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Ovarian cysts, vaginal bleeding and hypothyroidism in a 4-year-old female with Down Syndrome: A case of Van Wyk-Grumbach Syndrome



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ABSTRACT

Van Wyk-Grumbach Syndrome (VWGS) is a constellation of symptoms including precocious puberty without adrenarche, delayed bone age, ovarian cysts, and hypothyroidism. We report here a four-year-old Down Syndrome patient who presented for evaluation of abdominal distension, vaginal bleeding, and bilateral ovarian cysts. Her work-up and management demonstrates the importance of screening for hypothyroidism in Down Syndrome, as well as considering the diagnosis of VWGS when evaluating a patient with precocious puberty and an apparent intra-abdominal surgical process. Given the presence of ovarian masses, a surgical emergency such as ovarian torsion or rupture must be ruled out. Even when the diagnosis of VWGS is confirmed, practitioners must be vigilant to consider surgical intervention in the presence of uncontrolled vaginal bleeding, hemodynamic instability, or failure of regression of ovarian cysts with exogenous thyroid hormone replacement.

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This case presents a pediatric patient with both Down Syndrome (DS) and Van Wyk-Grumbach Syndrome (VWGS). To our knowledge, similar cases have been presented only eight times before in the literature [1]. This indicates that this case is a rare intersection of the hypothyroidism associated with DS and VWGS and presents several educational opportunities through detailed examination of the case [2–4].

1. Case report

The patient is a 4-year 6-month African-American female with a history of DS, seasonal allergies, and tympanostomy tube placement who presented to an emergency department for evaluation of an 8-day history of vaginal bleeding and abdominal distension. No history of trauma, abuse, or vaginal foreign bodies. Mother of the child reported no history of hematuria, hematochezia, or melena. This patient was initially evaluated at an outside facility and found to have bilateral adnexal structures on ultrasound, measuring 4.49×3.86 cm on the left and 4.46×6.09 cm on the right (Fig. 1).

She was transferred to our facility for further evaluation. Given the patient's presentation with abdominal distention, vaginal bleeding, and bilateral ovarian masses, it was deemed most appropriate to admit to the pediatric surgical service to rule out an oncologic process or surgical emergency such as ovarian torsion or rupture.

Her vital signs were within normal limits and she was in no apparent distress. She presented with Tanner stage II breast development without galactorrhea, Tanner Stage II pubic hair, and Tanner Stage I axillary development. She underwent a pelvic exam under anesthesia, with no palpable masses on bimanual exam, normal external genitalia, pink cervix, and normal rectum. Bone age was delayed at 2 years and 6 months.

An abdominal CT scan was performed in the emergency department to adequately evaluate for any acute intraabdominal processes that would result in the patient's presentation. The CT showed bilateral adnexal cysts with multiple septations, measuring 4.18×3 cm on the left and 4.35×5.36 cm on the right (Fig. 2). Upon discussion with pediatric radiology and gynecology, an MRI was recommended to better define the patient's ovarian, fallopian, and uterine anatomy and to assess for any underlying oncologic processes. MRI was performed under the same episode of anesthesia as the patient's pelvic exam. The MRI verified the finding of bilateral ovarian cysts with multiple septations (left 4.27×3.03 cm, right

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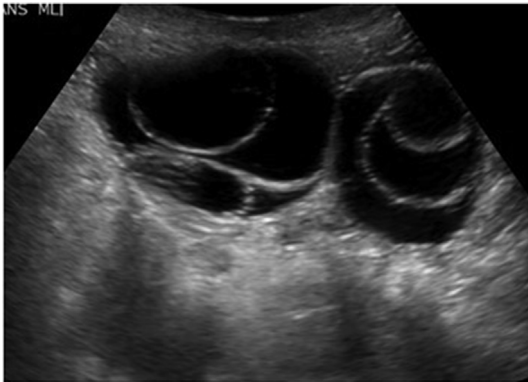


Fig. 1. Patient's ultrasound showing bilateral cystic ovaries.

3.14 × 6.02 cm) and better defined an enlarged uterus and enlarged vagina (Fig. 3).

Laboratory evaluation is summarized in Table 1. We found elevated thyroid-stimulating hormone (TSH), low free thyroxine (T4), and positive thyroid peroxidase (TPO) antibodies. Thyroglobulin (Tg) levels were elevated but Tg antibodies were negative. Hemoglobin was not measured. She had elevated estrogen and prolactin; her luteinizing hormone (LH) and follicle-stimulating hormone (FSH) were within normal limits. Beta-hCG was negative. Tumor markers were also obtained with normal cancer antigen 19-9 (CA 19-9), and elevated cancer antigen 125 (CA-125) and alpha-fetoprotein (AFP).

Given her altered endocrine profile, she was evaluated by endocrinology. The diagnosis of VWGS was made. She was started on thyroid hormone replacement with levothyroxine at 50mcg daily. Discussions with the patient's mother revealed no recent thyroid testing by her primary care provider. The patient was set up for outpatient follow up with a pediatric endocrinologist. She was also evaluated by reproductive endocrinology, who stated that a prolactinoma was an unlikely source of the elevated prolactin but rather likely secondary to elevated thyroid-releasing hormone (TRH). A brain MRI was not recommended given the alignment of endocrine findings. Gynecologic oncology had also evaluated the patient's pelvic masses and concluded that the ovarian cysts were likely an endocrine-related consequence of the patient's hypothy-



Fig. 2. CT scan showing patient's bilateral adnexal cysts with multiple septations.

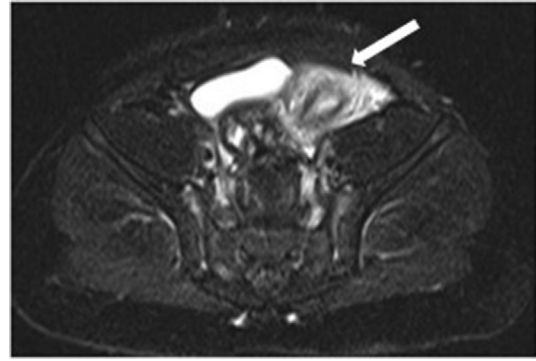


Fig. 3. Patient MRI illustrating her enlarged uterus (white arrow).

roid state. Thus, all involved clinical teams agreed that there was no indication for surgical intervention. Her hemodynamic stability also negated her needs for intervention.

Most recent contact with the patient's endocrinologist revealed continued outpatient titration of the levothyroxine, and resolution of vaginal bleeding and abdominal distention. Her growth stature is improving and there has not been further progression of Tanner staging. Given this, additional outpatient imaging has been deferred to date. This patient presentation represents a unique opportunity to review the intersection of hypothyroidism, DS, and VWGS, to avoid unnecessary operative intervention.

2. Discussion

2.1. Hypothyroidism & Down Syndrome

2.1.1. Epidemiology and screening protocols

Children with DS are known to have an increased risk of thyroid disease compared to the general population, with reported incidence of 3–54%. The risk of thyroid disease increases with age to an estimated prevalence of 30% among DS adults [5]. The American Academy of Pediatrics (AAP) recommends a rigorous screening protocol for thyroid function among children with DS. This starts with the state newborn screen, which tests TSH and free T4. Pediatricians should then repeat TSH levels at 6 months, 1 year, and annually thereafter to age 21 [6]. Pediatricians are also advised to screen for symptoms consistent with hypothyroidism, such as lethargy, dry skin, and reduced growth velocity, which could be masked by the DS phenotype.

2.1.2. Hypothyroidism presentations

DS patients can present with a range of hypothyroid disease, including congenital hypothyroidism, subclinical hypothyroidism, primary hypothyroidism, and autoimmune (Hashimoto's) thyroiditis. DS newborns are at a 1% risk of congenital hypothyroidism, making the state newborn screen extremely important for timely diagnosis and treatment [6]. In newborns without DS, the rate of congenital hypothyroidism is estimated at 1:3000–4000 live births, versus 1:141 among newborns with DS [7,8]. Other risk factors for congenital hypothyroidism in DS include female sex, low birth weight (<2000g), macrosomia (≥4500 g), and Hispanic, Middle-Eastern, Asian, and Hawaiian ethnicities [7].

Subclinical hypothyroidism is considered an elevated TSH with a normal "compensated" T4 level [9]. DS neonates have been found to have lower T4 concentrations and mildly elevated TSH compared to non-DS neonates [10]. This is postulated to be secondary to delayed hypothalamus-pituitary-thyroid maturation, which can be present until the third decade of life [11].

Table 1
Patient lab values.

Lab	Value on Presentation	Interpretation	Reference Range
TSH (mIU/L)	880.90	Elevated	0.27–4.20
Free T4 (ng/dL)	0.17	Low	0.93–1.79
TPO Ab (U/mL)	108.5	Elevated	<0.3
Thyroglobulin Ab (IU/mL)	<20	Normal	<20
Thyroglobulin (ng/mL)	183.0	Elevated	2.0–35.0
Estradiol (pg/mL) [36]	113	Elevated	<20–53
Prolactin (ng/mL)	134.8	Elevated	4.8–23.3
LH (mIU/mL) [36]	<0.1	Normal	<0.1–3.3
FSH (mIU/mL) [36]	5.7	Normal	<0.1–7.1
Beta-hCG (IU/L)	<1	Normal	0–5
CA 19-9 (U/mL)	26	Normal	0–35
CA-125 (U/mL)	68	Elevated	0–35
AFP (ng/mL)	24.5	Elevated	0.0–8.7

Patients with DS can also develop primary hypothyroidism, with elevated TSH levels and low T4. DS patients' predisposition to hypothyroidism may be secondary to alterations of the thyroid as part of the trisomy 21 phenotype. Thyroid hypoplasia is seen in the DS population. Therefore, the increased incidence of hypothyroidism with age in DS patients may be a reflection of increased metabolic demands with increased body size [5,10].

The most common cause of primary hypothyroidism in DS patients is autoimmune, or Hashimoto's, thyroiditis. This appears to be the cause of our patient's untreated hypothyroidism. Hashimoto's thyroiditis is the most common autoimmune disorder in DS [5,12–14]. DS patients present at a younger age with negative family history, and tend to have a significantly lower concentration of TPO or Tg antibodies [12].

2.1.3. Treatment options

Once diagnosed, the hypothyroid DS patient is treated similarly to a non-DS hypothyroid patient, with exogenous thyroid hormone replacement and close clinical and laboratory follow-up.

2.2. Van Wyk-Grumbach Syndrome

2.2.1. Definition

VWGS is a constellation of symptoms first reported by Van Wyk and Grumbach in 1960. They noted three cases of precocious menstruation, breast development, and galactorrhea associated with delayed bone age and hypothyroidism. The patients' symptoms and precocious puberty resolved with administration of exogenous thyroid hormone, which Van Wyk and Grumbach found to be an essential component of this syndrome [15].

2.2.2. Previous case reports

After the initial report of VWGS, there have been numerous case reports describing female pediatric patients presenting with precocious puberty (breast development, menarche, and/or galactorrhea) without adrenarche (no body odor, no pubic hair, no axillary hair), elevated TSH, low T4, delayed bone age, and ovarian cysts [1–4,16–28]. To our knowledge, there have been fewer than 10 previous case reports in the literature of patients with both DS and VWGS [1–4]. Kumar et al. presented the only reviewed VWGS case series without ovarian cysts on imaging [26]. Post-pubertal VWGS patients presented with profound hypothyroidism, irregular menses, and elevated prolactin levels with or without galactorrhea [24,27]. Pre- and post-pubertal VWGS patients also presented with reduced or arrested linear growth, with concern for “crossing percentiles” that was confirmed with delayed bone age on radiographs.

2.2.3. Pathophysiology

On their initial study, Van Wyk and Grumbach found one of their patients to have an enlarged sella turcica without classical visual field deficits suggesting an underlying etiology of pituitary hyperplasia rather than adenoma. The enlarged sella turcica resolved with exogenous thyroid hormone replacement, which suggested the pituitary hyperplasia was associated with precocious puberty. One of the patients in this study also had evidence of Hashimoto's thyroiditis on thyroid biopsy. The authors concluded that the patients in their case series had hypothyroidism due to primary failure of the thyroid gland rather than a TSH deficiency [15]. The reduced circulating thyroid hormone stimulated hyperplasia of TSH-secreting pituitary cells, leading to compression of the pituitary stalk, disrupted inhibition of prolactin secretion, elevated prolactin levels, and eventual elevation in TRH levels in response to high prolactin levels [22,29]. The cross-sensitivity between TSH and prolactin pituitary cells to TRH stimulation may further contribute to elevated prolactin levels [21]. The elevated levels of prolactin also can increase ovarian sensitivity to circulating LH and FSH and decrease the frequency of gonadotropin-releasing hormone (GnRH) pulses, thereby increasing FSH levels, reducing LH levels, and increasing the risk of precocious puberty [30,31].

Several case reports of VWGS demonstrated elevated FSH levels in their patients [4,20,22,25]. This led to the discovery that high concentrations of TSH can act as a competitive antagonist for FSH at ovarian FSH-receptors (FSH-R), demonstrating a possible link between hypothyroidism and precocious puberty. This is particularly important in VWGS, with consistently elevated TSH in the prepubertal patient [32,33]. TSH stimulation of FSH-R without concomitant LH stimulation leads to the clinical findings of thelarche and gonadarche without adrenarche, consistent with the findings of precocious puberty with no pubic or axillary hair in VWGS patients [25]. The stimulation of ovarian FSH-receptors leads to follicle recruitment, ovarian cysts, and elevated estrogen levels, which in turn stimulates precocious puberty with breast development and vaginal bleeding. The elevated estrogen levels can also reduce prolactin inhibitory factor levels, which prevents negative feedback on prolactin and increases the risk for galactorrhea [4,24].

Some VWGS patients present with elevated tumor markers. Our case and several others report an elevated CA-125 level [21,24,27]. Importantly, CA-125 can be non-specific and elevated in endometriosis, uterine fibroids, and tubo-ovarian masses, which would fit the clinical picture of VWGS [21]. Our patient also presented with elevated AFP, which has been related to dysgerminomas and other germ cell tumors. AFP has been found to normalize after thyroid hormone replacement [21]. Another VWGS case with elevated AFP resulted in oophorectomy, with pathology showing cystic follicles without neoplasm [34]. Thus, the elevated tumor markers may not

be due to neoplasm, but rather are secondary to ovarian hyperstimulation and cyst formation. It is important to keep in mind that bilateral ovarian cysts are likely secondary to an endocrine pathology rather than malignancy, although it is possible to present with VWGS and a unilateral ovarian cyst [21]. Knowledge of the etiology of ovarian cysts and patterns of presentation is important for the pediatric surgeon to prevent unnecessary operative interventions.

Other symptoms of VWGS relate directly to the patient's profound hypothyroidism. Myxedema can result in ascites, pleural effusions, and pericardial effusions [17]. Ovarian pathology reports after biopsy or ovarian cystectomy have shown myxedematous infiltration into ovarian stroma [23,27]. Several VWGS case reports found patients to be anemic, which could be secondary to vaginal bleeding from precocious puberty, or directly due to their hypothyroid state [16,22–24,27,35]. The delayed bone age seen in these patients is classically associated with untreated hypothyroidism [15]. Delayed bone age is also an important diagnostic clue for VWGS, as most other causes of precocious puberty are associated with advanced bone age [22]. In our patient, delayed bone age was indicated on bone scan.

2.2.4. Treatment options

As suggested in Van Wyk and Grumbach's initial report, exogenous thyroid hormone replacement results in negative feedback on pituitary hyperplasia, allowing hypothyroid symptoms to regress [15]. Several reported cases treated VWGS with levothyroxine and followed in the outpatient setting for normalization of lab values and regression of ovarian cysts on serial imaging [3,17,19–21,24,28]. Others followed for resolution of precocious puberty and return of linear growth [4,16,26]. Vaginal bleeding can persist in some patients after starting thyroid hormone replacement due to endometrial hyperplasia from long-term estrogen exposure. Treatment of persistent vaginal bleeding with progestogen was successful in one case series [3].

Several authors have agreed that surgical intervention for ovarian cystectomy or oophorectomy should be reserved for patients who may have associated ovarian torsion, ovarian rupture, hemodynamic instability, or failure to regress with thyroid hormone replacement. In one instance of failure to regress, a post-pubertal patient underwent ovarian wedge resection which showed myxedema and hemorrhage in a benign ovarian cyst [27]. A VWGS patient with severe anemia and hemodynamic instability secondary to persistent vaginal bleeding necessitated bilateral percutaneous ovarian cyst aspiration. The procedure was modeled after aspiration techniques used to treat ovarian hyperstimulation syndrome; the patient's vaginal bleeding resolved [22]. Given our patient's hemodynamic stability and lack of evidence for an emergent indication for surgery once VWGS was established, she was treated with levothyroxine and has had resolution of her menses-like symptoms and advanced Tanner staging. Overall, operative management on ovarian findings in VWGS should be reserved for lack of symptom resolution or normalization of physiology.

3. Conclusion

Through our literature review, we explored the epidemiology, pathophysiology, presentation, and treatment associated with both hypothyroidism in DS and VWGS. Our case study emphasizes the importance of adhering to the AAP's recommendations for screening for hypothyroidism in DS patients, as there can be severe consequences with the development of untreated hypothyroidism in the pediatric patient. Surgery was not performed on this patient; it was appropriately avoided by the recognition of VWGS. With

early recognition of the syndrome, CT or MRI could also have been avoided, as ovarian cyst regression with thyroid hormone replacement can be monitored with serial ultrasounds [4,20,23,25]. The size and complexity of the cysts contributed to concerns of misdiagnosing the child without thorough imaging during her evaluation. By examining this patient's presentation of VWGS associated with untreated autoimmune hypothyroidism, we also hope to encourage practitioners to maintain this rare syndrome in their differential when presented with a pediatric patient with apparent ovarian pathology, and experiencing inconsistent signs of precocious puberty.

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Conflict of interest

The authors declare that they have no conflict of interest.

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