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Sotos syndrome with a novel mutation in the *NSD1* gene associated with congenital hypothyroidism

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ABSTRACT

Childhood overgrowth syndromes are relatively rare. A generalized overgrowth syndrome should be suspected when tall stature and macrocephaly are present, after ruling out nutritional excess and endocrinopathies. Sotos syndrome is a well-described overgrowth syndrome due to haploinsufficiency of the *NSD1* gene. We present a case of an infant with permanent congenital hypothyroidism, who had tall stature and macrocephaly by 7 months of age. He was noted to have typical facial features, mild gross motor and speech delay, and scoliosis by 13 months of age. Gene sequencing revealed a heterozygous novel c6076_6087del12: p.Asn2026_Thr2029del variant in exon 20 of the *NSD1* gene, pathogenic for Sotos syndrome. Congenital hypothyroidism with Sotos syndrome has been infrequently reported and may expand the spectrum of disease characteristics. Early diagnosis of overgrowth syndromes is important for developmental follow up and multidisciplinary care coordination.

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1. Introduction

Overgrowth describes either generalized and symmetric or localized and segmental excess growth [1]. Growth in infancy is nutritionally driven until after 6 months of age, when growth hormone, insulin like growth factor-1, and thyroid hormone become important factors impacting growth [2]. Children with height more than the 97th percentile and outside of their predicted genetic height potential may need to be evaluated for causes of overgrowth [3]. The most common causes of tall stature are familial or due to growth acceleration driven by over nutrition. However, potential endocrinopathies such as precocious puberty, hyperthyroidism, congenital adrenal hyperplasia, or growth hormone excess should be excluded [3]. A specific overgrowth syndrome should also be considered in any child with dysmorphic features and a height and head circumference greater than +2 SDS (standard deviation score) of predicted genetic potential, particularly if associated with developmental delays or learning difficulties [1,3].

Typical dysmorphic features for overgrowth syndromes have been well described, but these may be more recognizable after infancy.

Sotos syndrome is a pre- and postnatal overgrowth syndrome with characteristic facial features and intellectual disability [4]. Here, we describe an infant with permanent congenital hypothyroidism, macrocephaly, significant tall stature (SDS +4) and an advanced bone age without the evidence of an endocrinopathy; who was diagnosed with a novel mutation in *NSD1* (Nuclear receptor SET Domain containing protein-1), consistent with Sotos Syndrome. Congenital hypothyroidism has been rarely reported in Sotos syndrome. Thus, this case presents a novel mutation and may expand the phenotype of this syndrome.

2. Case presentation

A 3-week-old male infant, born to non-consanguineous parents presented for the evaluation of congenital hypothyroidism. No family history of thyroid abnormalities was reported. He was macrosomic (birth weight 4.16 kg, SDS +1.6). He had neonatal jaundice with unconjugated hyperbilirubinemia requiring phototherapy.

His first newborn screen demonstrated a normal TSH at 24 h of life. Second newborn screen at 11 days was abnormal with a TSH of 25.3 mIU/ml (normal < 16) confirmed by serum TSH of 23 mIU/ml

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at 2 weeks of age (normal < 6.5). A Tc99 (Technetium 99) thyroid uptake scan showed decreased uptake in a eutopic thyroid gland. At 3 weeks of age, levothyroxine 50 mcg daily was initiated. Thyroid ultrasound at 2 years of age demonstrated a normal-appearing thyroid gland other than a 5-mm hypochoic nodule in the left lobe with characteristics similar to thymic tissue. At 3 years of age, he was biochemically and clinically euthyroid on 62.5 mcg (2.9 mcg/kg) of levothyroxine, and failed the attempt to trail off therapy, demonstrating a persistent need for thyroid hormone replacement indicative of permanent congenital hypothyroidism.

At 3 weeks of age, his weight was 4.42 kg (SDS +0.2), length 58.6 cm (SDS +2.3), and head circumference 40.2 cm (SDS +2.8). By 7 months of age, he continued to have tall stature, accelerated growth velocity and macrocephaly, with weight 9.1 kg (SDS +0.3), length 78.8 cm (SDS +4.22), and head circumference 48.4 cm (SDS +3.8) (Fig. 1). Weight for length was at the 7th percentile (SDS -1.46). Mid parental height was 170 cm, between the 10th and 25th percentile.

On examination at 13 months, he had triangular facies, frontal bossing, prominent occiput, and low set ears, without coarsening of features. Dentition was normal for age. No organomegaly was noted. Testes were descended and pre-pubertal in size. He had deep creases on the soles of his feet and an increased gap between his first and second toes. He had the prominence of the right rib cage with curvature of his spine. Hand length was 11 cm (SDS +2.5). Feet measured 14 cm (SDS +3.0).

As his linear growth parameters were large for family history and weight for length was normal (Fig. 1), he did not have evidence of familial tall stature or nutritionally driven overgrowth. Laboratory work up included thyroid function tests, calcium, vitamin D, growth factors (IGF-1 and IGF-BP3), and gonadotropins (LH, FSH), which were normal for age and pre-pubertal status (Table 1). Bone age was advanced, between 1-year 3-month, and 1-year 6-month standards of Greulich and Pyle, at a chronological age of 9 months. Brain MRI demonstrated macrocrania with the prominence of subarachnoid spaces overlying the frontal and temporal lobes and a mild prominence of the lateral and third ventricles. Renal ultrasound was normal.

By 13 months of age, he had symptoms of obstructive sleep apnea and mild gross motor and speech delay. He developed kyphodextroscoliosis of the thoracic spine and levoscoliosis of the lumbar spine requiring bracing. With these features, a gene-sequencing panel for overgrowth syndromes was done. The panel uses next-generation sequencing of all exons of genes and detects large deletions and duplications in: *ABCC9*, *AKT1*, *AKT3*, *BRWD3*, *CCND2*, *CDKN1C*, *CUL4B*, *DEPDC5*, *DNMT3A*, *EED*, *EZH2*, *GLI3*, *GNAQ*, *GNAS*, *GPC3*, *HEPACAM*, *KCNJ8*, *KIF7*, *MED12*, *MLC1*, *MTOR*, *NFIA*, *NFIX*, *NSD1*, *PIK3CA*, *PIK3R2*, *PTCH1*, *PTEN*, *RAB39B*, *TIN2*, *RNF135*, *SETD2*, *STRADA*, *TBC1D7*, *TSC1*, *TSC2*. Analysis revealed a heterozygous novel c6076_6087del12: p.Asn2026_Thr2029del variant in exon 20 of the *NSD1* gene, pathogenic for Sotos syndrome.

3. Discussion

Sotos syndrome is an overgrowth syndrome with an estimated incidence of 1 in 15,000 [3]. Tatton et al. [4] described three cardinal features of the syndrome that were present in more than 90% of individuals: characteristic facial appearance, learning disability, and overgrowth. Facial dysmorphism in Sotos syndrome is most recognizable between 1 and 6 years of age [5]. Dolicocephaly, broad and prominent forehead, sparse fronto-temporal hair, downward slant of palpebral fissures, malar flushing with a narrow jaw and long chin are classically described [6]. Delay in speech and language as well as motor milestones due to hypotonia and large size or poor coordination are common [5,7]. Rapid linear growth occurs from the prenatal through early childhood years. Height and/or head

circumference measurements are typically more than +2 SDS [4]. De Boer et al. also reported an increased arm span/height ratio, decreased upper to lower segment ratio, and increased hand length [6]. Height normalizes in adulthood but macrocephaly persists [5]. Major features such as advanced bone age, cardiac anomalies, cranial MRI abnormalities, scoliosis, neonatal jaundice, renal anomalies, seizures, joint hyperlaxity, and maternal preeclampsia are present in 15%–89% of individuals [4]. Several additional features including behavioral problems, astigmatism, cataracts, conductive hearing loss, cryptorchidism, hypercalcemia, hypospadias, hypothyroidism, neonatal hypoglycemia, tumors, and vertebral anomalies are reported in 2%–15% of patients [4].

This patient initially had two of the cardinal features in infancy: overgrowth and motor and speech delay. His facial features were not suggestive of classic Sotos syndrome in the first few months of life, but later became apparent. He had an advanced bone age but endocrine causes of overgrowth were excluded. Additional features of Sotos syndrome in this patient included neonatal jaundice and severe scoliosis.

The patient was also noted to have congenital hypothyroidism. Given findings of the Tc99 scan, thyroid ultrasound and failure to trail off therapy at 3 years of age, possible etiology of his permanent congenital hypothyroidism includes thyroid hypoplasia or a partial iodine-trapping defect. In the current literature, one case of Sotos syndrome with congenital hypothyroidism has been reported due to thyroid hypoplasia with p.R1984X mutation [4]. Smith et al. have reported primary acquired (not congenital) hypothyroidism due to Hashimoto's disease in autosomal-dominant inheritance of Soto syndrome [8].

In 2002, it was established that Sotos syndrome is caused by haploinsufficiency of *NSD1* on chromosome 5q35 [9]. Known genetic causes of congenital hypothyroidism are located on chromosome 14 (transcription factor *TTF-1*), chromosome 2 (transcription factor *PAX8* and thyroid peroxidase gene), chromosome 19 (sodium-iodine symporter defect), or chromosome 8 (Thyroglobulin gene) [10]. A syndromic form of congenital hypothyroidism has been identified due to *MCT8*, mapped to Xq13.2 [10]. Thus, currently known genetic causes of congenital hypothyroidism have not been mapped to the locus of *NSD1* gene on chromosome 5q35.3.

Tatton et al. have described the largest cohort of Sotos syndrome patients with >200 patients [4]. Their findings indicated that in at least 90% of patients, Sotos syndrome is attributable to *NSD1* mutations. Of those, 77% of patients had small intragenic mutations, 6% with partial-gene deletions, and 10% with whole-gene deletions. Only 7% of patients did not have an identifiable abnormality in *NSD1*. *NSD1* contains two distinct nuclear receptor interaction domains (NID^{-L} and NID^{+L}), five zinc-finger plant homeodomains, two proline – tryptophan – tryptophan – proline domains, a SET domain, and a C5HCH motif [5,9]. The *NSD1* gene plays a role in the regulation of transcription by methylation of histone lysine residues. Differential binding of two domains leads to either a corepressor or coactivator of genes [5,9]. Mechanism of overgrowth in Sotos syndrome is still unclear, but *NSD1* likely acts as a corepressor of genes that promote growth [5]. Our patient has a novel heterozygous c6076_6087del12 mutation that causes an in-frame deletion of four amino acids, denoted p.Asn2026_Thr2029 pathogenic for Sotos syndrome, associated with permanent congenital hypothyroidism. This variant has not been reported in published databases as a known pathogenic variant, nor has it been reported as a benign variant. However with the constellation of signs and symptoms present in our patient, this is in fact a pathogenic novel mutation.

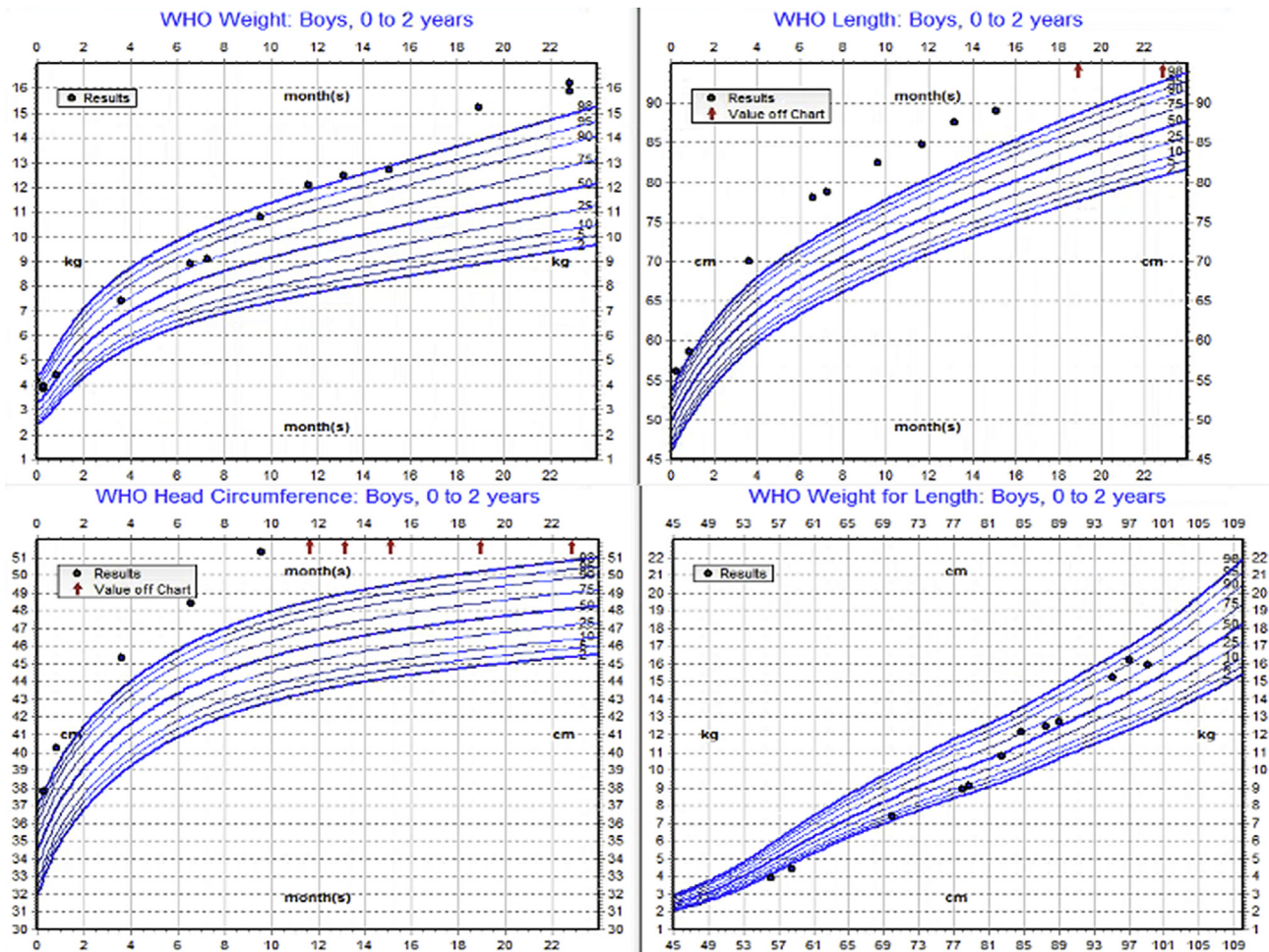


Fig. 1. WHO growth charts (0–2 years) for our patient: (from left to right clockwise) weight for age, length for age, head circumference for age, and weight for length.

Table 1
Initial lab workup for linear growth excess.

Laboratory test	Value	Reference range
TSH	1.98 mIU/ml	0.5–4.5
Free thyroxine level	1.7 ng/dl	0.8–2.0
IGF-1	36 ng/dl	27–157
IGF BP3	1.6 mcg/ml	1.1–3.2
Ultrasensitive LH	0.2 mIU/ml	<0.5
FSH	<0.7 mIU/ml	<5
Calcium level	10.6 mg/dl	8.7–10.7
Phosphorus level	6.4 mg/dl	3.9–6.5
Vitamin D 25-OH	49 ng/mL	≥ 30

4. Conclusion

Overgrowth syndromes must be considered in patients who present with a height and head circumference over +2 SDS and facial dysmorphism. Because of associated anomalies, early diagnosis is important for developmental follow up, multidisciplinary care coordination, and prognosis. Congenital hypothyroidism is underreported as an associated feature in Sotos syndrome. More frequent and earlier thyroid function screening may be appropriate in this population.

Declaration of competing interest

The authors declare that they have no competing or conflicts of interests.

List of abbreviations

IGF-1 Insulin like growth factor-1
SDS standard deviation score

Ethics approval and consent to participate

Ethics committee approval was waived as this is a case report without any research intervention. Consent to participate was not applicable for this case report.

Consent for publication

Consent for publication was obtained from the parent of this child, which was signed by the patient's mother, dated: October 9, 2019.

References

- [1] Kamien B, Ronan A, Poke G, Sinnerbrink I, Baynam G, Ward M, et al. A clinical review of generalized overgrowth syndromes in the era of massively parallel sequencing. *Mol Syndromol* 2018;9:70–82.
- [2] Murray PG, Clayton PE. Endocrine control of growth. *Am J Med Genet C Semin Med Genet* 2013 May;163C:76–85.
- [3] Neylon OM, Werther GA, Sabin MA. Overgrowth syndromes. *Curr Opin Pediatr* 2012;4:505–11.
- [4] Tatton-Brown K, Douglas J, Coleman K, Baujat G, Cole TR, Das S, et al. Genotype-phenotype Associations in Sotos syndrome: an analysis of 266 individuals with NSD1 aberrations. *Am J Hum Genet* 2005;77:193–204.
- [5] Tatton-Brown K, Cole TRP, Rahman N. Sotos syndrome. *GeneReviews*®

- [Internet]; 1993-2019.
- [6] de Boer L, le Cessie S, Wit JM. Auxological data in patients clinically suspected of Sotos syndrome with NSD1 gene alterations. *Acta Paediatr* 2005;94:1142–4.
- [7] Ball LJ, Sullivan MD, Dulany S, Stading K, Schaefer GB. Speech-language characteristics of children with Sotos syndrome. *Am J Med Genet A* 2005;136A:363–7.
- [8] Smith A, Farrar JR, Silink M, Judzewitsch R. Investigations in dominant Sotos syndrome. *Ann Genet* 1981;24:226–8.
- [9] Kurotaki N, Imaizumi K, Harada N, Masuno M, Kondoh T, Nagai T, et al. Haploinsufficiency of NSD1 causes Sotos syndrome. *Nat Genet* 2002 Apr;30:365–6.
- [10] Park SM, Chatterjee VK. Genetics of congenital hypothyroidism. *J Med Genet* 2005;42(5):379–89.