Familial Partial Lipodystrophy

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The lipodystrophies are rare disorders characterized by insulin resistance and the absence or loss of body fat. The 4 subtypes of lipodystrophy are characterized by onset and distribution. Partial lipodystrophy is rare, with loss of fat from the extremities and excess fat accumulation in the face and neck; recognizing this phenotype and subsequent referral for endocrinologic care may improve outcome and reduce mortality.

Lipodystrophies are rare disorders characterized by insulin resistance and the absence or loss of body fat.[1] Classification of the 4 main subtypes of lipodystrophy is based on onset (congenital/familial vs acquired/sporadic) and distribution (total/generalized vs partial). Congenital total lipodystrophy (also known as Berardinelli syndrome, Seip syndrome) is a rare autosomal-recessive disorder marked by an almost complete lack of adipose tissue from birth. Familial partial lipodystrophy (also known as Kobberling-Dunnigan syndrome) involves loss of subcutaneous fat from the extremities and accumulation of excess fat in the face and neck and to a lesser extent in the hands and feet. Acquired total lipodystrophy (also known as lipoatrophy, Lawrence-Seip syndrome) presents with generalized loss of fat beginning in childhood. Acquired partial lipodystrophy (also known as progressive lipodystrophy, partial lipoatrophy, Barraquer-Simons syndrome) is characterized by loss of fat only from the upper extremities, face, and trunk.[2]

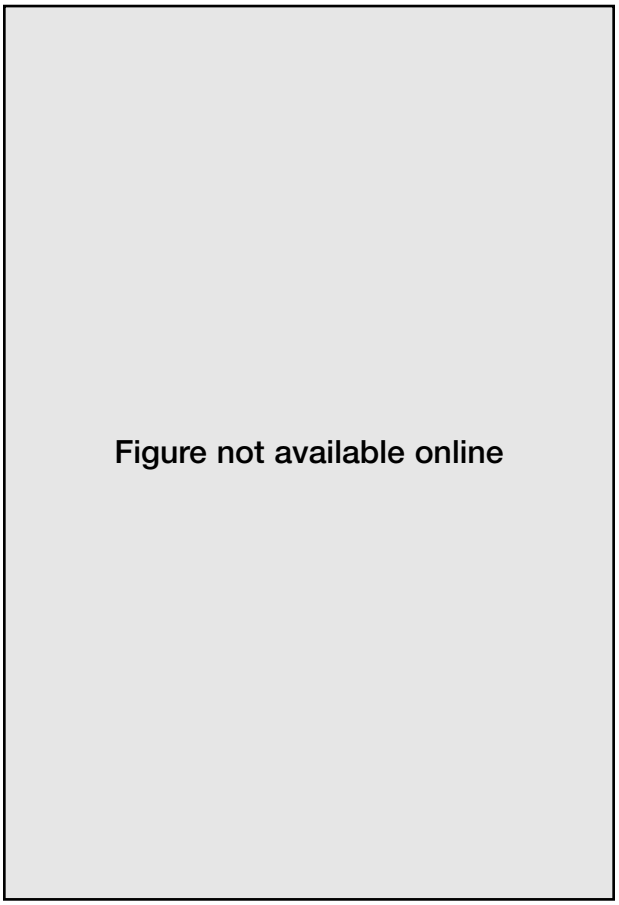

Figure 1. Accentuation of fat pads in the face and neck.

Case Report

A 39-year-old white woman presented with the complaint of thickened brown skin on the neck and medial thighs. Her medical history was significant for poorly controlled diabetes mellitus (onset age, 36 years), hirsutism, hypothyroidism, and dysfunctional uterine bleeding (gravida 2, para 1, AB 1) necessitating total hysterectomy. On physical examination, accentuation of fat pads in the face and neck (Figure 1), central obesity, and prominent musculature in the extremities (Figure 2) were noted. On cutaneous examination, acanthosis nigricans was noted on the posterior area of the neck (Figure 3), on the dorsal interphalangeal areas, on the medial area of the thighs, and on the labia majora; 1- to 2-mm taglike papules studded the velvety plaques on the thighs and genitalia. The chin and the cutaneous upper lip and infraumbilical areas were hirsute; scalp hair was thin and in an androgenic pattern.

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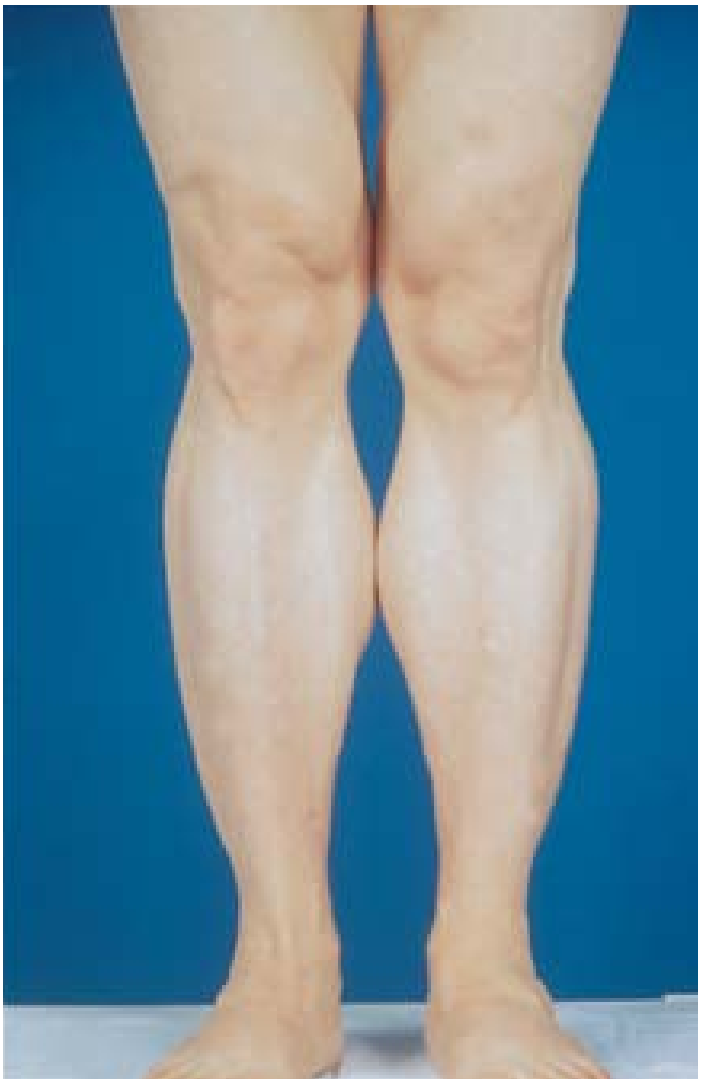

Figure 2. Pseudomuscular appearance of legs.

Lipodystrophy with associated endocrinologic abnormalities was suspected. Endocrinology tests were performed. Results of lipid tests were normal. Family history was positive for hyperlipidemia and early myocardial infarction (patient's father), partial lipodystrophy (paternal grandmother, paternal aunts), and lipodystrophy and polycystic ovary syndrome (sister). Given this history, we confirmed the diagnosis of familial partial lipodystrophy.

Comment

In 1973, Ozer et al[3] were the first to describe familial partial lipodystrophy; a year later, Dunnigan et al[4] described this entity in 2 families. The work of these authors paved the way for the *familial partial lipodystrophy* classification. In 1986, Kobberling and Dunnigan[5] identified types 1 and 2. In type 1, subcutaneous fat is lost only from the limbs (the face and trunk are spared). In type 2, fat is also lost from the trunk; the face and vulva are spared (sparing of the vulva results in an appearance of labial hypertrophy). Since these first cases were reported, approximately 15 other families (>100 patients) with the disease have been identified.[2] The prevalence of familial partial lipodystrophy was estimated to be less than 1 in 15 million individuals.[2]

Children with familial partial lipodystrophy look normal; loss of subcutaneous adipose tissue from the extremities begins during adolescence.[2-10] Absence of palpable or visible fat in the extremities may create an appearance of muscular hypertrophy with prominent veins.[2,5] Possible later developments include a round face, a double chin, and an excess of supraclavicular fat[2] (sometimes clinically mistaken as cushingoid features[6]); broad or acromegalic facial features may also be present.[5]

Figure 3. Velvety brown plaque of acanthosis nigricans on posterior area of the neck.

Associated clinical features variably expressed with familial partial lipodystrophy are hirsutism, acanthosis nigricans, hepatosplenomegaly, tuberous eruptive xanthoma, elevated basal metabolism, essential hypertension, carpal tunnel syndrome, polycystic ovary syndrome, and menstrual abnormalities.[2,4,5,8]

Individuals with familial partial lipodystrophy usually develop insulin-resistant diabetes after 20 years of age.[2] A high concentration of serum triglycerides and a low concentration of serum high-density lipoproteins predispose affected individuals to develop sequelae such as chylomicronemia, fatty liver, and acute pancreatitis,[2] and death may occur from cardiovascular complications between the ages of 40 and 60 years.[4] Females tend to be far more severely affected by the metabolic complications of insulin resistance.[8] A defect in the capacity of insulin to suppress lipolysis in adipose tissue could explain the insulin resistance of carbohydrate metabolism in familial partial lipodystrophy.[9] Presence of acromegalic features, acanthosis nigricans, and polycystic ovary syndrome in patients with familial partial lipodystrophy is thought to be mediated by the direct effect of an increased amount of insulinlike growth factor-1.[10] Laboratory studies should include tests of levels of fasting glucose, plasma free fatty acids, serum triglycerides, and a complete lipid panel. The Table lists diagnostic and laboratory findings in patients with familial partial lipodystrophy.[8]

Because the clinical features of this disease are more easily recognized in females, there is often an underreporting of cases in males.[2-5,8,11] Other reports with an examination of pedigrees have found that disease transmission is autosomal-dominant[12] and that the chromosome is 1q21-22.[13,14] Mutations connected to familial partial lipodystrophy are in LMNA, a gene that encodes nuclear lamin A and lamin C.[6,15-19] Lamins A and C are intermediate filament protein components of the nuclear envelopes of cells, including adipocytes,[6,15-19] and changes in these proteins may lead to the highly specific adipocyte wasting seen in familial partial lipodystrophy.[6,15-19]

With the onset of puberty, hormones also become influential in lipoatrophy[2-9]; they may trigger the expression of LMNA mutations in mutant gene carriers.[18] The specific LMNA mutation R482Q is strongly associated with hyperinsulinism, lipodystrophy, dyslipidemia, hypertension, and diabetes.[17-19] This mutation also is associated with a reduced concentration of plasma leptin. Leptin directs delivery of free fatty acids into adipocytes and limits the delivery of free fatty acids to nonadipocytes (liver and muscle cells), thus protecting nonadipocytes from lipotoxicity. Leptin deficiency results in an increase in exposure of muscle cells to free fatty acids and allows uptake of free fatty acids for oxidation and energy utilization, resulting in resistance to glucose-mediated insulin action.[19] An increase in serum free fatty acids is hypothesized to lead to a decrease in peripheral glucose utilization and an increase in hepatic gluconeogenesis, thereby resulting in the insulin resistance observed.[20]

Familial partial lipodystrophy, a disease with effects that model extreme insulin resistance, is

Types of Lipodystrophy*[8]

Lipodystrophy	Diagnostic Criteria	Metabolic Derangements
Congenital total lipodystrophy (Berardinelli syndrome, Seip syndrome)	Extreme muscularity and generalized loss of body fat from birth Acanthosis nigricans Acromegalic features Umbilical hernia Severe fasting or postprandial hyperinsulinemia Early-onset diabetes and glucose intolerance Hypertriglyceridemia/low HDL-C level Hirsutism and clitoromegaly in females Characteristic body-fat distribution (MRI)	Euglycemic Hyperinsulinemia Marked insulin resistance Low level of plasma leptin
Familial partial lipodystrophy (Kobberling-Dunnigan syndrome, Dunnigan variety)	Extreme muscularity and lack of subcutaneous fat in all extremities Normal physical appearance at birth; onset of lipoatrophy during puberty Excessive amount of adipose tissue in face and neck Acanthosis nigricans Mild-to-moderate fasting or postprandial hyperinsulinemia Impaired glucose tolerance or diabetes after 20 y of age Hypertriglyceridemia/low HDL-C level Characteristic body-fat distribution (MRI)	Diabetes after 20 y of age High concentration of serum triglycerides with predisposition to chylomicronemia and acute pancreatitis Elevated level of plasma free fatty acids Reduced rate of insulin-mediated glucose disposal
Acquired total lipodystrophy (lipoatrophy, Lawrence-Seip syndrome)	Extreme muscularity and generalized lack of fat during childhood or later Loss of subcutaneous fat from palms and soles Severe fasting or postprandial hyperinsulinemia Impaired glucose tolerance or diabetes Hypertriglyceridemia/low HDL-C level Panniculitis at onset of lipodystrophy Presence of other autoimmune diseases	Insulin resistance Hyperinsulinemia Hypertriglyceridemia Low serum HDL-C level Elevated level of plasma free fatty acids Excessive lipolysis Resistance to ketolysis
Acquired partial lipodystrophy (progressive lipodystrophy, partial lipoatrophy, Barraquer-Simons syndrome)	Gradual-onset loss of subcutaneous fat from face, neck, trunk, and upper extremities during childhood Normal or excess amount of subcutaneous fat in hips and lower extremities Proteinuria or biopsy-proven mesangiocapillary glomerulonephritis Low serum complement (C3) levels and presence of C3 nephritic factor Absence of insulin resistance and metabolic complications Presence of other autoimmune diseases Characteristic body-fat distribution (MRI)	Seldom develop insulin resistance, diabetes, dyslipidemia, acanthosis nigricans, hirsutism, or menstrual abnormalities

*HDL-C indicates high-density lipoprotein cholesterol; MRI, magnetic resonance imaging.

Data from Garg A. *J Clin Endocrinol Metab.* 2000;85:1776-1782.

treated primarily through strict control of diabetes and hyperlipidemia.[6,10,20] Much remains to be done to unravel the underlying mechanisms of insulin resistance and related strategies for prevention and treatment. Dermatologists who recognize this phenotype can direct patients toward appropriate endocrine care and thereby help reduce associated morbidity.

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