REVIEW

Familial gigantism

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Familial GH-secreting tumors are seen in association with three separate hereditary clinical syndromes: multiple endocrine neoplasia type 1, Carney complex, and familial isolated pituitary adenomas.

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HISTORICAL OVERVIEW

In 1886, Dr Pierre Marie used the term ''acromegaly'' for the first time and described the full clinical characteristics of this condition (1). However, twenty-two years prior in 1864, Dr. Andrea Verga had already named the same disorder ''prosopo-ectasia'' [widening of the face] (2). At the postmortem examination of an acromegalic woman (with ''prosopo-ectasia''), he found a walnut-sized sellar tumor and displacement of the optic nerves (2). A normal pituitary gland was not found. He wondered whether the normal pituitary gland had disappeared because of pressure from the tumor or whether the tumor itself was a degeneration of the gland (2). Also, Dr. V. Brigidi described in 1877 a case report that included findings obtained at the autopsy of the acromegalic Italian actor Ghirlenzoni (3). Dr. V. Brigidi had diagnosed this condition as ''rheumatitis deformans'' and made the significant observation of a hypertrophied pituitary gland on the first microscopic examination of a pituitary tumor (3). In 1887, Dr. Oskar Minkowski reported that pituitary enlargement is found in all postmortem studies on patients with acromegaly (4). In 1892, Dr. Roberto Massalongo was able to correlate acromegaly with increased pituitary function by demonstrating that a pituitary tumor taken from a patient with acromegaly contained specific granulated cells (5). At the end of the 19th century, the relationship between pituitary hyperfunction-hypertrophy (or a hyperfunctioning pituitary tumor) and acromegaly was clearly established and confirmed by many investigators (6–12). Dr. Henri Henrot had already published in 1877 an autopsy report of a patient with gigantism, in whom a 4.5 × 3.0 cm tumor was found in the position of the pituitary body (13,14).

Initially, it was believed that acromegaly and gigantism were two totally different diseases. Dr. Pierre Marie (15–21), his intern Dr. J.D. Souza-Leite (22) and Dr. Georges Guinon (23) were convinced that acromegaly and gigantism were two entirely different disorders. Gigantism was considered an exaggerated variant of normal development, whereas acromegaly was considered as a pathological condition. However, in 1884, Drs. Christian F. Fritsche and Theodor Albrecht Edwin Klebs (24), supported by the work of Dr. Karl Langer (1872) (25), concluded that in contrast to gigantism, which they considered a congenital disorder, acromegaly is an acquired variety of gigantism that occurs at a later age after growth is completed. In 1894, Dr. M. Sternberg concluded that there are many similarities between acromegaly and gigantism (26). However, in 1897 he changed his view and agreed with Dr. Pierre Marie and others that both disorders have different origins (27). In 1891, Dr. D.J. Cunningham, after studying the skeleton of the Irish giant Cornelius Magrath (1736–1760; height: 2.26 m [7 ft, 5 in]), pointed out the connection between acromegaly and gigantism (28–30). In 1893, Dr. Charles Dana (31) and Dr. Woods Hutchinson (32) described the case report and postmortem studies of the French giantess Emma Aline Bataillard (also known as Lady Aama, 1877–1895; height: 2.03 m [6 ft, 8 in]) and reached the same conclusion. After studying the acromegalic giant Jean-Pierre Mazas (1847–1901; height: 2.30 m [7 ft, 6½ in]), the so-called ''giant of Montastruc'' (Monastruc, Haute-Garonne, France) in 1895, Drs. Édouard Brissaud and Henry Meige also concluded that acromegaly and gigantism can coexist in the same person (33,34).

It gradually became evident that acromegaly and gigantism have the same pathogenetic mechanism, but differ regarding the age of onset. Gigantism occurs much earlier in life when the skeleton still has the potential to grow, a developmental phase now known as ''prepubertal'' (33–35). Finally, the cause of acromegaly and gigantism — the overproduction of pituitary growth hormone — became known in the early years of the 20th century (36).

Familial acromegaly and familial gigantism are extremely rare. The earliest report of familial gigantism may be that of Goliath, described in in the Bible, where it is stated that his father and three brothers were also giants. The first description of familial acromegaly in the medical literature is most likely a report by Fraenkel that was published in 1901 (37,38). The Ugo brothers, or Hugo brothers, also

No potential conflict of interest was reported.

known in France as ''les Géants des Alpes'' (''the Giants of the Alps'') (Figure 1), were two famous giants who traveled the world and appeared at fairs and circuses at the end of the 19th century and the beginning of the 20th century. Battista Ugo (in French: Baptiste Hugo, 1876–1916) attained a height of 2.30 m (7 ft, 7 in) and Paolo Antonio Ugo (in French: Antoine Hugo, 1887–1914) attained a height of 2.25 m (7 ft, 5 in) (39–41). Their parents, three brothers and two sisters were of average size. The postmortem examination of Baptiste Hugo was performed and published by Dr. D. Symmers at the William Parker Hospital in New York. The report describes a pituitary adenoma measuring $5 \times 2.5 \times 2.3$ cm ($2 \times 1 \times 0.9$ in) and weighing 5.94 g with suprasellar expansion that compressed both optic nerves. Left parasellar and retrosellar expansion were also found.

In his famous monograph, ''The Pituitary Body and its Disorders'', published in 1912, Dr. Harvey Cushing (42) hinted at ''*Mendelian tendencies*'' in two patients with familial gigantism (case XIII, surgical No. 27784, pp. 8–92; case XXXI, surgical No. 27011½, pp. 158–162) (42).

Figure 1 - Familial gigantism in the two Hugo brothers. Top row: Battista Ugo (Baptiste Hugo), 1876–1916, reached a height of 2.30 m (7 ft, 7 in) and Paolo Antonio Ugo (Antoine Hugo), 1887–1914, reached a height of 2.25 m (7 ft, 5 in). Bottom row: the parents of the Ugo brothers, Teresa Chiardola (1849–1905) and Antonio Ugo (1840–1917), and their sister, Maddalena Ugo (1885–1960). Picture from the collection of Dr. W. W. de Herder.

Since these initial reports, several authors have reported the coincidence of acromegaly and gigantism in first-degree relatives (43–55).

Clinical relevance

Growth hormone (GH)-secreting pituitary adenomas have an annual incidence of about 3 per 1,000,000 and a prevalence of about 60 per 1,000,000. The likelihood of multiple GH-secreting tumors presenting among first-degree relatives within a single family is, therefore, statistically very uncommon, and their occurrence has prompted many researchers to consider this an inheritable disorder (56).

Familial GH-secreting tumors are seen in association with three separate hereditary clinical syndromes: (1) multiple endocrine neoplasia type 1 (MEN1), (2) Carney complex (CNC), and (3) familial isolated pituitary adenomas (FIPA).

Multiple endocrine neoplasia type 1 (MEN1)

Autosomal-dominant MEN1 syndrome is associated with a loss of heterozygosity (LOH) on chromosome locus 11q13 (57). The *MEN1* gene tumor suppressor gene encodes a 610-amino acid protein known as menin. More than 550 mutations of the *MEN1* gene have been identified. Pituitary tumors occur in approximately 30–50% of patients with MEN1 (58), but the frequency of GH-producing pituitary tumors in MEN1 patients is only about 10% (59).

Carney complex (CNC)

Pituitary adenomas occur in 10–20% of patients with the autosomal-dominant CNC, and these are invariably GH-secreting tumors (60).

CNC is associated with a LOH on chromosomal locus 17q22–24. Germline mutations in the protein kinase A (PKA) regulatory subunit 1 (*PRKAR1A*) gene have been identified (61). Loss of function of this regulatory subunit results in constitutive activation of PKA that increases signaling through a pathway that enhances proliferation of the GH-producing cells in the pituitary.

Familial isolated pituitary adenomas (FIPA)

Inactivating germline mutations in the aryl hydrocarbon receptor that interacts with tumor suppressor protein (AIP) can be found in 40–50% of families that have a case of acromegaly occurring along with FIPA (62–66). To date, about 50 different AIP mutations have been identified.

AIP mutation-positive acromegaly or gigantism is generally diagnosed 10 years earlier than sporadic acromegaly. GH-producing tumors in AIP-positive patients (mostly males) more frequently display extrasellar growth, exhibit more aggressive characteristics, and have a tendency for higher accelerated growth than sporadic tumors. These tumors are also more frequently associated with onset in childhood and adolescence, thus presenting more frequently with gigantism (67,68). Furthermore, AIP mutation-positive GH-producing tumors appear to be less responsive to medical therapy with somatostatin analogs and dopamine agonists.

In 2010, Chahal and co-workers extracted DNA from a tooth of the Irish giant, Charles Byrne (1761–1783; 2.31 m, [7 ft 7 in]), and identified a germline mutation in the *AIP* gene. Four contemporary Northern Irish families who

presented with gigantism, acromegaly, or prolactinoma have the same mutation and haplotype associated with the mutated gene. Using coalescent theory, they came to the conclusion that these persons share a common ancestor who lived about 57–66 generations earlier (69).

Familial acromegaly and gigantism only account for a very tiny proportion of all pituitary adenomas and can be related to MEN 1 and CNC syndromes as well as to mutations in the *AIP* gene. *AIP* mutations are very common in gigantism.

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