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Annales d'Endocrinologie 76 (2015) 629–634

Annales d'Endocrinologie
Annals of Endocrinology

Clinical case

Growth hormone deficiency and pituitary malformation in a recurrent Cat-Eye syndrome: A family report

Déficit en hormone de croissance et malformation hypothalamo-hypophysaire dans une forme familiale de syndrome Cat-Eye

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Abstract

Growth hormone deficiency affects roughly between one in 3000 and one in 4000 children with most instances of growth hormone deficiency being idiopathic. Growth hormone deficiency can also be associated with genetic diseases or chromosome abnormalities. Association of growth hormone deficiency together with hypothalamic–pituitary axis malformation and Cat-Eye syndrome is a very rare condition. We report a family with two brothers presenting with growth delay due to a growth hormone deficiency associated with a polymalformation syndrome. They both displayed pre-auricular pits and tags, imperforate anus and Duane retraction syndrome. Both parents and a third unaffected son displayed normal growth pattern. Cerebral MRI showed a hypothalamic–pituitary axis malformation in the two affected brothers. Cytogenetic studies revealed a type I small supernumerary marker chromosome derived from chromosome 22 resulting in a tetrasomy 22pter-22q11.21 characteristic of the Cat-Eye syndrome. The small supernumerary marker chromosome was present in the two affected sons and the mother in a mosaic state. Patients with short stature due to growth hormone deficiency should be evaluated for chromosomal abnormality. Family study should not be underestimated.

Keywords: Cat-Eye syndrome; Growth hormone deficiency; Pituitary malformation; Mosaicism

Résumé

Le déficit en hormone de croissance affecte entre 1 enfant sur 3000 et 1 enfant sur 4000. Le plus souvent, il est idiopathique. Rarement, il est dû à une maladie génétique ou à une anomalie chromosomique sous-jacente. L'association d'un déficit en hormone de croissance à une malformation de l'axe hypothalamo-hypophysaire et à un syndrome de Cat-Eye est très rare. Nous rapportons une famille dans laquelle deux frères présentant un retard de croissance dû à un déficit en hormone de croissance avaient à un syndrome polymalformatif évocateur du syndrome Cat-Eye. Ils présentaient tous deux des anomalies pré-auriculaires, une imperforation anale et un syndrome de Duane. Leurs parents et leur frère sain avaient une

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http://dx.doi.org/10.1016/j.ando.2015.02.002
0003-4266/

croissance normale. L'IRM cérébrale montrait une malformation de l'axe hypothalamo-hypophysaire. Les explorations cytogénétiques retrouvaient la présence d'un marqueur chromosomique surnuméraire dérivé du chromosome 22 de type 1, ayant pour conséquence l'existence d'une tétrasomie 22pter-22q11.21. Ce marqueur chromosomique surnuméraire était présent chez les deux frères atteints et leur mère à l'état de mosaïque. Devant un retard de croissance associé à un déficit en hormone de croissance, il est important de rechercher une anomalie chromosomique. De plus, l'importance de l'enquête familiale, en cas de syndrome Cat-Eye, ne doit pas être sous-estimée.

Mots clés : Syndrome Cat-Eye ; Déficit en hormone de croissance ; Malformation hypothalamo-hypophysaire ; Mosaïcisme

1. Introduction

Congenital growth hormone deficiency (GHD) is a frequent and treatable cause of growth delay. GHD can be an isolated phenomenon or associated with other pituitary hormone deficiency. Both congenital and acquired factors can be responsible for isolated GHD (IGHD). Yet, in a majority of cases, isolated GHD is idiopathic, without identifiable etiology [1]. Clinical presentation varies depending on the association of other pituitary hormone deficiencies or extra-pituitary malformations. IGHD and multiple pituitary hormone deficiencies can also be associated with hypothalamic–pituitary axis malformations in cases of mutations in genes involved in the pituitary gland development [2]. More rarely, *de novo* chromosomal anomalies have also been reported in such cases (associating GHD and hypothalamic–pituitary axis malformations): 15q24 microdeletion syndrome [3], Prader–Willi syndrome [4], 22q11.2 microdeletion syndrome [5], Jacobsen syndrome [6] and Cat-Eye syndrome [7].

Cat-eye syndrome (CES), or Schmid–Fraccaro syndrome (OMIM 115470), is a rare genetic disease with a prevalence estimated between 1 in 50,000 and 1 in 150,000. The phenotype of CES is heterogeneous, the most notable clinical features include: pre-auricular pits and/or tags, anal atresia, iris coloboma, congenital cardiac defects, and intellectual disability. Growth delay is reported in 15% of cases [8]. CES is due to the presence of a small supernumerary marker chromosome (sSMC) derived from chromosome 22, which results in a partial tetrasomy of the 22p-22q11.21 region.

We report a familial recurrence of CES in which two brothers presented with a growth hormone deficiency (GHD) due to a hypothalamic–pituitary axis malformation. The two affected brothers and their mother carry the sSMC responsible for CES in a mosaic state.

2. Subjects and methods

2.1. Clinical report

2.1.1. Patient 1

Patient 1 was the first child of non-consanguineous healthy parents. He was born at 41 weeks of gestation (WG) after an uneventful pregnancy. At the time of birth, his height was 53 cm (1.5 SD), weight was 3680 g (0.5 SD), and head circumference was 37 cm (1.5 SD). Clinical examination identified bilateral pre-auricular tags and pits and an imperforate anus, which required a surgical treatment. No genitourinary malformation was found. A detailed ophthalmologic examination was performed which excluded coloboma of iris but revealed a bilateral type I Duane retraction syndrome. Transthoracic echocardiography identified an atrial septal defect, which closed spontaneously. Ultrasound examination of the abdomen found a transitory and moderate dilation of the collecting system of right kidney. At the age of 4 years, his height was 91 cm (–3 SD) and weight was 12.8 kg (–3 SD). A workup for short stature was then undertaken. Hormonal investigations revealed that insulin-like growth factor 1 (IGF1) level was below 25 ng/dL (normal: 76–500 ng/dL), a basal GH level was 1.4 μg/dL with no response to insulin. The values for adrenocorticotrophic hormone (ACTH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), testosterone, thyroid stimulating hormone (TSH), free tri-iodothyronine (FT3), free tetra-iodothyronine (FT4), and cortisol were found to be normal (Table 1). At the age of 4 years 10 months, cerebral MRI examination of the subject revealed a small intrasellar anterior pituitary gland, measured at 2 mm, and an ectopic neurohypophysis located in the postero-superior region of the pituitary stalk (Fig. 1). Neurocognitive development was normal with absence of delayed psychomotor milestones. GH replacement therapy at the dose of 0.035 mg/kg/day, six days a week was introduced. It allowed the patient to attain a normal growth after 2.5 years of treatment (Fig. 2). At the age of 9 years, his height was 132 cm (0.5 SD) and weight was 29.6 kg (0.5 SD) on the same medical treatment.

2.1.2. Patient 2

Patient 2 was the brother of patient one and third child of the couple. He was born at 38.5 weeks of gestation after an uneventful pregnancy. At the time of birth, his height was 51 cm (0.5 SD), weight was 3540 g (–0.5 SD), and head circumference was 34 cm (–0.5 SD). Clinical examination identified the presence of bilateral pre-auricular tags, an imperforate anus associated with a rectal fistula, and a micropenis with a hypospadias. Detailed ophthalmological examination found a bilateral type I Duane retraction syndrome without iris coloboma. Renal and cardiac ultrasound scans of the subject were normal. Hormonal screening performed at the age of one year found an isolated GHD. Results of hormonal investigations revealed that IGF1 level was below 25 ng/mL (normal: 49–171 ng/mL), a basal GH level was 3.9 μg/dL with no response to insulin (Table 1). At the age of 1 year 9 months, cerebral MRI found a hypotrophic intrasellar anterior pituitary gland, measured at 2 mm, and an ectopic neurohypophysis (Fig. 1). Like his brother,