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Posted Date: 12 June 2024

doi: 10.20944/preprints202406.0736.v1

Keywords: Puberty, Precocious; Ovarian Cysts; gonadectomy; Van Wyk Grumbach Syndrome

 doi:10.20944/preprints202406.0736.v1

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Van Wyk Grumbach Syndrome and Gonadectomy

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Abstract: Van Wyk Grumbach syndrome refers to the development of peripheral precocious puberty, long-standing hypothyroidism, and gonadal masses; when not diagnosed, an unnecessary gonadectomy may be done; Here we present a case of a 10-year-old girl with Down syndrome, short stature, and vitiligo presented with vaginal bleeding, and a pelvic mass, in whom bilateral gonadectomy was performed. Most cases of Van Wyk Grumbach syndrome present in women, and classic hypothyroidism symptoms always precede the diagnosis; 11% of patients have Down Syndrome, sometimes tumor markers get elevated, and some develop severe symptoms (myopathy, short stature, mental delay, ascites, pericardial effusion, Cullen sign, pituitary hyperplasia, and severe anemia), that respond to levothyroxine treatment; Conclusions: Children with peripheral precocious puberty and gonadal masses, must be studied for hypothyroidism before any radical decision is made.

Keywords: puberty; precocious; ovarian cysts, gonadectomy; Van Wyk Grumbach Syndrome

1. Introduction

Unnecessary gonadectomies are frequent in girls with benign ovarian masses (21 to 77% of cases), resulting in infertility, osteopenia, and increased cardiovascular risk. Preoperative risk stratification algorithms can reduce unnecessary oophorectomies and prevent negative lifelong consequences [1,2].

Hypothyroidism has a significant burden of disease [3]; congenital hypothyroidism affects 1:2000 to 1/4000 newborns, but the screening only covers 30% of them worldwide [4,5]. Hypothyroidism symptoms are subtle and insidious, so populations with high risk, such as people with Down syndrome, must be screened annually to prevent severe symptoms (short stature, pericardial effusion, muscle injury, dyslipidemia, mental retardation) [6].

Thyroid-stimulating hormone (TSH) can activate the human FSH receptor because glycoproteins share a common α-subunit. As a result, hypothyroidism patients may present symptoms related to FSH stimulation, including precocious puberty and ovary cysts[7].

We present the case of a girl with Down syndrome who underwent bilateral gonadectomy for benign cysts caused by a non-treated chronic primary hypothyroidism. Moreover, we analyze the literature related to the Van Wyk-Grumbach Syndrome.

2. Materials and Methods

We present a case and review the literature. In brief, the terms van Wyk Grumbach Syndrome, precocious puberty, ovarian cyst, children, and hypothyroidism were searched in PubMed, Imbiomed, Google Academic, and Scopus. We included all articles that describe Van Wyk Syndrome compatible phenotype. From each article, we described the sex, age at presentation in the hospital, age at first hypothyroidism sign, continent of origin, comorbidities, hypothyroidism typical signs, bone age, height in cm, height in standard deviation by CDC charts, TSH concentration at diagnosis,

 doi:10.20944/preprints202406.0736.v1

pubertal sings, severe hypothyroidism signs, ultrasound findings, surgical treatment. SPSS V25 was used to analyze data.

3. Results

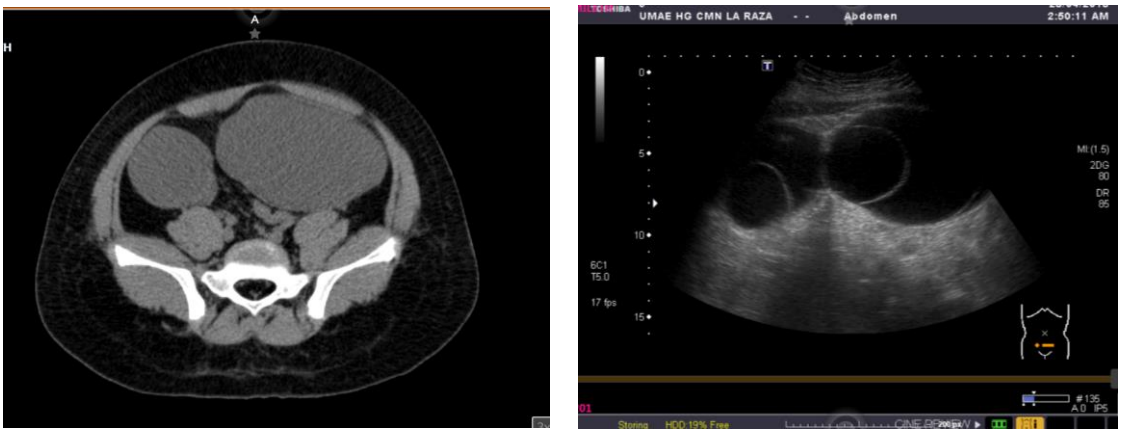
3.1. Case Presentation

A 10 year-old female with Down syndrome (karyotype 47XX(20)+21), vitiligo, and a two-month history of vaginal bleeding presented to Pediatric consultation with abdominal pain. An abdominopelvic ultrasound revealed an ovarian tumor of 21 x 8 cm.

The patient was referred to our hospital, where a second ultrasound found anechoic abdominal lesions with a round, dense material inside. A subsequent CT showed two pelvic lesions of 20 HU, one of 174 cc (right ovary) and the other of 333 cc (left ovary). The left one had a round interior image of 250 HU inside. The radiological diagnosis was adnexal vs. mesenteric cystic tumors (Figure 1a,b). Blood tumor markers were negative (Table 1).

Table 1. Initial laboratory findings in this case.

Laboratory	Result	Normal range
Alpha-fetoprotein	4.86 ng/mL	0 to 7 ng/mL
Carcinoembryonic antigen	3.84 ng/mL	0 to 3.8 ng/mL
Chorionic gonadotropin	<0.10	non detectable
CA-125	25.39 UI/mL	0 to 35 UI/mL
TSH	367.3 mUI/mL	0.27 to 4.2 mUI/mL
Total T4	0.49 mg/dL	5.1 a 14.1 mg/dL
Free T4	0.06 ng/dL	0.93 to 1.7 ng/dL
Total T3	<0.20ng/mL	0.8 to 2 ng/mL
Free T3	1.59 pmol/L	1.73 to 6.3 pmol/L
Anti thyroglobulin	150.5 ()	5 to 100
LH	<0.10 mUI/mL	<0.10 mUI/mL
Estradiol	63.53 pg/mL	Non detectable
FSH	5.19 mUI/mL	0 to 5 mUI/mL
Total cholesterol	305 mg/dL	120 to 200 mg/dL
Triglycerides	332 mg/dL	35 to 135 mg/dL



(**a**) (**b**)

Figure 1. (**a**) Tomography image from two pelvic tumors; (**b**) Ultrasound image from a pelvic tumor.

 doi:10.20944/preprints202406.0736.v1

A bilateral gonadectomy and salpingectomy were performed on the patient, and the histopathological study found normal salpinges, mucinous cystadenoma, and follicular cysts of the ovaries.

Biochemical tests performed after surgery because of Down syndrome showed severe primary hypothyroidism, LH suppression, elevated estrogens, and hyperlipidemia (Table 1). An endocrine-targeted approach of the patient revealed a history of asthenia, bone pain, progressive weight gain, and dry skin one year before surgery, obesity (BMI 59.7 Kg/m2), short stature (120 cm), and signs of peripheral puberty (Tanner stage 1 in breast and pubic hair, and vaginal bleeding).

Finally, a Van Wyk-Grumbach syndrome (severe primary hypothyroidism and isosexual peripheral precocious puberty) was diagnosed; she was treated with levothyroxine, and obesity, dry skin, asthenia, and short stature were resolved. Sexual hormone replacement started at the age of 13 years.

3.2. Literature Review

We found 54 patients reported with Van Wyk-Grumbach syndrome [8–53], most from Asia. Their main characteristics are in Tables 2–8. The age at diagnosis was from 1.5 to 24 years. Every but one [12] case had typical hypothyroidism findings, and short stature was present in more than 60% of the patients. The most common symptoms that led to the diagnosis were abdominal pain and vaginal bleeding. Other manifestations were severe anemia [27,28,30,33], ascites [12,28,35], ovarian torsion [13,52], intracranial mass effect [21], and Cullen's sign [45]. Ultrasound findings included cysts in 80% of cases and complex images in 6.7%. In some cases, tumor markers were measured (31.5%), resulting in positive in less than one-fifth of the cases (18.5%). Although thyroid substitution can reverse ovary cysts, seven patients underwent surgery (13%) (11,24,44,51), and in one case, an oophorectomy was avoided just in time [10].

Table 2. Main characteristics of reports of Van Wyk-Grumbach Syndrome.

Variable	Result N (%) or *median (interquartile range).
Place of report	
Asia	29 (53.7)
America	18 (33.3)
Europe	7 (13)
Female Sex	51(94)
Age at diagnosis years.	9.95 (7.37 to 14)*
Comorbidities	9 (16.6)
Down syndrome	6 (11.1)
Alport syndrome	1(1.9)
Hemangioma	1 (1.9)

Table 3. Hypothyroidism typical findings at presentation.

Variable	n (%) from all studies or *median (interquartile range).	Percentage of studies that report the symptom
Mental retardation	12 (22.2)	13 (24.1)
Edema/myxedema	18 (33.3)	19 (35.2)
Dry skin	22 (37)	22 (37)
Puffy facies	19 (33.3)	19 (33.3)
Hypoactivity or asthenia	23 (38.9)	23 (38.9)
Constipation	13 (24.1)	14 (24.1)
Bradycardia	8 (14.8)	8 (14.8)
Anemia	27 (46.3)	25 (48.1)
Hb g/dL.	9 (7.9 to 10)*	
Alopecia	1 (1.9)	1 (1.9)

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Menstrual irregular rhythm	6 (11.1)	6 (11.1)
Myopathy or muscular weakness	6 (11.1)	6 (11.1)
Short stature	34 (63)	39 (72)
Height (CDC sz)	-3.47 (-2.45 to -4.76)*	
Obesity	15 (27.8)	17 (31.5)
Hypercholesterolemia	7 (13)	7 (13)
Total Cholesterol mg/dL.	345 (299 to 444)*	
Delayed bone age	31 (57.4)	36 (64.7)
Bone age delay, years	-3 (-4 to -1.5)*	
Number of findings		
0	1 (1.9)	
1 to 5	35 (64.6)	
6 to 10	18 (33.5)	
Time from typical hypothyroidism findings to diagnosis, years	2 (1 to 5)	
TSH mUI/mL	490 (100 to 939)*	35 (63.3)
TSH >100	42 (77.8)	
TSH <100	10 (18.5)	

Table 4. Symptoms that led to medical consultation.

Symptom	n(%)
Vaginal bleeding	23 (42.3)
Abdominal pain	15 (27.8)
Abdominal bloating	3 (5.6)
Abnormal menstruation (irregularity or metrorrhagia)	4 (7.4)
Other (ascites, headache, clitoromegaly, Cullen's sign, abdominal mass, precocious puberty, short stature, muscular weakness)	9 (16.6)

Table 5. Puberal or gonadal related findings of hypothyroidism at diagnosis.

Symptom	**n(%)**
Puberal or sexual symptom	
Vaginal bleeding	33 (61.1)
Macroorchidism	3 (5.6)
Clitoromegaly	2 (3.7)
Puberal delay	1 (1.9)

Table 6. Severe findings of hypothyroidism at diagnosis.

Symptom	**n(%)**
Anemia requiring transfusion	2 (3.8)
Ascites	4 (7.4)
Pericardial effusion	5 (9.2)
Intracranial mass effect	1 (1.9)
Cullen's sign	1 (1.9)

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Ovarian torsion	3 (5.5)
Pituitary hyperplasia	18 (33.3)
Hyperprolactinemia	29 (53.7)
Elevated AST	1 (1.9)

Table 7. Gonadal ultrasound findings at diagnosis.

Findings	n(%)
Multiple cysts	23 (51.1)
Cysts	13 (28.9)
Ovarian enlargement	5 (11.1)
Ovarian tumor or complex images	3 (6.7)
Other	1 (2.2)

Table 8. Surgery indications.

Type of surgery	n(%)
Cystectomy	2 (28.5)
Ovary detorsion	2 (28.5)
Ovary biopsy	1 (14.2)
Bilateral oophorectomy	1 (14.2)
Aborted oophorectomy	1 (14.2)

4. Discussion

Van Wyk-Grumbach syndrome is caused by peripheral gonadal stimulation mediated by elevated TSH, which results in peripheral precocious puberty. Absent negative feedback by thyroid hormones causes pituitary hyperplasia. Gonadal enlargement and vaginal bleeding in girls can lead to gonadectomy and subsequent lifetime hormonal function loss [19].

The pathophysiology of Van Wyk-Grumbach syndrome remains unclear. It is associated with variable FSH receptor sensitivity and ovarian overstimulation by elevated TSH. This phenomenon is seen not only in children but also in adults with recombinant TSH treatment [54–56]. Some cases have demonstrated typical FSH receptors.

In almost every case of Grumbach syndrome, hypothyroidism classic symptoms precede precocious puberty, and some symptoms may be severe or life-threatening, such as severe hypercholesterolemia, anemia, intracranial mass effect, myopathy, galactorrhea, or mental retardation. In some reports, ovarian cysts due to hypothyroidism may elevate tumor markers.

In all cases, treatment with levothyroxine reversed the precocious puberty, the ovarian cysts, the tumor marker elevation, and dyslipidemia. Typical symptoms of hypothyroidism were also improved.

As in this case, delayed diagnosis of hypothyroidism results in unnecessary medical visits, tests, and treatments (gonadotrophin tests for precocious puberty, invasive tests for short stature, surgery).

About 11% of patients with Van Wyk-Grumbach syndrome have Down syndrome. Persons living with Down syndrome must be screened for thyroid disorders annually, before any surgery or when another autoimmune disease appears, 50% will develop any thyroid dysfunction in their lives (hypothyroidism 39%, congenital hypothyroidism 7%, hyperthyroidism 3%) [57] [58].

Irreversible treatment decisions in children, such as gonadectomy, must be based on reliable tools to avoid overtreatment and its long-term consequences [2].

Author Contributions: Conceptualization, Arellano-Llamas and Hernández Caballero; methodology, Arellano-Llamas and Hernández Caballero.; software, Arellano-Llamas and Hernández Caballero.; validation, Delgado-

 doi:10.20944/preprints202406.0736.v1

Mendoza and Catalán-Ruiz.; formal analysis, Arellano-Llamas.; investigation, Efren y alejandro.; resources, Arellano-Llamas.; data curation, Arellano-Llamas.; writing—original draft preparation, Arellano-Llamas.; writing—review and editing, Hernández Caballero.; visualization, Hernández Caballero.; supervision, Hernández Caballero.; project administration, Hernández Caballero.; funding acquisition, Hernández Caballero. All authors have read and agreed to the published version of the manuscript." Please turn to the CRediT taxonomy for the term explanation. Authorship must be limited to those who have contributed substantially to the work reported.

Funding: "This research received no external funding".

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board of Instituto Mexicano del Seguro Social (R-2024-3504-023).

Informed Consent Statement: "Written informed consent has been obtained from the patient(s) to publish this paper".

Data Availability Statement: We encourage all authors of articles published in MDPI journals to share their research data. In this section, please provide details regarding where data supporting reported results can be found, including links to publicly archived datasets analyzed or generated during the study. Where no new data were created, or where data is unavailable due to privacy or ethical restrictions, a statement is still required. Suggested Data Availability Statements are available in section "MDPI Research Data Policies" at https://www.mdpi.com/ethics.

Acknowledgments: We acknowledge Instituto Mexicano del Seguro Social for its support.

Conflicts of Interest: The authors declare no conflicts of interest.

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 doi:10.20944/preprints202406.0736.v1