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"Role of Radiological Imaging in detecting Van Wyk Grumbach syndrome: A Case series."

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Abstract
Van Wyk and Grumbach syndrome is characterized by long-standing history of hypothyroidism, high levels of thyroid-stimulating hormone, unilateral or bilateral ovarian cysts, delayed bone age and precocious puberty but lacking pubic and axillary hair growth. All of the features can be reversed with treatment of the underlying hypothyroidism with thyroxine.Two cases having features of Van Wyk and Grumbach syndrome suspected on radiological imaging and confirmed with clinical findings and raised levels of TSH hormone are discussed here. Both the patients promptly responded to L-thyroxine with regression of the ovarian cysts and other symptoms. This case series highlight the importance of radiology in clinching this rare diagnosis.
Key words: Enlarged multicystic ovaries, Computed tomography, Hypothyroidism, MRI, Precocious puberty, Pituitary hyperplasia, Radiological Imaging, USG

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I. Introduction

The term 'Van Wyk Grumbach Syndrome' (VWGS) was coined in 1960 to describe a constellation of hypothyroidism, precocious puberty and ovarian mass(1).Central precocious puberty occurs due to GnRH dependant activation of hypothalamic pituitary gonadal axis. Pseudo-precocious puberty or GnRH independent sexual precocity is characterized by extra-pituitary secretion of gonadotropins(2).

The presence of precocious puberty in the background of enlarged ovaries usually suggests an estrogen secreting ovarian tumor. However, presence of severe hypothyroidism and delayed bone age narrows down the diagnosis to Van WykGrumbach Syndrome. High circulating TSH with pre-pubertal LH further confirms the diagnosis. Auto-immune thyroiditis needs to be ruled out in these patients as a cause of hypothyroidism (3). The following case series highlight the importance of radiological imaging in detection of the salient findings (enlarged mutlicystic ovaries, pituitary hyperplasia and thyroiditis) of this rare disorder as well as the role of radiology in documenting response to the treatment without the need of invasive diagnostic procedures or surgery(4).

II. Case Series

Case 1

A 9-year-old girl presented with right iliac fossa pain for last six to seven months, aggravated during menstural cycles and relieved temporarily by medications. According to her parents, the patient had early menarche at approximately 8 years of age. Presently the patient weighed 25 kg and her height was 130 cm. She exhibited Tanner stage 3 breast and stage 2 pubic hair development. On palpation lower abdomen was tender predominantly in right iliac fossa. Patient was referred for pelvic ultrasound which revealed normal sized uterus and bilateral enlarged multicystic ovaries (right ovary, measuring approximately 4.7 cm x 4.3 cm x 4.3 cm, volume ~47-48cc and left ovary 4.1 cm x 3.4 cm x 5.0 cm , volume ~ 36-37 cc with largest measuring spproximately 3.7 x 2.7cm in the right ovary).

CECT whole abdomen confirmed the USG findings and showed bilateral enlarged ovaries with multicystic appearance, right ovary measuring approximately 5.4 cm x 4.5 cm x 4.7 cm, volume ~ 57 cc and left ovary measuring approximately 4.2 cm x 4.4 cm x 4.9 cm, volume ~ 45 cc. Based on USG and CT findings possibility of ovarian hyperstimulation by hormonal disorder was suggested. As part of further workup CE MRI brain was done revealing diffusely enlarged pituitary gland measuring 16 mm CC x 18 mm TR x 10mm AP

with volume approximately 1440mm^3,showing homogeneous enhancement and mildly compressing the optic chiasm superiorly suggesting pituitary hyperplasia. Based on the imaging and clinical findings thyroid function examination was conducted and revealed profound hypothyroidism: thyroid-stimulating hormone (TSH) was 1367uIU/L, triiodothyronine (T3) was0.33ng/ml and thyroxine (T4)was0.49 ug/dl. Neck ultrasonography revealed heterogenous thyroid gland with multiple fibrous echogenic septae suggesting thyroiditis. Patient was diagnosed with precocious puberty and large multicystic ovaries with primary hypothyroidism and given thyroidreplacement therapy. By the fourth week of therapy the thyroid function test showed normal values, thyroid-stimulating hormone (TSH) was 25uIU/L, triiodothyronine (T3) was 1.84ng/ml and thyroxine (T4)was 14.77 ug/dl and ultrasonography showed a significant decrease in the size of bilateral ovaries.

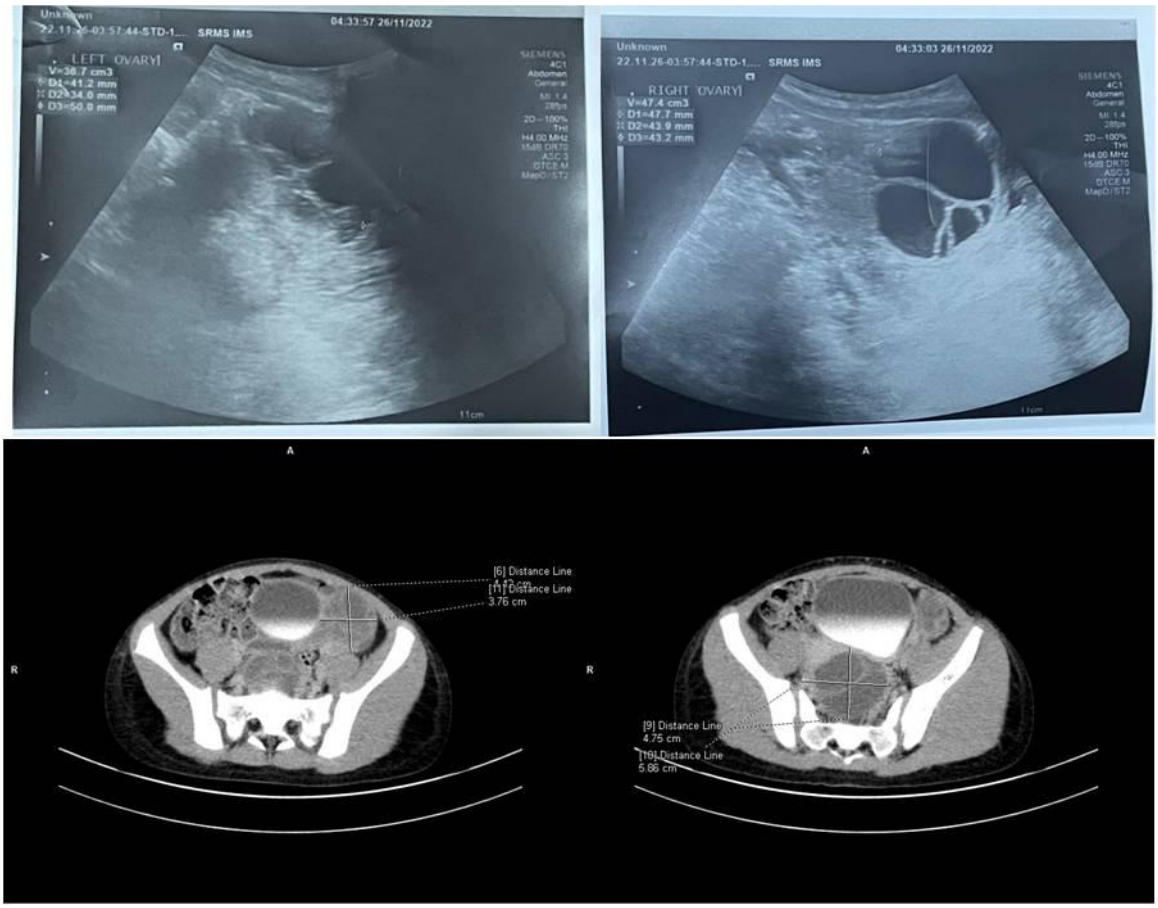

Figure 1 Top row images of transabdominal pelvic USG and bottom row images of CECT pelvis reveal bilateral enlarged multicystic ovaries

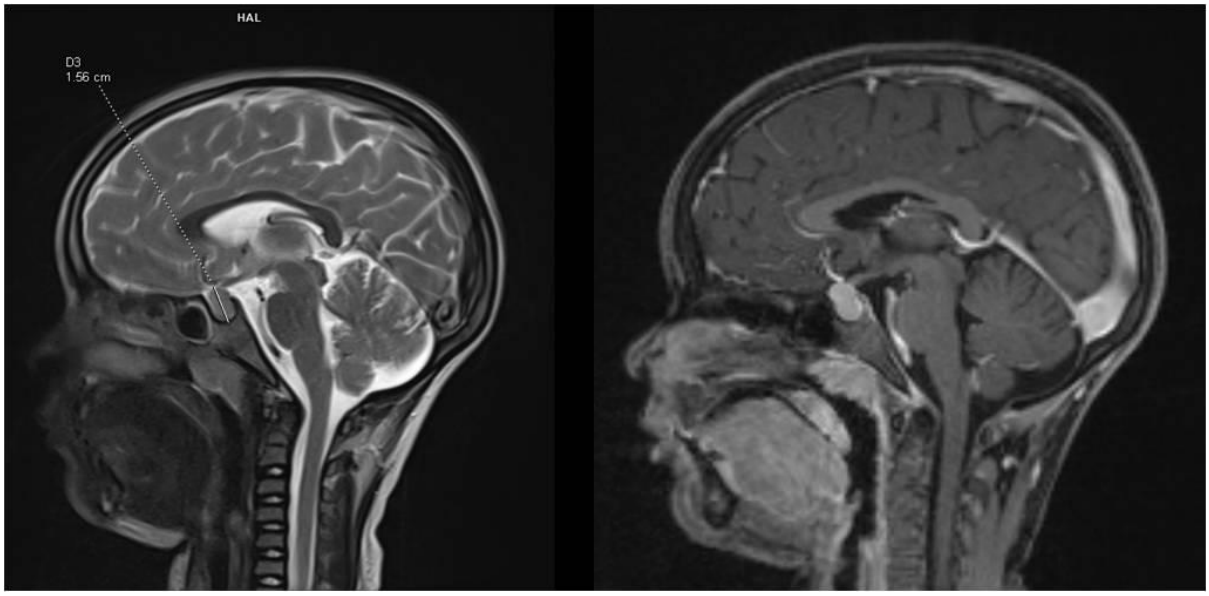

Figure 2. Sagittal T2WI and post gadolinium T1WI images reveal homogeneously enhancing pituitary hyperplasia

Case 2

A 17-year-old girl presented with complains of menorrhagia and lower abdominal pain for last few months with severe anaemia with haemoglobin 3.8 g/dl. She had early menarche at approximately 7 years of age. She had sub normal IQ and short stature. On palpation there was lower abdominal tenderness. Patient was referred for pelvic MRI to evaluate uterus, endometrial cavity and ovaries, and revealed bulky arcuate uterus and bilateral enlarged multicystic ovaries, (right ovary measuring approximately 8.0 cm x 4.5 cm x 4.7 cm, volume ~ 85 cc and left ovary measuring approximately 9.0 cm x 6.0 cm x 5.0 cm, volume ~ 135 cc) with thin walls and internal septations suggestive of possibility of ovarian hyperstimulation syndrome vs bilateral ovarian cystic neoplasms. Based on the MRI findings, thyroid function examination was conducted and revealed profound hypothyroidism: thyroid-stimulating hormone (TSH) was 343uIU/L, triiodothyronine (T3) was 0.66 ng/ml and thyroxine (T4) was6.72 ug/dl. With the diagnosis of hypothyroidism suggesting Van Wyk-Grumbach syndrome, treatment was begun with levothyroxine. By the fourth week of therapy the thyroid function test showed normal values, thyroid-stimulating hormone (TSH) was 11.57uIU/L, triiodothyronine (T3) was 1.56 ng/ml and thyroxine (T4) was 6.46 ug/dl and follow up ultrasonography of abdomen showed a significant decrease in the size of bilateral ovaries right ovary measuring approximately 15-16 cc and left ovary measuring approximately 10-11 cc and improvement of other symptoms.

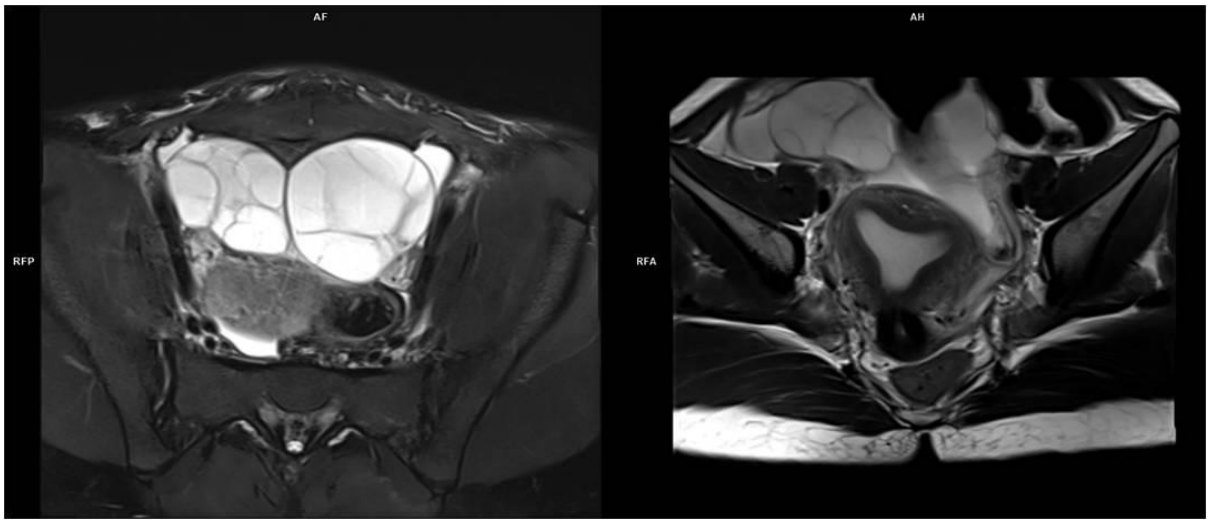

Figure 3. MRI pelvis axial T2 fat suppressed images showing bilateral enlarged multicystic ovaries and arcuate uterus.

III. Discussion

Van WykGrumbach syndrome includes chronic hypothyroidismwith high levels of TSH, precocious puberty with lack of pubic and axillary hair growth, and delayed bone age(1).Children with primary hypothyroidism generally present with delayed pubertal development and short stature. Rarely, juvenile hypothyroidism can manifest as isosexual precocity in the form of isolated menarche in conjunction with delayed bone age, retarded growth, pituitary enlargement, and multicystic ovaries (5-10).High levels of TSH acts via the FSH receptor causing gonadal stimulation resulting in increased oestrogen production, which stimulates the development of secondary sexual characters like breast development, follicular cysts and menstruation. Several theories have been postulated to explain the mechanism that occurs in VWGS. Van Wyk and Grumbach originally attributed it to a hormonal overlap in pituitary feedback mechanism. TSH, FSH, LH and human chorionic gonadotropin (hCG) are glycoprotein hormones which share a common alpha subunit but different beta subunits. Thus, TSH, in high concentrations, stimulates the FSH receptor leading to an increase in gonadal size and steroidogenesis(11). Chronic hypothyroidism can interfere with gonadotropin secretion by increasing serum prolactin levels(12).Ovaries are sensitized to GnRH as Granulosa cells TSH receptors are activated which causes ovarian hyper-stimulation & myxedematous infiltration of the ovary resulting in multicystic enlargement of the ovaries (13).

In our case series both the patients presented with precious puberty without pubic or axillary hair growth clinically, had multicystic enlarged ovaries with hypothyroidism with high circulating TSH levels consistent with the Van Wyk and Grumbach syndrome. There was further confirmation of the diagnosis with regression of symptoms and bilateral ovarian cysts on USG and normal thyroid hormone levels after treatment with the thyroid hormonal replacement therapy with thyroxine.

Long-standing hypothyroidism resulting in loss of negative feedback at the hypothalamus with secondary hypertrophy of thyrotropic cells in the anterior pituitary. This anterior pituitary enlargement is seen as homogeneous diffuse enlargement of the pituitary on contrast enhanced MRI Brain. In our case series, the first case shows the diffusely enlarged pituitary gland on CEMRI brain that also favours our diagnosis of Van Wyk and Grumbach syndrome.

IV. Conclusion

Van Wyk Grumbach Syndrome is, an atypical presentation of a common endocrinal disorder and should be considered in juvenile girls with precocious puberty, delayed bone age & hypothyroidism. Even without subjecting patients to skeletal X-rays the diagnosis could be ascertained with the help of multimodality radiological imaging, clinical correlation and confirmatory hormonal assay. The regression of features of this syndrome with thyroxine supplementation also was well documented on follow up ultrasounds preventing unnecessary invasive interventions. Hence knowledge of the varied presentations and its association to the practicing radiologists can help in early recognition of this condition and preventing unnecessary investigations and surgical interventions in young girls preserving the fertility.

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