Case Report

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Van Wyk-Grumbach Syndrome: Atypical Presentation in Childhood Pituitary Macroadenoma with Primary Hypothyroidism

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Abstract

Van WykGrumbach syndrome is a constellation of hormonal abnormalities which includes hypothyroidism, precocious puberty and ovarian cysts in pre and pubertal girls. The usual presentation is ascites, pericardial and pleural effusion, enlarged pituitary, elevated prolactin, ovarian hormones. Here, we present a 6 year old female, who presented with precocious puberty associated with hypothyroidism and had features suggestive of Van Wyk– Grumbach syndrome. This is presented to highlight the rare presentations of Pediatric Sellar Pituitary enlargement with bleeding PV, walking difficulty, thelarche her hormonal profile showed elevated TSH, Prolactin, Inhibin B and LDH, USG abdomen showed multiple ovarian cysts with adrenal mass, MRI brain showed enlarged pituitary gland and bone scans revealed a delayed bone age. This rare entity should be kept in mind in cases of ovarian cysts, especially those with isosexual precocity, to prevent delay in medical management and unnecessary surgical misadventures.

Keywords: Hypothyroidism; Pituitary; Vanwyk Grumbach.

Case Report

Written informed consent was obtained from the parent of the child. A 6 year old female presented to the Neurosurgery outpatient department with progressive breast enlargement and episodes of irregular vaginal bleeding for past 3 months with gait disturbance in the form of left side high stepping gait since 1 year. She was full-term delivered vaginally, was born of non-consanguineous marriage and was first in the birth order. Her birth weight was 2.5 kg (between 3rd and 15th centiles; WHO growth charts). She has not joined school because of her declining socialistic performances. There was no history of headache, vomiting, or visual symptoms. There was no other significant past history. There was no history of autoimmune disorder in the family.

Her height is 114 cm (<3rd percentile, IAP chart), her weight is 11 kg (between 25th and 50th centiles; IAP growth chart). Her pulse rate is 74/min and blood pressure is 100/62 mmHg (50th centile). She had dry skin, pallor and there were no café au lait spots. Child had gait disturbances in the form of left high stepping gait with lateral deviation of left toes.

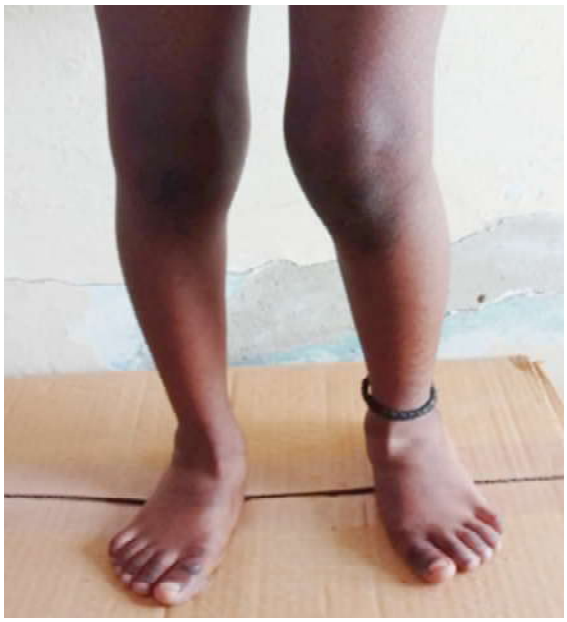
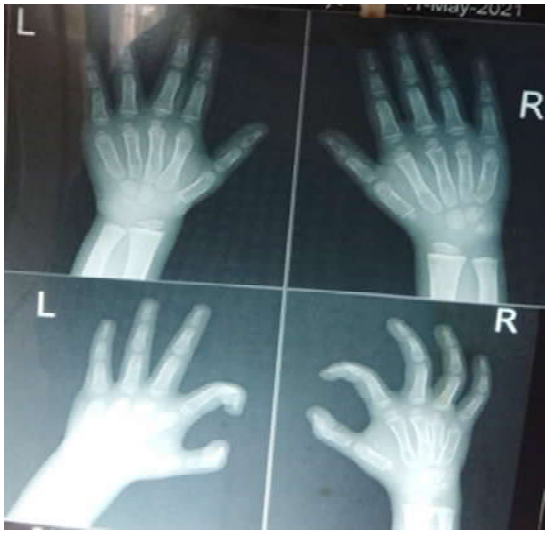


Fig. 1: Clinical picture showing left high stepping foot with lateral deviation of left toes.

There was no goitre on palpation. She was having Tanner's staging II, and there were no axillary or pubic hairs. Visual acuity and fields were normal. Her hormonal profile showed TSH - > 1000 micro IU/ml, Serum prolactin -75 ng/ml, Inhibin B level is 439.5 ng/l, LDH – 394 u/l and others hormonal values are normal.

Ultrasonography (USG) of the Abdomen and pelvis suggested multi-septated right ovarian cyst measuring around 4.9x 2.5 cm with bulky left ovary for the age with large follicles with mildly bulky left adrenal gland. USG screening of both breast shows prominent retroglandular areolar tissue, Screening of thyroid gland shows diffuse altered with increased vascularity. Skeletal survey was done of hands and feet



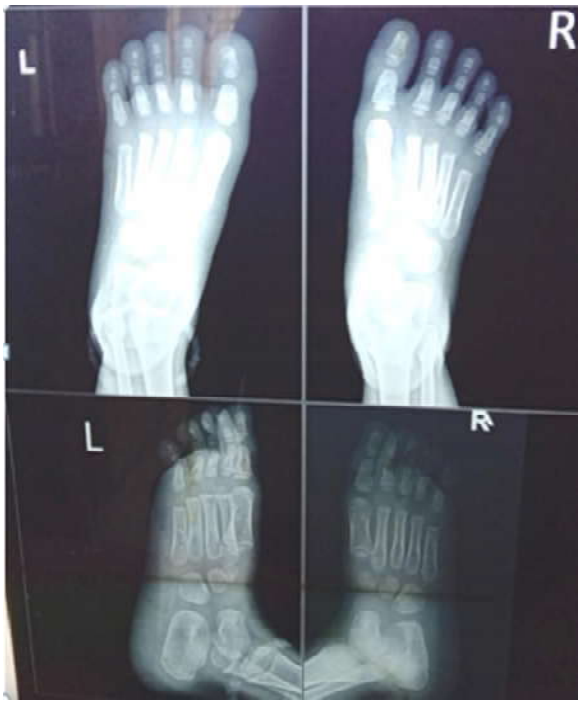


Fig. 2 & 3: x-ray of hand and foot.

Magnetic resonance imaging (MRI) scan of the brain revealed an enlarged anterior pituitary gland showing intense enhancement on contrast of size 11mm x 16mm without invasion of 3rd ventricle or parasellar extension into cavernous sinus.

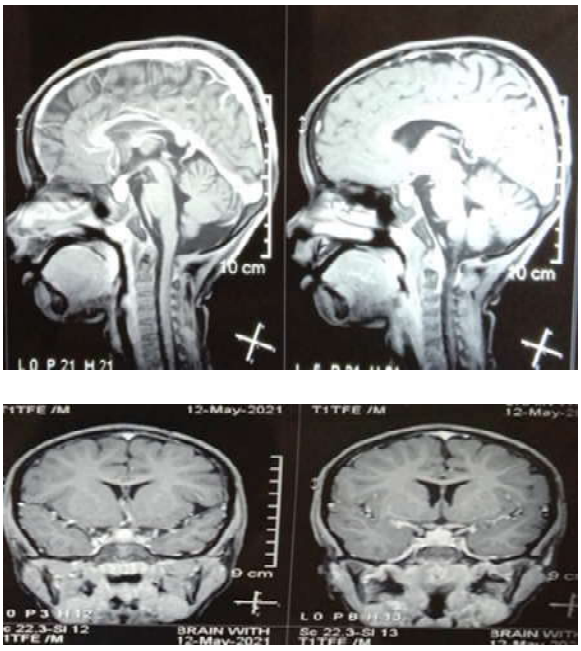


Fig. 4 & 5: Sagittal and coronal view of Magnetic resonance imaging brain contrast revealed an enlarged anterior pituitary gland showing intense enhancement on contrast of size 11mm x 16mm without invasion of 3rd ventricle or parasellar extension into cavernous sinus.

The child was managed with thyroid replacement therapy and was started on tablet L-thyroxine at a dose of 25 μg, which was escalated weekly to a daily dose of 50 μg, given in the early morning on an empty stomach and within a month of starting the therapy, her bleeding cycles stopped. She was referred to Pediatric surgery department ICH Chennai for further treatment of ovarian mass.

Discussion

Our patient presented with features of growth retardation and a delayed bone age with iso-sexual peripheral precocious puberty. The most common differentials of growth failure were juvenile hypothyroidism, Cushing's disease and panhypopituitarism. Short stature without obesity initially pointed towards juvenile hypothyroidism as the diagnosis.

Precocious puberty with adnexal masses is always associated with an advanced bone age with an elevated basal cortisol level, which was not seen in the index case. Severe growth retardation is also observed in patients with panhypopituitarism (due to the combined deficiency of growth hormone and TSH). It is associated with secondary hypothyroidism and delayed puberty, which was not seen in this patient. Hence, we came to the diagnosis as primary hypothyroidism in view of the linear growth failure with a delayed bone age and features of thyroid hormone insufficiency with pituitary lesion. The association of long-standing thyroid insufficiency with sexual precocity has been described in literature as Van Wyk and Grumbach syndrome (VWGS).

The exact mechanism of the development of precocious puberty in VWGS remains undefined and has been explained with several theories.[1] The most widely accepted of which is hormonal overlap in the pituitary feedback mechanism due to molecular mimicry between TSH and follicle-stimulating hormone (FSH) receptors. TSH in high concentrations leads to stimulation of gonadal FSH, as they share the common alpha subunit, which, in turn, increases the oestrogen levels, thereby manifesting as peripheral sexual precocity in females and macroorchidism in males. Pubic and axillary hairs are characteristically absent as there is no effect on adrenal hormone synthesis, thus it is also known as incomplete sexual precocity.[2]

Multiple cysts in the ovaries develop secondary to the enhanced production and decreased clearance of FSH due to hyperstimulation of its receptors by elevated thyrotropin-releasing hormone (TRH). In addition, high circulating TSH acts on the FSH receptors present on the ovarian follicle due to specificity spillover, resulting in the follicular cyst formation.[3] Pituitary adenoma reported on imaging is basically thyro-lactotrope hyperplasia, which is an indication of a long-standing, severe thyroid deficiency state. High circulating levels of TRH due to lack of thyroxine-mediated feedback inhibition result in hyperstimulation of thyro-lactotropes in the pituitary gland, thus presenting as a macroadenoma on imaging studies. The similar mechanism is also responsible for the stimulation of Prolactin secretion, thereby leading to hyperprolactinaemia.[4] Hyperplastic pituitary causes compression of the pituitary stalk that disrupts the hypothalamic inhibition of prolactin secretion, which further explains the presence of high prolactin levels with long-standing hypothyroidism.

The most common cause of thyroid insufficiency in an iodine sufficient area in young females has been attributed to immune-mediated destruction of the thyroid gland (Hashimoto's thyroiditis)[5] which is not the case in our patients as anti-TPO antibody titre was normal and screening of thyroid gland showed diffuse altered echo pattern with increased vascularity. Hypothyroidism in our patient could have been due to severe iodine deficiency or a delayed onset dyshormogenesis. Several methods have been devised for the estimation of bone age in children, of which the most frequently used and practically feasible is through Greulich and Pyle atlas. In females aged three years and above, assessment of the bone age is done through comparison between ossification centres of the epiphysis and metaphysis of proximal and intermediate phalangeal joints, in an X-ray of hand. This can also be done by comparison with age-matched standards derived from healthy children, published in the atlas.[6-8]

Our patient at presentation had a bone age of four years, which was delayed by two years from the chronological age. Thyroxine is needed for the secretion and action of growth hormone. It acts directly on the growth plate and promotes differentiation of chondrocytes to hypertrophic chondrocytes, which is required for the growth of long bones.[9] Deficiency states as seen in primary hypothyroidism lead to growth failure and a delayed bone age, as was seen in our patient. Thyroid replacement therapy in VWGS will lead to complete resolution of all the symptoms along with complete regression of ovarian cyst and pituitary hyperplasia without any need of surgical management.

Conclusion

Pediatric pituitary macroadenoma can be associated with Juvenile severe long-standing primary hypothyroidism with precocious puberty along with

the presence of pituitary hyperplasia and ovarian cysts. It is essential to know about this type of rare presentation and levothyroxine therapy can lead to complete resolution of all the signs and symptoms without any surgical intervention of non compressive pituitary tumors without hydrocephalus. Management of precocious puberty in a protocol-based algorithm not only helps in early diagnosis and management but also prevents any invasive surgical interventions for associated ovarian cystic lesions and pituitary hyperplasia.

Consent of patient and attenders

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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