De novo NSD1 Mutation Leading to Sotos Syndrome – First Case Report from Oman

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Abstract

Multiple factors control the growth of a child, including genetics, nutrition, and socioeconomic factors. Referral of tall boys who are otherwise well is very rare. However, sometimes, extraordinary tall stature for the age can be a cause of great concern to the parents. We report a case of an Omani child with a de novo mutation of NSD1 that led to his overgrowth and diagnosis of Sotos syndrome (SoS). This syndrome is a rare genetic disorder. Only two cases of genetically proven diagnosis were reported from the Middle East and North Africa region. Therefore, we describe a case and highlight the comorbidities associated with this condition, encouraging colleagues from the region to report their cases to understand better the phenotype–genotype and the natural history of this disorder in this part of the world.

Keywords: NSD1, Oman, overgrowth, tall stature

INTRODUCTION

NSD1 gene was first isolated about 20 years ago. In 2002, the gene of Sotos syndrome (SoS) was identified. Since then, almost 400 mutations in the NSD1 gene have been recognized in patients with SoS. It is a rare genetic disorder that was described previously by Juan Sotos in 1964. However, some authors would refer to Schlesinger as the first reporter of this condition as he initially described its symptoms in 1931.

The incidence of SoS in the Middle East and North Africa (MENA) region is unknown. Literature review and searching PubMed, MEDLINE, and Embase databases, using “NSD1 mutation” and “Sotos syndrome” as keywords, showed only two case reports from MENA; the first was from Egypt in 2016[1] and the other one was from Saudi Arabia in 2018. The second paper referred to a Saudi report from the nineties describing 14 children diagnosed clinically to have SoS and another case report from the same period. The incidence worldwide is not precise. A Swedish report suggested the estimated incidence is 5–10 children are born with SoS every year.[2]

Ninety years since it was first described, but given the condition’s rarity or perhaps its underreporting, there is a concern that some clinicians are not well aware of managing this condition or counseling the patient and parents at diagnosis and whether a multidisciplinary team approach is needed. Therefore, we aimed to raise the awareness of health care professionals about this condition, as raising awareness may result in a better recognition of SoS and subsequently an early management. Hence, the recommendations afterward would be more efficient.

CASE REPORT

A 10-year-old boy was referred to pediatric endocrine services due to his tall stature and large head compared to his peers, associated with a history of learning difficulty. Some behavioral changes were first noticed at age of 6 years, described as “being rude to others” and “disrespectful”. But that had then progressed to bouts of anger and aggression.
The child was born to a consanguineous parent, at term, with a birth weight of 3.9 kg (+0.74 SDS). Normal antenatal scans and uncomplicated pregnancy. Postnatally, he received phototherapy in the 1st week of life due to jaundice attributed to G6PD deficiency. There was a delay in achieving milestones, for example, walking and speech, but eventually, they were achieved. A history of obstructive sleep apnea and recurrent chest infections was reported since preschool age. Furthermore, there was a history of recurrent ear infections and hearing difficulty for 2 years before presentation. There is no family history of tall stature. He has nine other healthy siblings.

Examination revealed a child with macrodolichocephaly, frontal bossing, elongated face, deep-seated eyes with dislocation of lenses, thin philtrum, prominent chin, elongated fingers, normal teeth, and no chest deformity. His height and weight were above the 99th centile for age and sex; height was 160 cm (+3.72 SDS), weight of 56.7 kg (+2.67 SDS), head circumference of 57.5 cm (+3.63 SDS), body mass index (BMI) of 21.9 kg/m² (+2.1 SDS), and growth velocity of 9.2 cm/year (+5.61 SDS). The rest of the examination was unremarkable. Tanner staging showed A1, P2, G2, and testicular volume of 4 mL bilaterally. Parental adjusted height (+3.87 SDS). Further evaluation revealed conductive hearing loss bilaterally.

Biochemical investigations showed normal levels of follicular-stimulating hormone 1.8 IU/L and luteinizing hormone 1.8 IU/L. Normal thyroid function test and normal cortisol, prolactin and alpha fetoprotein levels. Growth hormone was appropriately suppressed by a glucose load using 75-g anhydrous glucose and diluted in 200-mL water [Table 1].

Ultrasound abdomen revealed mildly enlarged liver with normal echogenicity, otherwise normal intra-abdominal organs. Bone age was advanced. Using the radiographic atlas of skeletal development of the hand and wrist by Greulich and Pyle, the bone age was 13 years and 6 months when the chronological age was 10 years and 8 months (+2 SD for his chronological age is 22.8 months). Normal magnetic resonance imaging (MRI) of the pituitary with no intracranial abnormalities. Genetic studies revealed a pathogenic heterozygous variant in the NSD1 (NM_022455.4: c. 5990A > G: p. Tyr1997Cys) mutation. Both parents had normal growth during their childhood, and now they have normal stature, and they are not planning to have further children; therefore, they were not tested. There is no family history of such phenotypic features which made us think it is a de novo mutation. The genetic study was done by Fulgent Genetics, based in California, USA. Genomic DNA was isolated from the specimen, and DNA was barcoded and enriched for the coding exons of targeted genes using hybrid capture technology. The prepared DNA libraries were then sequenced using a next-generation sequencing technology. Following alignment to the human genome reference sequence (assembly GRCh37/hg19), variants were detected in regions of at least 10x coverage. For this patient’s specimen, 99.99% and 99.92% of coding regions and splicing junctions of genes listed had been sequenced with coverage of at least 10x and 20x, respectively, or by Sanger sequencing.

Adenotonsillectomy was performed around the time of diagnosis. The surgery was indicated to improve the obstructive sleep apnea caused by adenoid hypertrophy. Bilateral grommet insertion also took place due to recurrent ear infections.

**DISCUSSION**

According to a French report, tall stature affects almost 2.5% of the population, according to a French report, and it is a much infrequent reason for a consultation in pediatrics compared to short stature as it is usually perceived as a good sign. During the endocrine consultation, the clinician would study the birth anthropometric records, postnatal health issues (for example, hypoglycemia and feeding difficulty), followed by focusing on growth and development. The growth velocity can be an instrumental piece of information to differentiate the causes of overgrowth, but this depends on the availability of previous growth parameter records to study the growth velocity properly. Accelerated growth velocity can be seen in acromegaly, hyperthyroidism, obesity, precocious puberty, and estrogen resistance in females. Family history and parental height could give a clue whether it is familial tall stature or not. The clinical examination mainly focuses on studying the relation between height (standing and sitting), weight, arm span, BMI, and head circumference. It extends to evaluate any signs of dysmorphism, skeletal deformities such as scoliosis, and congenital anomalies, including congenital heart disease. These are required to consider some genetic diseases that manifest with overgrowth, for example, Klinefelter, Marfan, Beckwith–Wiedemann, Weaver, Simpson–Golabi–Behmel, Perlman, Bannayan–Riley–Ruvalcaba, fragile X syndrome, Marshall–Smith syndrome, Nevo syndrome, and SoS. The

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**Table 1: Summary of biochemical investigations**

<table>
<thead>
<tr>
<th>Value</th>
<th>Reference range</th>
</tr>
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<tbody>
<tr>
<td>ACTH</td>
<td>32.4 ng/L</td>
</tr>
<tr>
<td>Morning cortisol</td>
<td>237 nmol/L</td>
</tr>
<tr>
<td>OGTT</td>
<td></td>
</tr>
<tr>
<td>Fast glucose</td>
<td>4.5 mmol/L</td>
</tr>
<tr>
<td>Glucose at 2 h</td>
<td>4.8 mmol/L</td>
</tr>
<tr>
<td>Growth hormone in response to the glucose load</td>
<td>0.97 mg/mL at 0 min</td>
</tr>
<tr>
<td></td>
<td>0.22 ug/mL at 120 min</td>
</tr>
<tr>
<td>IgF-1</td>
<td>25 nmol/L</td>
</tr>
<tr>
<td>IgF-BP3</td>
<td>3071 ng/mL</td>
</tr>
<tr>
<td>Prolactin</td>
<td>246 mIU/L</td>
</tr>
<tr>
<td>TSH</td>
<td>1.51 mIU/L</td>
</tr>
<tr>
<td>FT4</td>
<td>15.3 pmol/L</td>
</tr>
<tr>
<td>Alpha-fetoprotein</td>
<td>&lt;2 KIU/L</td>
</tr>
<tr>
<td>LH</td>
<td>1.8 IU/L</td>
</tr>
<tr>
<td>FSH</td>
<td>2.7 IU/L</td>
</tr>
</tbody>
</table>

ACTH: Adrenocorticotropic hormone, OGTT: Oral glucose tolerance test, LH: Luteinizing hormone, FSH: Follicular-stimulating hormone, TSH: Thyroid-stimulating hormone, FT4: Free thyroxine, IgF-1: Insulin-like growth factor, IgF-BP3: IgF-binding protein-3
primary differential diagnoses for Sotos are Weaver syndrome, Beckwith–Wiedemann syndrome, fragile X syndrome, Simpson–Golabi– Behmel syndrome, and 22qter deletion syndrome.[9]

The investigations would include assessing the bone age, as usually markedly advanced bone age is associated with pathological tall stature rather than a physiological cause. Even though we know that physiological or constitutional tall stature is the most common cause of tall stature, performing MRI brain and oral glucose suppression test (OGTT) as part of growth hormone suppression test is helpful to rule out acromegalogigantism as the constitutional tall stature is a diagnosis by exclusion.[4] The central role of a pediatric endocrinologist is to evaluate whether there is a treatable endocrine cause for the tall stature such as precocious puberty, hyperthyroidism, or growth hormone excess. Those conditions are usually present with an abrupt recent growth spurt, and the patient would have no dysmorphism. Patients with dysmorphic features should be assessed whether their growth is proportionate or not? If it is disproportionate, then Beckwith–Wiedemann, Klinefelter, Marfan syndromes, and homocystinuria are likely to be the cause. Otherwise, if the child has proportionate overgrowth, cerebral gigantism (SoS) and Weaver syndromes are likely to be the case.

In this case report, we focus on SoS caused by NSD1 mutation at chromosome 5q35. The characteristic triad of this syndrome is an overgrowth, learning difficulty, and facial dysmorphism, including frontal bossing, high anterior hairline, downward slanting palpebral fissures, and prominent jaw.[10] Cole and Hughes suggested four criteria to diagnose patients with SoS including child overgrowth, advanced bone age, distinctive facial gestalt, and developmental delay.[10] The clinical diagnosis itself perhaps is not sufficient for counseling and future follow-up planning. Genetic studies could give a better idea of the disease and its associated morbidities. Mutations can be either microdeletion encompassing the NSD1 gene as in most Japanese SoS patients or intragenic mutations like most European SoS patients. The implication of that can be reflected in the associated congenital disabilities. For example, congenital heart defects were reported more in patients with microdeletion (55%, n = 27),[11] compared to patients with intragenic mutations (8.7%, n = 23).[12] The described mutation of this patient is intragenic.

The endocrinologists are commonly the first specialists receiving referrals regarding tall stature, but the condition is not always easy to diagnose. The importance of establishing an appropriate diagnosis at an early stage could get translated into better health care, as children could be assessed and evaluated by the relevant specialists at appropriate times. The following section will detail the reported associated disorders that could manifest in patients with SoS.

**Associated features and disorders with Sotos syndrome**

**Behavior and development**

delayed development is one of the criteria to diagnose this syndrome, as Cole and Hughes outlined in 1994. Autistic spectrum disorder was reported in patients with SoS. Learning difficulty can be variable even between the same family members who have familial inherited SoS.[9]

**Hearing**

The sensorineural hearing loss was reported. However, conductive hearing loss is more frequent as patients with SoS tend to have more frequent upper respiratory tract infections (URTIs) and otitis media, leading to some degree of conductive hearing loss.[13]

**Respiratory tract**

The reason for the recurrent URTIs in the SoS patients is not very well known. The authors suggest it could be linked to some immune defect as the NSD1 gene is known to be expressed in the thymus, so its mutation could affect the T-lymphocyte’s function and hence the recurrence of respiratory tract infections. Further studies by immunologists would be very beneficial. Recurrent pneumothoraces secondary to multiple subpleural lung blebs were reported in two cases living in the UK and both of them required thoracoscopy to diagnose.[10] It is unusual for a child to present with recurrent spontaneous pneumothoraces during the prepubertal period. Thus, having a child with prepubertal spontaneous pneumothorax should raise suspicion for SoS as a differential diagnosis.

**Cardiovascular**

Antenatal diagnosed critical aortic stenosis was reported in a case of recessive IL36RN mutation and an NSD1 microduplication. Secundum ASD and a bicuspid aortic valve were also reported.

**Central nervous system and neuroimaging**

A Brazilian study of 34 patients with SoS suggested a prenatal onset of mutation effects on brain development resulting in cerebellar vermis hypoplasia.[11] Seizure, behavioral problems, and psychiatric disorders are common associations with SoS. Early recognition and treatment are advisable. Characteristic neuroimaging may include ventricular dilatation and the thinning of the corpus callosum (especially the posterior third).[12]

**Endocrinopathies**

Although the overgrowth in SoS is said to be nonendocrine in origin, reports are suggesting an involvement of the growth hormone–insulin growth factor axis. This area is still yet to be explored. Furthermore, individual case reports suggest some other associated endocrine disorders with NDS1 mutation, such as hypoparathyroidism and congenital hyperinsulinism. The latter was transient in most of the affected babies.[13]

**Musculoskeletal**

Height and head circumference are usually >2 standard deviations above the mean for the sex and age in patients with SoS. However, the adult height is usually within the upper normal limit or just normal. Scoliosis is a common feature in SoS, and sometimes, patients would present to orthopedic surgeons firstly due to scoliosis.
Skin
Severe pustular psoriasis was reported in a Moroccan child living in France.[14]

Malignancy
NSD1 mutation is known to be associated with several cancers such as head-and-neck squamous cell carcinoma[15] and neuroblastoma in children and adolescents.[16] Therefore, surveillance for such malignancies is crucial for early detection and treatment on time.

Conclusion
The patient in this case report has some disorders associated with NSD1 mutation, such as learning difficulty, recurrent chest infection, and hearing loss. It is essential to continue monitoring him in the future. By reporting this case, we encourage our pediatric colleagues from different subspecialties to try linking the clinical findings with you and think about it when overgrowth is evident. In addition, we encourage colleagues from the MENA to report their cases, when possible, to have a better understanding of the natural history of this condition in the region. Having a registry for rare diseases in the MENA countries is desirable.

Declaration of patient’s consent
The authors certify that they have obtained the appropriate consent from the patient’s parents. They have given consent for images and other clinical information to be reported in the journal. The patient’s parents understand that no names and initials will be published, and all due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

Authors’ contribution
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Conflicts of interest
There are no conflicts of interest.

Compliance with ethical principles:
No prior ethical approval is required for case reports and small case series provided the patients provide consent as stated above.

References