A GIRL WITH TRISOMY 21 PRESENTS WITH VAN WYK-GRUMBACH SYNDROME, A RARE DIAGNOSIS

E.Dikaiakou[1], E.Vlachopapadopoulou[1], I. Kosteria[1], A.Panos[2], E.Dede[2], E.Koutrouveli[3], C.Zouridaki[3], S.Michalacos[1]

[1]Dept.of Endocrinology Growth and Development, Children's Hospital "P. & A. Kyriakou", Athens, Greece
[2]2nd Department of Paediatrics, University of Athens, "P&A Kyriakou" Children's Hospital, Athens, Greece
[3] Radiology Department, Children's Hospital "P. & A. Kyriakou", Athens, Greece

ESPE 2021 The 59th Annual Meeting Online 22-26 September 2021

BACKGROUND

Van Wyk-Grumbach syndrome (VWGS) is a rare diagnosis that should be suspected in children with signs of peripheral precocious puberty and hypothyroidism. It is characterized by multicystic enlarged ovaries, in the presence of long-term severe hypothyroidism. Treatment of VWGS consists of hormonal replacement with levothyroxine. Usually, ovarian cysts and increased ovarian volume subside within an average of 2 months but can persist up to 12 months after treatment.

CASE PRESENTATION

An 8yrs old girl with known Trisomy 21, presented with **recurrent vaginal bleeding** for 3 days prior to admission.

Personal & Family History: She was born full-term, with normal birth weight. Medical history was remarkable for occasional constipation episodes that were treated with dietary interventions.

Physical examination: Her height was 109 cm (5th %ile), her weight was 25 kg (50th %ile), with normal blood pressure (112/74 mmHg) and bradycardic (HR: 74/min). Tanner stages were prepubertal (PH I, AH I, B I). She also appeared sluggish and apathic. Her face and eyelids were puffy (myxedema) and had a protruding tongue, features, that were initially attributed to the typical facies of the syndrome. She had dry skin and shallow lacerations perianally and at the vaginal opening, with an intact hymen. Her thyroid was not palpable.

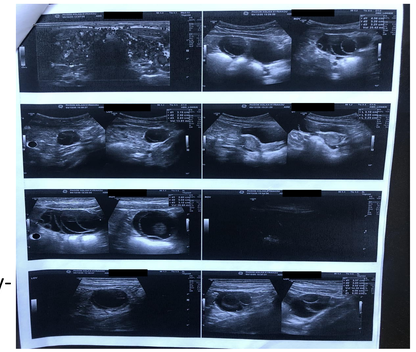
Further evaluation: Causes of vaginal bleeding such as sexual abuse, trauma, foreign body insertion and urethral prolapse were excluded by surgical examination and psychosocial evaluation of the child and the family. Infections were excluded by urine, vaginal and skin cultures. Cardiological evaluation confirmed the bradycardia, and revealed non specific ST abnormalities and a small pericardial effusion surrounding the right atrium.

The constellation of Trisomy 21, myxedema, dry skin, bradycardia and pericardial effusion was suggestive of hypothyroidism and the child was referred for an endocrinologic evaluation.

Laboratory work-up: TSH>1000μIU/ml (0.4-5), fT4: 0.65 μg/dl (0.90-1.90), T3:0.204 ng/ml (0.94-2.41), Anti-Tg: 361.7 IU/ml (<100), Anti-TPO: 521.30 IU/ml (<16) FSH 9,22 m IU /ml (<3,80), LH< 0,1m IU /ml, E2 256,00 pg/ml, B-hCG < 0,1mU/ml, PRL 1832 μIU/ml (58-471)

Imaging:

①*Pelvic ultrasound*
Uterus: 6.39* 3.04*2.22 cm, thin endometrial stripe.
Bilateral ovarian cystic masses (V:3.6*5.04*3.12 cn-26.69 ml and 3.57*3.05*2.52-14,38 ml), right and left, respectively), repressing the ovarian parenchyma peripherally-Functional ovarian cysts



②*Thyroid ultrasound:*
Increased thyroid volume [7,5 ml (<6.9 ml)] Hypoechoic parenchyma, lobulated borders, multiple hyperechoic septa, no focal lesions, increased vascularization
③*Bone age (GP atlas): 6.5 years (CA: 8 years)*

Diagnosis:
Van-Wyk Grumbach Syndrome - Long standing, severe hypothyroidism stimulating isosexual precocious pseudopuberty & multicystic enlarged ovaries

Treatment: LT4 treatment was initiated (4 μg/kg/day), combined with LT3 for 2 weeks. Due to continuing bleeding after 15 days, letrozole was added to treatment for 2 weeks. (2.5 mg/day)

	Pre-treatment	Post -treatment
TSH (μU/ml)	>1000	2.73
fT4 (ng/dl)	0.65	2.52
T3 (ng/ml)	0.204	
FSH (mU/ml)	9.22	0.45
LH (mU/ml)	<0.1	<0.1
E2 (pg/ml)	256	<5
PRL (μU/ml)	1832	

Pelvic Ultrasound		
At diagnosis	15 days later	1 month later
Uterus: 6.39* 3.04*2.22 cm, thin endometrial stripe Bilateral ovarian cystic masses (V:3.6*5.04*3.12 cn-26.69 ml and 3.57*3.05*2.52-14,38 ml), right and left, respectively), repressing the ovarian parenchyma peripherally Functional ovarian cysts	Uterus: 3.95*1.68*1.84 cm Bilateral ovarian cystic masses (1.88.*1.99*2.05 cm and 2.78*1.75*2.03), right and left, respectively	Uterus: maximal diameter 2.46 cm, endometrial stripe 0.9mm, complete regression of ovarian cysts V(R): 1.4 ml V(L): 1.5 ml

DISCUSSION

The VWGS was first described in 1960 by van Wyk and Grumbach and is characterized by long standing profound hypothyroidism, FSH dominant sexual precocity (breast development-vaginal bleeding-macrorchidism), delayed bone age and multicystic enlarged ovaries. Possible mechanisms include **(1) Overlap of TSH, FSH, LH and hCG, all glycoprotein hormones which share a common alpha subunit but different beta subunits and all act through GPRCs. It is believed that TSH, in high concentrations, stimulates the FSH receptor leading to an increase in gonadal size and steroidogenesis (2) Direct TRH effect on FSH secretion**

Other findings include: (1) Hyperprolactinemia, caused by increased TRH and estrogen levels and, in turn, decreases GnRH pulse frequency and leads to the suppression of-mainly-LH (FSH dominant precocity) **(2) Pituitary enlargement**, misidentified as "adenoma", due to the trophic effect of TRH **(3) Hyperpigmentation** (overlap with MSH) **(4) Elevated aFP, CA-125 levels** (produced by cysts)

Patients with Trisomy 21 may have clinical features that overlap with hypothyroidism such as short stature, developmental delay, hypotonia, and dry skin. Increased awareness and regular screening for thyroiditis is of outmost importance, as 13-46% of patients with Trisomy 21 have thyroid autoantibodies which also appear earlier in life.

CONCLUSION

It is important to think about VWGS and investigate for thyroid status during the evaluation of ovarian cysts or isolated premature menarche. Early recognition can eliminate unnecessary extensive workup and/or surgery to remove ovarian cysts, as appropriate treatment with levothyroxine leads to complete remission of symptoms. Children Trisomy 21 are more likely to develop hypothyroidism, so they should be screened annually.

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