



EDITORIAL COMMENT

Familial amyloid polyneuropathy, sympathetic denervation and liver transplantation[☆]



Polineuropatia amiloidótica familiar, desnervação simpática e transplante hepático

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The various forms of amyloidosis are characterized by the extracellular deposition of amyloid substances. These consist of insoluble, non-functional fibrils derived from different precursor proteins that accumulate in characteristic conformations. Amyloid infiltration into organs causes them to fail, and cardiac amyloidosis is a major cause of death.¹

The common denominator of both hereditary and acquired forms of amyloidosis is prolonged exposure to an abnormal protein or to excessive quantities of a normal protein. More than 30 amyloid precursor proteins are known,² the most common being immunoglobulin light chain, wild-type transthyretin, and mutant forms of transthyretin, apolipoprotein A1 and fibrinogen alpha chain.³

Mutant variants of transthyretin are the cause of the most common type of autosomal dominant hereditary systemic amyloidosis, familial amyloid polyneuropathy (FAP).⁴

Transthyretin is a plasma transport protein mainly synthesized by the liver. FAP is the result of mutations in *TTR*, the gene that codes for transthyretin, with the Val30Met mutation being responsible for 50% of cases. Clinically, FAP is characterized by sensory, motor and autonomic

neuropathy, gastrointestinal alterations, and heart and renal failure that can rapidly lead to death. The phenotype varies according to geographic origin of the mutation, age of onset, and gender.^{4,5}

The first cases of FAP were described by Corino de Andrade in northern Portugal (Vila do Conde and Póvoa do Varzim) in 1952.⁶ Its prevalence in the endemic areas of Portugal and Sweden ranges between 1/1000 and 1/10 000 individuals.⁴

Effective treatment requires an accurate diagnosis based on histopathology and genetics. Imaging studies such as echocardiography, magnetic resonance and scintigraphy aid assessment of the extent and severity of involvement of different organs and enable stratification of associated risk.^{4,5}

Liver transplantation has made it possible to slow the progression of the disease, and recently there have been promising reports of drugs, including tafamidis and diflunisal, that appear to stabilize transthyretin.^{4,5}

The article by Coutinho et al.⁷ in this issue of the *Journal* analyzes the use of MIBG scintigraphy to assess cardiac sympathetic denervation and how it is affected by liver transplantation in FAP patients. Their work is of particular interest due to the high prevalence of the disease in some regions of Portugal. It is a prospective observational study of 232 carriers of the Val30Met mutation who underwent annual clinical assessment and serial ¹²³I-MIBG scans.

¹²³I-MIBG scintigraphy provides information on cardiac autonomic neuropathy, but its role in clinical practice is as

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yet unclear. ^{123}I -MIBG is an analog of norepinephrine and behaves similarly; when injected peripherally it is taken up by presynaptic nerve endings at concentrations that are dependent on the release and uptake of norepinephrine and thus on the integrity of the autonomic nervous system. The heart-to-mediastinum ratio is a measure of relative uptake of the radioisotope in the heart and mediastinum and is lower in cases of sympathetic denervation.⁸

Coutinho et al. report that decreased heart-to-mediastinum ratio was associated with risk of death, and that this ratio stabilized during a median follow-up of 4.5 years in 70 patients who underwent liver transplantation. They conclude that sympathetic denervation is common in this variant of FAP and that MIBG scintigraphy is useful for risk stratification in these patients. Their results suggest that liver transplantation halted progression of sympathetic denervation.

^{123}I -MIBG scintigraphy is used to study cardiac denervation in various conditions including ischemic heart disease, heart failure, arrhythmias and sudden death; risk of the latter has been shown to be associated with sympathetic denervation assessed by ^{123}I -MIBG scintigraphy in certain contexts.^{8,9}

There are few studies in the literature on the use of ^{123}I -MIBG scintigraphy in FAP. One of the first was a case report in Japan in 1995.¹⁰ In 1999 a study by Delahaye et al. published in the *European Journal of Nuclear Medicine* concluded that ^{123}I -MIBG scintigraphy was of value for assessing cardiac sympathetic denervation in FAP,¹¹ and in 2006, in a study of 31 patients, the same group reported that liver transplantation helped stabilize denervation and that patients with worsened neurological status after transplantation were those who had had the most severe denervation before surgery.¹²

Coutinho et al.'s group have already published two articles on ^{123}I -MIBG scintigraphy in FAP: a study of 34 patients in the *Journal* in 2004 that demonstrated a high incidence of cardiac denervation in FAP type I,¹³ and another of 143 patients in *Circulation: Cardiovascular Imaging* in 2013, in which they concluded that sympathetic denervation as assessed by ^{123}I -MIBG scintigraphy was a prognostic marker in FAP patients.¹⁴

The article under discussion⁷ is thus part of a research line they have followed for some years and that now covers a substantial population of FAP patients assessed by ^{123}I -MIBG scintigraphy. They have related the findings with prognosis and conclude that sympathetic denervation does in fact stabilize following liver transplantation.

Conflicts of interest

The author has no conflicts of interest to declare.

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