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NT-proBNP and High-Sensitivity Cardiac Troponin T Fail to Detect Cardiac Involvement in Erdheim-Chester Disease

To the Editor: Erdheim-Chester disease (ECD) is a rare non–Langerhans cell histiocytosis belonging to the L-group of the 2016 revised histiocytosis classification.[1] Although frequent and associated with clinical complications, cardiac involvement is underdiagnosed in ECD.[2] Cardiac magnetic resonance (CMR) imaging is the most robust way to detect cardiac involvement.[3] However, access to this technique is limited. We evaluated the utility of B-type natriuretic peptides and troponin for the diagnosis of cardiac involvement in ECD.

We retrospectively included patients with a biopsy-proven diagnosis of ECD who were referred to the internal medicine department of a French tertiary care center or the hematology department of an Israeli tertiary care center and had undergone both CMR and assessment of B-type natriuretic peptide and troponin levels, at least once, between 2007 and 2019.

Cardiac magnetic resonance imaging was performed on a 1.5T scanner (Siemens Aera). All images were re-read in a blind fashion by an experienced radiologist (M.B.). Cardiac involvement was defined as abnormal epicardial or pericardial enhancement or infiltration. Cardiac biomarker levels were determined at the physician's discretion, in the routine clinical care setting. Natriuretic peptide test assessment was performed using *N*-terminal pro–brain natriuretic peptide (NT-proBNP) at the French center (normal, <300 pg/mL) and brain natriuretic peptide (BNP) at the Israeli center (normal, <100 pg/mL). Troponin assessment was performed using high-sensitivity cardiac troponin (hs-cTnT) at the French center (normal, <14 μg/L) and troponin I at the Israeli center (normal, <0.04 μg/L). Only NT-proBNP and hs-cTnT were considered in quantitative analysis.

The study was approved by the appropriate ethics committee (*Comité de Protection des Personnes d'Ile de France III* [#2011-A00447-34]) and was conducted in accordance with the Declaration of Helsinki.

We included 122 patients in total (118 in France, 4 in Israel), with a mean age of 58.7 years (±13.9 years). Most of the patients (70%) were male. $BRAF^{V600E}$ mutations were detected in 75 patients (61.5%). Biologic assessment was performed a median of 12 months (1 to 33 months) after cardiac imaging. Coronary artery disease was present in 28 patients (23.1%). Mean left ventricular ejection fraction was 57% (±7%). Erdheim-Chester disease–related cardiac involvement was present in 57 patients (46.7%).

Median NT-proBNP concentration was 173 (73 to 470) pg/mL (normal, <300 pg/mL). Median NT-pro-BNP levels were similar between patients with and without right atrioventricular sulcus infiltration (195 vs 154 pg/mL; *P*=.3; Figure A). Area under the curve was 0.68 for cardiac involvement detection using NT-proBNP (Figure C). With an optimal threshold of 114 pg/mL, NT-proBNP diagnostic performances were as follows: sensitivity, 0.79; specificity, 0.58; accuracy, 0.68; negative predictive value, 0.76; and positive predictive value, 0.62. The NT-proBNP/BNP levels were high in 38 (32.8%) patients. Cardiac involvement was detected on imaging in 22 (57.9%) of the patients with high NT-proBNP/BNP levels and in 30 (38.5%) of those with normal NT-proBNP/BNP levels (*P*=.08). High levels of NT-proBNP/BNP were associated with the presence of coronary artery disease (*P*=.001), atrial fibrillation (*P*=.001), older age (*P*=.001), and higher serum creatinine concentration (*P*=.02; Table).

Median hs-cTnT concentration was 9 (6 to 16) μg/L (normal, <14 μg/L). Median hs-cTnT levels were similar between patients with and without right atrioventricular sulcus infiltration (10.3 vs 9 μg/L; *P*=.3; Figure B). Area under the curve was 0.64 for cardiac involvement detection using hs-cTnT (Figure D). With an optimal threshold of 4.8 μg/L, hs-cTnT diagnostic performances were as follows: sensitivity, 0.96; specificity, 0.25; accuracy, 0.59; negative predictive value, 0.88; and positive predictive value, 0.54. Troponin levels were high in 39 patients (32%). Cardiac involvement was detected on imaging in 20 patients with high troponin levels (51.3%) and 37 (45.1%) patients with normal troponin levels (*P*=.7). High troponin levels were associated with the presence of atrial fibrillation (*P*=.001), older age (*P*=.001), and higher serum creatinine concentration (*P*=.001; Table).

In other infiltrative diseases, such as amyloidosis and Fabry disease, cardiac biomarkers have been

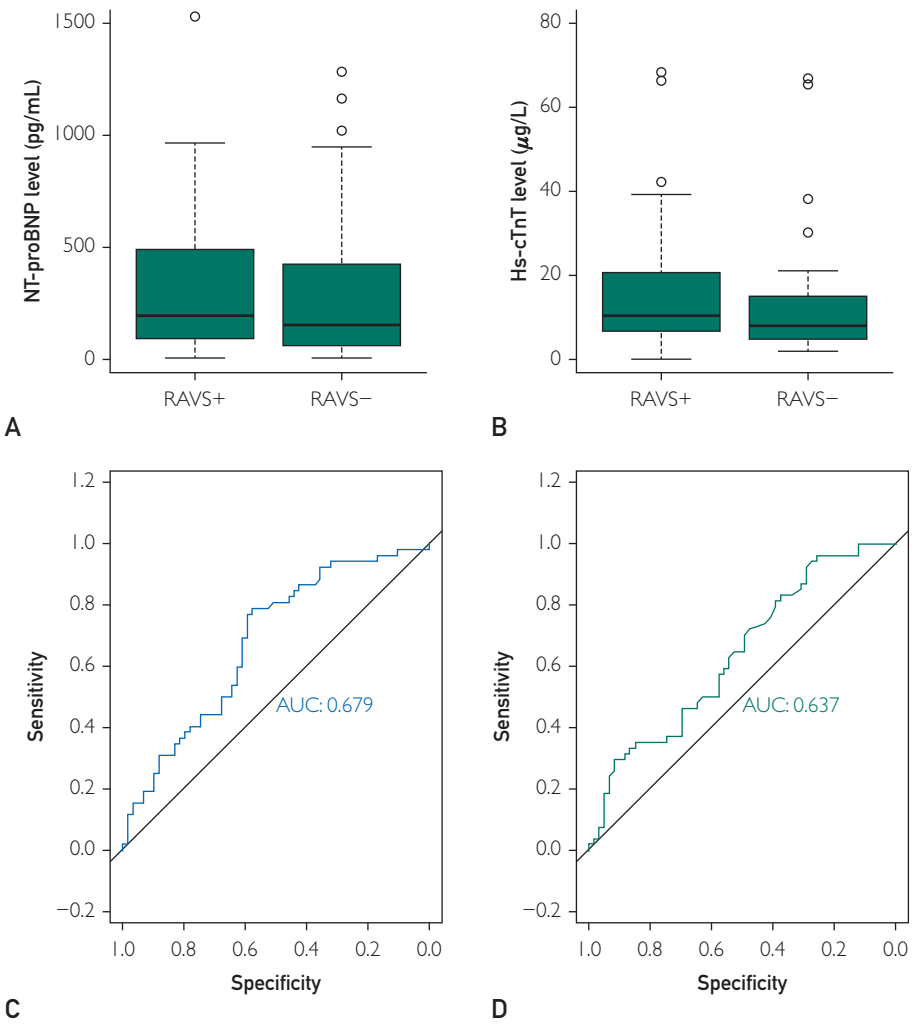

FIGURE. *N*-Terminal pro—brain natriuretic peptide (NT-proBNP) and high-sensitivity cardiac troponin T (hs-cTnT) were measured in 118 patients. A, The NT-proBNP levels according to right atrioventricular sulcus (RAVS) infiltration. B, The hs-cTnT levels according to RAVS infiltration. C, The NT-proBNP area under the receiver operating characteristic curve (AUC) for cardiac involvement. D, The hs-cTnT AUC for cardiac involvement.

shown to be highly sensitive and specific for both diagnosis and the prediction of prognosis.[4,5] Our findings suggest that they are much less sensitive and specific in the setting of ECD. There are 2 pathophysiologic explanations for this discrepancy. First, unlike amyloidosis and other infiltrative diseases, ECD rarely leads to infiltration of the ventricle, with the infiltrates located mostly in the atria. Second, histiocytes predominantly infiltrate the adventitial tissue, particularly the perimyocardial white fat, in such a way that they may not necessarily cause myocardial damage.

These findings further highlight the need for a coronary artery disease assessment, especially in patients with elevated NT-proBNP, and the need for CMR imaging to unravel cardiac involvement in ECD.

In conclusion, NT-proBNP and hs-cTnT concentrations are not a reliable surrogate for cardiac involvement in ECD, but their elevation should prompt coronary artery disease assessment.

POTENTIAL COMPETING INTERESTS

The authors report no competing interests.

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TABLE. Clinical and Cardiovascular Features According to NT-proBNP and Troponin Levels in Patients With ECD[a,b,c]

Clinical features	All	Normal NT-proBNP/BNP levels	High NT-proBNP/BNP levels	*P* value	Normal troponin levels	High troponin levels	*P* value
No. of patients	122	78	38		82	39	
Mean age, years	58.7(14)	55.7 (14)	64.2 (12)	.001	55.5 (14)	65.3 (12)	.001
Female	37 (30)	27 (35)	10 (26)	.5	29 (35)	8 (22)	.1
$BRAF^{V600E}$ mutation	75 (62)	45 (58)	24 (63)	>.99	51 (62)	24 (62)	.7
Death	22 (18)	11 (14)	11 (29)	.1	13 (156)	8 (21)	.7
Confounding factors							
Creatinine, μmol/L	97.5 (38)	90.5 (33)	111 (45)	.02	87.5 (29)	118 (48)	.001
C-reactive protein, mg/L	15.7 (20)	10.8 (16)	25.9 (25)	.001	12.5 (17)	22.2 (24)	.03
BMI, weight (kg)/height $(cm)^2$	26.5 (4)	26.4 (4)	26.8 (5)	.7	26.5 (4)	26.6 (5)	.9
LVH	17 (14)	10 (13)	6 (17)	.8	8 (10)	8 (22)	.09
CAD	28 (23)	11 (14)	16 (43)	.001	15 (18)	13 (34)	.09
AF and/or flutter	10 (8)	0 (0)	9 (26)	.001	2 (2.44)	7 (19)	.003
LVEF, %	57.1 (7)	58.2 (5)	54.7 (9)	.03	57.6 (6)	55.8 (9)	.3
CMR findings							
Cardiac ECD	57 (47)	30 (39)	22 (58)	.08	37 (45)	20 (51)	.7
Pseudomass	38 (31)	24 (31)	10 (26)	.8	27 (33)	11 (28)	.8
RAVS infiltration	44 (36)	26 (33)	14 (37)	.9	31 (38)	13 (33)	.8
RA free wall infiltration	20 (17)	10 (14)	10 (26)	.2	12 (15)	8 (21)	.7
RA posterior wall infiltration	28 (23)	16 (21)	11 (29)	.5	17 (21)	11 (28)	.5
IA septum infiltration	28 (23)	17 (22)	9 (24)	>.99	18 (22)	10 (26)	.8
LAVS infiltration	9 (7)	5 (6)	4 (11)	.5	6 (7)	3 (8)	>.99
Left atrium infiltration	13 (11)	6 (8)	6 (16)	.2	7 (9)	6 (15)	.4
Pericardial effusion	27 (22)	14 (18)	9 (24)	.6	16 (20)	11 (28)	.4
Pericardial enhancement	14 (12)	7 (9)	5 (13)	.5	7 (9)	7 (18)	.1
Pericardial thickening	18 (15)	8 (10)	8 (21)	.2	9 (11)	9 (23)	.1

[a]AF, atrial fibrillation; BMI, body mass index; BNP, brain natriuretic peptide; CAD, coronary artery disease; CMR, cardiac magnetic resonance; ECD, Erdheim-Chester disease; IA, interatrial; LAVS, left atrioventricular sulcus; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; NT-proBNP, *N*-terminal pro—brain natriuretic peptide; RA, right atrial; RAVS, right atrioventricular sulcus.

[b]To convert C-reactive protein values to nmol/L, multiply by 9.524.

[c]Categorical variables are presented as number (percentage). Continuous variables are presented as mean (standard deviation).

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