
TSH	576.051	0.64-6.27 mIU/L
FT3	0	2.3-4.2 pg/ml
FT4	1.24	0.89-1.76 ng/dL
PTH	52.8	11.1-79.5
Prolactin	147.74	2.8-29.2 ng/mL
AFP	11	less than 8.1 ng/ml
B-HCG	0.7	<10 mIU/mL
FSH	10.48	mIU/ml
LH	0.2	mIU/ml
Estradiol	80.9	6-27 pg/ml
ACTH	15.1	5.0-46.0 pg/mL
Cortisol AM	12.73	4.3-22.4 ug/dL
Cortisol PM	28.13	3.09-16.6 ug/dL
Serum Insulin	9.9	5-10 uU/ml
Serum Growth hormone	0.61	0.02-4.76 ng/ml
Intact PTH	52.8	11.1-79.5 pg/mL
Vitamin D (Total)	<8.1	9.3-48.5 ng/ml

antibody revealed positive, confirming a diagnosis of autoimmune thyroiditis. Repeat pelvic ultrasound after 3 months showed normal-sized uterus measuring 4.7cm x 2.9cm x 1.5cm with thin endometrium and polycystic right ovary, which gradually decreased in size into 3.6cm x 3.1cm x 2.4cm. With the return to euthyroid state five months later, the mother noticed her child now became more alert, active and playful. Her myxedematous features and breast budding also gradually disappeared and the vaginal bleeding did not recur. The patient had shown improvement physically and mentally.

Discussion

The early onset of menstruation at the age of 6 in the patient is pathognomonic of isosexual pseudoprecocious puberty. The presence of breast buds (Tanner Stage 2) and the absence of axillary and pubic hair imply that the etiology of her precocity is not central or due to the early maturation of the hypothalamic-pituitary-gonadal axis but because of the elevated levels of estrogen. The high levels of estrogen may be secondary to exogenous or endogenous sources.[4] The bilaterally enlarged ovaries indicate ovarian hyperstimulation as the cause of her hyperestrogenic state.

Her myxedematous features, short stature, delayed bone age and poor mental development all point to severe untreated hypothyroidism. All of these features became evident at age 4, signifying that the hypothyroidism was acquired after birth. Generally, hypothyroidism is associated with delayed sexual maturation and delayed puberty. However, in cases of long standing untreated acquired hypothyroidism as in our patient, there is a rare occurrence of precocious puberty.[5,6]

In 1905, Kendle first reported a 9-year-old girl with acquired hypothyroidism who developed precocious puberty with breast maturation and menarche at age 5. It has been considered that the etiology of acquired hypothyroidism may be undiagnosed autoimmune thyroiditis or an ectopic thyroid. Since this was reported, there were a few number of case reports of children with hypothyroidism and precocious puberty.[6]

However, it was only in 1960 that Judson Van Wyk and Melvin Grumbach first correlated hypothyroidism with precocious puberty in their case report of 3 girls with juvenile hypothyroidism, early menarche, galactorrhea, absence of pubic hair and enlargement of sella turcica.[1] They theorized 2 possible etiologies: 1) The follicle stimulating hormone (FSH) theory states that thyroid stimulating hormone (TSH) could mimic the action of follicle stimulating hormone (FSH) on the ovaries because they share the same alpha subunit.[1,3,5] The hyperstimulation of ovaries causes it to enlarge and produce high levels of estrogen, which now explains the breast enlargement, early menarche and bilateral multicystic ovarian enlargement in the patient. Since androgens are not increased, axillary and pubic hair are absent. The pituitary adenoma of the patient is explained by the 2) prolactin theory, which states that prolactin and thyroid stimulating hormone share the same regulating hormone – the thyroid regulating

hormone (TRH). With severe hypothyroidism, the thyroid regulating hormone increases. This does not only cause hyperplasia of the thyroid stimulating hormone (TSH)-secreting cells but also the prolactin-secreting cells in the pituitary, which eventually leads to hyperprolactinemia.[1,7] Simultaneously, the high estrogen levels reduce the prolactin inhibitory factor via a negative feedback mechanism which further increases the prolactin levels. The hyperestrogenic state also promotes enhanced sensitivity of the ovaries to the circulating gonadotropins, thereby accelerating follicular maturation and ultimately resulting to precocious puberty.[2]

The incidence of Van Wyk Grumbach Syndrome is still unknown since only few cases have been reported worldwide. In a literature search since its year of discovery using PubMed Central, only 20 case reports have been cited. To date, no written reports of this syndrome have been made locally.

Van Wyk Grumbach syndrome remains a diagnostic challenge. Long standing hypothyroidism in children is more known to cause delayed puberty and stunted growth.[5] On the other hand, true precocious puberty presents with pubertal growth spurt and advanced bone age. This unique and rare syndrome combines hypothyroidism and isosexual pseudoprecocious puberty, making it a diagnostic dilemma.

It is unfortunate to report that the recognition and treatment of hypothyroidism in the patient had been delayed, which eventually led to the development of Van Wyk Grumbach Syndrome. Although it can be treated medically, surgical emergencies may still ensue from ovarian torsion and rupture of the enlarged ovaries. This happened in the patient because of the delayed diagnosis. This could have been a preventable complication if only she had been diagnosed early and given adequate hormonal replacement. Case reports have demonstrated that medical treatment alone resulted in complete resolution of symptoms such as regression of breast enlargement, reversal of multicystic ovaries and cessation of vaginal bleeding.[9]

In conclusion, though a very rare disease, it is of great significance that clinicians are aware and able to recognize the associated clinical features of Van Wyk Grumbach Syndrome in order to prevent the undesirable effects in the physical and mental growth of the child and its possible surgical complications if left untreated medically, and more importantly, to preserve her future reproductive capacity.

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