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CASE REPORT

VAN WYK GRUMBACH SYNDROME: CASE REPORT

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ABSTRACT

BACKGROUND: Children with primary hypothyroidism usually presents with delay in linear growth and pubertal development, but in rare instances they can present with precocious puberty. In 1960, presentation of primary hypothyroidism with precocious puberty was first reported and labelled as Van Wyk Grumbach syndrome (VWGS). We report a case of VWGS in a six years old girl.

CASE PRESENTATION: A six years old girl presented with precocious puberty accompanied by short stature and delayed bone age due to untreated hypothyroidism. On examination she had Tanner's stage B3 (breast development) and P2 (pubic hair). She had normal external genitalia. On workup her Thyroid Stimulating Hormone was 100 mIU/ml, Free-T4 0.7 was ηg/dl, Follicle Stimulating Hormone 8.1 mIU/ml, Luteinizing Hormone 0.12 mIU/ml, estradiol 58 ρg/ml and prolactin 177 ηg/ml. Pelvic ultrasound revealed a uterine size of 5.4 × 3.2 × 3.6 cm and enlarged ovaries with multi cystic appearance. She was started on 50 μg of Levo-thyroxine per day and then was reassessed after 9 weeks of treatment which showed improvement in her Tanner's Stage and hormonal profile.

CONCLUSION: The girl was diagnosed as VWGS and responded to the treatment which was evident by improvement in her physical and biochemical assessment.

KEYWORDS: Van Wyk Grumbach syndrome (Non-MeSH); Hypothyroidism (MeSH); Puberty, Precocious (MeSH); Short Stature (Non-MeSH); Sexual Maturation (MeSH); Thyroid Hormones (MeSH); Gonadal Steroid Hormones (MeSH).

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INTRODUCTION

Children with primary hypothyroidism usually presents with delay in linear growth and pubertal development, but in rare instances they can present with precocious puberty. Boys usually presents with enlarged testicles whereas girls present with vaginal bleeding.[1] In 1960, presentation of primary hypothyroidism with precocious puberty was first reported by Van Wyk and Grumbach and labelled it as Van Wyk Grumbach syndrome (VWG). VWG Syndrome primarily presents with precocious puberty in the form of early vaginal bleeding, development of breasts, galactorrhea, and delayed bone age.[2] Female children with this syndrome usually presents with hypothyroid facies, short stature, isosexual incomplete precocious puberty with thelarche, menstrual bleeding and multi cystic ovaries with absent pubic and axillary hair.[3] The underlying mechanism is thought to be related to the elevated thyroid stimulating hormone (TSH) levels acting via the follicle stimulating hormone (FSH) receptors owing to the structural homology between the glycoprotein receptors of these two hormones.[4]

We report the case of a young girl whose presentation was with precocious puberty, short stature and delayed bone age due to untreated hypothyroidism.

CASE DESCRIPTION

A 6-years young girl, referred by the gynecologist to the department of endocrinology for assessment and workup for precocious puberty. She initially presented to the department of gynecology with 4 months' history of abdominal pain, abdominal swelling, and progressive breast enlargement. She also reported recent weight gain with no increase in height, low mood, and loss of appetite. There was no history of vaginal bleeding. She belonged to Afghanistan and was born through normal vaginal delivery and the pregnancy was uneventful with no postnatal complications. She was product of non-consanguineous marriage and was full term at the time of birth, weighing 2.25 kgs. Routine neonatal laboratory investigations were unremarkable. She was of normal intelligence and had normal developmental milestones. There was no history of vomiting, headache or visual disturbance. Family history was unremarkable for any thyroid disorder, precocious puberty or any other autoimmune disorder. There was no history of any drug intake.

On physical examination she was pale with dry skin and some facial puffiness. Her height was 98 cm (<3rd centile, SDS of – 3.4) and weight was 22 kg (50th centile). She had distended abdomen with no organomegaly, however there was tenderness in both iliac fossae. She had Tanner's stage B3 for breast development and Tanner's stage P2 for pubic hair. Her external genitalia were normal. There was no expressive galactorrhea.

On workup, her bone age was 4 years at the time of consultation revealed on the Xray left wrist. Hormonal profile including Luteinizing Hormone (LH), FSH, TFTs, Prolactin, Testosterone and Estradiol done (Table 1). Abdominal ultrasound was unremarkable whereas

pelvic ultrasound revealed a uterine size of 5.4 × 3.2 × 3.6 cm and enlarged ovaries with multi cystic appearance with right ovarian size of 7.9 × 5.2 cm and left ovarian size of 4.2 × 3.9 cm. The largest cyst in the left ovary measured about 28 × 34 × 36 mm and largest right ovarian cyst was about 57.8 × 45.2 × 63.2 mm. The fore mentioned workup leads to the diagnosis of VWG Syndrome with incomplete isosexual precocious puberty and the patient was started on 50 ug of Levo-thyroxine per day.

First follow up was at 9 weeks and patient reported an improvement in her facial appearance, mood, and appetite. Breast size decreased from Tanner's stage B3 to B2. There was marked improvement in the hormonal profile as well (Table 1). She was continued on same dose of levothyroxine.

TABLE 1: HORMONAL WORKUP AT DIAGNOSIS AND 9 WEEKS FOLLOW UP

Laboratory Parameter	Normal Range	At time of diagnosis	At time of 1st follow up (9 weeks)
Follicle Stimulating Hormone	1.5 - 12.5 mIU/ml	8.1	
Luteinizing Hormone	1.7 - 8.6 mIU/ml	0.12	
Prolactin	4.49 - 19.5 ηg/ml	177	95
Estradiol	< 29 ρg/ml	58	40
Testosterone	0.04 - 0.4 ηg/ml	0.025	
Thyroid Stimulating Hormone	0.7 - 6.4 mIU/ml	100	4.3
Free Thyroxine (FT_4)	0.8 - 2.0 ηg/dl	0.7	1.5
Triiodothyronine (T_3)	1.08 - 3.14 ηmol/ml	0.98	2.01

DISCUSSION

The common presentation of primary hypothyroidism is usually in the form of nonspecific features like gain in weight, reduced concentration, weakness, depressive symptoms, lethargy, short stature in children and menstrual irregularities in females.[5] Very rarely, it may present in an unusual form like VWG Syndrome. For the first time this syndrome was reported by Van Wyk and Grumbach in three girls, whose presentation was with precocious puberty; precocious thelarche and galactorrhea but with delayed bone age along with hypothyroidism. Importantly, there were no axillary and pubic hair.[2] Moreover, there is incomplete isosexual precocious puberty in VWGS.[6] The patient described in our case report had breast development in the absence of uterine bleeding, suggesting an incomplete isosexual precocious puberty. Furthermore, an estrogen secreting ovarian tumor was initially suspected because of precocious puberty with enlarged ovaries presence of delayed bone age on X ray of the wrist leads to the suspicion of primary hypothyroidism, proven further on performing thyroid function tests. Radiological studies in VWGS usually reveals enlarged ovaries with multiple cysts due to development of the follicles, an enlarged uterus of puberty and delayed bone age instead of advanced bone age as expected in a case of sexual precocity. Biochemical findings in VWGS include low free thyroxine along with raised TSH, prolactin and oestradiol.[3]

Autoimmune destruction of the thyroid gland is one of the most common etiologies of hypothyroidism in these patients. Enlargement of the Sella turcica has also been observed in a number of cases and this is due to the thyrotroph hyperplasia.[6] It is of paramount importance to diagnose this syndrome in time as appropriate treatment with thyroid hormone regresses the symptoms and patients usually attain spontaneous puberty at an appropriate time and also achieve an improved final height.[3] The exact mechanism of sexual precocity in VWGS is unknown however, Van Wyk and Grumbach postulated that the increased production of TSH, prolactin, gonadotropins and estradiol might be because of the overlap of hormones in the pituitary feedback mechanism.[7] Moreover, a common alpha subunit is shared by TSH, FSH and LH which are all glycoprotein hormones however, they have unique beta subunit conferring specificity to each hormone. Due to this molecular homology, they have a tendency to cross react.[8]

Furthermore, there is possibility that ovarian hypersensitivity to the gonadotropins could be either directly from the hypothyroid status or indirectly due to raised prolactin level. Prolactin also sensitizes ovaries to gonadotropins and promotes maturation of the follicles. In primary hypothyroidism, Thyrotropin-releasing hormone (TRH) levels are high due to absence of negative feedback by the thyroid hormones, this high TRH leads to thyrotroph hyperplasia and increased prolactin secretion.[9]

A unique characteristic feature of isosexual precious puberty produced by primary hypothyroidism is retarded growth with a delay in the bone age, paradoxical to rest of the causes of precocious puberty where there is advancement in bone age. This is because of the extremely low levels of thyroid hormones. Although the exact pathogenesis is still not clear, the treatment approach is quite straightforward. All the symptoms and signs regresses with thyroid hormone replacement. There is resolution of the hormonal derangements and reduction in the ovarian cyst sizes or even regression of these cysts altogether. Timely diagnosis and treatment are of paramount importance because it can save the patient from unnecessary investigations or interventions.

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AUTHORS' CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under:

SK, ZU: Identification and diagnosis of case, drafting the manuscript, approval of the final version to be published

SEM: Identification, diagnosis and management of case, critical review, approval of the final version to be published

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

CONFLICT OF INTEREST

Authors declared no conflict of interest

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