Original Research

VAN WYK-GRUMBACH SYNDROME- A CASE REPORT

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ABSTRACT

Van Wyk-Grumbach Syndrome (VWGS) is an exceptional clinical entity defined by the triad of untreated juvenile primary hypothyroidism, isosexual precocious puberty, and bilateral multicystic ovarian enlargement. While typical central precocious puberty is characterized by accelerated skeletal maturation and increased linear growth, VWGS is uniquely distinguished by significant growth retardation and delayed bone age. This report describes a female child in her ninth year, born out of a 3rd degree consanguineous marriage, who presented with abdominal distension and vaginal spotting. Investigations revealed ovarian cyst, profound primary autoimmune hypothyroidism (TSH >100 uIU/ml) and a pathognomonic bone age delay. Initiation of levothyroxine replacement therapy facilitated the stabilization of pubertal progression and initiated regression of ovarian masses. This case highlights the necessity of systematic endocrine screening in paediatric adnexal masses to prevent unnecessary surgical interventions which was planned earlier and ensure correct diagnostic pathways and the right treatment with thyroxine reversed all the pathology.

Keywords: Thyroid, Growth Failure, Precocious Puberty, Ovarian Cysts.

BACKGROUND

The complex intersection of the hypothalamic-pituitary-thyroid (HPT) and hypothalamic-pituitary-gonadal (HPG) axis has long been a subject of investigation and discussion , yet few conditions illustrate this relationship as dramatically as Van Wyk-Grumbach Syndrome (VWGS).[1,2]First characterized in 1960, this syndrome represents a rare manifestation of long-standing, untreated primary juvenile hypothyroidism in which features of sexual precocity paradoxically replace the typical developmental deceleration associated with thyroid deficiency.(3) In the standard paediatric population, primary hypothyroidism is an established cause of linear growth failure, metabolic slowing, and delayed pubertal onset; however, VWGS stands as a critical exception where profound thyroxinedeficiency,is known to trigger a GnRH-independent form of precocious puberty.[3,4]

The fundamental clinical challenge of VWGS is that it mimis more ominous pathologies.

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Prepubertal girls often present with varying degrees of thelarche, irregular vaginal bleeding, and substantial bilateral ovarian enlargement, frequently leading to a misdiagnosis of ovarian malignancy or central precocious puberty as in our case .[2,5-7] The presence of large multicystic ovaries, sometimes reaching the dimensions of giant abdominal masses, coupled with elevated tumor markers such as Cancer Antigen 125 (CA-125), has historically prompted unnecessary and potentially devastating surgical interventions.[8]

Pathophysiologically, the syndrome is driven by a particular phenomenon known as "specificity spillover" or "hormonal overlap".[2] TSH, Follicle-stimulating hormone (FSH), and luteinizing hormone (LH) are all members of the glycoprotein hormone family, characterized by a common alpha-subunit and a hormone-specific beta-subunit.[6,8] In states of extreme primary hypothyroidism, the absence of negative feedback results in supraphysiological TSH levels that may exceed 100 uIU/ml. At these concentrations, the TSH molecule also exhibits cross-reactivity with the FSH receptor, directly stimulating follicular maturation and estrogen production without the involvement of the central gonad tropic axis. Furthermore, the elevated thyrotropin-releasing hormone (TRH) levels

associated with primary hypothyroidism stimulate prolactin secretion and may cause thyrotrophic hyperplasia, which can radiologicallybe similar to a pituitary adenoma.[6,9]

High index of suspiscion and Recognizing VWGS is of paramount importance because the condition is entirely reversible with thyroid hormone replacement therapy. This report details the clinicalfeatures of a pediatric patient whose presentation underscores the diagnostic paradox of isosexual precocity occurring in the setting of severe skeletal retardation and metabolic failure.

CASE PRESENTATION

A female child in her ninth year was referred to the PediatricOut patient department for an urgent evaluation of bilateral multicystic ovarian masses. She was the third child born to parents in a third-degree consanguineous marriage. Her early developmental milestones were reported as normal, and she had been immunized according to national guidelines for her age.

The patient's clinical course began approximately two months before presentation with the insidious onset of intermittent abdominal pain and progressive abdominal distension. During this period, her parents also noted a distinct change in her physical appearance, characterized by generalized facial puffiness and a dull and lack of lusterin the skin texture. One week before the referral, the child experienced a single episode of vaginal spotting. Upon further focused clinical history, the parents reported that the child had exhibited significant, cold intolerance and a persistent history of constipation for several months.

Before her arrival at our centre, the patient had been evaluated at a secondary healthcare facility where an abdominal ultrasound identified large, complex bilateral ovarian cysts. Given the size of the adnexal masses and the history of vaginal bleeding, the patient had been opined and scheduled for an exploratory laparotomy and cyst excision under the presumptive diagnosis of an ovarian germ cell tumor. There was no documented family history of autoimmune thyroid disease, childhood endocrinopathies, or early puberty.

Physical examination revealed a child who appeared clinically hypothyroid, exhibiting noticeable facial puffiness, a sallow complexion, and dry, thickened skin. Growth monitoring was critical; her height was recorded at 104 cm and her weight at 18 kg, both of which were significantly below the 3rd percentile for her chronological age. Her pulse rate was 98 beats per minute, and her blood pressure was 100/60 mmHg (within the 50th–90th percentile for her height).

Pubertal assessment according to Tanner staging revealed Stage III breast development (thelarche). However, there was a stark absence of pubic or axillary hair (adrenarche), and her external genitalia were otherwise prepubertal.[1]Abdominal examination confirmed moderate distension, but no firm solid mass or fluid thrill was elicited on palpation. No features of virilization or neurofibromatosis (such as café-au-lait spots) were observed.

Investigations

Initial laboratory investigations confirmed a state of profound primary hypothyroidism and secondary hormonal disturbances as shown in figure 3.

Table 1: Biochemical and Hormonal Investigations at Presentation

Parameter	Patient Value	Reference Range	Clinical Significance
Serum TSH	>100 uIU/ml	0.5–5.0 uIU/ml	Severe primary hypothyroidism.
Serum FSH	12 mIU/ml	0.3–2.0 mIU/ml	Inappropriately elevated for age.
Serum LH	<1 IU/L	0.1–6.0 IU/L	Suppressed/Prepubertal.
Anti-TPO Antibodies	265.3 U/ml	<35 U/ml	Confirms autoimmune thyroiditis.
CA-125	Mildly Elevated	<35 U/ml	Mimics malignancy in hypothyroid states.

The severe elevation of TSH, coupled with positive Anti-TPO antibodies confirmed autoimmune thyroiditis as the underlying etiology. The hormonal profile demonstrated a low LH level, which is characteristic of VWGS and stands in contrast to the high LH/FSH ratio seen in normal central puberty.

Radiological Assessments

Radiological studies were pivotal in confirming the cystic nature of the adnexal masses and assessing skeletal maturity as shown in figure 1 and 2.

Table 2: Radiological assessments

Modality	Key Findings	Rationale and Influence on Management
USG Pelvis	Bilateral complex ovarian cysts (4.7 x 3 cm and 6.4 x 4.1 cm); enlarged uterus.	Initial identification of adnexal pathology.
Pelvic MRI	Right: Unilocular cyst (8.3 x 6.1 x 7.2 cm); Left: Unilocular cyst (5.6 x 6.7 x 4.2 cm).	Confirmed benign cystic morphology over solid neoplasm.

Neck USG	Features of thyroiditis.	Radiographic confirmation of thyroid pathology.
Wrist Radiography	Bone age: 2–2.5 years (Chronological age: 9 years).	Definitive diagnostic clue; excluded central precocity.

Most important diagnostic finding was the severe delay in bone age (2–2.5 years in a 9-year-old child). In central precocious puberty, bone age is typically advanced due to early epiphyseal maturation driven by estrogen. The presence of delayed bone age in the setting of thelarche and vaginal bleeding is nearly pathognomonic for VWGS.

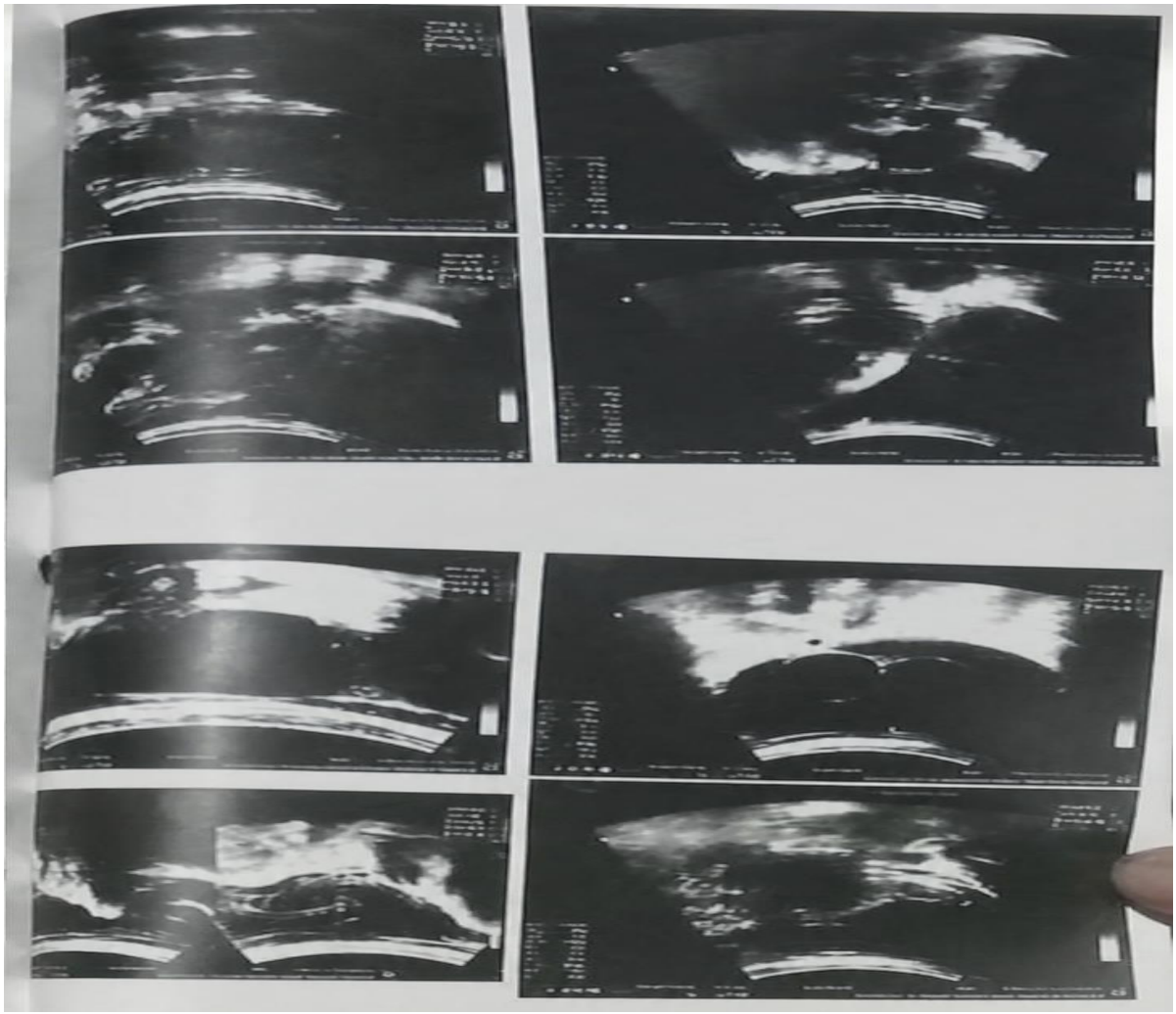
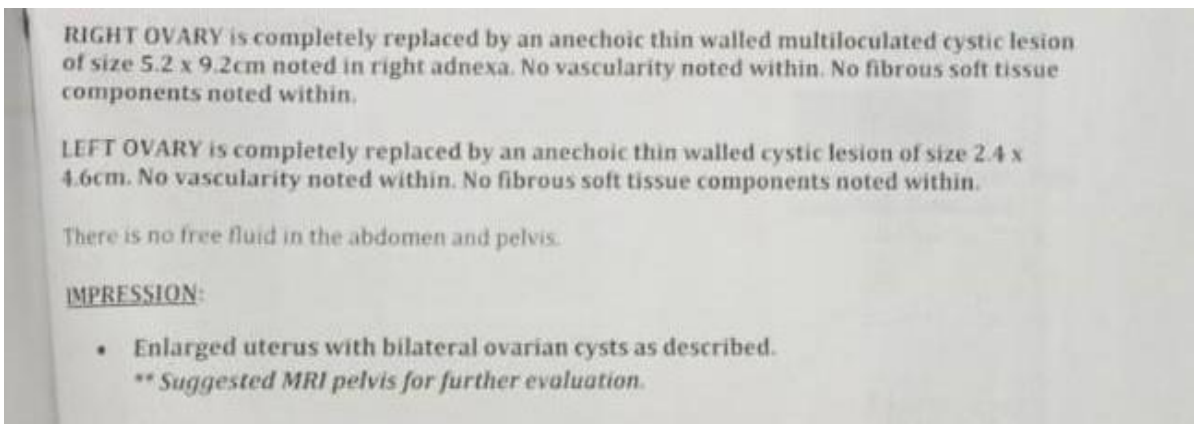


Fig 1: Ultrasound Images of Ovaries



RIGHT OVARY is completely replaced by an anechoic thin walled multiloculated cystic lesion of size 5.2 x 9.2cm noted in right adnexa. No vascularity noted within. No fibrous soft tissue components noted within.

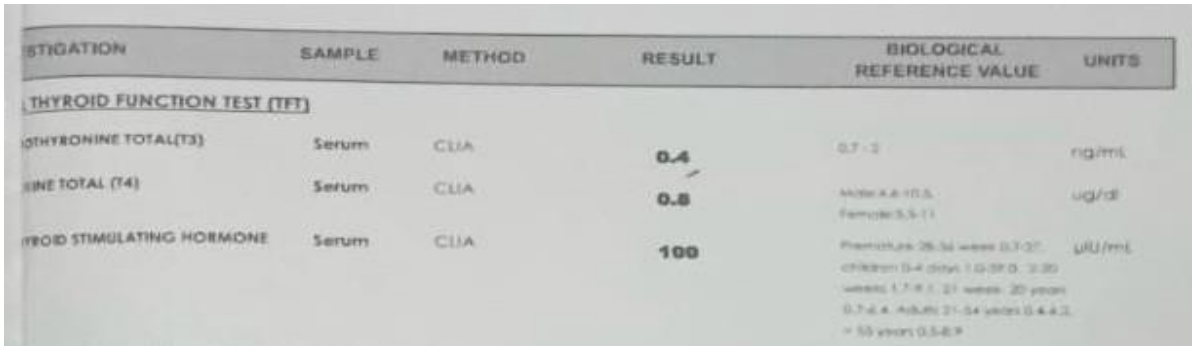
LEFT OVARY is completely replaced by an anechoic thin walled cystic lesion of size 2.4 x 4.6cm. No vascularity noted within. No fibrous soft tissue components noted within.

There is no free fluid in the abdomen and pelvis.

IMPRESSION:

- Enlarged uterus with bilateral ovarian cysts as described.
  *** Suggested MRI pelvis for further evaluation.*

Fig 2: Ultrasound Report



STIGATION	SAMPLE	METHOD	RESULT	BIOLOGICAL REFERENCE VALUE	UNITS
THYROID FUNCTION TEST (TFT)					
OTHYRONINE TOTAL(T3)	Serum	CLIA	0.4		
INE TOTAL (T4)	Serum	CLIA	0.8		
ROID STIMULATING HORMONE	Serum	CLIA	100		

Fig 3: Thyroid Function Test Report

Differential Diagnosis

The diagnostic reasoning followed a step-by-step exclusion of common pediatric conditions presenting with adnexal masses and sexual precocity.

- **Ovarian Germ Cell Malignancy**

The initial clinical suspicion was an ovarian neoplasm due to the large size of the bilateral complex cysts and vaginal bleeding. However, the markers alpha-fetoprotein (AFP) and beta-hCG were not elevated, and CA-125 elevation is known to be non-specific in hypothyroid states.[10]

- **Central Precocious Puberty (CPP)**

Central precocious puberty involves the early activation of the GnRH pulse generator. While CPP presents with similar physical signs, it is characterized by an advanced bone age and an elevated LH/FSH ratio.[3]

- **Autonomous Ovarian Cysts (GnRH-Independent)**

Autonomous cysts, such as those seen in McCune-Albright Syndrome, can cause pseudo precocity. However, McCune-Albright typically presents with classic café-au-lait spots and polyostotic fibrous dysplasia, and like other forms of precocity, it usually leads to an advanced bone age.[11]

- **Pituitary Adenoma**

The profound lack of thyroxine leads to a massive increase in TRH, which induces hyperplasia of the pituitary thyrotrophs. On MRI, this can appear as a bulky pituitary with suprasellar extension, which is often misdiagnosed as a macroadenoma. In our clinical reasoning, the knowledge that pituitary enlargement in this syndrome is reversible with thyroxine led to a conservative approach with planned follow-up imaging rather than neurosurgical intervention.[12]

Treatment

The management of Van Wyk-Grumbach Syndrome is pharmacological and focuses on restoring thyroid homeostasis.

Pharmacological Intervention

The patient was commenced on oral levothyroxine replacement therapy as per protocol.[1]The initial dosage was 50 mcg daily, which corresponded to approximately 2.8 mcg/kg/day given her weight of 18 kg. The therapeutic rationale was rooted in the physiological negative feedback loop: as serum thyroxine levels normalize, TSH levels decline, thereby removing the "spillover" stimulus at the FSH receptors in the ovaries.The scheduled surgery for ovarian cyst excision was cancelled. The parents were extensively counseled on the benign nature of the ovarian masses and the expected clinical course under medical therapy.

Outcome and Follow-up

The patient was discharged on a maintenance dose of levothyroxine with a structured plan for outpatient monitoring and asked to come for regular follow up and following review to be done.

- **Hormonal Review:** Repeat thyroid function tests are required to ensure TSH suppression and cessation of vaginal bleeding.
- **Radiological Review:** Repeat pelvic ultrasonography is indicated to document the regression of ovarian cysts, which typically resolve or return to polycystic morphology within 2–6 months.
- **Growth Monitoring:** Serial height and weight measurements are essential to track "catch-up growth".

The patient's symptoms of constipation, dry skin, and facial puffiness were expected to resolve within the first month of therapy.

DISCUSSION

Pathophysiology of Specificity Spillover

The defining mechanism of VWGS is the "hormonal overlap" phenomenon at the level of the pituitary and ovaries. TSH, FSH, and LH share an identical alpha-subunit. While the beta-subunit ensures receptor specificity, this system fails when one hormone is present in extreme excess. In the absence of thyroid hormone feedback, the resulting surge in TSH allows the molecule to bind to the FSH receptors in the ovaries. This "specificity spillover" directly stimulates the granulosa cells, leading to follicular maturation, multicystic changes, and estradiol secretion. This pathway is GnRH-independent, explaining why LH levels remain suppressed while the patient manifests signs of estrogenic exposure.[4,13–15]

Table 3: Comparison with Previously Published Cases

Author	Age / Sex	Key Clinical Features	Hormonal Findings	Imaging Findings	Treatment	Outcome
Jagadhish TK (2002)[3]	9-year-old girl	Breast enlargement, vaginal bleeding, short stature	Elevated TSH, increased FSH, low LH	Bilateral polycystic ovaries, pituitary enlargement	Levothyroxine therapy	Resolution of precocious puberty and normalization of pituitary size
Waghmare M et al. (2016)[14]	9-year-old girl	Abdominal mass, vaginal bleeding, growth retardation	TSH >150 µIU/mL, low LH, raised prolactin	Giant bilateral ovarian cysts, enlarged uterus	Levothyroxine	Regression of ovarian cysts and normalization of TSH
Kamatham V et al. (2023)[16]	12-year-old girl	Abdominal pain, irregular menstruation, short stature	Severe hypothyroidism with elevated anti-TPO antibodies	Large bilateral ovarian cysts, pituitary enlargement	Thyroxine replacement	Complete regression of cysts after treatment
Ambekar AN et al. (2025)[17]	10-year-old girl	Abdominal pain, vaginal bleeding, breast development	TSH markedly elevated, low LH, mildly raised FSH	Multicystic ovaries with elevated CA-125	Levothyroxine therapy	Resolution of ovarian cysts within 2 months
Singhania P et al. (2022)[15]	7-year-old girl	Menstrual bleeding, breast development	Elevated TSH, low LH	Multicystic ovaries and pituitary hyperplasia	Levothyroxine	Disappearance of cysts and normalization of hormones
Present Case	9-year-old girl	Abdominal pain, vaginal spotting, breast development without pubic hair	TSH >100 µIU/mL, low LH, raised FSH, anti-TPO positive	Bilateral ovarian cysts, enlarged uterus	Levothyroxine therapy	Follow-up planned for cyst regression

CONCLUSION

VWGS must be considered in any girl presenting with isosexualprecocity, multicystic ovarian enlargement, and growth retardation.A delayed bone age in a child with signs of puberty is nearly pathognomonic for VWGS.Ovarian cysts in VWGS are a physiological response to high TSH levels and are reversible with thyroid hormone replacement.Elevated CA-125 and pituitary enlargement in these patients are secondary to hypothyroidism and do not necessarily indicate malignancy or primary pituitary tumors. The syndrome occurs due to spillover where supraphysiological TSH levels activate FSH receptors.The primary clinical implication is the validation of the thyroid screening rule: every child with an adnexal mass and sexual precocity must have thyroid function and bone age assessed to avoid therapeutic

Misadventure, such as unnecessary and potentially disastrous surgery.

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