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CASE REPORT

Clinical and genetic characteristics of a child with Sotos syndrome and attention-deficit/hyperactivity disorder: A case report

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Abstract

BACKGROUND

Sotos syndrome is an autosomal dominant disorder, whereas attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental condition. This report aimed to summarize the clinical and genetic features of a pediatric case of Soros syndrome and ADHD in a child exhibiting precocious puberty.

CASE SUMMARY

The patient presented with accelerated growth and advanced skeletal maturation; however, she lacked any distinct facial characteristics related to specific genetic disorders. Genetic analyses revealed a paternally inherited heterozygous synonymous mutation [c.4605C>T (p.Arg1535Arg)]. Functional analyses suggested that this mutation may disrupt splicing, and bioinformatics analyses predicted that this mutation was likely pathogenic. After an initial diagnosis of Sotos syndrome, the patient was diagnosed with ADHD during the follow-up period at the age of 8 years and 7 months.

CONCLUSION

The potential for comorbid ADHD in Sotos syndrome patients should be considered to avoid the risk of a missed diagnosis.

Key Words: Sotos syndrome; Attention-deficit/hyperactivity disorder; Nuclear receptor binding SET domain protein 1; Case report; Developmental disabilities; Diagnosis; Como-

rbidity; Management

Core Tip: This case presents an overview of the clinical and mutational patterns observed in a pediatric patient diagnosed with Sotos syndrome and comorbid attention-deficit/hyperactivity disorder. Clinical features included accelerated growth, advanced skeletal maturation, and a normal intelligence quotient. Clinicians must remain aware of the potential for an attention-deficit/hyperactivity disorder diagnosis in Sotos syndrome patients to avoid missed diagnoses and to ensure the prompt provision of appropriate interventions, thereby improving patient quality of life and prognostic outcomes.

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INTRODUCTION

Sotos syndrome is an autosomal dominant disorder caused by deletions or mutations in the histone methyltransferase-encoding *NSD1* gene, which is an important regulator of chromatin[1]. This syndrome is diagnosed based on specific facial features (including a protruding forehead, hypertelorism, mandibular elongation, a high palatal arch, and/or bitemporal hair degeneration), accelerated growth (including height and head circumference values above the 97th percentile for age-matched children with normal development), advanced bone aging, and developmental delays (including defects in short-term memory, abstract thinking, learning, and language development), with the potential for some degree of mental retardation. Other nonspecific symptoms in affected patients can include epilepsy, poor coordination, clumsy movement, jaundice, and early feeding difficulties[2]. Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by inattention, hyperactivity, and/or impulsivity that are frequent, pervasive, and impairing[3]. ADHD manifests during childhood and can adversely impact the social, familial, academic, and overall development of the affected children[4]. Before the age of 4 years, differentiating between motor stagnation and variations along the normal developmental spectrum can be difficult. Inattention tends to become more pronounced and deleterious among children of primary school age who are subjected to greater external demands. Motor restlessness tends to decline during adolescence in affected patients, ultimately culminating in feelings of inner restlessness and/or drive that are considered subjectively unpleasant, whereas impulsivity, poor planning, and concentration difficulties tend to persist. The primary symptoms of ADHD during adulthood can include mood dysregulation, irritability, reduced tolerance for frustration, and pronounced mood swings[5]. To date, there have been few reports of comorbid ADHD in patients with Sotos syndrome. This study provides an overview of the clinical and mutational presentation of a pediatric patient who was diagnosed with both Sotos syndrome and ADHD.

CASE PRESENTATION

Chief complaints

A 7-year-old girl presented with accelerated growth, advanced bone maturation, and a normal intelligence quotient. In July 2019, she was admitted to the hospital to evaluate the cause of her rapid increase in height over the past 2 years.

History of present illness

The patient was born at full term *via* vaginal delivery following *in vitro* fertilization in 2012 to a mother who had not previously been pregnant. At birth, the child weighed 2.9 kg, was 50 cm long, and had no history of asphyxia. She was exclusively breastfed until 6 months of age and did not exhibit any evidence of hypotonia or feeding difficulties. Developmental milestones included turning over at 4 months of age, teething at about 8 months, and walking at 13 months. Her family members reported her tendency to be taller than her peers during early childhood, with no recent changes in breast development or vaginal discharge over the past 2 years.

History of past illness

The patient did not exhibit any relevant medical history.

Personal and family history

The patient was born to two unrelated, nonconsanguineous parents, and none of her relatives exhibited a similar medical history. Her grandparents had a history of diabetes mellitus and poor dietary control, but no other familial medical

conditions were noted, and no history of fractures was reported.

Physical examination

Physical examination revealed that the patient's blood pressure was 100/66 mmHg, heart rate was 113 bpm, and respiratory rate was 22 breaths/min. On admission, her body temperature was 36.5 °C.

Laboratory examinations

Five months before the current visit (in February 2019), the patient was 6 years and 6 mo of age, with a height of 135 cm and a weight of 40.2 kg. Her luteinizing hormone level in the gonadotrophin-releasing hormone stimulation test was under 5 mIU/mL; the same results were observed when the test was repeated in July 2019. At this point, the patient's height had increased to 137.5 cm and weight had increased to 42.5 kg, with an average growth rate of 2.3 cm every 4 months. Her uric acid level was 592 μmol/L (normal range: 155-357 μmol/L), blood glucose level was 4.7 mmol/L (normal range: 3.9-6.0 mmol/L), growth hormone levels were < 0.05 ng/mL (normal range: 0.06-5.0 ng/mL), insulin-like growth factor 1 level was 225 ng/mL (normal range: 50-410 ng/mL), fasting insulin level was 19 μU/mL (normal range: 2.6-24.9 uIU/mL), follicle-stimulating hormone level was 0.25 IU/L (normal range: 3.5-12.5 IU/L), and luteinizing hormone level was < 0.2 IU/L (normal range: 2.4-12.6 IU/L).

Imaging examinations

Bone age analyses revealed a bone age of 10 years (Figure 1A). Magnetic resonance imaging scans revealed mucus membrane thickening in the left maxillary and ethmoid sinuses, without any apparent pituitary gland abnormalities (Figure 1B). Ultrasonography revealed bilateral breast development, the absence of any bilateral axillary lymph node involvement, a left ovary measurement of 10 mm × 5 mm, and a right ovary measurement of 10 mm × 4 mm, without any apparent abnormalities in shape or internal echogenicity. Neither the uterus nor the bilateral adnexa exhibited any significant abnormalities, and all other results were within the expected parameters. Ultrasound reports indicated the slight thickening of the glandular layers in both breasts, visible bilateral axillary lymph nodes, a left ovary measuring 13 mm × 8 mm containing 3-4 follicles, and a right ovary measuring 10 mm × 8 mm containing 1-2 follicles. The uterus and bilateral regions did not exhibit any apparent abnormalities.

Genetic analyses

Methods: After obtaining informed consent from the patient's parents and approval from the Ethics Committee of Beijing Children's Medical Center, genetic testing of the patient and both parents was conducted. A 2-mL volume of whole blood was obtained from the patient and her parents and used to isolate genomic DNA for individual whole-exome sequencing (category B), with a focus on the exonic regions of about 20000 genes. These sequencing results were cross-referenced with the OMIM database (2018. 11) based on the patient's primary findings to identify potential pathogenic genes. After the fragmentation of genomic DNA and library preparation, exon and splicing region-associated DNA capture and enrichment were performed using a chip-based approach. A high-throughput sequencing platform was then used to detect mutations. This approach can detect a range of variants including point mutations, insertions, and deletions in a 20 bp range within exons and adjacent introns, while also offering insight into exon-level copy number variations. This approach cannot detect genomic structural variations such as large deletions, duplications, or inversions, AlU-mediated insertions or other types of large insertions, mutations present within deep intronic regions or regulatory areas, or more unusual mutation types including complex recombination and dynamic mutations. This approach is also limited with respect to its ability to capture pseudogene regions, high-repeat regions, regions with high GC content, and regions with high levels of complex heterozygosity; however, it can achieve a total coverage of > 95%.

Genetic testing results: The patient was found to harbor the synonymous c.4605C>T (p.Arg1535Arg) mutation in the gene encoding NSD-1 (Figure 2). This mutation was present in her father in a heterozygous state and was predicted to affect splicing. Bioinformatics analyses supported the pathogenic nature of this point mutation (Figure 3).

Additional tests

At 8 years and 7 months of age, the patient was admitted to the psychological clinic of Beijing Children's Hospital affiliated with Capital Medical University. Testing for autism spectrum disorder at this time revealed a severity score of 113 points, a total score of 33 on the Conners Parent Symptom Questionnaire test, and adherence to eight items in Group A and three items in Group B on the ADHD scale, suggestive of ADHD. Visual sustained attention test results supported the diagnosis of a potential attention disorder. On the Child Difficulty Inventory, the patient achieved a normal score of 37, while on Raven's intelligence test, she exhibited an average intelligence quotient of 96.

FINAL DIAGNOSIS

The patient was diagnosed with Sotos syndrome and ADHD.

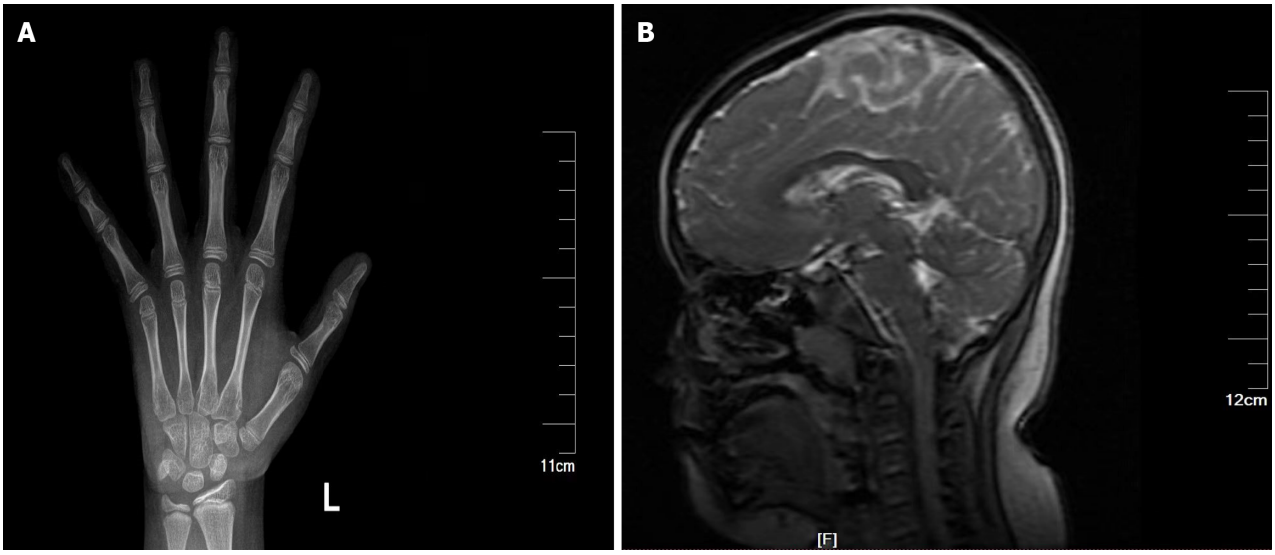

Figure 1 X-ray image of the patient's left hand and magnetic resonance image of the pituitary gland. A: X-ray image of the patient's left hand; B: Magnetic resonance image scans of the patient's pituitary gland.

Serial number	Genes	Chromosomal location	Transcript numbering Nucleotide changes (Amino acid changes)	Genetype	Pathogenic classification	Related diseases/ genetic model	References
1	NSD1	Chr5: 176675289	NM_022455.4: c.4605C > T (p.Arg1535Arg)	Heterozygosis	Unclear meaning	Central giant syndrome type 1 (OMIM: 117550) / AD	-

Figure 2 Genetic sequencing results for the proband.

TREATMENT

The treatment consisted of oral atomoxetine, metformin (0.25 g, 3 times per day), and polyene phosphatidylcholine capsules (2 capsules, 3 times per day).

OUTCOME AND FOLLOW-UP

On July 11, 2021, after 2 years, the patient was evaluated at Hebei General Hospital. Examinations revealed uterine measurements of 19 mm × 18 mm × 11 mm, with a linear endometrium. Her left ovary measured approximately 25 mm × 15 mm and contained more than 15 follicles, including 8-10 measuring more than 4 mm in diameter. Her right ovary measured approximately 21 mm × 19 mm and contained more than 20 follicles, including 10 measuring 4 mm. The changes in the weight and height of the patient over time are presented in Figure 4, while her fasting insulin levels are presented in Table 1.

DISCUSSION

Sotos syndrome, also referred to as cerebral macrosomia syndrome or cerebral gigantism, was first described as a form of autosomal dominant congenital overgrowth disorder in 1964 by Sotos *et al*[6]. This disease is characterized by low incidence, with sporadic onset and only a small number of cases of familial inheritance. Sotos syndrome is related to abnormalities in the *NSD1* gene in the chromosome 5q35 region[7], which regulates a range of biological processes including cellular differentiation and embryonic development. Specific splicing isoforms and changes associated therewith have recently been demonstrated to be important in the context of development[8]. Different splicing changes can give rise to different protein isoforms that are related to development but warrant further functional characterization. Few studies to date have explored the particular molecular and cellular regulatory networks related to particular *NSD1* isoforms. There is, thus, a pressing need to explore different protein isoforms encoded by *NSD1* and to evaluate their expression in a range of cell types under both physiological and pathological conditions, including cancer and Sotos

Table 1 Genetic sequencing results of the proband

Age in yr	FINS
7	19
7.5	24.18
8	40.92
8.5	49.81
9	14.55
10.10	74.88

FINS: Fasting insulin, normal range of 2.6-24.9 μU/mL.

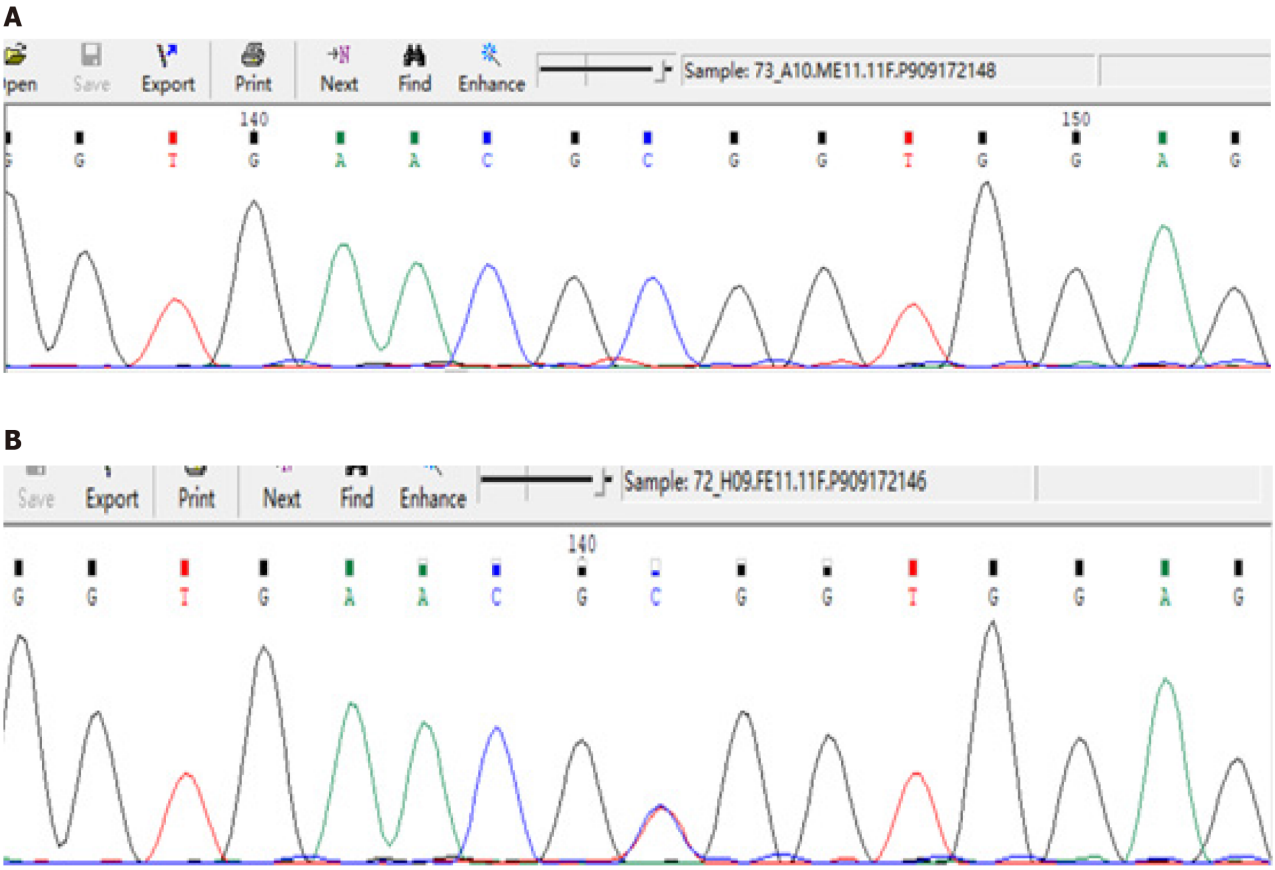

Figure 3 Genetic sequencing results for the proband's parents. A: *NSD1* c.4605C>T mutation not present in the proband's mother; B: *NSD1* c.4605C>T mutation present in the proband's father.

syndrome[9].

NSD1 is a histone methyltransferase associated with histone modification and the remodeling of the chromatin expressed in the brain, kidneys, and leukocytes in the peripheral blood. NSD1 is particularly important in the context of embryonic development. While this enzyme has been linked to histone H3 methylation at lysine 36 and associated transcriptional changes, the underlying molecular mechanisms remain unclear. Pathogenic variants in the *NSD1* gene are the cause of Sotos syndrome, with over 90% of affected children presenting with microdeletions in the region of chromosome 5q35 that encodes *NSD1* or *NSD1* gene mutations, which can include splice site, nonsense, missense, and frameshift mutations[1]. *NSD1* haploinsufficiency, as in cases of deletions, nonsense mutations, or missense mutations, has been suggested to be linked to increased growth in terms of height and facial development. *NSD1* gene haploinsufficiency in the distal long arm of chromosome 5 (5q35.2-q35.3) is, thus, the primary cause of Sotos syndrome. However, there have been some cases of so-called "reverse Sotos syndrome" characterized by shorter stature and microcephaly without distinctive facial characteristics in patients harboring 5q35 microduplications[10].

No correlations between the location of disease-related mutations and clinical phenotypes have been observed in Sotos syndrome, with high levels of clinical variability being evident among patients, even in cases associated with the exact same mutation. Patients harboring 5q35 microdeletions are more likely to present with severe learning disabilities as

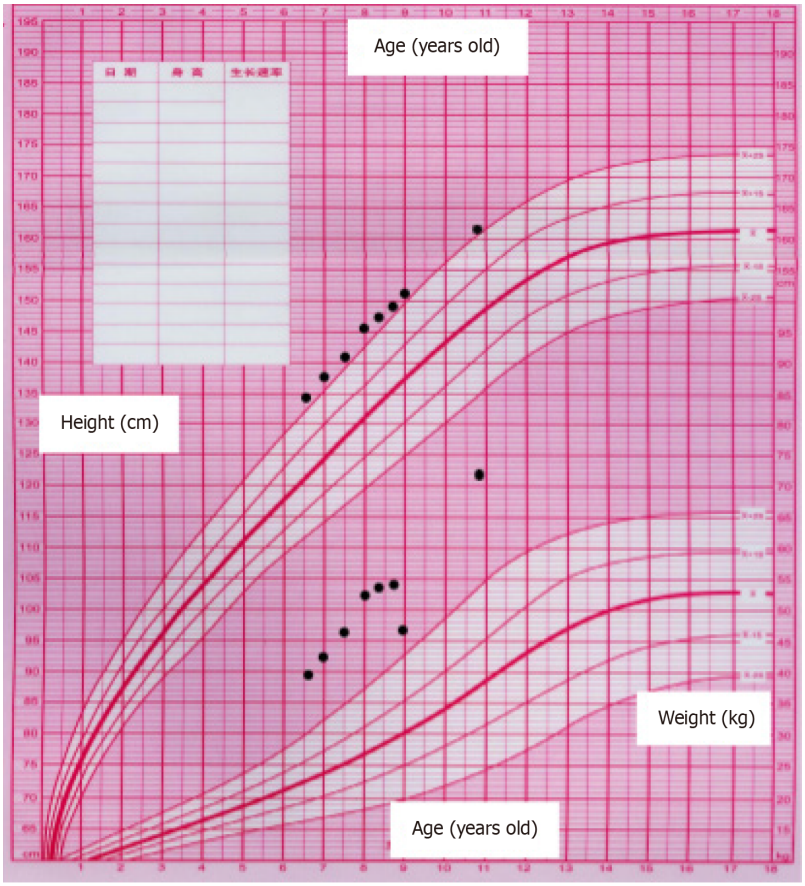

Figure 4 Trends in height and weight changes.

compared to cases of intragenic *NSD1* mutations, often coinciding with inconspicuous overgrowth[11]. The presence of genetic deletions may significantly increase the risk of a lower intelligence quotient independent of age or problematic behavioral patterns. With respect to the behavioral profile of Sotos syndrome patients, significant differences were observed in terms of the extent of externalizing behaviors, particularly symptoms consistent with ADHD, with these behavioral problems being more common or severe in cases harboring 5q35 microdeletions. These findings suggest that behavior (specifically, problematic behavior) is significantly associated with the adaptive functioning of children. Sotos syndrome patients harboring 5q35 microdeletions are, thus, more likely to experience impaired behavioral, cognitive, and adaptive development[12]. In the present case, the patient was found to harbor an intragenic mutation associated with an average intelligence quotient and the absence of any form of severe learning disability. An estimated 10% of patients in Europe and the United States harbor *NSD1* gene 5q35 microdeletions, and genotypic distributions vary among populations.

Substantial variations have been reported among cases of Sotos syndrome in China and other countries, likely owing to both mutation site differences and ethnic variations[13]. Patients with Sotos syndrome can present with a range of otolaryngologic conditions such as hearing loss, otitis, hypothyroidism, hyperthyroidism, dyspnea, speech disorders, feeding difficulties, head and neck tumors, and congenital abnormalities such as high palatal arches, macroglossia, and cleft lip/palate. However, further studies are required to better study this relationship, and patients should be monitored carefully for breathing and feeding difficulties, head and neck tumors, otitis, and hearing loss during infancy. When the results of physical examination suggest the presence of these conditions, patients should be referred to an ENT physician to undergo further assessment[14].

Sotos syndrome patients often experience sleep difficulties, failing to exhibit expected reductions in the duration of sleep over the course of maturation relative to infancy. While developmental disabilities are common in Sotos syndrome patients, they exhibit sleep patterns distinct from those of patients with intellectual disabilities. Nocturnal awakenings and apnea are more common in Sotos syndrome patients, in addition to lower odds of daytime sleepiness or delayed sleep onset. Sotos syndrome generally appears to be associated with abnormal but not dangerous changes in sleep habits [15]. Comparisons of the relationship between sleep symptoms and behavioral issues among children with Sotos syndrome have revealed that more severe sleep issues are related to externalizing and internalizing symptoms, particularly those of the impulsivity and hyperactivity domains. In contrast, milder sleep issues tend to coincide with more typical adaptive behaviors. Early detection of sleep disorders is vital to ensure that they can be quickly rectified, minimizing the risk of any adverse effects on the caregiver's quality of life. Efforts to overcome behavioral issues may also have a positive impact on sleep, as the two are bidirectionally connected[16].

The patient in this case presented with elevated fasting insulin levels consistent with hyperinsulinemia; however, her blood glucose levels were within the normal range. She was administered symptomatic oral metformin treatment. Reports of congenital hyperinsulinemia in Sotos syndrome patients are rare, and patients tend to respond well to diazoxide treatment. Beckwith-Wiedemann is an overgrowth syndrome that is more commonly linked to hypoglycemia stemming from hyperinsulinemia, although just 5% of patients present with hypoglycemia persisting beyond the neonatal period. Persistent hyperinsulinemia-related hypoglycemia is not a common finding in Sotos syndrome patients [17]. The mechanistic basis for dysregulated insulin secretion in patients with Sotos syndrome remains uncertain. *NSD1* encodes a histone methyltransferase that is important for controlling chromatin accessibility and gene expression, with indirect evidence suggesting a potential role for this protein in the control of islet β cell insulin regulation[18]. In this case, the patient exhibited hyperinsulinemia but not hypoglycemia, and her symptoms were attributed to the paternally inherited synonymous 4605C>T (p.Arg1535Arg) mutation. She presented with overgrowth, advanced bone age, and other features characteristic of Sotos syndrome, albeit without any evidence of renal or cardiac abnormalities or mental retardation, consistent with the possible involvement of distinct genetic loci.

Over the course of follow-up, the patient was diagnosed with ADHD. Relative to age-matched children without ADHD, those affected by this disorder present with difficulty focusing, a shorter attention span, and impulsivity. Pediatric Sotos syndrome patients frequently present with learning difficulties, irritability, hyperactivity, behavioral issues, social problems, inappropriate speech, stereotypy, and sleep issues of varying severity. ADHD is among the most common neurobehavioral disorders of childhood, characterized primarily by developmentally inappropriate inattention and hyperactivity/impulsivity, resulting in the impairment of emotional, social, and/or academic function. In addition to their tendency to exhibit impaired emotional and academic function, children affected by ADHD face higher odds of developing concurrent language, cognitive, motor, learning, and mental health difficulties. Children suffering from developmental disabilities are also at a greater risk of developing ADHD[19].

Children with Sotos syndrome exhibit intelligence levels ranging from average to severely disabled, with most falling within the borderline range. This study found that the average level of intelligence of the patient was significantly higher than that observed in control children. These patients generally exhibit language development to a level consistent with their overall intellectual ability. While patients present with higher rates of parent- and teacher-reported behavioral problems, with the exception of a tendency toward irritability, these rates do not differ from those of normal controls. ADHD is evident in approximately 38% of children with Sotos syndrome. Relative to controls, these children are typically more withdrawn and irritable, in addition to exhibiting inappropriate speech and stereotyped behaviors[20]. ADHD can lead to significant distress and impairment throughout life, with affected patients facing a higher risk of accidental injuries, worse relationships with peers and parents, poorer academic performance, and poorer overall quality of life[3]. ADHD can also coincide with a greater risk of disorders including oppositional defiant, mood, and conduct disorders [21], and patients are also more likely to engage in substance abuse and other destructive disorders as they age, contributing to poor outcomes[22]. Long-term follow-up analyses suggest that the academic performance of children who achieve adequate symptom control tends to be better, with these children experiencing lower rates of mood disorders, substance abuse, criminal behavior, motor vehicle accidents, injuries, and traumatic brain injuries[19]. While the patient in this case lacked rigid language skills, she did exhibit difficulties in peer communication and the establishment of boundaries, together with irritability. After diagnosis, follow-up efforts should, thus, focus on monitoring the emotional well-being, personality development, and cognitive performance of the affected patients.

Current clinical guidelines recommend the use of individualized multimodal treatment approaches for the management of ADHD in children, including education as well as pharmacological and non-pharmacological interventions. Drugs available for the management of ADHD include stimulants (amphetamine, methylphenidate) and non-stimulants (atomoxetine, guanfacine, clonidine). In this case, the patient was treated using atomoxetine, which is a norepinephrine reuptake inhibitor that binds to norepinephrine transporters to increase synaptic norepinephrine levels. Norepinephrine transporters in the prefrontal cortex also control dopamine reuptake, owing to the presence of few dopamine transporters in this region of the brain. Atomoxetine treatment thus leads to increased synaptic norepinephrine and dopamine levels in the prefrontal cortex. When administered orally, the metabolism of atomoxetine primarily occurs *via* the cytochrome P450 2D6 pathway[23].

Chromosomal microarray or exome sequencing analyses of amniotic fluid or chorionic villi specimens can enable the prenatal diagnosis of Sotos syndrome. However, only fetal ultrasound imaging can be used to screen for this condition, enabling the recommendation of appropriate genetic testing based on the observed findings. Thus, an understanding of the perinatal findings associated with Sotos syndrome and expertise in neurosonography are both very important for accurate prenatal diagnostic efforts[24]. The treatment of Sotos syndrome relies on coordinated efforts across multiple areas of medicine, with symptomatic treatments being the most common. During the neonatal period, managing Sotos syndrome generally entails phototherapy-based jaundice treatment, together with efforts to address any feeding difficulties, hypoglycemia, and gastroesophageal reflux. During infancy and childhood, routine pediatric follow-up efforts are vital to address issues including respiratory infections, constipation, seizures, scoliosis, and tumor risk[25]. No forms of radical treatment are currently available for Sotos syndrome. In children with delayed motor and mental development, rehabilitative evaluation and treatment should be provided as soon as possible. Scoliosis affects an estimated 30% of Sotos syndrome patients. A system of routine follow-up should be implemented to monitor these patients, with timely treatment for related symptoms. During follow-up, patients should be evaluated for growth and developmental abnormalities, particularly in cases with irregular cranial magnetic resonance imaging, electroencephalography, hearing, cardiac, urinary, and digestive findings, shortening the interval between follow-up visits as appropriate. When patients are diagnosed with Sotos syndrome, clinicians should be attentive to the potential for comorbid ADHD to avoid a missed diagnosis, ensuring that early interventions can be provided to improve patient quality of life and prognostic outcomes[13].

CONCLUSION

The potential for comorbid ADHD should be taken into consideration when diagnosing Sotos syndrome.

FOOTNOTES

Author contributions: Yang YJ, Li BY, Gan KX, Liu J, Lv XQ, and Zhang DM substantially contributed to the conception, design, and interpretation of the article and carefully revised important substantive content; Liu J and Ma HJ contributed to the final version of the manuscript. All authors have agreed to the publication of this manuscript.

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REFERENCES

1 **Tatton-Brown K**, Rahman N. Sotos syndrome. *Eur J Hum Genet* 2007; **15**: 264-271 [PMID: 16969376 DOI: 10.1038/sj.ejhg.5201686]
2 **Cole TR**, Hughes HE. Sotos syndrome: a study of the diagnostic criteria and natural history. *J Med Genet* 1994; **31**: 20-32 [PMID: 7512144 DOI: 10.1136/jmg.31.1.20]
3 **Leffa DT**, Caye A, Rohde LA. ADHD in Children and Adults: Diagnosis and Prognosis. *Curr Top Behav Neurosci* 2022; **57**: 1-18 [PMID: 35397064 DOI: 10.1007/7854_2022_329]
4 **First MB**. Diagnostic and statistical manual of mental disorders, 5th edition, and clinical utility. *J Nerv Ment Dis* 2013; **201**: 727-729 [PMID: 23995026 DOI: 10.1097/NMD.0b013e3182a2168a]
5 **Banaschewski T**, Becker K, Döpfner M, Holtmann M, Rösler M, Romanos M. Attention-Deficit/Hyperactivity Disorder. *Dtsch Arztebl Int* 2017; **114**: 149-159 [PMID: 28351467 DOI: 10.3238/arztebl.2017.0149]
6 **Sotos JF**, Dodge PR, Muirhead D, Crawford JD, Talbot NB. Cerebral gigantism in childhood. a syndrome of excessively rapid growth and acromegalic features and a nonprogressive neurologic disorder. *N Engl J Med* 1964; **271**: 109-116 [PMID: 14148233 DOI: 10.1056/nejm196407162710301]
7 **Kurotaki N**, Harada N, Yoshiura K, Sugano S, Niikawa N, Matsumoto N. Molecular characterization of NSD1, a human homologue of the mouse Nsd1 gene. *Gene* 2001; **279**: 197-204 [PMID: 11733144 DOI: 10.1016/s0378-1119(01)00750-8]
8 **Baralle FE**, Giudice J. Alternative splicing as a regulator of development and tissue identity. *Nat Rev Mol Cell Biol* 2017; **18**: 437-451 [PMID: 28488700 DOI: 10.1038/nrm.2017.27]
9 **Conteduca G**, Testa B, Baldo C, Arado A, Malacarne M, Candiano G, Garbarino A, Coviello DA, Cantoni C. Identification of alternative transcripts of NSD1 gene in Sotos Syndrome patients and healthy subjects. *Gene* 2023; **851**: 146970 [PMID: 36261088 DOI: 10.1016/j.gene.2022.146970]
10 **Liu X**, Chen C, Wan L, Zhu G, Zhao Y, Hu L, Liang Y, Gao J, Wang J, Yang G. A novel nonsense variant in NSD1 gene in a female child with Sotos syndrome: A case report and literature review. *Brain Behav* 2023; **13**: e3290 [PMID: 37908045 DOI: 10.1002/brb3.3290]
11 **Tatton-Brown K**, Douglas J, Coleman K, Baujat G, Cole TR, Das S, Horn D, Hughes HE, Temple IK, Faravelli F, Waggoner D, Turkmen S, Cormier-Daire V, Irrthum A, Rahman N; Childhood Overgrowth Collaboration. Genotype-phenotype associations in Sotos syndrome: an analysis of 266 individuals with NSD1 aberrations. *Am J Hum Genet* 2005; **77**: 193-204 [PMID: 15942875 DOI: 10.1086/432082]
12 **Siracusano M**, Riccioni A, Frattale I, Arturi L, Dante C, Galasso C, Gialloreti LE, Conteduca G, Testa B, Malacarne M, Coviello D, Mazzone L. Cognitive, adaptive and behavioral profile in Sotos syndrome children with 5q35 microdeletion or intragenic variants. *Am J Med Genet A* 2023; **191**: 1836-1848 [PMID: 37066965 DOI: 10.1002/ajmg.a.63211]
13 **Jin HY**, Li HF, Xu JL, Hui W, Ruan WC, Lv CC, Xu RA, Qiang S. Case Report of Neonatal Sotos Syndrome with a New Missense Mutation in the NSD1 Gene and Literature Analysis in the Chinese Han Population. *Medicina (Kaunas)* 2022; **58** [PMID: 35888687 DOI: 10.3390/medicina58070968]
14 **Danis DO 3rd**, Bodamer O, Levi JR. The otolaryngologic manifestations of Sotos syndrome 1: A systematic review. *Int J Pediatr Otorhinolaryngol* 2021; **143**: 110649 [PMID: 33640723 DOI: 10.1016/j.ijporl.2021.110649]
15 **Stafford CF**, Ward C, Ward SLD, Sanchez-Lara PA. Characterization of sleep habits of children with Sotos syndrome. *Am J Med Genet A*

2021; **185**: 2815-2820 [PMID: 33893755 DOI: 10.1002/ajmg.a.62212]

16 **Frattale I**, Sarnataro R, Siracusano M, Riccioni A, Galasso C, Valeriani M, Conteduca G, Coviello D, Mazzone L, Moavero R. Sleep disturbances and behavioral symptoms in pediatric Sotos syndrome. *Front Neurol* 2024; **15**: 1360055 [PMID: 38434199 DOI: 10.3389/fneur.2024.1360055]

17 **González Casado I**, De la PuenteArévalo A, López Moreira O, Lapunzina P, Gracia Bouthelier R. [Hypoglycaemia due to persistent hyperinsulinism in a patient with Sotos syndrome]. *An Pediatr (Barc)* 2012; **76**: 232-234 [PMID: 22206879 DOI: 10.1016/j.anpedi.2011.11.004]

18 **Zenker M**, Mohnike K, Palm K. Syndromic forms of congenital hyperinsulinism. *Front Endocrinol (Lausanne)* 2023; **14**: 1013874 [PMID: 37065762 DOI: 10.3389/fendo.2023.1013874]

19 **Rajaprakash M**, Leppert ML. Attention-Deficit/Hyperactivity Disorder. *Pediatr Rev* 2022; **43**: 135-147 [PMID: 35229109 DOI: 10.1542/pir.2020-000612]

20 **Finegan JK**, Cole TR, Kingwell E, Smith ML, Smith M, Sitarenios G. Language and behavior in children with Sotos syndrome. *J Am Acad Child Adolesc Psychiatry* 1994; **33**: 1307-1315 [PMID: 7995798 DOI: 10.1097/00004583-199411000-00013]

21 **Tandon M**, Pergjika A. Attention Deficit Hyperactivity Disorder in Preschool-Age Children. *Child Adolesc Psychiatr Clin N Am* 2017; **26**: 523-538 [PMID: 28577607 DOI: 10.1016/j.chc.2017.02.007]

22 **Dalsgaard S**, Mortensen PB, Frydenberg M, Thomsen PH. Long-term criminal outcome of children with attention deficit hyperactivity disorder. *Crim Behav Ment Health* 2013; **23**: 86-98 [PMID: 23576439 DOI: 10.1002/cbm.1860]

23 **Bymaster FP**, Katner JS, Nelson DL, Hemrick-Luecke SK, Threlkeld PG, Heiligenstein JH, Morin SM, Gehlert DR, Perry KW. Atomoxetine increases extracellular levels of norepinephrine and dopamine in prefrontal cortex of rat: a potential mechanism for efficacy in attention deficit/hyperactivity disorder. *Neuropsychopharmacology* 2002; **27**: 699-711 [PMID: 12431845 DOI: 10.1016/s0893-133x(02)00346-9]

24 **Bornstein E**, Reiss S, Malinger G. Prenatal characterization of novel neurosonographic findings in a fetus with SOTOS syndrome. *Prenat Diagn* 2024; **44**: 360-363 [PMID: 38152001 DOI: 10.1002/pd.6504]

25 **Lesinskiene S**, Montvilaite R, Pociute K, Matuleviciene A, Utkus A. Neuropsychiatric Aspects of Sotos Syndrome: Explorative Review Building Multidisciplinary Bridges in Clinical Practice. *J Clin Med* 2024; **13** [PMID: 38673476 DOI: 10.3390/jcm13082204]

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