

Sotos syndrome

A case report of 1st genetically proven case from Saudi Arabia with a novel mutation in *NSD1* gene

Naglaa M. Kamal, MD^{a,b,*}, Jwahr M. Althobiti, MBBCh^b, Abdulaziz Alsaedi, MD^b, Ayman Bakkar, MD^b, Tahani Alkaabi, MBBCh^c

Abstract

Rationale: Sotos syndrome is a rare genetic disorder characterized by rapid growth during infancy and childhood; ≥ 2 SD for height and head circumference; distinctive facial appearance and developmental delay.

Ten clinically diagnosed cases have been reported from Saudi Arabia; none of them was genetically confirmed.

Patient concerns: A male Saudi patient, who had a birth length and head circumference above 97th centile, presented with abnormal rapid growth, delayed motor and mental milestones, aggressive behavior, obsession to close doors, nail biting, defective attention, and hyperactivity.

Diagnoses: Sotos syndrome was suspected

Interventions: Molecular genetic analysis for *NSD1* gene was carried for the patient.

Outcomes: A novel heterozygous deletion of all exons 1 to 23 of the *NSD1* gene was detected. Genetic counseling was carried for the family with extended genetic testing for the parents and his siblings with normal results.

Lessons: Despite its worldwide distribution, Sotos syndrome may be under-reported. Besides its characteristic clinical picture, molecular genetic testing is also extremely recommended.

Abbreviations: Hc = head circumference, Ht = height, MLPA = multiplex ligation-dependent probe amplification, NR = nuclear receptor, *NSD1* = nuclear receptor-binding SET domain protein 1, PHD = plant homeodomain protein, PWWP = proline-tryptophan-tryptophan-proline, SA = Saudi Arabia, VSD = ventricular septal defect.

Keywords: cerebral gigantism, novel mutation, *NSD1*, Saudi, Sotos syndrome

1. Introduction

Sotos syndrome or cerebral gigantism (OMIM 117550),^[1] 1st described by Sotos in 1964,^[2] is an autosomal dominant genetic disorder. It is characterized by overgrowth in childhood, distinctive facial appearance and mental and movement disabilities.^[3]

The affected infants and children tend to grow quickly with large hands/feet.^[4,5] They are all taller than their peers.^[4,5] Patients have characteristic facial features including broad and prominent forehead, sparse fronto-temporal hair, down slanting

palpebral fissures, malar flushing, long and narrow face, small pointed chin with unusual macrocephaly.^[4,5] Their milestones are usually delayed with associated intellectual impairment and mostly behavioral problems. Some patients may have scoliosis, seizure disorders, congenital heart defects, kidney abnormalities, hearing loss, and visual problems.^[1,3,6]

Most cases of Sotos syndrome are sporadic and may represent new dominant mutation in *NSD1* gene (nuclear receptor-binding SET domain protein 1) located on chromosome 5q35.2-35.3.^[1] Some authors suggest that its incidence is around 1 in 10,000 to 14,000 newborns^[1] while others suggested a higher incidence of 1: 5000.^[3] This is due to the fact that many of its features can be attributed to other conditions and hence it is under diagnosed.^[3]

The *NSD1* is a unique bi-functional cofactor with 2 distinct nuclear receptor (NR)-interaction domains called NID^{-L} and NID^{+L}.^[5] *NSD1* belongs to a family of NRs. These receptors bind to DNA response elements upon binding of congeneric ligands such as steroid and thyroid hormones, or retinoids.^[5] *NSD1* also contains several conserved functional domains, such as, SET, SAC, proline-tryptophan-tryptophan-proline (PWWP), and plant homeodomain protein (PHD). *NSD1* contains a Cys-rich region, which is composed of different arrangements of 3 conserved motifs, corresponding to a protein domain that has been called SAC for SET-associated Cys-rich domain.^[5] The SAC domain may have a function in chromosome binding. In addition to the SET and SAC domains, *NSD1* contains 6 other domains including 2 PWWP domains and 5 PHD domains.^[5]

The SET domain (su(var)3-9, enhancer-of-zeste, trithorax) was 1st identified as a motif present in the *Drosophila* proteins SU

Editor: Zelena Dora.

The study was approved by the Alhada Armed Forces Hospital research and ethical committee. Written informed consent was obtained from the patient's parents for publication of details of the case report. Personal information was not mentioned in a way which can lead to identification of the patient or his family.

All data generated or analyzed during this study are included in this published article.

The authors have no funding and conflicts of interest to disclose.

^a Cairo University, Cairo, Egypt, ^b Alhada Armed Forces Hospital, ^c Department of Pediatrics, Taif Children Hospital, Taif, Saudi Arabia.

* Correspondence: Naglaa M. Kamal, Cairo University, Cairo, Egypt (e-mail: nagla.kamal@kasralainy.edu.eg).

Copyright © 2018 the Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial License 4.0 (CCBY-NC), where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.

Medicine (2018) 97:47(e12867)

Received: 29 July 2017 / Accepted: 25 September 2018

<http://dx.doi.org/10.1097/MD.0000000000012867>

(var)3–9, E(z), and TRx. The SET domain was also found in a number of eukaryotic proteins.^[5] The SET domain was shown to play a role in cell growth and differentiation, and it is associated with chromatin. It also functions as a transcriptional repressor and/or a transcriptional activator.^[5]

It has been suggested that the PHD finger domains involve chromatin-mediated transcriptional regulation. The PWWP domain is thought to be involved in protein–protein interactions. Adjacent to the C-terminus of the PHD-V domain is another region rich in cysteines and histidines, possibly corresponding to a zinc-finger-like motif.^[5]

The function of *NSD1* remains largely unknown; however, its role includes activating as well as silencing domains and binding liganded as well as unliganded NRs. This suggests that *NSD1* could be a versatile NR intermediary factor controlling transcription either negatively or positively. It has been observed that the haplo-insufficiency of *NSD1* induces overgrowth which prompted Kurotaki et al to suggest that *NSD1* acts as a co-repressor of genes that promote growth.^[7]

Three reports were released from Saudi Arabia (SA), 14 cases were reported by al Rashed and 2 single cases, were reported by Alhumaidi and Al-Mulla et al.^[8–10] All of them were diagnosed based on their clinical findings and radiologic abnormalities. Although all the reported cases were similar to our patient clinically, none of them had undergone molecular genetic studies to confirm their diagnosis.

The 5-year-old patient described below is 1st Sotos syndrome proven case by molecular genetic analysis from SA.

2. Case presentation

A 5-year-old Saudi male patient born at term with a weight of 3.25 kg “50th centile,” length of 57 cm “>97th centile,” occipitofrontal head circumference 38 cm “99th centile,” small muscular ventricular septal defect (VSD) and minimal bilateral hydronephrosis.

Follow-up visits were planned, but the patient did not show until he was 1 year when he was hospitalized with bronchopneumonia. His body system review revealed delay in both motor and mental developmental milestones. For instance, he was unable to sit, stand or produce single words. He had stuttered speech and was wearing glasses. His height (Ht) and head circumference (Hc) were more than 97th centile; 89 and 50 cm, respectively. He had high forehead, long narrow face, down slanted palpebral fissure, large ears, right eye strabismus, and left eye estropia. Fortunately, he had no hearing deficits.

On further follow-up, the patient started pronouncing mummy and daddy at the age of 18 months, and started walking at the age of 24 months. After that the patient did not attend follow-up visits until he was 5 years when his parents presented suffering from his aggressive behavior toward his siblings, obsession to close doors, nail biting, defective attention and hyperactivity, and an evident abnormal rapid growth compared to his siblings as he was much taller than his elder 7 years brother. His Ht and Hc were more than 99th centile. He had mild mental disability with attention-deficit-hyperactivity disorder and obsessions. VSD was closed and the hydro-nephrosis status was static. His brain magnetic resonance imaging (MRI) revealed prominent ventricles and sulci as shown in Figure 1.

There was no similar presentation of this syndrome in his family and his parents were nonconsanguineous. Patient’s family pedigree is shown in Figure 2.

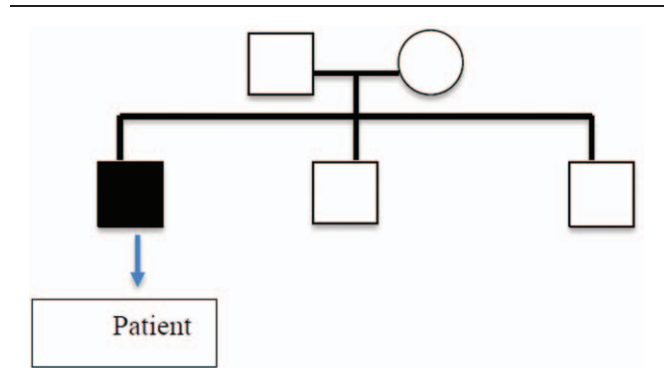


Figure 1. Patient’s family pedigree.

Molecular genetic analysis for *NSD1* gene was done for the patient and proved the diagnosis of Sotos syndrome with a novel *NSD1* gene mutation. Genetic counseling was carried for the family with extended genetic testing for the parents and his siblings with normal results, which shed light to the fact that the mutation found in the proband is denovo. Multidisciplinary team management has been provided for the patient, in conjunction with regular follow-ups with the neurologist, cardiologist, general pediatrician, speech therapist, psychiatrist, and ophthalmologist.

2.1. Molecular genetic analysis of the *NSD1* gene

Deletion/duplication analysis of *NSD1* gene on chromosome 5q35 (OMIM 606681)^[11] was performed. This was done by applying multiplex ligation-dependent probe amplification (MLPA) using the SALSA P026-D1 kit (Fig. 3).

The MLPA analysis revealed a heterozygous deletion of the complete *NSD1* gene (exons 1–23). The result was confirmed by an independent MLPA analysis. Heterozygous deletions of the *NSD1* gene have been reported to be causative for Sotos syndrome.

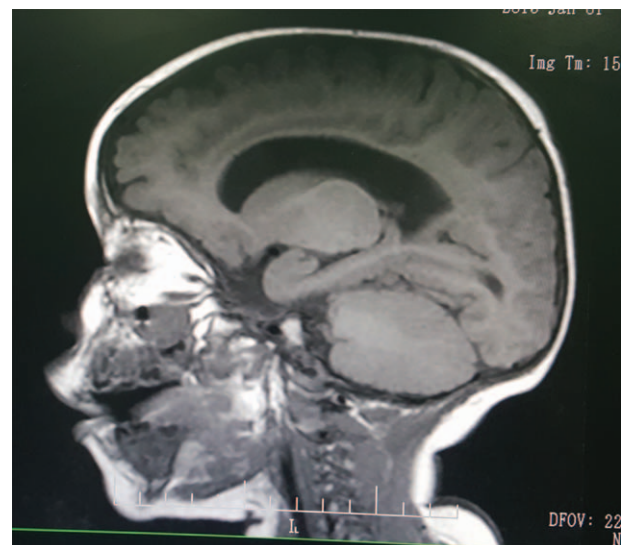


Figure 2. Brain magnetic resonance imaging of the patient, sagittal view, demonstrating prominent sulci and ventricles.

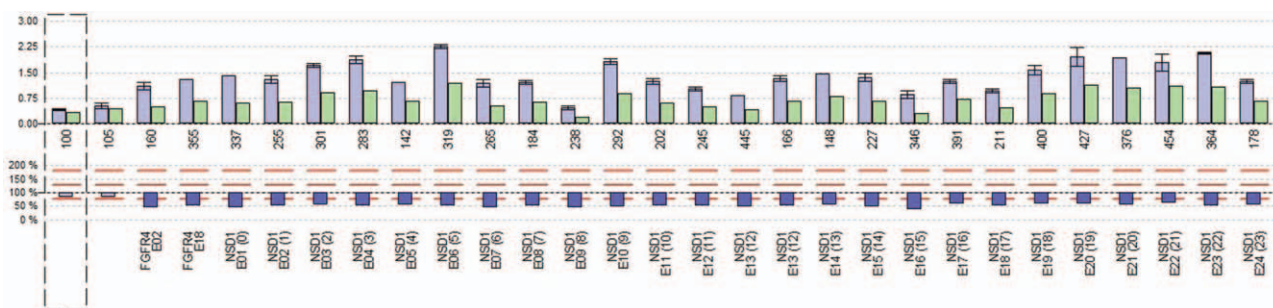


Figure 3. Multiplex ligation-dependent probe amplification genetic testing of the patient's with deletion of the complete *NSD1* gene (exons 1–23).

3. Discussion

Sotos syndrome, described in 1964, is a genetic disorder due to haplo insufficiency of the *NSD1* gene on chromosome 5q35.2-35.3 in 90% of the patients: Sotos syndrome 1. Recently, heterozygous mutations in the NFIX gene (nuclear factor I, X type) on chromosome 19p13.3 were identified in a few children with the Sotos syndrome phenotype: Sotos syndrome 2.^[11]

Clinically, it has cardinal, major and associated features occurring in $\geq 90\%$, 15% to 89%, and ≥ 2 and < 15 of the affected patients, respectively.^[12] Its cardinal features are the characteristic facial appearance, learning disability, and overgrowth while the behavioral problems, advanced bone age, cardiac anomalies, cranial MRI/computed tomography abnormalities, joint hyperlaxity/*pes planus*, maternal preeclampsia, neonatal complications, renal anomalies, scoliosis, and seizures are among the major features.^[6] The other associated features include: astigmatism, cataract, cholesteatoma, conductive hearing loss, constipation, contractures, craniosynostosis, cryptorchidism, gastroesophageal reflux, hemangioma, hemihypertrophy, hydrocele, hypercalcemia, hypermetropia, hypodontia, hypoplastic nails, hypospadias, hypothyroidism, inguinal hernia, myopia, neonatal hypoglycemia, nystagmus, pectus excavatum, phimosis, skin hyper/hypo-pigmentation, strabismus, talipes equinovarus, umbilical hernia, vertebral anomalies, and 2 to 3 toe syndactyly.^[6]

Sotos syndrome has worldwide distribution. Reviewing literature regarding genetically proven cases of Sotos syndrome revealed; deletion encompassing *NSD1* gene in a Japanese patient. In addition, point mutations have been identified in the majority of European Sotos syndrome patients.^[5] The *NSD1* gene in 42 Japanese patients with sporadic Sotos syndrome was analyzed. This revealed that 19 of them had a 2.2 mb microdeletion of 5q35 encompassing *NSD1*, and 4 of them had intragenic *NSD1* mutation predicted to inactivate the protein.^[7]

Another study evaluated 75 patients with childhood overgrowth for intragenic mutations and large deletion of *NSD1* gene. This study revealed that there were 3 deletions and 32 mutations (13 frame shift, 8 nonsense, 2 splice site, and 9 missense).^[13] On the contrary, upon analysis of 266 patients with *NSD1* aberrations, 233 had 180 different intragenic *NSD1* mutations and the remaining 33 individual had 5q35 microdeletions encompassing *NSD1* gene.^[12]

Previously reported data suggest that 93% of patients, who have been clinically diagnosed with Sotos syndrome, have identifiable *NSD1* abnormalities, of which 83% were intragenic mutations and 10% were 5q35 microdeletions.^[12]

Tatton-Brown et al^[12] evaluated 234 Sotos syndrome patients with an *NSD1* abnormality, and found that those with a 5q35

microdeletion have less overgrowth and more severe learning disability than individuals with an intragenic pathogenic variant while no genotype–phenotype correlations were detected for cardiac abnormalities, renal anomalies, seizures, and scoliosis. In addition, they found no correlations between type of intragenic pathogenic variant (missense vs truncating) and phenotype or between position of pathogenic variant (5' vs 3') and phenotype.

From Arab world, a total of 17 cases with typical clinical features of Sotos syndrome have been reported, among them 10 were Saudi. None of the those patients was proved by molecular genetic studies.^[8–10,14] Al Rashed et al^[8] diagnosed his 14 cases based on clinical features, 8 Saudis, 3 Egyptians, 2 Sudanese, and 1 Syrian. Alhumaidi^[9] described a patient with typical clinical features of Sotos syndrome with normal chromosomal studies.^[11] A similar patient, described by Al-Mulla et al,^[10] was clinically diagnosed as Sotos syndrome and treated for acute myelocytic leukemia. Our patient is the 1st genetically proven case from Saudi Arabia with a novel heterozygous deletion of the complete *NSD1* gene (exons 1–23). We recommend genetic testing of other cases from SA for better characterization of the Saudi cohort.

Author contributions

NMK: diagnosed the patient, did investigations, followed up him.

NMK, AA, AB, JMA: reviewed literature, drafted the manuscript, and reviewed the manuscript final.

JMA, TA: collected data of the patient and helped to draft the manuscript.

All authors read and approved the final manuscript.

Conceptualization: Naglaa M Kamal.

Data curation: Naglaa M Kamal, Jwahr Althobiti, Ayman Bakkar, Abdulaziz Alsaedi, Tahani Alkaabi.

Formal analysis: Ayman Bakkar, Abdulaziz Alsaedi, Tahani Alkaabi.

Investigation: Naglaa M Kamal.

Methodology: Naglaa M Kamal.

Project administration: Naglaa M Kamal.

Supervision: Naglaa M Kamal.

Writing – original draft: Naglaa M Kamal.

Writing – review & editing: Naglaa M Kamal, Jwahr Althobiti, Ayman Bakkar, Abdulaziz Alsaedi.

Naglaa M Kamal orcid: 0000-0002-8535-3838.

References

- [1] Sotos syndrome 1. Available at: www.omim.org/entry/117550. Accessed January 15, 2018.

- [2] Tatton-Brown K, Rahman N. Sotos syndrome. *Eur J Hum Genet* 2007;15:264–71.
- [3] Sotos syndrome. Available at: ghr.nlm.nih.gov/condition/sotos-syndrome. Genetics home reference. Accessed January 31, 2018.
- [4] Sotos syndrome. Genetic and rare disease information center. Available at: <https://rarediseases.info.nih.gov/diseases/10091/sotos-syndrome>. Accessed January 17, 2018.
- [5] Türkmen S, Gillissen-Kaesbach G, Meinecke P, et al. Mutations in NSD1 are responsible for Sotos syndrome, but are not a frequent finding in other overgrowth phenotypes. *Eur J Hum Genet* 2003;11:858–65.
- [6] Tatton-Brown K, Cole TRP, Rahman N. Sotos Syndrome. *GeneReviews*. Seattle (WA): University of Washington, Seattle. Initial posting: December 17, 2004; Last update November 19, 2015.
- [7] Kurotaki N, Imaizumi K, Harada N, et al. Haploinsufficiency of NSD1 causes Sotos syndrome. *Nature Genet* 2002;30:365–6.
- [8] Al Rashed AA, Al-Jarallah AA, Salih MA, et al. Sotos syndrome (cerebral gigantism): a clinical and radiological study of 14 cases from Saudi Arabia. *Ann Trop Paediatr* 1999;19:197–203.
- [9] Alhumaidi M. Sotos syndrome: a case report. *Ann Saudi med* 1994;14:514–6.
- [10] Al-Mulla N, Belgaumi AF, Teebi A. Cancer in Sotos syndrome: report of a patient with acute myelocytic leukemia and review of the literature. *J Pediatr Hematol Oncol* 2004;26:204–8.
- [11] Sotos JF. Sotos syndrome 1 and 2. *Pediatr Endocrinol Rev* 2014;12:2–16.
- [12] Tatton-Brown K, Douglas J, Coleman K, et al. 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.
- [13] Douglas J, Hanks S, Temple IK, et al. NSD1 mutations are the major cause of Sotos syndrome and occur in some cases of Weaver syndrome but are rare in other overgrowth phenotypes. *Am J Hum Genet* 2003;72:132–43.
- [14] al Talabani J, Shubbar AI, Mustafa KE. Major congenital malformations in United Arab Emirates (UAE): need for genetic counselling. *Ann Hum Genet* 1998;62(Pt 5):411–8.