Journal of Molecular Neuroscience (2022) 72:149–157
https://doi.org/10.1007/s12031-021-01897-5

Neurodevelopment and Genetic Evaluation of Sotos Syndrome Cases with a Novel Mutation: a Single-Center Experience

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Received: 9 October 2019 / Accepted: 28 July 2021 / Published online: 12 August 2021

Abstract

Sotos syndrome is a non-progressive neurological disease with overgrowing, increased bone age, and developmental retardation. The aim of this study is to evaluate the prenatal, natal, and postnatal clinical findings of patients with Sotos syndrome. Sixteen patients suspected to have Sotos syndrome with clinical findings were examined retrospectively, ranging in ages between 3 and 23. In our file screening, we screened the FISH results of all 16 patients, but not all patients had NSD1 gene analysis results. We collected NSD1 gene analysis results, if there were any. The parameters that we investigated for these patients are birth weight, birth length, Apgar score at the 5th minute, dysmorphological face appearance, bone age, seizure, learning disability, feeding difficulties, surgical operation, and other accompanying abnormalities (brain MRI, abnormal echocardiographic findings, chronic otitis media, etc.). The anamnesis, clinical examination findings, and genetic reports of the patients were examined. For this, the hospital registration system was used. Breech presentation, Apgar score in the 5th minute of between 4 and 7, atrial septal defect at echocardiography, and consanguineous marriage rate were detected to be increased in individuals with Sotos syndrome compared to the normal population. When compared to the general population, delayed psychomotor development was determined. Macrocephaly, increased bone age, chronic otitis media frequency, and hernia operation frequency were determined to see if all patients were consistent with the literature. As a result of NSD1 gene sequencing analyses (NSD1 gene analysis was performed in 6 patients and a mutation was detected in 3 of them), three were found to have NSD1 gene mutation (one of them was novel). A novel deletion-type mutation that was not previously reported in the literature in the 19th exon of the NSD1 gene was determined. Xiphoidal protrusion was detected on this patient that had the novel mutation, and this situation has not been reported in the literature previously. If a patient has rapid growth, difficulty in learning, macrocephaly, speech delay, and timid personality, Sotos syndrome can be considered at the pre-diagnosis stage.

Keywords Sotos syndrome · Macrocephaly · Fetal macrosomia

Abbreviations

OFC	Occipitofrontal circumference
NSD1	Nuclear receptor binding SET domain protein 1
OMIM	Online Mendelian Inheritance in Man
LGA	Large for gestational age
SGA	Small gestational age
AGA	Appropriate for gestational age

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Background

The clinical features of Sotos syndrome (OMIM 117,550) were first described in 1964 as large body size and early accelerated growth, increased bone age, acromegaloid features, developmental retardation, and non-progressive neurological disease (Agwu et al. 1999). The main features of this syndrome are overgrowth in childhood, macrocephaly, diffuse facial gestalt, varying degrees of learning difficulty, and variable minor clinical features. The diagnosis is usually suspected after birth because of the increase in height, occipitofrontal circumference (OFC), and bone age. Neonatal complications including hypotonia and feeding difficulties and characteristic facial features are seen. Other clinical features are scoliosis, cardiac and genitourinary abnormalities, and seizures. Also, in this syndrome, various degrees

of motor and cognitive development delay are seen (Baujat and Cormier-Daire 2007).

In Sotos syndrome, most of the patients have a sporadic mutation but autosomal dominant inheritance has also been reported (Edery et al. 2003). Thus, the existence of other individuals with the same symptoms in the family is an important factor. In 2002, Kurotaki and colleagues investigated NSD1 (nuclear receptor binding SET domain protein 1) from a 5q35 break point on an individual with Sotos syndrome with chromosomal translocation. As a result, they showed that haploinsufficiency of NSD1 is the main cause of Sotos syndrome (Kurotaki et al. 2002).

For Sotos syndrome, characteristic facial features are frontal bossing, high anterior hairline, increased head circumference (above the 97th percentile), downslanting palpebral fissures, and prominence of the jaw. The hands and feet are also overgrown (Agwu et al. 1999). Prenatal overgrowth is a well-known feature of Sotos syndrome. The most commonly recorded growth parameter at birth is weight, but weight is a poor diagnostic indicator in Sotos syndrome. Usually seizures have been reported that 50% were febrile convulsion. Neuroimaging anomalies are considered to be specific for this syndrome. Among these, ventricular dilatation (particularly in the trigone region) is most frequently identified while other abnormalities include midline changes (hypoplasia or agenesis of the corpus callosum, cavum septum pellucidum), cerebral atrophy, and small cerebellar vermis (Visser and Matsumoto 2003).

Patients with Sotos syndrome have a non-progressive neurological dysfunction that includes reduced skillfulness and coordination. Cole and Hughes reported an average developmental/intelligence quotient (DQ/IQ) of 78 in Sotos cases ranging from 40 to 129 ($n = 23$). Boer et al. found that the mean IQ was 76 (range 47 to 105) in 21 individuals with NSD1 gene variants. Especially during infancy, the disease expresses itself as delay in language and motor development. The level of learning disability appears highly variable (Baujat and Cormier-Daire 2007).

The Apgar score, which is used for fetal well-being, is another parameter questioned for this study. This score includes color, heart rate, reflexes, muscle tone, and respiration. There are 3 categories according to the results of the Apgar score: low (0–3), intermediate (4–6), and normal (7–10). Low Apgar scores at birth are consistently associated with increased risk of neurological diseases, such as cerebral palsy, epilepsy, and cognitive impairment (Tweed et al. 2016) (Cnattingius et al. 2017).

Other parameters we searched for the patients with Sotos syndrome referred to our clinic were the history of a previous surgery (inguinal hernia operation, hypospadias operation, etc.) and having a chronic disease (such as chronic otitis media, congenital heart diseases). We could not find such a descriptive study done in the literature for this patient population.

Sotos syndrome is a syndrome that has broad clinical heterogeneity as seen in the studies above. We investigated a total of around 50 parameters for this study.

Methods

In this study, we selected patients with clinical characteristics of Sotos ranging in ages from 3 to 23 who applied to our Medical Genetics Department between 2012 and 2017. Seven male and nine female patients were evaluated retrospectively. In this context, we used the hospital registry system and the patient reports. The patients were selected according to the criteria in GeneReviews. In addition, parameters that were questioned in our study are prenatal history (oligohydramnios, polyhydramniosis), natal history (delivery type, birth length, birth weight), postnatal history (history of neonatal intensive care, hypoxic birth history, hypotonia, sucking difficulty), speech and walking time, surgery history, seizure history, and presence of any individuals with similar symptoms in the family.

Denver Developmental Screening Test II (DDST II) was developed to provide a simple screening method for slow development in infants and preschool children. The test covers four functions: gross motor, language, fine motor, and adaptive and personal-social skills (Glascoe et al. 1992). We used DDST II to determine the motor-mental developmental stages of our patients.

After a detailed anamnesis and clinical examination, we analyzed the pedigree chart. We used online diagnostic databases, Online Mendelian Inheritance in Man (*OMIM*), and GeneReviews for the diagnosis of Sotos syndrome.

There are no formal clinical diagnostic criteria published for Sotos syndrome. We used suspected criteria in GeneReviews for the patients we concluded to have Sotos syndrome (Table 1).

We used clinical differential diagnosis of major macrosomic syndromes (Beckwith-Wiedemann, Proteus syndrome, Weaver syndrome, etc.) with the Sotos syndrome. We did MRI, echocardiography and wrist graphy for the bone age of the patients we concluded to have Sotos syndrome. The reports of patients who underwent fluorescent in situ hybridization (FISH) analysis with the NSD1 probe for the 5q35 region were scanned to detect the deletion causing the disease. The results of NSD1 gene sequence analysis of the patients who had no deletion detected in FISH analysis were screened. Then, pathogenicity according to ACMG (American College of Medical Genetics and Genomics) classification of detected mutations was evaluated. The VarSome mutation scoring system was also used.

Table 1 Suspected criteria for Sotos syndrome in GeneReviews (Tatton-Brown et al. 2004)

• Characteristic facial appearance — easily recognizable between ages 1 and 6 years
○ Broad, prominent forehead with a dolichocephalic head shape
○ Sparse frontotemporal hair
○ Downslanting palpebral fissures
○ Malar flushing
○ Long narrow face (particularly bitemporal narrowing)
○ Long chin
Note: Facial shape is retained into adulthood; with time the chin becomes broader (squarer in shape)
• Learning disability
○ Early developmental delay
○ Mild to severe intellectual impairment
• Overgrowth
○ Height and/or head circumference is two or more SD above the mean (which approximates to the 98th centile)
○ Height may normalize in adulthood
○ Macrocephaly is usually present at all ages

Collected data were analyzed by Statistical Package for Social Sciences version 18.0 (SPSS Inc., SPSS IBM, Armonk, NY, USA). Continuous data were expressed as mean ± standard deviation (range: minimum–maximum) whereas categorical data were denoted as numbers or percentages where appropriate. Chi-square test was used for the statistical comparisons. Two-tailed p values less than 0.05 were accepted to be statistically significant.

Results

Clinical findings of our 16 patients are summarized in Table 2. Sotos syndrome was suspected for all of our 16 patients who have a characteristic facial appearance, learning disability, and overgrowth symptoms. All patients come from different families.

The increased birth weight according to the gestational week was seen in 10 patients (> 97 percentiles at same gender) (P1, P2, P4, P5, P7, P8, P10, P13, P15, P16). The increased birth length according to the gestational week was seen in 15 patients (> 97 percentiles at same gender) (P1, P2, P3, P4, P5, P7, P8, P9, P10, P11, P12, P13, P14, P15, P16). There were chronic otitis media in 5/16 patients (P3, P5, P11, P12, P14). Bone age was assessed with hand wrist graphy, and all patients were found to have an advanced bone age. When we evaluated the learning disability, 8 patients had mild symptoms, 6 patients had moderate learning difficulty, and only 2 patients had severe learning difficulty. At the same time, all of the patients had distinct personality traits like shyness, cowardice, and timidity. Seizures were reported by seven patients (P1, P2, P4, P8, P9, P14, P16). We questioned the parents of the patients for the presence of consanguineous marriage. In the presence of consanguineous marriage, we distinguished the relationship between parents as 1st degree, 2nd degree, 3rd degree, and as from the same village. In 11 of our patients, kinship among the parents was not reported. One of our patients had 1st degree of parental consanguinity (P13), 2 of them had 2nd degree of parental consanguinity (P9, P14), one of them had 3rd degree of parental consanguinity (P5), and one of them had parents from the same village (P16). Furthermore, when we examined the dysmorphological features of the patients, macrocephaly (increased at occipitofrontal circumference) was present in all cases. Other dysmorphological features were broad, prominent forehead; dolichocephalic head shape; sparse frontotemporal hair; epicanthus; hypertelorism; downslanting palpebral fissures; and prominent chin.

Another important aspect of pedigree analysis was the presence of any other genetic diseases in the family. All patients were from different families. There were no individuals with similar findings in the family of 4 of our patients. The father of 4 patients had similar symptoms (P2, P3, P4, P5). Two patients' mothers had similar symptoms (P9, P10). Uncles of two of the patients had similar symptoms (P12, P15). Cousins of 2 of the patients (P13, P14) and fathers' cousins of 2 (P1, P16) had similar symptoms.

When we evaluated the 5th-minute Apgar score of the patients, we found 11 of them normal (7–10) and 5 of them intermediate (4–6) (respective percentages are 68.8% and 31.1%) (Fig. 1).

When we categorized the fetal presentation type in our patients, we divided it into 2: vertex and breech presentation. Eleven (61%) of the 16 patients were born with vertex presentation, and 5 (39%) were born with breech presentation (Fig. 1).

Table 2 Clinical findings of 16 patients (present study)

	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12	P13	P14	P15	P16
Age* (yo)	16	9	3	3	14	7	11	17	14	5	23	14	5	9	7	7
Sex	M	M	F	F	F	F	M	F	M	F	F	F	M	M	F	F
Birth weight (kg)	4.5	4.2	3	5	4.6	2.7	4.5	4.2	3.4	4.4	3.5	3.2	4.8	3.8	4.3	5
Birth length (cm)	53	56	51	55	56	46	52	53	54	57	55	52	54	54	55	56
Apgar score at 5 min	8–9	8–9	4–7	8–9	8–9	4–7	8–9	4–7	8–9	8–9	4–7	8–9	4–7	8–9	8–9	8–9
Consanguineous marriage	–	–	–	–		–	–	–		–	–	–			–	
1st degree													+			
2nd degree									+					+		
3rd degree					+											
From same village																+
Have chronic otitis media	No	No	Yes	No	Yes	No	No	No	No	No	Yes	Yes	No	Yes	No	No
Bone age	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
Learning disability																
Mild	+		+			+			+		+		+	+	+	
Moderate		+		+	+		+	+								+
Severe										+		+				
Seizure	+	+	–	+	–	–	–	+	+	–	–	–	–	+	–	+
Dysmorphological findings																
Sparse frontotemporal hair	+	–	+	+	+	+	–	–	–	+	+	–	+	–	+	–
Broad, prominent forehead	+	+	+	–	–	–	+	+	+	+	+	–	+	+	+	+
Macrocephaly	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hypertelorism	+	–	–	–	–	–	–	–	+	+	+	–	–	+	+	–
Prominent chin	+	–	–	–	–	–	+	–	+	–	+	–	–	–	–	–
Epicanthus	–	–	+	–	–	–	+	–	–	+	+	–	+	+	+	+
Downslanting palpebral fissures	–	–	–	+	–	–	–	–	–	–	–	+	+	+	–	+
Dolichocephalic head shape	+	+	+	–	–	–	+	+	+	+	+	–	+	+	+	+

P patient number, + yes or present, – no or absent, ↑ increased, *yo* years old, *M* male, *F* female

*Age at first clinical assessment

Birth weight for gestational age was another parameter which was investigated in our patients. If a patient had a weight below the 10th percentile for the gestational age, this indicates a small gestational age (SGA). On the other hand, if he/she had a weight above the 97th percentile for the gestational age, this meant that they were large for their gestational age (LGA). Other newborns between the 10th and the 97th percentiles according to birth weight were categorized as appropriate for gestational age (AGA). According to these definitions, 38% of our patients were born with AGA, 56% were born with LGA, and 6% had no data to compare the birth weight to birth length (Fig. 1).

According to the classification made by Lubchenco and Battaglia's gestational week at birth, we classified the newborn maturity according to the birth week of the patients. According to this, a birth week earlier than the 37th gestational week was defined as premature, a birth week between the 37th and 42nd gestational weeks was defined as term, and a birth week later than the 42nd week was defined as postterm (Battaglia and Lubchenco 1967). Of our patients, 81% were term, while 13% were preterm and 6% were postterm (Fig. 1).

The mean times of neurological developmental stages of the patients with Sotos syndrome are also presented in Table 3. The patients' head neck control was at the 6th month, rolling from prone to supine position was at the 8th month, sitting with support was at the 9th month, sitting without support was at the 25th month, creeping was at the 15th month, walking was at the 22nd month, and fluent speech was at the 53rd month on average (Table 3).

Another parameter we questioned was previous surgical history. Four of the patients had undergone some surgery. One of them had hypospadias correction (P1), and 3 of them had inguinal hernia operation (P2, P3, P4), 1 of them being bilateral (P2).

We elevated patients' brain MRI. MRI reports showed that 6 patients had hydrocephaly and ventriculomegaly, 5 patients had cavum septum pellucidum varga, one had cavum septum pellucidum varga + hypoplasic cerebral parenchyma, and 4 patients had a normal imaging.

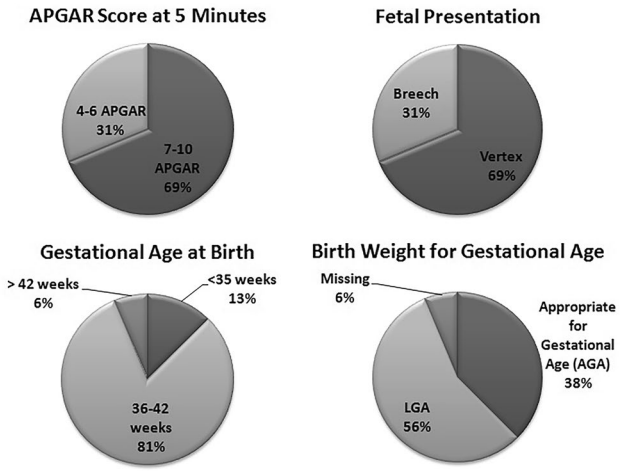

Fig. 1 Left top column, graph for rate of Apgar score at 5 min. Right top column, graph for fetal presentation at birth. Left bottom column, graph for gestational age at birth. Right bottom column, graph of birth weight for gestational age

According to the results, the most common finding was cavum septum pellucidum varga.

We also examined echocardiography reports of the patients. Eight of them were reported as normal, 7 of them were reported as atrial septal defect, and 1 case was reported as atrial septal defect with patent foramen ovale.

NSD1 mutation was detected in 73 to 93% of patients diagnosed with Sotos syndrome (Saugier-Veber et al. 2007). The detection rate of 5q35 microdeletions by FISH on patients with Sotos syndrome is between 66 (Kurotaki et al.) (Kurotaki et al. 2002) and 8% (Douglas et al. 2003) In our study, 5q35 microdeletions were detected by FISH in 3 patients who were siblings (P2, P10, P15). An NSD1 mutation was detected in 3 patients. The pathogenicity of these mutations is as follows: P3 is pathogenic, P7 is uncertain significance, and P14 is likely pathogenic. In one of the patients, an NSD1 mutation that was not previously described in the literature was detected (P14) (Table 4). This novel mutation was at the 19th exon of NSD1 gene (C.5908_5911delGAGT heterozygous). The sequence image of this mutation is shown in Fig. 2.

This mutation is considered "likely pathogenic" according to the ACMG classification. ACMG's identification criteria were PVS1 and PM2. These criteria are defined as follows: PVS1 (pathogenic very strong), null variant (frameshift) affecting gene NSD1, which is a known mechanism of disease (330 pathogenic variants out of 492 classified variants = 67.07%, which is greater than threshold = 10.0%), associated with Sotos syndrome, Weaver syndrome, and Beckwith-Wiedemann syndrome; PM2 (pathogenic moderate), variant not found in gnomAD exomes (good gnomAD exome coverage = 90.1); and variant not found in gnomAD genomes (good gnomAD genome coverage = 32.5) (Kopanos et al. 2019).

Discussion

In the literature, we found a few publications that investigate the Sotos syndrome and clinical manifestations.

A breech presentation occurs at 3–4% of all births. The percentage of breech deliveries decreases from 22 to 25% of births before gestational week 28 to 7–15% of births at the 32nd week to 3–4% of births in term births due to gestational age progression (Hickok et al. 1992). Eleven of the 16 patients were vertex birth; 5 were breech presentation. The prevalence of breech presentation in Sotos syndrome has never been reported before. In our study, the breech presentation rate was 31.3%. Therefore, there could be a point that needs attention for Sotos syndrome.

We did not find any study about the Apgar scores and Sotos syndrome relationship in the literature. A 5th-minute Apgar score between 4 and 7 is seen in 0.05% of the normal population, whereas in our study, a 5th-minute Apgar score between 4 and 7 was found in 31.3% of the Sotos syndrome patients (Thorngren-Jerneck and Herbst 2001).

Tatton-Brown and colleagues found that 76% of patients with Sotos syndrome were between 75th and 91st percentiles of birth weight for the gestational week (Tatton-Brown and Rahman 2004). In our study, we found that 56% of the patients were over the 97th percentile of birth weight. At the same time, the percentage of patients between 75th and 91st percentiles was found to be 38%. One patient (P6) had a

Table 3 Neurological development times (month)

		Head and neck control	Rolling from prone to supine position	Sitting with support	Sitting without support	Creeping	Walking	Lingual development	
								Simple words	Fluent speaking
N	Valid	16	16	16	16	16	16	16	16
	Normal	0	0	0	0	0	0	0	0
Mean (mouth)		6	8	9	25	15	22	25	53
Std. deviation (mouth)		2	3	3	57	6	10	11	107

Table 4 Results for 5q35 microdeletion and NSD1 sequencing

Patient number	Mutation detected with fluorescent in situ hybridization (FISH)	Mutation detected with NSD1 gene sequencing	Pathogenicity of mutation according to ACMG
P1	Normal	Mutation not detected	
P2	5q35 microdeletion (+)	Missing	
P3	Normal	Mutation detected (NSD1 c.1492C > T R498* protein conversion in exon 5)	Pathogenic
P4	Normal	Missing	
P5	Normal	Missing	
P6	Normal	Mutation not detected	
P7	Normal	Mutation detected (NSD1 c.4709G > T C1570F protein conversion in exon 12)	Likely pathogenic
P8	Normal	Missing	
P9	Normal	Missing	
P10	5q35 microdeletion (+)	Missing	
P11	Normal	Mutation not detected	
P12	Normal	Missing	
P13	Normal	Missing	
P14	Normal	Mutation detected (NSD1c.5908_5911delGAGT p.Glu1970Metfs*6)	Pathogenic
P15	5q35 microdeletion (+)	Missing	
P16	Normal	Missing	

twin, and their birth weight was between 10 and 5th percentiles. We concluded that this low birth weight was associated with twin birth.

In the study by Cole and Hughes, increased birth-length frequency was reported in 85% of individuals with Sotos syndrome (Cole and Hughes 1994). In our study, we found that 15 out of 16 (93%) patients had an increased birth weight. As Baujat and Cormier-Daire showed, as well as our study, the birth length is increased more than the birth weight (Baujat and Cormier-Daire 2007).

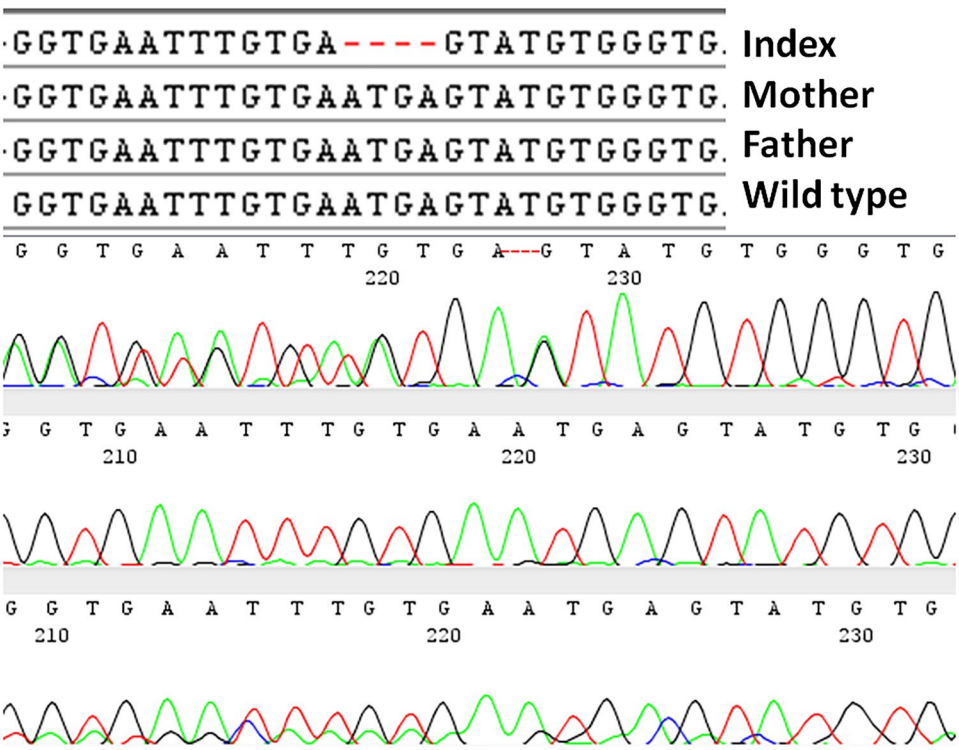

Fig. 2 NSD1 sequence image for novel mutation

The classic method of skeletal age assessment is based on the difference in the radiographic appearance of the maturity indices of wristband radiographs when compared to a reference atlas (Płudowski et al. 2004). Agwu et al. found that all Sotos syndrome patients had an increased bone age (Agwu et al. 1999). Also in our study, we found that all the children with Sotos syndrome had an increased bone age compared to the same-aged children in the general population.

Cole and Hughes have found a seizure frequency of 50% among individuals with Sotos syndrome. In our study, this proportion (7/16) corresponds to 43% (Agwu et al. 1999). The rate of seizure in our study is also consistent with the literature.

Cole and Hughes found that chronic otitis media prevalence was 72% in Sotos syndrome. In our study, this rate was 31.2% (Cole and Hughes 1994). The presence of chronic otitis media is thought to cause hearing loss in patients. This situation is likely to cause learning difficulty as well.

We could not find any study about consanguineous marriage in Sotos syndrome in the literature. In our study, parents of one patient had 1st degree of consanguinity (P13), those of two patients had 2nd degree of consanguinity (P9, P14), those of one had 3rd degree of consanguinity (P5), and those of one were from the same village (P16).

In children with Sotos syndrome, there is a delay in psychomotor development compared to normal development. This delay is present in all patients, and it is thought that the probable cause is hypotonia in the early period, as noted in the article of Cole and Hughes (Cole and Hughes 1990). At the same time, the presence of learning difficulties and behavioral problems makes this syndrome difficult in the school age.

The typical facial appearance may be helpful for predicting this syndrome. As in our study, macrocephaly was seen in 100% of patients in the literature (Cole and Hughes 1990). Sotos syndrome can be considered in a patient with macrocephaly and typical facial dysmorphology.

In the literature review we conducted, there was no information about gestational age at birth in Sotos syndrome. The preterm birth ratio is between 8 and 18% in the general population (Blencowe et al. 2012). In our study, the preterm birth rate was found to be 13% and there is no increase.

The presence of an abnormal MRI in Sotos syndrome is not a surprise (Schaefer et al. 1997). In our study, MRI was normal in 25% of patients. In addition, ventriculomegaly, which was reported as 62.5% in the literature, was the most frequent MRI finding in our study. The frequency of ventriculomegaly in our study was found to be 37.5%. The second most common MRI finding in our study was cavum septum pellucidum varga, which we found in 31.5% of the cases. The frequency of this finding was 40% in the literature (Schaefer et al. 1997).

The incidence of congenital heart disease in Sotos syndrome is between 8 and 23.5% (Tatton-Brown and Rahman 2004) (Noreau et al. 1998). In our study, this rate was 50%. In echocardiography, the atrial septal defect was detected in 43.7% of the patients. But none of these patients had a heart failure that required surgery.

Inguinal hernia and hypospadias is another minor finding (2% and 15%) for Sotos syndrome patients as noticed in the study of Tatton-Brown et al. (2005). In our study, 1 out of 16 cases, which also had a novel mutation, had hypospadias.

The variant detected at P3 causes a non-sense mutation. It is classified as pathogenic according to ACMG criteria

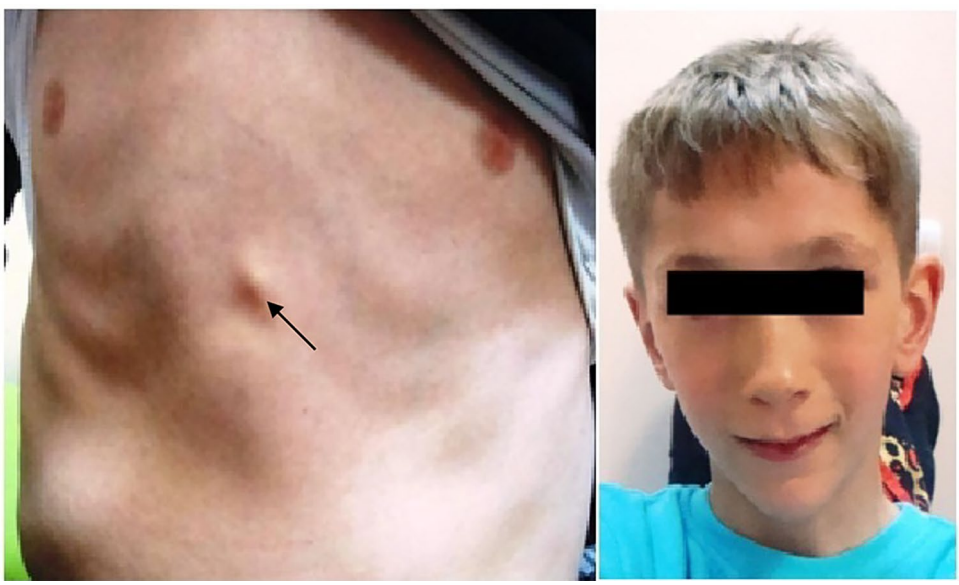

Fig. 3 NSD1 gene (p.Glu1970Metfs*6 (c.5908_5911delGAGT) novel mutation detected in patient (P14). At the tip of the arrow, there is a xyphoidal protrusion which may be specific to this mutation

because of the match with PVS1 (null variant (non-sense), in gene NSD1, for which loss of function is a known mechanism of disease (gene has 306 pathogenic loss-of-function (LOF) variants and gnomAD loss of function observed/expected = 0.0452, which is less than 0.763), associated with Sotos syndrome 1, Weaver syndrome, and Beckwith-Wiedemann syndrome), PM2 (variant not found in gnomAD exomes (good gnomAD exome coverage = 84.7), variant not found in gnomAD genomes (good gnomAD genome coverage = 30.9)), PP3 (pathogenic computational verdict based on 5 pathogenic predictions from BayesDel_addAF, DANN, EIGEN, FATHMM-MKL, and MutationTaster vs no benign predictions), and PP5 (ClinVar classifies this variant as pathogenic, rated 1 star, criteria provided, single submitter, with 1 submission). At the same time, the variant detected in P7 is a likely pathogenic missense mutation. It appropriates with PM1 (UniProt protein NSD1_HUMAN zinc finger domain "PHD-type 1" has 1 non-VUS missense/in-frame/non-synonymous, variant (1 pathogenic and 0 benign), pathogenicity = 100.0%, which is more than threshold of 50.0%), PM2 (variant not found in gnomAD exomes (good gnomAD exome coverage = 87.6), variant not found in gnomAD genomes (good gnomAD genome coverage = 33.9)), PP2 (the gnomAD missense *Z*-score = 3.41, which is greater than 0.647), and PP3 (pathogenic computational verdict based on 11 pathogenic predictions from BayesDel_addAF, DANN, DEOGEN2, EIGEN, FATHMM-MKL, LIST-S2, M-CAP, MVP, MutationAssessor, MutationTaster, and SIFT vs 1 benign prediction from PrimateAI). Alteration in the NSD1 gene detected in P14 causes frameshift mutation, and it is classified as pathogenic. Because it is scored as PVS1 (null variant (frameshift), in gene NSD1, for which loss of function is a known mechanism of disease (gene has 306 pathogenic LOF variants and gnomAD loss of function observed/expected = 0.0452, which is less than 0.763), associated with Sotos syndrome 1, Weaver syndrome, and Beckwith-Wiedemann syndrome), PM2 (variant not found in gnomAD exomes (good gnomAD exome coverage = 92.9), variant not found in gnomAD genomes (good gnomAD genome coverage = 32.7)) and PP3 (pathogenic computational verdict based on 1 pathogenic prediction from GERP vs no benign predictions).

Xiphoidal protrusion was present in the patient with the novel mutation (Fig. 3). No similar condition has been reported in patients with Sotos syndrome in the literature. Could this mutation be responsible for this phenotype? The accuracy of this claim can only be determined by further cell culture and enzyme assays.

Clinical heterogeneity is seen in Sotos syndrome as it is in most syndromes. As a good example in our case whom we detected a novel mutation, there were findings that did not exactly match with Sotos syndrome diagnosis criteria at first. For instance, the birth height was 54 cm and the birth weight was 3800 g. In the dysmorphological examination, there was no frontotemporal sparse hair. But the most important finding was rapid growth and rapid development compared to peers and a cowardly, funky, shy personality trait.

Conclusion

As Hippocrates said, "It is more important to know what sort of person has a disease than to know what sort of disease a person has." There are differences between clinical findings in individuals with Sotos syndrome. If one patient has macrocephaly, macrosomia, rapid growth, learning difficulty, speech delay, cowardly personality, typical dysmorphological facial findings, and advanced bone age, then Sotos syndrome should be considered in differential diagnosis.

Acknowledgements We would like to thank the patients and families.

Author Contribution M.E. and B.G. conceived and designed the study. A.G. and B.D. performed clinical assessments. M.S. performed experiments and contributed to data acquisition, analysis, and interpretation. B.G. drafted the manuscript. All authors contributed to critical revision of the manuscript for intellectual content and final approval of the manuscript.

Availability of Data and Materials The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics Approval and Consent to Participate All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from the guardians of the patients included in this study.

Competing Interests The authors declare no competing interests.

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