How to diagnose a lipodystrophy syndrome

Comment diagnostiquer un syndrome lipodystrophique

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Abstract

The spectrum of adipose tissue diseases ranges from obesity to lipodystrophy, and is accompanied by insulin resistance syndrome, which promotes the occurrence of type 2 diabetes, dyslipidemia and cardiovascular complications. Lipodystrophy refers to a group of rare diseases characterized by the generalized or partial absence of adipose tissue, and occurs with or without hypertrrophy of adipose tissue in other sites. They are classified as being familial or acquired, and generalized or partial. The genetically determined partial forms usually occur as Dunnigan syndrome, which is a type of laminopathy that can also manifest as muscle, cardiac, neuropathic or progeroid involvement. Gene mutations encoding for PPAR-gamma, Akt2, CIDEc, perilipin and the ZMPSTE 24 enzyme are much more rare. The genetically determined generalized forms are also very rare and are linked to mutations of seipin AGPAT2, FBNI, which is accompanied by Marfan syndrome, or of RAN1, which is characterized by a progeroid syndrome without insulin resistance and with early bone complications. Glycosylation disorders are sometimes involved. Some genetically determined forms have recently been found to be due to autoinflammatory syndromes linked to a proteasome anomaly (PSMB8). They result in a lipodystrophy syndrome that occurs secondarily with fever, dermatosis and panniculitis. Then there are forms that are acquired. They may be iatrogenic (protease inhibitors in HIV patients, glucocorticosteroids, insulin, graft-versus-host disease, etc.), related to an immune system disease (sequelae of dermatopolymyositis, autoimmune polyendocrine syndromes, particularly associated with type 1 diabetes, Barraquer-Simons and Lawrence syndromes), which are promoted by anomalies of the complement system. Finally, lipomatosis is currently classified as a painful form (adiposis dolorosa or Dercum’s disease) or benign symmetric multiple form, also known as Launois-Bensaude syndrome or Madelung’s disease, which are sometimes related to mitochondrial DNA mutations, but are usually promoted by alcohol. In addition to the medical management of metabolic syndrome and the sometimes surgical treatment of lipodystrophy, recombinant lepntin provides hope for

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Le spectre des pathologies du tissu adipeux s’étend des obésités aux lipodystrophies et s’accompagne d’un syndrome d’insulino-résistance, favorisant la survenue d’un diabète de type 2, d’une dyslipidémie et de complications cardiovasculaires. Les lipodystrophies représentent un groupe de maladies rares congénitales ou acquises caractérisées par une absence généralisée ou partielle du tissu adipeux, plus ou moins associée à une hypertrophie de ce tissu adipeux dans d’autres sites. Elles sont classées en formes familiales ou acquises, généralisées ou partielles. Les formes génétiquement déterminées partielles correspondent le plus souvent au syndrome de Dunnigan, une forme de laminothmie qui peut également s’exprimer sous forme d’atteinte musculaire, cardiaque, neuropathique ou progeroïde. Les mutations des gènes codant pour PPAR-gamma, Akt2, CIDEC, pérlipine et l’enzyme ZEMPSTE 24 sont beaucoup plus rares. Les formes génétiquement déterminées généralisées sont également très rares et sont liées à des mutations de la seipine, d’AGPAT2, des désordres de la glycosylation, des mutations de FBN1 qui s’accompagnent d’un syndrome marfanoïde ou de BANF1 caractérisées par un syndrome progeroïde sans insulino-résistance et avec complications osseuses précoces. Certaines formes génétiquement déterminées ont été récemment rapportées à des syndromes auto-immunatoires liés au protéasme (PSMB8). Ils se traduisent par un syndrome lipodystrophique d’apparition secondaire dans un contexte fébrile de dermatose et de panniculite. Il existe enfin des formes considérées comme acquises. Celles-ci peuvent être iatrogènes (antiprotéases chez les patients HIV, glucocorticoïdes, insuliné, réaction greffon contre hôte...), liées à une pathologie dysimmunitaire (séquelles de dermatopolymyosite, polyendocrinopathies autoimmunes notamment associées au diabète de type 1, syndromes de Barraquer-Simons et de Lawrence) favorisées par des anomalies du complément. Enfin les lipomatoses sont actuellement classées en formes douloureuses (adiposis dolorosa ou maladie de Dercum) et formes multiples bénignes symétriques encore appelées syndrome de Launois-Bensaude ou de Madelung, parfois liées à des mutations de l’ADN mitochondrial, mais le plus souvent favorisées par l’alcool. Outre la prise en charge médicale du syndrome métabolique, et parfois chirurgicale de la lipodystrophie, la leptine recombinante apporte des espoirs dans les syndromes auto-immunatoires génétiquement déterminés, tandis que les modifications de traitement antirétroviral et la tesamoreline, un analogue du GHRH, est efficace dans le syndrome métabolique des patients HIV. D’autres pistes thérapeutiques seront sans doute développées en fonction des avancées physiopathogéniques qui tendent aujourd’hui à classer les lipodystrophies génétiquement déterminées en formes laminopathiques, d’une part, et formes liées à une pathologie de la gouttelette lipidique, d’autre part.

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1. Introduction

The spectrum of adipose tissue diseases is modified by quantitative, qualitative and distribution factors [1]. White adipose tissue disorders promote insulin resistance, type 2 diabetes, dyslipidemia and cardiovascular complications.

Anomalies in adipose tissue distribution, even when the total quantity is decreased (lipoatrophy versus obesity), are the cause of metabolic syndrome, particularly when the adipose tissue is located viscerally (compared to subcutaneous distribution), when it is predominant on the upper part of the body (compared to the lower part) and when it proves to be dystrophic (through inflammation, fibrosis, oxidative stress and hypoxia) in genetically determined or acquired syndromes [1].

The objective of this review is to help the clinician in the identification of lipodystrophy syndromes, which are not so rare, particularly within the type 2 diabetic population.

2. Adipose tissue

2.1. Composition

Adipose tissue is a highly vascular, innervated organ, which is made up of different cell types: adipocytes, as well as preadipocytes, endothelial cells, blood components and macrophages. By virtue of its ability to regulate fatty acid storage and to secrete numerous adipokines (leptin, adiponectin, tumor necrosis factor-alpha, interleukin-6, resistin, visfatin), adipocytes appear to be an essential endocrine cell for the control of energy metabolism and innate (through macrophages [2] and dendritic cells [3]) or adaptive (through T lymphocytes [4,5]) inflammatory and immune responses. Adipose tissue also promotes the aromatization of androgens into estrogens and has a mechanical supportive role, particularly on the soles of the feet and the buttocks.

2.2. White and brown adipose tissue

There are two subtypes of adipose tissue in mammals: white adipose tissue, which stores surplus energy in the form of triacylglycerols, and brown adipose tissue, rich in mitochondria characterized by the uncoupling protein 1 (UCP1) enzyme, which dissipates energy in the form of heat (endogenous thermogenesis). As with subcutaneous white adipose tissue, it has beneficial metabolic effects. There has been renewed interest in the study of brown adipose tissue since the FDG-PET scan studies showed this tissue was present in adults, particularly in the cervical, supraclavicular, mediastinal and interscapular regions. Glucose consumption in brown adipose tissue is indeed elevated, which explains its uptake on PET scan imaging. Moreover, its water content, which is also higher than in white adipose tissue, results in visible contrast on nuclear magnetic resonance (NMR), thus enabling its identification; this latter exam is less irradiating [6].

2.3. Differentiation of adipose tissue

Adipocytes originate from mesodermal stem cells, which also give rise to the muscular and cartilaginous cell lines. Certain
transcription factors, such as peroxisome proliferator-activated receptors (PPAR) or CCAAT/enhancer-binding protein (C/EBP) play a vital role in adipocyte differentiation.

2.4. Transdifferentiation of white and brown adipose tissue and muscle tissue

Brown adipose tissue can be generated in vitro from white adipose tissue preadipocytes (or at least PET scan negative adipose tissue) [7]. Conversely, recent studies have shown that the adipose tissue of patients with LMNA gene mutations or protease inhibitor-induced lipodystrophy accumulated prelamin A and underwent restructuring towards a brown adipose tissue phenotype, with overexpression of UCP1 and mitochondrial alterations [8]. The PRDM16 transcription factor is capable of controlling the cell fate between brown adipocytes and myoblasts and is an autonomous cellular differentiation determinant of brown adipose tissue in the subcutaneous white adipose tissue [9].

2.5. Role of muscle in insulin resistance

The role of the muscle in insulin resistance continues to be the subject of many research studies. It indeed involves more than the malfunctioning generated by intramuscular deposit of excessive triglycerides. Mitochondrial dysfunction [10], modification of intracellular signaling (AMP-activated protein kinase) [11], and specific proteins of the muscle and lipid droplets [12,13] appear to modify the insulin sensitivity of muscle.

3. Clinical diagnosis of lipodystrophy

3.1. Definition

Lipodystrophy refers to a group of rare congenital or acquired diseases that are characterized by the general or partial absence of adipose tissue, with a variable degree of hypertrophy of this adipose tissue in other sites. These distribution anomalies are the source of metabolic syndrome with insulin resistance, the distinctive features of which are shown in Fig. 1. The waist-to-hip ratio is not reliable here, since a certain number of lipodystrophy syndromes occur in the absence of clinically visible abdominal fat accumulation. Hypertriglyceridemia may be extremely severe, leading to acute pancreatitis with diabetic ketoacidosis. Hepatic steatosis is also very common and can be complicated by metabolic cirrhosis.

3.2. Classification

Lipodystrophy is classified as being familial or acquired, and generalized or partial (Table 1), but there are some exceptions. Certain genetically determined forms however can indeed appear only secondarily (at puberty in Dunnigan syndrome; after inflammatory episodes for monogenic autoinflammatory diseases). Some causes (autoimmune, laminopathic) may moreover induce forms of lipodystrophy that are either partial or generalized.

Table 1

Main lipodystrophic syndromes.

**Genetically determined or familial**

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial lipodystrophies with neck and face accumulation of fat (FPLD)</td>
<td>FPLD 2 or Dunnigan syndrome: autosomal dominant mutations of LMNA gene</td>
</tr>
<tr>
<td></td>
<td>FPLD 3: autosomal dominant mutations of PPAR (gamma peroxisome proliferator-activated receptor gamma) gene</td>
</tr>
<tr>
<td></td>
<td>AKT2 autosomal dominant</td>
</tr>
<tr>
<td></td>
<td>CIDECK cell death-inducing Dff-like effector C, autosomal recessive</td>
</tr>
<tr>
<td></td>
<td>PLIN1 autosomal dominant</td>
</tr>
<tr>
<td></td>
<td>Mandibulare-acral dysplasia (type A): autosomal recessive mutations of LMNA or ZMPSFE24</td>
</tr>
<tr>
<td>Generalized lipodystrophies or Berardinelli-Seipsyndrome (BSCL)</td>
<td>Agpat2 (BSCL1)</td>
</tr>
<tr>
<td></td>
<td>Seipin (BSCL2)</td>
</tr>
<tr>
<td></td>
<td>Caveolin 1(CAV1) and Cavin (PTRF)</td>
</tr>
<tr>
<td></td>
<td>Mandibulacral dysplasia (type B): autosomal recessive mutations of ZMPSFE24</td>
</tr>
<tr>
<td>Type 8 subunit of immunoproteasome (PSMB8) autosomal recessive</td>
<td>FBN1 associated to Marfan syndrome</td>
</tr>
<tr>
<td></td>
<td>BANF1 associated chronic progeria with severe bone complications</td>
</tr>
</tbody>
</table>

**Acquired lipodystrophies (or unknown gene)**

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial iatrogenic</td>
<td>Antiretroviral treatment (thymidine analogs and protease inhibitors)</td>
</tr>
<tr>
<td></td>
<td>Glucocorticosteroids</td>
</tr>
<tr>
<td></td>
<td>Localized post-injection: insulin, somatostatin analog, pegvisomant</td>
</tr>
<tr>
<td></td>
<td>Graft-versus-host disease after bone marrow transplantation</td>
</tr>
<tr>
<td>Immune</td>
<td>Immune</td>
</tr>
<tr>
<td></td>
<td>Dermatopolymyositis sequeale</td>
</tr>
<tr>
<td></td>
<td>Barraquer-Simons syndrome: cephalo-thoracic lipoatrophy and lipohypertrophy of lower limbs (complement anomaly)</td>
</tr>
<tr>
<td></td>
<td>Generalized lipoatrophy or Lawrence syndrome</td>
</tr>
<tr>
<td>Truncal lipodystrophies or Köbberling syndrome (FPLD1)</td>
<td>Lipodystrophies of unknown origin</td>
</tr>
</tbody>
</table>

**Lipomatosis (acquired or unknown gene)**

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beginn multiple symmetrical or Launois-Bensaude syndrome or Madelung disease (often alcohol-related, sometimes related to mitochondrial mutations)</td>
<td>Dercum disease or adiposis dolerosa</td>
</tr>
</tbody>
</table>

3.3. Typical presentation: familial partial lipodystrophy: Dunnigan syndrome

3.3.1. Definition

The most common form is the familial partial lipodystrophy known as Dunnigan syndrome (FPL2; OMIM 151660). It is characterized by loss of adipose tissue in the limbs and trunk beginning in puberty, with an accumulation of fat in the face and neck (Figs. 2a and d) [14].

3.3.2. Reason for medical consultation

The functional signs are fairly rare. There may be cramps or generalized pain, but the most commonly reported pain is hand pain, with sometimes infiltration of the fingers (Fig. 2b). Besides pain, hirsutism, spaniomenorrhea and especially diabetes are the most common reasons for medical consultation. As lipodystrophy syndromes are little known to the general population, the
anomaly of adipose tissue distribution is rarely the cause for seeking medical attention.

3.3.3. Patient interview

During the patient interview, a careful investigation must be done with regard to the personal or family history of atypical myopathy, sudden death, heart rhythm disorders or cardiomyopathy. If there is a history of cardiomyopathy, the diagnosis is directed more towards a laminopathy. A family history of a lipodystrophy phenotype is important to record.

3.3.4. General signs

The body mass index (BMI) is nearly always less than 25 kg/m². Variations have been described according to geographic origin, with the mean BMI of these patients being higher in North America than in Europe. In spite of the lipodystrophy, certain patients are able to gain weight with age (Figs. 2 c and d). The appetite is often voracious in lipodystrophy syndromes (even more so with the generalized types than the partial ones), and the presence of uncontrolled diabetes sometimes adds to this hyperphagia.

3.3.5. Physical signs

The physical examination is the most important part of the diagnosis. It should be done with the patient in undergarments (i.e. underwear and/or bra). The patient should be examined frontally and in profile, with their arms alongside the body, as well as frontally with the arms crossed horizontally and in motion. Photos can be used to follow the progression of lipodystrophy. Measurements of the waist circumference, hips, limb circumference and the thickness of the skin folds are used to assess the fat mass.

3.3.5.1. Lipodystrophy. In the Dunnigan variety of lipodystrophy, the adipose tissue is distributed in an odd and unharmonious manner on the face and trunk, with lipoatrophy to the abdomen and legs. Patients of this type have a large build.

In the familial type of lipodystrophy related to a laminopathy, the “pseudo-Cushing’s syndrome” type of lipodystrophy can be distinctly recognized (a “frog’s neck” appearance due to the widening of the neck in relation with the accumulation of fat), whereas other types have more of an appearance of premature aging, or sometimes pseudo-acromegaly.

Conversely, an emaciated face with atrophy of the buccal fat pads suggests generalized lipoatrophy, related to a laminopathy, or a Barraquer-Simons syndrome (see below).

The absence of adipose tissue makes the muscles and the veins of the extremities prominent. However lipoatrophy may occur with genuine muscular hypertrophy, which can be related to the extent of insulin resistance, although this mechanism is hypothetical. The pseudohypertrophy of the calves is nearly always a sign of the Dunnigan type of familial partial lipodystrophy that has been present since childhood. The increase of biceps relief signifies perihumeral lipoatrophy [15] (Fig. 3).

Hypomastia (Figs. 2c and 3c) is always very distinct in Dunnigan syndrome and can be used to differentiate partial lipodystrophy from classical android obesity. In some cases of Dunnigan syndrome, adipose tissue is deposited in the pubic and vulva areas, which can result in gynecological infections and make the wearing of pants difficult (Figs. 2d and 3a and b).

The diagnosis is made easier in women than in men, in whom an athletic appearance is more common. In the latter, discordance between a low level of physical activity and an athletic appearance or prominent muscle structure for age can direct the diagnosis towards laminopathy.

The spectrum of diabetes extends from hyperinsulinism (rarely if ever absent and often marked) to diabetic ketoacidosis secondary to acute pancreatitis; it also includes glucose tolerance disorder. This form of diabetes is never
completely deprived of insulin. Insulin resistance can be extreme, requiring insulin doses of 20 to 30 U/hour, even by intravenous route. The clinical complications of diabetes must be investigated early since the insulin resistance syndrome is inherited.

3.3.5.2. **Distinctive anthropometric features.** In addition to the absence of subcutaneous adipose tissue with muscular hypertrophy, there are some distinctive anthropometric features that also aid in the diagnosis of Dunnigan syndrome. Bi-acromial diameter (distance between the two acromions) is greater than the bi-trochanteric diameter (distance between the two trochanters) in women (Fig. 2c); this fact gives this impression of large build suggestive of Dunnigan syndrome at least in women. The lower limbs are also relatively short, with a ratio of height to leg length (as measured in a standing position between the iliac spine and heel) that is greater than 2 (Fig. 2c). The hands are small and wide with tapered infiltrated fingers (Fig. 2b). More to the point, it is essential that investigations be performed for anomalies of posture, kyphosis, scoliosis, shoulder ptosis, spine straightness, mandibular hypoplasia and winged scapulae (Figs. 4b and c).
3.3.5.3. **Muscle signs: pelvic and shoulder girdle deficiency [16–18].** Patients should be examined while moving by asking them to walk, squat and rise up, with the clinician being alert to small signs of muscle and tendon involvement. Amyotrophy might be severe (Fig. 4a).

In addition to the pseudohypertrophy of the calves that is constant in Dunnigan syndrome, it is important to look for retraction of the Achilles tendons or elbows, making it difficult to stand on the heels and making the patient tend to walk on tiptoe. A deficiency of the shoulder girdle muscles should be suspected if, when the person is undressing, they do not raise their arms to take off a sweater. A Trendelenburg’s sign (swinging of the pelvis while walking) and difficulties getting up from a squatting position attest to a proximal deficit of the pelvic girdle.

Finally, many lipodystrophy syndromes that are genetically determined (e.g. *LMNA, PPAR-g, PTRF*) or acquired (autoimmune diseases, dermatopolymyositis) occur with muscle involvement that could be mediated by immunological, inflammatory, hypoxic, lipotoxic or oxidative mechanisms;
mitochondrial anomalies or an interference in the myoadipogenesis mechanisms might also intervene.

3.3.5.4. Cutaneous signs. Cutaneous signs are not rare. Independent of any hirsutism, the skin is often thick and seborrhea or acne may be present.

Assessment of the quality of the adipose tissue (supple, fibrous, indurated) is done through palpation, and it is important to look for the presence of small subcutaneous lipomas, particularly in the abdomen. Axillary or more generalized acanthosis nigricans, particularly around the belt area or the neck, may be present (Fig. 5). Leuko-melanoderma (finely dappled skin color) has been reported [19].

Scleroderma-like syndrome with telangiectasia, limitation in the opening of the mouth and of the joint range of motion, tendon retraction, is especially noted in the N-terminal mutations of the lamin A/C gene with generalized lipoatrophy and sometimes retrognathia (Fig. 5). Its mechanism is poorly understood: it could be a consequence of severe insulin resistance involving a protein glycosylation anomaly or a developmental skin defect related to the laminopathy itself [20,21]; these could also be manifestations relative to nuclear injury that induces antigen release, which will trigger an autoimmune reaction [22].

3.3.5.5. Polycystic ovary syndrome (PCOS). The diagnosis of PCOS is based on classification using the Rotterdam consensus criteria:

- menstrual cycle anomaly;
- clinical and/or biological hyperandrogenism;
- ultrasound finding of PCOS.

Two out of three criteria are needed once other diagnoses have been ruled out.

In lipodystrophy, the clinical signs of hyperandrogenism (hirsutism, androgenetic alopecia) are not always present in spite of the insulin resistance but may be extremely severe and associated with oligomenorrhea or amenorrhea [23]. The Ferriman-Galway score should be calculated.

Infertility may require special management, generally after genetic counseling that takes into account the dominant autosomal transmission of laminopathies. There is an increased risk of gestational diabetes, as well as complications such as early spontaneous abortion and pre-eclampsia, compared to related controls without mutation [24].

3.3.5.6. Endocrine signs other than polycystic ovary syndrome (PCOS). The clinical diagnosis of goiter is difficult due to the...
presence of a cervical adipose panicle, which is often pronounced. An increased incidence of goiter is suspected, whether it is promoted by the hyperinsulinism or the laminopathy itself [26].

Otherwise, there has been one reported case of primary hyperaldosteronism with normal adrenal glands [26].

3.3.5.7. Cardiovascular signs [16,25]. Investigations must always be done for complications of insulin resistance syndrome, such as hypertension, carotid or femoral bruit, or an absence of pulse related to arteritis.

Investigations for silent myocardial ischemia should be carried out relatively early considering the congenital character of insulin resistance syndrome. Cardiac rhythm anomalies sometimes occur very early, especially in generalized lipodystrophy, through proximal mutations of the lamin gene, even if they do not require immediate therapeutic intervention.

The frequency of rhythm or conduction disorders in lamin A/C gene mutations usually responsible for lipodystrophy syndromes, appears to be relatively low. Nevertheless, increased caution is called for if there is (a) a family or personal history of cardiac rhythm or conduction disorders since childhood, especially when the lipodystrophy syndrome is associated with (b) mutations that are “non-classical” in lipodystrophy syndromes or (c) that have been described in cardiomyopathy or myopathy (LMNA N-terminal mutations).

Sleep apnea syndrome does not appear to be more common in lipodystrophy, especially those that are partial, although this has been debated.
3.3.5.8. Gastrointestinal signs. Hepatomegaly with steatosis is common and can progress to cirrhosis. Very severe acute pancreatitis can complicate insulin resistance syndrome. Rectal prolapse does not appear to be rare and might be promoted by the lipo-amyotrophy.

3.3.5.9. Neurological signs. It is essential that a work-up be done for neuropathy due to diabetes or sometimes to the laminopathy itself [16]. Parkinson’s syndrome occurring relatively early has been reported [16]. Insulin resistance syndrome can be complicated by cerebral vascular accidents. Intellectual ability is usually normal in familial partial lipodystrophy. It may be altered in some forms of generalized lipoatrophy, generally not related to a laminopathy, and without a clear identification of the involved mechanisms. Endoplasmic reticulum stress [27], or cerebral phospholipid anomalies might be involved.

4. Clinical differential diagnosis

4.1. Dunnigan familial partial lipodystrophy syndrome

Dunnigan familial partial lipodystrophy syndrome must be differentiated from Cushing’s syndrome and acromegaly. Alcohol addiction is often wrongly suggested in this context. Some types of android obesity and Launois-Bensaude syndrome or proximal multiple lipomatosis are difficult to differentiate from metabolic laminopathies, in which the lipoatrophy is sometimes less pronounced.

4.2. Generalized lipoatrophy

Generalized lipoatrophy must be differentiated from constitutional body thinness or weight loss with its classical causes, especially pheochromocytoma.

4.3. Voracious appetite

Voracious appetite can wrongly result in the diagnosis of food behavior disorders, particularly when the lipoatrophy syndrome is revealed at puberty with amenorrhea.

4.4. Barraquer-Simons syndrome

The Barraquer-Simons syndrome form of lipodystrophy is quite specific and has few differential diagnoses, other than generalized lipoatrophy when lipohypertrophy of the lower limbs is absent. This diagnosis should come to mind in the presence of glomerulonephritis.

4.5. Pain

Pain sometimes suggests fibromyalgia. In this context of metabolic syndrome and/or autoimmune disorders, iron overload, adrenal insufficiency, etc. should be ruled out.

5. Laboratory diagnostic testing for lipodystrophy

5.1. Glucose tolerance disorders

A systematic work-up should be done for fasting hyperglycemia, carbohydrate intolerance (2-hour blood glucose between 1.40 and 2 g/L after oral glucose tolerance test [OGTT]) and diabetes (2-hour blood glucose greater than 2 g/L after OGTT). Fasting hyperinsulinism greater than or equal to 20 mU/L is common, with OGTT values often exceeding 200 mU/L.

5.2. Lipid panel

A lipid panel including measurements of total, HDL cholesterol, and triglycerides should be done. Hypertriglyceridemia with low HDL is frequently found. Hypertriglyceridemia can be significant, resulting in acute pancreatitis, particularly when the patient is taking estroprogestative combinations, the initiation of which must be carefully monitored.

5.3. Hepatic disturbances

Transaminase levels are often high, predominantly ALT, which reflects hepatic steatosis.

5.4. Muscle enzymes

Creatine kinase (CK) plasma concentrations are frequently increased but the values rarely exceed 500 U/L.

5.5. Hyperandrogenism

An increase in serum testosterone with decrease in sex binding protein (SBP) is common in non-menopausal women.

5.6. Adipocytokines

Serum leptin is less than 10 ng/mL with 69% sensitivity and 78% specificity in our experience. However, distinctly higher values are seen depending on the BMI of the patients. Nevertheless, serum leptin levels appear to be lower in laminopathies of patients with a BMI comparable to those of obese subjects [28]. The study of other cytokines is not routinely done. Published studies however cite low concentrations of adiponectin and interleukin-6.

In familial partial lipodystrophy, serum levels of leptin and adiponectin are inversely correlated to the fat mass and degree of insulin resistance. TNF-alpha concentrations are high and are proportional to the fat mass. Interleukin-6, interleukin-1 beta and resistin are not correlated to the metabolic syndrome [29,30].

5.7. Genetics

The clinical phenotype and the familial character can direct the diagnosis towards a genetic anomaly. A 10 mL blood sample..
with EDTA will be taken after the informed consent and signature of the patient for gene study in an authorized laboratory. The reported gene anomalies are autosomal dominant, except for CIDE C mutations in familial partial lipodystrophy, as well as some lamin and ZEMPSTE 24 gene mutations in lipodystrophy associated with acromandibular dysplasia (Table 1).

6. Paraclinical diagnostic testing for lipodystrophy

6.1. Characterization of fat mass

This characterization is especially done based on clinical investigation. It is not essential to the diagnosis but often helps to direct it, particularly in the atypical phenotypes.

6.1.1. Impedance measurement

Impedance measurement provides an approximation of the fat mass by weight, and is an easy technique that is actually quite well correlated to absorptiometry in our experience.

6.1.2. Dual-energy absorptiometry

Dual-energy X-ray absorptiometry is however the gold standard test for quantifying the fat mass percentage. The measurement furthermore enables an assessment to be made of both the total and truncal fat mass, with the latter being equivalent to an estimation of the visceral fat mass in patients with lipodystrophy. In patients with lipodystrophy, this percentage of total fat mass is about 23% but can be as low as 10% (for a normal value of around 30%).

6.1.3. Metabolic MRI

Metabolic MRI is used to quantify the intra-abdominal fat (a quantitative estimate of the visceral fat), the abdominal subcutaneous fat and hepatic steatosis. It may confirm the presence of liver dysmorphia, which can promote progression to cirrhosis of metabolic origin.

In the Dunnigan lipodystrophy syndrome, the total abdominal fat value on MRI is generally around 200 cm³ versus 100 cm³ for intraperitoneal fat with a total abdominal fat/BMI ratio less than 10 and a total abdominal fat/intraperitoneal fat ratio less than 2 [28]. These assessments show that the visceral fat in patients with laminopathy constitutes on average 50% of the total abdominal fat versus about 25% in patients with adipose tissue distribution anomalies other than generalized lipoatrophy [28,31].

6.1.4. Ultrasound and elastography

Ultrasound is currently not highly used but could be a low-cost and low-invasive means of exploration in the future [32]. Measurement of adipose tissue elasticity could be used as an index of fibrosis and insulin resistance, along the same principle as liver fibrosis measurement with FibroScan [33].

6.2. Complications of insulin resistance syndrome

The investigation for complications of diabetes must be done according to the current recommendations, particularly those that concern complications involving:

- hypertension (measurement of outpatient blood pressure, echocardiography);
- atheromas (Doppler ultrasound of the lower limbs and neck vessels);
- silent myocardial ischemia (e.g. stress test, myocardial scintigraphy, etc.);
- or microalbuminuria.

6.3. Polycystic ovary syndrome

An ovarian ultrasound is used to look for stigmas of polycystic ovary syndrome.

6.4. Cardiological assessment

In laminopathy, systematic ECG, echocardiography and Holter monitoring should be carried out together with the cardiology teams at least on diagnosis and then with a frequency that depends on the type of mutation and the symptoms. Laminopathy should be considered in patients with early familial types of heart disorders and/or those associated with diabetes.

6.4.1. Echocardiography

Cardiac septal hypertrophy can be seen on echocardiography in lipodystrophy-type laminopathy, while dilated cardiopathy is usually noted in cardiac laminopathy.

6.4.2. Holter electrocardiogram monitoring

The Holter electrocardiogram monitor is used to detect cardiac rhythm disorders, the spectrum of which extends from complete arrhythmias with atrial fibrillation to ventricular arrhythmias. Conduction disorders can also occur.

6.4.3. Exploration of the bundle of His

An exploration of the bundle of His may be done, especially if there is a history of familial rhythm disorders, in laminopathies and if the patient has bursts of ventricular tachycardia activity on Holter monitor or an ejection fraction less than 45%.

6.4.4. Cardiac MRI

Finally, cardiac MRI with lipid profile analysis is used for more detailed myocardial study [34].

6.5. Neuromuscular assessment [16,18,25,35]

6.5.1. Muscle MRI

Muscle MRI of the calves, quadriceps and the shoulder girdle can show evidence of atrophy or moderate adipose degeneration of certain muscle fascicles, particularly in the thighs, while the calf muscles are hypertrophied, sometimes with mild adipose infiltration of the muscle fascicles and a near total absence of subcutaneous adipose tissue.

6.5.2. Electromyogram

The electromyogram can show myogenic disturbances especially in lipodystrophy with severe myopathic complications. It

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can also demonstrate signs of neuropathy, usually in diabetic patients.

6.5.3. Muscle biopsy

Muscle biopsies that are occasionally done in the lipomyopathic forms of laminopathy have shown signs of dystrophy and excessive lipid droplets between the type 2 myofibrils. The expression and the location of nuclear emerin and lamin A/C are normal, as are those for calpain-3, except in the severe myopathic forms. It should be noted that the severity of the lipodystrophy and the myopathy are not correlated, but the presence of lipid droplets might be linked to the degree of insulin resistance [16,33].

7. Etiologic diagnosis of lipodystrophy

The etiologic diagnosis is based on the clinical analysis of the adipose tissue distribution and the knowledge of familial or acquired disease, keeping in mind that certain genetically determined forms can appear later (Dunnigan syndrome at puberty). Patients often are very well aware when there are other cases in the family.

7.1. Genetically determined lipodystrophy syndromes

7.1.1. Partial lipodystrophy with facial-truncal predominance. Partial lipodystrophy with facial-truncal predominance are autosomal dominant except for CIDE and MAD which are autosomal recessive

7.1.1.1. Laminopathy. Lipodystrophy syndrome with facial-truncal predominance usually involves mutations of the lamin A/C gene, located on chromosome 1. It is also called Dunnigan syndrome (FPLD2) and is by far the most common of the genetically determined lipodystrophy syndromes. Its estimated prevalence, one out of 15 million, might be much higher (close to one out of 100,000 inhabitants and about 50% of the lipodystrophy syndrome cases in our experience).

Laminopathies, which are also called nucleopathies, are disorders related to lamina dysfunction. The lamina, which is mainly composed of laminas A, C B1 and B2, is a network of intermediate filaments lining the internal face of the nuclear membrane. The lamina assures the structural organization of the nucleus and chromatin, communication with the cytoplasm, gene transcription and cell multiplication. Lamin A alterations lead to defects in the replication and repair of DNA mediated by SREBP1, and results in increased genome instability, thus promoting degenerative (lamin mutations) or tumoral (defects in lamin expression) disorders [36,37]. Lamina A/C intervenes in adipocyte differentiation, and insulin and PPARγ signaling.

The laminopathies have a very vast phenotypic spectrum, which sets them apart within the lipodystrophy syndromes (Table 2). Indeed, besides classic R482 mutations, which associate insulin resistance and lipodystrophy, there have been descriptions of predominantly metabolic phenotypes, in which lipodystrophy can be less severe [14–16,19,20]. Anthropometric anomalies are nevertheless seen (particularly enlargement of the bi-acromial diameter, broaden but small hands, postural anomalies, hypomastia, pseudohypERTrophy of the calves). A predominant proximal myopathy can sometimes complicate these syndromes, even within the classical mutations. Acanthosis nigricans is common, as is polycystic ovary syndrome. Laminopathies are also the source of generalized and borderline forms of lipodystrophy syndromes with myopathic, progeroid or sclerodermoid-like forms. The leptin level is not always severely reduced.

Similarities to laminopathy can be found in mutations of the ZMPSTE 24 gene, encoding for a zinc metalloprotease enzyme that intervenes in pre-prolamin maturation. Mutations of this gene are the source of premature aging syndromes such as Hutchinson-Gilford [38]. The absence of cleavage of prelamin A by mutation of the LMNA or ZMPSTE 24 genes results in an accumulation of prenylated prelamin A, which is the cause of progeria syndromes.

7.1.1.2. Peroxisome proliferator-activated receptor gamma mutations (PPAR-γ) (FPLD3). PPAR proteins are transcription factors, which belong to the hormonal nuclear receptor family. They heterodimerize with RXR (retinoid X receptor) and there are three subtypes: PPAR-alpha, PPAR-delta and PPAR-gamma. PPAR-gamma plays a major role in lipid regulation and glucose metabolism, adipocyte differentiation, suppression of the inflammatory response of the macrophages and other cellular regulatory processes.

The loss-of-function mutations of PPAR-γ are much more rare than the preceding forms (ratio of about one out of 100 lipodystrophy syndrome cases in our experience). The main reported mutations are V299M and P467L, F388L, R425, Y355X and more recently D424N, C190S, R194W and Y151C [39].

Lipoatrophy is less severe and occurs with a pronounced metabolic syndrome, having a “pseudo-acromegaly” presentation (Fig. 6). The diagnosis is made all the more difficult as the patient complaint might be profuse sweating. Early childhood diabetes with severe hypertriglyceridemia and recurrent pancreatitis has been reported for the most recently identified mutations. Muscle enzymes may be elevated without any clear reason. The therapeutic response to thiadizolidinediones seems to be more variable.

7.1.1.3. AKT2. This serine/threonine-protein kinase is involved in glucose regulation, insulin and mTOR signaling and adipocyte differentiation.

AKT2 gene mutations are very rare [40]. Lipoatrophy mainly affects the extremities and occurs with severe insulin resistance.

7.1.1.4. Autosomal recessive cell death-inducing DFFA-like effector C (CIDE). The first homozygote mutation of a lipid
droplet protein called cell death-inducing Dff4-like effector C (CIDEC) (E186X) was reported in a case of partial lipodystrophy with lipoatrophy affecting the lower limbs, buttocks and subcutaneous abdominal tissue in combination with insulin-resistant diabetes. The lipid droplets were multilocular [41].

7.1.1.5. Perilipin. Perilipin is another lipid droplet protein and is the most abundant. It is essential for the incorporation and release of lipids from this droplet. Two heterozygous mutations were recently reported in the perilipin gene (PLIN1) in three families with partial lipodystrophy, severe dyslipemia and insulin-resistant diabetes. The adipocytes of the subcutaneous tissue of these patients were smaller, with macrophage infiltration and fibrosis [13].

7.1.1.6. Partial lipodystrophy associated with autosomal recessive mandibuloacral dysplasia (MAD). Subcutaneous lipoatrophy especially affects the extremities, preserving the neck and trunk in the A-type, which is linked to homozygote mutations of the LMNA gene. In the B-type, which is linked to composite heterozygous mutations of the ZMPSTE24 gene, lipoatrophy is generalized [42] (see below). Hypertriglyceridemia, insulin resistance or glucose intolerance, musculoskeletal anomalies (such as retrognathia and sloping shoulders), and signs of premature aging are present.

7.1.2. Autosomal recessive generalized lipodystrophy (Berardinelli-Seip syndrome)
Generalized lipodystrophy is characterized by a near total absence of adipose tissue from birth, except for the supportive adipose tissue in the palms and soles, scalp and joints. The face often appears emaciated due to atrophy of the buccal fat pads. The patient has a voracious appetite, and statural growth is accelerated, with an advance in bone age. Metabolic syndrome occurs early and is severe. Mental retardation may be present.

7.1.2.1. AGPAT2 mutations. The AGPAT2 or BSCL1 gene, located on chromosome 9, encodes for 1-acylglycerol-3-phosphate-O-acyltransferase 2, which is involved in triacylglycerol synthesis. Mutations of AGPAT2 result in a very insulin-resistant diabetes with severe lipoatrophy and a distinct acromegaly presentation with muscular pseudohypertrophy from childhood [43]. Mental retardation may be present (personal observation; Fig. 7), although it is usually found more often in seipin mutations. Supportive adipose tissue is generally intact.

7.1.2.2. Seipin mutations. Seipin mutations on chromosome 11q13 are loss-of-function mutations encoding for type 2 congenital generalized lipodystrophy (or BSCL2), a severe form of lipoatrophy with insulin resistance and hypertriglyceridemia. Certain gain-of-function mutations (N88S and S90L mutations) have been identified in autosomal dominant diseases of motor neurons (Silver syndrome, spastic paraplegia 17 and distal hereditary neuropathy type V). Seipin is an autonomous determinant of cAMP/PKA-mediated lipolysis, which is essential for adipocyte differentiation [44]. All of the adipose tissue (metabolically active and supportive) is affected.

7.1.2.3. Cavin (PTRF-Cavin) and caveolin (CAV1) mutations. Caveolae are small invaginations of the plasma membrane, which are made up of surface proteins (caveolins and cavin) involved in lipid storage, membrane signaling and endocytosis. Mutations of the caveolin gene and its associated proteins (PTRF, or polymerase I and transcript release factor/Cavin-1) result in a clinical presentation of lipoatrophy of the limbs and the face, with diabetes, associated with muscular and cardiac dystrophy. Sometimes pulmonary hypertension, and prostate or breast cancer, might be associated particularly for caveolin three mutations. Caveolin 1 and cavin anomalies are rather the source of generalized lipoatrophy, although the lipoatrophy can be predominant on the upper part of the body, at least for CAV1 [45,46].

7.1.2.4. Type B mandibuloacral dysplasia from ZMPSTE24 mutations. In type B, which is linked to composite heterozygous mutations of the ZMPSTE24 gene, lipodystrophy is generalized and often associated with musculoskeletal anomalies and progeroid traits [42].
7.1.3. Proteasome-associated autoinflammatory syndromes

An autosomal recessive autoinflammatory lipodystrophy has been recently reported. It is due to a proteasome subunit β type 8 (PSMB8) mutation. PSMB8 encodes for the β5i subunit of immunoproteasome. These mutations are the cause of Nakajo-Nishimura syndrome, Japanese autoinflammatory syndrome with lipodystrophy, Candle syndrome (fever spikes, panniculitis, chronic atypical neutrophilic dermatosis with partial secondary lipodystrophy) and the syndrome of joint stiffness with post-panniculitis and muscle atrophy [47]. It should be remembered that proteasome is one of two protein degradation pathways, in addition to lysosome. It involves a multi-protein enzymatic complex, which assures proteolysis of ubiquitinated proteins. Disturbance of this degradation by mutation of a gene encoding for one of the proteasome subunits results in an accumulation of ubiquitinated and oxidized proteins in the cells expressing the immunoproteasome, with a secondary increase of interleukin (IL)-6 and interferon (IFN)-γ inducible protein (IP)-10, which is responsible for the inflammatory response. These seemingly acquired lipodystrophies result from an innate immune regulation anomaly inducing autoinflammatory disorders [48]. Their discovery confirms the relationship between adipose tissue, inflammation and immunity, and shows that certain types of secondary lipodystrophy are in fact genetically determined.

7.1.4. Glycosylation disorders (autosomal recessive)

Moderate lipodystrophy was reported in a 9-month-old child with a phosphomannomutase 2 (PMM2-CDG) deficiency, which is very often accompanied by cerebellar involvement [49]. The semi-quantitative measurement of sialotransferrin by isoelectrofocusing is used to make the diagnosis.

7.1.5. FBN1 mutations

The FBN1 gene encodes a fibrillin involved in the genesis of Marfan syndrome. Severe generalized lipodystrophy accompanied by marfanoid syndrome with lens dislocation and neonatal progeroid syndrome with muscular involvement was attributed to mutations or heterozygous deletions of the 3’ end of the FBN1 gene (exon 64) [50]. Insulin resistance syndrome was not always present.
7.1.6. BANF1 mutations (autosomal recessive)

This premature aging syndrome, which is also called Nestor-Guillermo syndrome, involves a generalized decrease in subcutaneous adipose tissue and has the distinctive feature of not being associated with early insulin resistance [51]. The classical components of progeroid syndromes such as Hutchinson-Gilford or mandibuloacral dysplasia are present: premature aging, growth retardation, spindle limbs and joint stiffness. However, bone complications are often significant and occur early; the longer than usual survival is due to the absence of cardiovascular complications. Homozygous mutations of BANF1 (c.34G>A [p.Ala12Thr]), encoding barrier-to-autointegration factor 1 (BAF), are the cause of this syndrome.

7.2. Acquired lipodystrophy

7.2.1. Iatrogenic lipodystrophy

7.2.1.1. Partial facial/trunkal lipodystrophy related to antiretroviral treatment. About 50% of the lipodystrophy cases associated with HIV are a group of anomalies of adipose tissue distribution (lipatrophy and lipohypertrophy) and metabolic alterations (dyslipidemia and insulin resistance), which result from complications of antiretroviral treatment use (thymidine analogs or reverse transcriptase inhibitors and protease inhibitors). This metabolic syndrome is associated with an increased cardiovascular risk. The lipodystrophy syndrome often generates anxiety and depression. Its genesis is affected by multiple factors that are dependant on the host, the disease and the treatment, such as inflammation, immune reaction and lymphocytic depletion. A recent study showed that immune deficiency (lymphocyte T CD4+<500 mm³) was itself a factor of insulin resistance, associated with higher age and BMI [52,53], as was the viral load and co-infection with hepatitis C virus. Antiprotease drugs seem to inhibit the transcription factors that regulate adipocyte differentiation, such as PPARγ and C/EBP-α and induce increased oxidative stress. Reverse transcriptase inhibitors can lead to mitochondrial dysfunction. These two factors may explain the metabolic lipodystrophy syndrome.

7.2.1.2. Partial facial/trunkal lipodystrophy related to glucocorticosteroids. Anomalies of adipose tissue distribution associated with steroids are accompanied by a different adipokine profile before and after glucocorticosteroid use. Serum leptin more than 5.9 ng/mL is predictive of the occurrence of lipodystrophy related to corticosteroids [54].

7.2.1.3. Localized lipodystrophy. Localized lipodystrophy is generally iatrogenic and secondary to medication injections (somatostatin analogs, pegvisomant, insulin), vaccines or repetitive pressure trauma. They involve small body areas and are not usually accompanied by the metabolic syndrome. It should be noted that localized lipodystrophy can also be secondary to panniculitis and undetermined causes.

Insulin-induced lipodystrophy is often related to inappropriate injection technique or equipment (needle length). They are very clearly promoted by the absence of injection site rotations and are the source of severe glycemic imbalance or instability. Their mechanism was the subject of a recent study: adipocytes that were chronically exposed to high insulin concentrations appeared to become severely insulin-resistant, which led to increased lipolysis and thus their atrophy. Active secondary recruitment of preadipocytes would explain their possible regression when insulin exposure was interrupted [55].

7.2.1.4. Graft-versus-host reaction. Lipodystrophy can also involve a graft-versus-host reaction, particularly after bone marrow transplantation [56].

7.2.2. Lipodystrophy occurring with immune system disorders

7.2.2.1. Lipodystrophy sequelae of dermatopolymyositis. Many isolated clinical cases of lipodystrophy associated with dermatopolymyositis have been described in the literature. Two series of 20 to 30 children confirmed that generalized, partial or focal lipodystrophy are common sequelae of juvenile dermatopolymyositis. The time to their appearance was about 5 years. Their frequency was correlated to the severity of the initial clinical assessment with regard to the degree of amyotrophy, skin rashes, joint stiffness and the presence of calcinosis. These lipodystrophy syndromes resulted in metabolic complications, mainly hypertriglycerideremia. There was no demonstration of the pathogenic role of cytokine polymorphisms, C3 nephritic factor (C3Nef), anti-insulin receptor antibodies or the lamin gene [57]. In another series that was studied for an average of 14 years after the initial episode, lipodystrophy was found in 13% of the 53 patients. The frequency of the most prominent sequelae, which included cutaneous scarring and muscle dysfunction, was related to the duration of the initial disease (especially when over 4 years) [58].

7.2.2.2. Acquired partial lipodystrophy or Barraquer-Simons syndrome. Barraquer-Simons syndrome (Fig. 8) is characterized by a selective loss of adipose tissue from the upper half of the body, appearing in childhood or at puberty, with cephalo-thoracic progression and fat accumulation in the thighs and buttocks. Metabolic complications are rare, with the exception of hepatomegaly; in our experience however, the frequency of these metabolic complications increase with age. There is activation of the alternative complement pathway by the C3 nephritic factor (a polyclonal immunoglobulin G, which stabilizes C3-convertase), with a low C3 level and frequent membranoproliferative glomerulonephritis. This C3Nef seems to destroy the adipocytes secreting adipin or factor D, a serine protease, which is predominant in the cephalo-thoracic adipocytes, thus explaining the location of the lipodystrophy ([59]; Section 7.2.2.4). Autoimmune diseases such as lupus, dermatomyositis or infections such as measles can also trigger the disease. There is usually no family history.

In four out of nine patients with “acquired” lipodystrophy, three heterozygous LMNB2 mutations were also identified in the intron 1-6G→T; exon 5 c.643G→A (p.R215Q; in two patients), and exon 8 c.1218G→A (p.A407T) [60]. Other groups have not confirmed these results however.
7.2.2.3. **Acquired generalized lipodystrophy (Lawrence syndrome) of autoimmune origin.** Acquired generalized lipodystrophy, or Lawrence syndrome, usually found in women, develops in association with panniculitis, autoimmune diseases (autoimmune hepatitis, possibly type 1 diabetes) or remains idiopathic [61]. Some autoimmune forms are associated with a marked decrease of C4 linked to activation of the classic complement pathway, certain components of which are also synthesized by the adipocytes that could be secondarily destroyed.

7.2.2.4. **Pathophysiology of acquired lipodystrophy with immune system disorders: complement?** Indeed, the adipocytokines secreted by the adipose tissue include a certain number of proteins that intervene in the complement system, such as adipsin or factor D, a protein that stimulates acylation and similar to C3a, and adiponectin, which has many homologies with C1q. Yet the complement system is part of the innate immune system. The classical complement pathway is activated by IgG or IgM antigen complexes, while the alternative pathway is activated directly by C3 on the antigen surface. Also both pathways generate C3-convertase protease, which is capable of activating C3 and causing membrane cytolysis. The complement proteins also exert metabolic effects but are liable to make adipocytes more sensitive to autoimmune assaults [62].

In addition, the antinuclear antibodies present in systemic autoimmunee diseases are in fact nuclear anti-envelope antibodies, particularly anti-lamin, providing possible new pathophysiological explanations [22].

Finally, the question about genetic susceptibility remains unanswered, with hereditary anomalies possibly underlying immune dysregulation.

7.2.3. **Partial lipodystrophy with predominant truncal involvement or Köbberling syndrome (FPLD 1)**

Köbberling syndrome is a type of lipodystrophy characterized by lipodystrophy of the limbs and, in contrast to Dunnigan syndrome, fat accumulation in the trunk [63]. Its cause remains unknown, although it is often classified as a familial form and is therefore apparently genetically determined. In the absence of known genes, it is difficult to confirm the clinical diagnosis and differentiate it from other more common forms of obesity.

7.2.4. **Many causes of lipodystrophy syndromes remain undetermined**

For instance, generalized familial lipodystrophy with muscle weakness and cervical spine instability are not linked to AGPAT2, BSCL2 and CAV1 anomalies. . .

7.3. **Lipomatosis**

The definition of lipomatosis is not easy, despite most of lipomatosis syndromes have been recognized more than one century ago. They are characterized by multiple deposits of adiposis tissue, generally unencapsulated, but without lipodystrophy. It is the reason why they are at the frontiers of lipodystrophy syndromes, which are characterized by lipohypertrophy in some sites and absence of adipose tissues in other sites. In this review, we
considered that lipomatosis could be considered as lipodystrophy syndromes in their lipohypertrophic component (no lipoatrophy). These rare diseases are today split in two main groups: benign multiple symmetric lipomatosis (Madelung’s disease or Launois-Bensaude syndrome) which might be acquired or rarely inherited, and Dercum disease (adiposis dolorosa). Roch-Leri mesosomatous lipomatosis characterized by the development of many small lipomas, mainly on the trunk, upper thighs and forearms is not anymore mentioned in medical literature.

Lipomatosis could result from growth of brown adipose tissue cell strains, with secondary lymphatic dysfunction in multiple symmetric lipomatosis, or primary vascular or lymphatic dysfunction in Dercum’s disease.

7.3.1. Benign multiple symmetric lipomatosis (Madelung’s disease or Launois-Bensaude syndrome)

7.3.1.1. Phentype. Madelung’s disease is a rare disease characterized by multiple deposits of uncapsulated (in contrast to lipoma) adipose tissue distributed symmetrically:

- in the face, neck, nape of the neck, sometimes the superior mediastinum, shoulders and arms (type 1 with a ‘pseudo-athletic’ build);
- more rarely in the lower limbs (type 2 with an appearance of generalized obesity) [64,65] (Fig. 9).

Two series of 35 and 65 cases, respectively, were reported by Madelung in 1888 and Launois and Bensaude in 1898. It affects middle-age men that usually have chronic alcoholism, although there are primary forms. It can have esthetic and psychological implications. Deep mediastinal infiltration with vascular and nerve compression may complicate these syndromes. The adipocytes are smaller and are multivacuolar compared to the normal adipose tissue.

7.3.1.2. Pathophysiological hypotheses. Different pathophysiological hypotheses have been suggested, including:

- brown adipose tissue hypertrophy or dysfunction;
- mitochondrial dysfunction. Mitochondrial DNA mutations have been identified in certain familial forms of symmetric lipomatosis associated with MERFF cytopathy (myoclonic epilepsy with ragged red fibers or Fukuharaou disease) [66];
- alcohol is a co-factor in 60 to 90% of cases of Madelung’s disease, which promotes lipogenesis, reducing lipolysis and altering mitochondrial functioning. Ethanol induces positive regulation of lipin-1 gene expression mediated by AMPK inhibition and SREBP-1 activation [67,68].

7.3.1.3. Complications. Metabolic disorders are commonly associated with lipomatosis (diabetes, dyslipidaemia, hepatic steatosis). Sensorimotor or autonomic neuropathy are present

Fig. 9. Launois-Bensaude syndrome or benign symmetric lipomatosis.
in 85% of cases, often occurring several years after the lipomatosis; it is histologically characterized by progressive axonal atrophy and not the demyelination and axonal degeneration known with alcohol.

7.3.1.4. Preoperative assessment. Computed tomography and MRI are useful in the preoperative assessment for plastic surgery.

7.3.1.5. Differential diagnosis. The specific differential diagnoses include simple trunk obesity; angiolipomas; neurofibromas; encapsulated lipomas; hibernomas, mainly composed of brown adipose tissue, and which have the distinctive feature of having positive uptake on FDG-PET scan; liposarcoma; and lipoblastomatosis. Additional differential diagnoses are salivary gland anomalies and congenital or acquired facial/trunkal partial lipodystrophy.

7.3.1.6. Disease course. The disease course is characterized by an initial period of rapid growth followed by slower progression over the years, with no spontaneous regression after alcohol intake is stopped. Malignant transformations are extremely rare (a single case reported in the literature).

7.3.2. Dercum’s disease or adiposis dolorosa

Adiposis dolorosa is a syndrome described for the first time in 1888 by the American neurologist Francis X. Dercum. It is found in obese as well as non-obese individuals and is characterized by painful non-encapsulated lipomatosis in the subcutaneous tissue. Fatigue is present in 50% of cases. This disease appears to be more common in women. The adipose tissue is characterized by excess collagen and multinucleated giant cells. Metabolic disorders may occur with Dercum’s disease, depending on the extent of adipose tissue inflammation. The differential diagnosis is lymphedema. Energy expenditure at rest is lower than in controls when the body mass index is taken into account [69]. Elevated stearoyl-CoA desaturase activity has been described in obese states, with an increased desaturation index suggesting enhanced lipogenesis. This vaccenic/stearic index is lower in Dercum disease in comparison to obese controls, suggesting presence of other factors involved in fat accumulation in addition to lifestyle [70].

8. Therapeutic strategy

Treatment should target the metabolic syndrome, as well as the lipodystrophy syndrome and, if necessary, associated complications. Some specific treatments are beginning to emerge [71].

8.1. Insulin resistance syndrome

Diabetes and dyslipidemia should be treated as part of the regular standard care for insulin-resistant diabetes, in particular with regard to dietary control, physical exercise and the use of biguanides, although these have not been subjected to specific studies in this domain [72].

PPAR agonists (peroxisome proliferator-activated receptor agonist), which improve insulin sensitivity, also increase adipogenesis, though the increase occurs more in the areas that are already lipodystrophic. There is often a distinct improvement in hepatic steatosis. Pioglitazone seems to be more effective than rosiglitazone on glucose metabolism in the limited number of studies that have been performed [73–75]. The hematological and bladder effects must be monitored. The availability of new PPAR-g agonists is highly anticipated in these diseases, especially in France where pioglitazone and rosiglitazone are no longer available.

The use of GLP-1 receptor agonists can help limit the tendency for weight gain, which is seen in a certain number of Dunnigan syndrome cases [76]. The effect of gliptins has not been specifically studied.

There may still be a need for insulin therapy. Sometimes the insulin resistance requires insulin to be administered via a flow pump providing several tens of units per hour subcutaneously. There may also be a need for intravenous or intraperitoneal insulin therapy, at least temporarily [72].

8.2. Lipodystrophy

Lipodystrophy is not responsive to calorie reduction or to bariatric surgery, at least with regard to the lipomatous component. The obesity component that is sometimes associated with Launois-Bensaude or Dunnigan syndrome can improve however.

Plastic surgery via liposuction can be performed if the adipose tissue is not too fibrous, or via lipectomy, which offers better protection of the vascular and nervous networks. These plastic options are offered when there are clinical consequences such as compression or effects that are mechanical (difficulty dressing) or psychological. The risk of hematoma is not negligible, and metabolic control must be optimal before the care is started. Recurrence is however common.

8.3. Specificities of management of lipodystrophy associated with HIV

Modifications of the antiretroviral treatment may improve the lipodystrophy syndrome. However some studies mention the existence of hyperinsulinism in HIV-infected patients that still had not undergone treatment.

Treatment with metformin must be particularly monitored due to a theoretical increased risk of lactic acidosis.

Tesamorelin, a growth hormone releasing factor analog (GHRH), was validated by the Food and Drug Administration (FDA) in November 2010 for the treatment of HIV-associated lipodystrophy. This treatment was effective in decreasing the visceral fat in two Phase III clinical trials that were extended for 1 year and showed no harmful effects on glucose-lipid metabolism. There are currently no longer-term safety studies available [77].

Meteleptin (Section 8.4.1.1) also seems to be effective in lipodystrophy syndromes in HIV patients.
8.4. Specificities of laminopathy management

8.4.1. Metreleptin and adiponectin

8.4.1.1. Metreleptin. Metreleptin, or recombinant leptin, proved to be effective in lipodystrophy syndrome cases that were severely (leptin <3 ng/mL) or moderately hyperleptinemic (leptin 4 to 6 ng/mL) at a dose of 0.04–0.08 mg/kg per day per subcutaneous injection. Most studies have been performed in laminopathy, which is the main cause of lipodystrophy syndromes. Dyslipidemia and hepatic steatosis overtly improve. Insulin needs may be considerably reduced in the more severe forms. An improvement of lipodystrophy has also been seen, although often associated with a loss of thin mass and mild weight loss. Menstrual disorders may also improve [78,79]. Metreleptin has also been used in PPAR-gamma mutations and/or hyperandrogenism. The systematic analysis of the role of lamin and its vast phenotypic spectrum could also open new hope to patients, in whom the level of social disability is mild and body weight is still preserved. Metreleptin has been used in patients with a typical clinical presentation, but also a large number of borderline forms with type 2 diabetes.

The study of these lipodystrophies finally provide new insights on insulin resistance syndrome, its relationship with the liver and muscle, the major role of the distribution and quality of adipose tissue, and lastly on aging. These advances will progressively enable targeted care for these syndromes, the knowledge of which will probably improve the prevention and treatment of metabolic syndrome and type 2 diabetes.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References


9. Conclusion

Lipodystrophy syndromes were identified over a century ago, and the first genetic causes over 10 years ago. Since the recognition of the role of lamin and its vast phenotypic spectrum in these disorders, a plethora of other genes have been discovered, progressively unraveling the importance of the lipid droplet in lipid metabolism. In addition, antiretroviral treatments form an iatrogenic model of acquired lipodystrophy, and specific lipodystrophy treatments are progressively emerging, offering new hope to patients, in whom the level of social disability is often underestimated.

Considered rare, lipodystrophy syndromes also seem to be under-recognized. Their diagnosis remains primarily a diagnosis of inspection and the physical examination is of utmost importance for directing the etiological diagnosis of patients with diabetes and/or hyperandrogenism. The systematic analysis of adipose tissue distribution in these situations can reveal cases with a typical clinical presentation, but also a large number of borderline forms with type 2 diabetes.


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