Cardiovascular complications of lipodystrophic syndromes – focus on laminopathies

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Complications cardiovasculaires des syndromes lipodystrophiques - focus sur les laminopathies

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Introduction : lipodystrophy and cardiovascular diseases

Lipodystrophic syndromes are genetic or acquired rare diseases characterized by a partial or generalized lack of adipose tissue leading to insulin resistance, hypertriglyceridemia and hepatic steatosis. These heterogeneous diseases are of familial or sporadic occurrence, of congenital or delayed clinical expression during childhood or adulthood, and are associated or not with different multi-organ comorbidities, including cardiovascular manifestations [1].

Lipodystrophy-associated cardiovascular involvement is expressed as heterogeneous disorders, either heart muscle diseases, with hypertrophic or dilated cardiomyopathies, rhythm and conduction system diseases, and/or coronary artery disease [2]. Cardiovascular alterations, which are important causes of morbi-mortality in patients with lipodystrophy, result from several non-mutually exclusive mechanisms. Besides the deleterious role of insulin resistance, diabetes, and dyslipidemia, some studies point to additional pathophysiological factors such as cardiac fatty infiltration, fibrosis, autonomic neuropathy, precocious cellular senescence, and cell-autonomous consequences to each specific pathogenic molecular variant [3-7].

The example of laminopathies, due to pathogenic variants in *LMNA* encoding A-type lamins, illustrates well the challenges of multiple cardiovascular phenotypes associated with lipodystrophy and their consequences for clinical practice.

Laminopathies : a broad spectrum of diseases with different cardiovascular phenotypes

Although *LMNA* is ubiquitously expressed in all differentiated tissues, laminopathies form tissue-specific diseases that may clinically translate into skeletal and/or cardiac muscular dystrophies (Emery-Dreifuss muscular dystrophy (EDMD), limb girdle muscular dystrophy 1B (LGMD1B), congenital muscular dystrophy (L-CMD)), dilated cardiomyopathy with conduction defects (DCM-CD), axonal neuropathies (Charcot-Marie-Tooth disease type 2), lipodystrophies or premature ageing syndromes (mandibuloacral dysplasia, Hutchinson-Gilford progeria syndrome (HGPS), atypical progeroid syndromes, and restrictive dermopathy) [8]. Dunnigan syndrome, also known as familial partial lipodystrophy type 2 (FPLD2), is due to heterozygous *LMNA* pathogenic variants, with a mutational hot spot

located at residue Arg482 in the C-terminal part of the protein. It is the most frequent form of genetically-determined lipodystrophy, characterized by partial lipoatrophy with insulin resistance, hypertriglyceridemia, hepatic steatosis, and frequent ovarian hyperandrogenism [9, 10].

The heart and the vascular wall appear as recurrent targets in most forms of laminopathies. On the one hand, laminopathies of the striated muscle, including EDMD, LGMD1B, L-CMD and DCM-CD, are frequently associated with dilated cardiomyopathy [11]. On the other hand, in *LMNA*-linked lipodystrophies, frequent and early atherosclerotic cardiovascular events have been reported [3,12]. In addition, HGPS and *LMNA*-associated premature ageing syndromes are associated with lipoatrophy and with very precocious and severe atherosclerosis and valvular calcifications [13].

Complexity of cardiovascular involvement in the different types of lipodystrophic laminopathies

In addition to premature atherosclerosis, cardiomyopathic features have been reported in few patients with typical FPLD2 carrying heterozygous substitutions at the codon 482 of the *LMNA* gene [7]. Furthermore, lipodystrophic complex laminopathy phenotypes, mostly due to non-codon 482-associated *LMNA* pathogenic variants have been described, associating lipodystrophy and skeletal and/or cardiac dystrophic features [14-19]. Frequent dilated or to a lower extent hypertrophic cardiomyopathies are observed in such patients [7].

Lipodystrophy can also reveal *LMNA*-associated atypical premature ageing syndromes [20,21]. In affected patients, the cardiovascular phenotype mainly results from valvulopathy and/or atherosclerotic features. However, cardiomyopathy has also been described, and could be worsened by insulin resistance and/or diabetes [22, and personal results].

In *LMNA*-linked lipodystrophies, premature and severe atherosclerosis is not systematically associated with major cardiometabolic risk factors [3,12,23]. Recent studies showing mesodermal and endothelial differentiation defects upon expression of the *LMNA* p.Arg482Trp variant suggest that developmental alterations could contribute to both lipodystrophy and premature atherosclerosis in FPLD2 [24]. Other pathophysiological

mechanisms could include defects in prelamin A post-translational maturation leading to both myocardial inflammation and premature senescence of endothelial and smooth vascular muscle cells [12,25,26] and/or laminopathic alterations in extracellular matrix leading to fibrosis [27].

Consequences for clinical practice

In patients diagnosed with a lipodystrophic syndrome, whatever its etiology, cardiovascular investigations, including at least ECG and echocardiography should be systematically performed [1].

A clear-cut classification of cardiovascular phenotypes among the different tissue-specific laminopathies, involving either heart muscle or the cardiac vasculature, may be challenging. Indeed, in *LMNA*-linked lipodystrophies, both cardiac muscle and arteries can be affected. Therefore, in each patient diagnosed with lipodystrophy due to a *LMNA* pathogenic variant, in addition to systematic ECG and echocardiography and even in the absence of any specific sign, other cardiovascular investigations should be systematically discussed, based on genotype, cardiovascular family history, age at diagnosis, and other cardiovascular risk factors. These include a 24-hour Holter ECG monitoring to detect rhythm and/or conduction disturbances, and stress test and/or coronary CT angiogram to detect coronary artery disease. Cardiac MRI should also be discussed evaluating cardiac steatosis and fibrosis.

Cardiovascular specific therapies should be discussed with cardiologists trained in the management of *LMNA*-associated diseases. It should be emphasized that *LMNA*-associated cardiomyopathy may require the implantation of cardioverter-defibrillator to prevent sudden death [28].

Therapeutic management of lipodystrophy-associated metabolic alterations should follow the current international recommendations, with lifestyle and dietary measures being essential for prevention and treatment of metabolic complications [1]. Exercise should be strongly encouraged in the absence of cardiovascular contraindications. Dyslipidemia should be managed in accordance with guidelines for the general population. However, even in patients without diabetes, strict lipid targets (LDL-cholesterol <100 mg/dL, non-HDL-cholesterol

<130 mg/dL, triglycerides <200 mg/dL) are recommended in the context of lipodystrophy-associated increased cardiovascular risk [1]. The association of statins and fibrates should be used with caution in the case of associated muscular dystrophy or inflammatory muscular involvement. The cardiovascular effects of metformin, used as a first-line drug therapy in most patients with lipodystrophy-associated diabetes, and of other non-specific antidiabetic drugs, have not been specifically evaluated in patients with lipodystrophy. The orphan drug metreleptin, a leptin analog, has recently obtained an European Marketing Authorization and is available in France for the treatment of metabolic complications associated with leptin deficiency in selected lipodystrophic patients. In addition to its beneficial effects on insulin sensitivity, insulin secretion and hypertriglyceridemia, metreleptin could decrease LDL-cholesterol and PCSK9 serum levels, and improve the atherogenic lipid profile in patients with lipodystrophy [29-31].

Conclusion - Cardiovascular evaluation and management : a systematic requirement for patients with lipodystrophic syndromes

The clinical and molecular heterogeneity of lipodystrophic syndromes requires a multidisciplinary expertise for each affected patients. At the cardiovascular level, it translates into several manifestations, including cardiomyopathies, rhythm and conduction disturbances and/or coronary artery disease. It is particularly the case for laminopathies, for which cardiovascular evaluation and management requires a close collaboration between endocrinologists and cardiologists.

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