Diagnosis and treatment

Uncommon lipodystrophic syndromes

Síndromes lipodistróficos infrecuentes

Cristina Guillín-Amarelle, Sofia Sánchez-Iglesias, David Araujo-Vilar

* Servicio de Endocrinología e Nutrición, Complejo Hospitalario Universitario de Santiago de Compostela, Departamento de Medicina, Instituto de Investigaciones Sanitarias de Santiago-Universidade de Santiago de Compostela, Santiago de Compostela, A Coruña, Spain

b Grupo de Patología Molecular-UETeM, CIMUS, Universidade de Santiago de Compostela, Santiago de Compostela, A Coruña, Spain

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Introduction

Lipodystrophies are disorders characterised by a total or partial loss of adipose tissue. Sometimes the fat loss in certain areas of the body is accompanied by an increase of body fat in other areas.

Excluding lipodystrophy related to antiretroviral drug therapies in aids, the rest of lipodystrophic syndromes are extremely infrequent. Its prevalence is estimated to be around 1:40,000 and a few dozens, according to the subtypes. On the other hand, most cases start at birth, during childhood or in adolescence, and are a diagnosis challenge for the clinician, given its low prevalence.

Classification

Fat loss may be generalised, partial or localised, and these symptoms may be genetic or acquired (Table 1).

Diagnosis

The diagnosis in lipodystrophic syndromes lays in a thorough clinical assessment, mainly focused on the extent of the loss of adipose tissue, onset age, progression of the fat loss and, in the case of partial forms, identification of body areas with lipohypertrophy. It is relatively frequent to observe a marked emphasised venous tree (flebomegaly) in lipoatrophic limbs, as well as a hypermuscular appearance which sometimes corresponds to a clear muscular hypertrophy. Due to the frequent association with a severe insulin resistance (IR), the presence of acanthosis nigricans is not infrequent, even in unusual areas of the body (for instance, abdomen), and in the most severe forms we usually observe abdominal distension caused by fatty liver. Certain clinical signs are characteristic of certain subtypes of lipodystrophy and may help the diagnosis, such as acromegalooid features in the case of the Berardinelli-Seip syndrome, or signs of premature ageing (the latter in progeroid syndromes). Although they do not appear in all forms, metabolic alterations (diabetes mellitus, hypertriglyceridaemia) and non-alcoholic steatohepatitis are not infrequent. The presence of similar clinical symptoms in the patient’s family is very helpful for genetic forms, especially in autosomal dominant forms, but also in recessive syndromes, and the existence of consanguinity must be investigated.

In genetic cases, the diagnosis for certainty is reached through molecular studies, provided they are mutations already known, although in more than 50% of the cases the responsible gene is not identified.

Assessment of natural history, morphotype and distribution of adipose tissue

Generalised lipodystrophies

Congenital generalised lipodystrophy or Berardinelli–Seip syndrome

Congenital generalised lipodystrophy (CGL) is an autosomal recessive disorder diagnosed at birth or during the first year of life. These children have characteristic clinical manifestations: generalised absence of adipose tissue, coarse and triangular facies, well defined muscles which gives them a muscular appearance, flebomegaly and distended abdomen related to hepatomegaly (Fig. 1). Umbilical hernias are frequent. The rate of growth is accelerated, although the final size will be consistent with parental...
Hypertrichosis is also frequent (Fig. 1F), although it tends to disappear over time. Depending on the case, it is usual to observe acanthosis nigricans, which usually worsens over the years. Over time, acrochorda usually appear, in general in the neck and armpits (Fig. 1E). Although there may be suction problems during the first months, the appetite is characteristically voracious. The absence of fat affects both subcutaneous and visceral fat, while there will be mechanical and retro-orbital fat according to the subtypes. As they grow, facial features tend to accentuate, acquiring an acromegaloïd facial appearance (Fig. 1B and C). Likewise, the muscular appearance worsens with age, and muscular hypertrophy is common, especially in gastrocnemius muscles (Fig. 1G).

The prognosis is conditioned by hepatic, metabolic and cardiac complications. Without treatment, patients may die prematurely due to severe acute pancreatitis, and before the age of 60 due to complications of diabetes or cirrhosis.

**Acquired generalised lipodystrophy or Lawrence syndrome**

Typically recognised during childhood or adolescence, frequently after an infection, with progressive loss of adipose tissue affecting the face, limbs, buttocks and abdomen, with variable changes in intra-abdominal fat (Fig. 2); intramedullary and retro-orbital deposits are preserved, and the fat loss in palms and soles is variable. The loss of adipose tissue may be rapid (weeks) or extend over the years with periods of stagnation. From childhood, affected individuals have a voracious appetite, acanthosis nigricans and hepatic steatosis, and may develop diabetes mellitus (Fig. 2B, C and F). Acquired generalised lipodystrophy (AGL) has been classified based mainly on clinical attributes: AGL associated with autoimmune disorders (≈25% of cases), AGL associated with panniculitis (≈25% of cases) and idiopathic form (≈50%). In one out of four cases, panniculitis (which appears clinically as subcutaneous inflammatory nodules) precedes the fat loss. The autoimmune form is associated with diseases such as juvenile dermatomyositis and autoimmune hepatitis, which proves that AGL is an autoimmune disease in itself, and in some patients, low levels of C4 have been detected.

**Partial lipodystrophies**

**Familial partial lipodystrophy**

This is, in most cases, an autosomal dominant disorder, and therefore the identification of relatives with the same phenotype is critical for the diagnosis. Due to the particular distribution of the adipose tissue and the age of onset, affected males are usually diagnosed after the women in the family. Characteristically, patients with familial partial lipodystrophy (FPL) start the phenotype during puberty, mainly in the classical form of Dunnigan disease (FPL type 2), linked to mutations in LMNA. However, there have been descriptions of patients with fat loss starting in adulthood, generally associated with mutations in PPARG (FPL type 3).

The loss of adipose tissue affects the limbs, buttocks and hips, while an accumulation of fat in the face, jowl, armpits and supra-spinacular region is observed, although in certain subtypes (FPL type 3), facial fat accumulation is less frequent. Subcutaneous deposits in the torso are variable, while visceral fat is preserved (Fig. 3). In Köberling syndrome (FPL type 1) there is a clear accumulation of trunk subcutaneous fat and patients are usually obese.

The absence of fat in patients with FPL gives them a hypermuscular appearance, and superficial veins are very visible. The presence of IR is premature, and its severity will condition the appearance of acanthosis nigricans.

**Acquired partial lipodystrophy or Barraquer–Simons syndrome**

The symptoms usually start during childhood or adolescence, although cases of onset in adulthood have been described, and it is much more frequent in women (8:1). The affected individuals show a loss of adipose tissue in the face, neck, upper limbs, thorax and upper half of the abdomen, with a cephalo-caudal trend.
Fig. 2. Acquired generalised lipodystrophy or Lawrence syndrome. (A) Phenotypic evolution of a girl with Lawrence syndrome. Fat loss began at 3 years old, affecting lower limbs and buttocks, progressively extending to the torso and, finally, the face, although in a less pronounced way. (B) Acanthosis nigricans in this patient’s armpit. (C) Abdominal distension caused by hepatomegaly and umbilical hernia in this patient. (D) Flebomegaly in limbs. (E–G) Pronounced fat loss in the torso, buttocks and limbs.

Fat deposits in glutei, hips and lower limbs (including soles of the feet) are preserved or may even be excessive, especially in women. The loss of fat in the palms is variable, but no retro-orbital or medullary fat loss has been reported. This disorder has been frequently associated with autoimmune diseases such as systemic lupus erythematosus, dermatomyositis, hypocomplementaemia and membranoproliferative glomerulonephritis, the latter affecting one out of five patients. Subjects with renal disease develop lipodystrophy earlier than those who do not have renal disease. More than 80% of patients have low C3 values and high C3 nephritic factor, which contributes to confirm the certainty diagnosis. Certain autoimmune or infectious diseases may act as triggers of this condition.1,2,7

The prognosis is conditioned by the evolution of the renal disease, when present, or cardiovascular complications of metabolic syndrome, although these last ones are much less frequent than those observed in other forms of lipodystrophy.

Localised lipodystrophies

Localised lipodystrophies are presented as focal subcutaneous fat losses, causing one or more depressions in the skin. In some
patients there may be large adjacent areas affected, or different patched areas in any part of the body. Localised lipodystrophy is usually related to subcutaneous injections of different drugs, pancreaticitis, pressure or other mechanisms (Table 1).8

Premature ageing syndromes

Hutchinson–Gilford progeria

This is the classical form of premature ageing and is associated with de novo heterozygous mutations in LMNA. The disease characteristically starts to manifest after the first year of life. Patients show a delay in growth, short stature, alopecia, osteolysis, characteristics of facial ageing, joint stiffness, abnormalities in teething, pointy nose, high-pitched voice, osteoporosis and generalised lipodystrophy affecting the limbs, face and torso, but preserved intra-abdominal deposits (Fig. 5). Patients usually die before 15 years of age due to myocardial infarction or stroke.9

Fig. 4. Acquired partial lipodystrophy (APL) or Barraquer–Simons syndrome. (A) Evolution of the fat loss in a patient from 5 to 10 years old. Fat loss began at 6 years and a half, shortly after suffering from bacterial pneumonia, initially affecting the face. (B) APL on a 10 and a half-year old girl: fat loss initially affecting the face and neck, then extending to the pectoral girdle. At that age the patient had no other complications, even though complement C3 values were low.

Mandibuloacral dysplasia

Mandibuloacral dysplasia (MD) is an extremely rare autosomal recessive disorder appearing in early childhood and characterised by multiple skeletal anomalies (acro-osteolysis, clavicular resorption and mandibular hypoplasia, which cause retrognatia and depressed shoulders), progeroid features (skin atrophy with marked superficial vasculature and mottled hyperpigmentation, slim pointy nose and alopecia), delay in teething and fontanelle closure, dental crowding and joint stiffness. There are 2 types of lipodystrophy: a (partial, with fat loss in the limbs, not in the neck and torso) and B (generalised).10,11

Werner syndrome

Recessive condition characterised by short stature and progeroid features of late onset (middle childhood–adolescence), such as premature ageing, cataracts, cutaneous manifestations of scleroderma and osteoporosis. Also, these patients have lipodystrophy affecting the torso, face and limbs, high-pitched voice, bird-like facial appearance with pointy nose, hypogonadism, muscle atrophy in the limbs, calcification of blood vessels and premature death (third-fourth decade) due to cardiovascular disease or cancer. The typical habit is short stature, appearance of ageing, slim limbs and robust torso.12

Atypical Werner syndrome and other progeroid syndromes associated with mutations in LMNA

Certain, and generally de novo, heterozygous LMNA gene mutations cause premature ageing different to the classical Hutchinson–Gilford progeria syndrome (HGPS). In all of these conditions there is lipodystrophy, although in a variable degree, from generalised forms to partial forms affecting only distal extremes of the limbs.

Table 1

<table>
<thead>
<tr>
<th>Classification of non-frequent lipodystrophic syndromes.</th>
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<tbody>
<tr>
<td><strong>Genetic</strong></td>
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<tr>
<td>Generalised</td>
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<tr>
<td>Berardinelli–Seip syndrome (CGL)</td>
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<tr>
<td>Type 1: mutations in ACMAT2</td>
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<tr>
<td>Type 2: mutations in ESCLD2</td>
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<td>Type 3: mutations in CAV1</td>
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<td>Type 4: mutations in PTRF</td>
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<tr>
<td>Partial</td>
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<tr>
<td>Familial partial lipodystrophy</td>
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<tr>
<td>Type 1 or Köbberling syndrome: no recognised genes</td>
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<tr>
<td>Type 2 or Dunnigan syndrome: mutations in LMNA</td>
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<td>Type 3: mutations in PPARC</td>
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<td>Type 4: mutations in PLIN1</td>
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<td>Type 5: mutation in CIDEC</td>
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<tr>
<td>Due to mutations in AKT2</td>
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<tr>
<td>Associated with muscular dystrophy</td>
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<tr>
<td>Premature ageing syndromes</td>
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<td>Hutchinson–Gilford progeria: mutations in LMNA</td>
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<tr>
<td>Mandibuloacral dysplasia</td>
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<td>Type A: due to mutations in LMNA</td>
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<td>Type B: due to mutations in ZMPSTE24</td>
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<td>Werner syndrome: mutations in RECQL2</td>
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<tr>
<td>Atypical progeria and atypical Werner’s syndrome: mutations in LMNA</td>
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<tr>
<td>Néstor-Guillermo progeroid syndrome: mutation in BAVFT1</td>
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<tr>
<td>Neonatal progeroid syndrome or Wiedemann–Rautenstrauch syndrome</td>
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<tr>
<td>MDPL syndrome: mutation in POLD1</td>
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<td>ALDD syndromes</td>
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<tr>
<td>Nakajo–Nishimura syndrome: due to mutations in PSMB8</td>
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<td>JUMP syndrome: due to mutations in PSMB8</td>
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<tr>
<td>CANDLE syndrome: due to mutations in PSMB8</td>
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<tr>
<td>Other syndromes which are hard to classify</td>
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<tr>
<td>SHORT syndrome: due to mutations in PIR3R</td>
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<td>Congenital disorders of glycosylation due to mutations in PMM2-CDG</td>
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<tr>
<td>Mutations in FBN1 associated with Marfan syndrome</td>
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<tr>
<td><strong>Acquired</strong></td>
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<tr>
<td>Generalised</td>
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<tr>
<td>Lawrence syndrome</td>
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<tr>
<td>Partial</td>
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<tr>
<td>Barraquer–Simons syndrome</td>
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<tr>
<td>Localised</td>
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<tr>
<td>Drug-related</td>
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<tr>
<td>Glucocorticosteroids</td>
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<tr>
<td>Postinjection: insulin, somatostatin analogues, pegvisomant</td>
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<tr>
<td>Lipoatrophy semicircularis</td>
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<td>Panniculitis-induced lipodystrophy</td>
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ALDD: autoinflammation, lipodystrophy, and dermatosis syndrome; CANDLE: chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature syndrome; JUMP: joint contractures, muscular atrophy, microcytic anaemia, and panniculitis-induced lipodystrophy; CGL: congenital generalised lipodystrophy; MDPL: mandibular hypoplasia, deafness, progeroid features and lipodystrophy; SHORT: short stature, hiperextensibility of joints, oculare depression, Rieger (ocular and dental), anomaly, and teething delay.
The so-called atypical Werner syndrome shows symptoms similar to the classic form of this condition, though with some differences. In general, the onset of the first signs (premature greying) is at earlier ages, and the progression of the disease is more accelerated in atypical forms than in the classical form. Cases have also been described as associated to dyslipidaemia, hepatospleno-megaly, cardiomyopathy, joint contractures and leucomelanodermic papules; however, the phenotypic heterogeneity is large. In general terms, these patients have short stature, premature greying, lipodystrophy and appearance of ageing.

The atypical progeroid syndrome (APS) is related to LMNA mutations, mostly de novo in heterozygosis. These patients show progeroid signs such as short stature, pointy nose, premature greying, partial alopecia and high-pitched voice, in addition to skin lesions (mottled hypopigmentation and scleroderma-like changes, mostly in the back of the hands and feet), but no acanthosis nigricans. Other characteristics that may appear are: mandibular hypoplasia, mild clavicular resorption, acro-osteolysis, dental crowding and ogival palate. Many patients have contractures affecting elbows, wrists, knees and ankles. In more than 50% of cases valvular heart disease has also been described, and, based on our experience, one case of severe dilated cardiomyopathy which required a heart transplant (Fig. 5). Lipodystrophy is of a variable degree, from generalised and severe to only partial, affecting the limbs, and medullary fat is always preserved. Although the phenotype is heterogeneous, there are characteristics distinguishing it from HGPS and AMD. In contrast to these 2 syndromes, there is minimum or no acro-osteolysis in PAS, affecting distal phalanges, and mandibular hypoplasia is rare or mild. Alopecia is barely relevant. The beginning of clinical symptoms is more delayed than for HGPS or AMD, and, at least as regards HGPS, the survival rate is higher.

Néstor-Guillermo progeria syndrome

This is an autosomal recessive disorder that begins manifesting from 2 years old, with delay in growth, short stature, partial alopecia, but preserving eyebrows and eyelashes, ocular protrusion, generalised lipodystrophy, severe osteolysis affecting jaws, clavicles, ribs and phalanges, dental crowding, joint stiffness, delay in fontanelle closure, loss of nasal bridge, appearance of ageing with dry wrinkled skin, mottled pigmentation, severe scoliosis and valve disease. Laboratory studies only revealed a vitamin D2 deficit and severe hypoleptinaemia. Unlike HGPS and AMD, these patients did not have metabolic alterations, hepatic steatosis or atherosclerosis.

Neonatal progeroid syndrome

Also called Wiedemann–Rautenstrauch syndrome, this condition follows an autosomal recessive inheritance pattern, although its molecular bases are unknown to date. Affected children show progeroid characteristics since birth, generalised lipodystrophy and cranial deformities.

Mandibular hypoplasia, deafness, progeroid features and lipodystrophy syndrome

Disorder characterised by mandibulo-acral hypoplasia, hearing loss, progeroid manifestations, undescended testicles, male hypogonadism and generalised lipodystrophy. Some women show scarce breast development. This syndrome is caused by de novo mutations of heterozygosis in the gene POLD1.

Autoinflammation, lipodystrophy and dermatosis syndromes

Nakajo–Nishimura syndrome

This condition begins in early childhood as erythema pernio and nodosum, slim face, partial lipo-muscular atrophy, long fingers,
febrile crises and joint contracture. They may present micro-
cytic anaemia, hepatosplenomegaly, basal ganglia calcification and hypergammaglobulinaemia.18

**Joint contractures, muscular atrophy, microcytic anaemia, and panniculitis-induced lipodystrophy syndrome**

Characterised by joint contractures, muscular atrophy, micro-
cytic anaemia and panniculitis-induced generalised lipodystrophy. Other characteristics are intermittent fever, hypergammaglobu-
laemia, increase of sedimentation rate, hepatosplenomegaly and basal ganglia calcification.19

**Chronic atypical neutrophilic dermatosis syndrome with lipodystrophy and elevated temperature syndrome**

Recessive condition beginning during childhood with recurrent fever and annular violaceous plaques on eyelids and lips, evolving through childhood to subcutaneous fat loss in the face and upper limbs. They also present hepatosplenomegaly, arthralgia, micro-
cytic anaemia, increase in sedimentation rate and basal ganglia calcifications.20

It seems reasonable to deduce that these 3 syndromes, all associated with *PSMB8* mutations, are clinical variations of the same disorder.

**Metabolic and hepatic complications**

In general, the more adipose tissue loss, the more severe the metabolic complications associated with these conditions are. Most lipodystrophy conditions are presented with hypertriglyceridaemia, which, if severe, may cause acute pancreatitis episodes and/or eruptive xanthomas, and low levels of cholesterol with high-density lipoproteins. IR is usually associated with alterations in metabolism of glucose, from altered basal blood sugar levels, glucose intolerance or gestational diabetes, to clear nonketotic diabetes mellitus, which is very common in generalised lipodystrophies, especially after the first decade of life. In general, controlling diabetes is difficult. Non-alcoholic steatohepatitis is frequent, and may evolve into hepatic cirrhosis in adulthood in generalised lipodystrophies. Plasma leptin and adiponectin levels go from undetectable in generalised lipodystrophies to low in partial forms in relation to the body mass index.

**Cardiovascular complications**

As expected, the association of atherogenic dyslipidaemia and diabetes mellitus increases the cardiovascular risk in these patients.21 Besides, 25% of patients with type 2 CGL (due to BSCL2 mutations) present hypertrophic cardiomyopathy, while type 4 CGL, due to PTRF mutations, is associated with rate disorders including long-QT, exercise-induced ventricular tachycardia and sudden death.22 In some patients with type 2 FPL (due to LMNA mutations) we observed valve disease, hypertrophic cardiomyopathy and heart rate disorders.23

**Neurological complications**

In addition to an increased risk of stroke in most of these condi-
tions, 80% of patients with type 2 CGL have a mild–moderate mental disability,24 as well as hyperactivity and attention deficit during early childhood. Our group has recently described a vari-
ation associated with the BSCL2 gene that presents with a lethal neurodegenerative condition in middle childhood.25

**Musculoskeletal complications**

In some cases of type 1 CGL (due to mutations in *AGPAT2*), there are focal lytic lesions in appendicular bones after puberty, although there is no increase in the risk of fracture.24,25 Type 4 CGL is associated with other conditions, such as myopathy, percussion-induced myoedema, pyloric stenosis and atlantoaxial instability.22,27 Gastrocnemius muscle hypertrophy is a character-
istic feature, except for progeroid conditions, autoinflammatory syndromes and Barraquer–Simons syndrome.2 A new type of FPL associated with muscular dystrophy has been recently described,28 though its metabolic bases are unknown.

**Other complications**

In CGL, women may present clitoromegaly, polycystic ovary syn-
drome (POS), hirsutism and menstrual disorders, and gestation is an exception.29 Sexual function in males with these conditions is nor-
mal and they are fertile, although some cases of hypogonadism have been reported.1,29 In type 2 FPL, we can also observe POS, increase in the abortion rate and perinatal mortality (although the reproduc-
tive capacity is normal),30 hypoplastic breasts, rough hands with short fingers, encapsulated lipoma31 and muscle pains.

**Complementary tests**

Although the disappearance of adipose tissue is evident, it is advisable to confirm it in patients with diagnosis of suspected partial or generalised lipodystrophy, not only via pylemetry, but also through imaging tests (DEXA, magnetic resonance imaging). Likewise, potential metabolic complications shall be assessed through the corresponding plasma determinations of basal glu-
cose, haemoglobin A1c, and fractional cholesterol, as well as plasma transaminase, insulin and leptin levels. In acquired partial lipodys-
trophy cases, plasma complement C3 and C4, and nephritic factor levels shall be assessed, as well as urine protein and kidney function, in addition to monitoring the appearance of membranoproliferative glomerulonephritis.

Potential heart complications shall be assessed via EKG/Holter and echocardiogram. The abdominal ultrasound can will allow identification of hepatic steatosis.

**Molecular diagnosis**

To date, 17 loci associated to infrequent lipodystrophy syn-
dromes have been described (Table 2). All CGL subtypes are recessive disorders, while FPL subtypes are dominant conditions, except for the type associated with *CIDEC*.32 Progeroid syndromes are usually caused by de novo mutations of heterozygosis, although there are recessive forms.

**Treatment**

These conditions have no cure and the treatment addresses its complications, in addition to cosmetic treatment.

Since adipose tissue recovery is not possible, plastic surgery may improve appearance, but should only be indicated once the develop-
ment is complete. Lipohypertrophic areas can be treated with liposuction or lipoectomy, although recurrence is frequent,33 while lipoatrophic areas may be treated with autologous transplant of adipose tissue, if feasible, or with fillings with certain polymers such as polyactic acid or polycrylamide gel to improve facial appearance.34 Patients with Berardinelli–Seip syndrome may be subject to reconstructive facial surgery.
To improve metabolic complications, all patients should be advised to follow a diet of low animal fats and refined sugars to reduce hypertriglyceridaemia and the risk of acute pancreatitis; but in children and teenagers the amount of proteins shall not be reduced, and the caloric intake shall warrant a proper growth and development. Physical exercise, especially aerobics, is advisable to improve IR, although patients with lipodystrophy associated with LMNA mutations and cardiomyopathy should avoid exhausting exercises. Drug therapies for metabolic complications will depend on the age of the patients. In children, when hypertriglyceridaemia is significant (>500 mg/dl), fibrates and n – 3 fatty acids may be used, and in very severe cases, plasmapheresis may be used to treat eruptive xanthomas and reduce the risk of pancreatitis. If there is diabetes mellitus, the only drugs authorised for paediatric age are insulin and la metformin. The latter is a first line drug in children older than 12 years. In patients over 18 years old, pioglitazone may be associated as sensitiser, taking into consideration that not only does it increase adipose tissue in lipotropic areas but it may also increase it in lipohypertrrophic areas. The use of traditional secretagogues associated with metformin is only indicated for adults. The same occurs with agonists of the GLP1 receptor, which in the case of FPL may help to lose weight. Many patients with generalised lipodystrophy (and not few with FPL) need insulin therapy, generally in large doses. When insulin doses exceed 200 UI/day, U-500 insulin should be used. Recombinant human leptin drastically improves metabolic control, hypertriglyceridaemia and hepatic steatosis, especially in cases of generalised lipodystrophy. The use of this hormone in elderly cases (from 2 years of age) in some cases also improves physical appearance and acanthosis nigricans. Our group has been treating several patients with familial lipodystrophies with this hormone for 5 years with excellent results in generalised forms. Recombinant human leptin has been authorised last year in Japan (Japanese Ministry of Health, Labour and Welfare), and more recently by the U. S. Food and Drug Administration for its used in CGL and AGL, but not yet by the European Medicines Agency, and therefore its use in Spain is compassionate. The drug is well tolerated, with no relevant adverse events described, with the exception of 3 cases of lymphoma in patients with Lawrence syndrome.

Some adult patients with FPL have benefited from bariatric surgery, although generally they do not have a body mass index allowing treatment under the National Health System (Sistema Nacional de Salud).

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Conflict of interests
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