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Case report

Central Precocious Puberty in an Infant with Sotos Syndrome and Response to Treatment

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What is already known on this topic?
Sotos syndrome is characterized by overgrowth, typical facial appearance, learning disability. While advanced bone age can be detected in some cases, precocious puberty reported only in three cases until now

What this study adds?
In some specific syndromes with precocious puberty such as Sotos syndrome, treatment can be difficult, maximum dose GnRH analog could not successful for control of pubertal progression. Cyproterone acetate would be aid for benefit of treatment.

Abstract
Sotos syndrome is characterized by overgrowth, distinctive facial appearance, and learning disability. It is caused by heterozygous mutations, including deletions of *NSD1* located at chromosome 5q35. While advanced bone age can occur in some cases, precocious puberty (PP) is reported only in three cases until now.
Here, we reported a case of Sotos syndrome diagnosed at the infancy period with central precocious puberty. The discovery of potential factors that trigger puberty is one of the central mysteries of pubertal biology. Depot gonadotropin-releasing hormone (GnRH) analogs constitute the first-line therapy in central precocious puberty (CPP), which has proven to be both effective and safe. In our cases, leuprolide acetate in maximum dose could not be successful for the control of pubertal progression, and cyproterone acetate (CPA) was added to therapy. Then, pubertal progression was controlled.
In some specific syndromes with precocious puberty, such as Sotos syndrome, treatment can be challenging. Cyproterone acetate would be an asset for the benefit of treatment.
Keywords: Sotos syndrome, Precocious Puberty, NSD1, cyproterone acetate

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Introduction

Sotos syndrome (SS) is a rare syndrome with an incidence of approximately 1 in 14,000 live births (1). This childhood overgrowth syndrome of prenatal onset is characterized by increased birth length or head circumference typically greater than two standard deviations from the mean, distinctive facial features, excessive growth during the first four years, and advanced bone age. Children with SS have macrodolichocephaly, broad and prominent forehead, and bitemporal narrowing (2). Also, they may present with neonatal hypotonia, delays in motor development and intellectual disabilities (2). The majority of cases have the mutation of nuclear receptor-binding SET domain-containing protein 1 (*NSD1*), which occur mostly de novo (3). SS results from the loss of function mutations, primarily truncating mutations and whole gene deletions (1,4,5) .The four major diagnostic criteria were based on the systematic assessment of 41 typical cases as overgrowth with advanced bone age, macrocephaly, distinctive facial appearance, and learning difficulties. Features of this syndrome reevaluated after the identification of *NSD1* mutations, and the Childhood Overgrowth Collaboration Consortium reviewed the clinical features of cases with *NSD1* abnormalities (6).
Several endocrine problems could occur in SS (7). While advanced bone age can be detected in some cases, precocious puberty (PP) reported only in three cases until now, and the reason for PP remains unknown (8,9,10). Also, long time follow-up characteristics and response to treatment had not been discussed in the literature. Here, we reported a case of SS associated with central precocious puberty (CPP) and the difficulties of its management.

Case: A 6.5-month-old male infant presented with neuromotor delay and macrogenitalia. He was the second child of non-relative parents, and his birth-weight was 4200g. There was no pathological feature in physical examination, excluding the height as 81 cm (SDS: +5.6), testicular volumes as 4 ml bilaterally, and penis length as 6.7 cm. Mild facial dysmorphism with global developmental delay was noticed. High basal testosterone level (88 ng/dl), and high basal and stimulated gonadotropins (basal luteinizing hormone (LH): 1.56 mIU/ml, basal follicle-stimulating hormone (FSH): 1.02 mIU/ml, stimulated LH: 43.3 mIU/ml, stimulated FSH: 3,65 mIU/ml) confirmed the CPP. Cranial imaging studies revealed normal

pituitary gland with dilated perivascular cavities in subcortical white matter, dilatation of cerebral lateral ventricles, and cavum septum pellucidum. The patient's bone age was found to be one-year-old.
GnRH analog at a dose of 250 mcg/kg/month was started. Due to the inefficient hypothalamic-pituitary-gonadal (HHG) axis control, the GnRH analog dose increased to 500 mcg/kg/month. At the age of 2.5, an increase of testicular volume to 8 ml and penile length to 9 cm was observed, and his bone age advanced to 4.5 years by 20 months of treatment with GnRH analog. The basal LH level was 1.6 mIU/ml, and the basal testosterone level 58 ng/dl. Because of the pubertal progression and unsuccessful suppression of LH and testosterone level, cyproterone acetate (CPA) 50 mg/day was added to his treatment. Over the next three years with combined treatment, the patient's clinical and laboratory progression was finally controlled. At the last examination, he was 6.24 years old, and his height was 139 cm (SDS: +4.52). The patient's testicular volume regressed to 5 ml, and basal testosterone level was suppressed to prepubertal level. **Laboratory results of the patient before and during treatment have been shown in Table 1.**
As his phenotype resembled Sotos syndrome, we performed *NSD1* analysis, and a heterozygous mutation NM_022455.4: c.5177C>G (p.Pro1726Arg) was detected. This variant not found in gnomAD exomes and gnomAD genomes. There are several other pathogenic mutations very near this codon in this gene. Pathogenic computational results detected based on 12 pathogenic predictions from BayesDel_addAF, DANN, DEOGEN2, EIGEN, FATHMM-MKL, M-CAP, MVP, MutationAssessor, MutationTaster, PrimateAI, REVEL and SIFT versus no benign predictions. ClinVar classifies this variant as Pathogenic. That's why this variant evaluated as pathogenic due to ACMG criteria. Informed consent was received from his parents.

Discussion:

Sotos syndrome is characterized by overgrowth and typical facial features, but other clinical features and their molecular bases have been identified as well. Additional features may be present potentially as a consequence of micro-deletions encompassing other genes in addition to *NSD1* (11,12). Our patient was large for his gestational age (birth weight was 4200 gr, gestation age was normal). He had distinctive facial features with macrodolichocephaly, marked frontal bossing, long and thin face besides global developmental delay. While CPP was the most striking feature of the patient, other clinical characteristics were compatible with SS. He was clinically considered SS, then *NSD1* analysis was performed, and a heterozygous mutation NM_022455.4: c.5177C>G (p.Pro1726Arg) was detected.
Many benign and pathogenic variants of *NSD1* have been identified. However, the way how functional abrogation of *NSD1* results in SS remains unknown. It is thought that there may be a link between SS and rat sarcoma–mitogen-activated protein kinase (RAS-MAPK) signaling pathway, which is downregulated in SS (13). RAS-MAPK pathway, also known as the Ras-Raf-MEK-ERK (MAPK/ERK). On the other side, the Ras interacting protein 1, a downstream Ras effector interfering with the MAPK/ERK pathway, is identified upregulated in SS (14).The deregulation of the MAPK/ERK-signaling cascade causes a hypertrophic differentiation of *NSD1*-expressing chondrocytes with subsequent statural overgrowth and accelerated skeletal maturation in patients with SS (14).
Our case was presented with CPP at a very early age. CPP in SS is an infrequent condition, although some endocrine problems such as hypoglycemia, hypothyroidism, hypospadias, and cryptorchidism in infancy could occur (7).
Cases such as ours caused by central activation of the HHG axis are referred to as CPP, the etiology of which can be idiopathic, familial, or secondary to structural brain anomalies (15,16). CPP may have critical underlying causes, including acquired and congenital central nervous system (CNS) lesions or congenital causes without CNS lesions, such as complex syndromic phenotypes with or without known chromosomal abnormalities or genetic changes. Most of the time, the common cause of CPP in females is idiopathic, while in males, there is usually an underlying pathology. CPP may develop in infancy in male patients with organic lesion (17).
For SS, only three cases with precocious puberty have been reported until now in the literature (8,9,10). The first case with CPP of SS was reported in 1995. Although we could not obtain detailed information about this case, she was reported to have premature pubarche and premature pubertal development (8). Second case was presented at the European Society for Paediatric Endocrinology (ESPE) meeting at 2016. He was diagnosed at 6.8 years of age as CPP with a global developmental delay. *NSD1* gene deletion was determined after the diagnosis of precocious puberty. This case had normal pituitary and brain magnetic resonance imaging (MRI) (9). As the third case, a 3-month-old boy reported by Saniya Gupta et al., presented with enlargement of genitalia and rapid growth noticed since birth was diagnosed CPP and SS, and genetic analysis identified a pathogenic heterozygous mutation in the *NSD1* gene (c.2362C>T; p. Arg788Ter) (10).
The pathogenesis of CPP is not yet fully understood in this syndrome. Some structural brain abnormalities, which usually develop in SS, might induce CPP by activating the HHG axis. In our patient, cranial MRI revealed brain formation anomalies (dilatation of cerebral lateral ventricles and cavum septum pellucidum), but the hypothalamus and hypophysis were normal. However, the cause of CPP could not be related to such cranial structural abnormalities since not all SS cases have CPP despite having similar radio imaging features. A disorder of the central activation of the HHG axis is likely, although the underlying pathophysiological mechanism is not yet to be determined (13).

Many factors that regulate the timing of puberty remains unclear despite recent advances. Some syndromes associated with disorders of pubertal timing provide opportunities to identify genetic regulation of puberty. RASopathies are developmental disorders caused by heterozygous activating germline mutations in rat sarcoma–mitogen-activated protein kinase (RAS-MAPK) pathway genes. RAS-MAPK pathway, also known as the Ras-Raf-MEK-ERK pathway, plays a central role in signal transduction from extracellular stimuli to the intracellular environment (18,19).

The RAS-MAPK pathway is one of the pathways involved in the regulation of the GnRH receptor signaling cascades. GnRH receptor signaling results in the secretion of LH and FSH. Therefore, genetic abnormalities in this pathway could theoretically lead to either delayed or precocious pubertal development. Because the RAS-MAPK pathway is one of the intracellular signaling pathways, although, as with precocious puberty, this association's exact etiology is not fully understood (20). It can be speculated that CPP in SS may be associated with these RAS-MAPK signaling pathways and

NSD1 gene relationships. Because of this unusual clinical condition, it is important to report such cases and find common points to help understand the etiology. Besides, future comprehensive studies of pubertal development in patients with SS will help to explore the pathophysiological relevance of mechanisms underlying the precocious onset of puberty in these disorders.

Although some cases showed difficulties with standard doses, GnRH analog treatment could effectively control the CPP in most cases (21). In our case, GnRH analog treatment in high doses could not effectively control the CPP, so CPA was added to therapy.

CPAs have both antigonadotropic and antiandrogenic features. In addition to blocking the GnRH analogs initial stimulatory effect on the pituitary somatotrophs, CPA has antiandrogenic activity, partly due to its Adrenocorticotropic Hormone (ACTH) suppressing activity but also to a direct antiandrogen effect (22). Over 20 months of treatment with GnRH analog the patient's basal LH was 1.6 mIU/ml, basal testosterone level 58 ng/dl, and his bone age advanced to 4.5 years. Because of the pubertal progression and unsuccessful suppression of the LH-testosterone level, CPA 50 mg/day was added to treatment. CPA is a beneficial therapy in central precocious therapy with gonadotropin suppressing and androgen inhibiting effects, which was not controlled by GnRH analog treatment.

Over the next three years with combined treatment, the patient's clinical and laboratory progression was finally under control.

CPA has adverse effects, mainly in adults and with high doses.[20] We found no alterations in liver function tests during three years of experience with CPA, which was checked routinely.

In conclusion, CPP can very rarely accompany SS, and overgrowth can be related either to syndrome itself or precocious puberty. Treatment can also be very challenging with a required high dose and combined treatment. Although we can not explain the reason for CPP in SS, it can be related to mutation characteristics of *NDS1* or other underlying reasons that need to be demonstrated. Also, the CPA can help control the pubertal progression.

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Age (year)	Bazal LH (mIU/ml)	Bazal FSH (mIU/ml)	Testosteron (ng/dl)	Peak LH (mIU/ml)	Peak FSH (mIU/ml)	Treatment
0.6	1.02	1.56	88	43.3	3.65	GnRH a (250 mcg/kg/month)
1.28	3.52	0.39	67	6	0.54	GnRH a (500 mcg/kg/month)
2.5	1.61	0.13	58	6.5	0.53	GnRH a (500 mcg/kg/month) + Cyproterone acetate
6.24	1.2	0.2	<10	3.1	0.36	GnRH a (500 mcg/kg/month) + Cyproterone acetate

Table 1.