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 *acromegaloidism.*
- Sotos syndrome (also known as cerebral gigantism syndrome) is a 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 97th)
- **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
- Ethinylestradiol 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 UPF3B.
- 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 reported[4], strongly suggesting the pathogenicity of our variant.

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

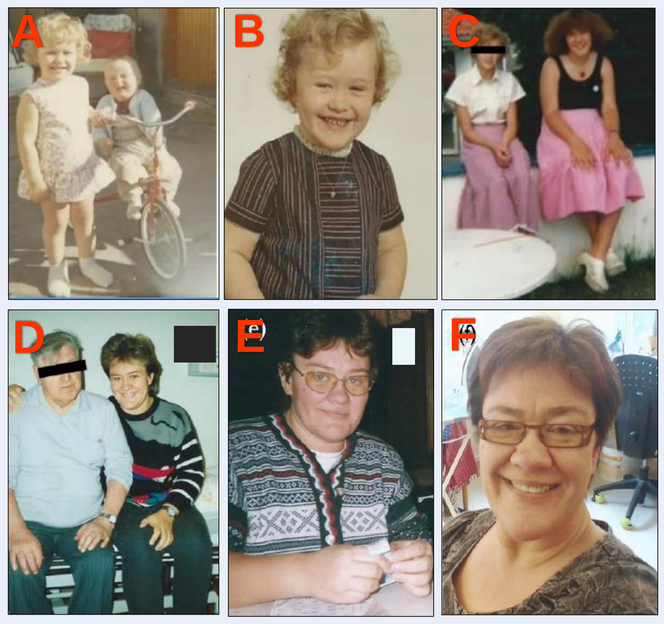
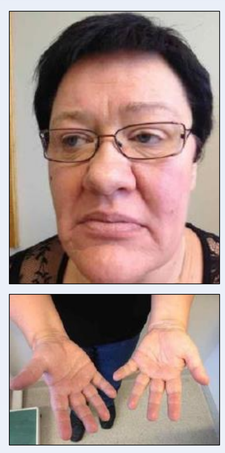


Figure 1: Patient´s pictures at the ages of 3 (**A**), 5 (**B**), 14 (**C**), 22 (**D**), 34 (**E**) and 45-years-old (**F**)



Height (cm)	175
Weight (kg)	112
BP (mmHg)	125/75
Index finger diameter (mm)	28
Shoe size (UK/EU)	10.5/45
Haemoglobin (g/L)	145
Fasting glucose (mmol/L)	5.4
IGF-1 (µg/L)	213 (54-307)
GH day curve and OGTT	Normal
MRI sella	Normal

Table 1: Some clinical parameters, laboratory and imaging data from the last evaluation (prior to the genetic testing)

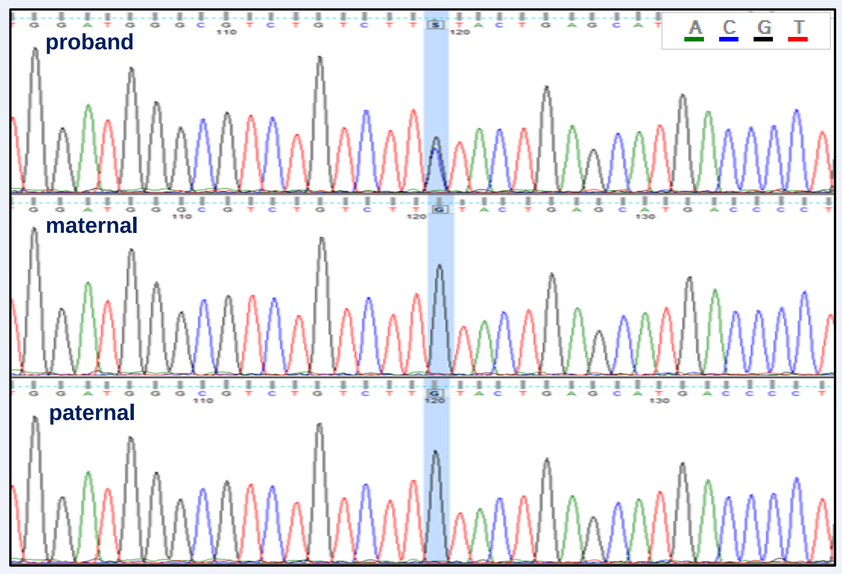


Figure 2: Sequencing electropherogram of *NSD1* exon 23 from the patient (**above**) and her parents (**below**). The double peak (in blue) confirms the presence of a *de novo* heterozygous missense mutation at c.6605G>C (p.Cys2202Ser). No mutation was found in her mother and father.

1. Baujat G, Cormier-Daire. Sotos syndrome. *Orph J Rare Dis* 2007; 2:36.
2. Fickie M, Lapunzina P, Gentile J, *et al*. Adults with Sotos syndrome: Review of 21 adults with molecularly confirmed *NSD1* alterations, including a detailed case report of the oldest person. *Am J Med Genet Part A* 2011; 155:2105-11.
3. Kurotaki N, Harada N, Yoshiura K, *et al*. Molecular characterization of NSD1, a human homologue of the mouse Nsd1 gene. *Gene* 2001; 279
4. Boer L, Kant S, Karperien M, *et al*. Genotype-phenotype correlation in patients suspected of having Sotos syndrome. *Horm Res* 2004; 62:197-207.

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