Case Report

Untreated primary hypothyroidism presenting as two rare syndromes

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ABSTRACT

The association of chronic untreated primary hypothyroidism, delayed skeletal growth, and isosexual incomplete precocious puberty together describes Van Wyk Grumbach syndrome (VWGS). Sporadic case reports of this syndrome have been reported. Laboratory investigations reveal high levels of thyroid-stimulating hormone and delayed bone growth. VWGS has seldom been reported in a case of cerebral palsy. Here, we present the cases of two girls aged 11 years and 8 years who presented to our hospital with VWGS, one of whom was a case of spastic quadriparesis cerebral palsy. They were started on thyroxine supplements and showed favorable outcomes, thus emphasizing the importance of recognizing these rare manifestations of hypothyroidism, which on treatment show reversal to the prepubertal state.

Key words: Cerebral palsy, Kocher–Debre–Semelaigne syndrome, Precocious puberty, Primary hypothyroidism, Van Wyk Grumbach syndrome

Central precocious puberty (PP) is due to gonadotropin-releasing hormone (GnRH)-dependent activation of the hypothalamic-pituitary-gonadal axis. The secretion of gonadal steroids independent of pulsatile GnRH stimulation may lead to pseudo PP or GnRH-independent sexual precocity. Chronic untreated primary hypothyroidism is associated with growth retardation and delayed puberty, but rarely with isosexual incomplete PP. This was first described in 1905 by Kendle and named by Van Wyk and Grumbach in 1960 [1,2]. Investigation reveals very high level of thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), and prolactin with suppressed/prepubertal luteinizing hormone (LH).

Elevated TSH acts at the FSH receptor as TSH, FSH, and LH share a common β-subunit. Therefore, high TSH stimulates the FSH receptors of the ovary, leading to high estrogen levels and bilateral ovarian enlargement and onset of menarche [3]. Tendency to manifest sexual precocity is directly related to severity of TSH elevation. Another rare presentation of juvenile hypothyroidism is calf pseudohypertrophy called the Kocher–Debre–Semelaigne syndrome (KDSS) [4]. The simultaneous occurrence of Van Wyk Grumbach syndrome (VWGS) and KDSS has been described twice in the literature [5,6]. The pseudohypertrophy is due to the increased glycogen accumulation and mucopolysaccharide deposition in the muscle tissue. We report two cases of VWGS, one with cerebral palsy and other with KDSS, on treatment showed reversal to the prepubertal state.

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CASE PRESENTATION

Case 1

An 11-year girl, case of spastic quadriparesis cerebral palsy, presented with wet cough for 2 weeks and low-grade fever for 1 week. She was weighing 1.75 kg at birth and had birth asphyxia. There was a history of progressive breast enlargement and menstruation every month after achieving menarche at 8 years and was on non-hormonal contraceptive pill Ormeloxifene. There was a positive pulmonary Koch's contact history in younger sibling on treatment.

On examination, her height was 115 cm (<-3SD, height age 7 years; target height: 154–170 cm) and weight was 15 kg (<-3SD). She had disproportionate short stature with upper to lower segment (US:LS) ratio of 1.3:1. Her pulse was 110/min and blood pressure 96/60 mmHg. She had microcephaly (45 cm), coarse facies, dry and lusterless easily pluckable hair, dental caries, and multiple significant cervical lymph nodes. She had limb contractures, post-surgery scar marks, and dry scaly skin. There was no goiter. As per Tanner's staging, her sexual maturation score was $B_3P_1A_0M+$.

Her HRCT thorax showed necrosis and cavitation in the left upper and lower lobe. CBNAAT of gastric lavage was positive for *Mycobacterium tuberculosis*; ESR was 130 mm/1st h, and

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Mantoux test was positive (23 mm × 20 mm). The hormonal investigations are stated in Table 1. Her bone age was 18–24 months (bone age < height age < chronological age). Radiograph of the skull showed widened sella turcica, as shown in Fig. 1.

Ultrasound of pelvis revealed bulky ovaries and cystic change in the endometrium. Ultrasound of neck showed normal size, shape, and vascularity of the thyroid gland. The magnetic resonance imaging (MRI) brain revealed an enlarged pituitary gland measuring 10 mm × 12 mm (Fig. 2) and periventricular leukomalacia with enlarged bilateral lateral ventricles and cystic changes suggestive of perinatal insult. The child was started on anti-tubercular therapy as per National TB Elimination Program (NTEP) regimen and on thyroxine at 25 mcg daily. Her menses stopped post-treatment. She is on regular follow-up for thyroid function test and titration of thyroxine dose.

Table 1: Hormonal investigations of cases

Hormonal investigations	Case 1	Normal range	Case 2
TSH (μIU/ml)	>150 (very high)	0.5–5.5	>100 (very high)
FT3 (pg/ml)	1.1 (low)	2.3–6.5	< 0.88 (low)
FT4 (ng/ml)	0.3 (increased)	0.08–0.23	<0.3 (increased)
FSH (mIU/ml)	8.5 (high)	0.3–2.0	9.29 (high)
LH (mIU/ml)	0.00 (very low)	0.1–6.0	0.3
Prolactin (ng/ml)	80.7 (very high)	2.8–9.2	68.49 (very high)
Estradiol (pg/ml)	96.82 (high)		-
Anti-TPO antibody	Positive		Positive

FSH: Follicle-stimulating hormone, LH: Luteinizing hormone

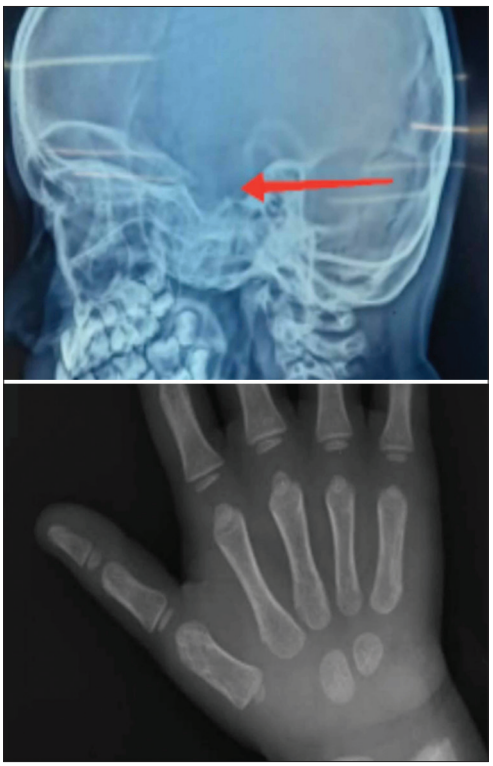

Figure 1: Radiograph of the skull showed widened sella turcica and X-ray wrist showing bone age of 18–24 months

Case 2

Our second case was an 8-year-old girl with short stature and dysmorphic facies. She had achieved premature menarche at 8 years of age with periorbital puffiness for 1 year. History of diabetes mellitus in mother was elicited. On examination, her weight was 14 kg (<−3 SD), height 91 cm (<−3 SD), target height: 147 cm approximately (as father had expired), and height age of 4 years, US:LS ratio being 1.3:1. As per Tanner's staging, her sexual maturity rating was $B_2P_1A_0M+$, had some pallor, hoarse voice, rough skin, sparse hair, and bilateral calf hypertrophy. Systemic examination was normal. An impression of VWGS with KDSS secondary to long-standing untreated hypothyroidism was made.

Investigations revealed blood urea nitrogen 8.22 mg/dl and serum creatinine 1.2 mg/dl. The endocrinological investigations are tabulated in Table 1. Ultrasound of pelvis showed bilateral multicystic ovaries. Her bone age was 3–4 years (bone age < height age < chronological age). Radiograph of the skull showed widened sella turcica. MRI scan for pituitary size is awaited. She was started on T. thyroxine 50 mcg daily and after 3 months; showed recovery with an increase in height, decrease in the puffiness of face, and stoppage of menses, as shown in Fig. 3.

DISCUSSION

PP is the premature pubertal development due to elevated sex steroids – estrogen in girls and testosterone in boys leading to the appearance of physical changes of pubertal maturation before 8 years in girls and 9 years in boys [7]. Menarche before 9.5 years in girls is also considered precocious, which can be either GnRH dependent (central) or independent (peripheral). The incidence of central PP is 20 times more with cerebral palsy [8], due to the intense activation of hypothalamic-pituitary-gonadal axis. Long-standing untreated hypothyroidism manifests as delayed puberty.

PP may occur rarely in hypothyroidism. A retrospective review over 10 years reports 24% incidence of PP among children with profound hypothyroidism [9]. Acquired pediatric hypothyroidism occurs in 1.3–4% of children. A report of three

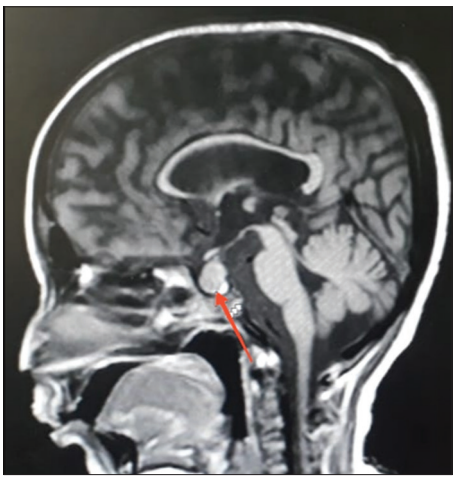

Figure 2: The magnetic resonance imaging brain scan of case 1 showing an enlarged pituitary gland measuring 10 mm × 12 mm

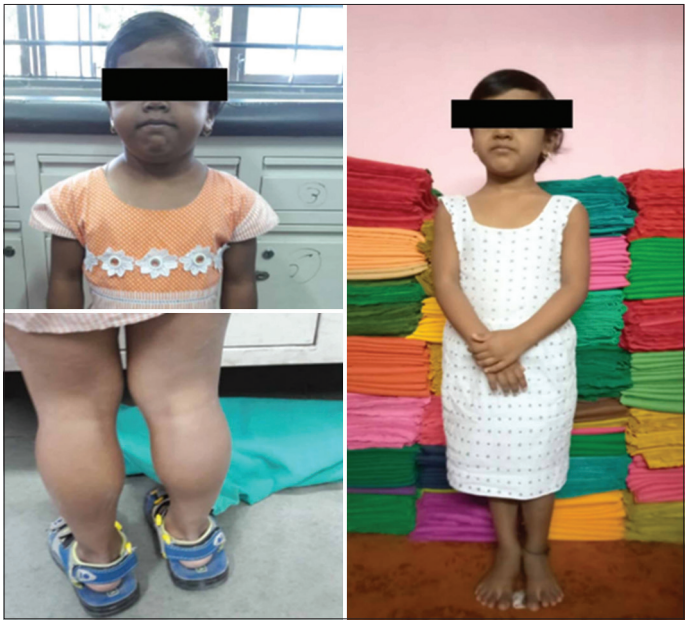

Figure 3: Pre-treatment and post-treatment clinical photograph of case 2

cases of long-standing hypothyroidism presented with menarche, premature thelarche, and galactorrhea. It was postulated that a lack of specificity in the feedback mechanism leading to an overproduction of multiple hormones characterized by juvenile hypothyroidism, delayed bone age, and isosexual PP. Reversal to a prepubertal state with thyroid hormone was seen. The symptoms were directly related to the TSH elevation. The clinical manifestation in girls is vaginal bleeding, rarely breast development or galactorrhea and lack of pubic hair; and in boys is macroorchidism without significant signs of virilization [10]. The common cause is autoimmune thyroiditis [11] which was found in our cases as anti-TPO antibody was positive. Sella turcica enlargement is due to thyrotrope hyperplasia in the pituitary gland. The pathology of macroorchidism in males is the over proliferation of Sertoli cells [12].

In females, the multicystic ovaries are due to elevated levels of circulating gonadotropins. In patients with isosexual pseudo precocity, the presence of palpable adnexal mass would suggest ovarian tumors but in such cases, the bone age is advanced. The presence of delayed bone age with PP is an important clue for the diagnosis of VWGS. A rare presentation of juvenile hypothyroidism is the KDSS which was first reported by Emil Theodore Kocher in 1892, the occurrence of muscular pseudohypertrophy was emphasized by Robert Debre and Georges Semelaigne in 1935. It is a syndrome which affects children aged 18 months–10 years and presents as pseudohypertrophy of affected muscles, delayed contraction, and relaxation of deep tendon reflexes, myokymia, and pseudomyotonia. Decreased enzyme activity and glycogen accumulation explain the hypothyroid myopathy [5]. VWGS and KDSS are rare and should be thought of in cases of chronic untreated hypothyroidism.

CONCLUSION

VWGS is the only form of PP with delayed bone age. It is reversible with early identification and prompt thyroid hormone replacement therapy. It needs to be emphasized that one should have high index of suspicion to prevent these disastrous consequences.

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