Pseudoacromegaly – a differential diagnosis problem for acromegaly

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Introduction

• Acromegaly is usually not a difficult condition to diagnose, if the suspicion of this disease has been raised. However, there are a few conditions presenting with some aspects of acromegaly or gigantism, but without excess of GH excess - pseudoacromegaly or acromegaloaldism.

• Sotos syndrome (also known as cerebral gigantism syndrome) is an overgrowth condition characterized by four cardinal features: excessive growth during the childhood with advanced bone age; macrocephaly; characteristic facial appearance; learning difficulties.1

Case report

In 1974, a 10y girl presented with tall stature since infancy (>P97):
• She was 160cm tall and weighed 60kg (both over 99th)
• Acromegalic features: large hands and feet (shoe size UK8/EU43), macroglossia, prognathism and deep voice (Figure 1)
• Her bone age was advanced (15y) and she had already a full set of permanent teeth
• Headaches and mild learning difficulties
• Pubertal development was corresponding to her chronological age (Tanner stage I)
• Sella X-ray and endocrine evaluation were normal
• Ethynylestradiol and medroxyprogesterone was started, with cessations of linear growth within 2y. No increase of shoe and glove size since the age of 15y. Final height=171cm.

Over the next 40 years:
• Acromegaly screening was initiated by different doctors on 2 more occasions, both negative
• Surgery for carpal tunnel syndrome and hallux valgus (31y)
• 3 unsuccessful IVF attempts
• Endometriosis: left salpingo-oophorectomy (31y) and total hysterectomy (34y)
• Radioiodine treatment for an hyperfunctioning thyroid nodule (34y)

Current presentation at age 49y:
• Weight gain, sweating, sleep apnoea, headaches, joint pain, together with acromegalic facial features, lead to reassessment of GH axis and MRI scan – normal (Table 1)
• Genetic testing with a panel for macrocephaly/overgrowth syndrome genes: CUL4B, EZH2, GLI3, NSD1, PTEN and UPS3B.
• A heterozygous mutation in NSD1 gene known to cause Sotos syndrome was identified (c.6605G>C; p.Cys2202Ser) (Figure 2).
• DNA samples from her parents found no mutation, suggesting a de novo mutation.

Discussion

Sotos syndrome is a rare disorder, which diagnosis can be challenging and delayed.

Overgrowth, macrocephaly, acromegalic features and learning difficulties should raise suspicion for this condition, especially in those cases with normal GH axis.1

In addition to acromegaly, the differential diagnosis list includes several syndromes such as Weaver, Beckwith-Wiedeman, Simpson-Golabi-Behmel, Cowden, Malan syndrome, Fragile-X-syndrome (in males), or Marshall syndromes.2

NSD1 (Nuclear receptor binding SET Domain protein 1) gene contains 23 exons located on 5q35, encoding a histone methyltransferase implicated in transcriptional regulation.3 The variant we found was not previously described, but pathogenic mutations affecting the same cysteine residue have been reported4, strongly suggesting the pathogenicity of our variant.

The patient has agreed to the presentation of her case and all photographs