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Growth hormone treatment for short stature associated with duplication of the *NSD1* Sotos syndrome gene

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Summary

NSD1 deletions are associated with the Sotos syndrome, a syndrome of overgrowth in childhood without evidence of endocrine disturbance. Duplications involving the *NSD1* gene have been reported to be associated with a 'reverse Sotos syndrome' phenotype, characterised by short stature, microcephaly, dysmorphic features and developmental delay. A 2-year-old girl with short stature, dysmorphic features and developmental delay was found to have duplication of 5q32.2–5q32.3, which includes the *NSD1* gene. Growth hormone stimulation testing was normal. Growth hormone therapy was initiated at 5 years of age due to severe short stature and growth failure, with height 3.35 standard deviations (SDS) below the median. Growth velocity increased markedly, by +4.91 SDS in the first year of treatment. At the time of last follow-up at 9 years and 11 months, she had achieved a height within 1 SDS of the median. This is the first report of growth hormone therapy for the short stature associated with duplication of the *NSD1* gene, showing that despite normal pituitary function, exogenous growth hormone can dramatically improve linear growth.

Learning points:

- Sotos syndrome is a disorder of childhood overgrowth caused by *NSD1* deletions.
- Duplications involving *NSD1* cause a 'reverse Sotos syndrome' phenotype characterised by short stature and microcephaly.
- The contrasting phenotypes of *NSD1* deletions and duplications suggest a dose effect.
- Stimulated growth hormone secretion is normal in children with *NSD1* deletions and duplications.
- Growth hormone therapy can be very effective in children with *NSD1* duplications, comparable to the response seen in severe growth hormone deficiency.

Background

The nuclear receptor SET domain-containing protein-1 (*NSD1*) gene, located in the region 5q35.2–5q35.3, encodes for a histone methyltransferase. *NSD1* is an important regulator of growth; however, the precise mechanism has not yet been established. *NSD1* can act to increase or decrease transcription depending on the cellular context, possibly via methylation of lysine residues on histone K36H3 or K20H4 (1). Inactivating mutations of the *NSD1* gene and microdeletions involving 5q35 underlie over 90% of cases of Sotos syndrome, which is clinically characterised by somatic overgrowth in childhood, macrocephaly, distinctive facial features and developmental delay (1, 2).

More recently, duplications at the 5q chromosomal locus encompassing the *NSD1* gene have been reported in 14 individuals. This was associated with short stature,

poor growth, microcephaly and developmental delay (3, 4, 5, 6, 7). To our knowledge, there are no reports of whether growth hormone treatment is effective in patients with *NSD1* duplications.

Case presentation

A 2-year-old girl was referred for evaluation of short stature. She was the third child of non-consanguineous Caucasian parents. The older siblings and parents were of normal stature with no significant health problems. The adjusted mid-parental height was 161.85 cm (25th–50th centile). Birth weight was 2800 g at 37 weeks gestation (45th centile), with length 48 cm (50th centile) and head circumference 33 cm (15th–50th centile). APGAR scores were 9 at 1 minute and 10 at 5 min and the neonatal period was uncomplicated.

Hypotonia was noted at 5 months of age and subsequently, she developed global developmental delay. At 2 years of age, she could speak single words but no two-word sentences, and could walk with one hand held but not independently. She developed bilateral serous middle ear effusion and hearing loss requiring myringotomy tube insertion.

On examination at 2 years and 2 months of age, she was proportionately short, with length 78.5 cm (−2.81 standard deviation scores (SDS)), weight 9.22 kg (−2.99 SDS) and head circumference 46.2 cm (9–25th centile). There were subtle dysmorphic features including small, posteriorly rotated ears, epicanthic folds, small nose with anteverted nostrils, an under-developed philtrum, thin upper lip and bilateral clinodactyly of the fifth fingers.

Investigation

Investigations for short stature and hypotonia were all normal, including standard karyotype, fragile X probe, thyroid function, full blood count, liver function, vitamin B12, folate, ferritin, creatine kinase and urine organic and amino acids. She had a secundum atrial septal defect with fenestrations on echocardiogram. Bone age was consistent with the Greulich and Pyle standard for 2 years, at the chronological age of 2 years and 2 months. Chromosomal microarray revealed a 780 kB duplication, involving the interstitial region 5.35.2–5.35.3, which includes the *NSD1* gene. Peak growth hormone responses to arginine and clonidine were 6.1 and 9.1 µg/L, respectively. Growth hormone > 5 µg/L is considered normal for the current automated sandwich-type immunoassay, using monoclonal antibodies, in New Zealand (8).

Treatment

Given that there was no evidence of growth hormone deficiency, and the New Zealand criteria for funded growth hormone therapy were not met, the patient's progress was monitored regularly. At 5 years of age her height was 94.4 cm (−3.35 SDS) with height velocity 3.88 cm/year (−2.6 SDS). Growth hormone therapy was started at 1 mg/m²/day. Baseline plasma IGF-1 was 65 ng/mL (−1.3 SDS), and bone age was most consistent with the Greulich and Pyle standard for 4 years and 2 months.

Outcome and follow-up

The patient demonstrated an excellent response to growth hormone therapy with a maximum growth velocity of 11.0 cm/year (+4.91 SDS) in the first year of treatment (Fig. 1A and B). Over time, the dose was progressively increased to maintain it at 1 mg/m²/day. Serum IGF-1 was monitored and was maintained in the range of +0.7 to +1.9 SDS. Growth hormone therapy was well tolerated throughout with good compliance and no known adverse effects.

At the time of last follow-up, the patient was 10 years 2 months of age, with a height of 135.4 cm (−0.64 SDS) and weight 27.78 kg (−0.98 SDS). Height velocity was 6.04 cm/year (+ 0.65 SDS). Arm span was 134.7 cm and head circumference was 52.4 cm (just below the 50th centile). She had evidence of early adrenarche with Tanner stage 2 pubic hair but no axillary hair or breast development. Bone age was between 7 years 10 months and 8 years 10 months, at a chronological age of 9 years 8 months. IGF-1 was 353 ng/mL (+1.0 SDS).

Discussion

We report the case of a child with short stature associated with a duplication of the 5q35.2–5q35.3 region including the *NSD1* gene. Our patient had similar clinical findings to the 14 previously reported individuals with this duplication, with short stature, and normally stimulated growth hormone secretion. We now report that the exogenous GH therapy was associated with a marked increase in growth velocity and sustained catch-up growth. This finding has implications for the mechanism of short stature associated with *NSD1* duplications, and conversely, the overgrowth in Sotos syndrome.

Sotos syndrome is characterised by somatic overgrowth with macrocephaly, dysmorphic features and neuro-developmental problems, including seizures (1).

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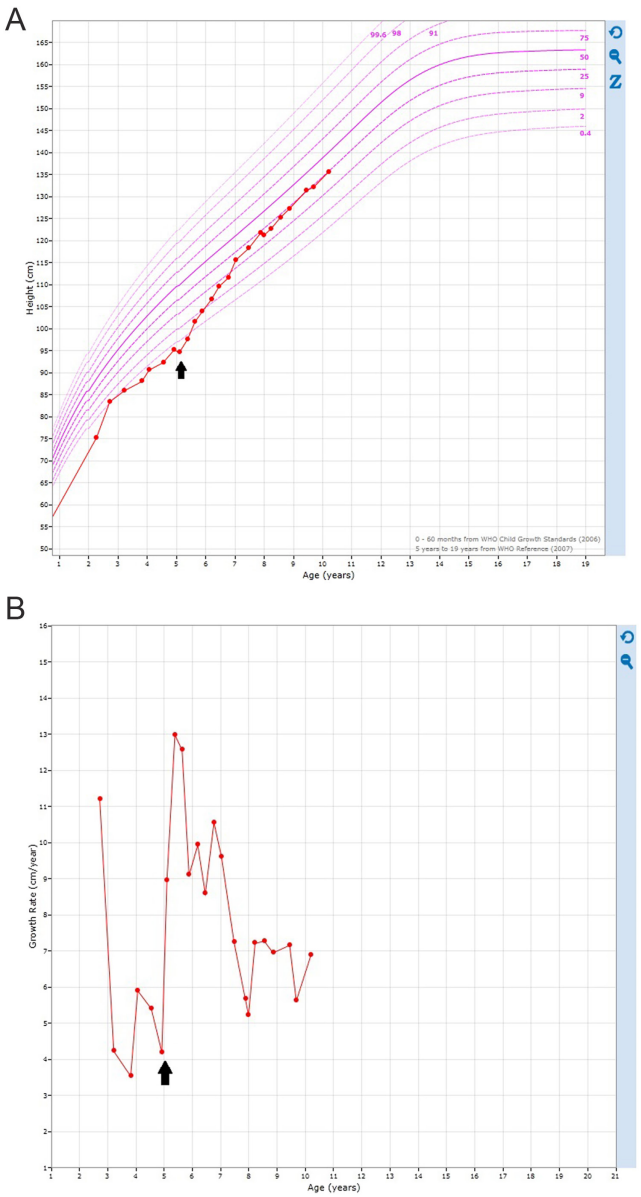

Figure 1
(A) Height prior to and during growth hormone treatment. The red dots indicate height in centimetres, pink lines indicate centile lines according to WHO Child Growth reference data, and the black arrow indicates initiation of growth hormone therapy. (B) Height velocity prior to and during growth hormone treatment. The red dots indicate height velocity in centimetres per year, and the black arrow indicates initiation of growth hormone therapy.

The overgrowth does not appear to have an endocrine basis, and IGF-1 and growth hormone secretion are normal in these individuals. The bone age is advanced compared to the chronological age, but appropriate for the height centile. Accelerated growth begins prenatally and continues into childhood but normalises after 5 years of age. Although children with somatic overgrowth and tall stature due to Sotos syndrome achieve adult heights taller than their calculated target height, they do not usually exceed the 97th centile for adult height. For this reason, treatment to limit adult height is usually not recommended (9).

In 2006, Chen *et al*. described the first reported case of direct duplication of 5q32.2–5q32.3 in association with short stature and microcephaly, and they hypothesised a dosage effect of the *NSD1* gene (4). Subsequently, Dikow *et al*. reviewed phenotypic and genetic data from 14 patients with 5q35.2–5.35.3 duplications involving the *NSD1* gene (3). They found a consistent clinical phenotype including short stature, microcephaly and learning difficulties, as well as distinctive facial features comprising periorbital fullness, short palpebral fissures, a long nose with broad or long nasal tip, a smooth philtrum and a thin upper lip vermillion border. Although these patients had *NSD1* duplications, it has been noted that there were nine additional Online Mendelian Inheritance in Man (OMIM) genes within the 'smallest region of overlap', including three genes known to be associated with the disease. They concluded that the relative contribution of these genes to the clinical phenotype is not established, and therefore it is not clear whether this condition should be considered 'Reverse-Sotos syndrome'. However, the respective phenotypes of individuals with *NSD1* deletions and duplications do seem to suggest a dosage effect for linear growth and head circumference.

Of the reported cases of *NSD1* duplications, the adult height is recorded in three patients, two of whom had low-normal height (3rd–10th centile), and the other having marked short stature <3rd centile (−2.6 SDS) (3). Therefore, some of these patients may experience significant 'catch-up growth' in puberty, analogous to the childhood overgrowth seen in Sotos syndrome.

Our patient had evidence of normal growth hormone secretion, consistent with existing hypotheses regarding the mechanism of disordered growth in *NSD1* deletions and duplications, as accelerated growth occurs in the absence of GH excess in patients with Sotos syndrome (9). Of the various indications for growth hormone therapy in childhood, individuals with severe growth hormone deficiency have the greatest increase in height velocity, compared to children with small for gestational age or Turner syndrome and other syndromic causes of short stature (10). The increase in growth velocity is greatest in the first year of therapy, and then progressively diminishes thereafter. Our patient had a growth velocity of 10.98 cm/year (+ 4.91 SDS) in the first year of treatment, compared with reported median values of 10.3–11 cm/year in

5-year olds with severe growth hormone deficiency, and 8.8–9.3 cm/year in 5-year olds with mild GH deficiency, SGA and syndromic short stature. The Δ-height SDS was +2.31, compared to median reported values of +1.1–1.3 in those with severe GH deficiency and +0.7–0.9 in those with other indications (10). Thus this patient's response was at least as good or better than the typical patient with growth hormone deficiency despite being growth hormone sufficient, suggesting that the *NSD1* pathway is growth hormone responsive.

Our patient highlights the clinical features of 5q35.2–5q35.3 duplication with characteristic dysmorphic features and short stature in the absence of any apparent endocrine disturbance. She had a substantial increase in linear growth with growth hormone therapy, comparable or even better than that seen in growth hormone-deficient individuals. Long term follow-up will be important to document adult height, cranial growth and developmental outcome. Further work is required to delineate the contributory role of the *NSD1* gene to this syndrome and the precise pathophysiological mechanism by which the *NSD1* gene product acts to regulate growth.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent

Signed, written consent has been obtained from the patient's guardian, and consent form filed in the patient's notes.

Author contribution statement

I T Bernhardt wrote the first draft of the manuscript. I T Bernhardt, A J Gunn and P J Carter edited and submitted the manuscript. P J Carter was the patient's named physician and supervised the overall preparation of the manuscript. All authors reviewed the final manuscript and approved it for publication.

References

1 Tatton-Brown K & Rahman N. Sotos syndrome. *European Journal of Human Genetics* 2007 **15** 264 – 271. (https://doi.org/10.1038/sj.ejhg.5201686)

2 Kurotaki N, Imaizumi K, Harada N, Masuno M, Kondoh T, Nagai T, Ohashi H, Naritomi K, Tsukahara M, Makita Y, *et al*. Haploinsufficiency of *NSD1* causes Sotos syndrome. *Nature Genetics* 2002 **30** 365–366. (https://doi.org/10.1038/ng863)

3 Dikow N, Maas B, Gaspar H, Kreiss-Nachtsheim M, Engels H, Kuechler A, Garbes L, Netzer C, Neuhann TM, Koehler U, *et al*. The phenotypic spectrum of duplication 5q35.2–q35.3 encompassing NSD1: is it really a reversed Sotos syndrome? *American Journal of Medical Genetics: Part A* 2013 **161A** 2158–2166. (https://doi.org/10.1002/ajmg.a.36046)

4 Chen CP, Lin SP, Lin CC, Chen YJ, Chern SR, Li YC, Hsieh LJ, Lee CC, Pan CW & Wang W. Molecular cytogenetic analysis of de novo dup(5)(q35.2q35.3) and review of the literature of pure partial trisomy 5q. *American Journal of Medical Genetics: Part A* 2006 **140** 1594–1600. (https://doi.org/10.1002/ajmg.a.31329)

5 Franco LM, de Ravel T, Graham BH, Frenkel SM, Van Driessche J, Stankiewicz P, Lupski JR, Vermeesch JR & Cheung SW. A syndrome of short stature, microcephaly and speech delay is associated with duplications reciprocal to the common Sotos syndrome deletion. *European Journal of Human Genetics* 2010 **18** 258–261. (https://doi.org/10.1038/ejhg.2009.164)

6 Kirchhoff M, Bisgaard AM, Bryndorf T & Gerdes T. MLPA analysis for a panel of syndromes with mental retardation reveals imbalances in 5.8% of patients with mental retardation and dysmorphic features, including duplications of the Sotos syndrome and Williams-Beuren syndrome regions. *European Journal of Medical Genetics* 2007 **50** 33–42. (https://doi.org/10.1016/j.ejmg.2006.10.002)

7 Zhang H, Lu X, Beasley J, Mulvihill JJ, Liu R, Li S & Lee JY. Reversed clinical phenotype due to a microduplication of Sotos syndrome region detected by array CGH: microcephaly, developmental delay and delayed bone age. *American Journal of Medical Genetics: Part A* 2011 **155A** 1374–1378. (https://doi.org/10.1002/ajmg.a.33769)

8 Davidson J. Harmonisation of growth hormone assays in Australasia. *Clinical Biochemist: Reviews* 2012 **33** 101–102.

9 Agwu JC, Shaw NJ, Kirk J, Chapman S, Ravine D & Cole TR. Growth in Sotos syndrome. *Archives of Disease in Childhood* 1999 **80** 339–342. (https://doi.org/10.1136/adc.80.4.339)

10 Ranke MB, Lindberg A & KIGS International Board. Observed and predicted growth responses in prepubertal children with growth disorders: guidance of growth hormone treatment by empirical variables. *Journal of Clinical Endocrinology and Metabolism* 2010 **95** 1229–1237. (https://doi.org/10.1210/jc.2009-1471)

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