



## Lipodystrophy

The lipodystrophies are a heterogeneous group of diseases characterized by generalized or partial loss of subcutaneous fat. In addition to clearly exhibiting selective loss of adipose tissue, patients are also at risk for abnormalities such as insulin resistance, hyperinsulinemia, type 2 diabetes mellitus, hyperlipidemia, glomerulonephritis, and autoimmune disorders. Advances in molecular biologic techniques have allowed greater understanding of the molecular mechanisms underlying the clinical features as well as the myriad metabolic and endocrinologic abnormalities that are associated with these acquired and inherited syndromes. This chapter provides an overview of the various types of acquired and inherited lipodystrophies.

## ACQUIRED LIPODYSTROPHIES

### Epidemiology

The acquired lipodystrophies are more common than the inherited forms but are still quite rare. They include human immunodeficiency virus (HIV) infection-associated lipodystrophy (HIV-L), acquired partial lipodystrophy (APL), acquired generalized lipodystrophy (AGL), and localized lipodystrophy.

HIV-L has become the most common form of lipodystrophy and is rapidly increasing in prevalence as more patients receive highly active antiretroviral therapy (HAART) and survive long term with HIV infection. The incidence of this complication increases with duration of therapy and affects one-third to two-thirds of patients treated for 1 year or longer. The exact prevalence of HIV-L is unknown, but at least 100,000 patients in the United States have this form of acquired lipodystrophy.<sup>1</sup> APL is much less common. Approximately 250 patients of various ethnic origins (male-female ratio of 1:4) have been found to have APL since it was first described by Mitchell, Barraquer, and Simons more than 100 years ago.

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Even more rare is AGL, which has been reported in approximately 80 patients, most of whom are Caucasian (male-female ratio of 1:3).

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## LIPODYSTROPHY AT A GLANCE

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- · Acquired:

- 1. o
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- · Inherited:

- 1. o Familial partial [Dunnigan type, peroxisome proliferator-activated receptor- $\gamma$  (PPAR- $\gamma$ )-associated] lipodystrophy: autosomal dominant mutation in LMNA gene or PPAR- $\gamma$ .
- 2. o Congenital generalized (Berardinelli-Seip) lipodystrophy: autosomal recessive mutation in AGPAT2 (type 1) or Seipin gene (type 2).
- 3. o
- 4. o

#### Human Immunodeficiency Virus Infection-Associated Lipodystrophy

#### ETIOLOGY AND PATHOGENESIS

Soon after the introduction in the mid-1990s of HAART for the treatment of patients with HIV disease, redistribution of body fat in treated patients was reported. Although the incidence of HIV-L clearly increased markedly after the introduction of protease inhibitors (PIs), there are also cases in patients treated with nucleoside reverse transcriptase inhibitors (NRTIs) as well as in patients receiving combinations of the two. Rarely, cases are seen in treatment-naive HIVpositive individuals.

The pathogenesis of HIV-L is unknown and is likely multifactorial. Risk factors consistently observed in cohort studies include increasing age, use of certain types of medication, current use of antiretroviral therapy (excluding non-NRTIs), and longer total duration of such therapy. In particular, combination therapy using two NRTIs and a PI is associated with more severe disease.<sup>3,4</sup> Hierarchical effects of responsible drugs have not been established because it is

difficult to identify specific effects of individual drugs when patients are receiving multidrug therapy with agents from different classes.

PIs may induce lipodystrophy by inhibiting several lipid and adipocyte regulatory proteins. These include sterol regulatory element-binding protein 1c and peroxisome proliferator-activated receptor- $\gamma$  (PPAR- $\gamma$ ).<sup>5</sup> In vitro studies have shown PIs both to inhibit lipogenesis and adipocyte differentiation and to increase lipolysis.

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NRTI-induced lipodystrophy may be due to mitochondrial injury.

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NRTIs inhibit adipogenesis and promote lipolysis as is observed with PIs and therefore demonstrate strong synergistic toxicity with PIs in vitro and in vivo.

Other factors that may increase the risk of developing lipodystrophy have been suggested but are less clear. These include gender, diagnosis of acquired immunodeficiency syndrome, low body weight before therapy, and better therapeutic response to HAART, as measured by rapid recovery of peripheral blood CD4<sup>+</sup> lymphocytes and decreased HIV RNA levels.<sup>5</sup> In addition, changes in fat distribution have been reported in a limited number of HIV patients who were never treated with antiretroviral therapy, but HIV-L is far more common in treated patients, which argues against HIV infection itself as a strong factor.

## CLINICAL FINDINGS

As early as several months after institution of HAART, HIV-infected individuals may begin to develop loss of subcutaneous fat from the face and extremities. Facial lipoatrophy leads to an emaciated appearance with loss of buccal fat, triangular depression below the cheekbone, nummular depression at the temples, and a seemingly protuberant mouth due to the surrounding atrophy. Several rating scales are available to grade the severity of facial atrophy, which can be classified as mild, moderate, or severe. Fat increases at the posterior neck and upper back, which results in a "buffalo hump" similar to that seen in patients with Cushing disease. Fat may also increase in the abdomen, with increased waist-hip ratio and feelings of bloating and distention ("protease paunch" or "crix belly"), as well as in the breasts, sometimes with marked pain. Insulin resistance and impaired glucose tolerance often develop, progressing in some cases to frank diabetes

mellitus, hypertriglyceridemia, and hypercholesterolemia. This constellation of metabolic abnormalities is clearly associated with accelerated atherosclerosis in the non-HIV population, so it is expected that HIV-infected individuals may also be at increased risk for cardiovascular disease.

Acquired Partial Lipodystrophy (Barraquer-Simons, "Classic" Partial)

## ETIOLOGY AND PATHOGENESIS

Although the pathogenesis of APL is unclear, C3 levels are decreased in up to 90 percent of patients. Associated with this decrease is the presence of C3 nephritic factor, a circulating polyclonal immunoglobulin G that blocks degradation of the enzyme C3 convertase, which allows unopposed activation of the alternative complement pathway and increased consumption of C3. Furthermore, serum containing C3 nephritic factor has been shown to be toxic to adipocytes in vitro, which suggests that this factor contributes directly to the loss of fat.<sup>10</sup> Factor D is another protein (identical to a serine protease, adipsin) that is produced by adipocytes and is also a key component of the alternative pathway. In the presence of C3 nephritic factor, the alternative pathway becomes dysregulated, which leads to hypocomplementemia and direct adipocyte loss, possibly of those adipocytes that express Factor D.

Approximately 20 percent of patients with APL develop membranoproliferative glomerulonephritis after a median of approximately 8 years after the onset of lipodystrophy.<sup>12</sup> The aforementioned serologic abnormalities may also be found in patients with glomerulonephritis without APL, and currently the weight of evidence favors the hypothesis that the nephritic factor predisposes to glomerulonephritis via direct toxicity and/or hypocomplementemia.

<sup>13,14</sup>

Also, because APL often occurs after a febrile illness, it remains to be shown whether there may be a viral trigger leading to autoimmunity.

## CLINICAL FINDINGS

APL (Barraquer-Simons syndrome) develops in most patients before the age of 15 years, most often between 8 and 10 years of age. Patients show gradual loss of subcutaneous fat in clearly

demarcated, generally symmetric areas of the body. The loss usually begins on the face and spreads downward, and may stop at any point, most often just at or above mid-thigh level. Occasionally, the lower portion of the body may be affected while the upper portion remains uninvolved. The unaffected part of the body often appears obese, partly due to the contrast with the gaunt appearance of the thin portion. Excess fat deposition over the hips and thighs frequently occurs in postpubertal women with APL.

The face appears cachectic. Buccal fat pads disappear, leaving a relative prominence of the chin and zygomas. With loss of retro-orbital and periorbital tissue, the eyes may sink deeply into the sockets. Smiling produces many wrinkles and a prematurely aged expression. Unshielded by the usual blanket of fat, the veins and muscles of the trunk and upper extremities appear hypertrophied. The overlying skin itself is of normal color, texture, and elasticity. Visceral fat stores underlying the thin areas are also absent.

A clinically apparent inflammatory phase does not precede the fat loss, but patients often correlate the onset with an acute febrile illness. In addition to the glomerulonephritis mentioned earlier, other autoimmune diseases have been described in association with APL, including systemic lupus erythematosus and dermatomyositis.<sup>12</sup> In general, APL patients develop insulin resistance less frequently than patients with the generalized lipodystrophies.

### Acquired Generalized Lipodystrophy (Lawrence Syndrome)

## ETIOLOGY AND PATHOGENESIS

The exact etiology and pathogenesis of AGL are unknown. In approximately 25 percent of patients, onset of fat loss is preceded by the development of subcutaneous inflammatory nodules. Histologic evaluation of the nodules demonstrates a granulomatous reaction with a mixed lymphohistiocytic infiltrate and multinucleated giant cells, findings consistent with panniculitis. These nodules heal with localized loss of the subcutaneous fat underlying them, followed by generalized loss of all subcutaneous fat. These patients have less severe fat loss and metabolic dysfunction than is seen in the other forms of AGL. Another 25 percent of patients have associated autoimmune diseases, particularly juvenile dermatomyositis,<sup>2, 16</sup> and it is thought that their fat loss is likely immune mediated. The remaining 50 percent of patients (with an idiopathic variety) have neither panniculitis nor associated autoimmune diseases, and other pathogenic mechanisms are likely involved.

## CLINICAL FINDINGS

The clinical findings of AGL are similar to those of congenital generalized lipodystrophy (CGL), but onset of fat loss is later and associated features are more mild. The patient's loss of fat may be extremely rapid and typically occurs in childhood or adolescence. Subcutaneous fat loss is severe and usually affects the face, abdomen, and extremities but has also been shown to involve the palms and soles and in some cases the intra-abdominal region.<sup>2</sup> Children often have a voracious appetite and acanthosis nigricans. Hepatic steatosis is commonly present, which may lead to hepatomegaly. Most AGL patients have significant metabolic derangements as well as low levels of high-density lipoprotein cholesterol and low levels of the key adipocytokines leptin and adiponectin, which are involved in adipocyte production and migration. Diabetes mellitus and hypertriglyceridemia are less prevalent in the panniculitis variety than in the idiopathic and autoimmune varieties.

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## Localized Lipodystrophy

Localized lipodystrophy is the loss of subcutaneous fat in small areas of the body, often due to exogenous causes. Injection of drugs such as insulin, steroids, or antibiotics can cause localized lipodystrophy.<sup>17</sup> It can also be pressure induced or can develop in the location of resolved panniculitis. A centrifugal type of localized lipodystrophy has been described in children that spreads in a band around the abdomen. The etiology is unknown, and it was self-limited in half of the patients described.

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## INHERITED LIPODYSTROPHIES

### Epidemiology

The inherited lipodystrophies are rare entities. The familial partial lipodystrophies (FPLs) are a heterogeneous group of disorders with autosomal dominant inheritance. The most common is the Dunnigan variety, which has been identified in over 200 patients, primarily of European descent, since it was first described over 30 years ago.<sup>18</sup> The FPL associated with the PPAR- $\gamma$  mutation (see next section) has been reported in 10 patients since it was first described in 2002.<sup>19</sup>

Lipodystrophy associated with mandibuloacral dysplasia shows autosomal recessive inheritance and has been demonstrated in approximately 40 patients since its initial description in 1971.

CGL has autosomal recessive inheritance and has been reported in approximately 250 patients of various ethnic origins. With allowance for incomplete reporting of cases, the estimated prevalence of CGL is 1 in 10 to 12 million people.

Familial Partial Lipodystrophies (Dunnigan Type, Peroxisome Proliferator-Activated Receptor- $\gamma$  Associated)

## ETIOLOGY AND PATHOGENESIS

The locus for the Dunnigan variety has been mapped to chromosome band 1q21-22, which led to the identification of a missense mutation in the gene encoding lamins A and C (LMNA gene)<sup>2</sup>

and subsequent identification of other missense mutations within this gene. The nuclear lamins belong to the family of intermediate filament proteins that are attached to the inner surface of the nuclear envelope. Adipocyte loss in patients with LMNA mutations is likely due to disruption of nuclear function and loss of structural integrity of the nuclear envelope, which leads to cell death. Other mutations in the same gene can cause autosomal forms of muscular dystrophy, dilated cardiomyopathy, Charcot-Marie-Tooth neuropathy, and mandibuloacral dysplasia. These individuals develop multisystem involvement in addition to the lipodystrophy, depending on the site of mutation within the gene.

For dermatologists, the most important disorder that results from mutations in lamin A is progeria (Hutchinson-Gilford progeria syndrome). Generalized lipodystrophy in progeria is progressive and spares only the intra-abdominal fat deposits. Other features include very short stature, poor weight gain, early alopecia, scleroderma, osteolysis with decreased joint mobility, and premature aging. Lipodystrophy is the presenting sign in approximately 20 percent of



patients.<sup>24</sup> The mean age at diagnosis is approximately 3 years, although subtle features are detectable during the first 6 months of life. Cerebral vascular accidents and coronary artery dysfunction are the most common cardiovascular problems and tend to be the cause of death at a mean age of 12.6 years. Classic progeria is an autosomal dominant disorder, although virtually all cases result from spontaneous mutation. The late-onset or non-classic form of progeria is associated with a more slowly progressive lipodystrophy, as well as less retardation of growth, longer persistence of scalp hair, and survival into adulthood. This non-classic form of progeria is distinct from Werner syndrome and is most likely autosomal recessive.

## CLINICAL FINDINGS

In patients with the Dunnigan variety of FPL due to LMNA mutation, the fat loss of the extremities and trunk begins at puberty and is accompanied by fat deposition on the face, upper back, and intra-abdominal region as well as increased intermuscular fat in the arms and legs.<sup>30</sup> Affected men are often more difficult to identify than women because normal men are often quite muscular at baseline. Although some fat is maintained, the acanthosis nigricans and metabolic complications of insulin-resistant diabetes, coronary heart disease, and hyperlipidemia in these patients more closely resemble those of patients with general lipodystrophy rather than partial lipodystrophy. These metabolic abnormalities are more common in women than in men with FPL.

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The 10 patients who have been described with FPL due to the PPAR- $\gamma$  mutation showed loss of subcutaneous fat from the distal extremities that began after the second decade of life.

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## Congenital Generalized Lipodystrophy (Berardinelli-Seip)

## ETIOLOGY AND PATHOGENESIS

Patients with CGL cluster in consanguineous families, most of whom have linkage evidence of abnormalities at two loci: the 1-acyl-glycerol-3-phosphate-O-acyltransferase 2 (AGPAT2) gene on chromosome band 9q34<sup>33,34</sup> (CGL type 1) and the Berardinelli-Seip congenital lipodystrophy 2 (BSCL2) or seipin gene on chromosome band 11q13<sup>35</sup> (CGL type 2).

The AGPATs are involved in the biosynthesis of glycerophospholipids and triglycerides.<sup>36</sup> Therefore, defective AGPAT2 function in CGL type 1 may cause lipodystrophy either by reducing the amount of triglyceride in adipocytes or by reducing levels of glycerophospholipids, which causes defective cell signaling and membrane function. This theory is supported by the fact that metabolically active fat is affected in this syndrome but mechanical fat is normal because of the presence of other AGPAT isoforms in mechanical fat that likely counterbalance the defective AGPAT2 product.

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The seipin gene encodes a protein with unknown function. However, seipin's strong expression in normal brain tissue and absent expression in normal adipose tissue supports the hypothesis that the central nervous system is involved in the pathogenesis of CGL type 2.<sup>1</sup> Furthermore, there is higher prevalence of mental retardation in these patients. Patients with CGL type 2 lose both metabolically active and mechanical fat.

## CLINICAL FINDINGS

Patients with CGL have nearly absent subcutaneous fat from birth and are therefore born with a muscular appearance. The loss of fat is similar to that described for AGL, but it occurs much earlier and is more severe than in the acquired form. Because of the generalized absence of fat at birth, the muscles appear hypertrophic. However, the age at which the child sits and walks is usually normal, and muscle strength is not increased.<sup>38</sup> During infancy and childhood, linear growth is accelerated, and adult height may be greater than that predicted by the height of the parents. Most patients have a prominent umbilicus or umbilical hernia. Patients develop marked acanthosis nigricans in the neck, axilla, groin, and trunk, usually beginning in childhood.

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Focal lytic lesions have been shown to develop after puberty in the appendicular bones, which may be due to loss of bone marrow adipose tissue.

Daily energy consumption is increased noticeably. Children eat voraciously, perspire excessively, have an elevated basal metabolic rate, and are often heat intolerant despite normal thyroid function. Girls with CGL may develop hirsutism, clitoromegaly, and

oligomenorrhea or amenorrhea during puberty, and some may have frank virilization and polycystic ovarian disease. Some women have had successful pregnancies, but this is rare. Fertility is normal in men. Moderate mental retardation is frequent but not universal.

Characteristically, patients have decreased glucose tolerance, and the syndrome is often termed lipoatrophic diabetes, which usually starts in puberty. Hyperglycemia, glycosuria, and insulin resistance are often marked, requiring high doses of insulin for glucose control. Renal, retinal, and neuropathic diabetic changes may occur. Severe hypertriglyceridemia may lead to recurrent pancreatitis. As in AGL, leptin and adiponectin levels are markedly decreased.

Nearly all patients with GL have hepatomegaly, which results initially from increased fat in the liver, although the fat around the viscera is reduced. As with fatty liver resulting from other causes, cirrhosis may develop, and the patient may die of hepatic failure. Hypertrophic cardiomyopathy has also been seen in some patients.

CGL is also a feature of leprechaunism (also called Donohue syndrome).<sup>40</sup> This rare autosomal recessive disorder results from mutations in the insulin receptor (19p13.2). In addition to the generalized decrease in subcutaneous fat, clinical features include severe intrauterine growth retardation; small, elfin facies with protuberant ears; distended abdomen; relatively large hands, feet, and genitalia; thickened skin with acanthosis nigricans; and hypertrichosis. Affected individuals die during the first decade—most during the first months of life.

## TREATMENT

Treatment of the various types of lipodystrophy has proven quite difficult. The focus of treatment depends on the severity of the associated metabolic and endocrinologic abnormalities as well as the cosmetic effect of loss of subcutaneous fat in some areas and gain of fat in others in a disproportionate fashion. The major morbidity of these syndromes is due to the long-term sequelae of diabetes, dyslipidemia, and hepatic steatosis. However, the psychological side effects of facial lipodystrophy cannot be underestimated—particularly in patients with HIV, because it has often been the cause of discontinuation of critical HAART.

Aggressive glycemic control should be the focus of therapy in patients with diabetes and hyperinsulinemia associated with these syndromes. The goal of treatment is to decrease the

risk of development or slow the progression of neuropathy, nephropathy, and retinopathy. Glycemic control also leads to markedly decreased triglyceride levels, which in turn prevent pancreatitis and hepatic steatosis. Adherence to a verylow-fat diet, exercise, and consumption of  $\omega$ -3 fatty acids are logical to consider in all types of lipodystrophy. However, medications are often required. Metformin decreases insulin resistance and reduces appetite, and therefore may be a good oral hypoglycemic. Rosiglitazone is another oral hypoglycemic that is a PPAR- $\gamma$  agonist and may be beneficial in patients with mutations in PPAR- $\gamma$ . However, only two cases of its use have been reported (in patients with mutations in LMNA rather than PPAR- $\gamma$ ), and results have been equivocal. Avandamet, a combination of rosiglitazone and metformin, may also be effective. Unfortunately, lipodystrophy patients often require high doses of insulin in addition to, or as a better alternative to, oral hypoglycemics. Fibrates (PPAR- $\alpha$  agonists) and statins are often used to treat hypertriglyceridemia if it persists despite glycemic control, proper diet, and exercise. Experimental use of subcutaneous recombinant leptin led to significant improvement in mouse models<sup>43</sup> and was shown to significantly improve glycemic control and decrease triglyceride levels in nine female patients with lipodystrophy with minimal side effects.

Treatment of HIV-infected individuals with lipodystrophy is an increasingly important issue due to the number of patients receiving HAART who have developed this syndrome and the fact that facial lipodystrophy is rapidly becoming the hallmark look of HIV disease. In some patients, the cosmetic and symptomatic changes of HIV-L are so debilitating that they desire changes in their HIV drug regimens or, worse, they discontinue treatment altogether. Changes between or within classes of drugs may ameliorate the disease, and combinations that avoid the use of two PIs or a PI and an NRTI may slow the development of the complications of diabetes and dyslipidemia. Although the use of hypoglycemics, lipid-lowering medications, and other medications such as growth hormone-releasing hormone may be associated with improvement in intra-abdominal fat deposition and metabolic abnormalities, leading to reduction of risk of complications, the available options have not led to cosmetically significant re-accumulation of facial or limb fat.

Cosmetic procedures may be a useful adjunct to treatment of lipodystrophy, particularly in HIV-L. Liposuction of the upper back may reduce the cosmetic disfigurement of the buffalo hump. Fillers have now become more widely used to compensate for facial fat loss. These include permanent and temporary dermal fillers, such as transferred autologous fat, bovine collagen, hyaluronic acid, calcium hydroxyapatite (CaHa), liquid injectable silicone, polymethylmethacrylate, and injectable polyalkylamide gel in addition to other injectable polymers. In general, autologous fat transfer is less successful in HIV patients because there is often a dearth of fat available for transplantation at truncal donor sites, and the character and consistency of this fat may reduce its viability at the recipient site. Poly-L-lactic acid (PLA) is a longer-acting, prepackaged filler that has been approved by the U.S. Food and Drug Administration for the treatment of facial lipoatrophy in HIV patients and leads to expansion of the thickness of the dermis by stimulating fibroblasts.<sup>47</sup> Injectable CaHa can also provide cosmetically significant benefit for at least a year in the face. Like PLA, CaHa is completely biodegradable, and it is preferred by some patients and physicians because it does not require

reconstitution or multiple treatments. Also, the cosmetic effect of CaHa begins immediately and is not delayed for several months as with PLA .

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