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Case Report

Van Wyk Grumbach syndrome - a rare association of a common prepubertal condition

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ABSTRACT

Van Wyk Grumbach syndrome is a sequel of long standing untreated primary hypothyroidism. It occurs in both sexes. In boys, it is associated with testicular enlargement. Girls present with features of early onset menarche, enlarged bilateral multicystic ovaries and delayed skeletal growth. Prompt replacement therapy with Thyroxine corrects the menstrual abnormality and the ovaries also return to normal over a period of time. We describe an unusual case of irregular vaginal bleeding, giant bilateral ovarian cysts and delayed bone age in a young girl due to severe hypothyroidism who promptly responded to levo-thyroxine.

Keywords: Van Wyk Grumbach, Hypothyroidism, Pre-pubertal girls, Ovarian cysts

INTRODUCTION

Van Wyk and Grumbach in 1960 first described Van Wyk Grumbach Syndrome (VWGS) as the constellation of symptoms including juvenile hypothyroidism, precocious puberty and delayed bone age which regresses with thyroxine replacement.[1] We report a girl with a giant cystic abdominal lump and precocious puberty who was diagnosed as severe hypothyroidism.

CASE REPORT

A 9 year old girl presented with a gradually increasing large abdominal lump since 3 months. She had occasional vaginal bleeding accompanied with abdominal pain since two months. Her milestones were normal for her age. Patient had pallor and puffiness of face. Height was 125 cms (expected 130 cms below 25th percentile). Weight was 25 kg (expected 45 kg-below 5th percentile). Breast development was present. Axillary and pubic hairs were absent. There was a large abdominal lump 15x10cm arising from the pelvis and occupying the abdomen (Figure 1). Haemogram and Renal function tests were normal. Abdominal ultrasound (USG) showed a large 14x8x13 cm sized complex solid cystic lesion in pelvis, bilateral ovaries were not seen separately. Uterus was bulky and enlarged in size.

CT scan of the abdomen showed bilateral large multi-septate cystic lesions with solid components arising from the ovary with minimal ascites (Figure 2). Serum alpha fetoprotein and serum beta-HCG were normal. Serum CA-125 was raised (181.2 U/ml- ref range 0-35). In view of growth retardation with irregular vaginal bleeding, Thyroid function tests were done. Free T3 and free T4 were normal. Serum TSH (>150uIU/ml) and TPO antibodies (>1300 - normal upto 60 U/ml) were raised. Serum FSH was normal. Serum LH was low 0.0mlU/ml (2.5-10), while Prolactin was raised 49.6 ng/ml (5-25).

Ultrasonography of neck showed a bulky thyroid with heterogenous echotexture. Bone age as determined on skiagrams of the wrist and hand was below 7 years. MRI brain showed enlarged pituitary gland (15x11x20mm) with extension into suprasellar region (Figure 3). A provisional diagnosis of Van Wyk Grumbach syndrome with incomplete isosexual precocious puberty was made

in consultation with the endocrinologists. Patient was started on thyroid replacement therapy with Levo-thyroxine (Tab. Thyronorm) in weekly increasing doses starting with 50mcg/day reaching up to 125 mcg/day. Patient improved dramatically with decrease in the size of lump.

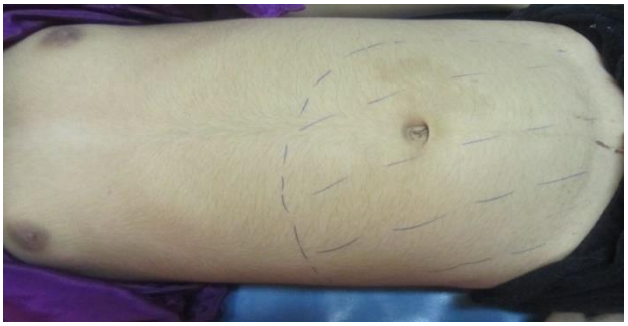

Figure 1: Clinical photograph of patient showing large abdominal lump.

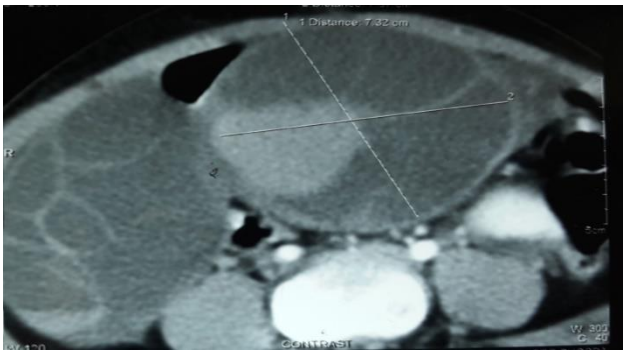

Figure 2: CT scan showing multicystic ovaries.

Follow up Ultrasonography after one month showed reduced size of the ovaries with right ovary measuring 5x4.7x3.7 cm and left ovary 3.6x3.1x3.2cm. Uterus was normal in size (Figure 4). Serum TSH returned to normal level 0.5mclU/ml (0.35-5). Levothyroxine at dose of 100mcg/day was continued. At 3months follow up, abdominal lump was not palpable and Ultrasonography showed bilaterally bulky ovaries with multiple follicles (1-15 mm) within.

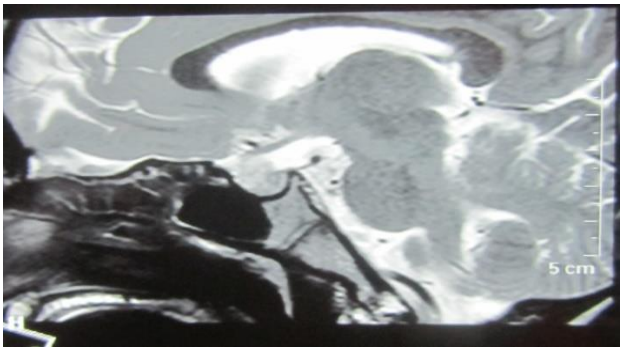

Figure 3: MRI brain showing enlarged pituitary gland.

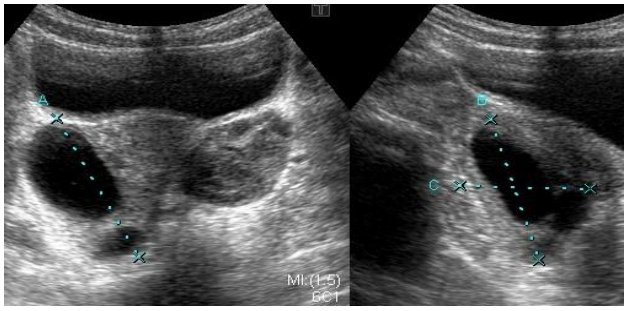

Figure 4: Follow up ultrasonography showing reduced size of bilalateral ovarian cysts.

DISCUSSION

Van Wyk and Grumbach in 1960 described a syndrome for the first time in which there is association of juvenile hypothyroidism, iso-precocious puberty and multicystic ovarian enlargement.[1] Van Wyk and Grumbach proposed that there was a 'hormonal overlap' in the pituitary feedback mechanism. This overlap is due to the fact that TSH, FSH and LH are all glycoproteins with common alpha chains and may thus cross react. High TSH could produce FSH and LH-like activity leading to luteinized ovarian cysts.[2] The current and most widely accepted theory is that high levels TSH act on FSH receptors because of the molecular similarities between the two hormones. This mechanism, known as "specificity spill over," has been demonstrated in vitro. Although hypothyroidism is classified as gonadotropin-dependent, the probable binding of TSH to FSH receptors removes the gonadotrop in from the process. Thyroid-stimulating hormone acts as gonadotropin in the ovaries or testes.[2] A convincing explanation of sexual precocity and bilateral ovarian enlargement is that high levels of thyroid stimulating hormone (TSH) seen in profound hypothyroidism could act through the follicle stimulating hormone receptor (FSHr) and cause gonadal stimulation. This causes uterine bleeding, multicystic ovaries in girls.[3] The most common cause of hypothyroidism in these patients is autoimmune thyroditis. The salient diagnostic features of the syndrome are untreated long-standing hypothyroidism with high levels of TSH, isosexual precocity with lack of pubic and axillary hair growth, and delayed bone age. The precocious puberty is always isosexual and incomplete in patients of VWGS. Sella turcica enlargement and pituitary adenoma may develop in some due to ling standing thyrotroph hyperplasia in response to hypothyroidism.[4] Hyperprolactinemia develops due to thyrotrophic hyperplasia or secondary to direct stimulation of prolactin release by TRH 5. 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. High circulating levels of TSH acting directly on FSH receptors may be the actual mediator of precocity.[6] The multicystic ovaries may result from elevated levels of circulating gonadotropins acting on it. It is also possible that increased sensitivity of the ovaries to the circulating

gonadotropins could result from the hypothyroid state directly or via increased prolactin. However, ovarian enlargement may be secondary to a myxedematous infiltration.[4] Girls with this syndrome have breast development, follicular cysts and menstruation in the absence of pubic or axillary hair, which depends on adrenal androgens. The clinical picture in the case discussed above was similar. In view of these features differentiation between ovarian malignancy and benign etiology was prudent. The clinical features and laboratory findings suggested severe hypothyroidism. Elevation of CA-125 levels is known to occur in hypothyroidism. Ascites is a rare complication of hypothyroidism (4%). Association of hypothyroidism, ascites (myxoedema) and high levels of CA-125 is very rare. Elevation of CA-125 probably is due to delay of clearance of CA-125 secondary to hypothyroidism, peritoneal inflammation or increased secretion of this marker by the ovarian cysts.[7] In patients with isosexual pseudo precocity, the presence of palpable adnexal mass would suggest ovarian tumors but in all such cases, the bone age is advanced. Hence, the presence of a delayed bone age in patients with precocious puberty is an important clue for the diagnosis. Diagnosing VWGS by recognition of the salient clinical features and appropriate confirmatory endocrine laboratory tests is essential as it responds very well to conservative management. A high clinical suspicion of complicating ovarian torsion is probably the only indication for surgery in these patients.[8] Although there is little consensus regarding the precise etiopathogenesis of this disorder, the treatment approach is clear. All symptoms subside with thyroxine replacement, the endocrine abnormalities resolve, and even the ovarian cysts decrease in size or altogether disappear, as seen in our patient during follow-up. Provided that the thyroid hormone is adequately replaced, and there is enough time for catch up growth before true puberty occurs, it is conceivable that patients can achieve a final height within normal limits.[9]

CONCLUSION

The presence of a delayed bone age in patients with precocious puberty is an important clue for the diagnosis of VWGS. Hypothyroidism should be included in the work-up of patients with ovarian cysts, especially if associated with high level CA-125 markers, in order to avoid unnecessary surgery. All symptoms subside with thyroxine replacement. The endocrine abnormalities resolve and the ovarian cysts decrease in size or altogether disappear.

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