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

E. Dikaïakou1, E. Vlachopapadopoulou1, I. Kosteria1, A. Panos2, E. Dede3, E. Koutrouveli4, G. Zouridakis5, S. Michalacos1

1Dept of Endocrinology Growth and Development, Children's Hospital “P. & A. Kyriakou”, Athens, Greece
22nd Department of Paediatrics, University of Athens, “P&A Kyriakou” Children's Hospital, Athens, Greece
3Radiology Department, Children's Hospital “P. & A. Kyriakou”, Athens, Greece

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 hypothryoidism. 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 8-year-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 percentile), her weight was 25 kg (50th percentile), with normal blood pressure (112/74 mmHg) and bradycardic (HR: 74/min). Tanner stages were prepubertal (PH 1, AH 1, B 1). 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 faces 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 no 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: 1000ng/mL (0.4-5), FT4: 0.65 μg/dL (0.90-1.90), T3: 20.24 ng/mL (0.94-2.41), Anti-Tg: 361.7 U/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 mU/mL (58-471)

Imaging:

Pelvic ultrasound

Uterus: 6.39*3.04*2.22 cm, thin endometrial stripe. Bilateral ovarian cystic masses (V:3.6*5.04*3.12 cm-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

Thyroid ultrasound

Increased thyroid volume [7.5 ml (<6.9 ml)] Hypoechoic parenchyma, lobulated borders, multiple hypoechoic septa, no focal lesions, increased vascularization

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

L4T treatment was initiated (4 μg/kg/day), combined with L3T for 2 weeks. Due to continuing bleeding after 15 days, letrazole was added to treatment for 2 weeks. (2.5 mg/day)

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 cm-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 cm), right and left respectively

VE: 1.4 ml (V/L): 1.5 ml

DISCUSSION

The VWGS was first described in 1960 by van Wyk and Grumbach. It 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 “adrenoma”, 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 utmost 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.

REFERENCES