Medical Expertise*

"Development of the European Network in Orphan Cardiovascular Diseases"
„Rozszerzenie Europejskiej Sieci Współpracy ds Sierocych Chorób Kardiologicznych"

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CASE SUMMARY

The presented case report elaborates on the middle-aged male diagnosed with Fabry disease (FD) in his 40-ties. Long before final diagnosis, asymmetric left ventricular hypertrophy (LVH) was observed on echocardiogram and he was initially diagnosed with hypertrophic cardiomyopathy (HCM). Ultimately, the correct diagnosis of FD was made after measurement of serum level of alfa-galactosidase, which was very low and typical for FD. The conformation of FD in the index patient, prompted the screening in his family, which revealed that his sister had also milder manifestation of the disease. It is unclear when and what indications were followed, nevertheless, the patient was started on enzyme replacement therapy (ERT) with agalsidase-α. Although the exact duration of ERT is unknown, at some point a significant left ventricular outflow tract (LVOT) gradient was observed on echocardiogram. Importantly, this was a new finding, as such thing had never been observed on serial echocardiograms. The nature and significance of LVOT gradient in FD, especially in patients on concomitant ERT, is unknown and is a subject of the present review.

LITERATURE REVIEW

Fabry disease, which is also known as angiokeratoma corporis difusum, ceramide trihexosidosis, or Anderson-Fabry disease, is an X-linked inborn error of metabolism of glycosphingolipid pathway. It is caused by the deficiency of the lysosomal enzyme – hydrolase α-galactosidase A, which results in the accumulation and subsequent tissue deposition of globotriaosylceramide, the glycolipid substrate for α-galactosidase A. Enzyme replacement therapy with agalsidase-α (Replagal©) or agalsidase-β (Fabrazyme©) stabilize disease in some patients, but long term benefits and safety are unclear.
Cardiac features observed in FD include LVH, valvular disease, myocardial ischemia, and electrophysiological abnormalities that are probably caused by the intracellular accumulation of glycosphingolipids in myocardium, valves, vascular endothelium, and conduction system. Paradoxically, glycoshingolipid accounts for only 1-2% of cardiac mass and thus others, not

defined yet signaling pathways have to be activated, leading to hypertrophy, apoptosis, necrosis, and fibrosis. Fibrosis of the heart, as well as kidneys and central nervous system, is one of the hallmark and an ominous sign of the advanced disease. It is postulated that ERT is less effective in patients who have already developed fibrosis.
Majority of patients develop concentric hypertophy, nevertheless, asymmetrical septal hypertrophy is observed in 5-10% cases. Although not always present, the echocardiograms typically reveal two-layered LV structure, comprising of thickened hyperechogenic layer of intracellular glycolipid deposition in the endocardium and epicardium and inner hypoechogenic layer of deposition-spared myocardium. Moreover, LVH probably also results from progressive myocardial fibrosis. The fibrosis almost always starts in the mid-myocardium of the posterior-lateral wall. The intensity of fibrotic process determines the development of diastolic and at later stages systolic dysfunction. The degree of hypertrophy correlates with age but even in severe LVH, LVOT obstruction is rarely observed.
Another aspects of FD are concomitant involvement of kidneys, central and peripheral nervous system, skin, gastro-intestinal tract that all shortens an average life span by at least 20 years. Kidney involvement is one of the cardinal feature of FD, and is observed in at least half of males and 20% of females. The severity of renal pathology usually increases with age. One of the first and most frequent symptom is an unspecific pain in various areas, particularly limbs, which is a consequence of nerve fibers damage of both systemic and autonomic system. It is estimated that 60-80% of young boys experience various degrees of pain in their first years of living.

ERT and the heart in Fabry disease
Although theoretically attractive, the role of ERT especially in the cardiac setting is unknown. The available evidence suggest that response to ERT is variable across patient subgroups and that agalsidase may slow progression of FD, with slight improvement of existing changes. Nevertheless, many uncertainties remain, especially about the optimal onset of the therapy (bearing in mind substantial cost of treatment), differences in natural course of the disease between female and male patients as well as different response to treatment, or significance of associated fibrosis. Likewise, there are conflicting data on the efficacy of ERT on cardiac morphology and function. Most studies indicate potential benefits of ERT on heart, nevertheless there are also studies with rather negative findings. Furthermore, observed improvement in the heart morphology and/or function did not translate to heard endpoints, such as cardiovascular mortality or stroke.
In one of the recent studies it was showed that early initiation of ERT had numerous beneficial effects on the heart, including decrease of LV mass and thickness of inter-ventricular septum and posterior wall, decrease of blood pressure and improvement of diastolic function. In another study, authors using more sophisticated technique of cardiac function assessment by means of tissue Doppler imaging (TDI), observed improvement in myocardial velocities in patients on ERT in comparison to those without therapy. The other study showed significant improvement of LV morphology, assessed by means of cardiac magnetic resonance, however, the observed changes did not correlate with patients' functional status (NYHA) or parameters of diastolic function. Conversely, in one study that compared 40 FD patients on ERT with 40 subjects from Fabry Registry matched for age, gender, chronic kidney disease state and previous transient ischemic attacks (TIA) no differences were

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observed in main outcome (a composite of stroke, end-stage renal disease and death). In another study, despite ERT cardiac mass increased in males but remained stable in females. There is very few data on the ERT in the setting of LVOT obstruction in FD as this is a rare phenomenon in those patients. The recent case report describes two patients with FD, who despite optimal pharmacological treatment including ERT, had no resolution of LVOT and subsequently had septal myomectomy operation done. Perhaps, not necessarily related to the presented case, nevertheless, in an autopsy study of whole hearts harvested from three FD patients who were long treated with ERT, the therapy did not have much effect on extensive cardiac fibrosis and myocyte disarray.

Despite extensive literature survey, no study/report was found that observed similar phenomenon on the LVOT obstruction in FD patient treated with ERT. Furthermore, as there is a detailed echocardiographic follow-up available for this patients (and never LVOT gradient was observed before), it can be even speculated that actually it was ERT that may have caused LVOT obstruction. Although rather improbable, this hypothesis should also be taken into account as decision has to be made on the further management of this patient.

EXPERT'S OPINION

The key question in the presented patient should be: what kind of the mechanism(-s) are responsible for observed LVOT gradient? The literature on LVOT obstruction in FD is scarce. Naturally, the analogy to LVOT obstruction in hypertophic cardiomyopathy (HCM) is obvious. In the setting of HCM with LVOT obstruction, there are two main mechanisms: abnormal flow vectors and systolic anterior motion (SAM) of the mitral valve. The obstruction can be either in the LVOT or in the LV cavity; occasionally in both areas. Knowing that LVOT obstruction is uncommon in FD, even less in known on this pathology and extrapolation to HCM does not have to be correct. Although rather improbable, the pathomechanisms of LVOT gradient in FD can be completely different from those observed in HCM.

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