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Cardiac Dysautonomia Predicts Long-Term Survival in Hereditary Transthyretin Amyloidosis After Liver Transplantation

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ABSTRACT

OBJECTIVES This study sought to compare techniques evaluating cardiac dysautonomia and predicting the risk of death of patients with hereditary transthyretin amyloidosis (mATTR) after liver transplantation (LT).

BACKGROUND mATTR is a multisystemic disease involving mainly the heart and the peripheral nervous system. LT is the reference treatment, and pre-operative detection of high-risk patients is critical. Cardiovascular dysautonomia is commonly encountered in ATTR and may affect patient outcome, although it is not known yet which technique should be used in the field to evaluate it.

METHODS In a series of 215 consecutive mATTR patients who underwent LT, cardiac dysautonomia was assessed by a dedicated clinical score, time-domain heart rate variability, ^{123}-meta-iodobenzylguanidine heart/mediastinum (^{123}-MIBG H/M) ratio on scintigraphy, and heart rate response to atropine (HRRA).

RESULTS Patient median age was 43 years, 62% were male and 69% carried the Val30Met mutation. Cardiac dysautonomia was documented by at least 1 technique for all patients but 6 (97%). In univariate analysis, clinical score, ^{123}-MIBG H/M ratio and HRRA were associated with mortality but not heart rate variability. The ^{123}-MIBG H/M ratio and HRRA had greater area under the curve (AUC) of receiver-operating characteristic curves than clinical score and heart rate variability (AUC: 0.787, 0.748, 0.656, and 0.523, respectively). Multivariate score models were then built using the following variables: New York Heart Association functional class, interventricular septum thickness, and either ^{123}-MIBG H/M ratio (S_{MIBG}) or HRRA ($S_{atropine}$). AUC of S_{MIBG} and $S_{atropine}$ were greater than AUC of univariate models, although nonsignificantly (AUC: 0.798 and 0.799, respectively). Predictive powers of S_{MIBG}, $S_{atropine}$, and a reference clinical model (AUC: 0.785) were similar.

CONCLUSIONS Evaluation of cardiac dysautonomia is a valuable addition for predicting survival of mATTR patients following LT. Among the different techniques that evaluate cardiac dysautonomia, ^{123}-MIBG scintigraphy and heart rate response to atropine had better prognostic accuracy. Multivariate models did not improve significantly prediction of outcome. (J Am Coll Cardiol Img 2016;■:■–■) © 2016 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

AUC = area under curve

CI = confidence interval

ECG = electrocardiogram

H/M = heart-mediastinum ratio

HRRA = heart rate responses to atropine

IQR = interquartile range

LT = liver transplantation

mATTR = hereditary transthyretin amyloidosis

^{123}-MIBG = ^{123}-meta-iodobenzylguanidine

NYHA = New York Heart Association

PND = polyneuropathy disability score

ROC = receiver-operating characteristic

SDNN = standard deviation of the normal sinus cycles

TTR = transthyretin

Amyloidosis due to hereditary transthyretin amyloidosis (mATTR) is a rare life-threatening, autosomal dominant disease caused by mutation of the transthyretin (TTR), a thyroxine transport protein. The mutation is associated with an unstable tetrameric structure of TTR leading to misfolding, promoting the deposition of amyloid fibrils predominantly in the peripheral nerves, heart, eyes, gastrointestinal tract, and kidneys. In endemic regions, Val30Met, Val122Ile, and Thr60Ala are the most prevalent TTR variants, although >100 variants have been reported worldwide. Depending on the mutation, the clinical manifestations of mATTR are as follow: 1) predominantly a polyneuropathy, known as familial amyloid polyneuropathy; 2) predominantly a cardiomyopathy with minimal or no neuropathy, known as familial amyloid cardiomyopathy; or 3) "mixed" forms of the disease, with cardiac and neurological manifestations (1,2). Cardiac involvement includes heart failure due to infiltrative and restrictive cardiomyopathy, cardiac arrhythmias, and cardiac denervation (3). This denervation affects both the sympathetic and the parasympathetic systems. The sympathetic system effect involves a decrease in pre-synaptic catecholamine stores with preserved cardiac β-receptor catecholamine responsiveness, which leads to an early and striking decrease in meta-iodobenzylguanidine (MIBG) uptake. On the other hand, parasympathetic denervation is associated with up-regulation of muscarinic acetylcholine receptors; however, because acetylcholine availability and binding is absent, parasympathetic tone is low and atropine has minimal or no effect on heart rate (4–6). By removing the main source of the circulating mutated TTR, orthotopic liver transplantation (LT) improves the course of the neuropathy and survival (7,8). More recently, pharmaceuticals have been developed as an alternative to LT (9–12). Nevertheless, LT remains the mainstay of familial amyloidotic polyneuropathy therapy and remains the historical reference for the evaluation of new treatments (13,14).

Several factors influence the prognosis after LT (7,15–20), including cardiac dysautonomia, and our group recently proposed a multivariate model to evaluate the risk of death in LT patients (21). This score is based on readily available clinical cardiac and neurological variables that included orthostatic hypotension, a typical symptom of dysautonomia. Numerous techniques exist to evaluate cardiovascular dysautonomia, including ^{123}-MIBG scintigraphy, heart rate variability, and heart rate response to atropine, and previous reports indicate that evaluation of cardiac denervation using these techniques could be of interest to assess prognosis in mATTR patients (18,22–25). To the best of our knowledge, no study thus far has evaluated and compared the prognostic accuracy of these techniques to predict overall mortality in mATTR patients after LT.

In this study, we aimed to evaluate and compare the ability to predict the overall mortality in mATTR patients after LT of 4 different techniques reflecting cardiac dysautonomia: clinical evaluation; time-domain heart rate variability; ^{123}-MIBG cardiac scintigraphy; and heart rate response after atropine injection.

METHODS

From the database of the French National Reference Center for Familial Amyloidotic Polyneuropathy, we identified 218 consecutive patients who underwent LT for mATTR between January 1, 1993 and January 1, 2011. mATTR was diagnosed by the observation of both amyloid deposits in biopsy specimens and a TTR mutation. After the exclusion of 3 patients who underwent combined heart and liver transplantation, 215 patients entered the analysis, of which 1 was censored at 65 months after LT when undergoing cardiac transplantation. Patient characteristics, clinical evolution, and outcomes, including the causes of death, were analyzed. This study complied with the ethical principles formulated in the Declaration of Helsinki and was approved by the ethics committee of the Hôpital de Bicêtre, Bicêtre, France. All patients who survived to the day of study initiation gave written, informed consent to participate in the registry (Commission Nationale de l'Informatique et des Libertés no. 1470960).

PREOPERATIVE EVALUATION. The cardiac evaluation included a physical examination and assessment of the New York Heart Association (NYHA) functional class, a surface electrocardiogram (ECG), and an echocardiogram. Pulmonary artery pressures, capillary wedge pressure, and cardiac index were measured during right heart catheterization in 200 patients. Arrhythmias and intracardiac conduction disorders were evaluated with 12-lead ECG, 24-h Holter ECG recordings, and electrophysiological studies as previously reported (26).

The neurological evaluation included a neuropathy impairment score and the polyneuropathy disability score (PND) (27,28). Nerve conduction studies of the extremities were performed by measuring the sensory action potential amplitude of the ulnar and sural nerves and the compound muscle action potential amplitude of the ulnar and peroneal nerves.