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Case Report

Thyroxine replacement promptly corrects vaginal bleeding in precocious menarche due to Van Wyk Grumbach syndrome

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ABSTRACT

Van Wyk Grumbach syndrome is a rare complication of a common endocrine disorder, i.e., hypothyroidism, but occurs when it is long standing during periods of pre-pubertal growth. It can occur in both sexes, in boys it is associated with testicular enlargement and in girls, the usual presenting features are early onset menarche, enlarged bilateral multicystic ovaries and delayed skeletal growth. Diagnosing this condition is very important as unnecessary surgical intervention for ovarian enlargement is avoided. Prompt replacement therapy with thyroxine not only corrects menstrual abnormality, but also ovaries return to normal over period of time. In this case report, we describe an unusual case of irregular vaginal bleeding, large multicystic ovaries and delayed bone age in a young girl due to autoimmune thyroiditis who promptly responded to levo-thyroxine.

Keywords: Van Wyk Grumbach syndrome, Precocious puberty, Delayed bone age, Multicystic ovaries

INTRODUCTION

Delayed pubertal development is commonly seen children with hypothyroidism. But, occasionally when hypothyroidism is left unattended for long duration, the result may be precocious puberty.[1,2] Van Wyk and Grumbach in 1960 described Van Wyk Grumbach Syndrome (VWGS) as the constellation of symptoms including hypothyroidism, precocious puberty, and delayed bone age which regresses with thyroxine replacement.[3] One of the explanation is that the high levels of Thyroid Stimulating Hormone (TSH) seen in long standing hypothyroidism stimulates release of pituitary gonadotrophins mainly the Follicular Stimulating Hormone (FSH), which in turn causes accelerated ovarian steroidogenesis.[4] It is well known that both TSH and FSH share α subunits and this can cause hormonal overlap at the level of G-protein coupled receptors.[5] As a consequence, serum oestrogen levels are increased and the affected girl may show precocious thelarche and menarche. As adrenal function is normal, pubic and axillary hair development does not occur simultaneously. Some girls may present with premenarcheal ovarian cysts.[6]

CASE REPORT

A ten year old girl presented with complaints of irregular bleeding per vaginum since 2 years, and minimal breast development from 8 years of age. Her menstrual cycles were irregular with 4-5 days of bleeding once in 1-5 months and minimal flow. She was on tranexamic acid during bleeding episodes as advised her family doctor. She had chicken pox 1 month ago. Her mother had attained menarche at 14 years.

On examination her BMI was 16.2 kg/m^2. She was pale, breast development was Tanner stage 2, pubic and

axillary hair development corresponded to Tanner stage 1. Thyroid was clinically normal, vital signs were stable, cardiovascular and respiratory systems were unremarkable. Abdomen was soft, non-tender, no mass or organomegaly. External genitalia were healthy, pubic hairs were absent and minimal bleeding per vaginum noted.

Transabdominal ultrasound done showed uterine dimensions of 6.3 x 2.7 x 1.7 cm and 8 mm thick endometrium. Right ovary measured 4x 3 cm with a clear 3 cm follicular and left ovary measured 4.5 x 3 cm with a clear cyst of 3 cm and multiple small follicles. Fluid collection of 4.8 x 2.8 cm noted in the vagina and lower part of cervix.

Lab parameters showed hemoglobin of 9.5 gm%, rest of complete blood counts and coagulation panel were normal. TSH was >100 mIU/ml, T_3 - 0.51 ng/ml, T_4 - 0.89 mcg/ml, anti-TPO and anti-TG antibodies done were high. FSH and LH were 5.4 & 0.1 mIU/ml respectively, prolactin levels corresponded to 42 ng/ml, calcium and vitamin D, PTH were within normal limits. Tumor markers for ovarian malignancy were normal.

Figure 1: X-ray of left hand for bone age determination.

Her bone age was determined by taking X-ray (Figure 1) of left wrist (including entire palm and distal radius and ulna) and employing Tanner-Whitehouse method which is gender specific.[7] Traditionally the bone age is determined by Greulich-Pyle method where in the radiographs of the whole hand and wrist are compared with images in the atlas.[8] The 20 different bones around the wrist joints were analysed and graded into 8 maturity stages (B, C, D, E, F, G, H & I, in some bones 7 stages). Then they were scored according to Tanner-Whitehouse maturity score for girls (Table 1).

The maturity of bones were assessed depending upon the size, shape, density, smoothness or thickening of the borders, thickness of epiphyseal line, extent of fusion and capping of epiphyseal regions.

Table 1: Twenty bone Tanner-Whitehouse maturity score for girls.

Bones assessed	Maturity scale & scores							
	B	**C**	**D**	**E**	**F**	**G**	**H**	**I**
Radius	17	19	25	33	54	85	99	106
Ulna	22	26	30	39	60	73	80	X
First metacarpal	5	6	11	18	24	29	31	33
Third metacarpal	3	5	7	11	17	23	24	26
Fifth metacarpal	3	4	7	12	18	22	24	25
Proximal phalanx of the thumb	5	5	8	14	24	29	30	32
Proximal phalanx of the third finger	4	4	7	13	20	24	25	26
Proximal phalanx of the fifth finger	4	4	7	13	19	23	24	25
Middle phalanx of the third finger	4	4	7	13	20	23	24	25
Middle phalanx of the fifth finger	4	5	8	14	20	22	22	23
Distal phalanx of the thumb	5	5	8	15	24	31	32	34
Distal phalanx of the third finger	3	4	6	10	17	22	23	24
Distal phalanx of the fifth finger	3	4	7	11	17	21	22	23
Capitate	53	56	61	67	76	85	113	X
Hamate	44	47	53	64	74	85	97	109
Triquetral	8	12	19	28	36	46	63	X
Lunate	10	14	20	27	35	46	60	X
Scaphoid	13	17	23	29	36	44	57	X
Trapezium	12	14	20	25	32	39	49	59
Trapezoid	13	16	20	24	31	40	57	X

The total score in our study was 565 and was equivalent bone age of 7.9 years (calculated from Table 2), which was delayed by 2 years.

Table 2: Tanner-Whitehouse girls bone age (GBA) for given maturity score (MS).

Tanner-Whitehouse girls bone age (GBA) for given maturity score (MS)																
MS	131	136	140	146	152	159	163	172	179	186	192	199	206	213	220	226
GBA	1	1.1	1.2	1.3	1.4	1.5	1.6	1.7	1.8	1.9	2	2.1	2.2	2.3	2.4	2.5
MS	233	240	247	253	260	267	274	281	287	293	299	303	311	317	324	331
GBA	2.6	2.7	2.8	2.9	3	3.1	3.2	3.3	3.4	3.5	3.6	3.7	3.8	3.9	4	4.1
MS	338	345	351	357	363	370	376	382	389	395	402	408	414	420	426	432
GBA	4.2	4.3	4.4	4.5	4.6	4.7	4.8	4.9	5	5.1	5.2	5.3	5.4	5.5	5.6	5.7
MS	438	444	450	456	462	468	474	480	485	491	497	503	510	516	522	529
GBA	5.8	5.9	6	6.1	6.2	6.3	6.4	6.5	6.6	6.7	6.8	6.9	7	7.1	7.2	7.3
MS	535	541	547	553	559	**565**	571	578	585	592	600	608	617	625	634	643
GBA	7.4	7.5	7.6	7.7	7.8	**7.9**	8	8.1	8.2	8.3	8.4	8.5	8.6	8.7	8.8	8.9
MS	653	662	670	680	690	700	710	721	731	742	752	762	772	783	794	803
GBA	9	9.1	9.2	9.3	9.4	9.5	9.6	9.7	9.8	9.9	10	10.1	10.2	10.3	10.4	10.5
MS	812	821	830	838	845	852	859	866	872	879	885	891	898	903	908	913
GBA	10.6	10.7	10.8	10.9	11	11.1	11.2	11.3	11.4	11.5	11.6	11.7	11.8	11.9	12	12.1
MS	918	923	928	932	937	940	944	948	953	956	960	963	966	969	972	974
GBA	12.2	12.3	12.4	12.5	12.6	12.7	12.8	12.9	13	13.1	13.2	13.3	13.4	13.5	13.6	13.7
MS	976	979	981	982	984	986	987	989	990	991	993	994	995	995	996	996
GBA	13.8	13.9	14	14.1	14.2	14.3	14.4	14.5	14.6	14.7	14.8	14.9	15	15.1	15.2	15.3
MS	997	997	998	998	999	999	103									
GBA	15.4	15.5	15.6	15.7	15.8	15.9	16									

In view of very high TSH levels, she was diagnosed as precocious puberty secondary to autoimmune Hashimotos thyroiditis and hence was started on tab. eltroxin 100 mcg OD. Follow up with thyroid function tests reports after one month were within normal limits and repeat transabdominal scan showed thin endometrium with no evidence of cysts in the ovaries and collection in vagina was regressed and patient did not have further episodes of bleeding per vagina since treatment. There was increment in the height by 5 cm. She was advised to continue eltroxin 100 mcg OD and regular follow up with pediatrician as well as with us.

DISCUSSION

Van Wyk Grumbach Syndrome (VWGS) consists of hypothyroidism, precocious puberty, and delayed bone age. The pathogenesis of precocious puberty or ovarian cyst is increased aromatization of androstenedione to oestrone, increased ovarian sensitivity to gonadotropins, increased sensitivity of mammotropes and gonadotropes to TSH. High levels of TSH acts via the FSH receptor causing gonadal stimulation resulting in increased oestradiol production, which stimulates the development of secondary sexual characters. Adrenal hormonogenesis is not increased; therefore pubic and axillary hairs are usually absent or sparse.[9] Pituitary adenoma may develop in some cases due to long standing thyrotroph hyperplasia in response to the decreased thyroid hormone.[10,11] Hyperprolactinemia develops either due to thyrotrophic hyperplasia in the pituitary compressing the pituitary stalk, thereby disrupting hypothalamic inhibition of prolactin or due to direct stimulation of prolactin release by TRH. Patients may be asymptomatic or can present with headache, visual disturbances and galactorrhoea. With thyroxine replacement TSH secreting cells reduce in number relieving compression, prolactin concentrations decreases.

In another case report, a 7 year old girl presented with abdominopelvic mass and vaginal bleeding. Goiter and secondary sexual characters were noted on clinical examination.[12] Based on clinical profile and investigations she was diagnosed with juvenile primary hypothyroidism due to autoimmune thyroiditis. Ovarian cysts and precocious puberty resolved spontaneously after thyroxine replacement.

VWGS in a 4.3 year old female patient with Down syndrome presented with hematuria on and off for 3 months.[13] Physical examination revealed typical morphologic features of Down syndrome and hypothyroidism. Pubertal development stages were: breast- stage III and pubic hair - stage I. Serum estradiol level was high (117.7 pg/ml). Bilateral multiloculated ovarian cysts were noted on transabdominal ultrasonography. TSH was > 500 mIU/ml and FT_4, FT_3 levels were as low as 0.4 ng/dl (0.7-1.48) and 1.0 pg/ml (1.71-3.71), respectively. With L-thyroxine - 100 mcg/day was started. Breast regressed and bleeding stopped after one month.

Children with Down syndrome have an increased risk for primary hypothyroidism; however, VWGS is not frequent

in them. In younger children, differentiation between macroscopic hematuria and vaginal bleeding may be difficult, and the diagnosis of precocious puberty may be delayed VWGS should be considered by the physicians in children with blood on their diaper; therefore, pubertal examinations must be performed carefully for all age groups. The cystic ovarian enlargement can be misinterpreted as a hormonally active ovarian neoplasm causing precocious puberty. It is imperative to recognize the clinical and imaging features of VWGS, including the relationship between juvenile hypothyroidism and cystic ovarian enlargement, to avoid unnecessary surgery.[14] The rare presentations of VWGS include microcytic anaemia, elevated Erythrocyte Sedimentation Rate (ESR), dermatological manifestations such as streaky hyperpigmented skin lesion on chest wall and axilla and parathyroid hormone suppression despite vitamin D deficiency.[15] CA-125, LDH, AFP, Inhibin were also elevated in few reported cases.[16] All of the tumor markers, including inhibin, returned to normal values after treatment of hypothyroidism.[17]

Urinary and vaginal bleeding in young children must be clearly differentiated, and hypothyroidism must be investigated in children who have precocious puberty to avoid inappropriate surgical treatment in these young girls.

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