

CASE REPORT

Van Wyk Grumbach Syndrome-A rare case report

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Abstract

Van Wyk and Grumbach syndrome is a rare condition characterized by breast development, uterine bleeding and multicystic ovaries in the presence of long-standing primary hypothyroidism. The patient with this syndrome was admitted in Shaheed Suhrawardy Medical College Hospital in November' 2013. Here this rare and interesting case was reported. [J Curr Adv Med Res 2015;2(1):24-27]

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Introduction

Van Wyk-Grumbach syndrome (VWGS) is characterized by juvenile hypothyroidism, delayed bone age, and isosexual precocious puberty with reversal to a prepubertal state following thyroid hormone replacement therapy¹. The gonadotropin releasing hormone (GnRH)-dependent activation of the hypothalamic-pituitary-gonadal axis leads to central precocious puberty (CPP). The extrapituitary secretion of gonadotropins or secretion of gonadal steroids independent of pulsatile GnRH stimulation may lead to pseudoprecocious puberty, or GnRH-independent sexual precocity².

Incomplete isosexual precocity is a consequence of premature increased sex hormone secretion, iatrogenic exposure of gonadal steroids, McCune-Albright syndrome, juvenile hypothyroidism in either sex, and, in boys, rarely hCG or LH secreting tumors. In Long standing primary hypothyroidism that is low level of serum T3 and T4 leads to increase TRH secretion which stimulates both TSH and Gonadotropins (FSH & LH) and prolactin from anterior pituitary. High

level of TSH acts on the FSH receptors of ovaries causing formation of multicystic ovaries³. Here there is iso-sexual precocious puberty, premature menarche, breast development, absent pubic and axillary hair growth and lump in lower abdomen. We have reported a girl with long-standing, untreated hypothyroidism who presented with precocious puberty.

Case Report

A 10 years old, Muslim, student, hailing from Sirajgong, admitted to this hospital with complains of cyclical per vaginal bleeding for last 1 year. Bleeding is scanty in amount and lasts for 3- 4 days per cycle. She also developed anorexia and gradually increased generalized weakness for same duration, which hampered her day to day activities. On query, she stated, for last 1 to 2 years she is experiencing excessive cold intolerance and occasional constipation. There was no H/O headache, vomiting or convulsion but she had delay in milestone of development. She was born at term without any complication in a poor illiterate family of non-consanguineous parents. There is no family history of similar

illness. With above complains she consulted at Sadar hospital and was referred to tertiary hospital for further management.



Figure1: Patient with VWGS (Before treatment)

On examination the patient was pale, anxious and severely anaemic, stunted and wasted having thin sparse hair, BMI 14.08 kg/m² (4th percentile). The patient was non edematous and skin was cold, dry, rough and scaly. Thyroid gland was not enlarged. Examination of Nervous system revealed moderate IQ level with normal visual field. All reflexes found normal. Alimentary system found normal except under developed teeth. Other system shows normal findings. Provisionally she was diagnosed as a case Precocious menarche with hypothyroidism with severe anemia. Laboratory data showed: hemoglobin 6 g/ dl, white blood cell count 4400/mm³. ESR was very high (90 mm in 1st hr); PBF showed microcytic hypochromic anaemia and platelet count was normal. RBC indices, RDW, SGPT, PT, PTT, fasting blood sugar, blood urea, nitrogen, creatinine, and electrolytes were normal. Urine analysis was normal. Chest X-ray was normal. Bone age (Greulich and Pyle) was delayed. Pelvic ultrasound: Bulky uterus (7.8x4.09x2.2cm) with right adnexal cyst

(8.5x5.3cm). USG of thyroid gland and CT scan of brain showed normal findings. Endocrinological evaluation revealed thyroxin (FT4) 0.22 pg/dl (normal 0.8-1.9), FT3 0.89 pg/ml (normal 1.5-4.1). Serum CA-125 was high (62.5U/ml); serum alpha fetoprotein was normal (2.45ng/dl). From history, examination & investigation findings suggested a case of Van Wyk Grumbach Syndrome (Precocious menarche with primary hypothyroidism with multicystic ovaries) with severe anaemia. This patient was treated by blood transfusion and Tab. Levothyroxin 4 µgm/kg body weight and her all symptoms subsided, the endocrine abnormality resolved and even the ovarian cyst decreased in size.



Figure1: Patient with VWGS (After treatment)

Now she is on regular follow up to this hospital. During follow up period the last measured biochemical test report have been documented and have been found that TSH (thyroid stimulating hormone) was high (485µIU/ml); antithyroid peroxidase antibody was also elevated (132 IU/L). Follicle stimulating hormone (FSH) was 1.28 miu. Lutenising hormone (LH) was 1.42miu. Prolactin was 33.6 ng/ml (1.9-25 adult female).

Discussion

The cause of vaginal bleeding must be sought when bleeding occurs in young girl and clinical presentations may help in establishing the correct diagnosis. Findings of delayed bone age in girls with precocious puberty narrows the differential diagnosis to hypothyroidism because other causes of precocious puberty should have an advanced bone age². Generally, children, precocious puberty with primary hypothyroidism present with delayed pubertal development and short stature². The presence of precocious puberty and enlarged ovaries suggested an estrogen-secreting ovarian tumor in the present case. But the finding of a delayed bone age in the patient with precocious puberty narrowed the differential diagnosis to long-standing hypothyroidism. High circulating levels of TSH along with prepubertal LH levels suggested Van Wyk–Grumbach syndrome. This case presented with precocious menarche, short stature and delayed bone development. These findings are consistent with other reports²⁻⁶.

The exact mechanism of the development of precocious puberty in VWGS remains speculative. Van Wyk and Grumbach postulated a lack of specificity in the feedback mechanism leading to an overproduction of multiple hormones¹. However, in other reported cases, 6 isolated menarche occurred in hypothyroidism in the absence of breast development. Interestingly, important clinical presentations that were reported previously and were detected in this case are bilateral ovarian enlargement with multiple cysts⁷⁻⁸, hyperprolactinemia and increased levels of gonadotropines mainly follicle stimulating hormone^{7,9,15}. 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 (FSH-r) and cause gonadal stimulation¹³. This causes uterine bleeding, multicystic ovaries in girls^{8,13-14}. Other mechanisms which may explain these manifestations are; an increased ovarian sensitivity to gonadotropines¹⁶. An increased aromatization of androstenedione to oestrone¹⁷ and hypothalamic encephalopathy impairs the normal tonic suppression of gonadotropine release by hypothalamus¹⁸. On the other hand, hyperprolactinemia reduces gonadotropine clearance and decreases dopaminergic and opioid tone at the hypothalamic pituitary axis¹⁹⁻²⁰.

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 prolactin¹⁹. However, ovarian enlargement may be secondary to a myxedematous infiltration²⁰. This patient also had multicystic ovaries with normal to low gonadotropins, suggesting that the increased sensitivity of ovaries to gonadotropins may be responsible for it.

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 of VWGS. Although there is little consensus regarding the precise etiopathogenesis of the disorder, the treatment approach is clear. The appropriate treatment of this case was thyroid hormone replacement which is consistent with other reports.¹⁵

Conclusion

Hypothyroidism should be considered especially when vaginal bleeding occurs in young girls, especially vaginal bleeding is accompanied with additional clinical presentations such as cold intolerance, constipation, delayed bone age and multicystic ovaries. Thyroxin replacement therapy should lead to complete resolution symptoms and promote normal physical and mental development.

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