Pituitary (2016) 19:560–564
DOI 10.1007/s11102-016-0743-0

Childhood acromegaly due to X-linked acrogigantism: long term follow-up

Rebecca J. Gordon[1] · Jennifer Bell[1] · Wendy K. Chung[1] · Raphael David[2] · Sharon E. Oberfield[1] · Sharon L. Wardlaw[3]

Published online: 8 September 2016

Abstract
Purpose Acromegaly in infancy is extremely rare. We describe a 32 year old woman who presented at 6 months of age with isolated macrocephaly, followed by accelerated linear growth. At 21 months of age, her head circumference was 55 cm (+5.5 SD), height was 97.6 cm (+4.4 SD) and weight was 20.6 kg (+6.2 SD). She had markedly elevated levels of growth hormone (GH) (135 ng/ml), IGF-1 (1540 ng/ml) and prolactin (370 ng/ml). A pituitary macroadenoma was surgically resected. Immunohistochemical staining was positive for GH. Post-operatively, she developed ACTH and TSH deficiency and diabetes insipidus.
Methods Long term clinical follow-up and genetic testing with chromosomal microarray analysis.
Results Despite GH deficiency, she grew well until 7 ½ years old, with subsequent decline in growth velocity, and received GH therapy for 5 years. Puberty was initiated with estrogen therapy. As an adult, she has no stigmata of acromegaly, with a height of 164.5 cm and non-acromegalic features. IGF-1 has remained in the low normal range. Prolactin has been mildly elevated. Serial MRIs have shown no evidence of tumor recurrence. She receives replacement therapy with hydrocortisone, levothyroxine and DDAVP. Chromosomal microarray analysis revealed that she has X-linked acrogigantism (X-LAG) due to a *de novo* duplication of Xq26.3 (516 kb). She recently became pregnant following ovarian stimulation and chorionic villus sampling revealed that she is carrying a male with the same duplication.
Conclusion This report provides detailed long term clinical follow-up of a patient with X-LAG syndrome.

Keywords Acromegaly · Pediatrics · Pituitary adenoma · X-linked acrogigantism syndrome

Introduction

Pituitary gigantism is caused by an excess of growth hormone (GH) before the closure of growth plates, either from a GH secreting pituitary adenoma or from pituitary hyperplasia. The genetic etiology of pituitary gigantism has been poorly understood, despite the fact that it can occur as a feature of many monogenic disorders. In a recent multicenter cohort study of over 200 patients with pituitary gigantism [1], half of the cases had an identifiable genetic etiology. The most frequent was an aryl hydrocarbon receptor interacting protein (*AIP*) gene mutation (29 %), followed by X-linked acrogigantism (X-LAG) (10 %). Other syndromes, such as McCune-Albright syndrome, Carney complex and multiple endocrine neoplasia type 1 (MEN1), were rarer. Non-syndromic gigantism can occur sporadically or be familial, with familial isolated pituitary adenomas (FIPA) occurring in families with two or more relatives having pituitary adenomas, of which *AIP* mutations have been found in 20 % and the remainder have no genetic cause identified.

✉ Sharon L. Wardlaw
sw22@cumc.columbia.edu

[1] Department of Pediatrics, Columbia University College of Physicians and Surgeons, New York, NY, USA

[2] Department of Pediatrics, New York University School of Medicine, New York, NY, USA

[3] Department of Medicine, Columbia University College of Physicians and Surgeons, 630 West 168th Street, New York, NY 10032, USA

We describe the long term follow up of a previously reported case of pituitary gigantism of childhood due to a GH secreting pituitary adenoma [2]. This report summarizes her initial presentation and over 30 years of follow-up, including recent genetic testing. A chromosomal microarray was performed and revealed that she has X-LAG syndrome [3] due to a 516 kb duplication of Xq26.3. She is now pregnant with a male fetus with the same Xq26.3 duplication. This case report provides detailed long term follow up of a patient with X-LAG syndrome.

Case report

The patient was born full term after an uncomplicated pregnancy and weighed 3.1 kg (50 % for age). Her initial history through 4 years demonstrated she had normal growth and development until about 6 months old, when she was noted to have rapid head enlargement; her head circumference increased from the 75th percentile at 1 month to greater than the 95th percentile at 5 months, with height of 69.2 cm at 6 months. Initially, this was attributed to familial macrocephaly, and serial CTs (at 8, 10 and 12 months) demonstrated normal ventricles, with slightly enlarged subarachnoid space and slightly broad infundibulum and repeated lumbar punctures showed normal intracranial pressure. Linear growth appeared normal through about 1 year old, with tall stature attributed to familial genetic potential. However, between 9 and 17 months, she grew 15 cm. Of note, she had a voracious appetite and frequent shoe size increases. She had no neurologic or ocular symptoms.

At 21 months old she was evaluated for accelerated growth, with a height of 97.6 cm (+4.4 SD), weight of 20.6 kg (+6.2 SD) and head circumference of 55 cm (+5.5 SD). She was tall and stocky with frontal bossing, slight hypertelorism, widened interdental spaces, high arched palate, prognathism with coarsened facial features and thickened hands and feet, heel thickness 21 mm (normal adult 22 mm), but no organomegaly (see Fig. 1). Initial work up revealed an elevated GH of 135 ng/ml, IGF-1 of 1540 ng/ml (normal for bone age 18–97, for chronologic age 14–60) and prolactin of 370 ng/ml (normal <20). She had prepubertal gonadotropins and normal thyroid function tests. Bone age was advanced to 3 years, at 21 months chronologic age. CT scan at 23 months showed a 1.75 × 1.25 cm homogeneous, solid lesion, well-circumscribed, minimally contrast enhancing, sellar and suprasellar mass (see Fig. 2).

At 24 months, she had a right pterional craniotomy, with total removal of an encapsulated marble sized tumor arising from the pituitary, filling the entire suprasellar region with deviation of the right optic nerve and chiasm. On immunohistochemical staining, 80 % of cells were positive for GH, but were negative for prolactin, ACTH, LH and FSH. Following tumor removal, on post-op day 4, there was a marked decrease in serum concentrations of GH to 4.7 ng/ml, IGF-1 to 221 ng/ml and prolactin to 27 ng/ml. Postoperatively, she developed hypopituitarism and diabetes insipidus, requiring treatment with hydrocortisone, levothyroxine and DDAVP.

Despite GH deficiency on repeated testing, between 2 and 7½ yo she grew normally, remaining above but parallel to the 95 % growth channel. This included GH stimulation tests with arginine, insulin and/or L-dopa or TRH stimulation tests, all of which demonstrated low peak GH responses, measured at 26 months, 34 months, 3½ and 5 yo were 2.8, 3.7, 3.3 and 2.0 ng/ml, respectively. 24 h basal GH levels measured every 2 h by RIA at 2½ and 7½ yo ranged from 2.1 to 3.4 ng/ml and 0.6 to 0.8 ng/ml, respectively. A 10 h sleep study at 5 yo showed a non-episodic pattern of GH secretion and subnormal values, with a mean GH level of 2 ng/ml and a peak GH level of 2.5 ng/ml. An oral glucose tolerance test demonstrated insufficient suppression of GH, with levels falling from a baseline of 3.1 ng/ml to a nadir of 2.1 ng/ml. During this time, she had serial bone ages that approximated her chronologic age. Furthermore, her general appearance normalized, with dramatic softening of her facial features, decreased spacing between her teeth and the development of normal sized hands.

At 7½ yo, her growth began to dramatically decline, falling from above the 95 % to between the 25 and 50 % by 11 yo (see Fig. 2) and serial bone ages were delayed by about 1 year. Repeat GH stimulation testing at 9½ yo showed persistent GH deficiency, with a peak of 2.04 ng/ml. IGF-1 levels were normal for age at 148–153 ng/ml (normal for chronologic age 117–771) until approximately 10 yo, when they decreased to 60–83 ng/ml. At 11 yo she was begun on GH therapy (0.15 mg/kg/wk), and her growth rate increased soon after starting GH and she subsequently had a mean growth velocity of 5.4 cm/year between 11 and 15 yo. Over this time period, her IGF-1 levels were mostly within normal limits for chronologic age, between 286 and 460 ng/ml, and bone age approximated her chronologic age. At 15 yo, her growth velocity decreased to 2.4 cm/year and continued at that rate. At 16 yo, she discontinued her GH therapy against medical advice with a final height of 164.5 cm, as both she and her family were satisfied with her achieved height. After discontinuing GH treatment, IGF-1 levels were low for age at 70–134 ng/ml (normal for chronologic age 182–780). Per patient and family preference, there was no further testing or treatment for GH deficiency.

Her prolactin remained elevated, but progressively declined, from levels on average of 87 ng/ml between 7

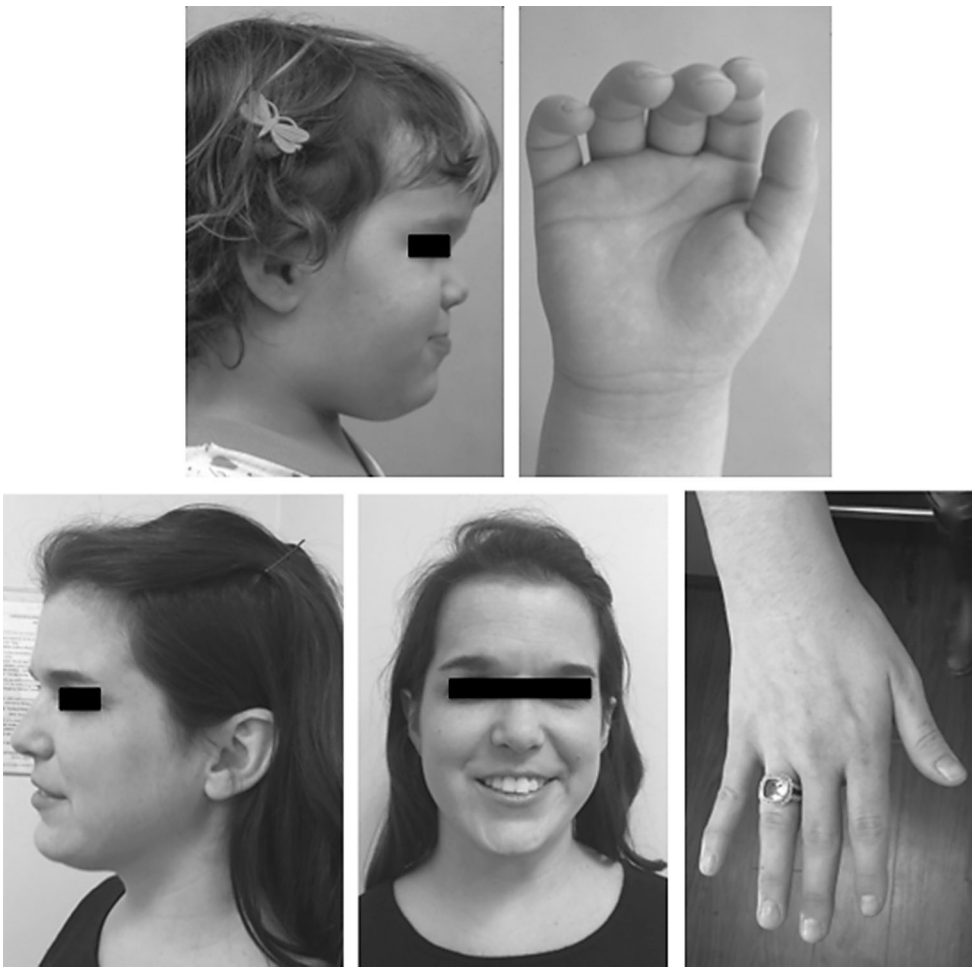


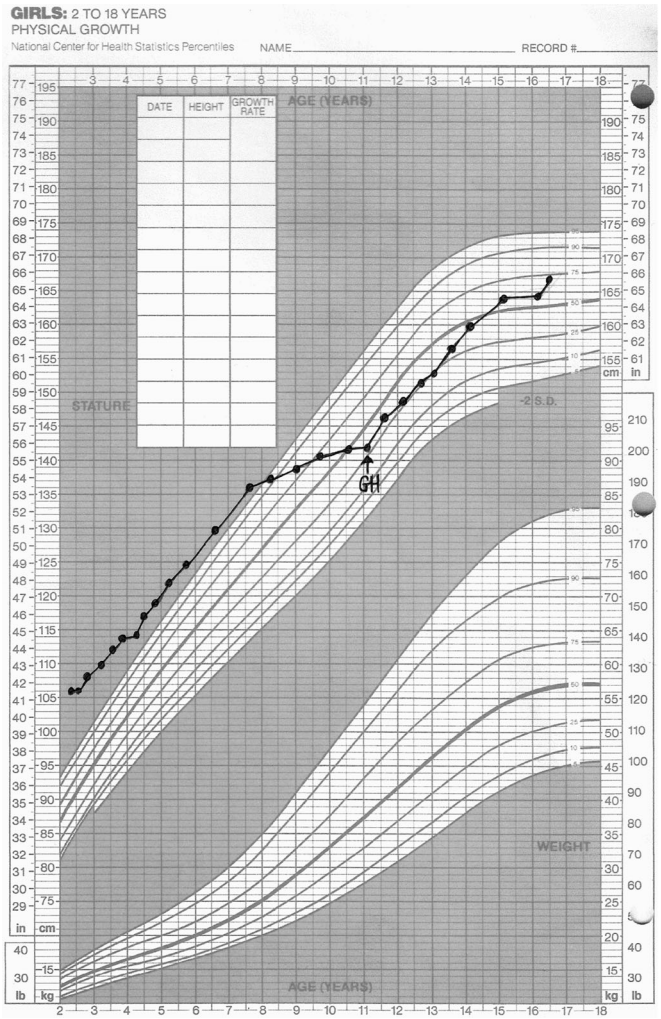
Fig. 1 Pictures of the patient at 21 months and 32 years of age. *Upper Panel* (21 months): facial profile showing coarsened features, frontal bossing, and prognathism as well as a thick stocky hand. *Lower Panel* (32 years): facial profile and hand, without acromegalic features

and 11 yo, to 47 ng/ml between 11 and 15 yo. She did not have onset of spontaneous puberty and just before 12 yo had a GnRH stimulation test with a peak FSH of 1.7 mU/ml and a peak LH of 1.4 mU/ml, indicating gonadotropin deficiency. At 13 yo, she had minimal clinical evidence of puberty, with minimal breast development (Tanner 1–2) and no axillary or pubic hair, and was subsequently started on estrogen (Premarin 0.15 mg qd). The dose was slowly titrated to 0.625 mg qd. At 15 yo, medroxyprogesterone acetate was added (10 mg qd × 7 days, monthly) and she shortly thereafter had menarche. At 16½ yo, the Premarin dose was increased (to 0.9 mg qd) to temporarily promote better breast development.

As an adult, she has no stigmata of acromegaly, with a height of 164.5 cm and non-acromegalic features including a small nose, normal jaw with normally spaced teeth, normal hands and feet size 10 with normal width, normal visual fields and no galactorrhea (see Fig. 1). She has been followed in our Neuroendocrine Unit for the past 10 years. Serial evaluations have demonstrated the following ranges: a GH 0.38–1 ng/ml, IGF-1 101–166 (normal range 117–329 ng/ml) and mildly elevated prolactin 19–43 ng/ml (normal <25), which may be due to post-surgical stalk effect. Serial MRIs have shown no interval change, with a partially empty sella turcica and no sellar or suprasellar mass. She continued to receive replacement therapy with hydrocortisone, levothyroxine, DDAVP and estrogen plus cyclic progesterone.

Her course has been complicated by seizures, attributed to post-surgical scar tissue. This occurred one time post-operatively and she was subsequently briefly on anti-epileptics. She had recurrence of seizures starting at 21 years of age. These have been well controlled with lamotrigine for the past 10 years. She has no problems with memory or concentration. She completed college, graduate coursework leading to teaching certification and a masters in public administration. She works full time as a special education elementary school teacher.

Based on the recent identification of a new infant-onset gigantism syndrome termed X-linked acrogigantism (X-LAG), of which she shares many features, and the potential implications it would have on her fertility treatment, whole genome array based comparative genomic hybridization (aCGH) and genotype analysis was



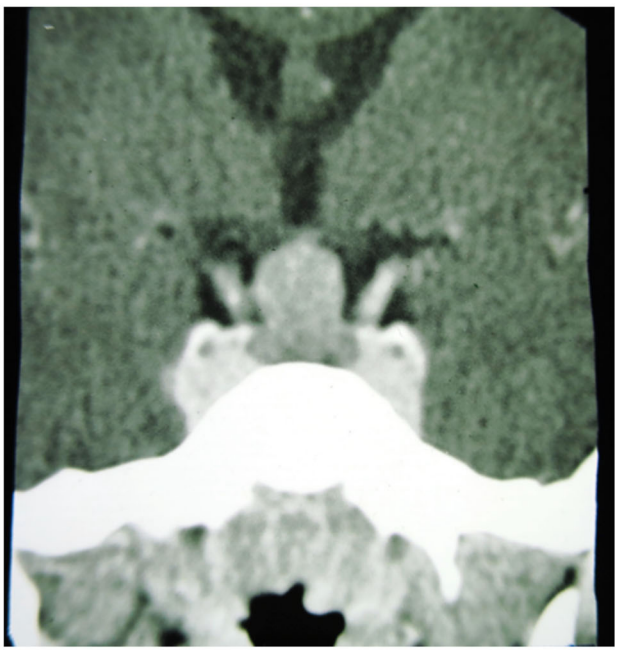


Fig. 2 CT scan at 23 months old showed a large (1.75 × 1.25 cm) homogeneous, solid, well-circumscribed sellar and suprasellar mass (*Right panel*). Growth curve from 2 to 17 years of age, including growth above and parallel to the 95 % growth channel, then dramatically declining, followed by her improved growth after starting growth hormone (*Left panel*)

performed on a custom designed oligonucleotide microarray (GenomeDx v5) with 115,000 copy number probes. Chromosomal microarray demonstrated a 516 kb microduplication in Xq26.3 of nucleotides 135,596,921-136,113,256, including *GPR101*, consistent with X-LAG syndrome. The duplicated interval contained four additional genes (VGLL1, CD40LG, ARHGEF6, RBMX), of which loss of function mutations but not duplications in CD40LG are associated with x-linked immunodeficiency with hyper-IgM and mutations in ARHGEF6 are associated with x-linked mental retardation, neither of which is present in the patient. This duplication was not present in either parent, confirming this as a *de novo* mutation.

Since there is a 50 % chance of passing this duplication on, with males more severely affected than females, she had genetic counseling as she had already started ovarian stimulation for the induction of fertility. This was not successful. She then initiated preimplantation genetic diagnosis (PGD) with in vitro fertilization (IVF). The first IVF cycle was unsuccessful and during the second cycle due to her poor oocyte response to stimulation, she opted to convert to intrauterine insemination (IUI). She conceived and chorionic villus sampling (CVS) revealed that she is carrying a male with the Xq26.3 duplication. The child will be followed by pediatric endocrinology with close monitoring of his growth parameters, IGF-1 and prolactin levels.

Discussion

This case report provides detailed long term (30 year) follow up of an infant with pituitary gigantism. There is minimal long term (<5 year) follow up of patients with pituitary gigantism and X-LAG syndrome [4]. Based on the patient's features of the recently identified X-LAG syndrome, including excessive growth beginning within the

first year of life, a GH secreting pituitary adenoma and hyperprolactinemia [5], a chromosomal microarray was performed and revealed a microduplication in Xq26.3(135,596,921-136,113,256 × 3), consistent with X-LAG syndrome. Her course has been complicated by hypopituitarism, diabetes insipidus and epilepsy. Of note, successful surgical cure of X-LAG syndrome is frequently complicated by hypopituitarism [3, 5]. Most patients with X-LAG syndrome typically have mixed GH and prolactin secreting tumors. Although in this case the immunohistochemical staining was reported to be only positive for GH, and not for prolactin, the markedly elevated serum prolactin at diagnosis, and rapid decline post-operatively, is consistent with a mixed GH and prolactin secreting tumor.

Patients previously identified with X-LAG syndrome had a common duplicate genomic segment of about 500 kb, ranging from Xq26.3 (135,627,637-136,118,269) [3]. Our patient's duplicated segment Xq26.3 (135,596,921-136,113,256) is likely the same as the duplication that has been previously described given the limits of the resolution of the array. Of note, there were several patients with X-LAG syndrome who had duplications of slightly different regions, but all include *GPR101*. Duplication of Xq26.3 causing X-LAG syndrome appears to be a relatively common genetic etiology of pituitary gigantism [6]. To date, 22 cases have been identified [7]. This duplication is associated with an overexpression of *GPR101*, which consists of a single 1.5 kb exon that encodes an orphan G protein-coupled receptor [3]. Although there were other genes duplicated within the 500 kb interval, duplication of the other genes was not associated with the gigantism phenotype. Subsequently, transfection of rat pituitary GH3 cells with the mutant *GPR101* construct led to increased GH secretion [3]. Therefore, X-LAG syndrome is likely solely due to *GPR101* duplication. However, the exact neurophysiologic mechanism of how overexpression of *GPR101* results in increased GH remains to be elucidated.

Further research into understanding the pathogenesis of X-LAG syndrome is ongoing. Recently, central dysregulation of growth hormone releasing hormone leading to chronic hypersecretion has been suggested to be a key feature that results in the pituitary pathology producing mixed GH and prolactin secreting adenomas seen in X-LAG syndrome [7]. Dysregulation of GH secretion may explain why the patient grew normally for years, but had repeated testing consistent with GH deficiency. Additionally, somatic mosaicism has been identified in the pathogenesis of X-LAG syndrome in males, with sporadic cases more affected than familial cases [8].

In over 30 years, our patient with X-LAG syndrome has done well, without recurrence of her pituitary tumor, on pituitary replacement therapy, without stigmata of acromegaly. Her genetic diagnosis has led to the prenatal diagnosis of X-LAG syndrome during her current pregnancy that will result in close monitoring and early treatment of the child. There are likely others with a history of early childhood pituitary gigantism that have unidentified X-LAG syndrome. Such patients should be looked for and identification would have implications for affected women of reproductive age, regarding fertility interventions and prenatal diagnosis.

Acknowledgments NIH/NIDDK T32DK065522 (RJG and SEO).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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