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ORIGINAL ARTICLE

Clinical and Genetic Characteristics of Chinese Patients with Sotos Syndrome: a Cohort Study of 51 Cases

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ABSTRACT

Background: **Sotos syndrome is a rare overgrowth disorder caused by mutations in the nuclear receptor SET domain-containing gene 1 (NSD1) or deletions encompassing NSD1 at 5q35. Comprehensive data on the clinical and genetic characteristics of Chinese patients remain scarce. This study aimed to elucidate the phenotypic and genotypic spectrum of Sotos syndrome in the Chinese population by analyzing the largest cohort of Chinese patients to date.**

Methods: **We conducted a retrospective cohort study. Data were derived from one index case diagnosed at our institution, supplemented by 50 additional cases reported domestically through a systematic literature review (1982 to January 2025). Descriptive statistical analysis was performed on the clinical characteristics and genetic findings of all patients.**

Results: **The cohort comprised 51 patients (36 males, 13 females, 2 of unknown gender). The median age at diagnosis was 12.5 months (range: 1 day - 43 years). The most prominent clinical features were distinctive facial features (96.1%), developmental delay (92.2%), and excessive growth (98.0%). Common systemic involvement included ventricular enlargement (62.7%), congenital heart disease (41.2%), epilepsy or febrile seizures (33.3%), and corpus callosum or brain hypoplasia (31.4%). Malignant tumor incidence was 7.8%. Among 44 patients with genetic results, pathogenic NSD1 gene variants accounted for 68.2%, and 5q35 microdeletions for 29.5%. In cases with defined inheritance patterns, 93.0% involved de novo mutations.**

Conclusions: **This study systematically characterized the clinical and genetic landscape of Sotos syndrome patients in China. The phenotypic spectrum aligns with international reports, but the genetic structure reveals a higher proportion of NSD1 point mutations compared to other East Asian populations. The findings underscore the core value of genetic testing in diagnosis and the necessity of comprehensive multisystem management for patients.**
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Sotos syndrome, NSD1, overgrowth syndrome, whole-exome sequencing, genotype-phenotype correlation

INTRODUCTION

Sotos syndrome, also known as cerebral gigantism or cerebral macrosomia syndrome, was first described by Sotos et al. in 1964 [1]. It is a rare genetic disorder with an estimated incidence of 1 in 14,000 in the general population [2]. The condition typically occurs sporadically, although a small number of familial cases have been documented. Sotos syndrome is an autosomal

dominant disorder characterized by overgrowth beginning in infancy, primarily caused by mutations in the NSD1 gene [3-9]. Numerous reports on Sotos syndrome exist in Western countries, but cases in China remain relatively rare and are mostly individual case reports, lacking comprehensive analysis of clinical and genetic characteristics based on larger samples. This study, based on a case initially misdiagnosed as congenital adrenal hyperplasia (CAH), integrates all previously reported domestic cases to systematically describe the clinical and genetic characteristics of the largest cohort of Chinese patients with Sotos syndrome to date, aiming to enhance overall understanding of this disease.

MATERIALS AND METHODS

Data source 1: index case report

A 28-day-old male infant was admitted for excessive growth and hyperpigmentation, presenting with characteristic facial features, ventricular enlargement, and congenital heart disease. Previously misdiagnosed with CAH, genetic testing confirmed a de novo NSD1 (NM_022455.4): c.3550G>T (p.Glu1184*) Heterozygous de novo missense mutation.

Data source 2: systematic literature review

We systematically searched Wanfang Data, China National Knowledge Infrastructure (CNKI), and PubMed databases from January 1982 to January 2025 using the keywords “Sotos syndrome,” “cerebral gigantism,” and “NSD1.” Inclusion criteria: Sotos syndrome patients with clinical and/or genetic diagnosis reported in mainland China. Exclusion criteria: Reports with insufficient clinical information to support diagnosis. Duplicate cases were avoided through careful verification of demographic, clinical, and genetic information. Standardized forms were used to extract demographic data, clinical manifestations, and genetic results.

Data analysis

Descriptive statistical methods were employed. This study primarily employs exploratory descriptive analysis to systematically characterize the clinical and genetic profiles of patients with Sotos syndrome in China. Categorical variables are presented as frequencies and percentages, with all percentages calculated based on the number of patients with valid records for the respective trait; the denominator (total number of cases or cases within a specific subgroup) is explicitly stated in the text and tables. Continuous variables with non-normal distributions are described using median and range. Data from index cases and literature cases were combined for unified analysis.

Genetic sequencing

We collected peripheral blood samples from the index patient and his parents. Genomic DNA was extracted using the genomic DNA extraction kit from Tiangen Biotech (Beijing) Co., Ltd. The DNA input was quantified using a Qubit fluorometer to ensure it was ≥ 100 ng. Exon capture and library preparation were performed using the Agilent SureSelect Human All Exon V8 kit. Dual-end 150 bp sequencing was conducted on the Illumina NovaSeq 6000 platform (also involving the Illumina HiSeq platform), yielding FastQ format data. Bioinformatics analysis included: raw data quality control using FastQC; mapping sequencing reads to the human reference genome GRCh38/hg38 via BWA (v0.7.17); and detection of single nucleotide variants (SNVs) and small insertions/deletions (Indels) using the GATK (v4.2) best practice workflow. Average sequencing depth ≥ 100×, with > 95% of target regions achieving ≥ 20× coverage. Detected variants were annotated by querying single nucleotide polymorphism (SNP) databases and the Human Genome Mutation Database (HGMD) (accessed January 15, 2025). For novel variants not listed in HGMD, pathogenicity was predicted using multiple bioinformatics tools including PROVEAN, SIFT, Mutation Taster, PolyPhen-2, Mutation Accessor, and FATHMM. All potentially pathogenic variants were interpreted and classified according to guidelines jointly published by the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP). For candidate variants in the NSD1 gene, validation was performed via Sanger sequencing in both the affected individual and their parental samples. For copy number variations (CNVs) such as the 5q35 microdeletion, we analyzed WES data using ExomeDepth (v1.1.16) software and conducted independent validation through quantitative PCR (qPCR).

Ethical considerations

This study was approved by the institutional research ethics committee of The Children’s Hospital Capital Institute of Pediatrics in accordance with regulatory and ethical guidelines pertaining to retrospective studies (SHERLLM2025012). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

RESULTS

Cohort characteristics and clinical spectrum

A total of 51 patients with Sotos syndrome from mainland China were ultimately included in the analysis (comprising 50 literature cases and the index case from this study). Demographic and core clinical characteristics of the cohort are summarized in Table 1 (Unless otherwise specified, the percentages for clinical characteristics in the following text and Table 1 are calculated using the total number of cases (n = 51) as the denominator. For characteristics applicable only to specific subgroups, the subgroup denominator is explicitly indicated). The male-to-female ratio was approximately 2.8:1. The median age at diagnosis was 12.5 months

Table 1. Demographic and core clinical characteristics of a cohort of 51 Chinese patients with Sotos syndrome.

Characteristics	Number/total number of cases	Percentage (%)
Demographic data	-	-
Male	36/51	70.6
Female	13/51	25.5
Age at diagnosis (median, range)	11 years (1 day - 43 years)	-
Birth status	-	-
Macrosomia/large for gestational age	22/51	43.1
Core diagnostic features	-	-
Special facial features (≥ 2 features)	49/51	96.1
Developmental delay	47/51	92.2
Overgrowth (giant deformity and/or excessive height increase)	50/51	98.0
Common system manifestations	-	-
Ventricular dilation/hydrocephalus	32/51	62.7
Congenital heart disease	21/51	41.2
Epilepsy or febrile convulsions	17/51	33.3
Corpus callosum or brain dysplasia	16/51	31.4
Cryptorchidism (in male patients)	3/35	8.6

"Macrosomia" refers to birth weight ≥ 4,000 g, "postmature infant" refers to birth weight exceeding the 90th percentile for gestational age.
"Distinctive facial features (≥ 2 features)" denotes meeting at least two typical facial signs of Sotos syndrome (e.g., long skull, prominent forehead, downward slanting palpebral fissures).
Denominator note: "Cryptorchidism" was calculated based on 35 male patients with available genitalia data (1 male patient lacked this information).
Data omission note: Due to incomplete clinical records in individual literature reports, certain indicators did not cover all 51 cases.

Table 2. Genetic profile of 44 Chinese patients with Sotos syndrome diagnosed by molecular testing.

Genetic alterations	Number of cases (n)	Percentage (%) *	Notes
NSD1 gene pathogenic variations (total)	30	68.2	-
Nonsense mutation	10	22.7	-
- Frameshift mutation	8	18.2	-
- Missense mutation	9	20.5	-
- Splicing site variation	3	6.8	-
5q35 microdeletion	13	29.5	-
No mutations were detected	1	2.3	tested but negative
Total	44	100	-

The percentage is based on 44 patients with genetic test results.
"Nonsense mutation": A variant introducing a premature termination codon, "Frameshift mutation": An insertion/deletion altering the reading frame of the gene, "Missense mutation": A variant causing a single amino acid change in the protein, "Splicing site variation": A variant affecting the splice donor/acceptor region of the gene, "5q35 microdeletion": A chromosomal deletion encompassing the NSD1 gene locus at 5q35.
Denominator clarification: All percentages (*) are calculated based on 44 patients who completed genetic testing (the remaining 7 cases in the cohort lacked genetic data). Missing data note: 1 patient tested negative for NSD1 variants and 5q35 microdeletion, the other 43 cases had confirmed genetic alterations.

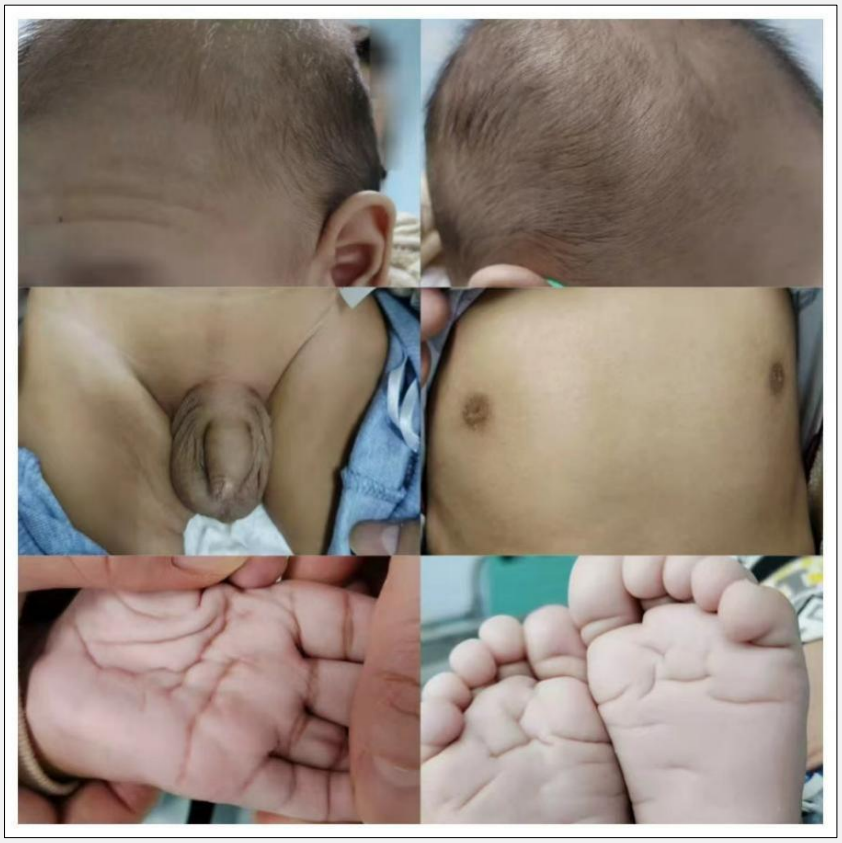

Figure 1. Clinical phenotypic manifestations of the index Sotos syndrome case.

(top row): Scalp and auricular region of the 28-day-old male index case, the left panel shows the infant's scalp (consistent with the macrocephaly feature of Sotos syndrome), and the right panel displays the posterior auricular skin and hair (no abnormal lesions). (middle row): Truncal skin and genital area, the left panel presents the infant's genital region (structure normal, no congenital malformation related to Sotos syndrome), and the right panel shows truncal skin (no specific pathological changes). (bottom row): Extremity features of the index case, the left panel displays the infant's palm (with prominent palmar creases), and the right panel shows the feet (with broad toes) - both are typical peripheral manifestations of Sotos syndrome.

(range: 1 day-43 years). At birth, 22 cases (43.1%) were macrosomic or postmature. The classic triad of Sotos syndrome was highly prevalent: distinctive facial features (96.1%), developmental delay (92.2%), and overgrowth (macrocephaly or excessive height gain, 98.0%). Systemic involvement was common (Table 1). The most frequent neurological/structural abnormality was ventricular enlargement/hydrocephalus (62.7%), followed by corpus callosum or brain hypoplasia (31.4%). Epilepsy or febrile seizures occurred in 33.3% of patients. Congenital heart disease was present in 41.2% of cohort members. Other notable features included macrocephaly (17.6%), hypoglycemia (13.7%), and various renal abnormalities (11.8%) (Supplementary Table S3). Typical clinical manifestations of index cases in this study are shown in Figure 1. Malignant tumors were reported in 4 patients (7.8%). Detailed case information (n = 50) underpinning all aggregated statistics - including demographics, birth data, clinical features, and genetic variants - is systematically compiled in Supplementary Table S2.

Genetic findings

Among all 51 patients, genetic testing results were obtained for 44 cases (86.3%), indicating data were missing for 7 cases (Table 2). All subsequent analyses of the genetic spectrum (including the percentages below) are strictly based on these 44 patients with test results. Pathogenic variants in the NSD1 gene were the most common, detected in 30 patients (68.2% of these 44 tested cases). Nonsense mutation (10/44, 22.7%) and frameshift variants (8/44, 18.2%) predominated. Micro-

deletions in the 5q35 region were detected in 13 patients (29.5%). Among cases with available information, the inheritance pattern was predominantly de novo (40/43, 93.0%), with a minority inherited from parents (3/43). One patient tested negative.

Dynamic changes in hormones and electrolytes in the index case

The index case in this study (case 51 in the cohort, with case details also listed in Supplementary Table S2) was misdiagnosed with congenital adrenal hyperplasia (CAH) due to early hormonal abnormalities. Key serial changes in adrenal axis hormones and electrolytes are shown in Supplementary Table S1. Data indicate that during neonatal stress (approximately 1.5 months of age), 17-hydroxyprogesterone (17-OHP) levels significantly increased (34.4 nmol/L). Following discontinuation of exogenous hormone therapy and resolution of the acute phase, hormone levels rapidly normalized: 17-OHP decreased to 2.03 nmol/L approximately 5 months after hospital discharge, and the cortisol response to the ACTH stimulation test exhibited a normal peak (30.81 μg/dL). Long-term follow-up until age 1 showed all indicators (including ACTH, cortisol, and electrolytes) maintained within normal physiological ranges. This complete dynamic process (Supplementary Table S1) provides direct evidence supporting the conclusion that "the early hormonal abnormalities stemmed from a stress state rather than an inherent adrenal disorder".

DISCUSSION

This study conducted a comprehensive analysis of the clinical and genetic characteristics of 51 Chinese patients with Sotos syndrome, constituting the largest cohort from mainland China to date. Our findings confirm that the hallmark features, characteristic facial appearance, developmental delay, and childhood overgrowth, are nearly universal among Chinese patients, consistent with reports from other global populations [10,13-16]. The high prevalence of ventricular enlargement, congenital heart disease, and epilepsy underscores the multisystemic nature of the disorder, emphasizing the necessity for comprehensive baseline evaluations. Notably, the incidence of epilepsy or febrile seizures in this cohort was 33.3%, exhibiting diverse phenotypes consistent with a recent international study involving 49 patients, which indicated that absence seizures, generalized tonic-clonic seizures, and febrile seizures were common presentations. Most patients achieved good seizure control, though a subset progressed to drug-resistant epilepsy [17]. Furthermore, Sotos syndrome is frequently associated with extensive neuropsychiatric comorbidities, including intellectual disability, autism spectrum features, attention-deficit/hyperactivity disorder, and behavioral-cognitive issues such as anxiety [18]. This underscores the necessity of incorporating neurodevelopmental and psychosocial assessments into clinical management. A key finding concerns the genetic architecture of Sotos syndrome in China. Within our cohort, NSD1 point mutations accounted for 68.2% of genetically confirmed cases, while 5q35 microdeletions constituted 29.5%. This pattern starkly contrasts with reports from Japan and South Korea, where 5q35 microdeletions predominate (50 - 60%) and point mutations are less common (10 - 20%) [19-21]. Instead, it aligns more closely with patterns observed in European and Hong Kong Chinese cohorts, where NSD1 point mutations constitute the overwhelming majority (83% and 88%, respectively) [10,13]. This suggests that despite geographical proximity, the genetic etiology of Sotos syndrome in China may follow a "European-like" pattern rather than a "Japan/Korea-like" pattern. This genetic heterogeneity has also been reflected in recent studies, with new NSD1 point mutations continually being reported [22]. The reasons for this regional variation warrant further investigation and may involve population-specific genetic backgrounds or differences in mutagenic mechanisms.

The tumor risk in our cohort was 7.8%, slightly higher than the commonly cited approximately 3% [9,23], though this may be influenced by publication bias in case series reports. Nevertheless, the occurrence of several malignant tumors underscores the importance of maintaining vigilance and considering appropriate monitoring in clinical management guidelines. Furthermore, the phenotypic spectrum of Sotos syndrome may be broader than traditionally recognized. A recent cohort study of 31 cases described atypical presentations including non-structural heart disease, rare tumors (such as pulmonary hamartomas), and recurrent urinary tract infections [24], suggesting clinicians should remain vigilant for seemingly atypical systemic symptoms to facilitate comprehensive multisystem follow-up.

The initial misdiagnosis experienced by the index case in this cohort highlights a significant clinical differential diagnosis challenge. The patient was initially misdiagnosed with CAH due to hormonal abnormalities, with the complete trajectory of hormonal and electrolyte dynamics presented in Supplementary Table S1. Although the co-occurrence of Sotos syndrome and CAH is extremely rare, transient adrenal hormone abnormalities may cause confusion [25]. Additional case reports suggest that Sotos syndrome may coexist with other endocrine abnormalities such as congenital hypothyroidism [26], but the hormonal changes observed in this indexed case are more consistent with a stress response. The NSD1 (NM_022455.4): c.3550G>T (p.Glu1184*) variant carried by this patient represents a novel pathogenic missense mutation. Notably, other loss-of-function variants affecting the same amino acid (Glu1184), such as c.3549-3550insT, have been reported in multiple studies as associated with classic Sotos syndrome, but none described an association with adrenal insufficiency or CAH [10-12]. Considering the patient's history of severe neonatal stress (pneumonia, hemorrhage) and the dynamic normalization of hormone levels upon resolu-

tion of stress, as demonstrated in Supplementary Table S1, the early transient abnormalities are more likely attributable to stress-induced transient alterations in the hypothalamic-pituitary-adrenal axis rather than a direct effect of NSD1 deficiency or concomitant CAH. The lesson from this case is that clinicians should broaden their diagnostic considerations for infants presenting with excessive growth and atypical CAH features (e.g., hyperpigmentation without classic salt-wasting or virilization), especially when hormone levels do not correlate with clinical manifestations or treatment response. Active pursuit of genetic testing (e.g., NSD1 gene analysis) is warranted to clarify the etiology and avoid unnecessary long-term hormone therapy.

Limitations

This study has several limitations. First, it is inherently a retrospective analysis with a relatively small sample size (n = 51), which limits our ability to conduct more in-depth subgroup analyses or detect rare phenotype-genotype associations with sufficient statistical power. Second, data primarily derived from published case reports inevitably reflects publication bias (e.g., cases with more typical clinical presentations or rare complications may be prioritized for reporting), and variations exist in data reporting completeness and standardization across different publications. Despite diligent efforts to verify and consolidate information, the possibility of unidentified duplicate cases cannot be entirely ruled out. Furthermore, missing records of certain clinical features in some cases may slightly affect the precise estimation of specific phenotype prevalence. Finally, the genetic analysis in this study primarily relied on prior testing reports and did not perform unified functional validation for some variants.

Future prospective, multicenter, large-scale studies will contribute to a more comprehensive characterization of the disease spectrum of Sotos syndrome in China.

CONCLUSION

In summary, through analysis of 51 Chinese patients, this study delineates the clinical and genetic spectrum of Sotos syndrome in China. Phenotypic presentation aligns with global experience, but the genetic basis reveals a unique pattern dominated by NSD1 point mutations-similar to European populations yet distinct from other East Asian cohorts. These findings underscore the pivotal role of molecular diagnostics in confirming Sotos syndrome and differentiating it from clinically similar disorders such as CAH. A multidisciplinary management approach is recommended, including monitoring for potential complications such as tumors.

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The entire content of this article was not assisted in any way by any form of artificial intelligence-generated tools during the writing process.

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Declaration of Interest:

The authors have no conflicts of interest to declare.

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