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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.

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 concentrons 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).

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

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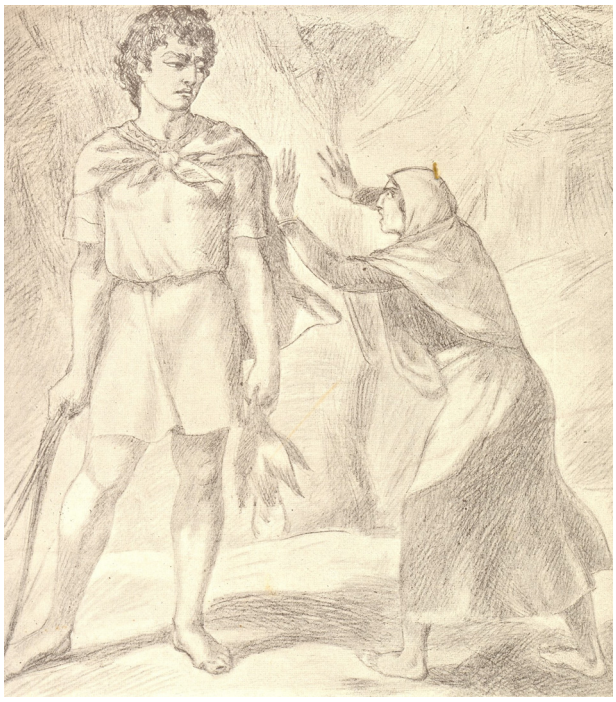

Fig. 1. David of Sassoun, the principal hero of Armenia's national epic "Daredevils of Sassoun" (an ancient oral history, first recorded by a bishop of the Armenian Apostolic Church Garegin Srvandzediants in 1873), who had a giant stature and outstanding strength since a young age (at the age of three years, he was the same size as a 12-year-old).
Illustration by Stepanyan (1939) [33].

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 approximatively 60–70% of cases, a mutation is detected in the *PRKAR1A* gene, encoding the type 1A 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 acrogigantism, Cushing'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 constitutively 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