Precocious puberty in a girl with Down syndrome due to primary hypothyroidism

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SUMMARY: Özgen T, Güven A, Aydın M. Precocious puberty in a girl with Down syndrome due to primary hypothyroidism. Turk J Pediatr 2009; 51: 381-383.

Van Wyk-Grumbach syndrome is a rare cause of precocious puberty due to hypothyroidism. We report a case of Van Wyk-Grumbach syndrome in a 4.3-year-old female patient with Down syndrome. She was investigated for hematuria for three months before she was referred to our clinic. Physical examination revealed typical morphologic features of Down syndrome and hypothyroidism. Pubertal development stages were: breast at stage III and pubic hair at stage I. In luteinizing hormone releasing hormone (LHRH) stimulation test, peak LH level remained less than 0.1 mIU/ml. Serum estradiol level was 117.7 pg/ml, which was higher than normal for her age (normal range: 2-15 pg/ml). The pelvic ultrasonographic evaluation revealed bilateral multicystic enlarged ovaries. Serum thyroid stimulating hormone (TSH) concentration was higher than 500 μIU/ml and free thyroxin (FT_4) and free triiodothyronine (FT_3) levels were as low as 0.4 ng/dl (0.7-1.48) and 1.0 pg/ml (1.71-3.71), respectively. L-thyroxin treatment at a dose of 100 μg/m²/day was started. Regression in breast development was obtained after one month and her bleeding did not repeat again. In conclusion, urinary and vaginal bleeding in young children must be clearly differentiated, and hypothyroidism must be investigated in children who have precocious puberty.

Key words: precocious puberty, hypothyroidism, Down syndrome.

The etiology of precocious puberty varies from idiopathic cases to those with an underlying serious illness. Different management protocols may be required[1]. Severe hypothyroidism is one of the rare causes of precocious puberty[1,2]. This condition was first described by Van Wyk-Grumbach[2] in a report of three cases presented with menarche, premature thelarche and galactorrhea.

We report a rare case of precocious puberty due to hypothyroidism in a girl with Down syndrome.

Case Report

A 4.3-year-old girl with Down syndrome was referred to our clinic because of genitourinary system bleeding. Her bleeding had started four months ago and lasted five days in each month. She did not have a history of any drug usage that included estrogens. She was operated for complete atrioventricular defect when she was 10 months old. She had been investigated for hematuria for three months.

On physical examination, she had typical morphologic features of Down syndrome. Her height, height z-score, and weight were 90.8 cm (<3rd percentile), -3.0 and 16.5 kg (25-50 percentile), respectively. Her bone-age and height-age were 1.5 and 2.5 years old, respectively. She had a dull facial expression, dry skin, and myxedema. She had a 2/6 systolic murmur at the left sternal border. Pubertal development was accelerated; breast development was at stage III and pubic hair was at stage I according to Tanner staging system.[3] The thyroid gland was not palpable. Her motor and mental development was retarded. She could not walk or speak.

Laboratory findings are given in Tables I and II. Peak luteinizing hormone (LH) response to luteinizing hormone releasing hormone (LHRH) was less than 0.1 mIU/ml. Serum estradiol level was 117.7 pg/ml higher than normal for her age (normal range: 2-15 pg/ml). Pelvic ultrasonography revealed bilateral multicystic enlarged ovaries. The largest cyst was 27 mm

Table I. Laboratory Findings at Diagnosis

Hb (g/dl)	9.9 (11.5-16)	Glucose (mg/dl)	70 (70-110)
MCV (fl)	75.6 (80-99)	AST (U/L)	19.3 (8-46)
Leukocyte/mm^3	6700 (4000-10000)	ALT (U/L)	12.7 (7-46)
Thrombocyte/mm^3	346000 (130000-400000)	BUN (mg/dl)	10.0 (5-24)
TT3 (ng/ml)	0.38 (0.6-1.81	Cr (mg/dl)	0.8 (0.4-1.4)
TT4 (μg/dl)	1.47 (4.5-10.9)	Calcium (mg/dl)	10.1 (8.1-10.7)
FT3 (pg/ml)	<1.00 (1.8-4.6)	Sodium (mEq/L)	139 (135-145)
FT4 (ng/dl)	<0.4 (0.93-1.70)	Potassium (mEq/L)	4.6 (3.5-5.5)
TSH (μIU/ml)	>500 (0.27-5.5)	Prolactin (ng/ml)	98.61 (1.9-25)
Urine analysis			
Density	1015		
pH	5.5		
Protein	Negative		
Glucose	Negative		
Microscopy	6 red blood cell/HPF, white blood cell negative, slender negative		

Hb: Hemoglobin. MCV: Mean corpuscular volume. TT3: Triiodothyronine. TT4: Total thyroxin. FT3: Free triiodothyronine. FT4: Free thyroxin. TSH: Thyroid stimulating hormone. AST: Aspartate aminotransferase. ALT: Alanine aminotransferase. BUN: Blood urea nitrogen. Cr: Creatine. HPF: High power field (40x magnification).
Reference values are given in parenthesis.

Table II. LHRH Stimulation Test

	0 minute	20th minute	40th minute	60th minute	90th minute	120th minute
LH (mIU/ml)	0.1	0.1	0.1	0.1	0.1	0.1
FSH (mU/ml)	9.7	9.3	9.6	9.5	9.1	9.3
Estradiol (pg/ml)	117				100	

LH: Luteinizing hormone. FSH: Follicle stimulating hormone.

in diameter. The sizes of the left and right ovaries were 50x36 mm and 44x30 mm, respectively.

Serum thyroid stimulating hormone (TSH) concentration was higher than 500 μIU/ml and free thyroxin (FT_4) and free triiodothyronine (FT_3) levels were low as 0.4 ng/dl (0.7-1.48) and 1.0 pg/ml (1.71-3.71), respectively. No autoantibodies (anti TPO and anti Tg) against thyroid gland were detected. Scintigraphy with Tc99 and ultrasonographic neck evaluation revealed a thyroid gland with normal localization and size. She was treated with L-thyroxin at a dose of 100 μg/m^2/day. Regression of breast development was seen after one month and bleeding did not repeat.

Discussion

Presence of myxedema, dry skin, vaginal bleeding, breast development, high TSH and low FT_3, FT_4 levels strongly suggested precocious puberty due to congenital hypothyroidism in the presented case. She had been investigated for months for hematuria. She was referred to our clinic when her doctor noticed the breast enlargement and enlarged ovaries on the ultrasonography. The delay in the diagnosis can be attributed to the difficulty of differentiating between urinary and vaginal bleeding in a child who had diaper and to the absence of a neonatal screening program for hypothyroidism. Additionally, retarded bone age and decreased growth velocity are not usual findings in precocious puberty. Association of hypothyroidism and precocious puberty could explain the pubertal acceleration with bone age retardation. This condition was first described by Van Wyk-Grumbach[2].

It is well known that thyroid dysfunction is a common finding in Down syndrome[4]. Hypothyroidism is a rare cause of precocious puberty.[1] The mechanism of this condition is not clear yet; however, there are several theories to explain the mechanism of precocious puberty due to hypothyroidism. TSH is composed of two subunits (α and β) and the structure of the α subunit is similar for TSH, LH and follicular stimulating hormone (FSH)[5]. High TSH concentration may stimulate ovaries using FSH receptors because of this structural similarity[6]. Another hypothesis involved increased prolactin (PRL) levels, which is an important part of

the syndrome. The stimulation of the pituitary gland by thyrotropin-releasing hormone leads to increased level of TSH and PRL, and the elevated PRL levels may enhance the sensitivity of the ovaries to circulating gonadotrophins by increasing LH receptors of ovaries[7-9]. The PRL level was found increased in our case.

A seven-year-old girl with Down syndrome who had vaginal bleeding due to primary hypothyroidism had been reported in the literature.[10] Clinical, radiological and laboratory findings of our case were similar to that reported case, but our patient was younger.

After two weeks of L-thyroxin treatment, symptoms like myxedema and dry skin resolved. Vaginal bleeding was not seen again and breast development returned to the prepubertal stage after six months of the L-thyroxin therapy.

In conclusion, children with Down syndrome have an increased risk for primary hypothyroidism; however, Van Wyk-Grumbach syndrome is not frequent in children with Down syndrome. In younger children, differentiation between macroscopic hematuria and vaginal bleeding may be difficult, and the diagnosis of precocious puberty may be delayed. Van Wyk-Grumbach syndrome should be considered by the physicians in children with blood on their diaper; therefore, pubertal examinations must be performed carefully for all age groups.

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