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Authors' reply

To the Editor,

We would like to thank Stöllberg et al. for their comments on our report about a Fabry disease patient with Wolff-Parkinson-White (WPW) and left ventricular noncompaction (LVNC)[1] and for the opportunity to discuss the case further.

Left ventricular noncompaction (LVNC), or spongy myocardium, is a rare abnormality of the left ventricular wall resulting from intrauterine developmental arrest of normal compaction process of myocardium in the first trimester leading to two layers of myocardium: the compacted and the noncompacted.[2] It may be genetically familial or sporadic. The familial types of LVNC are the most common, and follow autosomal-dominant, X-linked, or mitochondrial inheritance patterns.[3] Several gene loci were found to be associated with this cardiomyopathy: tafazzin (TAZ-G4.5),[4] alpha-dystrobrevin (DTNA),[5] LIM domain-binding protein 3 (ZASP/LDP3),[6] and lamin A/C (LMNA).[7] It can occur in isolation or coexist with other cardiac and/or systemic anomalies.[3] Anastomosing broad trabeculae, coarse trabeculae (resembling multiple papillary muscles), sponge-like interlacing smaller muscle bundles and absence of well-formed papillary muscles are histologic gross pattern of the disease.[8]

Clinical presentation of disease varies from patient to patient. Congestive heart failure symptoms are the most reported presentation. The disease leads to both systolic and diastolic dysfunction. Abnormal relaxation and restrictive filling caused by the numerous prominent trabeculae are the determinants of dyastolic dysfunction,[9] while subendocardial hypoperfusion and microcirculatory dysfunction determine the systolic dysfunction.[10]

WPW syndrome,[11] atrial fibrillation, and ventricular arrhythmias are rhythm disturbances associated with LVNC,[12] and sudden cardiac death is one of the major causes of death in this cardiomyopathy.[13] Increased thromboembolism risk is another clinical aspect of the disease. Stroke, transient ischemic attack (TIA), pulmonary embolism, systemic emboli, and mesenteric infarction may be seen.

Diagnosis is made mostly by echocardiography, though cardiac magnetic resonance imaging (CMRI), computed tomography (CT) scan, and contrast left ventriculography (LVG) are other options. Chin et al., 1990;[14] Stollberger et al., 2002;[15] and Jenni et al., 2001[16] suggested echocardiography criterion for diagnosis, but CMRI is the preferred imaging modality when echo image is insufficient.

We reported on a 28-year-old Fabry disease patient with WPW and LVNC.[1] Our patient's father suffered from cardiovascular disease (CVD) and died when he was 55-years-old from myocardial infarction (MI). He had kidney operation but the reason was not clear. Her mother has undergone coronary artery bypass graft surgery for 3 vessels and is alive. She has 3 paternal uncles, 2 of whom are dead (cardiovascular reasons are highly possible) and the other is alive with previous anamnesis of MI. She had 2 paternal aunts who were dead in their 50s from CVD. She has no maternal uncles, but 2 aunts. Both maternal aunts are alive and suffer from diabetes mellitus (DM). She has 3 brothers and 1 sister. Her sister has been diagnosed with DM. She has 2 sons and they have no chronic disease diagnosis as yet. Her sister's daughter is under nephrology surveillance, but the patient could not define proper anamnesis. It is clear that the patient's family did not undergo a thorough evaluation for Fabry disease.

Our patient's medical history was unremarkable until 2011, when she was diagnosed with Fabry disease at a university hospital. At the time she had multiple

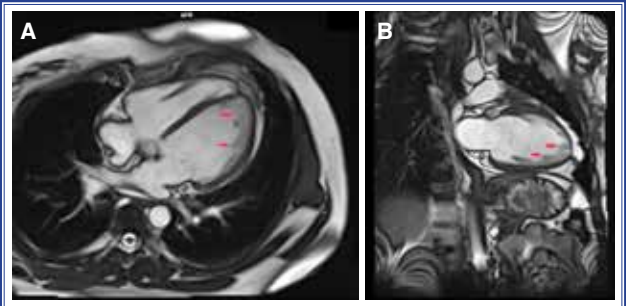

Figure 1. **(A)** Transverse cut view of MRI showing LVNC. **(B)** Coronal cut view of MRI showing LVNC.

angiokeratomas on knees, lower back, buttocks, hips, and thighs, and was suffering from acroparesthesia. Genetic analysis was attempted but did not find a clear mutation for disease. However, serum α-galactosidase A levels were found to be low. Enzyme replacement treatment (ERT) was discussed but was not started and the patient could not provide a specific explanation for not proceeding. Apart from Fabry disease, she was not diagnosed with any kind neuromuscular disorder, and she is not a competitive athlete. She had 2 successful term pregnancies and she did not recall any syncope or heart failure symptoms during pregnancies.

The question of the patient's LVNC being secondary to another underlying disease could be responded to as follows: 1) There is no specific underlying factor for such hypertrophy (no history of neuromuscular disease, hypertension, being competitive athlete, hypo or hyperthyroidism); 2) According to the anamnesis of the patient, this hypertrophy is thought to be a sporadic case of acquired LV hypertrabeculation, rather than familial type of LVNC; 3) LV hypertrabeculation has already been reported in patients with other lysosomal storage disorders (LSDs), including Pompe disease[17] and Danon disease,[18] and our patient's LVNC is attributed Fabry disease, rather than another etiology; 4) There is no clear conclusion as to whether or not LVNC is a primary genetic cardiomyopathy or a morphologic trait shared by different cardiomyopathies. Previously reported Fabry disease patients with LVNC are also female, but we do not have a specific suggestion for this preponderance.

None of her first-degree relatives has been diagnosed with Fabry disease or LVNC, but it is clear that none of her first-degree relatives has undergone a complete cardiological and neurological examination. Diagnosis of the patient was established with cardiac MRI (Figure 1); however, she meets most of the echocardiography criteria suggested by Jenni et al., Stollenberg et al., and Chin et al., despite not having proper echo window or echogenicity (Figure 2, Video 1–3). Subendocardial late gadolinium enhancement (LGE) showing myocardial fibrosis was observed in our patient, and MRI showed ratio of noncompacted to compacted layer of LV lateral of higher than 2.3. Patient did not give informed consent for myocardial biopsy and, unfortunately, we did not have tissue study of myocardium. Patient's control echocardiography showed similar extension and morphology of hypertrophied myocardium; no heart failure findings were observed.

Acroparesthesia, one of the neurological symptoms of Fabry disease, is the only neurological symptom present in this patient. There is no anamnesis of stroke, cerebral microbleeds or entrapment syndrome. Another issue is that LVNC could cause stroke and embolism apart from Fabry disease. Anticoagulation could have been an option if the patient had stroke anamnesis.

Angiokeratomas, multiple papules, are dermatological expression of Fabry disease, and our patient had several in various locations. During follow-up the number of angiokeratomas changed (decreased and increased), but they were always present. There is no diagnosed involvement of another system yet.

In summary, it is not certain if patient's Fabry disease is familial or not. Patient is reluctant to accept her disease and efforts of medical teams, and neglects follow-up. Instead of pursuing care under surveillance of university hospital, where all the sub-specialties are present, she chose to wander from hospital to hos-

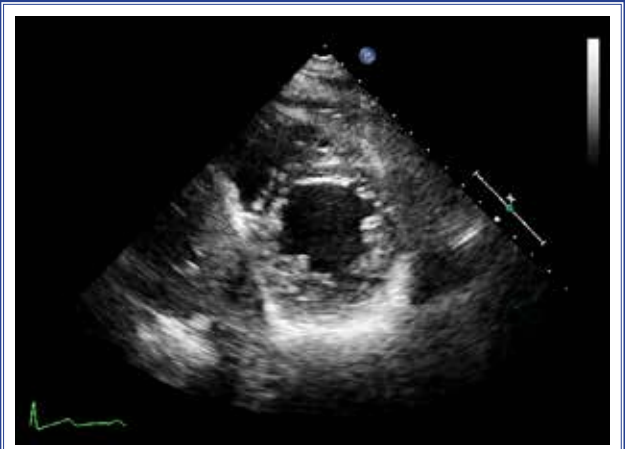

Figure 2. Parasternal short axis view of echocardiography showing LVNC.

pital in search of a cure. Therefore, disease anamnesis and system evaluations may be inconclusive. Family anamnesis of disease does not suggest pattern of inherited Fabry disease, but it is important to remember that none of the patient's relatives were examined properly. Nonetheless, we got the impression that this patient's Fabry disease is sporadic, rather than familial. To date, more than 600 Fabry disease mutations have been identified in human GLA gene, most of which are missense or nonsense nucleotide substitutions. As de novo mutations have been documented, the absence of Fabry disease family history does not rule out diagnosis of the disease,[20] nor does not being able to determine molecular diagnosis of Fabry disease rule it out.

Ahmet Taha Alper, M.D., Adnan Kaya, M.D., Ahmet İlker Tekkesin, M.D., Ahmet Öz, M.D.

Department of Cardiology, Dr. Siyami Ersek Cardiovascular and Thoracic Training and Research Hospital, İstanbul, Turkey

e-mail: adnankaya@gmail.com

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