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Case Report

Novel Variant in Sotos Syndrome: Second Case Report from Saudi Arabia

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Abstract

Background: Sotos syndrome (SS, OMIM#117550) is an uncommon autosomal dominant disorder, first identified by Sotos., *et al*. in 1964. It is characterized by three cardinal features unique facial features, learning disabilities, and overgrowth.

Case Presentation: We describe a 1-year-old Saudi male infant diagnosed with Sotos syndrome harboring a novel variant in the *NSD1* gene. This represents the second genetically confirmed case of Sotos syndrome reported from Saudi Arabia and the ninth from the Middle East and North Africa (MENA) region.

Conclusion: Sotos syndrome is likely underrecognized in clinical practice. Genetic testing plays a crucial role in confirming the diagnosis and in expanding the understanding of genotype-phenotype correlations.

Keywords: *Sotos Syndrome; NSD1 Gene; Saudi Arabia; Middle East and North Africa (MENA); Overgrowth Syndrome*

Introduction

Sotos syndrome (SS, OMIM#117550) is an uncommon autosomal dominant disorder, first identified by Sotos., *et al.* in 1964 [1]. It is characterized by three cardinal features unique facial features, learning disabilities, and overgrowth [2,3].

Global incidence of Sotos Syndrome is approximately 1 in 14,000 individuals [4].

Typical facial characteristics include a broad and prominent forehead, sparse hair at the front and temples, down-slanting palpebral fissures, malar flushing, a long and narrow face, a small, pointed chin, and unusual macrocephaly [5]. Other clinical features include scoliosis, seizures, and renal and cardiac anomalies [6,7]. The disease can be further complicated by ADHD, anxiety, aggression, tantrums, and autism spectrum disorder. Anxiety is notably more common in Sotos syndrome than in other intellectual disabilities [8].

Over 90% of Sotos syndrome cases are caused by heterozygous intragenic variants in the *NSD1* gene. The remaining cases result from a 5q35 microdeletion that involves either a partial or complete deletion of the *NSD1* gene and its surrounding region.

Molecular genetic testing is essential to confirm the diagnosis of Sotos syndrome [9].

In this report, we describe a 1-year-old Saudi male infant diagnosed with Sotos syndrome harboring a novel variant in the *NSD1* gene. This represents the second genetically confirmed case of Sotos syndrome reported from Saudi Arabia and the ninth from the Middle East and North Africa (MENA) region.

Case Presentation

One-year-old Saudi male infant, was delivered via emergency cesarean section due to previous cesarean section to a G9P6+2 mother at a gestational age of 33 weeks plus 6 days who had gestational diabetes otherwise was healthy throughout pregnancy. He cried immediately after birth with a good posture and Apgar scores of 7 and 9 at 1 and 5 minutes respectively. He was initially managed with noninvasive ventilation but due to deterioration in his respiratory status, he was intubated with initial ventilatory setting PC/AC mode with PIP 16 PEEP 6 rate 40 and FIO_2 50%. His initial blood gas was PH 7.37 PCO_2 37 mmHg HCO_3 19.8 mmol/L. Chest x-ray (Figure 1) showed respiratory distress syndrome (RDS) picture, and he was given two doses of surfactant after which there was marked improvement in his respiratory status and ventilatory setting were weaned successfully gradually to low setting.

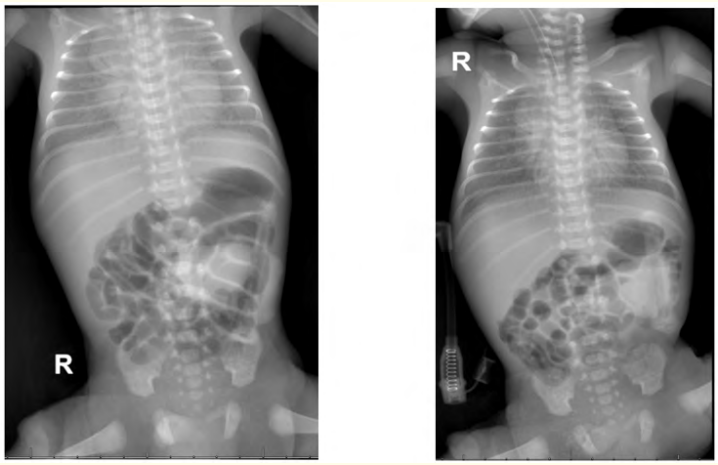

Figure 1A and 1B: 1A: *Chest x ray pre surfactant therapy. 1B: Chest x ray post surfactant therapy.*

The initial examination showed a preterm baby boy with no obvious dysmorphic features, in a moderate respiratory distress with a Ballard score compatible with the gestational age of 33 weeks. His growth parameters at birth were as follows: the weight was 1.5 kg (on the 3rd centile), the Length was 44 cm (between 10th - 50th centile) and the head circumference was 31 cm (on 50th centile).

Vital signs were stable. The systemic examination was unremarkable.

The patient started on total parenteral nutrition, complete blood count (CBC) was normal, blood culture was taken and started on antibiotics. Due to the unavailability of bed in our Neonatal Intensive Care Unit (NICU), the baby was transferred to another hospital at the age of 18 hours. The baby returned to our unit at the age of 25 days. He was on low setting mechanical ventilation there and was extubated to high flow nasal cannula 4 L/min, FIO_2 21% one day prior to transfer. The echocardiogram was done there and showed a large Patent Ductus Arteriosus (PDA) for which he received two courses of paracetamol and repeated echogram at the age of 17 days revealed small PDA. He was on orogastric tube feeding. There was suspension of dysmorphic baby in the previous hospital. Evaluation in our unit

showed evidence of hospital acquired infection with fever of 38.5°C, tachycardia with heart rate of 170 beats/min, lethargy and increased respiratory distress. The baby was intubated, blood urine and CSF cultures were taken and started on vancomycin and ceftazidime. Patient recovered soon after intubation and antibiotics, did not require inotropic support and all cultures were negative. patient was successfully extubated to noninvasive ventilation at 27 days of life.

Regarding the dysmorphism, family history (Figure 2) was reviewed, parents were non consanguineous. He has three full siblings, all born preterm, alive and healthy and has three healthy half siblings. His mother has had 2 abortions. Negative family history of neurological diseases.

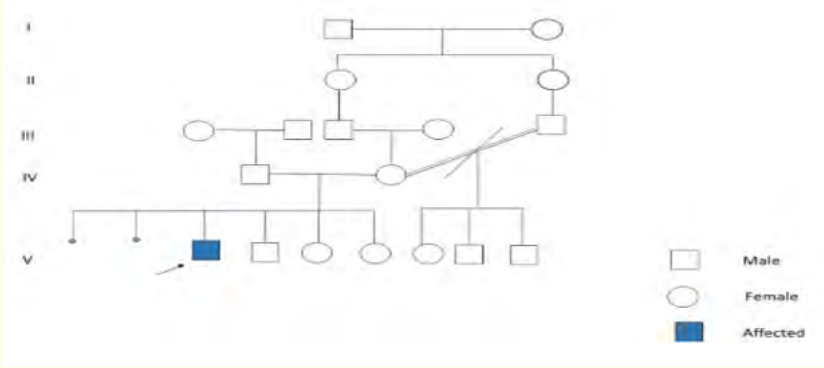

Figure 2: *Family pedigree.*

Genetic metabolic consultation has been done. The assessment was limited as the patient was intubated and there were no clear dysmorphic features apart from a pointed chin, low set, long ears and no hypotonia. This questionable dysmorphism can be normal variant as family were not yet encountered however, screening for internal organ anomalies was performed.

Renal US showed (Figure 3) bilateral grade I hydronephrosis. Cranial US was normal, Echocardiogram showed PFO with left to right shunt and no PDA, hearing screening was normal as well as ophthalmology examination. He required noninvasive ventilation CPAP/HFNC until the age 59 days, after which he was capable to breath comfortably and maintaining normal saturation. He was able to feed orally by the age of 60 days. The baby was discharged at the age of 71 days. Growth parameters upon discharge: weight 2.9 kg (below 3rd percentile) length 50 cm (on the 3rd percentile) and head circumference 35 cm (on the 10th percentile). He was given multidisciplinary clinic follow up.

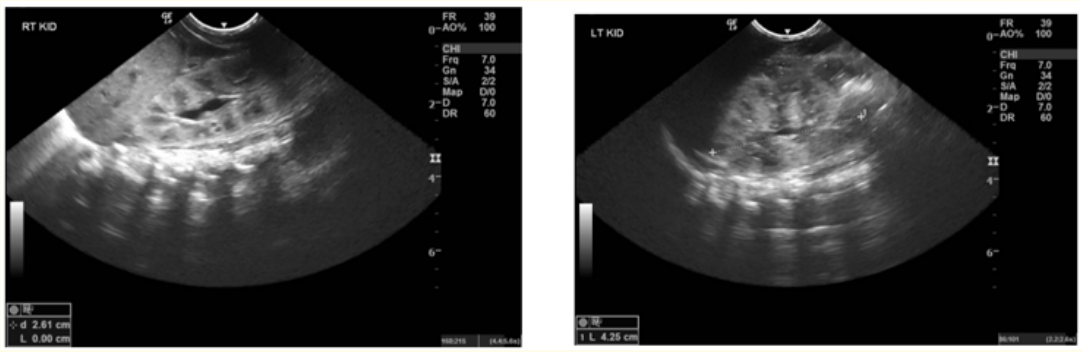

Figure 3: *Renal ultrasonographic at age of 1 month: bilateral grade I hydronephrosis.*

Patient was re-admitted to our hospital 2 days post discharge at the post-natal age of 3 months and 20 days as case of apnea to roll out sepsis with acute hypoxemic respiratory failure required intubation for 5 days then extubated to HFNC. He was diagnosed with ESBL Klebsiella pneumonia from endotracheal tube aspirate for which he was treated. He was revalued by genetic/metabolic service due to dysmorphism and hypotonia. Examination showed abnormal asymmetrical head shape, abnormal large, deformed ear more in the right side, epicanthal folds, hypertelorism, elongated face with normal neck and axial hypotonia. He was initially evaluated for hypotonia with a brain MRI, which demonstrated (Figure 4) bilateral, near-symmetrical, predominantly bi-fronto-parietal subcortical white matter T1 hypointense and T2 hyperintense signal abnormalities, with relative sparing of the deeper periventricular white matter. No diffusion restriction was observed. Basal ganglia and thalami showed normal signal intensity, while myelination was delayed for his age.

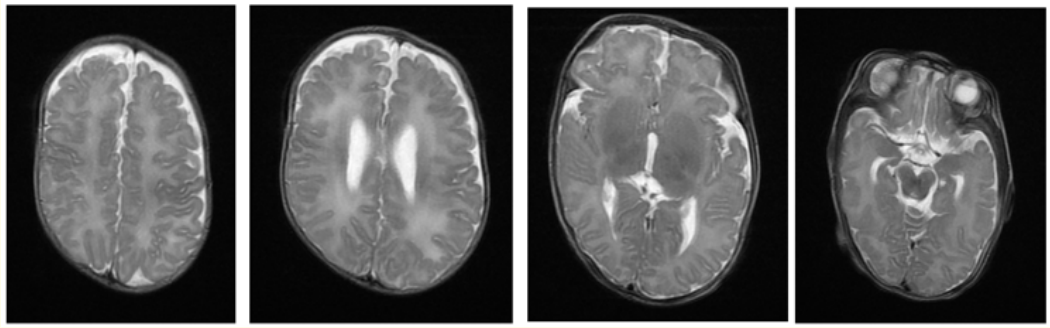

Figure 4: *Brain MRI.*

These findings concern neurometabolic disorders, so, serum ammonia, creatine kinase and lactate were extracted and all were normal. Acylcarnitine and urine for organic acids, and the result came later normal as well as chromosomal analysis. Neurology panels, and microarray were ordered and OPD followed up was given. The patient was discharged home with multidisciplinary follow up.

He was readmitted frequently with recurrent apnea and acute hypoxemic respiratory failure. Each time he required intubation for 48 - 72 hours followed by noninvasive ventilation then he was capable to breath comfortably and maintain normal saturation without oxygen. However, he was noticed to have irregularly triggering while he was on mechanical ventilation. Serial blood gas reviewed and showed non compensated mixed metabolic and respiratory acidosis which normalized later. Neurological assessment in subsequent admissions showed axial hypotonia, head lag, with normal power, tone and reflexes in upper and lower limbs bilaterally. The impression was this is most likely central type of apnea due to genetic causes. However, secondary chronic aspiration syndrome to the primary illness needs to be ruled out. He required through investigations such as electroencephalogram (EEG) which was repeated many times and was normal. Echocardiography was done to rule out some types of vascular ring and signs of pulmonary hypertension and was normal apart from PFO of 2-3 mm with left to right shunt. Barium swallow and meal was requested to rule anatomical abnormalities, such as H-type tracheoesophageal fistula (TEF), vascular ring, signs of Gastroesophageal Reflux Disease (GERD) and paresis and was normal. He was referred to ear, nose, and throat (ENT) specialists and flexible scope has been performed to rule out congenital dynamic airways anomalies like malacia, assessment of vocal cord movements and function, airway stenosis and signs of reflux. We do not have paediatric ENT in our hospital and their evaluation was limited. Signs of GERD was there for which they recommended to start proton pump inhibitors such as omeprazole. Bedside feeding evaluation by a bottle then by 3 teaspoons of puree showed adequate feeding skills with good coordination between the sucking and swallowing, no signs of respiratory distress, aspiration, symptoms of dysphagia or feeding difficulties. However, with recurrent admission with such complaint modified barium swallow to rule out silent aspiration is necessary. The patient had been referred to paediatric ENT, speech language therapist and modified barium swallow. Also, he was

referred for overnight pulse oximeter study and sleep study with/without CPAP/BiPAP titration and $EtCO_2$ monitoring to rule out central apnoea, hypopnea, and hypoventilations. Still the patient was not accepted due to technical issues and referral were sent again waiting for acceptance. At age of 4 months he was admitted as a case of poor feeding, with shortness of breath, cyanosis and seizure semiology in form of eye deviation and lip smacking for less than 5 minutes. He was brought to our emergency room with initial saturation of 25 - 30%, improved after suctioning (he had large amount of secretions) and high flow nasal cannula. The EEG revealed definitive seizure activity, which was effectively managed with phenobarbitone. The medication was successfully weaned off within six months of treatment.

Molecular genetic analysis results at the postnatal age of 5 months revealed a heterozygous likely pathogenic variant in the *NSD1* gene. This result is consistent with the genetic diagnosis of autosomal dominant Sotos syndrome.

The *NSD1* variant c.4233del p.(Lys1411Asnfs*8) creates a shift in the reading frame starting at codon 1411 in exon(s) no. 8 (of 23). This is a novel variant not previously reported in the literature. It is classified as likely pathogenic according to the recommendations of ACMG/AMP ClinGen SVI general recommendations.

The mutation was not detected in the father or mother of the affected child, which suggested that the *NSD1* gene variant in the present case was *de novo*.

Evaluation at the age of one year showed failure to thrive with current weight is 5.15 kg (far below the 3rd percentile), length is 65 cm (above 97th percentile), head circumference is 43 cm (between 3rd -15th percentile).

Physical examination (Figure 5) demonstrated characteristic facial features, including a broad, prominent forehead with dolichocephalic head shape, sparse frontotemporal hair, a long, narrow face with marked bitemporal narrowing, low-set ears, a prominent chin, and significant central hypotonia.

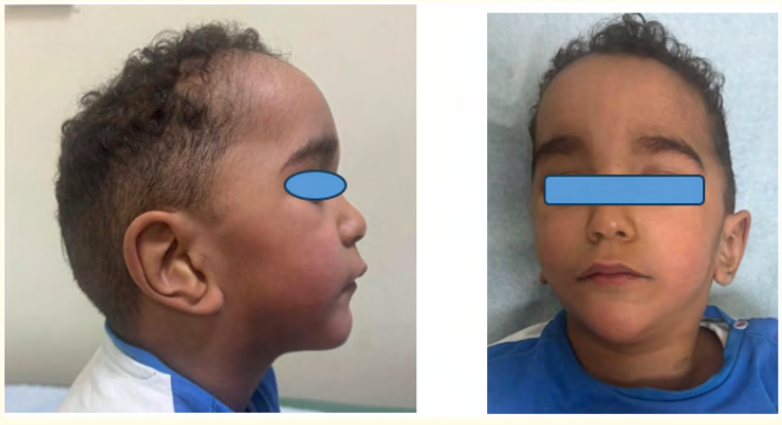

Figure 5: *Phenotype: Anterior posterior view and lateral view.*

The patient exhibits global developmental delay. He is unable to support his head, can grasp small light objects but is unable to transfer them between hands. He produces sounds and can recognize his mother's face, responding with a smile, but demonstrates no further social interaction.

Discussion

Incidence: Sotos syndrome is a rare overgrowth disorder inherited in an autosomal dominant pattern, with a global incidence of approximately 1 in 14,000 individuals. The incidence of Sotos syndrome in Saudi Arabia and the broader (MENA) region remains undetermined, with only eight confirmed cases reported to date. These include one case from Saudi Arabia reported in 2018 [10], one from Egypt in 2017 [11], two from Oman in 2022 and 2025 [12,13], and four recently published cases from Morocco in 2024 [14].

Phenotype: Sotos syndrome is defined by three cardinal features: a distinctive facial appearance, learning disabilities, and overgrowth-each observed in at least 90% of affected individuals. Beyond these primary characteristics, the syndrome is often associated with a range of major features, seen in 15 - 89% of cases. These include behavioural problems, advanced bone age, cardiac anomalies, cranial MRI or CT abnormalities, joint hyperlaxity (with or without flat feet), maternal preeclampsia, neonatal complications, renal abnormalities, scoliosis, and seizures. Additionally, 2-5% of individuals with Sotos syndrome may present with associated features such as tumors, constipation, and other less common findings [9].

Our case presents with all three cardinal features, along with five major features: seizures, renal abnormalities, cardiac anomalies, neonatal complications, and brain MRI abnormalities. However, scoliosis and other major criteria such as joint hyperlaxity, flat feet, and maternal preeclampsia were absent. No additional associated features were observed.

Cardinal criteria: The characteristic facial features in our case generally became apparent by the age of one year. Global developmental delay was evident from the neonatal period. Notably, from the intrauterine stage through the first year of life, he maintained a normal head circumference-an atypical finding, as macrocephaly is commonly observed in individuals with Sotos syndrome.

His height was within the normal range at birth but showed a marked acceleration, exceeding the 97th percentile by the age of one year.

Major criteria: Premature delivery has been reported in several neonatal cases of Sotos syndrome, including our patient. His neonatal course was complicated by hypotonia, failure to thrive, recurrent respiratory infections, repeated episodes of apnea, and acute hypoxemic respiratory failure.

Cardiac evaluation revealed a large PDA at birth, which was managed with two courses of paracetamol. Follow-up echocardiography at 17 days of age demonstrated a reduction to a small PDA, which closed spontaneously by 1 month of age.

Renal involvement included bilateral grade I hydronephrosis detected on ultrasound at 1 month of age, which resolved by 5 months. At that time, bilateral renal cysts were observed. Follow-up ultrasound at 1 year showed (Figure 6) two small right renal cysts with no recurrence of hydronephrosis.

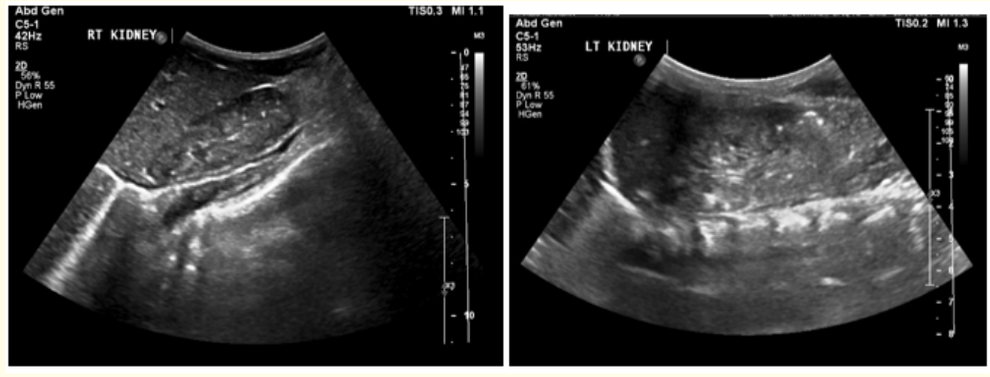

Figure 6: *Renal ultrasonographic at age of 1 year.*

Brain MRI at 3 months revealed bilateral, near-symmetrical, predominantly bi-fronto-parietal subcortical white matter T1 hypointense and T2 hyperintense signal abnormalities, with relative sparing of the deeper periventricular white matter. No diffusion restriction was observed. Basal ganglia and thalami demonstrated normal signal intensity, while myelination was delayed for age.

Seizures were first noted at 4 months of age and were successfully controlled with phenobarbitone, which was gradually tapered and discontinued after six months of therapy.

Additional associated features: No additional associated features were observed.

A summary of the phenotypic and genotypic features of reported Sotos syndrome cases from the MENA region, including our patient (case 9), is presented in the table 1.

			Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9
Sex			Male	Male	Male	Male	Male	Male	Female	Male	Male
Age			9 years	2 years 8 months	2 years	21 months	3 years	10 years	4 years	5 years	5 months
Country of origin			Morocco	Morocco	Morocco	Morocco	Egypt	Oman	Oman	Saudi	Saudi
Phenotype	Cardinal	Distinctive facial features	+	+	+	+	+	+	+	+	+
		Learning disabilities	+	+	+	+	+	+	+	+	+
		Overgrowth	+	+	+	+	+	+	+	+	+
	Major features	Behavioural problems	-	+	+	+	+	+	+	+	-
		Advanced bone age	+	NA	-	-	NA	+	NA	NA	NA
		Cardiac anomalies	+	+	+	-	NA	NA	_	+	+
		Carnial CT or MRI abnormalities	-	-	+	NA	+	-	NA	+	+
		Joint hyperlaxity (-\+ flat feet)	NA	NA	Flat feet	NA	NA	NA	-	-	-
		Maternal preeclampsia	NA	NA	NA	NA	NA	-	-	-	-
		Neonatal complications	-	NA	+	NA	+	+	+	-	+
		Renal abnormalities	-	NA	NA	NA	NA	NA	-	+	+
		Scoliosis	-	-	-	+	NA	NA	-	NA	-
		Seizures	-	-	+	+	NA	NA	NA	NA	+
	Associated	Tumor, constipation and others	-	GERD, Asthma, hyrdocephaly	Ogival palate	-	-	Conductive hearing loss	Chorioretinal coloboma involving the optic disc and macula	-	-
Genotype			Heterozygous Frameshift variants in the NSD1 gene c.5390_5397dup p.Gly1800SerfsTer24	Heterozygous Frameshift variants in the NSD1 gene c.2493dup p.Lys832GlufsTer13	Heterozygous Frameshift variants in the NSD1 gene c.6030del p.Gly2013GlufsTer7	Heterozygous Missense variant in the NSD1 gene c.4928G>C p.Cys1643Ser	5q35 microdeletion spanning approximately 1.9 Mb in size and including the complete NSD1 gene	Heterozygous Missense variant in the NSD1 gene (c. 5990A > G: p. Tyr1997Cys)	Heterozygous pathogenic Nonsense variant in the NSD1 gene (c.3958C>T; p.Arg1320Ter)	Heterozygous deletion of the complete NSD1 gene (exons 1–23)	Heterozygous Frameshift variant in the NSD1 gene c.4233del p.(Lys1411Asnfs*8)

Table 1: *Phenotype and genotype of our case and previously reported cases.*

While clinical features vary, all cases uniformly exhibit the core characteristics of intellectual disability, overgrowth, and a distinctive facial appearance.

Genotype: Among reported cases of Sotos syndrome in the MENA region, seven have been linked to intragenic variants of the *NSD1* gene. Of these, three are point mutations, including two missense mutations and one nonsense mutation. Four cases, including the present one, are due to insertions or deletions (indels) leading to frameshift mutations. The current case involves a novel intragenic frameshift mutation that introduces a premature stop codon. The remaining two cases are associated with copy number variations (CNVs), with one involving a large chromosomal deletion and the other a whole-gene deletion.

Phenotype to genotype correlation: A genotype-phenotype correlation has been noted in Sotos syndrome with respect to overgrowth and learning disabilities. Individuals carrying a 5q35 microdeletion typically show less pronounced overgrowth but more severe learning disabilities compared to those with intragenic pathogenic variants in *NSD1*. However, no consistent correlation has been identified between other clinical features and genotype. Furthermore, there is no significant phenotypic difference between individuals with missense variants and those with truncating intragenic variants [9,15].

Conclusion

Sotos syndrome, though variable in clinical presentation, consistently manifests with intellectual disability, overgrowth, and distinctive facial features. In the MENA region, reported cases exhibit diverse genotypic alterations, including point mutations, indels, and copy number variations in *NSD1*. Our case adds a novel intragenic frameshift mutation to the spectrum. Given the syndrome's frequent underdiagnosis, genetic testing remains essential for accurate diagnosis, management, and for establishing genotype-phenotype correlations that can guide clinical care.

Conflict of Interest

The authors declare that they have no affiliations with or involvement in any organization or entity with any financial or non-financial interest in the subject matter or materials discussed in this manuscript.

Ethical Approval

This case report was approved by the Scientific Research Ethics Committee at QCH.

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