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The Paradox of Hypothyroidism and Precocious Puberty: A Case of Van Wyk Grumbach Syndrome as a Clinical Puzzle.

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Abstract:
Van Wyk Grumbach syndrome (VWGS) is a rare presentation of long-standing prepubertal hypothyroidism. It was first described in 1960 by Van Wyk and Grumbach as a syndrome characterized by breast development, multicystic ovaries, and uterine bleeding in a patient with primary hypothyroidism. This report details the case of a 4-year-old female who presented with vaginal bleeding and signs of hypothyroidism, including easy fatigability and cold intolerance. Physical examination revealed short stature and other hypothyroid features. Laboratory tests showed significantly elevated TSH (699 IU/mL) and prolactin (66.35 ng/mL), with decreased free T3 and T4 levels. Imaging confirmed bilateral multiloculated cystic ovaries and pituitary hyperplasia. An X-ray of the wrist showed a delayed bone age by 12 months, which is a key diagnostic feature distinguishing VWGS from other forms of precocious puberty.
The diagnosis of VWGS was made based on the high TSH levels and radiological findings. Treatment with oral levothyroxine was initiated, leading to the cessation of vaginal bleeding and a gradual decrease in the size of the ovarian cysts after one month. This case emphasises the importance of early recognition of VWGS to prevent unnecessary surgical procedures and to demonstrate that thyroid hormone replacement alone can reverse the symptoms.
Keywords: *Ovarian Cysts, Delayed Bone Age, Van Wyk Grumbach syndrome, Precocious Syndrome, Hypothyroidism*

INTRODUCTION

Van Wyk Grumbach Syndrome (VWGS) is an infrequent yet fully reversible clinical entity predominantly observed in prepubertal girls. It is defined by protracted, unmanaged primary hypothyroidism, which initiates a complex cascade of endocrine alterations culminating in precocious pseudopuberty, ovarian enlargement, and pituitary hyperplasia [1,2]. The foundational pathological mechanism involves the chronic and substantial elevation of thyroid-stimulating hormone (TSH) levels, which exerts an overstimulating effect on the pituitary gland. This excessive TSH can then cross-react with follicle-stimulating hormone (FSH) receptors, thereby inducing anomalous ovarian follicular development, cyst formation, and increased estrogen production. These processes, in turn, manifest as features of precocious puberty, such as vaginal bleeding or breast development [3]. Furthermore, sustained high TSH concentrations can lead to hyperplasia of pituitary thyrotrophs [4]. Due to its uncommon incidence and diverse clinical presentations, VWGS frequently poses a diagnostic challenge, potentially resulting in unnecessary invasive medical interventions. This case report endeavors to delineate a quintessential presentation of VWGS in a 4-year-old female, elucidating the diagnostic pathway and highlighting the dramatic therapeutic response to thyroid hormone replacement.

Case Report

A 4-year-old female was admitted to the emergency department with a four-day history of vaginal bleeding. There was no history of trauma, foreign body insertion, or sexual assault. Her mother reported that for the last few months, the child had experienced easy fatigability, cold intolerance, and abdominal swelling. There was no family history of precocious puberty or autoimmune disease.
Upon physical examination, the child was conscious but irritable. She exhibited pallor, edema, bradycardia, and tachypnea. Her physical measurements were significantly below the average for her age: height was 85 cm (less than -3 SD), weight was 14 kg (between -1 SD to -2 SD), and head circumference was 45 cm (less than -3 SD). Other findings included global developmental delay, delayed dentition, coarse facies, a depressed nasal bridge, a protruded tongue, short stature, an umbilical hernia, and dry, rough skin with puffy hands and puffiness around the abdomen (Figure 1). Abdominal palpation revealed firm, non-tender, mobile masses of 7-9 cm in both iliac fossae.

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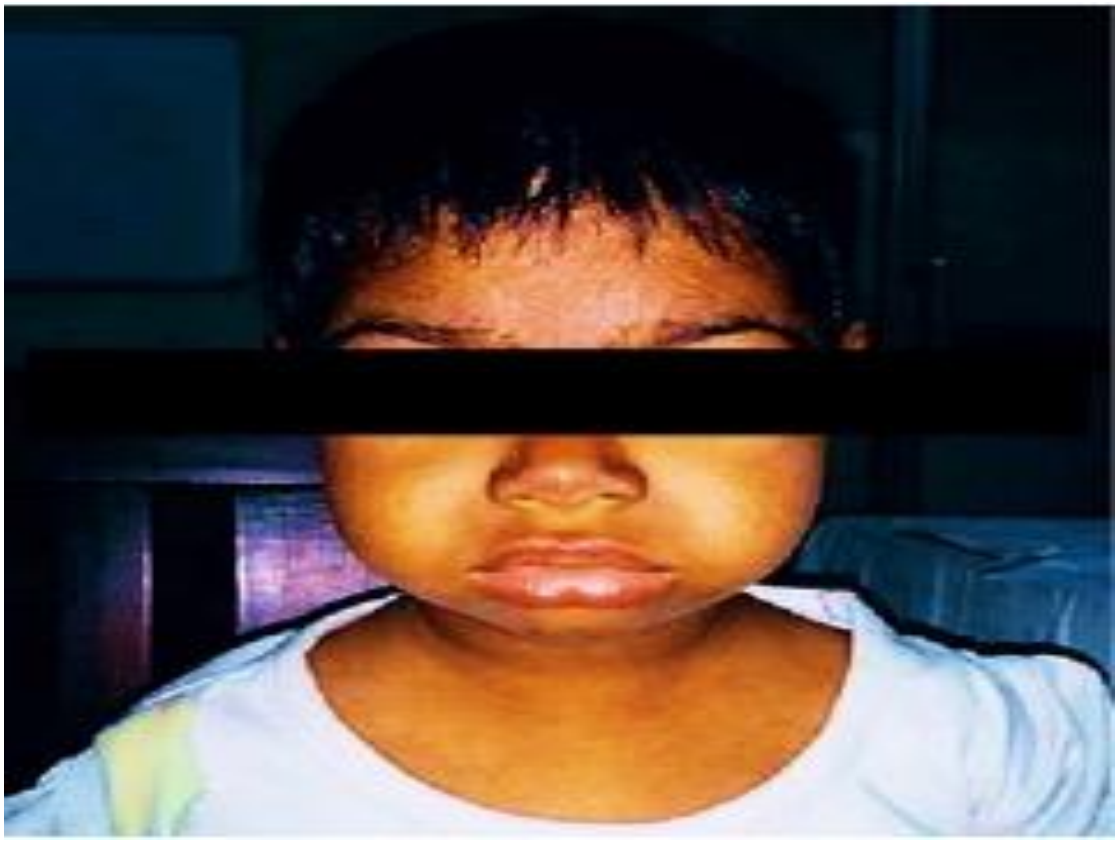

Figure 1: Clinical Photograph of Patient: A 4- year old female patient presenting with characteristic clinical features of severe hypothyroidism, including coarse facies, a depressed nasal bridge, and notable periorbital and facial puffiness. These findings were consistent with the global developmental delay, short stature and dry, rough skin observed on physical examination.

Hormonal profile tests showed an extremely high TSH level of 699 IU/mL and a high anti-TPO antibody level of >2152 IU/mL. Serum prolactin was also elevated at 66.35 ng/mL. Conversely, free T3 and free T4 levels were low, at <1 pg/mL and <0.4 ng/dL respectively. Serum LH was low at <0.01 IU/L. An ultrasonography (USG) of the abdomen and a CECT of the abdomen and pelvis revealed bilateral multiloculated cystic ovaries (Figure 2). USG of the neck showed a hypoplastic thyroid gland in a normal position. An MRI of the head indicated pituitary hyperplasia (Figure 3). An X-ray of the left wrist confirmed a delayed bone age by 12 months.

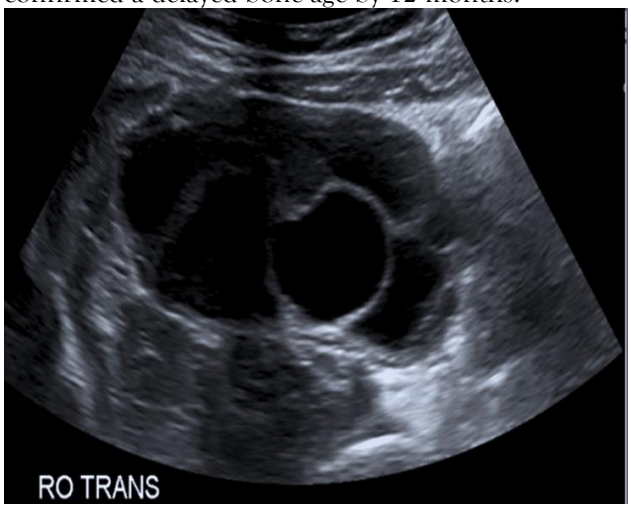

Figure 2: USG Whole abdomen showing Multiloculated Cystic Ovaries.

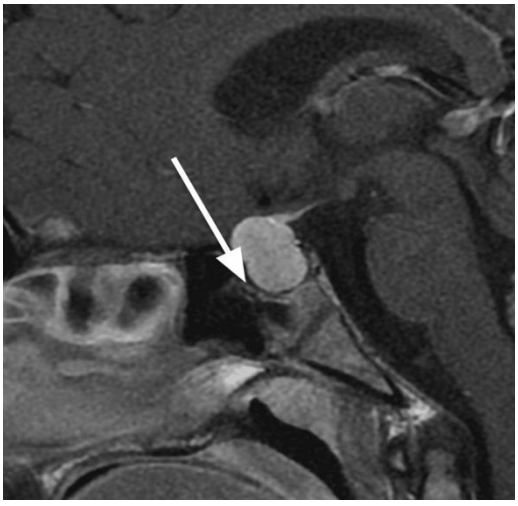

Figure 3: MRI Brain showing Pituitary Hyperplasia.

Based on the clinical presentation, the high TSH levels, and the radiological findings, a diagnosis of ovarian hyper-stimulation secondary to severe hypothyroidism, also known as Van Wyk Grumbach

Syndrome, was made.
The patient was started on oral levothyroxine at a dose of 75 ug daily. She also received a one-week course of Tab Dexamethasone 6 mg and Syrup Albendazole.
One month after starting levothyroxine therapy, the patient's vaginal bleeding had ceased. Her fT4 levels were rising, and concurrent imaging studies provided objective evidence of a gradual, yet significant, reduction in the size of the bilateral ovarian cysts.

Discussion

This particular case compellingly exemplifies the characteristic clinical tableau of Van Wyk Grumbach Syndrome, an infrequent yet diagnostically critical condition within pediatric endocrinology. The 4-year-old female presented with a broad spectrum of symptoms directly attributable to protracted, severe primary hypothyroidism. These manifestations encompassed profound growth retardation, clearly evinced by her significantly diminished height and head circumference (both below -3 SD), in conjunction with a delayed bone age. Other discernible features included global developmental delay, typical coarse facial characteristics (as vividly depicted in Figure 1), and dry, edematous skin. However, the most salient clinical elements were the precocious vaginal bleeding and the presence of bilateral ovarian masses, symptoms that frequently prompt initial diagnostic inquiries for ovarian neoplasms or alternative causes of precocious puberty [5,6,7].

The linchpin of establishing a diagnosis of VWGS resides in recognizing the profound degree of hypothyroidism. Our patient's exceptionally high TSH level of 699 IU/mL served as the primary impetus behind the observed pituitary hyperplasia and the subsequent cross-reactivity with FSH receptors [8]. The elevated anti-TPO antibodies strongly suggest an autoimmune etiology for her primary hypothyroidism, most plausibly Hashimoto's thyroiditis, although the presence of a hypoplastic thyroid gland could also point towards untreated or inadequately managed congenital hypothyroidism. The elevated serum prolactin level is a recurrent finding in severe hypothyroidism, resulting from augmented stimulation by thyrotropin-releasing hormone (TRH), which concurrently stimulates prolactin secretion [4].

The differential diagnosis for prepubertal vaginal bleeding accompanied by ovarian masses is extensive, encompassing true precocious puberty, various ovarian tumors (such as granulosa cell tumors or germ cell tumors), and other forms of pseudo-precocious puberty. Nevertheless, the simultaneous presence of severe hypothyroidism (e.g., short stature, bradycardia, coarse facies, and delayed bone age) in conjunction with the distinctive hormonal profile (markedly high TSH, low T3/T4) strongly inclined the diagnosis towards VWGS. Imaging findings of bilateral multiloculated ovarian cysts and pituitary hyperplasia offered further conclusive evidence, effectively distinguishing it from other potential conditions [9,10]. It is crucial to underscore that, once VWGS is diagnosed, unwarranted surgical interventions for the ovarian masses should be assiduously avoided, as these typically undergo spontaneous regression with appropriate thyroid hormone replacement therapy [11].

The therapeutic strategy for VWGS is direct and remarkably efficacious: immediate and sustained thyroid hormone replacement using levothyroxine. As palpably demonstrated by the rapid clinical improvement in this case, a dramatic therapeutic response manifested within one month, characterized by the complete cessation of vaginal bleeding and a significant reduction in the size of the bilateral ovarian cysts. Diligent long-term follow-up will be indispensable to monitor the patient's thyroid function, assess catch-up growth, observe the progression of normal pubertal development, and confirm the complete resolution of any ovarian and pituitary abnormalities. This case serves to underscore the critical importance of a meticulous clinical assessment and comprehensive endocrine evaluation in pediatric patients presenting with ambiguous signs of puberty, particularly when these are coupled with growth failure or other non-specific symptoms suggestive of underlying hypothyroidism.

CONCLUSION

Van Wyk Grumbach Syndrome, while rare, represents a completely reversible condition that precipitates precocious pseudopuberty and ovarian enlargement in prepubertal girls, originating from chronic and severe primary hypothyroidism. This case report illustrates a classic presentation in a 4-year-old female, whose array of symptoms, including vaginal bleeding, ovarian cysts, and pituitary hyperplasia, resolved promptly with the initiation of levothyroxine therapy. Consequently, clinicians should maintain a high index of suspicion for this syndrome and consistently integrate thyroid function tests into the diagnostic workup for girls presenting with precocious puberty or adnexal masses, thereby circumventing misdiagnosis and potentially intrusive medical procedures.

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