Case Report

Testotoxicosis with iron deficiency anemia: A case report

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ABSTRACT

Testotoxicosis is an autosomal dominant disorder causing early-onset peripheral precocious puberty in boys. This condition is predominantly caused by an activating mutation in the luteinizing hormone receptor (LHR) gene, which causes constitutive activation of the LHR, stimulating testosterone secretion in Leydig cells, despite suppression of luteinizing hormone. We are presenting a case report of a 2.6-year-old male child, who is a known case of Global developmental delay and spastic cerebral palsy. He presented with pubic hair development and penile enlargement as noticed by his mother at 10 months of age along with masculine features such as premature virilization of voice, acne, and breath holding spells. On further evaluation, he was diagnosed to have a rare genetic/heredofamilial disorder of testotoxicosis with iron deficiency anemia. The treatment consists of reducing hyperandrogenism in the children (sexual maturation, stature), with ketoconazole or a combination of antiandrogens and aromatase inhibitors. However, unfortunately, the treatment is not highly successful. Further, experience and controlled clinical trials are necessary to clarify the efficacy of combination therapy. Successful treatment can only be evaluated through long-term follow-up of these patients. The presenting case did not come for follow-up after the diagnosis and initial treatment advice.

Key words: Case report, Global developmental delay, Spastic cerebral palsy, Testotoxicosis

Testotoxicosis is a form of gonadotropin-independent precocious puberty, in which boys develop early onset of puberty. The disease presents between 2 and 4 years of age. Patients have accelerated growth, early development of secondary sexual characteristics and reduced adult height. Testotoxicosis is caused by an activating mutation of the luteinizing hormone receptor gene, which leads to increased levels of sex steroids in the context of low luteinizing hormone. The condition may be sporadic or transmitted as a dominant trait. It is only expressed in males [1-4]. There are different treatment regimens, such as combination of bicalutamide (antiandrogen agent) and a third-generation aromatase inhibitor, that are reported to be well-tolerated and successful in slowing bone age advancement and preventing progression of virilization. We report a case of testotoxicosis with iron deficiency anemia and global developmental delay with spastic cerebral palsy.

CASE REPORT

A 2.6-year-old boy was admitted with developmental delay, pubic hair development, and penile enlargement as noticed by his mother at 10 months of age with masculine features, premature virilization of voice, acne, and breath holding spells. The parents of the patient were healthy and had a non-consanguineous marriage. There was a positive history of familial testotoxicosis. Based on the family history, the patient most likely had familial testotoxicosis, but unfortunately, the other family members with probable case of testotoxicosis did not give permission for investigation who had all the presenting features like in our case.

The patient was born near term (36 weeks), small for gestational age weighing 2 kgs, with neonatal hypoglycemia. He developed neck holding and rolled over at the age of 1 year. The patient is presently unable to sit or stand even with support. He has not attained speech and language milestones. He was diagnosed to have spastic cerebral palsy with global developmental delay and is on occupational therapy but is irregular with follow-up.

On physical examination, his height was 94 cm (upper segment: 50 cm, lower segment: 44 cm; US: LS = 1:1.18) and weight was 15.6 kg. His blood pressure was 118/70 mmHg (95th centile 106/76 mmHg). The penile stretch length was 8.5 cm, with pubic hair and undescended testis on the left-hand side. The right testicular volume was recorded as 1.9 cc (Normal range – 0.49–0.91 cc) and left testicular volume was 1.6 cc (Normal range – 0.5–0.86 cc). The sexual maturity rate was observed to be at

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Tanner Stage III. The patient had pallor, bilateral hypereflexia, and hypertonia.

The bone age was determined to be >8 years by the Greulich-Pyle method. The mid-parental height was 162.75±8.5. Ultrasound scan of abdomen and scrotum showed undescended left testis situated in the left iliac fossa just beneath the anterior abdominal wall measuring 2.3×1 cm and right testis measuring 2.5×1 cm of normal size and echotexture.

The routine clinical and endocrinological findings at admission are summarized in Table 1. The patient's serum testosterone level

Table 1: Routine clinical investigations and specific endocrinological investigations

Routine investigations as on August 23, 2019				
S. No.	**Test Conducted**	**Result**	**Inference**	**Reference Range**
1.	Hb%	7.6 g%	↓↓	11–14 g%
2.	Total count	7630/mm^3	N	4000–11,000/mm^3
3.	Differential count			
	Neutrophil:	45	N	35–70%
	lymphocytes:	46	N	14–53%
	Eosinophils:	6	N	2–5%
	Monocytes:	3	N	3–13%
4.	Fasting blood sugar	80mg/dl	N	80–180 mg/dl
5.	Post-prandial blood sugar (PPBS)	94mg/dl	N	100–180 mg/dl
6.	RBCs	5.2 Lakhs	N	3.90–5.3 Lakhs
7.	MCV	53.5	↓	72.7–86.5 µm3
8.	MCH	14.6 pg	↓	24.1–29.4 pg
9.	MCHC	27.3	↓	32.4–35.3%
10.	RDW	17%	↑	13.2±0.9
11.	Menzer index	<11	N	<13
12.	Serum iron	6.0 mcg/dl	↓↓	35–168 mcg/dl
13.	Total iron binding capacity (TIBC)	606 mcg/dl	↑↑	250–450 mcg/dl
14.	Transferrin saturation	0.99 g%	↓↓	20–55 g%
15.	Serum ferritin	4.6	↓	15–230 ng/L
16.	Peripheral smear	MCHC with ADCC tear drop cells/target cells	-	-
17.	Serum calcium	10.5 mg/dl	N	8.5–10.5 mg/dl
18.	Serum albumin	5 g/dl	N	3.8–5.4 g/dl
19.	Phosphorus	4.3 mg/dl	↓	4.5–5.5 mg/dl
20.	Alkaline phosphatase	593 U/L	↑	<281 U/L
21.	Sodium	139 meq/L	N	135–145 mmol/L
22.	Potassium	5 meq/L	N	3.4–5.0 mmol/L
23.	Chlorides	106.1 meq/L	N	98–108 mmol/L
Specific endocrinological investigations				
1.	Total testosterone levels	611.90 ng/dl	↑	1–6 years: <19 ng/dl
2.	Free testosterone levels	10.69 ng/dl	↑	<0.5 ng/dl
3.	DHEAS	30 ng/ml	N	0–44 ng/ml
4.	17-OH progesterone levels	0.81 ng/ml	N	0.03–0.90 ng/ml
5.	LH levels	<0.07 mIU/ml	↓↓	<0.1–6.0 mIU/ml
6.	FSH levels	<0.3 mIU/ml	↓	1.55–9.74 mIU/ml
7.	Baseline serum cortisol levels	8.75 mg/dl	N	3–21 mcg/dl
8.	Beta-hCG	1.74 IU/L	↑	<1.4 IU/L
9.	Alpha-fetoprotein	0.22 mg/ml	N	<15 mg/ml
10.	GnRH stimulation test			
	10 mcg/kg of leuprolide given subcutaneous	• LH-0.6 mIU/ml	N	LH Peak<4mIU/ml (pre-pubertal response)
	• After 4 h sample	FSH-2.5 mIU/ml	N	<4mIU/ml (pre-pubertal response)
	• After 24 h sample	• LH-0.92 mIU/ml	N	<4mIU/ml (pre-pubertal response)
		FSH-1 mIU/ml	N	<4mIU/ml (pre-pubertal response)

***N: Normal ↑: Increased, ↑↑: Significantly Increased, ↓: Decreased, ↓↓: Significantly Decreased, LH: Luteinizing hormone, GnRH: Gonadotropin-releasing hormone, hCG: Human chorionic gonadotropin, MCHC: Mean corpuscular hemoglobin concentration, RBC: Red blood cell, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, RDW: Red cell distribution width, FSH: Follicle-stimulating hormone**

was very high and gonadotropin-releasing hormone stimulation test revealed prepubertal response and adrenal cortex hormone levels were within normal ranges. The findings were suggestive of peripheral precocious puberty with iron deficiency anemia. A normal serum beta-human chorionic gonadotropin (hCG) level excluded presence of a beta-hCG-secreting tumor. The patient met the criteria for the diagnosis of familial male limited precocious puberty, testotoxicosis. Testicular biopsy and orchidopexy were advised after 1 month of oral iron.

DISCUSSION

Testotoxicosis usually becomes symptomatic by 2–4 years of age [5]. However, in some cases, the clinical signs and laboratory findings of puberty appear earlier. Teles *et al*. [6] reported a healthy 10-month-old male baby investigated due to an older brother with familial testotoxicosis. In our case, the symptoms of precocious puberty were missed in the earlier evaluations.

Genetic workup is useful in patients with testotoxicosis, especially for diagnosis and follow-up. Several mutations were reported in Caucasian, Afro-American, and Brazilian populations. There has been genetic heterogeneity, but mutations were usually sited in exon 11 [5]. Our patient had family history of testotoxicosis as reported by his mother. But that, case was not evaluated and genetic studies were not done due to non-co-operation from the parents.

The treatment consists of reducing hyperandrogenism in children (sexual maturation, stature), with ketoconazole or a combination of antiandrogens and aromatase inhibitors [6-9]. Bicalutamide as an anti-androgen medication and anastrozole as an aromatase inhibitor have been proposed as agents that can be safely used in children [7]. The treatment is not highly successful, but if the parents are willing, combination of bicalutamide and anastrozole can be tried with a regular follow-up.

Parents were advised to start the child on bicalutamide and anastrazole, regular neurodevelopmental rehabilitation and timely follow-up. They were also counseled about the risk of transmission during subsequent pregnancy. In contradiction to the above-mentioned treatment strategies, a letter to the editor from Evliyaoğlu, mentioned that they could not see any benefit from bicalutamide treatment in our patients, whereas ketoconazole treatment is promising in short term [10]. Long-term studies with more patients are necessary for evaluation of the agents regarding prognosis, treatment efficacy, and long-term effects on adult height, fertility and on the metabolic parameters.

CONCLUSION

It is extremely difficult to treat a case with multiple genetic and congenital anomalies with the less hope for successful treatment. The risk of transmission is high in subsequent pregnancies. Successful treatment can only be evaluated in long-term follow-up of these patients.

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