RESEARCH PAPER | Medical Science | Volume : 5 | Issue : 8 | August 2015 | ISSN - 2249-555X

An Unusual Presentation of a Usual Disorder: Van Wyk-Grumbach Syndrome in a Downs Syndrome Patient

KEYWORDS

Dr. P. Sreenivasulu
I/c Professor, Dept of Endocrinology, KMC,Kurnool.

Dr. P. Padmaja
Asst. Prof KMC, Kurnool.

Dr.Rajani
M.D Post Graduate, Dept of Gen Medicine KMC,Kurnool.

Introduction

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 precocity.[1]

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.

Van Wyk-Grumbach syndrome (VWGS) is characterized by juvenile hypothyroidism, delayed bone age, and isosexual Pseudo precocious puberty with reversal to a prepubertal state following thyroid hormone replacement therapy.[2]

We report a girl with long-standing, untreated hypothyroidism who presented with Pseudo precocious puberty.

Case Report

A girl aged 7 years presented with per vaginal bleeding for 3 to 4 days in the form of spotting. She had two episodes, 4 months apart. There is no history of trauma, vulvar and perineal scratching, increased urinary frequency, no history of loose motions. History of hair loss from the age of 3 years started as patchy hair loss, later progressed to complete hair loss all over the scalp, associated with loss of eyebrows. History of cold intolerance and history of change in voice present. No history of seizures, vomitings, loss of vision, head injury, syncopal attacks, skin pigmentation or acne. No history of any swelling in the breast region. No history of baldder and bowel abnormalities. No history of cough, shortness of breath. No history of weakness of limbs.

PAST HISTORY

History of recurrent attacks of cough, shortness of breath during childhood. Diagnosed as large sub aortic VSD at the age of one year. She was on medical treatment from then and surgical closure was done at the age of 3 years. Diagnosed as hypothyroid 2 years back. Non compliant to treatment. No history of radiation exposure during childhood.

FAMILY HISTORY

No history of similar complaints in other sibling or any other family members.

ANTENATAL HISTORY

Her mother was 26 years at the time of conception. She has taken regular antenatal checkups and taken tetanus toxoid and IFA prophylaxis. No history of fever with rash during pregnancy. No history of pregnancy induced hypertension or gestational diabetes. No history of maternal drug usage/radiation exposure.

NATAL HISTORY

She was a term baby delivered through NVD at hospital and baby cried immediately after birth. Her Birth weight was 2.5kgs.

POSTNATAL HISTORY was uneventful.

DEVELOPMENTAL HISTORY

She had delayed milestones, global delay in development. She had delayed dentition. Her scholastic performance was poor.

IMMUNISATION HISTORY

She was immunised as per UNIVERSAL IMMUNISATION PROGRAMME SCHEDULE.

Volume : 5 | Issue : 8 | August 2015 | ISSN - 2249-555X

HEAD TO TOE EXAMINATION
On examination she had Facial puffiness, High arched palate, depressed nasal bridge, Hypertelorism , Low set ears, Broad nose, Short neck, Macroglossia and Alopecia.

	Patient details	EXPECTED	PERCENTILE
WEIGHT	15 kgs	22.4	3 SD 15th percentile
HEIGHT	95 cms	120.8	< 3 SD below 15th percentile

She had Mild pallor, no jaundice/clubbing/lymphadenopathy.

Pulse rate:62bpm

Respiratory rate:16cycles/min

Blood pressure:100/60mm of Hg noted in right arm in supine posture

Temperature:99·f

EXTERNAL GENITALIA
labia majora and labia minora separate, sparse pubic hair. No axillary hair/hyperpigmentation noted.

TANNERS STAGING
Stage 1: Breast changes shows prepubertal elevation of papilla only.
Pubic hair: Sparse corresponding to P_2

SYSTEM EXAMINATION
CARDIOVASCULAR SYSTEM:First and second heart sound are heard with normal intensity.no murmurs.

RESPIRATORY SYSTEM:bilateral air entry present,no added sounds.

ABDOMEN:soft,no organomegaly. No focal neurological deficit

INVESTIGATIONS
She had Haemoglobin level of 9 gm/dl, Wbc count : 5000/cumm, Differential count :N;70% , :L;22%, :E;4%, :M;2%, Platelet count : 4.70 lakhs/cumm, Blood group :0+ve. Random blood sugar:100mg/dl, Blood urea :22 mg/dl, Serum creatinine :0.7 mg/dl, Chest xray :normal, ECG : Normal, Viral screening : negative.

ULTRASOUND ABDOMEN showed multiple cysts with largest cyst measuring 2.4 ×3.5 cm noted in right ovary and cysts noted in left ovary, Bulky uterus, for, her age. Rest normal.

Hormonal investigations
THYROID PROFILE
T_3 :0.55ng/ml

T_4 :3.0 microgram/ml

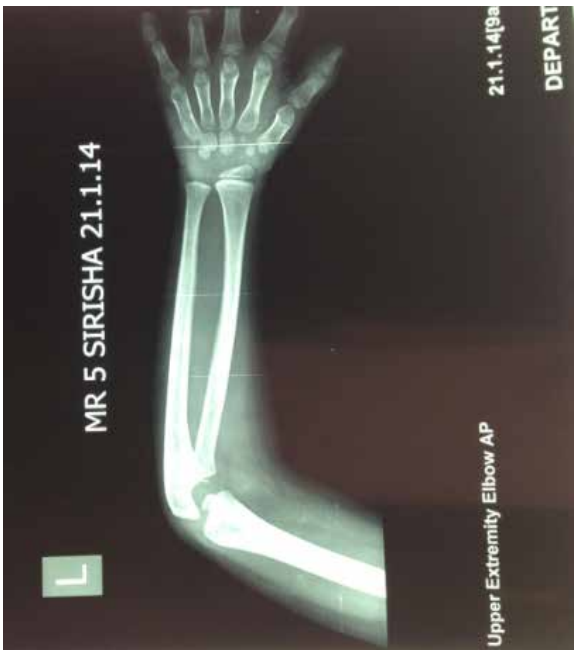
TSH :>750 microIU/ml

Estrogen :15.67pg/ml

Progesterone :0.03ng/ml

ULTRASOUND THYROID showed diffuse enlargement of the gland, altered echotexture of thyroid gland.

BONE AGE Corresponding to 4-5 yrs.

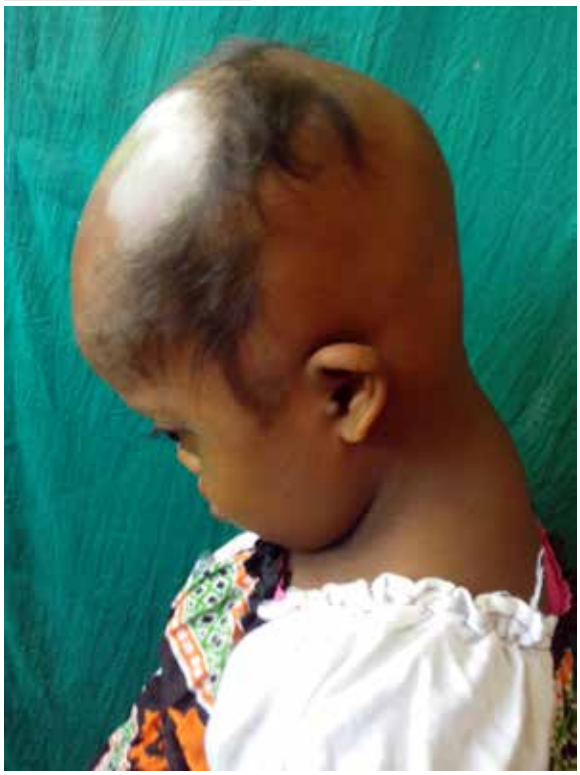


2D ECHO showed post VSD surgical closure, Patch intact, No residual shunt across the ivs patch, Trivial AR/no MR/no TR, Good biventricular function, No pericardial effusion/clot.

MRI BRAIN showed T1hypointense and T2 hyperintense signal noted in the pituitary fossa compressing the pituitary to the floor of the fossa. S/o Primary empty sella.

DERMATOLOGY REFERRAL

Volume : 5 | Issue : 8 | August 2015 | ISSN - 2249-555X



Impression:alopecia areata,ophiasis pattern.

treatment advised:tab.combit ½ tab od

lutica lotion for E/A

keratex oil for E/A

TREATMENT ADVISED

Tab.thyronorm 100µg od before breakfast

AFTER TREATMENT .

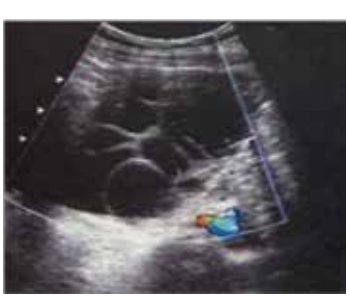
THYROID PROFILE

T_3Triiodothyronine:1.08 ng/ml. (Nanograms/ml)
T_4Thyroxine:11.30 µg/ml. (Micrograms/ml)
Thyroid stimulating hormone:1.34 µlu/ml (Micro lU/ml)

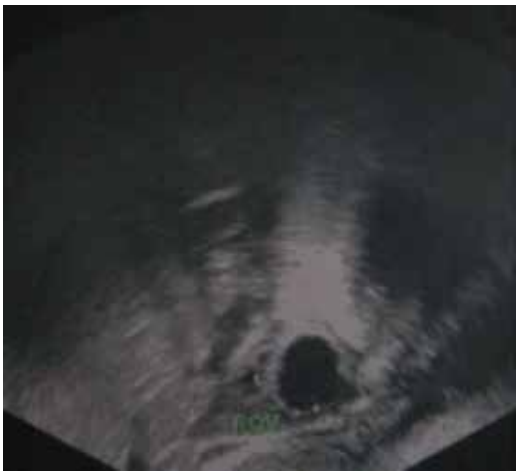
ULTRASOUND ABDOMEN showed Liver and spleen normal, Gall bladder normal,Kidney normal, Uterus normal, ovarian cysts regressed.

US Pelvis

BEFORE TREATMENT



AFTER TREATMENT



1.Phenotype
hypothyroid appearance delayed growth precocious uterine bleeding Presence of Sparse Public hair.

2.Imaging
enlarged ovaries pubertal uterus delayed bone age

3.Biochemistry
raised TSH
normal FSH
ALL THESE FEATURES GO IN FAVOUR OF Vanwyk Grumbach Syndrome

POSSIBLE MECHANISMS OF VAN WYK GRUMBACH SYNDROME
TSH and FSH and their receptors have related structures. high concentrations of TSH in hypothyroidism may be sufficient to cause activation of FSH receptors

FSHR activating mutations permitting amplified effect of TSH on follicles

TSH may sensitize the ovaries to gonadotrophins by stimulating receptors in granulosa cells,exacerbating ovarian hyperstimulation.

Myxedematous type infiltration also contribute to ovarian cystic changes

Discussion
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.

In girls, the condition usually presents with vaginal bleeding, and uncommonly with breast development or galactorrhea. Despite an early stage of puberty, there is lack of pubic hair. Boys have macroorchidism without significant signs of virilization. The salient diagnostic features include long-standing hypothyroidism,[2,3] high levels of TSH,[4] isosexual precocity with lack of public and axillary hair growth, and delayed bone age.[4] The precocious puberty is always isosexual and incomplete in patients of VWGS.[4]

The most common cause of hypothyroidism in these pa-

Volume : 5 | Issue : 8 | August 2015 | ISSN - 2249-555X

tients is autoimmune more so in Down's Syndrome.[5] Sella turcica enlargement may be seen at times and it has been attributed to thyrotroph hyperplasia. Primary empty sella in this patient may be due to defect in floor of diaphragm sella. Thus, VWGS can be diagnosed nonoperatively, by the recognition of the salient clinical features and appropriate confirmatory endocrine laboratory tests.[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 hormones. [1] The serum gonadotropin levels in these patients are relatively low for their degree of gonadal stimulation. Immunological activity is present but these gonadotropins are biologically inactive in *vitro* assay.[7] Thus, elevated gonadotropins alone cannot completely explain the gonadal stimulation seen in severe juvenile hypothyroidism.

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.[7] Using recombinant tools, it has been shown that human TSH can interact with the human FSH receptor to stimulate the adenylyl cyclase activity. Human recombinant TSH at a dose about 1000-fold greater than hFSH evoked a dose-dependent cyclic AMP response in Chinese hamster ovary (COS-7) cells transfected with the human FSH receptor[7] thus suggesting that relatively low FSH-like activity of TSH can be clinically significant at very high concentrations of TSH present in severe primary hypothyroidism.

A direct effect of severe hypothyroidism on the prepubertal testis, which leads to over proliferation of Sertoli cells is responsible for macroorchidism in males.[8] In females, 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.[9] However, ovarian enlargement may be secondary to a myxedematous infiltration.[10] Our 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. All symptoms subside with thyroxine replacement, the endocrine abnormalities resolve, and even the ovarian cysts decrease in size or altogether disappear, as also in the present case during follow-up.[11]

REFERENCE

1. Styne DM, Grumbach MM. William's textbook of Endocrinology. 11th ed . Philadelphia: Saunders (Elsevier); 2008. Puberty: Ontogeny, neuroendocrinology, physiology and disorders; pp. 969–1166. | 2. Van Wyk JJ, Grumbach MM. Syndrome of precocious menstruation and galactorrhea in juvenile hypothyroidism. An example of hormonal overlap in pituitary feedback. J Pediatr. 1960;57:416–35. | 3. Linsay AN, Voorhes ML, Mac Gillivry MH. Multicystic ovaries in primary hypothyroidism. Obstet Gynecol. 1988;61:433–7. | 4. Ever JL, Rolland R. Primary hypothyroidism and ovarian activity evidence for an overlap in the synthesis of pituitary glycoproteins. Br J ObstetGynaecol. 1981;88:195–202. [PubMed] | 5. Gordon CM, Austin DJ, Radovick S, Lufer MR. Primary hypothyroidism presenting as severe vaginal bleeding in a prepubertal girl. J PediatrAdolesc Gynecol. 1997;10:35–8. [PubMed] | 6. Browne LP, Boswell HB, Crotty EJ, O'Hara SM, Birkemeier KL, Guillerman RP. Van Wyk and Grumbach syndrome revisited: Imaging and clinical findings in pre- and postpubertal girls. Pediatr Radiol.2008;38:538–42. [PubMed] | 7. Anasti JN, Flack MR, Froehlich J, Nelson LM, Nisula BC. A potential novel mechanism for precocious puberty in juvenile hypothyroidism. J ClinEndocrinolMetab. 1995;80:276–9. [PubMed] | 8. Jannini EA, Ulisse S, D'Armiento M. Thyroid hormone and male gonadal function. Endocr Rev.1995;16:443–59. [PubMed] | 9. Chattopadhyay A, Kumar V, Marulaliah M. Polycystic Ovaries, precocious puberty and acquired hypothyroidism: The Van Wyk and Grumbach syndrome. J Pediatr Surg. 2003;38:1390–2. [PubMed] | 10. Hansen KA, Tho SP, Hanly M, Moretuzzo RW, McDonough PG. Massive ovarian enlargement in primary hypothyroidism. FertilSteril. 1997;67:169–71. [PubMed] | 11. Bhattacharya M, Mitra AK. Regressive of precocious puberty in child with hypothyroidism after thyroxine therapy. Indian Pediatr. 1992;29:96–8. [PubMed]