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Precocious Puberty with Primary Hypothyroidism due to Autoimmune Thyroiditis

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Summary:

Children with hypothyroidism generally have delayed pubertal development. Rare association with precocious puberty may occur especially in long standing untreated patients. The cardinal features of hypothyroidism induced pseudoprecocious pubertal development include thelarche, galactorrhoea & menarche . Other characteristic features are absence of sexual hair & retardation of linear growth. In this report a rare case of vaginal bleeding, large multicystic ovaries, precocious puberty, slow physical & mental growth in a seven and half years old girl with hypothyroidism due to autoimmune thyroiditis is described. It is important to recognize this syndrome because initiating simple thyroid hormone replacement completely resolves symptoms and hormone abnormalities, avoiding unnecessary investigations for malignancies or surgical intervention.

Key words: Precocious puberty, Hypothyroidism, Autoimmune thyroiditis.

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Introduction:

Sexual precocity is the onset of sexual maturation at any age that is 2.5 standard deviations earlier than the normal age for that population, being usually before the age of eight years. It may be classified as central, or GnRH dependent, precocious puberty (true precocious puberty) or peripheral, or GnRH independent precocious puberty (pseudo precocious puberty)[1]. Endocrine disorders such as hypothyroidism may accelerate hypothalamic pituitary axis maturation , resulting in precocious puberty[1]. Hence, precocious puberty secondary to hypothyroidism behaves like an incomplete form of gonadotropin dependent precocious puberty[2].

Juvenile hypothyroidism is a common disorder which usually presents with short stature and delayed puberty. Rarely sexual precocity can occur due to severe hypothyroid in young children. In girls precocity menifests as breast enlargement, uterine bleeding and multicystic ovaries[3]. In 1960, Van Wyk and Grumbach first described a syndrome characterized by breast development, uterine bleeding and multicystic ovaries in the presence of long standing primary hypothyroidism[4]. Looking for hypothyroidism in girls with ovarian masses and precocious puberty is important in order to avoid surgery on the ovaries[5]. This condition is very important to recognize as it is completely treatable with levothyroxine[3]. In this case hypothyroidism occurs due to autoimmune thyroiditis. Autoimmune thyroid disease (ATD) is the most common autoimmune condition, affecting approximately 2% of the female population & 0.2% of the male population[6]. In females it usually occurs early to mid puberty. Optimal quantities of thyroid hormone are critical to neurodevelopment and growth[6]. ATD arises due to complex interactions between environmental and genetic factors, that are yet to be completely defined . Even with identical twins the concordance rate is only about 50% , emphasizing environment play a role in disease pathogenesis[6]. Most cases of syndrome in the literature are secondary to autoimmune thyroid disease but there are some case reports where the syndrome is secondary to unrecognized congenital hypothyroidism[4]. Although rare, the exact incidence of pseudoprecocious puberty attributable to hypothyroidism is unknown[7].

Case report:

A seven and half years old girl was attended in Gynae outpatient department in Sir Salimullah Medical College Hospital because of a history of single episode of pervaginal bleeding for 5 days and slight enlargement of breast for one year. Bleeding was average in amount (use 2-3 pads/day). There was no history of local trauma or discharge, foreign body insertion, bleeding from any other site and difficulty in micturation. The patient did not have a history of convulsions, meningitis,

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encephalitis , head injury or hormonal therapy. She was born at term pregnancy without any complication in a lower middle class family. Her parents noticed that she had slow mental and physical development compared with her brother. They also complains that she has low memory, fatigue, cold intolerance and constipation and excessive weight gain. There is no family history of similar condition.

On examination, Patient looked lethargic , pale with puffy face. Her temperature was 98.4°F. Height was 115cm (<10th percentile), body weight was 32kg (>90th percentile) . Her blood pressure was 95/55mm of Hg , pulse was regular with a rate of 68/min. Thyroid gland was slightly enlarged, which was diffuse & non tender. Lymph nodes- not enlarged. Heart and chest were normal. Her breast buds were developed as tanner stage 2-3 (fig-6) without galactorrhoea or other external signs of sexual maturation. Abdomen was distended, no abnormal pelvic and abdominal mass was palpated. No pitting oedema. On genital examination no abnormalities were detected. No pubic or axillary hair growth. She was intolerant to cold.

Initial laboratory data showed: Haemoglobin-11.5g/dl, ESR- 15mm/1st hr, total WBC count- 7500/mm3, platelet -280,000/mm3, MCV- 88.4fl, MCH-30.3pg , RDW-CV-14.6%, RBS- 5.3mmol/L, Alkaline phosphatase- 156 U/L, Total cholesterol- 200mg/dl, Tryglyceride- 232mg/dl, HDL cholesterol- 33mg/dl, LDL cholesterol -120mg/dl, Urine RME- NAD.

Anti-Thyroglobulin Ab- 82.50IU/ml (normal<34), Anti-Thyroid Peroxidase Ab-163.70IU/ml (normal <12).

Endocrinological evaluation revealed: T3- 0.54ng/ml (normal 0.86-2.70), T4- 4.36ng/dl (normal 5.50-15.00), FT4-0.40ng/dl (normal .77-2.08), TSH >100.00mIU/ml (normal 0.70-5.70), LH- 0.62mUL/ml (prepuberty female <0.20), FSH 2.06 mIU/ml (prepuberty female <2.00), Prolactin 50.10ng/ml (normal 2.8-29..2),

Estradiol- 10.63pg/ml (child<10.00), Progesterone-0.02nmol/l, Testosteron- 0.10nmol/L, Cortisol- 2.56ug/dl, GH- 0.19ng/ml (normal 0.06-50), DHEA -S04 21.30µg/dl (normal 35-450) , Ca125- 12.50U/ml (normal <35.00).

Pelvic ultrasound: Uterus is anteverted in position. Longitudinal, side to side and anteroposterior diameter are about(6.2×3.1×2.6)cm. Myometrial and endometrial echotexture is uniform. Endometrial thickness is about 5-6mm.There are enlarged cystic mass in both adnexal region. Cyst in right ovary measures about 9.3×6.7cm. Cyst in left ovary measures about 9.1×5.3cm. Both cysts are closely applied with each other, wall of both cysts are thin and multiple thin septations are seen in both cysts (Figure-2).

Thyroid Ultrasound: Thyroid gland slightly enlarged.

Xray skull: Enlarged pituitary fossa. Sella turcica is widened and deep.

These results were consistent with diagnosis of Precaucious puberty with primary hypothyroidism as a result of chronic autoimmune thyroiditis.

After establishment of diagnosis, L-thyroxin 75ìg once daily was given. Within few days after treatment vaginal bleeding was stopped and there was no recurrence. In addition the patient was improved both physically and mentally and her weight decrease to 22Kg (<50th percentile). Over the last six months of follow up the post treatment laboratory data become normal except antithyroid antibodies remain raised. Pelvic ultrasound revealed normal uterus and ovaries.

Discussion:

The cause of vaginal bleeding must be saught when bleeding occurs in young girl and clinical presentation may help in establishing the correct diagnosis[8]. We report a typical case of vaginal bleeding that is caused by hypothyroidism & its successful treatment with thyroxin replacement therapy. Here hypothyroidism occurs due to autoimmune thyroiditis. .

Generally hypothyroidism is associated with delayed sexual maturation and delayed puberty. However, rarely it is associated with paradoxical precocious puberty, especially in longstanding untreated acquired hypothyroidism, a strikingly unphysiological association. This entity of hypothyroidism with precocious puberty was first described by Kendle in 1905[9]. Etiology of acquired hypothyroidism could be undiagnosed autoimmune thyroiditis. Van Wyck-Grumbach first reported the association of hypothyroidism with multicystic ovaries and precocious puberty . This is also called the Van Wyck Grumbach syndrome. There is no axillary and pubic hair development in both sexes. Exact pathophysiology for this paradoxical phenomenon is not clear[9]. But there are several explanations: A convincing explanation of sexual precocity and bilateral ovarian enlargement is that high levels of TSH seen in profound hypothyroidism could act through the FSH-r (FSH receptor) and cause gonadal

stimulation. This causes breast development, uterine bleeding, multicystic overies in girls[8]. The glycoproteins TSH, FSH, LH and hCG share a common alpha subunit but have a unique beta subunit that is specific to each hormone. They each act through transmembrane GPCRs to activate adenylate cyclase and stimulate c-AMP production[4]. Anasti et al[10] showed that recombinant human TSH elicited a dose-dependent response at the human FSH receptor. The TSH concentration required was several orders of magnitude higher than FSH, demonstrating that the FSH-like activity of TSH is very low[4]. Prolactin concentration was high as this hormone (prolactin) and TSH share the same hypothalamic releasing factor TSH releasing hormone (TRH). Continuous and high TRH concentrations have been shown to stimulate FSH secretion as well[11].

On the otherhand, hyperprolactinemia reduced gonadotrophic clearance and decrease dopaminergic and opoid tone at the hypothalamic pituitary axis . Pituitary enlargement with long standing profound hypothyroidism results from prolonged and or target organ failure in the absence of the appropriate hormone replacement, the loss of negative feedback of hypothalamus and secondary hypertrophy or hyperplasia of the thyrotrophic cells in the anterior lobe of pituitary gland[8]. Sometimes there is hyperplasia of not just thyrotrophs, but lactotrophs as well causing hyperprolactinemia[11]. Pubic and axillary hair is absent due to non arousal of adrenal gland. Unlike other precocious puberty, height acceleration does not occur in this condition and bone age gets retarded[3]. Thyroid hormone (TH) may actually be considered a growth factor, and TH deficiency impairs child growth and development, even when the growth hormone is present[12]. Providing TH is adequately replaced, and there is enough time for catch up growth before true puberty occurs, it is conceivable that patients can achieve a final height within normal limits[1].

Conclusion:

Where vaginal bleeding occurs in young girls, hypothyroidism should be considered especially when vaginal bleeding is accompanied with additional clinical presentations such as short stature, delayed bone age and multicystic ovaries[8]. Early recognition of thyroid dysfunction is necessary to prevent the negative effects of hypothyroidism on growth and metabolic function and to prevent deranged pubertal development [6]. Thyroxin replacement therapy lead to complete resolution of such disorder and promote normal physical and mental development of young girls[8] . Parents of children with AT should be advised that the hypothyroidism is likely to be permanent and monitoring of thyroid function for all patients should be lifelong [6].

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