A rare endocrine manifestation of Down syndrome: central precocious puberty: three cases report

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ABSTRACT

Background: Although peripheral precocious puberty has been reported due to untreated long-standing hypothyroidism in children with Down syndrome (DS), central precocious puberty (CPP) has been scarcely reported. The aim of this study is to describe our experience with this rare condition.

Case presentation: Three patients (two males and one female) who were receiving treatment for hypothyroidism and admitted with signs of precocious puberty were recruited in the study. Clinical and laboratory findings were compatible with CPP in all three patients with DS. They were euthyroid during investigations for CPP. A male patient had periventricular millimetric focuses in the supratentorial region in cranial magnetic resonance imaging. The other male patient developed central adrenal insufficiency during fallow-up and hence hydrocortisone was added to the treatment. All patients were successfully treated with gonadotropin-releasing hormone analogs; no adverse effects have been observed.

Conclusion: Our findings emphasize that CPP might be seen in rare cases with DS and hypothyroidism.

Keywords: Down syndrome, central precocious puberty, hypothyroidism, leuprolide acetate, case reports.

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Background

Endocrine disorders, especially short stature [1], thyroid dysgenesis [2], and thyroid dysfunction, caused by autoimmune thyroiditis, obesity, diabetes, and osteoporosis are common in patients with Down syndrome (DS). Previous reports have demonstrated that early onset primary gonadal deficiency is also common in patients with DS [3,4].

On the other hand, precocious puberty defined as the appearance of physical and hormonal signs of pubertal development before the age of 8 years in girls and before the age of 9 years in boys is a rare condition in these patients. Till date, there are several reports in the literature regarding peripheral precocious puberty (PPP) due to long-standing untreated hypothyroidism in patients with DS [3-6]. In all published cases, signs of puberty regressed with proper levothyroxine treatment. To the best of author's knowledge, central precocious puberty (CPP) in patients with DS has been reported in only one study thus far [1].

Here, three patients with DS who were treated for hypothyroidism and were diagnosed with CPP were presented; all of them were euthyroid while the signs of puberty began. Our aim is to contribute to the literature with three further cases with this rare condition and to draw attention to the fact that, when the signs of early puberty in DS children are detected, CPP can be seen in these rare cases.

Case presentation

Case 1

A 6 years and 3-month-old female patient with DS was diagnosed with hypothyroidism 6 months prior to admission and treatment with levothyroxine (LT4) was started. She was born to unrelated parents, in the 38th gestational week, and weighted 3630 g following an uneventful pregnancy. A ventricular septal defect was detected in the neonatal period which was closed spontaneously. During follow-up, the patient had pericarditis and acute respiratory distress syndrome. There was no history of precocious puberty in the extended family. The clinical findings of the patient are provided in Table 1.

During follow-up, the dose of LT4 was adjusted according to the thyroid function test (TFT) results. Pubic hair was noticed at 7.24 years, subsequently unilateral breast development compatible with Tanner stage II was detected on her routine examination at 7.56 years. A diagnosis of CPP was made based on clinical and laboratory findings (Table 2). The patient was treated with intramuscular leuprolide acetate 3.75 m/q28d. On follow-up, glandular tissue was regressed completely and no adverse effects were observed. The patient is still on treatment.

Table 1. *Clinical findings of cases.*

	CASE 1			CASE 2		CASE 3	
Gender	Female			Male		Male	
Karyotype	47,XX+21			47,XY+21		47,XY+21	
Age of hypothyroidism diagnosis, years	5.72			0.09		0.09	
	At the admission	**At the pubarche**	**At the diagnosis of CPP**	**At the admission**	**At the diagnosis of CPP**	**At the admission**	**At the diagnosis of CPP**
Chronological age, years	6.24	7.16	7.56	4.4	7.40	8.45	8.96
Bone age, years		8.80	10.48		8.48		6.48
Height-SD	1.02	2.14	2.2	0.49	-0.2	-0.55	-1.1
BMI-SD	-0.34	0.86	1.14	-0.79	-0.72	-0.66	-1.36
Tanner stage of pubarche	1	2	2	1	2	1	2
Tanner stage of thelarche	1	1	2/2	-	-	-	-
Size of testicles on examination	-	-	-	Right 1 ml/ left 1ml	Right 3-4 ml/ left 3-4 ml	Right 2 ml/ left 2 ml	Right 3 ml/ left 4 ml

Table 2. *Laboratory measurements and radiological findings and levothyroxine doses of cases.*

	CASE 1			CASE2		CASE3	
	AT THE ADMISSION	**AT THE PUBARCHE**	**AT THE DIAGNOSIS OF CPP**	**AT THE ADMISSION**	**AT THE DIAGNOSIS OF CPP**	**AT THE ADMISSION**	**AT THE DIAGNOSIS OF CPP**
Levothyroxine dose, mcg/ kg/d	0.92	1.45	1.87	1.66		2.5	
TSH, mIU/ml (N: 0.67-4.7)	4.49	4.69	3.26	1.69	2.51	7.18	0.71
fT4, ng/ml (N: 0.84-1.47)	1.18	1.21	1.41	1.15	1.11	1.16	1.26
Anti TPO, IU/ml (N < 5.6)		0.77			0.77		
Antithyroglobulin, IU/ml (N<4.10)		482			482		
LH, mIU/ml			0.16		0.38		0.61
FSH, mIU/ml			2.87		1.81		9.66
E2, pg/ml			23		-		-
TT, ng/ml			<0.13		0.13		0.1
Peak FSH, mIU/ml			37.03		8.61		36.29
Peak LH, mIU/ml			26.28		7.79		18.05
17OHP, ng/mL (N<2 ng/ml)		0.62			0.28		1.01
DHEAS, mcg/dl		60.8			96		8.96
Pelvic USG			Uterus length 34 mm, left ovary 0.83 ml, right ovary 0.25 ml				
Scrotal USG					Normal		Normal
Cranial and Pituitary MRI					Pituitary size decreased (4.3 mm)		Periventricular millimetric focuses in the supratentorial region
Thyroid USG, volume, ml	5.44 ml, parenchyma echogenicity was normal				2.28 ml, parenchyma echogenicity was normal		1.49 ml, parenchyma echogenicity was normal

Case 2

A male patient with DS who was treated in another clinic due to congenital hypothyroidism was admitted to our clinic at the age of 4.4 years. He was born to unrelated parents, in the 37th week of gestation, and his birth weight was 2,700 g. The dose of LT4 was increased as his serum TSH was found to be elevated on admission. During follow-up, the dose of levothyroxine was adjusted according to the TFT results. A slight testicular enlargement was detected on the physical examination at 7.4 years. He was diagnosed with CPP based on clinical (Table 1) and laboratory findings (Table 2). Treatment with leuprolide acetate was started at a dose of 3.75 mg/q28d intramuscularly. Cranial magnetic resonance imaging (MRI) revealed a hypoplastic pituitary gland for his age. During treatment, testicular volumes of the patient were found to be increased (5 ml), and his bone age was 8.48 years, while the TFTs were within normal limits (TSH: 3.06 m IU/ml, fT4: 1.02 ng/ml). The dose of leuprolide acetate was increased to 7.5 mg and testicular volumes regressed to prepubertal size during follow-up.At the age of 8.8 years, a low dose (1 mcg) adrenocorticotrophic hormone (ACTH) stimulation test was carried out since the patient had a complaint of fatigue. Basal cortisol and ACTH levels were 7.6 mcg/dl and 41.6 pg/ml, respectively, whereas his stimulated cortisol level was 10.2 mcg/dl. Treatment with hydrocortisone was added, with a dose of 10 mg/m^2/d.

Case 3

A male patient with DS receiving LT4 treatment due to congenital hypothyroidism was admitted to our clinic at the age of 8.45 years. He was born to unrelated parents, in the 35th gestational week, and weighted 2,700 g, following an uneventful pregnancy. At the age of 8.96 years, pubic hair developed and enlargement of left testis was detected on examination, these findings suggested a precocious puberty. The patient was euthyroid at that time. Laboratory findings were compatible with CPP (Table 2), while bone age was regressed (6.48 years). Treatment with intramuscular leuprolide acetate was started at a dose of 3.75 mg/q28d. Cranial MRI revealed periventricular millimetric focuses in the supratentorial region, but the pituitary gland was normal. On follow-up, his testicles shrank back to pubertal size.

Discussion

In this article, central precocious puberty detected in three cases, including one girl and two boys with DS who were treated for hypothyroidism, is presented.

Thyroid dysfunctions are often encountered in patients with DS [2]. While delayed puberty is frequently observed in patients with DS and untreated hypothyroidism, PPP is detected in rare cases. Peripheric or gonadotrophin-independent precocious puberty is more common in girls with DS than in boys. The most common cause of PPP in patients with DS is hypothyroidism due to thyroid hypoplasia or autoimmune thyroiditis [6-8]. A number of girls with DS and untreated hypothyroidism who presented with menarche and ultrasonographic examination of these patients revealed several large cysts in the ovaries [3,6,8].

There are limited publications in the current literature regarding the onset and progression of puberty in children with DS. Zemel et al. [9] determined that all patients were prepubertal before the age of 11 in their study, which included 56 children aged 1 day to 15 years and 44 patients older than 15 years with DS. In this large series, no patient with CPP was reported, and puberty was shown to start at an average of 13 years for boys and 12.2 years for girls. Serum gonadotropin levels were measured after 9 years of age in 12 boys and 13 girls in this group; FSH was found abnormally high in eight children (three boys) and LH was found abnormally high in five children (three boys).

Studies in adult males with DS demonstrated higher gonadotrophin levels compared to controls after 30 years of age [10]. However, follow-up studies have shown that there is no statistical difference, although adults with DS have higher gonadotropins than healthy adults [11]. While testosterone levels are not different from healthy adults, estrogen levels were found to be high [11,12]. Previously published studies indicate larger testicular volumes [12] or smaller testicular volumes than controls [11].

It was shown that the mean age of menarche in girls with DS was 13.6 years (SD = 20.9 months) and was not different from the controls. In this study, in which 15 patients older than 10 years with DS were examined, the youngest age of menarche was reported as 11 years [13]. Arnell et al. [1] reported in their long follow-up study of 44 patients with DS that the age of menarche was found to be at the earliest age of 11.8 years and the average age was 13.2 years.

Our two male patients were receiving LT4 for congenital hypothyroidism due to thyroid hypoplasia, and our female patient was receiving levothyroxine for autoimmune thyroiditis. All three patients were euthyroid while puberty findings were noticed. Therefore, CPP diagnosis was made by assessing bone age, by measuring serum gonadotropins, and by carrying out GnRH stimulation test. Cranial MRI was carried out in male patients. Periventricular leukomalacia was detected in Case 3, probably due to premature birth. Space-occupying lesions were not observed in either patient.

In the literature search, CPP in patients with DS was not observed except for the study by Arnell et al. [1]. The authors stated that CPP was detected in two males and one female patient with DS in their study, but they did not provide detailed information, such as the age of puberty onset, serum gonadotropin, testosterone, estradiol levels, and bone ages.

Conclusion

In children with DS and development of sexual characteristics at an early age, PPP should be considered first. On the basis of our experience, we aim to emphasize that gonadotropin-dependent true puberty might be seen in rare cases with DS and hypothyroidism.

What is new?

If signs of puberty develop before the expected time in patients with DS receiving thyroid hormone replacement therapy, it should be considered that these patients may have gonadotropin-dependent central precocious puberty.

Consent for publication

Written informed consent was obtained from the families of the patients.

Ethical approval

Ethical approval is not required at our institution for publishing an anonymous case report.

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Summary of the case

1	**Patient (gender, age)**	6 years and 3-month-old female; 7 years and 5-month-old male; 8 years and 11–month-old male
2	**Final diagnosis**	Down syndrome with hypothyroidism and precocious puberty, central adrenal insufficiency
3	**Symptoms**	Breast development, genital hair, enlarged testicles
4	**Medications**	Levothyroxine, leuprolide acetate, hydrocortisone
5	**Clinical procedure**	Levothyroxine dose was adjusted according to thyroid function test results; leuprolide acetate 3.75 mg/q28 days; hydrocortisone 10 mg/m2/d
6	**Specialty**	Pediatric Endocrinology