# Lipodystrophic syndromes: From diagnosis to treatment

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**Lipodystrophic syndromes : from diagnosis to treatment**
**Quand penser à un syndrome lipodystrophique et comment l'explorer ?**

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**Abstract**

Lipodystrophic syndromes are acquired or genetic rare diseases, characterized by a generalized or partial lack of adipose tissue leading to metabolic alterations linked to insulin resistance. They encompass a variety of clinical entities due to primary defects in adipose differentiation, in the structure and/or regulation of the adipocyte lipid droplet, or due to immune-inflammatory aggressions, chromatin deregulations and/or mitochondrial dysfunctions targeting adipose tissue. Diagnosis is based on clinical examination, pathological context and its comorbidities, and on results of metabolic investigations and genetic analyses, which together influence care procedures and genetic counseling. Early lifestyle and dietary measures focusing on regular physical activity and controlling energy intake are crucial. They are accompanied with a multidisciplinary follow-up adapted to each clinical form. For glycemic control, antidiabetic medications, with metformin as a first-line therapy in adults, are used in addition to lifestyle and dietary modifications. When standard treatments have failed, the orphan drug metreleptin, an analog of leptin, can be efficient for the treatment of metabolic complications in selected cases of lipodystrophy syndromes. Metreleptin therapy indications, prescription and monitoring were recently defined in France, representing a major improvement for patient care and outcomes.

**Résumé**

Les syndromes lipodystrophiques sont des maladies rares caractérisées par un déficit généralisé ou partiel du tissu adipeux corporel induisant secondairement des troubles métaboliques liés à une insulino-résistance marquée. Ces maladies, d'origine génétique ou acquise, regroupent des entités cliniques très diverses, dues à des altérations de la différenciation adipocytaire, de la formation et/ou de la régulation de la gouttelette lipidique adipocytaire, mais aussi à des agressions immuno-inflammatoires, des dérégulations chromatiniennes, et/ou des dysfonctions mitochondriales ciblant le tissu adipeux. Le diagnostic est basé sur l'examen clinique, l'analyse du contexte pathologique, la recherche d'atteintes associées, les explorations métaboliques et les analyses génétiques, qui orientent les modalités de prise en charge et le conseil génétique. L'instauration précoce de règles hygiéno-diététiques privilégiant l'exercice physique et évitant tout apport énergétique excédentaire est essentielle, avec un suivi multidisciplinaire adapté à chaque forme clinique. En cas d'hyperglycémie, les traitements antidiabétiques, avec en priorité chez l'adulte la metformine, sont utilisés en complément des mesures hygiéno-diététiques. Lorsque les traitements habituels ne suffisent pas à contrôler les troubles métaboliques, la metreleptine, un médicament orphelin analogue de la leptine, peut être efficace dans certaines formes de syndromes lipodystrophiques, Les indications, les modalités de prescription et de suivi du traitement par la metreleptine ont été récemment définies en France, ce qui représente une avancée majeure pour la prise en charge des patients.

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**Keywords** : lipodystrophy, insulin resistance, hypertriglyceridemia, metreleptin, genetics
**Mots-clés** : lipodystrophie, insulino-résistance, hypertriglycéridémie, metreleptine, génétique

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## Introduction

Lipodystrophic syndromes are genetic or acquired rare diseases, characterized by a lack of adipose tissue or a lack of adipose development leading to metabolic disorders associated with often severe insulin resistance, hypertriglyceridemia and hepatic steatosis. In France, the prevalence of lipodystrophic syndromes is estimated between 1/1 000 000 to 1/100 000 depending on generalized or partial forms. The discovery of lipodystrophy-causing variants has revealed that the structural and functional integrity of adipose tissue are essential for systemic glucose-lipid homeostasis. Advances in molecular genetics of lipodystrophy show that adipose tissue dysfunction can have very different origins. In addition, the clinical expression and severity of lipodystrophic diseases are gender-dependent, more specifically in familial partial lipodystrophy subtypes. The diagnosis of lipodystrophic syndromes extends to multi-organ pathologies. Investigations must be specifically oriented to improve disease management.

## Clinical diagnosis of lipodystrophic syndromes

Lipodystrophic syndromes are clinically heterogenenous diseases, that present as generalized or partial forms and may be familial or sporadic, associated or not with several comorbidities. They may be congenital or have a progressive clinical expression manifesting from adolescence to adulthood. Clinical assessment must include a thorough family and medical history and physical examination, looking for a deficit of subcutaneous body fat, generalized or partial but also for consequences of metabolic and endocrine complications (*acanthosis nigricans*, hepatomegaly, hirsutism). Less frequent associated manifestations, including dysmorphism, neuropathy, muscular, cardiac, digestive, inflammatory and/or premature aging signs may be important in orientating towards a specific etiology.

Subcutaneous adipose tissue loss is suspected after careful clinical examination, in the absence of undernutrition. Patients often exhibit hyperphagia due to leptin deficiency secondary to the fat deficit. At the extremities, an increased visibility of subcutaneous veins, (sometimes incorrectly qualified as “veinomegaly”), and increase of muscular reliefs, are often the first signs for suspecting a lipoatrophy (Figure 1). An evaluation of skinfold thickness, measured using a Harpenden caliper, appraises the loss of adipose tissue (less then 5mm in the absence of skin thickening).

Bichat's fat pad atrophy secondary to facial lipoatrophy gives a cachectic appearance. Bone structures can be exacerbated (prominent supraciliary arches and cheekbones) or be hypertrophic, leading to an acromegaloid morphotype due to the growth factor effect of

hyperinsulinemia, which is major in some patients. In generalized forms of lipoatrophy, the loss of mechanical adipose tissue (from palmoplantar or articular regions) favors ingrown toenails and static disorders of the feet (loss of fat pads on feet) [1]. In generalized congenital lipodystrophy (CGL), which are autosomal recessive diseases due to developmental adipocyte abnormalities (defects in differentiation and/or formation of adipocyte lipid droplet) (Table), infants show a generalized lipoatrophy associated with an important muscular hypertrophy. Nevertheless, even if metabolic disorders (insulin resistance, hypertriglyceridemia, hepatic steatosis) are precocious, they can be of favorable evolution in infancy under dietary measures only [2]. However, the disease can lead to atypical diabetes or episodes of acute pancreatitis in pubertal or post-pubertal period, so that the diagnosis of congenital generalized lipodystrophy can therefore, at times, be made by adult physicians. Other forms of "acquired" generalized lipodystrophy appear in a context of immune dysfunctions, such as organ-specific or systemic autoimmune diseases [3].

This review will not address the issue of generalized or partial lipodystrophy secondary to anti-retroviral therapy for HIV infection, which are less severe nowadays thanks to new therapeutic molecules, although most patients present with metabolic sequelae of the initial antiretroviral treatments [4].

In partial forms of lipoatrophy, the abnormal body fat distribution dominates the clinical picture, especially in women. Lipoatrophic regions frequently co-exist with zones of fat accumulation. In Barraquer-Simons syndrome which mostly affects women, the face and trunk are lipoatrophic whereas adipose tissue accumulates in the lower part of the body [3]. Conversely, the familial partial lipodystrophy, Dunnigan type (FPLD2) is characterized by a lipoatrophy of the limbs associated with facio-cervical adiposity (round face, double chin, supraclavicular fullness, "buffalo hump") giving patients a cushingoid morphotype. Nevertheless, the absence of skin fragility and the often-marked muscular hypertrophy direct the diagnosis toward a lipodystrophic syndrome rather than hypercortisolism. FPLD2 is inherited in an autosomal dominant manner and is generally noticed clinically from the pubertal period onwards. In affected women, in addition to the facial appearance, the accumulation of fat tissue deposited in the suprapubic and vulvar areas, are described as embarrassing. The android morphotype (bi-acromial diameter greater than bi-trochanteric diameter) with enlarged and infiltrated extremities (hands and feet), hypomastia, and signs of hyperandrogenism, may also be a reason for medical consultation. Thus, although this disease affects as much men as

women, diagnosis is easier in women (Figure 2). In addition, the metabolic complications in Dunnigan syndrome are also more common and severe in women than in men [5]. On the whole, the characteristic clinical picture makes it possible to clearly differentiate a Dunnigan syndrome from a "banal" metabolic syndrome with android morphotype. In particular, in Dunnigan syndrome, there is no or little accumulation of subcutaneous adipose tissue in the abdomen, the muscular hypertrophy is important, and, although a body mass index above 25 kg/m$^2$ should not be an exclusion criterion for the diagnosis, patients have a normal weight in the majority of cases [6]. In other etiological forms of partial lipodystrophic syndromes (Table), limb lipoatrophy is similar to that observed in Dunnigan syndrome, but in most cases, there is no characteristic cushingoid appearance. An acromegaloid morphotype may draw attention in other partial lipodystrophies with a different etiology [7,8].

A specific clinical presentation is observed in Launois-Bensaude lipomatosis (also known as Multiple Symmetric Lipomatosis; MSL) which is characterized by the development of pseudo-lipomatous fat masses in the neck, upper trunk and proximal upper limbs [9-11] (Figure 3). An autosomal recessive form, due to specific biallelic mutations in the *MFN2* gene has been recently discovered. *MFN2* encodes mitofusin-2, a mitochondrial fusion protein previously involved in Charcot-Marie-Tooth neuropathy. This *MFN2*-related form of MSL is very rare and mostly identified in consanguineous families. It can be classified as a lipodystrophic syndrome as a striking lipoatrophy of non-lipomatous areas is associated with metabolic complications such as insulin resistance, impaired glucose tolerance, hypertriglyceridemia, and hepatic steatosis. This contrasts with the most frequent form of MSL, linked to excessive alcohol consumption, which is not described with an associated lipoatrophy. In addition, patients with *MFN2*-associated MSL also present with a Charcot-Marie-Tooth neuropathy, characterized by a four-limb peripheral sensitive-motor axonal neuropathy of early onset, although of very heterogeneous severity.

Finally, other very rare etiological forms of lipodystrophic syndromes can be suspected from physical examination. In Hutchinson-Gilford progeria, or in progeroid syndromes clinically expressed in adolescence or adulthood, the general aspect suggests accelerated aging. Patients present with lipoatrophy associated with short stature and specific dysmorphic signs including bird-beaked nose, retrognatism, alopecia and/or clavicular hypoplasia, joint retractions, precocious cataracts, depending on the etiological subtype [12-14].

Some systemic auto-inflammatory syndromes associated with fever and multi-organ dysfunction affect not only skin, joints and heart, but also adipose tissue, resulting in a generalized lipoatrophy and insulin resistance [15].

**Metabolic abnormalities associated with lipodystrophic syndromes**

If there is a clinical suspicion of a partial or generalized lipodystrophy, it is necessary to look for associated metabolic abnormalities, to confirm the diagnosis. Indeed, the decrease in the capacity of adipose tissue to store the dietary energy surplus as triglycerides leads to both the clinical lipoatrophy, and to an ectopic lipid infiltration of non-adipose tissues (muscle, liver, pancreas) responsible for lipotoxicity. In conjunction with the endocrine defect of adipose tissue (decreased production of leptin and adiponectin), lipotoxicity induces abnormalities of insulin signal transduction ("post receptor" insulin resistance) with increased hepatic glucose production, hypertriglyceridemia and hepatic steatosis (Figure 4). This pathophysiology initiated by adipocyte dysfunction has been well demonstrated in mouse models of impaired adipocyte development, which recapitulate metabolic abnormalities observed in human lipodystrophic syndromes. Unlike wild-type mice, lipoatrophic mice do not gain weight in response to a high-fat diet but store ectopic lipids, particularly in the liver, and develop insulin resistance, hyperglycemia and hypertriglyceridemia [16]. Remarkably, the transplantation of functional adipose tissue corrects this metabolic phenotype [17].

Dual energy x-ray absorptiometry, which quantifies total and segmental fat mass, is useful to determine the severity of lipoatrophy and the regional distribution of fat. As an example, the percentage of global fat mass, as assessed by DEXA, is about 5 to 8% in patients with CGL [2], and was estimated at 20±5.5% in 39 women with FPLD2 as compared to 33.5±5.9% in 17 healthy women matched for age and BMI [6]. The serum leptin level, which is strongly correlated to total body fat, also helps to establish the diagnosis and is important regarding current therapeutic options (see below) [1]. However, it should be noted that the production of leptin is higher in subcutaneous than in visceral adipose tissue, and that circulating levels of leptin better reflect subcutaneous than visceral fat mass [18]. Patients with generalized lipodystrophies exhibit a profound leptin deficiency and in partial forms of lipodystrophies, serum leptin is relatively low with respect to body mass index.

Insulin resistance is habitually clinically reflected clinically in *acanthosis nigricans*, a hyperkeratotic and pigmented skin lesion occurring in large body folds (from axillary, inguinal,

cervical regions). *Acrochorda* (skin tags), in the same localizations, are considered semiological equivalents (Figure 5).

Biologically, assessment of fasting glucose and insulin levels can be sufficient to diagnose insulin resistance in a non-obese, non-diabetic patient. When a lipodystrophic syndrome is discovered in a patient with diabetes, the absence of specific autoantibodies associated with type 1 diabetes, a preserved insulin secretion (as assessed by peptide C levels), and/or the requirement of high insulin doses (> 2U/kg/day) are suggestive of insulin resistance (Figure 6). An oral glucose tolerance test can improve diagnosis, demonstrating post-stimulatory hyperinsulinemia and/or revealing impaired glucose tolerance. Over time, beta pancreatic cell dysfunction can appear and insulin resistance could thus become more difficult to demonstrate, except with the use of dynamic metabolic measures of insulin resistance (intravenous hyperglycemia, hyperinsulinemic euglycemic clamp, graded glucose infusion test) [19].

The lipid profile of affected patients typically shows a hypertriglyceridemia with low HDL-cholesterol. This metabolic dyslipidemia, which, when severe, can lead to episodes of acute pancreatitis, is common in insulin resistance states owing to abnormalities of insulin pathway signaling downstream of the insulin receptor, as is the case in lipodystrophic syndromes (Figure 4). In contrast, insulin resistance as a result of proximal defects in the insulin signal transduction pathway, in the case of abnormal insulin receptor or proximal signaling intermediates, is usually not accompanied by hypertriglyceridemia, nor hepatic steatosis [20-22]. The absence of hypertriglyceridemia associated with major insulin resistance can suggest these differential diagnoses of lipodystrophic syndromes. Measurements of serum adiponectin, sex hormone-binding globulin (SHBG), and/or insulin growth factor binding protein-1 (IGFBP1) which are low in lipodystrophic syndromes but normal or elevated in primary dysfunctions of the insulin receptor, can also be used as diagnostic indicators [23].

Hyperandrogenism of ovarian origin, of variable severity, is commonly associated with insulin resistance, and may be the initial reason for consultation in some women with lipodystrophic syndromes. Polycystic ovarian syndrome, or ovarian hyperthecosis, evolve in parallel to the insulin resistance due to the activation of the ovarian IGF1 receptor in response to massive circulating insulin concentrations [24,25]. The ovarian phenotype is nevertheless complex, especially in generalized lipodystrophies, due to the profound deficit in leptin secondary to lipoatrophy that may lead to a partial gonadotropic insufficiency [26,27]. Clinical examination

and exploration of the hypothalamic-pituitary-ovarian axis through biological testing and imaging are essential. The issue of contraception must be addressed and prescription of ethinyl estradiol should be avoided. Ethinyl estradiol is formally contra-indicated in case of pre-existing dyslipidemia, history of pancreatitis, or if an increase of circulating lipids, which should be very carefully monitored, occurs under treatment. Genetic counseling should be offered regarding the question of fertility and transmission of the disease [28].

Liver steatosis, resulting from both hyperinsulinemia and ectopic lipid storage, is an early complication in a lipodystrophy syndrome [2]. It is often at the forefront of the clinical picture in infants with congenital generalized lipodystrophy and should be carefully monitored as it may progress to cirrhosis with portal hypertension and hepatic insufficiency [29]. The potential risk of hepatocellular carcinoma also justifies periodic ultrasound screening.

**Specific clinical context in lipodystrophic syndromes**

Most lipodystrophic syndromes are associated, not only with the metabolic abnormalities described above, but also with other manifestations demonstrating multi-tissue involvement. Moreover, a lipodystrophic syndrome, associated with specific additional signs or pathological context, can reveal complex systemic diseases.

Bone involvement is not unusual in congenital generalized lipodystrophies (CGL) and occurs generally in the form of osteolytic cysts, which are usually asymptomatic but may help with diagnosis [30]. Moderate mental retardation and early hypertrophic cardiomyopathy are common in CGL2, due to pathogenic variants of *BSCL2* encoding seipin, a protein involved in the formation of the adipocyte lipid droplet [31]. In some rare forms of CGL2, a severe neurodegenerative syndrome has been described, related to abnormal protein aggregation in neurons [32]. The phenotype of CGL4 associated with bi-allelic mutations in *CAVIN1/PTRF* encoding cavin-1, is complex. CGL4 associates a lipodystrophic syndrome with muscular dystrophy, which can be at the forefront of symptomatology, but may also include cardiomyopathy with arrhythmia, and digestive signs, some of them being related to pyloric stenosis [33].

The example of laminopathies illustrates well the challenges of multiple clinical presentations of lipodystrophic syndromes. Indeed, diseases related to mutations in the *LMNA* gene, encoding type A lamins (ubiquitous nuclear intermediary filaments) can lead to familial partial

lipodystrophy, Dunnigan type (FPLD2) described above, but also, depending on the genotype, to a number of other clinical entities [34,35]. Certain monoallelic or bi-allelic variants of the *LMNA* gene lead to a partial or generalized lipoatrophy as part of accelerated aging syndromes (Hutchinson-Gilford progeria, acro-mandibular dysplasia, or atypical progeroid syndromes) characterized by facial dysmorphism, bone and cartilage abnormalities, alopecia, cutaneous trophic disorders in extremities, tendon retractions, and very early atherosclerosis with calcifications of arteries and/or heart valves. Other variants of *LMNA* are responsible for skeletal and/or cardiac muscular dystrophies, neuropathies, and to mixed phenotypes with neuromuscular signs, cardiomyopathies and/or progeroid signs [12,13,26]. Several pathophysiological mechanisms are involved in laminopathies. In particular, some variants of the *LMNA* gene impair the interactions of lamin A with chromatin, modifying the expression of genes involved in the differentiation of tissues of mesodermal origin, such as adipose tissue, muscles, bone, artery walls. This may explain the multiple pathological associations observed in laminopathies [37]. In practice, although the result of the molecular analyses makes it possible to predict, to a certain degree, the clinical type of laminopathy, it is nevertheless essential to search for other organ involvements that may be associated [1]. Echocardiography and Holter-ECG are recommended to detect potential cardiomyopathy associated to laminopathic lipodystrophy [38]. Indeed, cardiomyopathies associated with *LMNA* pathogenic variants may require the implantation of a defibrillator to avoid potentially life-threatening paroxysmal arrhythmias [39]. In addition, it is also necessary to plan tests for early detection of coronaropathy, as atherosclerosis can appear very early in Dunnigan syndrome and in other *LMNA*-associated lipodystrophies, probably modulated by environmental and other inherited factors [40]. Finally, probably due to epigenetic changes secondary to mutations in the *LMNA* gene that are both transmitted in families and sensitive to current environmental metabolic stress, it is noted that metabolic complications of laminopathies are earlier and more severe in younger generations [41]. This justifies pre-symptomatic genetic screening in pre-adolescents from families with laminopathic lipodystrophies, in order to provide patients with hygiene and dietary advices aiming to delay metabolic complications, and to screen for associated disorders as soon as possible [41].

Other lipodystrophic syndromes develop in the context of systemic dysimmune diseases (systemic lupus, scleroderma, and others) or of organ-specific auto-immune disorders (thyroiditis, auto-immune hepatitis, and others) [42]. These « acquired » lipodystrophies could be due to anti-adipose tissue autoantibodies, which however cannot be routinely investigated

today. In favor of this hypothesis, is the presence of autoantibodies directed against perilipin-1, an adipocyte lipolysis regulatory protein located on the lipid vacuole wall, observed in some patients with generalized forms of lipoatrophy occurring in a more general autoimmune context [43]. Anti-adipose tissue autoimmunity may also be associated with complex dysimmunity syndromes, possibly of genetic origin [44,45]. Barraquer-Simons syndrome, in which lipoatrophy of the upper body is associated with adipose tissue accumulation in the lower part of the body, is associated with glomerulopathic features, proteinuria and complement abnormalities in 20% of cases, which also suggest that impaired immune functions contribute to the pathophysiology [3].

Certain autosomal recessive systemic auto-inflammatory syndromes of pediatric onset, characterized by recurrent fever, and articular, cutaneous, hepatic, muscular, cardiac, cerebral and hematological manifestations, are accompanied by a lipoatrophy. Several clinical forms have been associated with homozygous pathogenic variants of the *PSMB8* gene, encoding a catalytic subunit of the immunoproteasome, a multimeric protease involved in protein degradation and in the production of peptides presented by MHC class I. Dysfunction of this pathway is accompanied by activation of pro-inflammatory signals and by inhibition of adipocyte differentiation *in vitro* [46]. Several auto-inflammatory syndromes of other genetic causes are also associated with lipodystrophy [15,47,48].

Lipodystrophy has also been reported following total body irradiation in patients treated with hematopoietic stem cells transplantation for hematologic malignancies. In agreement with what has been shown in mice [49], total body irradiation decreases differentiation capacities of adipocyte precursors in humans [50].

**Contribution of genetic analysis in diagnosis and management of lipodystrophic syndromes.**

The discovery of genes responsible for lipodystrophic syndromes has revealed the importance of energy storage capacities and endocrine functions of adipose tissue in systemic metabolic homeostasis (Figure 4, Table). The list of genes responsible for lipodystrophic syndromes continues to increase, and today there are more than 25 different genes whose pathogenic variants are responsible for monogenic forms of these syndromes. The overall clinical presentation and the recognition of lipodystrophy-associated co-morbidities contribute to prioritize genetic analyses. Family history of lipodystrophy, which is often underdiagnosed, but also of atypical diabetes (early, severe, unclassified, in a non-obese person), severe

dyslipidemia, spontaneous muscle hypertrophy, or hyperandrogenism in women suggest an autosomal form of lipodystrophic syndrome. Another important issue is parental consanguinity, either known or suspected, for example in case of endogamy (parents from neighboring villages) that would favor an autosomal recessive form of lipodystrophic syndrome. Some forms of lipodystrophy are more frequently associated with certain ethnic backgrounds. A specific *LMNA* pathogenic variant is associated with a complex form of laminopathy with co-dominant transmission in patients originating from the Reunion Island [35]. Some *BSCL2* CGL-causing variants have an ancestral Lebanese, Norwegian, or Hispanic origin, whereas a founder variant was identified in Northeast Brazil [29, 32]. Some *AGPAT2* pathogenic variants are more specifically observed in patients originating from Africa [31].

The genetic diagnosis of lipodystrophy is essential, as it allows to guide further investigation, patient monitoring and therapeutic options. Once diagnosis has been confirmed in the index case, family screening will allow to identify other disease carriers in a timely manner, avoiding diagnosis being made in sometimes dramatic circumstances (acute pancreatitis revealing an unknown hypertriglyceridemia for example).

**Treatment of lipodystrophic syndromes: initial measures**

Lipodystrophic syndromes are complex diseases requiring multidisciplinary management. At a metabolic level, no current therapeutic intervention is able to restore adipose tissue function in lipoatrophic zones. The management of insulin resistance is difficult, primarily based on the introduction of dietary and lifestyle rules, as early as possible after diagnosis, even in the absence of obvious metabolic alteration, focusing on regular physical activity and avoiding any excess energy supply [1].

In infants the use of medium-chain triglycerides oil formulas is often effective in limiting hypertriglyceridemia [2]. Patients should be educated on the importance of regular physical activity, which significantly improves insulin sensitivity. First-line non-specific therapeutic regimen includes the treatment of diabetes, dyslipidemia and related complications [1]. Metformin is used as a first-line therapy. Although GLP1 receptor agonists have not been specifically evaluated in the context of these rare diseases, they could be useful in treating hyperglycemia and reducing hyperphagia associated with leptin deficiency. The use of this therapeutic drug class is nevertheless limited to patients who have no major hypertriglyceridemia nor a history of acute pancreatitis.

The use of ultra-concentrated insulin analogs is useful when patients have very high daily insulin requirements. Fibrates are prescribed in case of significant hypertriglyceridemia. Synthetic estrogens are contraindicated because of the risk of hypertriglyceridemia. Affected patients, even before developing diabetes, are at high risk of cardiovascular disease and the use of statins is often required to reduce LDL-cholesterol below 1g/L. A cardiological follow-up must be systematically introduced and management must be adapted to cater the specific co-morbidities that exist in each etiological form [1].

The stigmatizing morphotype of patients can be a source of significant psychologic distress. The use of injectable fillers (volumizing facial fillers in particular) and/or plastic surgery (liposuction, surgical removal of adipose tissue, autologous adipose tissue injection) could be helpful. The patient association dedicated to lipodystrophy in France, AFLIP (Association Française des Lipodystrophies/ French Association of Lipodystrophies) offers support to patients and their families.

**Metreleptin replacement therapy in severe forms of lipodystrophic syndromes**

The use of recombinant leptin (metreleptin), in the context of leptin deficiency secondary to lipoatrophy, has not been studied in placebo-controlled studies in patients with lipodystrophic syndromes. Nevertheless, and although it does not improve lipodystrophy itself, it has been shown that metreleptin counteracts ectopic lipid storage, both by reducing hyperphagia, which is often difficult to manage in leptin-deficient lipodystrophy patients, and by activating insulin sensitizing pathways independent of decreased food intake [51]. Metreleptin improves insulin sensitivity and reduces hypertriglyceridemia, hyperglycemia and hepatic steatosis, and it has also been shown to improve insulin secretion [19]. The efficacy of metreleptin is better in generalized forms of lipoatrophy than in partial forms [52]. In accordance, in case of partial lipodystrophy, metreleptin could be proposed mainly to patients with severe metabolic alterations (HbA1c >8%, and/or hypertriglyceridemia >5g/L) and a pre-therapeutic serum leptin of less than 4 ng/mL [1,52]. Metreleptin obtained a European Marketing Authorization in 2018, for the treatment of metabolic complications associated with leptin deficiency in lipodystrophy patients, in addition to dietary measures, from 2 years of the age in congenital generalized lipodystrophy, and from 12 years of age in partial forms of lipodystrophy when standard first-line treatments failed to achieve sufficient metabolic control (Figure 6). These indications received a favorable opinion from the Transparency Commitee of HAS (French National Health Authority) in February 2019, who recommended this therapeutic option to be

validated and regularly re-evaluated at the national multi-disciplinary consultation meetings of the Rare Disease Reference Center PRISIS (Pathologies Rares de l'Insulino-Sécrétion et de l'Insulino-Sensibilité/Rare Diseases of Insulin Secretion and Insulin Sensitivity), and that treated patients are referred to a 'PRISIS' affiliated center at least once a year [53].

Metreleptin is administered as a daily subcutaneous injection. Patients have to learn how to prepare the solution for injection and how to correctly dose the product into a syringe, which may limit adherence with therapy [54]. The metreleptin dose, up to 10 mg/day (1 vial per day) is adapted to metabolic responses and to tolerance. Main side effects include local reactions at injection sites and hypoglycemia at the beginning of treatment, requiring anticipating a reduction of insulin doses. Metreleptin therapy usually results in weight loss, which is part of the therapeutic effect. The development of anti-leptin autoantibodies is common, but they are exceptionally neutralizing.

Very rare cases of lymphoma have been reported in patients with acquired generalized lipodystrophy treated with metreleptin. The underlying dysimmune pathology, responsible for pre-existing hematologic abnormalities of treatment in two of three described cases, was considered a significant risk factor, but the exact role of metreleptin on tumoral growth remains unknown. A post marketing surveillance register is planned. The price and terms of reimbursement of metreleptin are currently being evaluated by the National Health Authority in France.

**Conclusion**

Lipodystrophic syndromes are rare but very heterogenous diseases, associating adipose tissue deficiency and metabolic disorders with insulin resistance. Thorough clinical examination and research of metabolic abnormalities are the basis of the diagnosis. Genetic diagnosis can guide the search of specific co-morbidities, improve disease management, and allow to detect and treat affected relatives as soon as possible. Multi-disciplinary follow-up is essential. The management of metabolic complications requires first and foremost, the early introduction of hygiene and dietary measures, with regular physical exercise and no excessive food intake. The use of metreleptin should be reserved for lipodystrophy patients in therapeutic failure.

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