

## Letter to the Editor

## Editöre Mektup

**Cardiological and neurological implications in Fabry disease with noncompaction**

Dear Editor,

With interest we read the case report by Alper et al. about a female patient with Fabry disease (alpha-galactosidase deficiency), Wolff-Parkinson-White (WPW) syndrome, and left ventricular hypertrabeculation/noncompaction (LVHT).<sup>[1]</sup> We have the following questions and concerns:

The present case is the third case described in the literature with LVHT and Fabry disease. All 3 cases were young females.<sup>[2,3]</sup> How to explain the female preponderance, which is at variance with the male preponderance in patients with LVHT?

In contrast to the statement in the discussion, LVHT is not only congenital, but has been shown to develop during lifetime in patients with neuromuscular disorders, athletes, and pregnant females. Thus, it would be interesting to know if the presented patient had been already pregnant, if she suffered from a neuromuscular disorder, if she was an active athlete, and if there were any previous echocardiographic or electrocardiographic (ECG) recordings.

Fabry disease is associated with more than 600 mutations.<sup>[4]</sup> Was mutation screening carried out in the presented patient? Did any of her first-degree relatives also suffer from Fabry disease or LVHT? Were relatives investigated by cardiologists and neurologists?

How to explain that the diagnosis of LVHT was only established by cardiac magnetic resonance imaging (CMRI) and not by echocardiography? Did the patient show delayed enhancement indicating myocardial fibrosis when examined with MRI? Was myocardial biopsy carried out during the electrophysiological study? Was the cardiac conduction system affected by glycolipid infiltration, as described previously?<sup>[5]</sup>

Enzyme replacement with agalsidase  $\beta$  has been shown to be beneficial for patients with Fabry disease.<sup>[4]</sup> Did the presented patient receive enzyme replacement therapy (ERT)? If not, what were the reasons for withholding the therapy? If she received the enzyme

therapy, was radiofrequency ablation carried out before or after beginning this therapy?

It is indicated that the patient suffered from acroparesthesia, and made several visits to the neurology department. Neurological manifestations of Fabry disease include polyneuropathy with burning feet and neuropathic pain; ischemic cerebral stroke, especially in young adults; cerebral microbleeds; and entrapment syndromes, especially carpal tunnel syndrome. It would be interesting to know which of these neurological manifestations of Fabry disease were found in the presented patient, and how they developed during follow-up.

It is reported that the patient has been symptom-free for 2 years. Were echocardiographic follow-up studies carried out and did LVHT change in morphology and extension?

The patient suffered from multiple papules on knees and hips. Did these papules grow, regress or remain stable during follow-up? Since Fabry disease is a multisystem disorder, it should be indicated if the patient developed manifestations of other organ systems, like renal or ophthalmological problems, during follow-up.

In summary, it would strengthen the results if more cardiological and neurological data about other family members are provided, if more details about the applied treatment and its therapeutic effect are reported, and if the discussion about some inconsistencies as indicated above is extended.

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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)<sup>[1]</sup> 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 noncompact.<sup>[2]</sup> 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.<sup>[3]</sup> Several gene loci were found to be associated with this cardiomyopathy: tafazzin (TAZ-G4.5),<sup>[4]</sup> alpha-dystrobrevin (DTNA),<sup>[5]</sup> LIM domain-binding protein 3 (ZASP/LDP3),<sup>[6]</sup> and lamin A/C (LMNA).<sup>[7]</sup> It can occur in isolation or coexist with other cardiac and/or systemic anomalies.<sup>[3]</sup> 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.<sup>[8]</sup>

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 diastolic dysfunction,<sup>[9]</sup> while subendocardial hypoperfusion and microcirculatory dysfunction determine the systolic dysfunction.<sup>[10]</sup>

WPW syndrome,<sup>[11]</sup> atrial fibrillation, and ventricu-

lar arrhythmias are rhythm disturbances associated with LVNC,<sup>[12]</sup> and sudden cardiac death is one of the major causes of death in this cardiomyopathy.<sup>[13]</sup> 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,<sup>[14]</sup> Stollberger et al., 2002,<sup>[15]</sup> and Jenni et al., 2001<sup>[16]</sup> 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.<sup>[1]</sup> 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