CASE REPORT

Pseudoacromegaly in congenital generalised lipodystrophy (Berardinelli-Seip syndrome)

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SUMMARY

Pseudoacromegaly, or acromegaloidism, is characterised by a clinical appearance mimicking acromegaly in the absence of documented hypersomatotropism or past exposure to excess growth hormone. It can develop secondary to a number of congenital and acquired conditions of which severe insulin resistance is an important example. Lipodystrophy syndromes are a group of rare disorders of which autosomal recessive congenital generalised lipodystrophy is the most common type. Patients with this disorder are predisposed to insulin resistance and its associated complications such as diabetes mellitus, hypertriglyceridaemia, fatty liver, polycystic ovaries and acanthosis nigricans. Elevated circulating insulin levels in these patients rarely can give rise to soft tissue and bony overgrowth, with resultant acromegaloidism. We report an adolescent girl presenting with unusual prominence of her hands and feet; a thorough evaluation ultimately revealed a diagnosis of congenital generalised lipodystrophy.

BACKGROUND

Congenital generalised lipodystrophy (CGL), or Berardinelli-Seip syndrome, is a rare autosomal recessive condition with a prevalence of 1 in 10 million and is characterised by near complete loss of body fat, insulin resistance and its systemic consequences.¹ Acromegaly is a disease of excess circulating growth hormone (GH) with its characteristic somatic and metabolic effects. Patients with physical findings resembling acromegaly with normal insulin-like growth factor-1 (IGF-1) levels and suppressed GH following glucose load are considered to have pseudoacromegaly, or acromegaloidism. Circulating hyperinsulinaemia secondary to insulin resistance can occasionally give rise to an acromegaloid phenotype.

CASE PRESENTATION

A 13-year-old girl born of a consanguineous union presented with progressive enlargement of her hands and feet. She was otherwise asymptomatic, but the unusual prominence of her hands and feet compared to those of her peers prompted a medical consultation. Her parents had noticed that she had been 'unusually thin' since birth. Antenatal and postnatal periods were uneventful with normal developmental milestones. She had not attained menarche. Family history was unremarkable.

Clinical examination revealed the following:

Height: 135.6 cm (3rd to 5th centile), weight: 29.7 kg (5th to 10th centile), body mass index

(BMI): 16.2 kg/m² (3rd to 15th centile). The mid-parental height was also between 3rd and 5th centile. The anthropometric data suggested that the patient had familial short stature with low normal BMI. Her facial appearance was notable for loss of fat pads from cheeks, without a broad fleshy nose, macroglossia, prognathism, widely spaced incisors and a prominent forehead. She had near-total absence of subcutaneous fat on her face, trunk (figure 1), all extremities and buttocks (figure 2), suggestive of generalised lipoatrophy. However, subcutaneous fat over the palms and soles was preserved. Prominent acanthosis nigricans was present over the nape of the neck, axilla and groin. The patient's hands and feet were unusually large for

Figure 1 Acanthosis over both axillae, loss of subcutaneous fat from face and trunk.

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Figure 2 Loss of subcutaneous fat from buttocks.

her age and body habitus. Her breasts were of Tanner stage 2 and she had clitoromegaly (figure 3). She also had hepatosplenomegaly.

INVESTIGATIONS

Fasting plasma glucose: 168 mg/dL; post-glucose plasma glucose: 297 mg/dL; glycated haemoglobin (HbA1c): 8.1%; total cholesterol: 102 mg/dL; triglyceride: 196 mg/dL; high-density lipoprotein cholesterol (HDL-c): 19 mg/dL; low-density lipoprotein cholesterol: 44 mg/dL; very-low-density lipoprotein cholesterol: 39 mg/dL; bilirubin: 1.8 mg/dL; alanine transaminase: 88 U/L; aspartate transaminase: 54 U/L; uric acid: 9.4 mg/dL.

Serum IGF-1 and basal GH values were within age-specific and sex-specific reference range and the GH was adequately suppressed (<0.4 ng/mL) following oral glucose.

Morning total testosterone was 94 ng/dL (reference: 10–50 ng/dL).

Fasting, 1 h postmeal and 2 h postmeal insulin concentrations (in μ IU/mL) were 35.4, 89.5 and 54.7, respectively, which were suggestive of insulin resistance. Simultaneous C peptide values (in ng/mL) were 3.51, 13.1 and 8.78, respectively, indicating adequate β -cell secretory reserve. Abdominal ultrasound documented hepatosplenomegaly with fatty liver and multiple small cysts in both ovaries. The uterus was postpubertal with a uterine

Figure 3 Loss of fat from mons pubis, enlarged clitoris and acanthosis over groin.

Figure 4 X-ray showing multiple cysts over the metacarpals and some of the phalanges. The bone age is consistent with the chronological age.

volume of 2.6 mL. X-ray of the left wrist and hand revealed a bone age consistent with chronological age along with multiple lytic lesions over metacarpals and proximal phalanges (figure 4). Total body fat of only 4% was detected on whole body dual energy X-ray absorptiometry scan.

TREATMENT, OUTCOME AND FOLLOW-UP

The elevated blood sugar and dyslipidaemia were treated with medical nutrition therapy, lifestyle modification and metformin. The patient's blood sugars normalised within 3 months of presentation but no appreciable change in the appearance of her hands and feet was noticed after 1 year of follow-up.

DISCUSSION

There are four distinct forms of CGL: CGL types 1, 2, 3 and 4 resulting from mutations in 1-acylglycerol 3-phosphate-O-acyltransferase 2 (AGPAT2), Berardinelli-Seip congenital lipodystrophy 2 (BSCL2), caveolin-1 and polymerase I and transcript release factor (PTRF), respectively. The majority of cases are due to AGPAT2 and BSCL2 and have some difference in phenotype. For example, CGL type 2 is characterised by loss of metabolic fat, bone marrow fat and mechanical (palms, soles and orbits) fat. In CGL type 1, there is loss of metabolic and marrow fat and in CGL type 3 and 4, only metabolic fat is lost.² In most patients with CGL, diabetes develops around puberty; however, onset of diabetes around infancy has also been reported. Females usually present with oligomenorrhoea, hirsutism and clitoromegaly. Skeletal abnormalities include accelerated bone growth and focal lytic lesions in appendicular bones around puberty.³

This premenarchal girl had features of generalised lipodystrophy with acanthosis nigricans, clitoromegaly, hepatosplenomegaly, diabetes mellitus, elevated triglycerides, low HDL-c,

hyperuricaemia, fatty liver, elevated serum insulin and lytic lesions over metacarpal bones. Moreover, appearance of lipodystrophy from birth (as evidenced from the history and the photographs taken during infancy) led to the diagnosis of CGL. Presence of mechanical fat, however, excluded type 2 CGL.

Conditions giving rise to pseudoacromegaly include diseases associated with severe insulin resistance, pachydermoperiostosis (Touraine-Solente-Gole syndrome), Ascher's syndrome, multiple neuromas syndrome, drugs (minoxidil, phenytoin), primary hypothyroidism and syndrome of acromegaloïd facial appearance.⁴

The exact mechanism underlying acromegaloïd features in lipodystrophies and resultant insulin resistance is yet to be elucidated and a number of hypotheses have been put forward. Varying abnormalities in the GH values ranging from abnormally high levels with no suppression on dynamic testing to normal levels with adequate suppression have been reported.⁵ Although elevated GH has been proposed to be the underlying cause, many patients of lipodystrophy have normal GH values. Loss of fat mass with subsequent low leptin levels and uncontrolled diabetes attributing to hepatic GH resistance in the liver and central hypersensitivity at the level of the hypothalamus may partially explain the elevated GH level noted in some of these patients.^{6,7}

High insulin levels reduce the level of IGF-1 binding proteins and thus increase the ratio of IGF-1 to its binding protein,

which allows a relatively unopposed action of IGF-1 on its receptor and promotes growth.⁸ Another plausible explanation is the concept of pathway selective insulin resistance, in which resistance to the metabolic effects of insulin through phosphatidylinositol 3-kinase pathway and resultant hyperinsulinemia allows development of the acromegaloïd features due to preserved sensitivity to the growth promoting effect via the mitogen-activated protein kinase pathway.⁹

Since the first case reported in 1993, a handful of patients with insulin-mediated pseudoacromegaly have been described in the world literature. In all cases, severe hyperinsulinemia secondary to insulin signalling defects was the underlying mechanism. To the best of our knowledge, pseudoacromegaly in lipodystrophy has rarely been documented and acromegaloïdism as the presenting manifestation of CGL has not been reported.¹⁰

Contributors PPC and SD were involved in evaluation, workup and management of the patient, literature search and writing the manuscript. SM and SC were involved in patient management, intellectual inputs and finalising the draft.

Competing interests None declared.

Patient consent Obtained.

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Learning points

- Patients with clinical features resembling acromegaly but a normal growth hormone insulin-like growth factor-1 axis should be evaluated for pseudoacromegaly.
- Severe insulin resistance is an important cause of pseudoacromegaly.
- Lipodystrophy syndromes should be ruled out in all young individuals presenting with clinical and/or biochemical features of insulin resistance.
- Diabetes mellitus in non-obese adolescents having no family history of diabetes warrants evaluation for genetic causes of insulin resistance and lipodystrophies.

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