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A CASE OF SOTOS SYNDROME CAUSED BY A NOVEL VARIANT IN THE NSD1 GENE: A PROPOSED RATIONALE TO TREAT ACCOMPANYING PRECOCIOUS PUBERTY

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Abstract

Sotos syndrome is characterized by overgrowth, macrocephaly, distinctive facial features, and learning disabilities and is associated with alterations in the nuclear receptor binding SET domain protein 1 (NSD1) gene. Due to the advanced bone age, the eventual adult height is usually at the upper limit of normal. In this case report, a 6-year and 10-month old boy who presented with Sotos syndrome was described. He also had increased testicular volumes with advanced bone age. The stimulated levels of gonadotropins revealed central precocious puberty and brain magnetic resonance imaging (MRI) showed a pineal cyst. A heterozygous duplication variant [NM_022455.4:c.4560dup; p.(His1521Thrfs*9)] in the NSD1 was identified. Triptorelin acetate treatment was started. The aim was to report the novel duplication variant in the NSD-1 in a patient with Sotos syndrome accompanied by a pineal cyst and central precocious puberty, and also to discuss the rationale for treating precocious puberty.

Keywords: Central precocious puberty, GnRH analogue, NSD1 gene, Pineal cyst, Sotos syndrome.

INTRODUCTION

Sotos syndrome (OMIM#606681) (SS) is characterized by a distinctive facial appearance, learning disabilities and an advanced growth (1,2). Growth velocity is increased in early childhood but decreases especially after puberty and the final height is usually within the upper limit of normal. This normalization is thought to be due to the advanced bone age, which is also a characteristic of this syndrome (1). Early motor development is often delayed and the great majority of patients have some degree of intellectual impairment ranging from mild to severe. The disease course may be further complicated by attention deficit hyperactivity disorder (ADHD), anxiety, aggression, tantrums and autism spectrum disorder (ASD). In fact, anxious behaviour is more prevalent in SS than in intellectual disabilities due to other reasons (3). Neuroimaging abnormalities are common including dilatation of cerebral ventricles and midline changes. A small cerebellar vermis, an increased bilateral frontal subarachnoid space, bilateral optic nerve hypoplasia, Arnold-Chiari malformation type 1, cerebral cortical atrophy, megaloencephaly and pituitary incidentaloma may rarely associate (4-11). Cardiac, renal, ophthalmological and vertebral abnormalities and hypoplastic nails have also been reported in SS (1).

Haploinsufficiency of the nuclear receptor SET domain-containing protein 1 (NSD1) gene located on chromosome 5q35 is the major cause of the syndrome (1). The NSD1 is a histone methyltransferase that catalyzes methylation of nucleosomal histone H3 lysine 36 (H3K36) and is primarily associated with transcriptional activation (12). Intragenic mutations or 5q35 microdeletions and exon deletions have been reported as NSD1 abnormalities in SS (1). In the present case, a novel heterozygous variant, c.4560dup (p.His1521Thrfs*9) in exon 12 of the NSD1 was identified. The authors also aim to discuss the rationale to treat CPP in a case with SS, in which short stature due to the accelerated sexual maturation is not an expected problem.

CASE REPORT

Clinical findings

A boy was referred from Pediatric Neurology

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because of tall stature at 6 years and 10 months of age. The child comes from a consanguineous couple, after an uncomplicated gestation. He was born at 40 weeks of amenorrhea. The birth weight was 4320 g (+2.09 SDS), the height was 58 cm (+3.64 SDS) and the head circumference was 38 cm (+2.22 SDS). His parents reported that he had always been taller than his peers and displayed delayed neurological developmental steps. He was followed up for an atrial septal defect, tricuspid and mitral insufficiency and pulmonary hypertension. He also had hyperopia and amblyopia. A Wechsler lntelligence Scale for Children Revised (WISC-R) test performed at 34 months of age demonstrated a verbal quotient score of 81, a performance quotient score of 82 and a full-scale intelligence quotient score of 86.

At presentation, the height, weight and head circumference measurements were 133.6 cm (+2.63 SDS), 32.5 kg (+2.14 SDS), and 57 cm (+3.46 SDS), respectively. Macro-dolicocephaly, sparse fronto-temporal hair, a prominent forehead, a long narrow face with a prominent chin and down-slanting palpebral fissures were remarkable. He had kyphoscoliosis and distinctive nail hypoplasia (Fig. 1). Bilateral testicular volumes were 6 mL with no pubic hair. The stretched penile size was 6.5 cm. The mid-parental height was 171 cm (-1.1 SDS).

The bone age was 9 years. The luteinizing hormone (LH) level was 0.19 mIU/mL (N: 0-1.03 mIU/mL), follicle stimulating hormone (FSH) level was 0.21 mIU/mL (N: 0.95-11.95 mIU/mL) and total testosterone level was 0.19 ng/mL (puberty stage 2: 0.18-1.5 ng/mL). Considering his bone age of 9 years, a luteinizing hormone-releasing hormone (LHRH) stimulation test was performed. The stimulated levels of the gonadotropins showed central precocious puberty (CPP) (peak LH: 9.1 mIU/mL, peak FSH: 1.3 mIU/mL) (Table 1). Brain magnetic resonance imaging (MRI) revealed a pineal cyst 8x6 mm in size, bilateral dilated ventricles, a thin corpus callosum, cavum septum pellucidum and vergae (Fig. 2). Electroencephalography findings were normal. Hormone tests for further pituitary dysfunction were normal. In the light of these

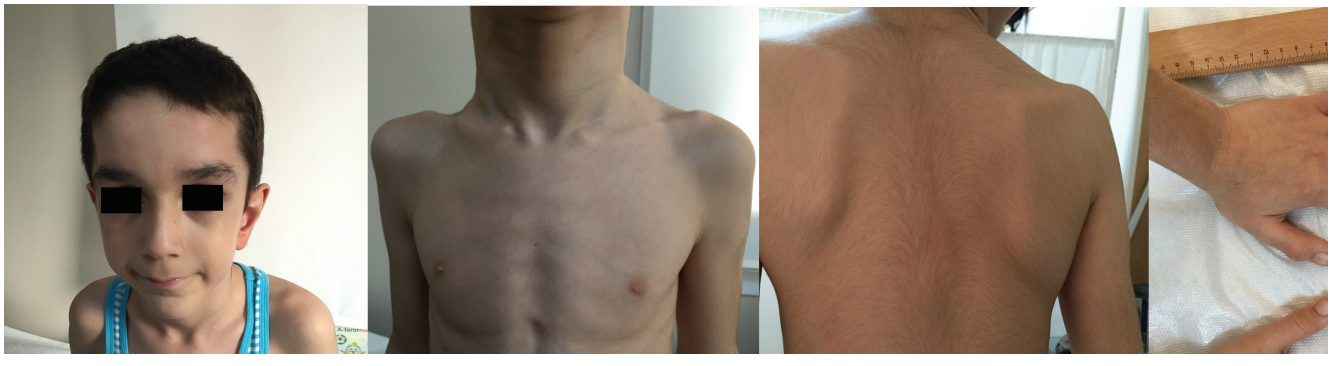

Figure 1. Facial gestalt (macro-dolicocephaly, sparse fronto-temporal hair, a prominent forehead, a long narrow face with a prominent chin), kyphosis and nail hypoplasia of the patient (consented by parents).

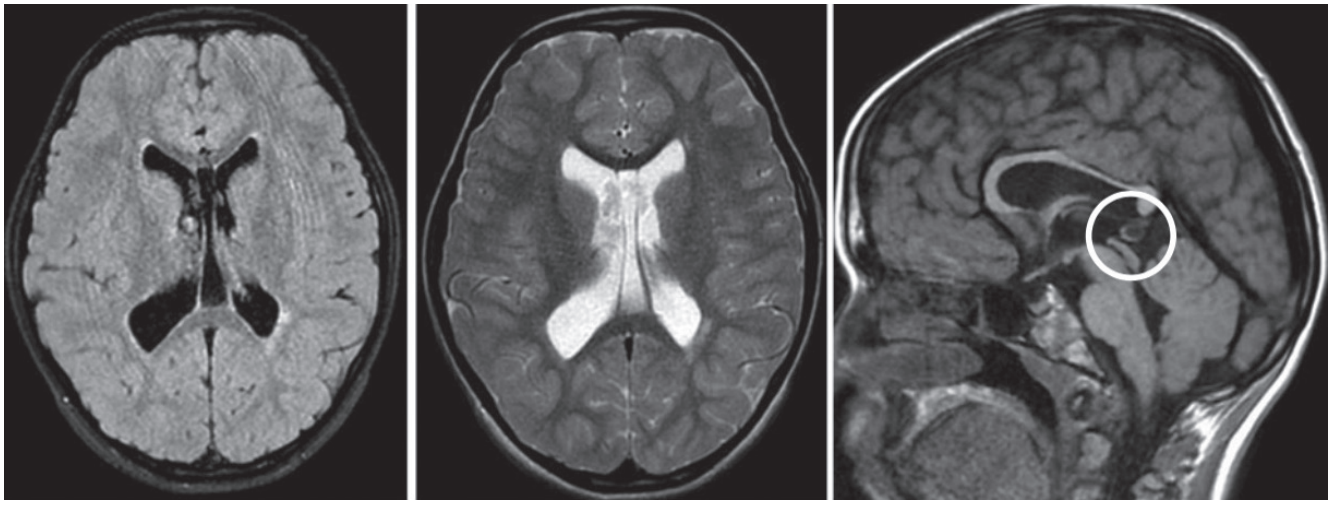

Figure 2. MRI findings of the patient (bilateral dilated ventricles, hydrocephalus, thin corpus callosum, pineal cyst shown in the white circle).

findings such as overgrowth, macrocephaly distinctive facial appearance and learning disability the patient was clinically diagnosed with SS.

Follow-up and treatment of the patient

At the age of 7 years 6 months, the height was 138.6 cm (+2.86 SDS) and the weight was 37 kg (+2.55 SDS). The height velocity was 5 cm in 7 months (8.6 cm/year). Bilateral testicular volumes increased to 8 mL. The stretched penile size was 6.5 cm without pubarche. The LH, FSH and total testosterone levels were 0.36 mIU/mL, 0.3 mIU/mL and 0.28 ng/mL respectively (Table 1). The bone age was 10 years and neuroimaging findings were the same as were on the previous brain MRI (Table1). The parents reported that he experienced problems at school because of his tall stature and accelerated sexual maturation. He refused to attend school because his overgrowth was negatively affecting his relations with his classmates and learning. A pediatric psychiatry consultation revealed a severe anxiety disorder. Because of psychosocial problems and school refusal due to accelerated growth and puberty, triptorelin-acetate treatment was started with a dose of 3.75 mg/28 days.

At one year of the treatment, the height was 146.1 cm (+3.28 SDS) and the weight was 42 kg (+2.64 SDS). The height velocity decreased from 8.6 cm/year to 7.5 cm/year. Bilateral testicular volumes and the stretched penile size remained unchanged and the bone age was 10.5 years. The parents reported reduced anxiety with no school rejection. The LH level after gonadotropin-releasing hormone analogue (GnRHa) injection was 1.48 mIU/mL (<2.1 mIU/mL), suggesting adequate suppression of the gonadotropin axis (13) (Table 1). Treatment with a GnRHa seemed to provide a satisfactory improvement in terms of psychosocial adjustment with his peers by delaying both his sexual maturation and pubertal growth acceleration.

Finally after 18 months of the treatment, the height was 150.5 cm (+3.41 SDS), the weight was 48 kg (+2.6 SDS) with bilateral testicular volume of 8 mL, pubarche at Tanner stage 2, stretched penile size of 9 cm and the bone age of 12 years with a predicted adult height of 185 cm (+1.22 SDS). The LH, FSH and total testosterone levels after GnRHa injection were 2.2 mIU/mL, 0.29 mIU/mL and 0.59 ng/mL respectively (Table 1). A dose increase was considered to be needed because of the absence of clinical and laboratory suppression (13). Later, the treatment had to be switched to another GnRHa, since triptorelin-acetate could not be found on market. At present the patient is receiving leuprolide-acetate with a dose of 11.25 mg / 3 months. The efficacy of treatment will be monitored with evaluation of pubertal development and linear growth velocity along with periodic bone age assessment annually and adult height prediction. We plan to continue treatment until the chronological age of 12 years or bone age of 13-13.5 years, as recommended in boys with CPP (14). The informed consent has been taken from the parents.

Molecular analysis of the NSD-1 gene

The clinical diagnosis of SS was confirmed by molecular genetic analysis. DNA sequencing analysis showed a novel heterozygous duplication variation (c.4560dup; p.His1521Thrfs*9) in exon 12 of the NSD1 gene, which has not been reported in the medical literature or has not been listed in the population frequency databases (http://exac.broadinstitute.org, http://gnomad.broadinstitute.org). Sanger sequencing confirmed the presence of the variant in the proband and its absence in both parents. This variation was thought to cause a frameshift and eventually a premature termination codon.

Table 1. Clinical and laboratory findings of the patient at presentation and under the treatment

Age (year)	Height (SDS)	Weight (SDS)	Testicular volume (mL)	Bone age (year)	LH (mIU/mL)	FSH (mIU/mL)	Total T (ng/mL)	LHRH stimulation test	Treatment
6.8	133.6 cm (+2.63 SDS)	32.5 kg (+2.14 SDS)	6 mL/6 mL	9	0.19	0.21	0.19	pLH: 9.1 mIU/mL, pFSH: 1.3 mIU/mL	-
7.5	138.6 cm (+2.86 SDS)	37 kg (+2.55 SDS)	8 mL/8 mL	10	0.36	0.3	0.28	-	triptorelin-acetate 3.75 mg/28 days
8.5	146.1 cm (+3.28 SDS)	42 kg (+2.64 SDS)	8 mL/8 mL	10.5	1.48	-	-	-	triptorelin-acetate 3.75 mg/28 days
9	150.5 cm (+3.41 SDS)	48 kg (+2.6 SDS)	8 mL/8 mL	12	2.2	0.29	0.59	-	leuprolide-acetate 11.25 mg /3 months

FSH: follicle stimulating hormone, LH: luteinizing hormone, LHRH: luteinizing hormone-releasing hormone, pFSH: peak follicle stimulating hormone, peak pLH: peak luteinizing hormone, Total T: total testosterone.

DISCUSSION

In our patient, SS was caused by a novel heterozygous duplication variation and was accompanied by CPP which was unclear whether it was associated with the pineal cyst shown by brain MRI or was idiopathic. Pubertal timing and progress are not very well defined for SS due to a limited number of case series in the literature. Martin-Herranz *et al.* (15) have recently reported that the loss of function mutations in the H3K36 histone methyltransferase NSD-1 accelerated epigenetic aging and that the normal aging process and SS shared methylation changes. They concluded that some of the methylomic alterations normally affecting the epigenome with age occurred at a faster rate in patients with SS than their healthy peers during their lifespan as opposed to the idea that the Sotos epigenetic changes were only acquired during prenatal development and remained constant afterwards (15). This interesting condition may play a role on the early pubertal progression in this syndrome.

Testicular volumes of larger than 4 mL and a stimulated LH level of >5 mIU/mL confirm the diagnosis of CPP in a boy younger than 9 years of age. Expert reports recommend that it is reasonable to consider GnRHa treatment in boys with progressive central puberty if they present before 9 years of age (14). However, management of a patient with an overgrowth syndrome and associated CPP is challenging since the treatment strategy for early puberty should consider the potential loss in the adult height. Accelerated bone age is the main reason of final height loss in early puberty (14). However, it is also a distinctive feature of patients with SS, which in turn provides an adult height at the upper limit of normal. That means, patients with SS can be considered to have little or no risk for a shorter stature than the target height in relation to their parents even if the puberty is accelerated.

Early developmental delay and learning disability, which are common features of SS, were present in our patient. Brain MRI revealed a pineal cyst of 6x8 mm in size. Pineal cysts have previously been reported to be associated with CPP (16). Although the prevalence of pineal cysts is reported to be 1.9% in healthy pediatric population, the presence of a pineal cyst has not been reported in a patient with SS (17).

As mentioned before, advanced bone age with overgrowth is common in SS (18). Büyükgebiz *et al.* (7). have previously reported a Turkish boy with SS at the age of 12.2 years with testicular volumes of 10 mL and a bone age of 14 years. Our patient was only 6 years and 10 months old when puberty was identified and increase in testicular volumes, somatic growth and bone age were notable within the 7 months of follow-up. Although we can speculate that the pineal cyst could be the underlying cause of early puberty or the rapid progression, it is difficult to conclude that there is a relationship between SS and the pineal cyst and accompanying CPP.

In previous studies, the majority of individuals with SS were found to have intellectual disability and behavioral problems such as aggression, ASD, ADHD and anxiety (3). Patients with CPP may also experience significant social and behavioral problems (19). In our case, when the negative effects of both SS and CPP became apparent and keen reluctance of the child to attend school, we started GnRHa treatment to counteract the acceleration in somatic growth and sexual maturation that were quite inappropriate for his age and intellectual status. After starting triptorelin-acetate injections, his school rejection disappeared, suggesting that the treatment had been beneficial.

So far, more than 500 different variants associated with SS have been identified: the small duplications -as our patient has- were detected in only 10% of the cases (http://www.hgmd.org). Moreover, the molecular analysis of other patients previously reported from Turkey did not show duplication in the NSD-1 (2,4,10). Although overgrowth and advanced bone age in childhood and finally normal adult height are well known characteristics of the syndrome, little is known about pubertal timing and progress. This novel duplication variant in the NSD1 may well be related with the early and accelerated pubertal development in this patient. The presence of a pineal cyst in the patient, whether or not related with this novel mutation, is another matter of consideration.

The main limitation of this case report is the lack of long-term follow-up, which would be more informative to understand the effect of the GnRHa in a patient with SS. A clinical and hormonal suppression of puberty at the first year of the treatment was obviously shown, except a missing total testosterone level because of a technical problem.

In conclusion, GnRHa treatment can be beneficial in patients with SS complicated by CPP by delaying puberty at least until the time of normal pubertal development. Further studies on a larger series of patients with SS are needed, with particular focus on the pubertal timing and progress, and the influence of puberty on psychiatric and behavioral disorders.

Conflict of interest

The authors declare that they have no conflict of interest.

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