Etiologies and Clinical Presentation of Gigantism in Algeria

Farida Chentli a  Said Azzoug a  Mohammed El Amine Amani c
Ali El Mahdi Haddam b  Dalal Chaouki d  Djamila Meskine b
Mohamed Lamine Chaouki d

a Endocrinologie et Maladies Métaboliques, Centre Hospito-Universitaire Bab El Oued, et b Service Endocrinologie, Etablissement Public Hospitalier, Bologhine, Alger; c Service d’Endocrinologie Diabétologie, Etablissement Hospitalo-Universitaire 1°Novembre, Oran, et d Service Endocrinologie, Centre Hospitalo-Universitaire Batna, Batna, Algérie

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Gigantism · Hypersomatotropism · Pituitary tumor · Sotos syndrome · Constitutional overgrowth

Abstract
Background/Aims: True gigantism is an exceptional and fascinating pediatric disease. Our aim in this study was to describe the different etiologies of a large group of children with gigantism and the natural history of their growth. Methods: In this multicenter study, we considered as giant children, adolescents and adults whose heights were ≥3 SD compared to their target stature or to our population average lengths. Isolated hypogonadism and Klinefelter syndrome were excluded from this series. All underwent clinical exam, and hormonal and neurological investigations. Results: From 1980 to 2010, we observed 30 giants: 26 males (86.6%) and 4 females (mean age 19.8 ± 11 years). Among the 13 patients (40.3%) who consulted before the age of 16 years, 9 had acromegaly and 6 had mental retardation and body malformations. Based on growth hormone (GH) secretion evaluation, 2 groups were observed: pituitary gigantism (n = 16): GH = 150 ± 252 ng/ml (n ≤ 5), and other causes with normal GH (0.7 ± 0.6 ng/ml): 6 Sotos syndrome and 8 idio-pathic cases. Only the first group had neurological, ophthalmological, metabolic and cardiovascular complications and received treatment. The result was not optimal as GH normalization was not observed. Reduction of tumor size and decreased GH plasma values were not observed. Conclusion: Gigantism predominates in males. The main cause is GH excess. The diagnosis was very late except for cerebral gigantism. Complications were observed in pituitary gigantism only.

Introduction

True gigantism is an exceptional disease due to an oversecretion of growth hormone (GH) or genetic disorders [1, 2]. Although gigantism has attracted a lot of attention, there are very few publications on this syndrome because of the extreme rarity of the condition. Complications are frequent in those cases. They are observed especially in patients with pituitary tumors. Our objective is to report a large group of giants observed in Algeria over a long period of 30 years, and to describe clinical presentation and etiologies of this very rare affection.
Subjects and Methods

In this retrospective and prospective multicenter study, we collected patients who were examined for gigantism from January 1, 1980 to December 31, 2010. These patients were observed in 6 different centers across the country.

Local body overgrowths and simple tallness between 2 and 3 SD observed in obesity, hyperthyroidism and in hypogonadism such as Klinefelter syndrome were excluded.

We considered as giant children, adolescents and adults whose heights were ≥ 3 SD compared to their target stature (TS) or to our population average height: 158 cm for women and 170 cm for men.

Clinical description of the patients was obtained as well as routine biological parameters. Endocrine evaluation was done at each institution; it was based especially on plasma GH and IGF1 measurement (when available) plus other hormones ( prolactin, ACTH, cortisol, TSH, FT4, FSH, LH, testosterone and estradiol). When GH was elevated, oral glucose suppression test was performed. All patients had cerebral CT scan, MRI or both. Genetic study was not available.

Results

We have collected 30 patients with gigantism: 26 males (86.6%) and 4 females, mean age: 19.8 ± 11 years (1–55). Thirteen (40.3%) were diagnosed before the age of 16 years. Pituitary gigantism was observed in 15 males and 1 female, Sotos syndrome in 6 boys, and in 8 (5 males, 3 females) no cause could be identified, so they were classified as idiopathic. The 30 cases were classified into 2 groups according to GH plasma values. In group 1 (G1), GH was elevated above normal values, and in group 2 (G2) GH was normal.

G1 was composed of 16 patients in whom GH was clearly elevated (150 ± 252 ng/ml, range 7.2–840, n ≤ 5), and was not suppressed during oral glucose loading (nadir 83.9 ± 132 ng/ml). Mean age at diagnosis was 25 ± 10.5 years. The diagnosis was made before the age of 16 years in 4 patients. Their mean height was 186 ± 6 cm for children and 196 ± 11 cm for men. The woman’s stature was 186 cm. Five patients had a lack of pubertal development, and 6 had experienced puberty, but they developed an acquired hypogonadism. Among these giants, 9 had signs of acromegaly (56%). A pituitary macroadenoma (≥10 mm) was found in 15 cases, and an isoadenoma (10 mm) in the female patient. In 4 patients, an increased secretion of GH and prolactin was observed. In 7 cases, a giant or very large tumor (defined as ≥4 cm) was found leading to intracranial hypertension in 5 patients. Complications of the macroadenomas were: ophthalmological troubles (7), psychiatric disorders (2) and pituitary deficien-
cits (13). GH excess complications were: glucose metabolism disorders (3), dyslipidemia (6), cardiomyopathy (3), arterioneuropathy (1) and vertebral abnormalities (4). In 2 patients, an associated tumor was observed: a pheochromocytoma and a hot thyroid nodule.

Except for 2 patients who refused surgery, they were all operated on (1–5 times). But, tumor resection was either partial or impossible. The 16 patients received additional conventional radiotherapy as somatostatin analogs were not available and high doses of bromocriptine were inefficient or not tolerated. The result of the combined treatment was good for the tumoricidal action as pituitary processes disappeared or were significantly reduced in all cases, but GH remained slightly high (13.9 ± 12 ng/ml, range 1–33). Metabolic and cardiovascular complications remained stable, but our prepubescent subjects continued to grow. Their final stature was 206 ± 16 cm (190–244; fig. 1).

In G2, plasma GH was normal as well as pituitary area on CT scan or MRI. Two types of patients were observed in this group: G2a and G2b.

In G2a, 6 boys with Sotos syndrome were classified. They were diagnosed during childhood at the age of 4.8 ± 3.7 years (1–12). They had a history of tall stature and mental retardation from birth. Several malformations were observed such as facial or body deformities, ectopic testis and/or cerebral asymmetry or atrophy.

Apart from psychological support, they did not receive any medication. The follow-up did not show any tumor development or metabolic disorders except for systemic hypertension (n = 1). In 2 of them, the final heights were 1.80 and 1.86 m (respective TS 1.69–1.62; fig. 1).

In G2b, 8 cases were classified. Except for a family history of gigantism (4) and pituitary adenoma (1), clinical exam was normal in all except one in whom prognathism was observed. Mean age at diagnosis was 19.7 ± 6.9 years (11–31), and statures were >3 SD in 3 subjects aged 11, 12 and 16 years, respectively, and equal to 194 ± 4.8 cm for the others. This group was considered familial or idiopathic gigantism as other diagnoses were excluded. No complications were observed either at diagnosis or during the follow-up. They did not receive any medications. One subject continued to grow until the age of 30 years (fig. 1).

Discussion

True gigantism is a very rare disease as only anecdotic cases have been reported [3–7]. The affection is prevalent in males. Although stature troubles were precocious, as they occur in childhood before epiphyseal long bone clo-

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sure, 60% were diagnosed very late. The diagnosis was delayed especially in subjects suffering from excess GH. For Sotos syndrome, the diagnosis was relatively precocious because of evident tallness at birth, large cranial perimeter and mental retardation.

Concerning the etiologies, similar to de Herder’s review [8] and contrary to the first reports, we found that the most important cause is pituitary gigantism. This disease caused the highest statures. In agreement with others, we found that most pituitary gigantisms were due to pure GH adenomas [9], sometimes to mixed adenomas [10] secreting prolactin and GH, rarely to pituitary hyperplasia [11]. Although the studied population was relatively young, one or more cardiovascular risk factors and

Fig. 1. a Male growth chart. b Female growth chart.
complications were present as reported in adults [12]. But, after treatment they were stabilized. In 2 cases, pituitary tumors were associated with a hot thyroid nodule and a pheochromocytoma. Other complications related to giant or very large pituitary tumors (>4 cm) were also observed, especially hydrocephaly, optic atrophy and pituitary insufficiency. In adult’s somatotroph adenomas, surgery is still considered as the best solution for limited tumors. But, for our patients, pituitary surgery was not very efficient because of the tumor size and cavernous system invasiveness. Radiotherapy was efficient as all the tumors disappeared or were significantly reduced, but GH normalization took many years. Of course, in this retrospective study over a long period of time, new treatments such as somatostatin analogues [6, 13] or GH receptor antagonists such as pegvisomant [5], which are now very helpful for giant tumors, were not available.

Idiopathic gigantism, also named family gigantism was the second etiology. But, if one considers simple tallness [14, 15], family or idiopathic cause would be the first. In idiopathic gigantism, there is not any dysmorphic syndrome, but some transitional cases with acromegaly features may exist with normal pituitary MRI, normal or even low GH and IGF1.

Sotos syndrome, also called cerebral gigantism [16–18] is the third etiology. This heterogeneous genetic disease is due to mutations and deletions of the NSD1 gene. Excessive stature may be present in the antenatal period [16]. The macrosomic newborns may also have psychomotor disorders, a dysmorphic aspect, and many malformations. Increase in tumor risk has also been reported [18]. In adulthood or in prepuberty, Sotos syndrome is generally misdiagnosed because prepuberty and definitive statures may be normal. In the follow-up, 2 boys had experienced puberty. Their final heights are superior to 3 SD compared to their TS.

Exceptional causes due to genetic disorders such as multiple endocrine neoplasms syndromes, and very complex syndromes, totally absent in our group, may also induce gigantism.

References