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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.

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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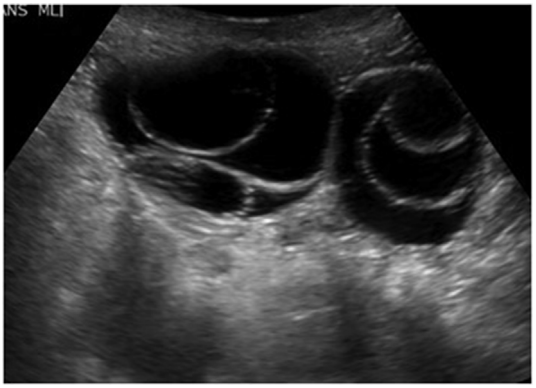

Fig. 1. Patient's ultrasound showing bilateral cystic ovaries.

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

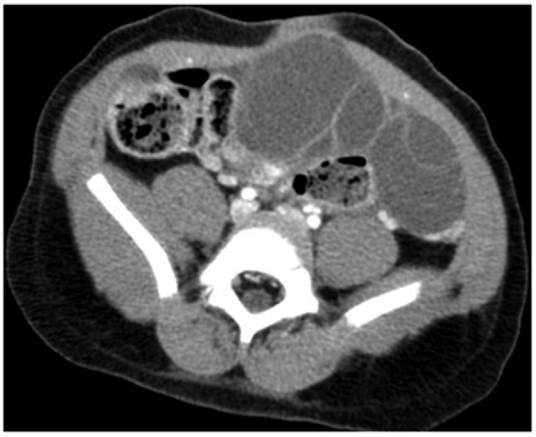

Fig. 2. CT scan showing patient's bilateral adnexal cysts with multiple septations.

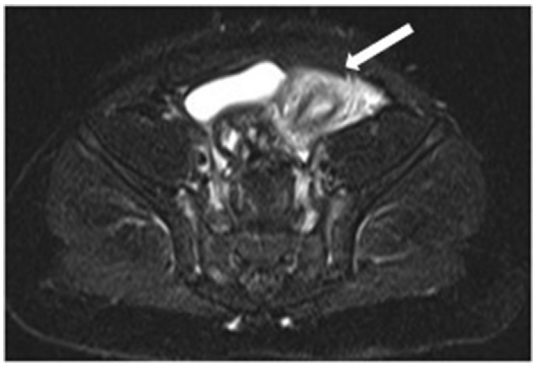

Fig. 3. Patient MRI illustrating her enlarged uterus (white arrow).

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].