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# Smith-Magenis syndrome and growth hormone deficiency

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**Abstract** Smith-Magenis syndrome (SMS) is a multiple congenital anomaly/mental retardation syndrome including physical and neurobehavioural features. The disease is commonly associated with a ca. 3.7 Mb interstitial deletion of chromosome 17p11.2, while a 1.1 Mb critical region has been identified, containing about 20 genes expressed in multiple tissues. Haploinsufficiency of one of them, RAI1, seems to be responsible for the neurobehavioural, craniofacial and otolaryngological features of the syndrome, but not for short stature, commonly seen in SMS patients with chromosome deletion, implying the role of other genes in the 17p11.2 region. Growth failure is a final result of several different mechanisms involving decreased growth hormone (GH) production, reduced tissue response to GH, or impaired activity of epistatic factors. To our knowledge, the association of GH deficiency with SMS has never been reported and rarely investigated, despite the very short stature of SMS patients. We describe a girl with a full SMS phenotype and a typical 3.7 Mb deletion of 17p11.2 who also has GH deficiency. After starting replacement therapy, growth has significantly improved, her stature being now above both the 10th percentile and her genetic target. *Conclusion*: We suggest that an investigation of both growth hormone secretion and function is carried out in patients with Smith-Magenis syndrome and 17p11.2 deletion.

**Keywords** Behavioural phenotype · Growth hormone deficiency · Short stature · Smith-Magenis syndrome · 17p11.2 deletion

**Abbreviations** FISH: fluorescent in situ hybridisation · GH: growth hormone · SMS: Smith-Magenis syndrome

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## Introduction

Smith-Magenis syndrome (SMS, OMIM 182290) is a multiple congenital anomaly and mental retardation syndrome including physical, neurodevelopmental, and behavioural features [2,8]. The facial appearance is characterised by a broad square-shaped face, brachycephaly, prominent forehead and mid-face hypoplasia; micrognathia is present in infancy changing to relative prognathism with age. Eyes are deep-set with up-slanting palpebral fissures, the nose is short and full-tipped, the mouth has down-turned corners and a fleshy everted upper lip with a "tented" appearance [1]. Gradual height and weight deceleration of post-natal onset is observed and short stature, small hands and feet and brachydactyly are the norm. Scoliosis, hearing loss and other otorhinolaryngological problems, including vocal cord nodules and polyps, and ophthalmological defects, especially strabismus and progressive myopia, are common. Hypercholesterolaemia, which may require medical treatment, is found in about 70% of patients [21]. Mild ventriculomegaly of the brain, and cardiac and renal abnormalities are observed in 33% of patients and hypothyroidsm and immunoglobulin deficiency in 20% to 25%. All patients have some level of cognitive impairment, mostly moderate, and expressive language is significantly impaired [19].

Infantile hypotonia with feeding difficulties is observed in most children. Marked hypersomnolence is noted in early infancy, shifting at about 2–4 years of age to the typical SMS pattern of sleep disturbances which include difficulty in falling asleep and frequent and prolonged night-time awakenings [20]. Other distinctive behavioural features of SMS are attention deficiency, hyperactivity, frequent outbursts, temper tantrums, aggression towards self and others, and stereotypies [19].

SMS is associated with an interstitial deletion of chromosome 17p11.2, the majority of patients having a common ca. 3.7 Mb deletion, flanked by large, highly homologous, low copy repeats [16]. These repeats are defined as proximal and distal SMS-REPs (SMS-REPP and SMS-REPD), while a third copy repeat, designed middle SMS-REP (SMS-REPM), lies between them with an inverted orientation. Homologous recombination and unequal crossing-over between the SMS-REPP and SMS-REPD represent the mechanism responsible for the common deletion and the reciprocal duplication. Some SMS patients have smaller or larger sized deletions and molecular analysis of ten patients with a different deletion from the common one allowed the delineation of a ca. 1.1 Mb SMS critical region (SMSCR) [3]. The discovery of three individuals with phenotypic features consistent with SMS, but without any fluorescence in situ hybridisation (FISH) detectable 17p11.2 deletion, led Slager et al. [17] to identify three different truncating mutations of the *RAI1*gene. In all cases the mutation was de novo confirming that haploinsufficiency of *RAI1*is responsible at least for the neurobehavioural and craniofacial features of the syndrome.

Adequate function of the growth hormone (GH) pathway is essential throughout childhood to maintain normal growth and bone maturation. While most cases of GH deficiency are idiopathic, a few single gene disorders, as well as a variety of other genetic disorders and syndromes, are associated with deficiency of GH or with its impaired activity [5]. In this context GH deficiency can be caused by alteration in the *GH* gene [13], in genes that affect the response to GH [26] or in other loci through epistatic effects [25]. To our knowledge, the association of GH deficiency with SMS has never been reported and GH secretion and bone age have been rarely investigated in these patients [10,18], despite their very short stature.

Here we describe a girl with a full SMS clinical phenotype and a typical 3.7 Mb deletion of chromosome 17p11.2 who also has GH deficiency and whose growth velocity dramatically improved after starting GH replacement therapy.

## Case report

Our patient, a girl, was born in 1994 to non-consanguineous parents. Her father died at the age of 41 years due to drowning; he had been diagnosed with brain astrocytoma at the age of 36. The mother and a 4-year-old sister are healthy.

During pregnancy, ultrasound examination demonstrated a mild intrauterine growth retardation and at birth (40 weeks of gestation) the girl's weight was 2730 g (3rd–10th percentile), length was 48 cm (25th percentile) and head circumference was 32.5 cm (3rd–10th percentile). Gradual height and weight deceleration had been noted since the age of 1 year. First tooth eruption was at 12 months and the anterior fontanelle closed at 24 months of age. When the girl was 5 years old, height had fallen to the 3rd percentile, growth velocity was 3.4 cm/year (−3 SD) and bone age was retarded (2.5 years). A partial GH secretion deficiency was demonstrated (GH peak: 6.68 ng/ml after arginine administration and 1.7 ng/ml after insulin tolerance test) and replacement therapy was started (0.2 mg/kg per week in six doses administered subcutaneously at bedtime). Early neuromotor milestones were achieved almost at the expected times (independent walking at 18 months), while language development was significantly retarded (at the age of 3 years, DQ was 78.8 on the Griffiths Developmental Scale). The girl also had mild hypotonia, swallowing difficulty and food textural aversion. Behavioural disturbances had been present since early infancy and escalated with age. They consisted of temper tantrums and outbursts, attention deficit, hyperactivity, self-injurious and stereotypic behaviours (particularly hand and nail biting and teeth grinding). Sleep disturbances improved greatly after starting therapy with acebutolol and melatonin [6]. During the first years of life, she exhibited occasional absence-like episodes and at the age of 7 years, during a bout of high temperature, she had seizures. Since the first months of life, she had suffered from recurrent otitis media and respiratory infections and has a selective IgA deficiency.

On our first clinical examination at the age of 7 years (Fig. 1b), height was 114 cm (10th percentile), weight was 17 kg (3rd percentile) and head circumference was 48 cm (far below the 3rd percentile). The girl presented with brachydactyly, an unusual gait on tiptoe, Brown syndrome of the right eye, mild astigmatism, and hoarse voice. She also had some dysmorphic features: mild up-slanting of the palpebral fissures, slight low-set and marked protrusion of ears, full-tipped nose, fleshy everted upper lip with "tented" appearance and slight micrognathia. On otolaryngological examination, mild bilateral conductive hypoacusia and a left vocal cord nodule were found. Brain MRI scan, echocardiography, renal ultrasound examination, vertebral column radiography and evaluation of thyroid function gave normal results. Repeated analyses (the last one at the age of 8 years) of blood triglycerides, cholesterol, LDL and HDL were always normal. After starting GH replacement therapy, growth velocity was 9 cm/year (+3 SD) in the first year and 8 cm/year (+2.5 SD) and 6.7 cm/year (+1.4 SD) during the 2nd and 3rd years respectively. At the age of 8 years and 3 months, her height was slightly above the 10th percentile (122.5 cm), and higher than

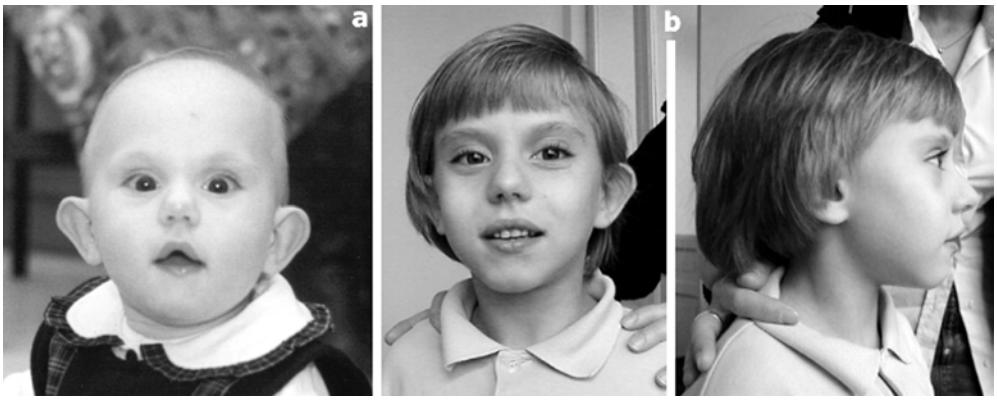


**Fig. 1** **a** Patient at age 1 year showing a characteristic broad square-shaped face and prominent forehead. **b** By 7 years, her general appearance seems to have changed and the girl only shows some SMS facial dysmorphism such as a full-tipped nose and a ''tented'' mouth appearance

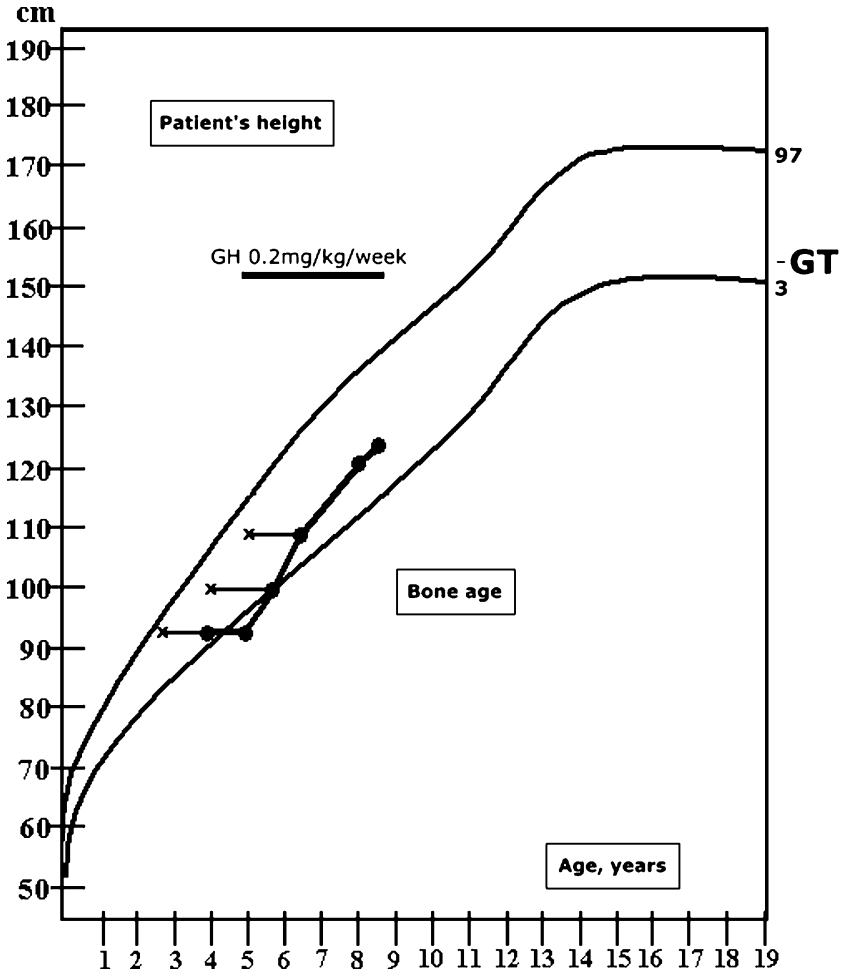


**Fig. 2** Growth curve of the patient. The *bar* above the 97th percentile indicates the duration and dosage of GH replacement therapy. Bone ages are indicated with an ''*x*'' at the end of a *horizontal line* from the actual age. The first evaluation of bone age was at 5 years (growth between 4 and 5 years was nil). Genetic target (GT) is at the 10th percentile

her genetic target for height (156 cm) (Fig. 2), span was 120 cm, upper/lower segment ratio was 1.16, while head circumference was around the 3rd percentile (50 cm).

## Materials and methods

Routine and high resolution chromosome studies were performed on phytohaemagglutinin-stimulated blood cultures by standard techniques. FISH analysis was carried out on chromosome preparations obtained from the patient's lymphoblastoid cell lines. BAC clones of 17p11.2 were selected from NCBI and UCSC web sites (http://www.ncbi.nlm.nih.gov/ and http://genome.ucsc.edu/) and purchased from the Childrens Hospital Oakland (BAC-PAC Resources), or provided free by the YAC Screening Centre (Dibit HSR, Milan, Italy), and Dr. M. Rocchi (http://biologia.uniba.it/eca/). The commercial probe for the SMS critical region was purchased from ONCOR (Gaithersburg). The probes

were labelled by nick-translation with digoxigenin-11-dUTP (Roche Mannheim, Germany). The analysis was performed according to Lichter and Cremer [11] with minor modifications.

## Results

Chromosome analysis after high resolution banding, performed when the girl was 7 years old, revealed a heterozygous interstitial deletion of the short arm of chromosome 17 (17p11.2) in all the analysed metaphases (Fig. 3). The mother had a normal karyotype; the father was unavailable for testing.

The involvement of the SMS region in the proband's deletion was confirmed by FISH experiments with the D17S258 SMS probe (Oncor) and a panel of contiguous region-specific BACs that gave a signal on one chromosome 17 only in all the analysed metaphases (data not shown). The centromeric deletion breakpoint was mapped within the SMS-REPP by FISH with RP11 218E15 (centromeric to the SMS-REPP [12]) that showed the presence of two signals (Fig. 4a), and RP11 121A13 (telomeric to SMS-REPP and mapping within the


**Fig. 3** Cutout of the normal and the deleted (*arrowed*) chromosomes 17

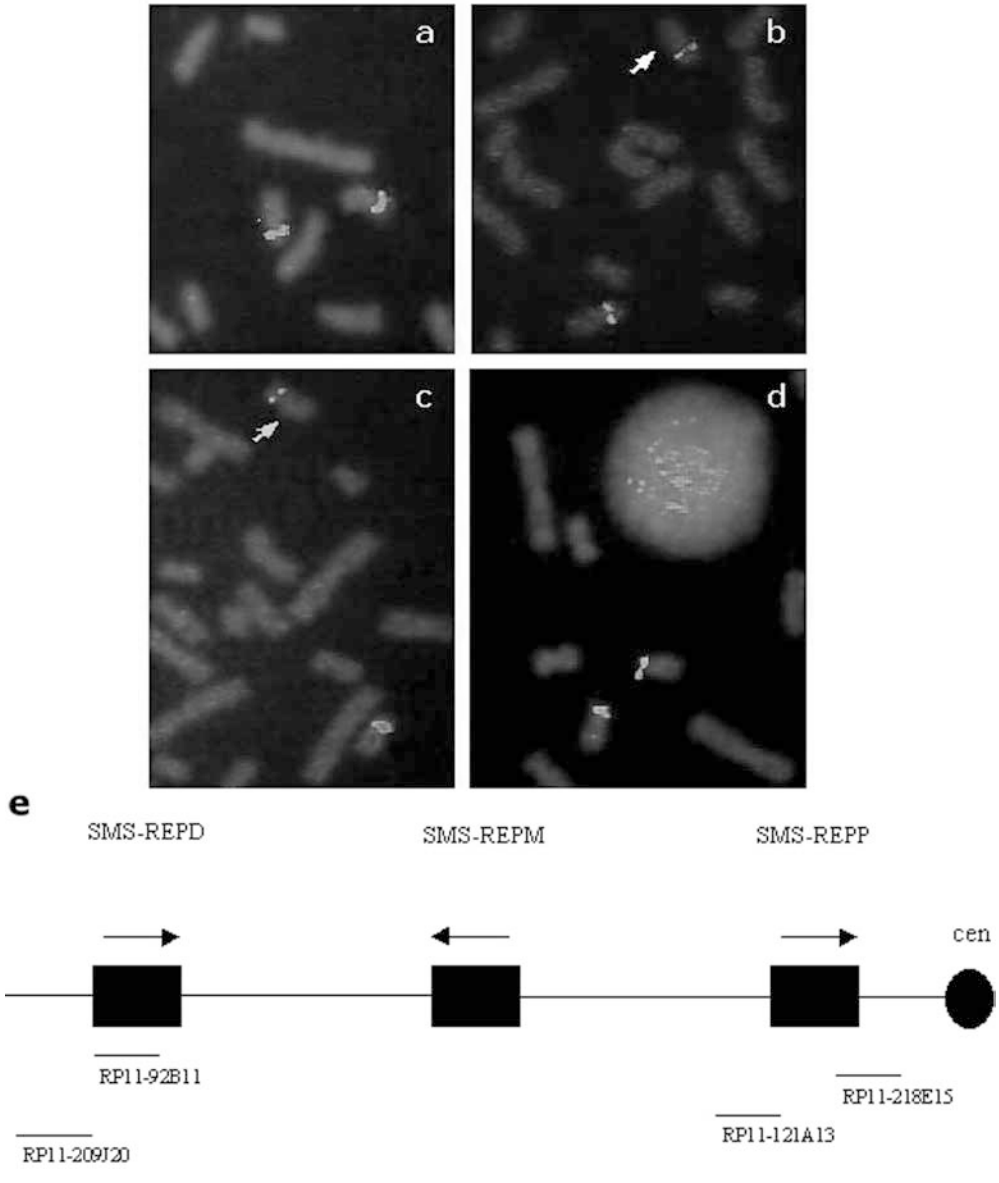


**Fig. 4** FISH characterisation of 17p11.2 deletion breakpoints. **a** RP11 218E15, centromeric to SMS-REPP, gives two distinguishable hybridisation signals. **b** RP11 121A13, telomeric to SMS-REPP, gives a signal of diminished intensity ( *arrowed*) indicating that the centromeric deletion breakpoint maps within SMS-REPP. **c** RP11 92B11, mapping within SMS-REPD, shows a signal of diminished intensity (*arrowed*). **d** RP11 209J20, telomeric to SMS-REPD, gives signals on both chromosomes allowing location of the telomeric breakpoint within SMS-REPD. **e** The diagram shows the map (not to scale) of chromosome 17p11.2 with the placement of the FISH clones used to define the deletion breakpoints. The *arrows* represent the orientation of the SMS-REPs

LCR17pC [23]) that showed a diminished signal on the deleted chromosome 17 in comparison to the normal homologue (Fig. 4b). The telomeric deletion breakpoint was located within the SMS-REPD by FISH with RP11 92B11 (mapping within the SMS-REPD [12]) which gave a signal of diminished intensity on the deleted chromosome 17 (Fig. 4c) and RP11 209J20 (telomeric to the SMS-REPD [23]) which gave signals on both chromosomes 17 (Fig. 4d). Our refined FISH study allowed us to establish that our patient had the common 3.7 Mb deletion located between SMS-REPP and SMS-REPD (Fig. 4e).

## Discussion

The patient we describe here is an 8-year-old girl with a 3.7 Mb deletion of chromosome 17p11.2, as observed in more than 90% of SMS patients. Her behavioural phenotype completely overlapped that observed in the syndrome. She had some facial dysmorphism strictly resembling that observed in SMS [1], namely a full-tipped nose and ''tented'' mouth, even if her general appearance seemed to have changed over the years, now lacking the characteristic broad square-shaped face, brachycephaly and prominent forehead (Fig. 1a,b). She lacked fasting lipid profile abnormalities and skeletal problems, both present in about 70% of SMS patients [21]. Orthopaedic manifestations of SMS have recently been revalued by Spilsbury and Mohanty in 22 patients [22]. They found that all the subjects had short stature with projected mean height of 143 cm when skeletally mature. At birth, our patient had a length of 48 cm (25th percentile), but since the age of 1 year gradual deceleration of height had been noted and, by the age of 5 years, her height had fallen to the 3rd percentile. Bone age was also delayed and an isolated partial GH secretion deficiency was demonstrated before the diagnosis of SMS was accomplished. After starting GH replacement therapy, growth has significantly improved and now the girl's height is above both the 10th percentile and her genetic target (Fig. 2).

To our knowledge GH deficiency and delayed bone age have never been reported in SMS, but they have been very rarely investigated [10,18]. The necessity of a good co-operation of patients and families and prolonged times to complete GH secretion testing may have led to the exclusion of this analysis from study protocols of SMS patients. On the other hand, if the diagnosis of SMS is made in early childhood, short stature can be regarded as a feature of the syndrome and thus not further investigated. Interestingly, one patient with 17p11.2 duplication has been reported having GH secretion deficiency [15].

It is probable that growth failure is a final common result of several different mechanisms involving decreased GH production, reduced tissue response to GH, or impaired activity of regulatory factors. GH deficiency has been demonstrated in chromosome deletion syndromes and implied in the pathogenesis of the associated short stature [7,14]. In a series of 33 subjects with the 18q syndrome, Cody et al. [4] identified a region of approximately 2 Mb that was deleted in every GH insufficient patient. They pointed to one gene included in this region, the galanin receptor 1, as candidate gene for the GH insufficiency phenotype, due to its hypothalamic involvement in GH regulation. No such genes, known to be important in growth, have been identified to date in the 17p11.2 region. The SMSCR contains about 20 genes widely expressed in multiple tissues [3]; haploinsufficiency of *RAI1* seems to be responsible for the neurobehavioural, craniofacial and otolaryngological features of the syndrome. However, the three SMS patients with *RAI1* mutations do not have short stature, implying that haploinsufficiency of another or other genes in the 17p11.2 region is responsible for this clinical feature in SMS patients with a chromosome deletion. Investigations of GH metabolism in children with chromosome deletion syndromes, such as SMS, might uncover novel mechanisms and new genes involved in normal and altered GH secretion and regulation pathways. This may also enhance the understanding of these disorders and suggest potential treatment approaches.

GH replacement therapy has proved beneficial in our patient, possibly reducing also her risk of hypercholesterolaemia and hypertriglyceridaemia as observed in adult GH deficient patients [24]. Similarly, in Prader-Willi syndrome, GH administration has been shown to improve body composition, sleep quality and pulmonary function [9]. Therefore we suggest that screening of GH secretion and function is carried out in other patients with SMS and a 17p11.2 deletion.

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