

Clinical and genetic characterization of pituitary gigantism: an international collaborative study in 208 patients

Liliya Rostomyan^{*}, Adrian F Daly^{*}, Patrick Petrossians, Emil Nachev¹, Anurag R Lila², Anne-Lise Lecoq^{3,4,5}, Beatriz Lecumberri⁶, Giampaolo Trivellini⁷, Roberto Salvatori⁸, Andreas G Moraitis⁷, Ian Holdaway⁹, Dianne J Kranenburg - van Klaveren¹⁰, Maria Chiara Zatelli¹¹, Nuria Palacios¹², Cecile Nozieres¹³, Margaret Zacharin¹⁴, Tapani Ebeling¹⁵, Marja Ojaniemi¹⁵, Liudmila Rozhinskaya¹⁶, Elisa Verrua¹⁷, Marie-Lise Jaffrain-Rea^{18,19}, Silvia Filipponi^{18,19}, Daria Gusakova²⁰, Vyacheslav Pronin²¹, Jerome Bertherat²², Zhanna Belaya¹⁶, Irena Ilovayskaya²³, Mona Sahnoun-Fathallah²⁴, Caroline Sievers²⁵, Gunter K Stalla²⁵, Emilie Castermans, Jean-Hubert Caberg, Ekaterina Sorkina²¹, Renata Simona Auriemma²⁶, Sachin Mittal²⁷, Maria Kareva¹⁶, Philippe A Lysy²⁸, Philippe Emy²⁹, Ernesto De Menis³⁰, Catherine S Choong³¹, Giovanna Mantovani¹⁷, Vincent Bours, Wouter De Herder¹⁰, Thierry Brue^{24,32}, Anne Barlier^{24,33}, Sebastian J C M M Neggers¹⁰, Sabina Zacharieva¹, Philippe Chanson^{3,4,5}, Nalini Samir Shah², Constantine A Stratakis⁷, Luciana A Naves³⁴ and Albert Beckers

Departments of Endocrinology and Human Genetics, Centre Hospitalier Universitaire de Liège, University of Liège, Domaine Universitaire du Sart-Tilman, 4000 Liège, Belgium

¹Clinical Center of Endocrinology and Gerontology, Medical University, Sofia, Bulgaria

²Department of Endocrinology, King Edward Memorial Hospital, Mumbai, India

³Assistance Publique-Hôpitaux de Paris, Hôpitaux Universitaires Paris-Sud, Service d'Endocrinologie et des Maladies de la Reproduction et Centre de Référence des Maladies Endocriniennes Rares de la Croissance, Le Kremlin-Bicêtre F-94275, France

⁴UMR 51185, Univ Paris-Sud, F-94276 Le Kremlin-Bicêtre, France

⁵INSERM U1185, Faculté de Médecine Paris-Sud, F-94276 Le Kremlin-Bicêtre, France

⁶Servicio de Endocrinología y Nutrición, Hospital Universitario La Paz, Madrid, Spain

⁷Section on Endocrinology and Genetics, Program on Developmental Endocrinology & Genetics & Pediatric Endocrinology Inter-Institute Training Program, Eunice Kennedy Shriver National Institute of Child Health & Human Development, National Institutes of Health (NIH), Bethesda, Maryland 20892, USA

⁸Division of Endocrinology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

⁹Department of Endocrinology, Greenlane Clinical Centre, Auckland, New Zealand

¹⁰Section of Endocrinology, Department of Internal Medicine, Erasmus Medical Centre, Rotterdam, The Netherlands

¹¹Section of Endocrinology and Internal Medicine, Department of Medical Sciences, University of Ferrara, Via Savonarola 9, 44121 Ferrara, Italy

¹²Servicio de Endocrinología, Hospital Universitario Puerta De Hierro, Majadahonda, Madrid, Spain

¹³Service d'endocrinologie-diabétologie, Centre Hospitalier Lucien Hussen, Montée du Docteur Chapuis BP127, 38 209 Vienne cedex, France

¹⁴Murdoch Children's Research Institute, Royal Children's Hospital, University of Melbourne, Parkville, Victoria, Australia

¹⁵Departments of Internal Medicine and Pediatrics, Oulu University Hospital, University of Oulu, Oulu, Finland

¹⁶Departments of Neuroendocrinology and Bone Diseases, and Department of Endocrinology, Endocrinology Research Centre, Moscow, Russia

¹⁷Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Unit of Endocrinology and Metabolic Diseases, Department of Clinical Sciences and Community Health, University of Milan, Via F. Sforza, 35, 20122 Milan, Italy

¹⁸Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, L'Aquila, Italy

¹⁹Neuromed IRCCS, Pozzilli, Italy

²⁰Andrology Department, NA Lopatkin Scientific Research Institute of Urology, Moscow, Russia

²¹Endocrinology Clinic, I.M. Sechenov First Moscow State Medical University, Moscow, Russia

²²INSERM U1016, Institut Cochin, Université Paris Descartes, Hôpital Cochin, Service d'Endocrinologie, 27, rue du Faubourg-Saint-Jacques, 75014 Paris, France

²³Endocrinology Department, Moscow Regional Research & Clinical Institute, Moscow, Russia

²⁴Aix-Marseille Université, CNRS, UMR7286, 13015 Marseille, France

²⁵Department of Endocrinology, Max Planck Institute of Psychiatry, Munich, Germany

²⁶Dipartimento di Medicina Clinica e Chirurgia, Sezione di Endocrinologia, University "Federico II", Naples, Italy

²⁷Department of Endocrinology, T.N. Medical College & B.Y.L. Nair Hospital, Mumbai, India

²⁸Pediatric Endocrinology Unit, Department of Pediatrics, Clinique Universitaire Saint-Luc, Université Catholique de Louvain, Brussels, Belgium

²⁹Service D'endocrinologie, CHR Orléans, Orléans, France

³⁰Endocrinology, Ospedale Generale Montebelluna, Montebelluna, Italy

³¹Department of Paediatric Endocrinology, Princess Margaret Hospital for Children and School of Pediatrics and Child Health, University of Western Australia, Perth, Western Australia, Australia

³²Department of Endocrinology, APHM Conception, 13385 Marseille, France

³³Laboratory of Molecular Biology, APHM Conception, 13385 Marseille, France

³⁴Department of Endocrinology, Faculty of Medicine, University of Brasilia, Brasilia, Brazil

* (L Rostomyan and A F Daly contributed equally to this work)

Correspondence should be addressed to A Beckers

Email
albert.beckers@chu.ulg.ac.be

Abstract

Despite being a classical growth disorder, pituitary gigantism has not been studied previously in a standardized way. We performed a retrospective, multicenter, international study to characterize a large series of pituitary gigantism patients. We included 208 patients (163 males; 78.4%) with growth hormone excess and a current/previous abnormal growth velocity for age or final height > 2 s.d. above country normal means. The median onset of rapid growth was 13 years and occurred significantly earlier in females than in males; pituitary adenomas were diagnosed earlier in females than males (15.8 vs 21.5 years respectively). Adenomas were ≥ 10 mm (i.e., macroadenomas) in 84%, of which extrasellar extension occurred in 77% and invasion in 54%. GH/IGF1 control was achieved in 39% during long-term follow-up. Final height was greater in younger onset patients, with larger tumors and higher GH levels. Later disease control was associated with a greater difference from mid-parental height ($r=0.23$, $P=0.02$). *AIP* mutations occurred in 29%; microduplication at Xq26.3 – X-linked acrogigantism (X-LAG) – occurred in two familial isolated pituitary adenoma kindreds and in ten sporadic patients. Tumor size was not different in X-LAG, *AIP* mutated and genetically negative patient groups. *AIP*-mutated and X-LAG patients were significantly younger at onset and diagnosis, but disease control was worse in genetically negative cases. Pituitary gigantism patients are characterized by male predominance and large tumors that are difficult to control. Treatment delay increases final height and symptom burden. *AIP* mutations and X-LAG explain many cases, but no genetic etiology is seen in $> 50\%$ of cases.

Key Words

- ▶ gigantism
- ▶ pituitary adenoma
- ▶ somatotropinoma
- ▶ growth hormone
- ▶ aryl hydrocarbon receptor interacting protein gene
- ▶ familial isolated pituitary adenoma (FIPA)
- ▶ X-linked acrogigantism (X-LAG) syndrome

Endocrine-Related Cancer
(2015) 22, 745–757

Introduction

Interest in the extremes of height stretches back into antiquity, and the occurrence of people with gigantism has contributed to popular myths across many cultures. Even with the recognition that many extreme cases of tall stature are disease manifestations, interest in gigantism has unfortunately remained focused on the visual spectacle, even today. Many forms of short stature are known and

screening activities in childhood are geared to identifying these cases for early investigation and intervention (Cheetham & Davies 2014). Overgrowth is less well understood and, particularly if unaccompanied by other syndromic features like developmental delay, its diagnosis may be slower. Societal factors may contribute to this, as tall stature is seen a less 'undesirable' physical feature than short stature

(Batty *et al.* 2009). However, increased height also carries risks in terms of disease (Lee *et al.* 2009), and excessive final adult height carries with it distinct disadvantages, particularly skeletal and orthopedic problems (Hazebroek-Kampschreur *et al.* 1994, Silventoinen *et al.* 1999). Surprisingly, the functional and psychological impacts of extreme tall stature have yet to be studied in detail.

Growth and stature are determined by highly complex processes involving genetic and environmental factors, such as endocrine function, nutrition, vitamin status and psychosocial wellbeing (Tanner & O'Keeffe 1962, Mascie-Taylor 1991, Wood *et al.* 2014). Diseases causing tall stature must be differentiated from other normal variations in height, in which underlying abnormalities are absent. Pathological tall stature can be isolated or syndromic; the latter is usually due to a chromosomal or genetic cause, such as Klinefelter syndrome, Marfan syndrome and Sotos syndrome among others (Davies & Cheetham 2014). Disorders of the growth hormone (GH) axis can lead to abnormal height, the most classical of which is pituitary gigantism, usually due to over-secretion of GH by a pituitary adenoma occurring before epiphyseal closure (Daughaday 1992, Eugster & Pescovitz 1999, Eugster 2000). In recent years a variety of genetic factors that predispose to somatotrope adenomas or hyperplasia have been identified. Mutations in genes such as *GNAS* and *PRKARIA* and particularly *AIP* are associated with acromegaly and gigantism (Daly *et al.* 2010a, Xekouki *et al.* 2010, Stratakis 2015). X-linked acrogigantism (X-LAG) syndrome is associated with a microduplication, including the *GPR101* gene, on chromosome Xq26.3 and leads to pituitary hyperplasia and adenomas in children and early onset gigantism beginning usually in the first year of life (Trivellin *et al.* 2014, Beckers *et al.* 2015).

Due to its rarity and despite the recent emphasis on pathophysiological causes, the clinical presentation, evolution, complications and responses to treatment of patients with pituitary gigantism have not been studied in a large cohort. To address these issues, we conducted an international collaborative study of the features of patients with pituitary gigantism.

Methods

This was a study that included patients with pituitary gigantism due to a pituitary adenoma or hyperplasia. The study was performed between 2011 and 2013 at the Department of Endocrinology, Centre Hospitalier Universitaire de Liège, Belgium, in collaboration with 46 other international centers in Argentina, Australia,

Belgium, Brazil, Bulgaria, Canada, Denmark, India, Italy, Finland, France, Germany, New Zealand, Romania, Russia, Spain, the Netherlands and the United States. This study was approved by the Ethics Committee of CHU de Liège (Belgian clinical trials number: B707201111968). Patients were identified at the participating centers and both historical and current follow-up data were collected; results of previous genetic tests were collected retrospectively, and other genetic analyses were also performed prospectively over the course of the study. Patients consented to the collection and use of clinical data and provided informed consent in their local language for genetic studies.

Eligibility criteria

The diagnosis of pituitary gigantism was defined as current or previous evidence of abnormal, progressive and excessively rapid growth velocity for age (>97th percentile, which corresponds to >+2 s.d.), or a final height >+2 s.d. above the mean for relevant population, associated with elevated GH/insulin-like growth factor 1 (IGF1) and imaging evidence of a pituitary lesion. Details on height sources for the countries are listed in [Supplementary Materials and methods](#), see section on [supplementary data](#) given at the end of this article.

Patient disposition

Patient information (demographics, medical and familial history, genetics, clinical examination, laboratory investigations, radiology, disease status during follow-up, treatment modalities and response to therapy) were systematically collected in each study center, recorded in the case report form and transmitted anonymized to the coordinating center. All patients with pituitary causes of gigantism diagnosed at any time at the participating centers were valid for inclusion. Overall, 229 patients were enrolled; 21 cases were ineligible and excluded (Klinefelter's syndrome ($n=5$), constitutional tall stature ($n=3$), Sotos syndrome ($n=2$), obesity ($n=2$), ectopic growth hormone-releasing hormone (GHRH) secretion ($n=1$) and tall stature of unknown etiology without GH axis excess ($n=8$)). The final study population consisted of 208 patients diagnosed with pituitary gigantism ([Supplementary Figure 1](#), see section on [supplementary data](#) given at the end of this article).

Study measures

Height was expressed as Z-scores above the mean value of height of the reference population. The mid-parental

height (MPH) was defined as the average of the parents' heights -6.5 cm for girls and $+6.5$ cm for boys. The difference of the final height from MPH was used to determine the variance from target stature.

The age at disease onset was derived from existing patient case files and following consultation with the patient and family. The age at diagnosis was assessed as the age at which a first definitive diagnosis of a pituitary gigantism was recorded in the case notes. Pituitary tumors were classified as per the local radiology reports according to the maximal diameter on magnetic resonance imaging or computerized tomography as microadenomas (<10 mm) and macroadenomas (≥ 10 mm); the latter included giant adenomas (those measuring ≥ 40 mm). Invasion of surrounding structures and extrasellar expansion was evaluated by neuroimaging and at surgical intervention.

Therapeutic modalities were assessed and details collected; a total treatment score was calculated as the sum of the use of somatostatin analogues (SSA), pegvisomant, dopamine agonists (DA), each individual surgery and radiotherapy (each was allocated one point). The multimodal treatment approach was considered with

≥ 3 modalities. Long-term disease control criteria (≥ 12 months of follow-up) were shrinkage or stable size of pituitary adenoma, the absence of clinical activity, an age/sex-appropriate IGF1 that was \leq upper limit of normal (ULN) for the assay used at the individual clinical center and a GH level < 1 ng/ml at last follow-up (pegvisomant-treated patients were assessed on IGF1 only).

Statistics

Statistical analysis (statistical computing and graphics) was performed using STATISTICA, version 10 (StatSoft, Tulsa, OK, USA), and R package, version 2.15.1 (R Core Team, Vienna, Austria). Absolute numbers and percentages were used to describe qualitative and categorical data. Continuous data did not fit parameterized distributions, therefore they were represented as medians and interquartile ranges (IQR) and non-parametric statistical tests were used for the analysis (Spearman's R and χ^2 tests for the association between variables and Mann–Whitney U and Kruskal–Wallis tests for comparison of independent subgroups). A P-value of < 0.05 was designated as the level of statistical significance.

Table 1 Clinical characteristics of patients with pituitary gigantism

Study criteria	Total group	Males (n=163) 78%	Females (n=45) 22%
Age at rapid growth onset (year) ^a	13 (9; 15)	13 (10; 15)	11 (3; 14)
Patients who had not attained final height (%)	15.9%	13.5%	25.6%
Age at which final height was attained (year)	20 (18; 22)	20 (18; 22)	18.5 (16; 23)
Age at first symptoms (year) ^a	14 (10; 16)	14 (11; 16)	12.5 (2; 14)
Age at diagnosis of PA (year) ^a	21 (15.5; 27)	21.5 (17; 28)	15.8 (10; 23)
Aged ≤ 19 years (%) ^a	42.4%	37.3%	61.9%
Delay from symptoms to diagnosis (year) ^a	5.3 (2.0; 11.0)	6.2 (3; 12)	2.5 (1.0; 6.0)
Height Z-score (s.d.)	3.1 (2.5; 4.0)	3.1 (2.5; 4)	3.1 (2.6; 4.1)
Age at height measurement (year)	29 (21; 37)	29 (22; 38)	28 (17; 35)
Difference from MPH			
Absolute (cm)	20 (15; 24)	19.5 (15; 23)	21 (15; 26.3)
% from MPH	11.6 (8.5; 14.8)	11.2 (8.4; 13.7)	12.9 (8.7; 16.4)
Maximal dimension of PA (mm)	22 (14; 34)	21 (14; 32)	24.5 (15; 36)
Macroadenoma (%)	84.3%	85.1%	81.6%
Giant adenoma (%)	15%	14.6%	16.7%
Extension (%)	77.2%	77%	78%
Invasion (%)	54.5%	54.9%	53.3%
GH level at diagnosis (ng/ml) ^a	35.5 (14; 83)	29 (12.3; 64)	62.3 (27.8; 95)
IGF1 level at diagnosis (% ULN)	254.5 (189.5; 359.5)	250 (188; 358.5)	268 (198; 421)
Prolactin co-secretion (%)	34%	31%	46.9%
Multimodal treatment (%)	32.2%	32.1%	32.5%
GH/IGF1 control at last follow-up (%)	45%	49%	32.5%
Age when GH/IGF1 control achieved (year)	23 (17; 30.5)	23.5 (17.8; 31)	17.7 (11; 29.5)
GH/IGF1 controlled ≤ 19 years (%)	36.6%	32.1%	55%
GH/IGF1 controlled before final height (%)	20.8%	19.2%	26.8%
Long-term control (%)	39%	42%	30%

All continuous data presented as median and IQR. PA, pituitary adenoma. Multimodal treatment: ≥ 3 separate modalities.

^aP-value < 0.05 when compared females and males.

Results

Characteristics at diagnosis

The pituitary gigantism population consisted of 208 patients, the majority of whom were male ($n=163$; 78%) (Table 1). Patients were diagnosed across a number of decades: 1950s (1%), 1960s (1%), 1970s (3%), 1980s (13%), 1990s (20%), 2000s (42%) and current decade, 2010s (20%). The median height Z-score was +3.1 (2.5; 4.0), the median age at height measurement was 29 (21; 37) years, and the majority of patients (84.1%) had reached their final height at a median age of 20 (18; 22) years. The median age at the onset of rapid growth was 13 (9; 15) years overall and was significantly younger in females than in males (11 (3; 14) vs 13 (10; 15) years, respectively; $P=0.003$). There was a median delay of 5.3 (2; 11) years between first symptom onset and pituitary adenoma diagnosis; this delay was significantly shorter in females than males (2.5 (1; 6) vs 6.2 (3; 12) years, respectively; $P=0.03$). Overall, 42.4% of patients were aged ≤ 19 years at diagnosis and significantly more female patients fell in this age group ($P=0.004$).

The most frequent first clinical sign was increased growth ($\sim 75\%$ of patients), followed by acral enlargement and facial changes (37%), headache (23%) and visual field defects (12%). Pubertal delay occurred in $\sim 29\%$ of males and females.

Nine cases of pituitary apoplexy were reported at baseline and seven patients had diffuse pituitary hyperplasia (radiological or surgical); the remainder had pituitary adenomas. Patients with diffuse pituitary hyperplasia presented in childhood/adolescence and were generally younger at first symptoms and had a higher height Z-score at diagnosis than the remainder of the gigantism cohort; these differences were not statistically significant. Pituitary tumors were predominantly macroadenomas (84.3%), with 15% of those being 'giant' adenomas. Extrasellar extension and invasion occurred in most cases (89% and 64% of macroadenomas, respectively). Radiological characteristics did not differ between males and females.

Despite the relatively young age of the patients, acromegalic features were present in almost all males (92%) and females (94%) at diagnosis (Supplementary Table 1, see section on supplementary data given at the end of this article). The median shoe sizes at diagnosis were 15.0 (13.0; 17.0) in males and 11.5 (10.5; 14.5) in females (European (EU) sizing, 48 (46.0; 50.0) and 42 (41.0; 45.0) in males and females respectively). Among 156 cases that had cardiac assessments reported, cardiac disease had already

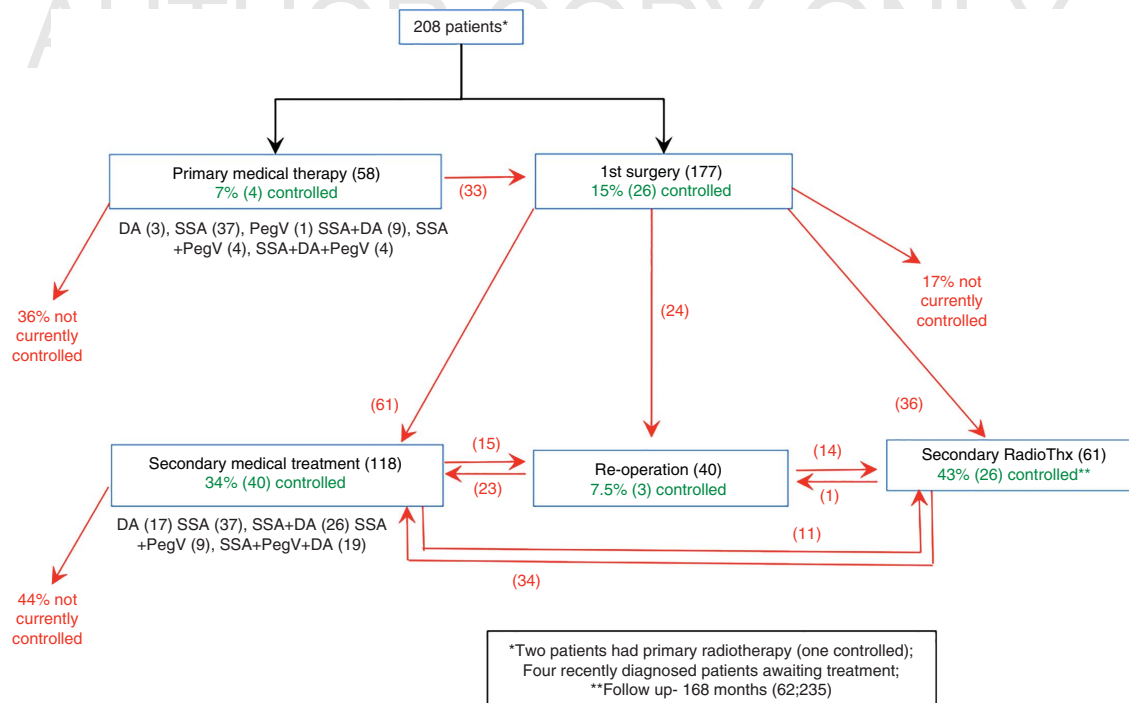
been diagnosed in 36.5% at baseline, mainly left ventricular hypertrophy (21%) and diastolic dysfunction (10%).

Females exhibited higher median GH levels at diagnosis than males (62.3 (27.8; 95.0) vs 29 (12.3; 64.0) ng/ml, respectively; $P=0.009$), but IGF1 levels were similar between genders. Co-secretion of prolactin occurred in 34% overall and was more frequent in patients with invasive macroadenomas with extrasellar extension. At diagnosis, 25% of patients had a deficit in ≥ 1 axis; among those aged ≤ 19 , hypopituitarism at baseline was seen in 18.3%.

Treatment and follow-up

Treatment regimens differed among centers due to the availability of medical therapies (Fig. 1). The median period of follow-up on treatment was 10.4 years (4; 20) overall. Initial surgery in 177 patients was associated with control in 15%. Among 40 cases that were then re-operated, 7.5% of those were controlled. Postoperative SSA were used in 66.7% ($n=118$) of the patients and disease control was achieved in 34% ($n=40$). A further 26% ($n=54$) of the patients received primary SSA treatment, but only 7% ($n=4$) of these were controlled. Pegvisomant was used preoperatively either alone ($n=1$) or in combination with SSA or DA ($n=8$); control was achieved in four cases. Pegvisomant was administered after surgery with SSA and/or DA in 28 patients; control was achieved in 53.5% ($n=15$) of these cases. A total of 63 patients were irradiated (two had primary radiotherapy) with control in 43% (median follow-up: 168 months (62; 235)); 56.5% of these also had received an SSA during follow-up. The median number of treatment modalities was 2 (1; 3). Overall, disease control was achieved in 45.6% of the patients. The median duration of follow-up post-treatment was 7 years (3; 17), and in those followed up for ≥ 12 months, disease control was achieved in 39.5% of cases. There was a significant correlation between larger tumor diameter and a greater number of treatment modalities ($r=0.18$, $P=0.02$). Macroadenomas required significantly more treatment modalities than microadenomas (≥ 3 modalities in 50% vs 19% respectively; $P=0.009$). Median maximal tumor diameter was smaller in patients who were controlled (19 (11; 25) vs 27 mm (17.0; 37.5) in uncontrolled cases; $P=0.0003$). However, there was better control at the last follow-up in those patients with tumors diagnosed at the age of ≤ 19 years than in older patients (58.5% vs 36.4% respectively; $P=0.02$). Maximal tumor diameter at diagnosis was correlated with GH (but not IGF1) levels ($r=0.34$, $P=0.002$) at diagnosis.

During follow-up, pituitary apoplexy occurred in nine patients. Hypopituitarism rose from 25% at baseline to

**Figure 1**

Schematic representation of treatments used in the management of patients with pituitary gigantism. Numbers in parentheses indicate the number of patients. RadioThx, radiotherapy; DA, dopamine agonists; SSA, somatostatin analogues; PegV, pegvisomant.

64% at the last follow-up. The proportions of patients with deficits in the various pituitary axes at the last follow-up were as follows: gonadal 62%, adrenal 47%, thyroid 41%, GH 10% and diabetes insipidus 8%. Among the patients with hypopituitarism, 92.6% had undergone surgery and 46% had received radiotherapy. In those aged ≤ 19 years at diagnosis, hypopituitarism was present at diagnosis in 18.3% and in 66% after treatment, with a deficiency of three pituitary axes in 29% and panhypopituitarism in 3%. The presence of hypopituitarism at the last follow-up was significantly related to larger tumor size (30 mm (20; 39) vs 15.5 mm (10; 25); $P=0.006$) but not to duration or control of the disease.

Seven patients (3.4%) died during follow-up; causes of death were thrombosis/embolism ($n=2$), hemorrhage, myocardial infarction, tumor progression, accident and suicide ($n=1$ each).

Growth responses

The height of each patient expressed in Z-scores above the mean and their age at the last measurement are shown in Fig. 2. The median height Z-score at diagnosis was higher in those who were still growing than those who

had attained their final height (+4.1 s.d. (2.8; 5.7) and +2.9 s.d. (2.5; 3.8) respectively; $P=0.004$).

Excess GH/IGF1 secretion was controlled before the end of linear growth in 20.8% of the total group; in 11 of these cases, hormonal control led to a normalization of the growth pattern and a height at last follow-up that was $< +2$ s.d. (Fig. 2). Hormonal control at ≤ 19 years of age was associated with an earlier halting of linear growth than in those controlled after that age ($P=0.0052$). Overall, patients' final height exceeded their MPH by a median difference of 20 cm (15; 24) and no gender differences were seen.

Height Z-score and the difference from MPH correlated significantly with tumor size ($r=0.2$, $P=0.03$) and GH (but not IGF1) at diagnosis ($r=0.29$, $P=0.0001$). Height Z-scores were also significantly greater in those who were younger both at first symptoms ($r=-0.3$, $P=0.01$) and at the start of rapid growth ($r=-0.19$, $P=0.01$). The difference of final height from MPH depended on age when first control was achieved ($r=0.23$, $P=0.02$), being significantly lower in those with disease control aged ≤ 19 years than thereafter (10.9% (7.7; 13.8) vs 12.7% (9.32; 16.3) respectively; $P=0.044$). Median excess over MPH was greater in patients with hypogonadism or pubertal delay than in those

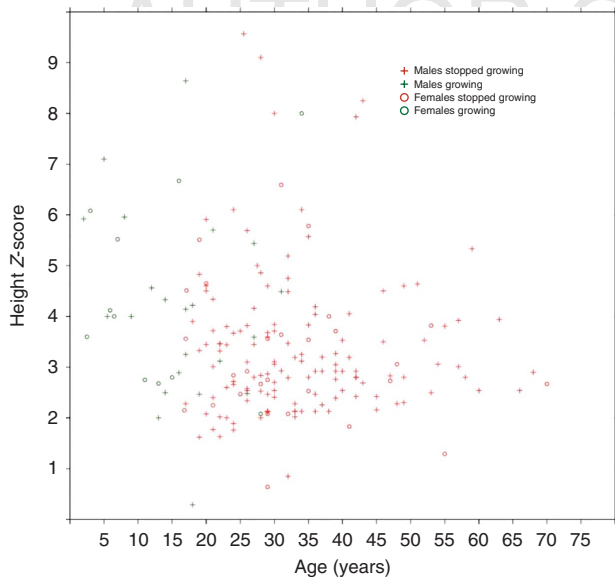


Figure 2

Age and Z-score for height of patients at the last follow-up. Of the total population of 208 patients, 57 patients had an absolute height > 200 cm at the last measurement (eight are still growing) and the tallest patient was 247 cm. Of those who were controlled before the end of the linear growth, 11 had a height at the last follow-up of < +2 s.d. (seven of these later had a disease recurrence).

with normal gonadal status (12.8% (8.8; 16.3) vs 10.7% (8.5; 13.3) respectively; $P=0.04$).

Genetic studies

In the study population, 143 pituitary gigantism patients consented to genetic testing (*AIP*, *MEN1*, *PRKAR1A*, *GNAS1*, Xq26.3 duplication) and 46% had genetic causes or inherited syndromes (Fig. 3). In total, 29% of the patients were positive for *AIP* mutations. There were 28 familial isolated pituitary adenoma (FIPA) patients (23 males) of whom 18 had *AIP* mutations. Four members of two FIPA families had Xq26.3 microduplications and X-LAG syndrome, as did a further ten sporadic cases. In addition, seven McCune-Albright syndrome, two familial Carney Complex and one *MEN1* gigantism case were observed; 54% of the patients had no genetic cause identified.

As compared with the *AIP* mutation-positive patients, those with no detected genetic cause were significantly more likely to be female, were older at first symptoms and at diagnosis (fewer cases were aged ≤ 19 years) and had a longer disease latency, with higher GH/IGF1 levels, more frequent multimodal therapy and poorer overall control rates (Fig. 4; Table 2). X-LAG cases were predominantly female and significantly younger at onset but had similar

tumor size and lower rates of invasion and extension as *AIP* mutation-positive cases (Fig. 4; Table 2).

Discussion

In this study we report the clinical and genetic characteristics of 208 patients with pituitary gigantism due to GH hypersecretion. This, the first extensive series of patients with radiologically and hormonally proven pituitary gigantism, provides insights into the disease profile of this rare disorder. Genetic or familial disease was seen in 46% of the cases tested. Of the tested cases, 29% had *AIP* mutations or deletions. Previous studies have noted that *AIP* mutations are associated with gigantism, either sporadic, within individual FIPA kindreds or in large historical studies (Naves *et al.* 2007, Jennings *et al.* 2009, Daly *et al.* 2010a, Chahal *et al.* 2011). This high frequency of *AIP* mutations among pituitary gigantism patients is logical, given that *AIP* mutations are characteristically common among children and young adults and most frequently lead to somatotropinomas (Stratakis *et al.* 2010, Tichomirowa *et al.* 2011). X-LAG syndrome is a recently described form of pituitary gigantism due to chromosome

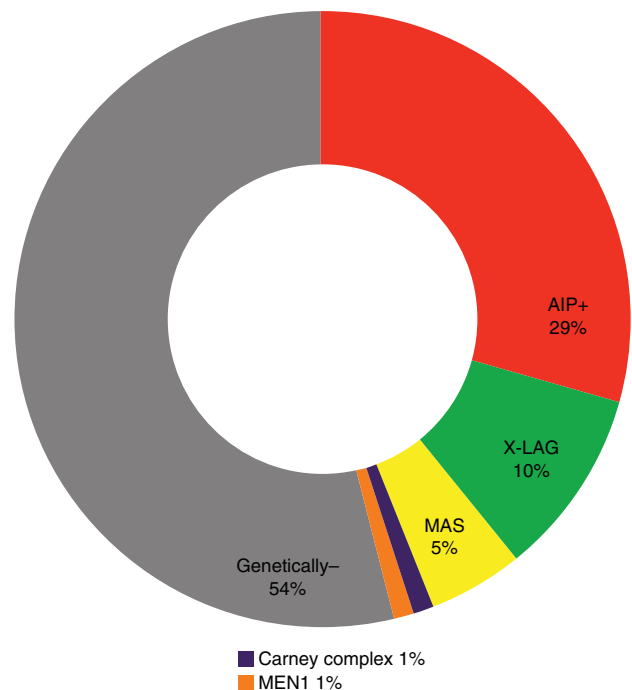
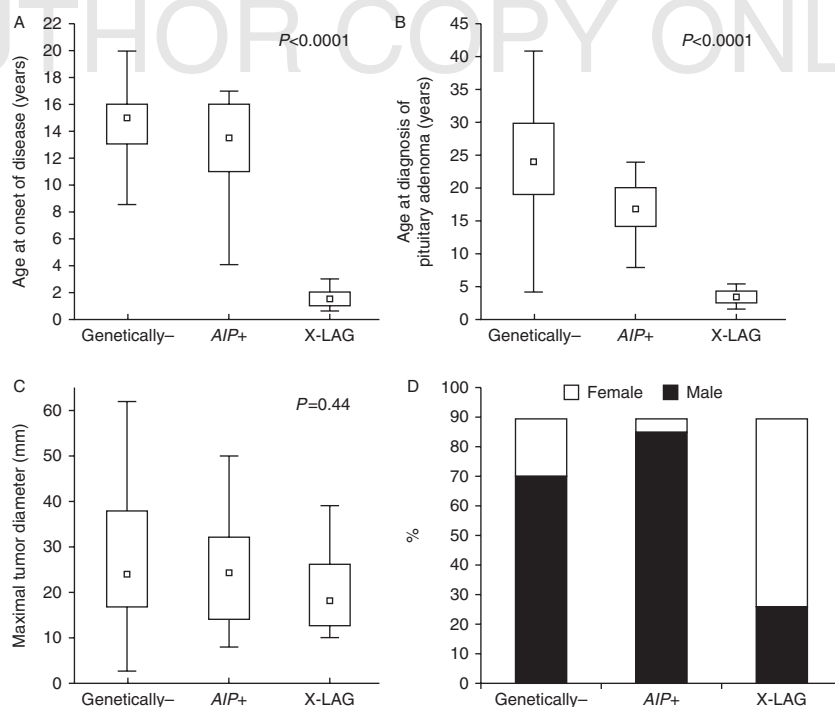


Figure 3

Genetic results in the study population. Numbers for each sector show the number of patients in the subgroup and its prevalence in the total group. AIP+, *AIP* mutation affected; Genetically-, genetically negative testing; MAS, McCune-Albright Syndrome; X-LAG, X-linked acrogigantism syndrome.

**Figure 4**

Comparisons of characteristics among genetically distinct groups of pituitary gigantism patients (genetically negative, *AIP*-mutation positive (*AIP*+) and X-linked acrogigantism syndrome (X-LAG)) showing statistically distinct patterns of age at first symptoms (A), age at diagnosis (B) and no

intergroup difference in terms of maximal tumor diameter at diagnosis (C). (D) demonstrates the female and male predominance of X-LAG and *AIP*+ related gigantism cases; the genetically negative group was also male predominant although less markedly so than the *AIP*+ group.

Xq26.3 microduplications (Trivellin *et al.* 2014, Beckers *et al.* 2015) and constituted 10% of the genetically studied cases in the current study. X-LAG syndrome has a particularly early age at onset, can present sporadically or as FIPA and predominantly affects females. We found no microduplication on Xq26.3 in any case diagnosed aged >5 years in our series, whereas the youngest *AIP* positive patient was 8 years old at diagnosis. Other genetic causes occurred less frequently; McCune-Albright Syndrome (MAS), Carney complex and MEN1 comprised 7% of gigantism overall. Although pituitary gigantism can occur in both genders, it predominantly affects males (78%). This is likely due to male predominance among *AIP*-mutated gigantism cases, as we reported previously in acromegaly (Daly *et al.* 2010b). This gender imbalance may have a number of causes, including unknown genetic factors. Likely contributors to the imbalance include the typical onset of *AIP* mutation-related somatotropinomas during puberty when GH excess coincides with the longer period of prepubertal growth and the greater pubertal peak growth velocity in males (Rogol *et al.* 2002). This could serve to augment the usual height difference

between males and females at the end of puberty and push more males than females into the gigantism height range. As *AIP* mutation-related adenomas are usually large, concomitant impingement on normal pituitary tissue could lead to hypogonadism, thereby further prolonging the time to final epiphyseal closure in males. Among patients without *AIP* mutations, the gender balance was heterogeneous: X-LAG syndrome cases are mainly female (Trivellin *et al.* 2014, Beckers *et al.* 2015), whereas cases that were negative on genetic testing were predominantly male but less markedly so than the *AIP*-mutated group. The genetically negative group comprised more than half of all cases studied. The clinical phenotype of patients with *AIP* mutations or X-LAG syndrome has shown to be aggressive (Daly *et al.* 2010a, Beckers *et al.* 2015). In this study we noted that genetically unexplained pituitary gigantism patients are even more aggressive (e.g., invasion, hormone levels, lower control rates) than *AIP* mutation cases. This group may be a priority for further genomic pathophysiological studies.

An important question regarding pituitary gigantism is whether earlier diagnosis and control of GH/IGF1 secretion

Table 2 Comparisons of characteristics between X-linked acrogigantism (X-LAG) syndrome group, *AIP* mutation positive (*AIP*mut) patients and genetically negative patients

Study criteria	Group I X-LAG syndrome n=14	Group II <i>AIP</i> mut n=42	Group III Genetically negative n=77	P1 (I vs II)	P2 (I vs III)	P3 (II vs III)
Gender (% of males)	29%	95%	78%	0.002	0.01	0.01
FIPA (number of patients/number of families)	4/2	18/16	5/5			
Age at rapid growth onset (year)	1.5 (1; 2)	13 (9; 15)	14 (11; 15)	<0.0001	<0.0001	0.09
Patients who had not reached final height (%)	76.9%	12.5%	12.2%	0.005	0.0001	0.8
Age at which final height was attained (year)	23.5 (18; 29)	19 (18; 21)	20 (18; 24)	0.6	0.6	0.16
Height Z-score (s.d.)	+4.82 (+2.8; +6.1)	+3.01 (+2.5; +4.1)	+2.99 (+2.4; +4.0)	0.009	0.007	0.9
Age at height measurement (year)	5 (3; 7)	26.5 (19; 33.5)	29 (24.8; 36.5)	<0.0001	<0.0001	0.11
Difference from MPH						
Absolute (cm)	10.9 (9.4; 12.4)	18.9 (16.2; 26)	21.5 (14; 24.5)	0.06	0.1	0.63
Relative (%)	6.52 (5.5; 7.5)	10.9 (8.9; 15.4)	12.7 (8.3; 16.2)	0.06	0.1	0.5
Age at first symptoms (year)	1.5 (1; 2)	13.3 (9; 16)	15.0 (13; 16)	<0.0001	<0.0001	0.04
Age at diagnosis PA (year)	3 (2.6; 3.7)	16.8 (14.0; 20.0)	24.0 (19.0; 29.5)	<0.0001	<0.0001	<0.0001
≤ 19 years of age (%)	100%	71.4%	28.6%			<0.0001
Delay from symptoms to diagnosis (year)	1.6 (1; 2.25)	3 (1; 6)	8 (4; 13)	0.06	<0.0001	0.0006
Macroadenoma (%)	76.9%	90.2%	92%	0.06	0.08	0.7
Giant (≥40 mm) adenoma (as a % of macroadenomas)	0.0%	10.8%	22%			0.07
Extension (%)	50.0%	77.8%	88.4%	0.02	0.001	0.07
Invasion (%)	30.0%	58.1%	66.7%	0.04	0.01	0.2
Maximal dimension of PA (mm)	18 (10; 27)	25 (14; 32)	24 (17; 37.5)	0.3	0.2	0.65
GH levels at diagnosis (ng/ml)	102 (58.5; 121)	23 (14.5; 50)	43 (21.6; 88.5)	0.01	0.09	0.05
IGF1 levels at diagnosis (% ULN)	385 (285; 463)	199.5 (116.8; 282.7)	285 (205; 403)	0.003	0.2	0.001
Prolactin co-secretion (%)	82.0%	33.3%	41%	0.02	0.01	0.4
Multimodal treatment approach (%)	46.0%	23.8%	42.7%	0.03	0.6	0.04
GH/IGF1 control at last follow-up (%)	58.0%	61.0%	43.0%	0.7	0.02	0.03
Age when first control achieved (year)	8.0 (4; 13)	17.3 (15; 20)	27 (18; 37)	0.006	0.0005	<0.0001
GH/IGF1 control ≤ 19 years (%)	85.7%	72.7%	22.7%			0.0001
GH/IGF1 control before final height (%)	54.5%	48.6%	10.9%	0.3	<0.0001	<0.0001
Long-term control (> 12 months) (%)	41.7%	55.3%	38.4%	0.05	0.1	0.08
Follow-up period on treatment (year)	3 (0.9; 8)	10.3 (4; 20)	7 (3; 13.5)	0.04	0.5	0.07
Hypopituitarism at follow-up (%)	75%	73%	66%	0.9	0.7	0.4

All continuous data are shown as median and IQR. FIPA, familial isolated pituitary adenomas; PA, pituitary adenoma; MPH, mid-parental height; ULN, upper limit of normal range.

can influence final height. As this study included patients with gigantism diagnosed at any time during their growth (not only on final adult height > +2 s.d.), we were able to address whether early recognition could limit excessive linear growth. In the group overall, the height at last follow-up was clearly in excess of MPH (11.6%; absolute difference, 20 cm) in both males and females. The median

age at which linear growth ceased was 23 years, which is later than in the general population – 20 years (Deaton 2007). This delay permitted a longer period of growth before epiphyseal closure, a factor that was exacerbated in those with concomitant hypogonadism who had a greater final height. We found that a greater final height Z-score was determined by earlier age of onset, larger tumor size

and greater GH excess. Moreover, these three features were interconnected, with younger patients developing larger tumors and higher GH secretion. Importantly, the age at which GH control was achieved had an important effect on final height. When control was achieved during the period of usual linear growth (≤ 19 years), the final height was lower, with a decrease in the difference between MPH and final height. These findings strongly suggest that an earlier diagnosis and a more rapid achievement of hormonal control can help reduce final height in pituitary gigantism patients. The delay between first symptoms of increased growth being noticed for the first time and the diagnosis of a pituitary adenoma relies on a number of factors. Not only is good awareness of the clinical features of excessive growth (including accompanying signs/symptoms) important in the general population but also the urgency of seeking and obtaining both general and specialized medical input depends on the patients and families and the attitude and efficiency of the health system. Access to expert diagnostics and treatment is not uniform, and particularly in economically disadvantaged regions, such access may be extremely difficult to obtain. Although these represent significant challenges, this study provides scientific evidence to support improvements in disease awareness and to improve the efficiency of current diagnostic and treatment networks.

In three-quarters of the cases abnormal growth was the first sign/symptom reported, and it was generally established by late prepubertal childhood or early adolescence (median 13 years). We found that signs/symptoms were noted significantly earlier in females than in males, which led to an earlier diagnosis and shorter latency period before diagnosis. A number of factors may have contributed to this earlier diagnosis. Disease onset overlapped with the earlier pubertal growth spurt in females. The superposition of abnormal acromegaly symptoms on top of accelerated vertical growth may have led to patients seeking medical attention earlier. In addition, tall stature even in healthy girls has long been viewed as less socially desirable (Lee & Howell 2006), possibly contributing to an earlier recourse to medical investigation by parents and doctors. However, despite the shorter latency period in females, the difference between final height and MPH did not differ between males and females. This was probably due to the similar duration between the time of diagnosis and the time of hormonal control in the two gender groups. This highlights that earlier recognition and diagnosis needs to be accompanied by rapid therapeutic intervention to control GH/IGF1 to influence final height.

Despite the young age at disease onset, pituitary adenomas were already large and most had extension and invasion at diagnosis. Elevated levels of GH and IGF1 (with prolactin co-secretion in one-third of cases) were seen at diagnosis and underpin the early and profound overgrowth seen among pituitary gigantism sufferers. Patients required multimodal treatment, with repeated surgeries and frequent use of radiotherapy. As the study was international and retrospective, not all modalities were uniformly available in all countries, particularly medical therapies like pegvisomant and SSA. Previous reports of individual cases or small series of pituitary gigantism have noted challenging disease control that required pegvisomant (Rix *et al.* 2005, Goldenberg *et al.* 2008). More uniform early recourse to medical therapies in patients not controlled by surgery alone could theoretically improve the poor responses seen in the current cohort. However, certain genetic forms of gigantism, such as AIP mutations and X-LAG syndrome, are poorly responsive to traditional SSA, further complicating the management (Daly *et al.* 2010b, Beckers *et al.* 2015). Radiotherapy has a relatively slow onset of effect and may not be sufficient alone following failed surgery, as in the setting of pituitary gigantism in which the window to provide effective therapy and to restrain overgrowth is quite narrow. Given these challenges, it would appear ideal that patients with suspected pituitary gigantism be referred to experienced centers with available multimodal therapy as soon as possible to improve chances of earlier effective disease control.

The clinical presentation included many typical disease features of adult acromegaly despite the relatively young age of the patients (Supplementary Table 1). The range of signs/symptoms was mainly influenced by the duration of GH/IGF1 hypersecretion and the delay in diagnosis. These included glucose metabolism disorders, arterial hypertension and heart disease, which are more typical of an older age group. Taking into account the poor hormonal control rate, it was not surprising that clinical symptom rates were not greatly ameliorated by surgery or on medical treatment (Supplementary Table 1). Moreover, hypopituitarism was diagnosed frequently in our cohort – probably due to high prevalence of macroadenomas – and rose from 25% of patients at baseline to 64% at the last follow-up due to cumulative effects of treatment (i.e., surgery and radiotherapy). Given the young age of disease-associated comorbidities, relatively low control of GH/IGF1 and the high rate of hypopituitarism, pituitary gigantism patients have significant morbidity. The impact of this morbidity on the lifespan as compared with what is established in adult

acromegaly is unknown (Biermasz 2014). In our group, seven patients died, all relatively young, but specific studies are required to better assess the effects of disease burden on mortality. In addition, the impact of the often dramatic physical overgrowth on quality of life in pituitary gigantism patients should be addressed.

Height is highly variable across human populations due to a variety of factors, including complex genetic influences (Silventoinen 2003, Wood *et al.* 2014). In addition, secular trends in anthropomorphic measures, including height, in national or regional sub-populations can lead to rapid changes over a few generations due to factors like improved nutrition (Hesse *et al.* 2003, Marques-Vidal *et al.* 2008, Jordan *et al.* 2012, Avila *et al.* 2013). For this reason, the diagnosis of abnormal height must be made based on appropriate population norms, which ideally are country specific and regularly updated. We chose such normal datasets for the current study, which allowed us to classify patients with gigantism according to Z-scores for height based on their own country of origin.

This is the first study to describe the clinical, genetic and therapeutic features of pituitary gigantism in a large international cohort. However, there are some limitations. This was an analysis conducted among patients with variable disease duration and treatment history, which could impact analyses of disease control. Changes in the availability of modalities across time and across geographic regions are an unavoidable issue in studies of this type and must be borne in mind. The methodology of the study was based on definitive measures to a large extent to make the analyses and conclusions more robust. However, certain aspects, such as the age at the onset of rapid growth, may suffer from imperfect recall. Similarly, the multicenter nature of the study has implications for hormonal and radiological assessments due to heterogeneity of testing kits and normal ranges and neuroradiological equipment and results. In such a rare condition, it is not feasible for an academic (i.e., noncommercial) study to recruit large numbers of patients at the same disease stage and receive the same diagnostic and therapeutic workup measured centrally in the same laboratory and by the same neuroradiologists. We recognize the important variability in hormonal measurement in the GH/IGF1 axis depending on standards and methods used, and the variability of normal values over time and among laboratories always requires caution (Clemmons 2011). As a follow-up study, we will examine the pituitary tumor characteristics of gigantism patients using the same neuroradiological methods and interpretation, albeit in a

small subset of the larger study group. Although this is the most extensive genetic study of patients with pituitary gigantism to date, only half of the patients consented to and underwent genetic testing; the final proportions of different genetic causes (and patients with unknown causes) could therefore vary from those we report here.

Pituitary gigantism patients are predominantly males diagnosed at a young age with macroadenomas, but females have their first symptoms and are diagnosed earlier than males. *AIP* mutations/deletions and X-LAG syndrome account for about 40% of the patients tested. However, a genetic cause remains to be found in more than half of the pituitary gigantism patients and these patients had aggressive disease features. Final height in gigantism was determined by an earlier age of onset, larger tumor size and greater GH excess; control of GH excess at a younger age led to a decreased final height. Treatment in patients with pituitary gigantism was complex and multimodal therapy was frequently needed. Pituitary gigantism is a challenging condition, and improved management to permit rapid diagnosis and treatment would likely be aided by greater general awareness of the condition, its genetic pathophysiology and the vital role of multidisciplinary surgical and medical teams.

Supplementary data

This is linked to the online version of the paper at <http://dx.doi.org/10.1530/ERC-15-0320>.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

This study was supported by an educational grant from the JABBS Foundation (UK Charity Number: 1128402) and from the Fonds d'Investissement de Recherche Scientifique of the Centre Hospitalier Universitaire de Liège, to A Beckers. This study is based in part on confidential data provided by Eurostat, the statistical office of the European Union: European Health Interview Survey (EHIS) 1 microdata. The responsibility for all conclusions drawn from the data lies entirely with the authors.

Acknowledgements

We would like to thank the following for contributing individual patient details: Daniel L Metzger, Hamilton Raúl Cassinelli, Satinath Mukhopadhyay, Natalia Strebkova, Monica Tome Garcia, Jens Otto Lunde Jorgensen, Jacob Dal, Annamaria Colao, Ismene Bilbao, Jose Ignacio Labarta Aizpun, Klaus Von Werder, Ann McCormack, Nadia Mazerkina, Dominique Maiter, France Devuyt, Marie-Christine Vantghem, Alexander Dreval, Simona Juliette Mogos, Diego Ferone, Elena Nazzari, Vincent Rohmer, Patrice Rodien,

Francoise Borson-Chazot and Sandrine Laboureau-Soares Barbosa. We also acknowledge the help of Nucleo de Apoio a Pesquisa from Instituto Sabin-Brasilia and CNPq, Brazil.

References

- Avila JA, Avila RA, Goncalves EM, Barbeta VJ, Morcillo AM & Guerra-Junior G 2013 Secular trends of height, weight and BMI in young adult Brazilian military students in the 20th century. *Annals of Human Biology* **40** 554–556. (doi:10.3109/03014460.2013.808696)
- Batty GD, Shipley MJ, Gunnell D, Huxley R, Kivimaki M, Woodward M, Lee CM & Smith GD 2009 Height, wealth, and health: an overview with new data from three longitudinal studies. *Economics and Human Biology* **7** 137–152. (doi:10.1016/j.ehb.2009.06.004)
- Beckers A, Lodish MB, Trivellin G, Rostomyan L, Lee M, Faucz FR, Yuan B, Choong CS, Caberg JH, Verrua E et al. 2015 X-linked acrogigantism syndrome: clinical profile and therapeutic responses. *Endocrine-Related Cancer* **22** 353–367. (doi:10.1530/ERC-15-0038)
- Biermasz NR 2014 Pituitary gland: mortality in acromegaly reduced with multimodal therapy. *Nature Reviews. Endocrinology* **10** 708–710. (doi:10.1038/nrendo.2014.193)
- Chahal HS, Stals K, Unterlander M, Balding DJ, Thomas MG, Kumar AV, Besser GM, Atkinson AB, Morrison PJ, Howlett TA et al. 2011 AIP mutation in pituitary adenomas in the 18th century and today. *New England Journal of Medicine* **364** 43–50. (doi:10.1056/NEJMoa1008020)
- Cheetham T & Davies JH 2014 Investigation and management of short stature. *Archives of Disease in Childhood* **99** 767–771. (doi:10.1136/archdischild-2013-304829)
- Clemmons DR 2011 Clinical laboratory indices in the treatment of acromegaly. *Clinica Chimica Acta; International Journal of Clinical Chemistry* **412** 403–409. (doi:10.1016/j.cca.2010.11.008)
- Daly AF, Tichomirowa MA, Petrossians P, Heliövaara E, Jaffrain-Rea M-L, Barlier A, Naves LA, Ebeling T, Karhu A, Raappana A et al. 2010a Clinical characteristics and therapeutic responses in patients with germ-line AIP mutations and pituitary adenomas: an international collaborative study. *Journal of Clinical Endocrinology and Metabolism* **95** E373–E383. (doi:10.1210/jc.2009-2556)
- Daly AF, Tichomirowa MA, Petrossians P, Heliövaara E, Jaffrain-Rea ML, Barlier A, Naves LA, Ebeling T, Karhu A, Raappana A et al. 2010b Clinical characteristics and therapeutic responses in patients with germ-line AIP mutations and pituitary adenomas: an international collaborative study. *Journal of Clinical Endocrinology and Metabolism* **95** E373–E383. (doi:10.1210/jc.2009-2556)
- Daughaday WH 1992 Pituitary gigantism. *Endocrinology and Metabolism Clinics of North America* **21** 633–647.
- Davies JH & Cheetham T 2014 Investigation and management of tall stature. *Archives of Disease in Childhood* **99** 772–777. (doi:10.1136/archdischild-2013-304830)
- Deaton A 2007 Height, health, and development. *PNAS* **104** 13232–13237. (doi:10.1073/pnas.0611500104)
- Eugster E 2015 Gigantism. In *Endotext*. Eds LJ De Groot et al. South Dartmouth, MA, USA: MDText.com, Inc. (available at: <http://www.ncbi.nlm.nih.gov/books/NBK279155/>).
- Eugster EA & Pescovitz OH 1999 Gigantism. *Journal of Clinical Endocrinology and Metabolism* **84** 4379–4384. (doi:10.1210/jcem.84.12.6222)
- Goldenberg N, Racine MS, Thomas P, Degnan B, Chandler W & Barkan A 2008 Treatment of pituitary gigantism with the growth hormone receptor antagonist pegvisomant. *Journal of Clinical Endocrinology and Metabolism* **93** 2953–2956. (doi:10.1210/jc.2007-2283)
- Hazebroek-Kampschreur AA, Hofman A, van Dijk AP & van Ling B 1994 Determinants of trunk abnormalities in adolescence. *International Journal of Epidemiology* **23** 1242–1247. (doi:10.1093/ije/23.6.1242)
- Hesse V, Voigt M, Salzler A, Steinberg S, Friese K, Keller E, Gausche R & Eisele R 2003 Alterations in height, weight, and body mass index of newborns, children, and young adults in eastern Germany after German reunification. *Journal of Pediatrics* **142** 259–262. (doi:10.1067/mpd.2003.85)
- Jennings JE, Georgitsi M, Holdaway I, Daly AF, Tichomirowa M, Beckers A, Aaltonen LA, Karhu A & Cameron FJ 2009 Aggressive pituitary adenomas occurring in young patients in a large Polynesian kindred with a germline R271W mutation in the AIP gene. *European Journal of Endocrinology* **161** 799–804. (doi:10.1530/EJE-09-0406)
- Jordan S, Lim L, Seubsman SA, Bain C, Sleigh A & Thai Cohort Study T 2012 Secular changes and predictors of adult height for 86 105 male and female members of the Thai Cohort Study born between 1940 and 1990. *Journal of Epidemiology and Community Health* **66** 75–80. (doi:10.1136/jech.2010.113043)
- Lee JM & Howell JD 2006 Tall girls: the social shaping of a medical therapy. *Archives of Pediatrics & Adolescent Medicine* **160** 1035–1039. (doi:10.1001/archpedi.160.10.1035)
- Lee CM, Barzi F, Woodward M, Batty GD, Giles GG, Wong JW, Jamrozik K, Lam TH, Ueshima H, Kim HC et al. 2009 Adult height and the risks of cardiovascular disease and major causes of death in the Asia-Pacific region: 21,000 deaths in 510,000 men and women. *International Journal of Epidemiology* **38** 1060–1071. (doi:10.1093/ije/dyp150)
- Marques-Vidal P, Madeleine G, Romain S, Gabriel A & Bovet P 2008 Secular trends in height and weight among children and adolescents of the Seychelles, 1956–2006. *BMC Public Health* **8** 166. (doi:10.1186/1471-2458-8-166)
- Mascie-Taylor CG 1991 Biosocial influences on stature: a review. *Journal of Biosocial Science* **23** 113–128.
- Naves LA, Daly AF, Vanbellinghen JF, Casulari LA, Spilioti C, Magalhaes AV, Azevedo MF, Giacomini LA, Nascimento PP, Nunes RO et al. 2007 Variable pathological and clinical features of a large Brazilian family harboring a mutation in the aryl hydrocarbon receptor-interacting protein gene. *European Journal of Endocrinology* **157** 383–391. (doi:10.1530/EJE-07-0533)
- Rix M, Laurberg P, Hojberg AS & Brock-Jacobsen B 2005 Pegvisomant therapy in pituitary gigantism: successful treatment in a 12-year-old girl. *European Journal of Endocrinology* **153** 195–201. (doi:10.1530/eje.1.01956)
- Rogol AD, Roemmich JN & Clark PA 2002 Growth at puberty. *Journal of Adolescent Health* **31** (6 Suppl) 192–200. (doi:10.1016/S1054-139X(02)00485-8)
- Silventoinen K 2003 Determinants of variation in adult body height. *Journal of Biosocial Science* **35** 263–285. (doi:10.1017/S0021932003002633)
- Silventoinen K, Lahelma E & Rahkonen O 1999 Social background, adult body-height and health. *International Journal of Epidemiology* **28** 911–918. (doi:10.1093/ije/28.5.911)
- Stratakis CA 2015 A giant? Think of genetics: growth hormone-producing adenomas in the young are almost always the result of genetic defects *Endocrine* [in press]. (doi:10.1007/s12020-015-0645-3)
- Stratakis CA, Tichomirowa MA, Boikos S, Azevedo MF, Lodish M, Martari M, Verma S, Daly AF, Raygada M, Keil MF et al. 2010 The role of germline AIP, MEN1, PRKAR1A, CDKN1B and CDKN2C mutations in causing pituitary adenomas in a large cohort of children, adolescents, and patients with genetic syndromes. *Clinical Genetics* **78** 457–463. (doi:10.1111/j.1399-0004.2010.01406.x)
- Tanner JM & O'Keeffe B 1962 Age at menarche in Nigerian school girls, with a note on their heights and weights from age 12 to 19. *Human Biology* **34** 187–196.
- Tichomirowa MA, Barlier A, Daly AF, Jaffrain-Rea ML, Ronchi C, Yaneva M, Urban JD, Petrossians P, Elenkova A, Tabarin A et al. 2011 High prevalence of AIP gene mutations following focused screening in young patients with sporadic pituitary macroadenomas. *European Journal of Endocrinology* **165** 509–515. (doi:10.1530/EJE-11-0304)

Trivellin G, Daly AF, Faucz FR, Yuan B, Rostomyan L, Larco DO, Scherthaner-Reiter MH, Szarek E, Leal LF, Caberg JH *et al.* 2014 Gigantism and acromegaly due to Xq26 microduplications and GPR101 mutation. *New England Journal of Medicine* **371** 2363–2374. (doi:10.1056/NEJMoa1408028)

Wood AR, Esko T, Yang J, Vedantam S, Pers TH, Gustafsson S, Chu AY, Estrada K, Luan J, Kutalik Z *et al.* 2014 Defining the role of

common variation in the genomic and biological architecture of adult human height. *Nature Genetics* **46** 1173–1186. (doi:10.1038/ng.3097)

Xekouki P, Azevedo M & Stratakis CA 2010 Anterior pituitary adenomas: inherited syndromes, novel genes and molecular pathways. *Expert Review of Endocrinology & Metabolism* **5** 697–709. (doi:10.1586/eeem.10.47)

Received in final form 14 July 2015

Accepted 16 July 2015

Made available online as an Accepted Preprint

17 July 2015