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Clinical Research Article

Van Wyk Grumbach Syndrome and Ovarian Hyperstimulation in Juvenile Primary Hypothyroidism: Lessons From a 30-Case Cohort

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Abstract

Context: Prolonged hypothyroidism in children commonly causes short stature with delayed bone maturation, and delayed puberty. However, a paradoxical occurrence of peripheral precocious puberty and pituitary enlargement in chronically untreated juvenile hypothyroidism was first reported by Van Wyk and Grumbach in 1960.

Objective: To create increased awareness and a better understanding of this clinical entity among emergency room physicians, pediatricians, surgeons, gynecologists and oncologists.

Methods: Case records of children diagnosed with Van Wyk–Grumbach syndrome (VWGS) were analyzed retrospectively.

Results: Twenty-six girls and 4 boys were identified (2005-2020). All had profound primary hypothyroidism (total thyroxine [T4]: 2.5-33.5 nmol/L, thyrotropin: > 75-3744 µIU/mL). Hypothyroidism was not the referral diagnosis in any of the girls. Among them, 17 were referred for precocious puberty, 5 with a diagnosis of pituitary tumor on magnetic resonance imaging, and others for acute surgical abdomen in 7 girls (painful abdominal mass—2, ovarian tumor—2, ovarian torsion—2, ruptured ovarian cyst—1), acute myelopathy in 1, and menorrhagia with headache in another. All girls were successfully managed with levothyroxine replacement alone, except for the 2 with ovarian torsion, who required surgery. Menstruation ceased promptly with T4 therapy in all girls, occurring at an age-appropriate later date. All boys had testicular enlargement at presentation that regressed partially after T4 treatment. Catch-up growth was remarkable during the first treatment year, but the final height was compromised in all.

Conclusion: Increased awareness of varied presentations of VWGS is vital among pediatricians to facilitate early diagnosis and targeted investigations, and to help in the initiation of the simple yet highly rewarding T4 replacement therapy to avoid all possible complications.

Key Words: ovarian hyperstimulation syndrome, hypothyroidism, child, precocious puberty

Abbreviations: AITD, autoimmune thyroid disorder; CH, congenital hypothyroidism; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; hFSH, human follicle-stimulating hormone; hTSH, human thyrotropin; LH, luteinizing hormone; MRI, magnetic resonance imaging; OHSS, ovarian hyperstimulation syndrome; T4, thyroxine; TRH, thyrotropin-releasing hormone; TSH, thyrotropin; VWGS, Van Wyk–Grumbach syndrome.

The principal manifestations of untreated hypothyroidism in children are hindered growth and maturation. Delay in skeletal maturity caused by low thyroxine (T4) levels is often associated with delayed pubertal development. However, in 1960, Van Wyk and Grumbach reported 3 girls with untreated, long-standing juvenile hypothyroidism presenting with the seemingly unusual combination of precocious menstruation, galactorrhea, early breast development, a conspicuous absence of pubic hair along with delayed bone age, and an enlarged sella turcica. All the abnormal clinical features including pituitary enlargement improved dramatically after thyroid hormone replacement therapy [1]. By giving a logical explanation to these and 4 other similar isolated cases reported earlier, Van Wyk and Grumbach grouped them all under the same umbrella term.

Over the years, a greater understanding of the phenotype of this syndrome emerged in several case reports, with the description of a diverse range of clinical manifestations varying from isolated breast development to premature menstrual bleeding, enlarged pituitary gland, multicystic ovaries resembling cystic ovarian tumor, or acute surgical abdomen due to ovarian torsion [2-8]. Although predominantly seen in older children with long-standing acquired hypothyroidism, cases were reported in association with congenital hypothyroidism as well [9]. Ovarian hyperstimulation syndrome

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(OHSS), seen in pubertal girls and young women with chronic untreated hypothyroidism, was considered to result from a similar pathophysiological process.

We analyzed the clinical, biochemical, and imaging findings of a series of children who presented with features of Van Wyk–Grumbach syndrome (VWGS) to survey the varied presenting manifestations. The underlying pathophysiology is also reviewed.

Materials and Methods

The case records of children diagnosed with VWGS syndrome between the years 2005 and 2020 from 3 pediatric endocrinology centers in southern India were reviewed retrospectively. Twenty-six girls and 4 boys were identified. Institutional ethics committee approval was provided and informed consent was obtained from the patients and their parents for use of anonymized data for publication.

Case Profiles

The median age at presentation was 9.0 years (range, 4.75-17.9 years) in girls and 8.83 years (range, 2.4-12 years) in boys. Nearly all the girls (24/26) were younger than 12 years and only 2 were in the postpubertal age group (17.4 and 17.9 years); 1 of them presented with menorrhagia and headache, and another with ovarian masses and menstrual irregularities.

Hypothyroidism was the referral diagnosis in none of the girls and in 3 of the 4 boys. The clinical symptoms and signs of hypothyroidism, namely, short stature; increasing weight gain; puffy face; cold, dry, rough skin; constipation, and dull behavior were elicited by history and physical examination in nearly all but were not the primary referral reasons in most cases. Five girls had palpable goiter: 4 with autoimmune hypothyroidism and 1 with congenital hypothyroidism (dyshormonogenesis). When plotted on Indian Academy of Pediatrics (IAP) growth charts [10], all except one child were short with a significantly delayed bone age, as assessed by the Greulich and Pyle Atlas [11] (Tables 1 and 2).

Biochemically, all cases had profound primary hypothyroidism, with extremely low total T4 (range, 2.5-33.5 nmol/L) and highly elevated thyrotropin (TSH) (range, > 75-3744 μIU/mL). Autoimmune hypothyroidism was diagnosed in 24 patients (significant elevations of antithyroid peroxidase antibodies in 16, antithyroglobulin antibodies in 5, and both antibodies in 3); congenital hypothyroidism in 6 (ectopic thyroid –1, dysgenesis—1, hypoplastic thyroid—1, dyshormonogenesis—3) (Table 3).

Clinical Details—Girls

Seventeen girls were referred with signs and symptoms of precocious puberty, 5 of them with a diagnosis of pituitary tumor. Referral diagnoses for the remaining 9 girls included abdominal mass with pain, ovarian tumor, ovarian torsion, ruptured ovarian cyst, myelopathy, and menorrhagia with headache (see Table 1).

Emergency presentation as acute surgical abdomen

Ovarian hyperstimulation (large, bulky ovaries with multiple enlarged cysts) was a constant finding in all the girls—7 presented as acute abdominal emergency. In 1 of the 2 girls in whom grossly enlarged, cystic ovaries resulted in ovarian torsion, emergency salpingo-oophorectomy was performed before the diagnosis of hypothyroidism, and levothyroxine therapy was initiated subsequently. Abdominal symptoms in the remaining 6 were managed conservatively with isolated levothyroxine replacement (see Table 1).

One of these children had severe abdominal pain for several days and was managed conservatively at a peripheral health care facility before she presented to the emergency room with tachycardia, hypotension, and a tender abdomen with bilateral palpable lower abdominal masses. An ultrasonogram showed enlarged ovaries with cystic masses. The torsed and gangrenous left ovary and fallopian tube had to be resected during an emergency laparotomy (Fig. 1). History and examination suggested premature menarche (at age 9 years) in a severely short child, and biochemistry confirmed severe primary hypothyroidism.

Another remarkable case was an 11.2-year-old girl diagnosed elsewhere as a having ovarian carcinoma due to elevated levels of the tumor marker CA-125 (358.64 U/mL, normal: < 46 U/mL). Even though she had several classic hypothyroid symptoms and signs including excessive weight gain, dry, rough skin, and delayed deep tendon reflexes, these remained undiagnosed and no medical treatment was given. She had diffuse goiter, body mass index of 23.3, and was short (height SD score [SDS]:—1.42) with delayed bone age (8.6 y). Bilateral palpable masses and free fluid were noted in the abdomen, and there was right pleural effusion (aspirated 150 mL of clear fluid). Abdominal computed tomography scan showed large lobular cystic masses (left: 14 × 6 × 11 cm with internal septations) in the ovarian region. Fine-needle aspiration cytology of these cysts revealed reactive mesothelial and hematogenous cells. Thyroid function tests suggested severe hypothyroidism due to autoimmune thyroiditis. The symptoms and signs—abdominal pain, palpable mass, ascites/hemoperitoneum, and pleural effusion—resolved completely with T4 monotherapy over the next 6 months.

Ovaries returned to normal size in all children during the 2-year follow-up, although 5 girls had a persisting polycystic appearance.

Peripheral precocious puberty

Though only 17 girls were referred with a complaint of precocious puberty, a history of early-onset vaginal bleeding (menarche at age < 10.5 years) was elicited in another 3 who presented primarily with abdominal complaints. Premature thelarche was present in all, but none had pubic or axillary hair. Basal gonadotropin levels, available for only 5 girls, showed prepubertal serum luteinizing hormone (LH) and normal to elevated serum follicle-stimulating hormone (FSH) levels (see Table 3).

Thyroid hormone replacement resulted in prompt cessation of further cycles of vaginal bleeding not only in those presenting with precocious puberty but also in the girls who had a history of early menarche. Subsequently, 9 girls went on to develop normal puberty with menarche at an appropriate later age (range, 11.4-13.6 years). Two developed true central precocity and needed gonadotropin-releasing hormone (GnRH) analogue therapy. Two were lost to follow-up, and the remaining have been progressing normally through puberty, and have not yet attained menarche.

Pituitary enlargement

Pituitary enlargement (reported as pituitary macroadenoma in some) was seen in 8 girls and 2 boys. Five girls were referred with a diagnosis of precocious puberty secondary to pituitary tumor, one of whom had a visual field defect (monocular

Table 1. Referral diagnosis and clinical features at presentation in girls (n = 26)

Clinical features	At presentation	At last follow-up
History of early vaginal bleeding	21/26	—
Age at onset of vaginal bleed, y[a]	7.3 (4-10.5)	—
Median age of girls, y (n = 26)	9.0 (4.75 to 17.92)	14.5 (7.8 to 20.8)
Weight SDS[a]	−0.94 (−3.77 to +2.01)	NA
Height SDS[a]	−2.83 (−6.67 to +1.07)	−2.06 (−6.4 to −0.21)
BMI[a]	17.45 (14.3 to 34.6)	NA
Bone age delay, y[a]	2.9 (0.2 to 5)	NA

Referral diagnosis and clinical features at presentation		No. of cases	Response to thyroxine monotherapy	
Precocious puberty	Idiopathic	12	Breast size regressed in 3 mo	Further menstrual cycles ceased promptly in those with early menarche
	Pituitary enlargement	1	Normal puberty started later appropriately	
	Pituitary enlargement associated with	1	Visual field defects improved in 6 mo	
	-Monocular temporal hemianopsia	1	Galactorrhea resolved in 2 wks	
	-Galactorrhea -Kocher-Debré-Sémélaigne syndrome	2	Calf muscle hypertrophy and tendon reflexes improved by 9-12 mo	
Paraparesis with short stature and pituitary enlargement		1	Lower limb weakness showed improvement in 1 wk; resolved fully in 1 mo	
Ovarian torsion		2	Enlarged ovarian cysts regressed in 1 girl The other required emergency unilateral salpingo-oophorectomy at initial presentation Contralateral ovary showed regression of enlarged follicles	
Ruptured ovarian cyst with hemoperitoneum		1	Acute abdominal symptoms resolved in 1 wk	
Ovarian "malignancy" (CA-125 positive)		1	Ovaries regressed to normal volume within 6 mo	
Ovarian tumor (? Cystadenoma)		1		
Painful mass per abdomen		2		
Menorrhagia with headache and pituitary enlargement		1	Resolved in next few mo	

Abbreviations: BMI, body mass index; NA, not available; SDS, SD score.
[a]Median (range).

temporal hemianopsia) in addition. The girl's field of vision was restored to normal within 6 months of T4 therapy. In the rest, pituitary enlargement was noted when cerebral imaging was performed to evaluate neurological symptoms like headache, paraparesis, and developmental delay. Follow-up magnetic resonance imaging (MRI), though available only in 3 for review, had shown a complete resolution of pituitary enlargement (Fig. 2).

Acute paraparesis

A 10.6-year-old girl presented to a tertiary neurology center with a 2-week history of progressive weakness of the lower limbs and inability to walk. She had proximal muscle weakness in both lower limbs with sluggish deep tendon reflexes, preserved cranial nerves, and bowel and bladder function. Nerve conduction velocity studies and spinal MRI were within normal limits. Pediatric endocrinology opinion was sought when brain MRI suggested a possible pituitary tumor. The child was lethargic, short (height SDS:—3.56) with severe bone age delay (3.8 years), had had early menarche at age 10.16 years, and had enlarged cystic ovaries on ultrasonography. Thyroid function tests were in favor of primary hypothyroidism. Within a week of initiating T4, she could walk with support and could climb stairs without support by 2 weeks. Her menstrual cycles ceased and subsequently, she had onset of normal puberty, attaining menarche at age 13.16 years with regular cycles thereafter. The pituitary returned to normal size as observed on the MRI conducted 1 year later.

Other features

One girl had galactorrhea at presentation. Two girls with delayed diagnosis of congenital hypothyroidism had clinical evidence of Kocher-Debré-Sémélaigne syndrome (thyroid myopathy secondary to long-standing hypothyroidism causing hypertrophied yet weak calf muscles). Two girls with congenital hypothyroidism had associated trisomy 21 and another developed idiopathic thrombocytopenic purpura a month after the diagnosis of autoimmune hypothyroidism (see Table 3).

Clinical Details—Boys

Two young boys (aged 2.42 years and 5.83 years) presenting with short stature had bilateral testicular enlargement that regressed with T4 therapy at 6-month follow-up. Another 11-year-old boy with severe short stature and "pituitary

Table 2. Referral diagnosis and clinical features at presentation in boys (n = 4)

Clinical features	At presentation	At last follow-up
Median age of boys, y (n = 4)	8.83 (2.42 to 12.42)	9.85 (3.7 to 20)
Weight SDS[a]	−0.24 (−3.66 to +0.24)	NA
Height SDS[a]	−2.63 (−6.00 to −1.14)	−2.05 (−4.77 to −0.71)
BMI[a]	19.95 (15.9 to 22.7)	NA
Bone age delay, y[a]	1.95 (1.4 to 6.4)	NA

Referral diagnosis and clinical features at presentation	No. of cases	Response to thyroxine therapy
Recurrent headaches with "pituitary macroadenoma" in a boy diagnosed with hypothyroidism and poor compliance to therapy	1	Headaches resolved in 3 mo when regular thyroxine therapy was ensured MRI at 6-mo follow-up showed normal pituitary gland
Developmental delay, short stature with enlarged testes (4-6 mL) on examination	1	Thyroxine replacement improved stature; developmental milestones are advancing Testicular size regressed to 3 mL by 6 mo
Short stature with enlarged testes (4-6 mL) on examination	1	
Short stature with "pituitary macroadenoma"	1	

Abbreviations: BMI, body mass index; MRI, magnetic resonance imaging; NA, not available; SDS, SD score
[a]Median (range).

macroadenoma" had 10 mL testes on both sides. After levothyroxine therapy, at 1.6-year follow-up, pituitary enlargement regressed completely, but the testes remained the same size, without further increase.

The fourth boy (aged 12 years) had an unusual course. He had been advised T4 replacement 2 years earlier when he presented with short stature and recurrent headaches. Although his headaches initially improved with T4, he was not compliant with therapy for many months and returned with recurrence of headaches, gross hypothyroidism (total T4: 33.5 nmol/L, TSH: 350 μIU/mL), delayed bone age (10 years), and a pituitary macroadenoma on neuroimaging. On recommencing T4 and ensuring compliance, his headaches disappeared and the pituitary reverted to normal size on the 6-month follow-up MRI scan. His testes regressed from 15 to 6 mL during the first follow-up and normal puberty began 2 years later. None of the boys had any signs of adrenarche at presentation (see Table 2).

Final Height—Boys and Girls

Two patients had attained their final height at the time of the initial presentation itself. Of the rest, follow-up height data were available only in 24 of 28 children. The mean height gain during the first year of treatment was 10.6 ± 3.26 cm. Ten children completed puberty and reached adult height, with a final height SDS of −1.94 (±0.96). The mean increment in height SDS was 0.72 (±1.19) after a mean duration of follow-up of 7.14 (±3.05) years. Of the 14 children who have not yet achieved final height, the mean height SDS at the last follow-up was −2.26 (±1.48), after a mean duration of follow-up of 2.70 (±2.44) years, with a mean increment in height SDS of 1.14 (±0.94). All the children belonged to lower socioeconomic strata, and none were treated with recombinant growth hormone because of financial constraints.

Discussion

It has been more than 6 decades since Van Wyk and Grumbach first described girls having untreated juvenile hypothyroidism presenting with the unusual association of sexual precocity, paradoxically delayed skeletal maturation, and sellar masses [1]. Though described occasionally in boys [12, 13], the affected child is typically a girl presenting with the clinical phenotype of classic hypothyroidism, along with the unexpected finding of precocious sexual maturation including features ranging from isolated breast development to galactorrhea and cyclical vaginal bleeding [14-16], adrenarche being characteristically absent. Imaging typically reveals delayed bone maturation, multicystic enlarged ovaries, and an enlarged pituitary gland. Biochemically, serum T4 levels are low with often extremely elevated TSH levels [4-6, 17-20].

The classic hypothyroid symptoms of lethargy, short stature, etc, are often overshadowed by the clinical picture resulting from ovarian hyperstimulation and pituitary enlargement. None of the girls in our cohort was referred with hypothyroidism as the primary working diagnosis. Though classically occurring in association with acquired autoimmune hypothyroidism, this syndrome may also be seen in those with long-standing untreated congenital hypothyroidism [21], as demonstrated in our cases.

The initial clinical manifestations in our case series were unique, exceptional, and varied in several of these children, some of them so intensive they required immediate emergency surgical care, while the others presented with the classic features as described originally by Van Wyk and Grumbach. A few earlier reports also demonstrated that in addition to precocious puberty, untreated hypothyroidism can result in ovarian hyperstimulation leading to enlarged, cystic ovaries that might undergo torsion and present with acute surgical abdomen in pubertal as well as postpubertal young women [8, 22-24]. Massive ovarian cysts due to hypothyroidism have also been reported in adult nonpregnant women between ages 19 and 26 years [3, 25-28]. Histology of resected ovaries has shown massive cystic follicles with no luteinization [2, 5, 6]. The basal gonadotropin levels in these patients are typically low [15, 20, 21], and the GnRH-stimulated values show a predominant FSH response with suppressed LH and elevated estradiol, suggesting a

Table 3. Investigation results at diagnosis and etiology of hypothyroidism

Laboratory investigation	Result
TT4, nmol/L, range	2.5-33.5
TSH, μIU/mL, range	> 75 to 3744
LH[a], IU/L, median and range	0.01 (0.01-0.1)
FSH[a], IU/L, median and range	5.55 (4.2-16.2)
Etiology of hypothyroidism[b]	AITD: 80% (n = 24) CH: 20% (n = 6)
Ultrasonogram of pelvis	Bulky, multicystic ovaries in all girls
MRI brain	Pituitary macroadenoma/hyperplasia n = 10 (8 girls, 2 boys)

TT4 reference range: 85 to 170 nmol/L, TSH reference range: 0.7 to 5.5 μIU/mL.
Abbreviations: AITD, autoimmune thyroid disorder; CH, congenital hypothyroidism; FSH, follicle-stimulating hormone; LH, luteinizing hormone; MRI, magnetic resonance imaging; TSH, serum thyrotropin; TT4, serum total thyroxine.
[a]Data available for only 5 girls.
[b]Two girls had trisomy 21 and one girl had idiopathic thrombocytopenic purpura as associated conditions.

peripheral etiology. Several mechanisms were postulated to explain the underlying pathophysiology.

Although thyrotropin-releasing hormone (TRH) induced excessive production of gonadotropins and prolactin was hypothesized earlier [1], the focus now has shifted to the molecular similarity between TSH and FSH, and their receptor interactions. FSH, LH, human chorionic gonadotropin, and TSH belong to a group of glycoprotein hormones made up of a common alpha subunit and specific beta subunits that share more than 40% amino acid sequences. Under physiological conditions, the specificity barriers of the receptors prevent cross-activation. Nevertheless, using recombinant human TSH (hTSH), it has been shown that hTSH can interact with and stimulate human FSH (hFSH) receptors and can also act as a competitive inhibitor of hFSH at its receptor. However, to produce half-maximal activity as that of hFSH, 3 times higher concentration of hTSH is required [29]. The search for a mutant FSH receptor having a higher susceptibility to stimulation by TSH, as seen in some pregnant women with OHSS [30, 31], has not been successful in patients with hypothyroidism [32, 33].

Hence, it is most probable that the extremely elevated TSH levels, typically associated with long-standing hypothyroidism might indiscriminately activate the wild-type FSH receptors causing ovarian hyperstimulation. This might be facilitated by a peripubertal gonad that is particularly sensitive to stimulation by TSH, as it is primed to be activated by even very low concentrations of FSH [33]. Finally, it can be speculated that some of these children might exhibit an unidentified variant of TSH possessing higher biological activity [32].

The stimulated ovaries produce estrogen, which causes premature thelarche and menarche. In our series, even though only 17 of 26 girls presented with concerns of precocious puberty, we identified early-onset vaginal bleeding (onset at age < 10.5 years) with irregular menstrual cycles in 3 others. Nonetheless, all these girls, including the latter 3, ceased to have menstrual cycles after T4 replacement, only to experience normal pubertal progression at a much later date. Two girls, however, developed central precocious puberty, reflecting the fact that chronic peripheral precocity could adversely affect the GnRH pulse generator and induce central precocity.

The severely hyperstimulated ovary and the resulting cystic mass can be large enough to undergo torsion and develop vascular compromise. If this is not recognized early, the ovary could become gangrenous and irrevocable [5], as happened in one of our patients (see Fig. 1). The massively enlarged ovaries may also result in hemorrhagic ascites and periumbilical ecchymosis [22].

Previous studies reported complete resolution of ovarian cysts within a mean duration of 3 to 6 months of initiation of T4 therapy [16, 21, 23, 24, 27]. Although ovarian size had regressed to normal in all, 5 girls in our series had ovaries that were still polycystic in appearance (multiple follicles, < 1 cm each), after a mean duration of 2.58 years (range, 1-6 years) of therapy with T4. The possible implications of this finding to the future reproductive and metabolic function of these young women need to be ascertained by longer follow-up.

Interestingly, elevated tumor markers like CA-125, alpha fetoprotein, and lactate dehydrogenase have been previously reported to be associated with hypothyroidism-associated OHSS, confounding the initial diagnosis and causing false alarm [23, 24, 34]. The CA-125 antigen is expressed in amnion and its derivatives such as müllerian epithelia, peritoneum, pleura, and pericardium, as well as in many adult tissues. Any pathology causing peritoneal irritation stimulates the production of peritoneally derived CA-125 that significantly contributes to circulating CA-125 concentrations, giving rise to high serum CA-125 [35]. One of our patients with an ovarian mass and elevated CA-125 was referred to us as a mistaken case of ovarian carcinoma. However, identification of the concurrent clinical phenotype of hypothyroidism led to biochemical confirmation and conservative treatment with T4 replacement, averting a potentially radical surgery.

The thyrotroph hyperplasia induced by elevated TRH in uncontrolled hypothyroidism can result in pituitary enlargement and be mistaken as an adenoma. When the underlying pathology is not understood, this becomes a major cause for concern, as with our patients who presented with visual field problems and headaches. Visual field defects are reversible, as the pituitary returns to normal size with appropriate T4 replacement [36]. Galactorrhea was a common associated feature in the first case series reported by Van Wyk and Grumbach. Elevated TRH due to loss of negative feedback by the thyroid could stimulate thyrotrophs as well as lactotrophs, leading to pituitary enlargement and hyperprolactinemia [14, 37]. One of our patients with pituitary hyperplasia had galactorrhea that ceased after T4 replacement.

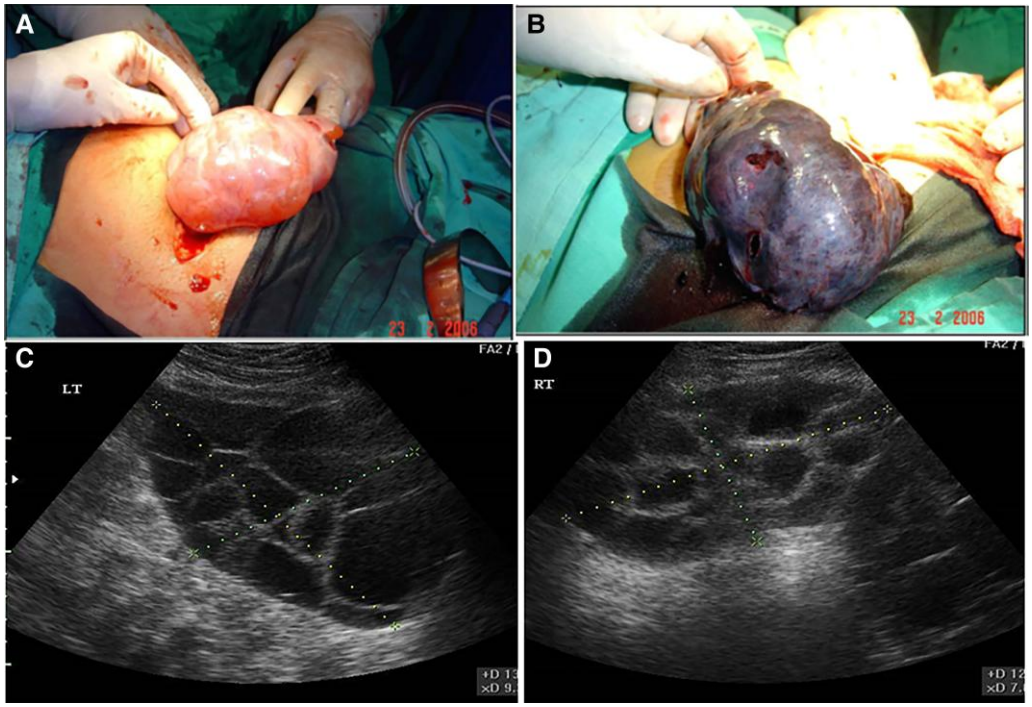

Figure 1. Ovarian hyperstimulation with chronic untreated hypothyroidism: A, Enlarged cystic left ovary, and B, torsed and gangrenous multicystic ovary that had to be resected, in a young girl who presented with hemodynamic compromise to the emergency room. C and D, Ultrasonographic evidence of enlarged and cystic ovaries in another young girl who presented with abdominal pain and elevated CA-125.

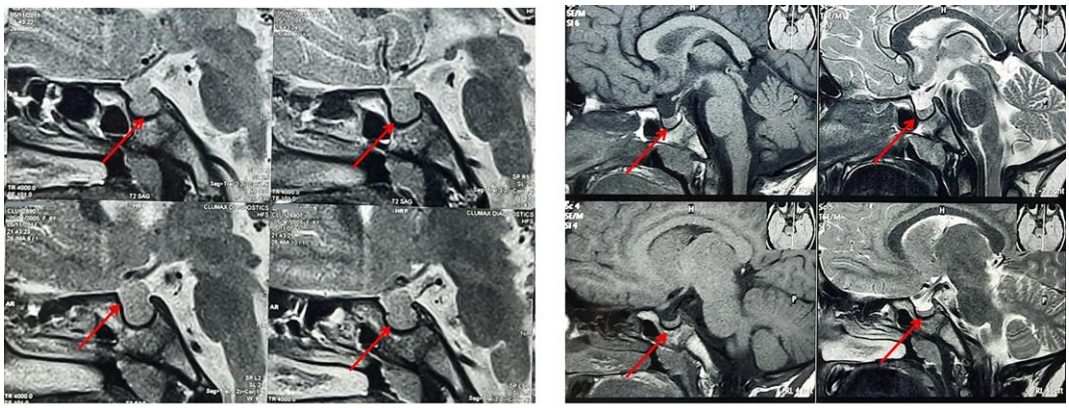

Figure 2. Left: Magnetic resonance imaging (MRI) of a girl with hemianopia at diagnosis showing "pituitary macroadenoma" with sellar and suprasellar components, superiorly compressing optic chiasm. Right: Repeat MRI in the same girl after 1 year of treatment with thyroxine is normal with complete resolution of pituitary enlargement.

Myopathy of hypothyroidism causing pseudohypertrophy of muscles (Kocher-Debré-Sémélaigne syndrome) has been well described in association with long-standing, untreated congenital hypothyroidism [38]. The hypothyroidism-associated polymyositis-like syndrome resulting in muscle weakness, and tenderness have also been described predominantly in adults, with few cases being reported in the pediatric age group [39, 40]. Typical findings are mild muscle weakness with delayed deep tendon reflexes with a slow relaxation phase, muscle tenderness, and induration, with normal electromyography in most cases. However, dramatic onset with acute paraparesis as seen in our case has not been reported previously in hypothyroidism. Neither has it ever been described before in association with VWGS. Our patient had suppressed deep tendon reflexes with delayed relaxation but did not have muscle tenderness or induration. All the symptoms rapidly reversed within 2 weeks of T4 replacement therapy.

Boys with this syndrome may present with macroorchidism without virilization in the background of the hypothyroid phenotype [12, 13]. In rare biopsies that were performed, histopathology of the testes revealed predominant tubular hyperplasia with precocious spermatogenesis up to spermatid and spermatocyte maturation, without any Leydig cell hyperplasia [31, 41, 42]. The molecular mechanisms of FSH receptor stimulation are similar to that of OHSS. Moreover, as triiodothyronine (T3) is responsible for the differentiation of

Sertoli cells, low thyroid hormone levels can result in overproliferation of Sertoli cells adding to an increase in the size of testes. With thyroid hormone replacement, testicular size might decrease or remain unchanged, as we observed [43].

Though all children showed remarkable catch-up growth in height during the first year of thyroid hormone replacement, height on long-term follow-up and final adult height were significantly compromised in many. It is well demonstrated that a delay in recognition and treatment of acquired hypothyroidism results in a significant reduction in final height despite appropriate thyroid hormone replacement [44]. The circulating estrogen resulting from peripheral and in some cases subsequent central precocity in VWGS could worsen the adult height restriction by hastening growth plate closure. However, our data in this regard are limited as we do not have midparental height records available for all with which to make more accurate interpretations.

Conclusion

We describe the varied ways in which the ever-intriguing VWGS can present, and how all the manifestations can be traced to a single underlying pathophysiology. Despite being clinically obvious, the diagnosis of hypothyroidism is often missed or considerably delayed and is left mostly to the specialist, as the unusual symptoms resulting from ovarian hyperstimulation and pituitary enlargement take precedence over the hypothyroid phenotype. The importance of recognizing hypothyroidism as the instigator in OHSS-related presentations cannot be overstated since the symptoms rapidly resolve with T4 replacement, avoiding complications of enlarged ovaries, such as torsion, and obviating unnecessary and potentially devastating ovarian surgery. Early diagnosis and treatment also allow timely puberty and remarkable early catch-up growth, although final height might be significantly compromised.

Over the years, widespread efforts have been made to increase awareness and improve the early recognition and diagnosis of hypothyroidism at all ages including neonates. However, we continue to encounter patients with long-standing, unrecognized hypothyroidism with its myriad complications as was evident in our series. There is an indispensable need to create awareness and a better understanding of this clinical entity among emergency room physicians, pediatricians, surgeons, gynecologists, and oncologists.

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Disclosures

The authors have nothing to disclose.

Data Availability

All data generated and analyzed during this study are included in this published article.

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