Review

Pituitary gigantism: Causes and clinical characteristics

Étiologies et caractéristiques cliniques du gigantisme hypophysaire

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Abstract

Acromegaly and pituitary gigantism are very rare conditions resulting from excessive secretion of growth hormone (GH), usually by a pituitary adenoma. Pituitary gigantism occurs when GH excess overlaps with the period of rapid linear growth during childhood and adolescence. Until recently, its etiology and clinical characteristics have been poorly understood. Genetic and genomic causes have been identified in recent years that explain about half of cases of pituitary gigantism. We describe these recent discoveries and focus on some important settings in which gigantism can occur, including familial isolated pituitary adenomas (FIPA) and the newly described X-linked acrogigantism (X-LAG) syndrome.

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Keywords: Gigantism; Aryl hydrocarbon receptor interacting protein gene; Familial isolated pituitary adenoma (FIPA); X-linked Acrogigantism (X-LAG) syndrome

Résumé

L’acromégalie et le gigantisme résultent d’une sécrétion excessive d’hormone de croissance (GH). Ces maladies rares sont habituellement dues à un adénome hypophysaire. Le gigantisme hypophysaire a lieu lorsque l’excès de GH se produit pendant la période de croissance linéaire rapide durant l’enfance ou l’adolescence. Jusqu’à récemment, son étiologie et les caractéristiques cliniques n’avaient pas été bien étudiés. Des causes génétiques et génomiques ont été identifiées au cours des dernières années qui expliquent environ la moitié des cas de gigantisme hypophysaire. Nous décrivons ces découvertes récentes et nous concentrerons sur certaines situations importantes dans lesquelles le gigantisme peut survenir, y compris les adénomes hypophysaires familiaux isolés (FIPA) et l’acrogigantisme lié au chromosome X nouvellement décrit (X-LAG).

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Mots clés: Gigantisme ; Aryl hydrocarbon receptor interacting protein gene ; Adénomes hypophysaires familiaux isolés (FIPA) ; Syndrome d’acrogigantisme lié au chromosome X (X-LAG)

1. Introduction

Giants are frequently depicted in popular art and literature as individuals with legendary abilities and strength (Fig. 1). In contrast, the description of patients with gigantism in the medical literature and the challenges faced by them was limited until very recently [1–3].

The pituitary gland and hypothalamus have a critical role in regulating the process of linear growth. Growth hormone (GH) overproduction by a somatotropinoma or pituitary hyperplasia in the young can lead to GH-dependent, or “pituitary”, gigantism. These cases can occur either sporadically or as a part of various endocrine neoplasia syndromes. In exceptionally rare cases, GH hypersecretion could be induced by GH-releasing hormone secreting ectopic neuroendocrine tumor.

2. Genetic predisposition in pituitary adenomas

Pituitary gigantism can occur as a part of several genetic disorders that lead to an increased risk of GH-secreting pituitary tumours. Hereditary pituitary adenomas are of great interest genetically and clinically. Recognition of the genetic causes of pituitary adenomas can permit closer follow-up and earlier
diagnosis of tumors in carriers of genetic mutations [4,5]. Clinical evidence suggests also that these tumors may be more aggressive than general sporadic equivalents.

GH producing pituitary adenomas seen in the context of inherited genetic abnormalities were traditionally considered to occur in cases of multiple endocrine neoplasia type 1 (MEN1) and Carney complex [6–8].

2.1. MEN1 syndrome

MEN1 syndrome is an autosomal dominant disease due to inactivating mutation in MEN1 gene (chromosome 11q13) encoding the protein menin that functions in cell cycle control and oxidative stress regulation. Up to the year 2010, more than 700 mutations in MEN1 had been described [9]. MEN1 occurs with the estimated prevalence of 0.02–0.2/1000 and is characterized by the association of parathyroid adenomas, neuroendocrine enteropancreatic tumors and pituitary adenomas. Pituitary lesions develop in about 40% and the majority of these pituitary lesions are invasive macroadenomas secreting prolactin; these tumors may have a poor response to treatment by dopamine agonists [10]. Excessive GH secretion was also described in the context of MEN1 that could lead to excessive stature in these patients [11]. Approximately 10–20% of patients with MEN1 do not have a detectable MEN1 mutation [10]. MEN4, a MEN1-like syndrome caused by germline mutations in the CDKN1B gene (chromosome 12p13), has been associated with a handful of cases of pituitary adenoma cases, including somatotropinomas [12,13].

2.2. Carney complex

Carney complex is a rare autosomal dominant disorder characterized by the association of cutaneous lesions, myxomas, schwannomas and glandular hyperactivity. In approximately 60–70% of cases, a mutation is detected in the PRKARIA gene, encoding the type I A regulatory subunit of protein kinase A [14]. In Carney complex, GH-secreting pituitary adenomas occurred about 10–13% of cases and usually have a slow progression [15,16]. Hypersecretion of GH associated with acromegaly or gigantism is often a consequence of a multifocal hyperplasia of somatotroph or somatomammotroph cells of anterior pituitary [13,15].

2.3. McCune–Albright syndrome

McCune-Albright syndrome presents usually as an association of polyostotic fibrous dysplasia, café au lait spots and precocious puberty. It is caused by postzygotic mutation that leads to mosaicism in GNAS1 gene (chromosome 20q13.3). As a consequence of this event occurring in endocrine cells, tumors with autonomous hormone secretion also form part of the clinical presentation, causing conditions like acrogeritism, Cush- ing’s syndrome etc. Hypersecretion of GH is present in 20–30% of McCune-Albright syndrome cases. It is caused by pituitary hyperplasia in the majority of cases but pituitary adenomas also are seen in one third of acromegalics with McCune-Albright syndrome [17,18]. A pathological increase in growth velocity caused by GH hypersecretion could be underestimated as a result of coexisting precocious puberty or hyperthyroidism – two conditions occurring frequently in McCune-Albright syndrome [19]. Mutations in GNAS1 could be inherited in cases of mosaicism affecting germinal cells. In a recent report, a constitu- tively active mutation was transferred in consecutive generations in transgenic mice [20]. However, in humans no cases of transmission in McCune-Albright syndrome are known.

3. Familial isolated pituitary adenomas (FIPA)

Cases of acromegaly in familial settings that were unrelated to known genetic syndromes were delineated in the 1990s [21]. A new condition with apparently inherited pituitary adenomas of all secretion types was identified in Liege in 1999–2000 and characterized as familial isolated pituitary adenomas (FIPA), consisting of families with two or more relatives having pituitary adenomas in the absence of known genetic causes (e.g. MEN1 and PRKAR1A) [22].

In 2006, Vierimaa et al. described AIP as being associated with predisposition to pituitary adenomas in a familial setting [4]. In FIPA families, adenomas usually occur earlier and are more aggressive than in sporadic cases. While in FIPA all types of pituitary adenomas can occur regardless of their AIP status, in AIP mutated patients, GH or GH and prolactin secreting adenomas are predominant (76.5%) [4]. We showed that patients with
GH secreting adenomas and AIP mutations are predominantly male and have larger and more aggressive tumors that occur more than 20 years before those without AIP mutations. AIP mutations have been demonstrated to be more frequent among specific subgroups of patients (e.g. children and young adults or FIPA families) than in sporadic cases. In particular, 10% of young patients (age at diagnosis less than 30 years) and 20% of children with sporadic macroadenomas are AIP mutation carriers [4,23–26]. We reported in 2010 that the number of acromegaly patients with gigantism among those with germline mutation in AIP gene was statistically significantly higher than in AIP negative cases (32% vs. 6.5%) [27].

A series of studies were performed for assessing the role and influence of predisposition genes (AIP, CDKN1B, MEN1) on pituitary tumor characteristics in aggressive pituitary adenomas and in FIPA. In 20% of FIPA families, AIP mutations have been found and in most of the remainder no genetic cause has yet to be discovered [5,23,24,27,28]. CDKN1B variants contribute little to the development of pituitary adenomas in FIPA [29].

4. Exploring the genetic causes of acrogigantism

As they are affected with GH secreting adenomas at a young age, this aggressive profile makes patients with pituitary gigantism a population of interest for genetic predisposition studies. We recently reported the results of the first specific multicenter study to characterize epidemiological, clinical, radiological, biological and genetic features in a cohort of 208 patients with pituitary gigantism [30]. In that study, 46% of cases tested had an identifiable genetic cause. Among these causes, the most frequent was AIP gene mutations (29%), while other known syndromes, such as McCune-Albright syndrome (5%), Carney complex (1%), and MEN1 (1%) were rarer.

The second most frequent cause of pituitary gigantism in the cohort (10%) was a microduplication at chromosome Xq26.3, which we recently described as a novel form of very early onset gigantism called X-linked acrogigantism (X-LAG) syndrome [31]. X-LAG syndrome can present either sporadically or in the setting of FIPA. In X-LAG syndrome patients, the rapid growth begins in infancy and is more frequent in females. Pituitary tumors were large mixed GH and prolactin secreting macroadenomas and secrete extremely elevated levels of GH (up to 1500 μg/L has been reported) and nearly all secreted have associated hyperprolactinemia. Pituitary adenomas were accompanied with pituitary hyperplasia in many cases and can rarely present with hyperplasia alone [31].

The Xq26.3 microduplication covers an approximately 500kb region involving CD40L, ARHGEF6, RBMX, and GPR101 (Fig. 2). However, a number of lines of evidence suggest that GPR101, which codes for an orphan G-protein coupled receptor, is responsible for the phenotype. In pituitary tumor tissue from patients with X-LAG syndrome, only GPR101 was upregulated on quantitative PCR. Variable upregulation of GPR101 can be seen on pituitary tumor samples from X-LAG syndrome patients. Crucially, chromosomal duplication of all of the other genes (CD40L, ARHGEF6, RBMX) that excluded GPR101 was not associated with a gigantism phenotype. In addition, an infrequent variant in the coding sequence of GPR101
Fig. 3. (Panel A) Physical changes in patients with X-LAG syndrome with Xq26.3 microduplication are shown at the age of 32 months at which time her height was +4 SDS (she had been growing at an abnormal rate since the age of 11 months). Of note are her large hands and feet and facial features that are moderately coarsened but well proportioned. Panel B shows widely spaced teeth and a patch of acanthosis nigricans on the left side of her neck [34].

(p.E308D), was identified in DNA from 4% of patients with sporadic acromegaly. In GH3 cells (rat somatomammotrope cell line), overexpression of the p.E308D GPR101 variant led to an increase in GH secretion as compared to the wild type GPR101 expressing controls [31]. Hence, X-LAG syndrome is likely due to GPR101 duplication alone.

More recently, we have described the clinical phenotype of X-LAG syndrome in an expanded cohort of 18 patients (at

Fig. 4. T1-weighted gadolinium-enhanced MRI images of sporadic female patient at diagnosis (age 2 years 11 months), revealing a large, hypoattenuated hourglass ('peanut')-shaped mass within the sella with expansion of the diaphragma sella (A and B). Panels C and D show coronal and sagittal T1-weighted postcontrast images at diagnosis of another female patient (age 3 years) showing a large pituitary mass with marked upward and posterior extension and areas of degenerative changes. Postoperative images (E and F) from the same patient reveal that the adenoma has been visibly resected (hormonal and growth control, however, required SSA and pegvisomant). Panels G and H show coronal and sagittal T1-weighted MRI images of the third female patient at diagnosis (aged 3 years), showing a large homogeneous pituitary mass extending superiorly and posteriorly ('bean shaped'); the posterior pituitary is clearly observed as a hyperattenuated posterior bright spot in panel H [35].
present, we have identified 21 X-LAG syndrome cases in our research project) [32]. In X-LAG syndrome begins usually during the first year of life in children that are generally normal at birth (Fig. 3) and leads to distinctive radiological findings (Fig. 4). There are a number of intriguing findings in X-LAG syndrome cases that require further investigation, including increased appetite or signs of insulin resistance in many cases. Also, a number of X-LAG syndrome patients have exhibited GH releasing hormone (GHRH) hypersecretion in the absence of peripheral sources of this hormone. This indicates that in some X-LAG syndrome cases, hypothalamic GHRH dysregulation may underlie the etiology of the disease. Treatment in the majority of cases was challenging. Aggressive surgical resection (up to and including anterior hypophysectomy) can result in effective halting of overgrowth although this is generally accompanied by permanent hypopituitarism. Pegvisomant enabled control of IGF-1 levels and slowed linear growth in patients not cured by surgery. Primary and secondary medical therapy with somatostatin analogues had poor efficacy, although this was not because of low expression of SSTR2 – the main target of traditional somatostatin analogues – as immunostaining showed moderate to high levels of these receptors. Other SSTR were also noted in analyzed tumors, such as SSTR5 and SSTR3, suggesting targeting these receptors could become an option.

Review of historical data strongly suggest many more cases of X-LAG syndrome are present in the literature on patients with pituitary gigantism [31,32] (Fig. 5). Interestingly, many of the best known cases of extreme pituitary gigantism, such as the tallest male and female cases in history (Robert Pershing Wadlow [272 cm] and Zeng Jinlian [249 cm]) match the phenotype of X-LAG syndrome very closely.

As noted above, the genetic background in more than half of cases of pituitary gigantism remains unknown (Fig. 6) [30]. Interestingly, there are some differences between this group of

Fig. 5. Photographs of two patients with pituitary gigantism. (a) Robert Pershing Wadlow (maximum height 272 cm) and (b) Dolores Ann Pullard (maximum height 227 cm), both pictured here as teenagers/young adults. In both cases, the patients were born to normally-sized parents in families without a history of gigantism, and had already established gigantism by the age of 3 or 4. Medical evidence confirms pituitary pathology underlying their dramatic overgrowth. Images courtesy of Dr. WW De Herder (Private Collection).

Fig. 6. Genetic causes in a large cohort of pituitary gigantism cases. AIP+: AIP mutation affected; MAS: McCune-Albright Syndrome; X-LAG: X-linked acrogigantism syndrome; MEN1: Multiple endocrine neoplasia type 1 [35].
The genetic etiologies of pituitary gigantism include mutations in \textit{AIP} – often in the setting of FIPA, McCune Albright syndrome, Carney complex and MEN1 syndrome. X-LAG syndrome is a new genetic entity that causes early onset overgrowth due to tumoral GH oversecretion in children who were normal (or underweight) at birth; hormonal control in X-LAG syndrome is challenging. Furthermore, X-LAG syndrome can occur as either a sporadic or inherited trait, and therefore represents a second genetic cause of FIPA. Further study of X-LAG syndrome may reveal more about novel regulatory pathways for growth. Similarly, ongoing studies of pituitary gigantism patients in general will help to uncover the pathophysiology mechanisms behind the more than 50% of cases in which no known genetic cause currently exists.

**Disclosure of interest**

The authors declare that they have no competing interest.

**References**


