Growth hormone deficiency as a cause for short stature in Wiedemann–Steiner Syndrome

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Summary

Wiedemann–Steiner Syndrome (WSS) is a rare condition characterised by short stature, hypertrichosis of the elbow, intellectual disability and characteristic facial dysmorphism due to heterozygous loss of function mutations in *KMT2A*, a gene encoding a histone 3 lysine 4 methyltransferase. Children with WSS are often short and until recently, it had been assumed that short stature is an intrinsic part of the syndrome. GHD has recently been reported as part of the phenotypic spectrum of WSS. We describe the case of an 8-year-old boy with a novel heterozygous variant in *KMT2A* and features consistent with a diagnosis of WSS who also had growth hormone deficiency (GHD). GHD was diagnosed on dynamic function testing for growth hormone (GH) secretion, low insulin-like growth factor I (IGF-I) levels and pituitary-specific MRI demonstrating anterior pituitary hypoplasia and an ectopic posterior pituitary. Treatment with GH improved height performance with growth trajectory being normalised to the parental height range. Our case highlights the need for GH testing in children with WSS and short stature as treatment with GH improves growth trajectory.

Learning points:

- Growth hormone deficiency might be part of the phenotypic spectrum of Wiedemann–Steiner Syndrome (WSS).
- Investigation of pituitary function should be undertaken in children with WSS and short stature. A pituitary MR scan should be considered if there is biochemical evidence of growth hormone deficiency (GHD).
- Recombinant human growth hormone treatment should be considered for treatment of GHD.

Background

Wiedemann–Steiner Syndrome (WSS, OMIM#605130) is a rare genetic disorder characterised by psychomotor delay, facial dysmorphism, hypertrichosis (especially of the elbow) and growth retardation (1, 2, 3). WSS results from heterozygous loss of function *KMT2A* mutations (4). Recently, it has been reported that 50% of patients with WSS have growth hormone deficiency (GHD) (5). However, no details of endocrine investigations were provided in these patients. We report endocrine and imaging studies in a patient with genetically confirmed WSS and GHD and his response to therapy with GH.

Case presentation

Proband (8.6 years, male) was born to non-consanguineous parents of White European origin by normal delivery at 39 weeks, weighing 2.6 kg (−1.8 SDS) with evidence of intra-uterine growth restriction on antenatal ultrasound

scanning. Vesico-ureteric reflux, mild hydronephrosis and hydroureter had been identified in early life. At 2.2 years of age, he presented with short stature (height: 75.5 cm, −4.1 SDS), decreasing height velocity and poor weight gain (weight: 6.8 kg, <−6.3 SDS) (Fig. 1A). A review at 3 years of age showed that his height (79.1 cm at age 3.0 years, −4.5 SDS) and weight (9 kg, −4.6 SDS) had remained suboptimal. His height was well below the mid-parental height (174.0 cm, −0.4 SDS). Investigations ruled out malabsorption. Although several allergies (soya and raw eggs) were noted, the coeliac screen was normal. Initial endocrine investigations showed low levels of the GH-dependent peptide IGF-I (20 µg/L (range: 28–247 for age)) with other pituitary functions remaining normal. The cause for low IGF-I was attributed to low body weight instead of GHD.

Although the patient did not have obvious features of GHD other than short stature, growth hormone dynamic stimulation testing was performed as per local protocol. Glucagon-stimulated GH levels were low (basal: 1.8, peak: 3.3 µg/L, expected values >7 µg/L), suggesting biochemical evidence for GHD. MR scanning of the pituitary and brain showed a hypoplastic anterior pituitary with an elongated posterior pituitary extending into the pituitary stalk (minor ectopic posterior pituitary), in keeping with a developmental abnormality of the pituitary gland (Fig. 1B). As the patient demonstrated an abnormal growth hormone response to stimulation and demonstrated radiological evidence of pituitary hypoplasia/ectopia, a second stimulation test was not performed in keeping with local protocol.

The patient was commenced on recombinant human GH treatment in a dose of 25 µg/kg/day, to which satisfactory height gain was achieved within the first year. While pre-treatment height velocity was 4.5 cm/year, post-treatment height velocity increased to 13.3 cm/year. Satisfactory height trajectory (height: 124.3 cm at 8.1 years, −0.8 SDS) was maintained in follow-up appointments with GH treatment administered in doses varying between 25 and 30 µg/kg/day. GHD continued to be isolated, with no evidence of wider pituitary dysfunction.

The patient was reviewed again at age 7.5 years; by this time, intellectual disability and an autistic spectrum disorder had been identified. Dysmorphism, including long eyelashes, thick arched eyebrows, downslanting and vertically narrow palpebral fissures, hypertelorism, low set ears, ptosis and mild facial asymmetry, was noted. The patient's DNA was analysed for a next generation sequencing (NGS)-based panel of 206 intellectual disability
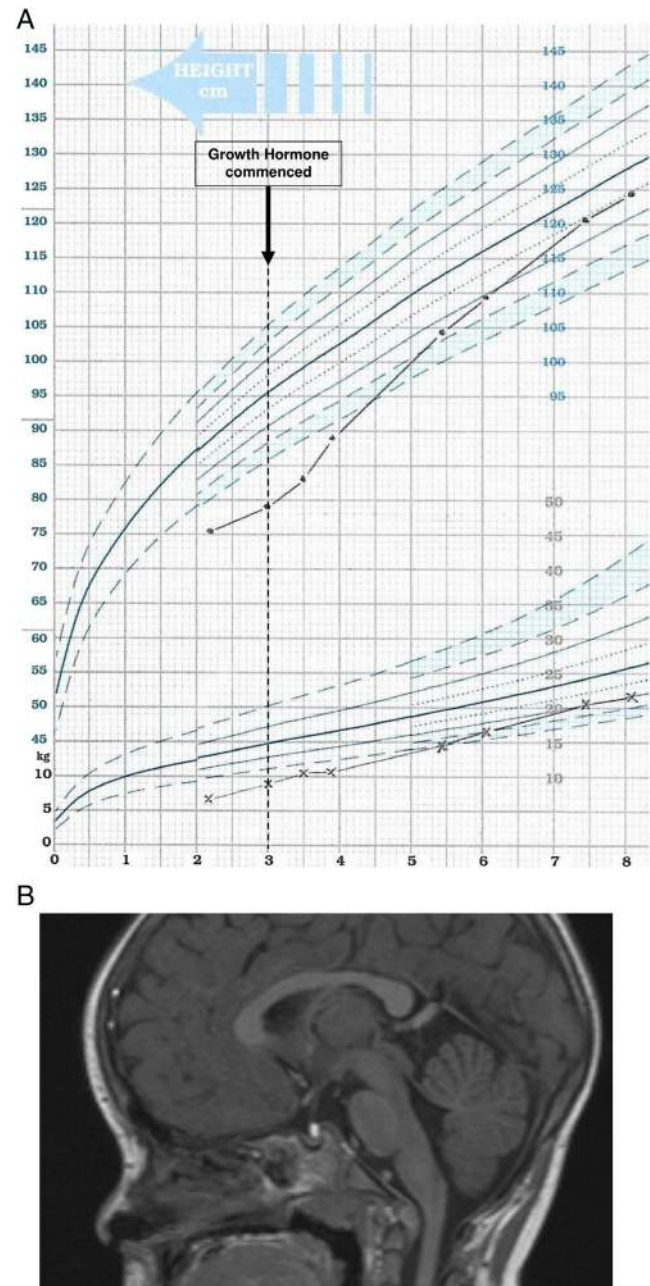

Figure 1

(A) Growth trajectory of patient with WSS demonstrating significant short stature prior to treatment and improvement in stature following treatment with growth hormone. (B) MR pituitary scan demonstrating hypoplastic anterior pituitary. The posterior pituitary is of abnormal configuration with elongation into the lower part of the pituitary stalk, suggesting minor ectopia. The combination of anterior pituitary hypoplasia and ectopic posterior pituitary is suggestive of abnormal pituitary development and explains biochemical evidence of GHD and short stature.

genes. A novel heterozygous *KMT2A* variant (c.7062delC p.(Ser2355LeufsTer18), RefSeq ID: NM_005933) predicted to be deleterious was identified. Reverse phenotyping

Endocrinology,
Diabetes & Metabolism
CASE REPORTS

G Stoyle and others

GHD as a cause for short stature in WSS

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confirmed that the phenotypic features were consistent with WSS (6). Targeted parental testing confirmed that the variant had arisen *de novo*.

Discussion

WSS is a rare genetic disease with variable phenotypes of presentation. Short stature is a recognised feature of WSS; the molecular basis for short stature has not been ascertained but had been assumed to be intrinsic to the genetic defect. A recent observational study suggested that GHD could be frequent in children with WSS (5). This study did not describe the methods by which GHD was diagnosed or report the response to GH treatment. As dynamic function testing has high false positive frequency, the validity of GHD diagnosis in WSS patients remains to be confirmed. In contrast, our case study has demonstrated auxological, biochemical and radiological evidence confirming GHD. Our findings suggest the possibility of a structural pituitary lesion in WSS causing GHD and short stature. Therefore, we would recommend thorough investigation of pituitary function in all children diagnosed with WSS, including a pituitary MR scan if there is biochemical evidence of GHD.

The combination of decelerating growth velocity, low GH to dynamic function testing, low IGF-I and MR scan findings of hypoplastic anterior pituitary/ectopic posterior pituitary and satisfactory and sustained treatment response to GH are highly suggestive of a diagnosis of GHD. The possibility of GHD occurring as a chance association remains to be confirmed, although the observation of GHD in 50% of WSS patients points towards a stronger and more intrinsic association (5). The latter is in contrast to the clinical experience in our centre where only one out of seven children with WSS had confirmed GHD.

The long-term outcome of GH treatment in patients with WSS has not been previously reported. In our patient, growth response was excellent to modest doses of GH treatment over a 6-year follow-up period. On regular monitoring, GH-dependent peptides IGF-I and IGFBP-3 remained within the normal range. No adverse events from GH administration were noted. There was no observed alteration in phenotypic characteristics of WSS. Our patient continues to be treated as any other child with GHD with strict monitoring for efficacy and adverse events arising from GH treatment; it remains to be seen if our patient develops wider pituitary dysfunction, experiences a pubertal growth spurt and if final height is appropriate for the parental height potential.

WSS is caused by *KMT2A* mutations (4). *KMT2A* encodes a histone 3 lysine 4 methyltransferase. Our observation indicates that *KMT2A* may have a role in pituitary development. Several other developmental disorders caused by mutations in histone lysine methyltransferases (KMTs) are known (7). Of these, *KMT2D* mutations that cause Kabuki syndrome (KS, OMIM#147920) are notable. This is because GH deficiency has also been described in patients with KS (8, 9). *CHD7* encodes a reader for H3K4 marks laid down by *KMT2D* (10). *CHD7* mutations cause CHARGE syndrome (OMIM#214800). Growth retardation is one of the cardinal features of CHARGE syndrome and GHD has also been described in patients with CHARGE (11).

We conclude that our case report illustrates the need to investigate pituitary function, in particular for GH secretion in all children diagnosed with WSS and short stature. Treatment with recombinant human GH could be considered as an option to improve height gain in patients with WSS and GHD.

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