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Case Report

Hypothyroidism gone awry: A Case Report on Van Wyk Grumbach Syndrome

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Abstract
Van Wyk Grumbach syndrome is a rare condition characterized by a triad of juvenile hypothyroidism, precocious puberty, and ovarian enlargement with multiple cysts. Here is a case of a 7-year-old female child presented with vaginal bleeding. On examination she had short stature. Family history of acquired hypothyroidism was present in both the parents. Laboratory tests confirmed severe hypothyroidism with TSH levels > 100 mIU / mL. Ultrasound revealed an enlarged uterus with fluid-filled internal echoes and polycystic ovaries. Thyroxine therapy was initiated and titrated, resulting in cessation of bleeding within three days.

Introduction

Van Wyk Grumbach syndrome (VWGS) is a rare medical condition characterized by a combination of hypothyroidism, precocious puberty with distinct features such as delayed bone age and lack of pubic hair, and ovarian cysts in pre- and post-pubertal girls or macroorchidism in boys.[1] Affected individuals often present with delayed bone age and enlarged ovaries that may mimic a germ cell tumor, accompanied by elevated tumor markers. Surgery is not indicated, and thyroid hormone replacement therapy is highly effective, leading to complete regression of ovarian enlargement and normalization of tumor markers with sequentially increasing doses.[2] Elevated TSH levels can stimulate FSH receptors in the ovaries due to molecular mimicry, as TSH, FSH, and LH share a common β-subunit. This aberrant stimulation leads to increased estrogen production, causing bilateral ovarian enlargement and precocious puberty, including symptoms like menarche.[3] Its incidence in youngsters, particularly in females, is believed to be between 1% and 2%.[4] Boys rarely develop classic VWGS. Instead, they present with isolated testicular enlargement (macroorchidism) without corresponding penile growth or pubic hair and with delayed bone age and short stature.[5]

Case Report

A 7-year-old female child with a history of congenital megacolon, treated with colostomy and modified Duhamel procedure, presented with vaginal bleeding. Child also had history of constipation. There was no history of headache, vomiting or visual symptoms. Her appetite was normal and she did not have excessive somnolence or cold intolerance. Her scholastic performance continued to be average. Both parents had history of acquired hypothyroidism and is on thyroxine supplements.

On examination child had fatigue, pallor and dry scaly skin. There was no goiter. Short stature was present. Despite having vaginal bleed child had no breast development or pubic hair on examination which strongly points to a phenomenon known as precocious pseudopuberty. Lab tests confirmed severe hypothyroidism with TSH levels > 100 mIU / mL. Ultrasound revealed an enlarged uterus with fluid-filled internal echoes and polycystic ovaries (Figure 1). Delayed bone age was also noted on comparison with Greulich Pyle atlas (Figure 2). Since the child had features consistent with VWGS, thyroxine therapy was initiated at 25 mcg, titrated to 50 mcg (Approx. 2.5 mcg / kg/ day) which is slightly below the typical range of thyroxine replacement), resulting in cessation of bleeding within three days, and the child was discharged on thyroxine 50 mcg. Since hypothyroidism is usually severe and longstanding in VWGS, a cautious approach to thyroxine replacement is necessary. Starting at a lower dose and titrating slowly helps prevent adverse effects from a sudden metabolic shift. Child is on regular follow up and our plan is to titrate the dose of thyroxine based on improvement.

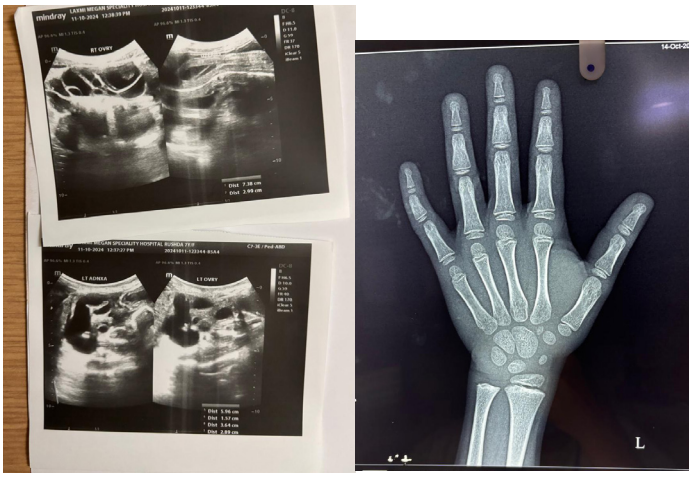

Figure 1 : Ultrasound of the abdomen of the child Figure 2 – X ray showing the delayed bone age

Discussion

VWGS is characterized by a combination of symptoms, including chronic hypothyroidism with elevated TSH levels, isosexual precocity without pubic and axillary hair growth, delayed bone age. The syndrome is thought to result from TSH stimulating the gonadal FSH receptor, leading to an FSH-dominant clinical picture with features like breast development, follicular cysts, and menstruation.[6] Acquired paediatric hypothyroidism, often caused by chronic autoimmune thyroiditis, affects 1.3 - 4% of children.[7] In our case, chronic hypothyroidism was attributed to autoimmune thyroiditis, supported by significantly elevated thyroid peroxidase antibody levels (> 1000 IU / mL). The TSH level was markedly elevated (> 100 microIU / mL even after 20-fold dilution), confirming severe hypothyroidism.

Elevated TSH levels stimulate the FSH receptor, leading to gonadal activation and increased estrogen production, which triggers the development of secondary sexual characteristics.[8] In the index case, breast development was consistent with Tanner stage 1 and pubic hair was not developed. FSH (O)-10.89 mIU / mL, estradiol-E2 estrogen - 53.4 pg / mL. In typical female puberty, thelarche is the first sign, followed by pubarche. However, in our index case, menarche occurred without either breast development or pubic hair. This unusual presentation of vaginal bleeding in the absence of other secondary sexual characteristics reflects the discordant or "precocious pseudopuberty" seen in VWGS, where severe primary hypothyroidism induces menarche without thelarche or pubarche.

Bone age is typically assessed through X-ray of the wrist and hand, evaluating epiphyseal development to determine linear growth. The Greulich and Pyle method is a common approach, comparing a patient's ossification centers to standardized age-matched references derived from healthy children.[9] Using the Greulich and Pyle's atlas, X-ray of left wrist revealed bone age of only five years in our case. VWGS is a unique form of precocious puberty characterized by delayed bone age, attributed to long-standing hypothyroidism. This distinguishes it from other forms of precocious puberty, where bone age is typically advanced.

Severe primary hypothyroidism in VWGS can mimic an ovarian tumor due to cystic ovarian enlargement, but recognizing its endocrine origin via thyroid function tests and hormonal profiling rather than jumping to surgery, is essential. In this case, elevated TSH and FSH revealed VWGS, with ovarian cysts likely arising from heightened ovarian sensitivity to gonadotropins, crossactivation of FSH receptors by high TSH and TRH induced prolactin elevation amplifying FSH effects. Thyroxine replacement resulted in regression of ovarian cysts, cessation of vaginal bleeding, and improvement of thyroid function tests within four months, highlighting the importance of accurate diagnosis and treatment to avoid unnecessary interventions.

Conclusions

Diagnosing VWGS requires a high index of suspicion due to its unique presentation. The characteristic features include pseudo pseudoprecocious puberty, absence of goiter, short stature, delayed bone age, elevated TSH with low T3 and T4, and high FSH with pre-pubertal LH levels. Prompt treatment with levothyroxine is essential, as early intervention can prevent short stature and help patients achieve their genetic height potential. Sometimes these individuals undergo surgery in view of ovarian torsion but simple replacement of thyroxine can reverse all this.

Conflict of Interest: None

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