Medical Expertise*

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

Title: Occurrence of intra-ventricular systolic gradient in the course of enzyme replacement therapy complicated by massive, LV hypertrophy.

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CASE SUMMARY

In a 50-year-old male with typical symptoms of severe hypertrophic cardiomyopathy and underlying Fabry disease, alpha galactosidase replacement therapy was introduced. After a year-long enzyme supplementation, the patient developed progressive cardiac hypertrophy with intraventricular gradient, what suggested an association of the complication with the employed therapeutic management.

At present, progressive circulatory failure poses a direct danger to the patient's life. In case of such a complex clinical problem, therapeutic management is extremely difficult, since it is necessary to exercise caution while considering pros and cons of enzyme substitution treatment. Terminating the causal enzyme replacement treatment would be a mistake, since, as it may be surmised, this might lead to destabilization of the achieved homeostasis, with the onset (or exacerbation) of disturbances involving other organs.

The management of restrictive cardiomyopathy should focus on symptomatic treatment; while undertaking such a therapy, one should bear in mind the underlying disease, i.e. the severe genetic syndrome that is associated with specific consequences. At the present stage of the patient's clinical state, the treatment may be based on several theoretically possible solutions. Thus, the therapy may consist in 1) initiation of conservative treatment (β-blocker), 2) performing a radical cardiological intervention, 3) a patency-restoring surgical procedure

(myotomy), and finally 4) heart transplant. Each therapeutic option has its limitations and is associated with a degree of risk.

LITERATURE REVIEW

BACKGROUND

Fabry disease is a severe genetic syndrome caused by a deficiency of the enzyme alpha galactosidase A. In consequence, glycosphingolipids are stored in the tissues and body fluids of the affected patient. The disease has its onset in adolescence – the patients present with neurological abnormalities (paresthesia, pains, fever), impairment of hearing, cataracts and skin lesions. Mature patients present with complications involving the kidneys (nephrosis) and heart – left ventricular hypertrophy, valvular regurgitations and arrhythmias. Clinical symptoms may – although on rare occasions – be limited to a single organ only.

Causal treatment of Fabry disease consists in supplementation of recombinant alpha galactosidase A, what may alleviate or arrest the development of the condition. The treatment may have adverse effects (vasculopathy, arrhythmias, etc.); however, a progressive increase of intraventricular LV systolic gradient as a side effect of enzyme replacement therapy is questionable. An accidental coincidence of the complication seems more likely[1]. In patients with Fabry disease, left ventricular hypertrophy is manifested as hypertrophic cardiomyopathy, which gradually closes the lumen of the left ventricle

Enzyme replacement therapy in Fabry disease may provoke certain adverse phenomena, however, most likely there is no simple association with progressive obstruction of the blood flow from the left ventricle [2], the more so that a logical interpretation of the sequence of events (cause-effect) is questionable and difficult to explain. Thus, the development of such a complication should not be taken in favor of termination the enzyme replacement therapy. Reported complications involving the circulatory system and associated with the enzyme alpha galactosidase supplementation include such phenomena as diffuse vasculopathy [3], also involving coronary vessels [4], conduction disturbances [5] and valvulopathies; even a sudden cardiac death has been described [6]. It does not necessarily mean that enzyme replacement therapy should be avoided, since it is the only reasonable management method even if improvement in the circulatory system is slight [7]. Patients treated with alpha galactosidase A usually demonstrate arresting of the hypertrophy process [8] or even significant resolution of left ventricular muscle hypertrophy [9]. Numerous authors highly value the beneficial effect exerted by enzyme replacement on the circulatory system, regardless of its local effect on hypertrophic lesions [10].

In case of diffuse LV hypertrophy with progressive intraventricular gradient one should seriously consider a cardiological intervention consisting in inducing controlled myocardial infarction in a well-defined zone of muscle mass that is responsible for obstructing the outflow tract from the ventricle. After many years devoted to accumulating experience, the method is recognized to be proven and effective, especially in the most severely ill,

symptomatic patients with significant LVOL gradients. A decrease in obstruction in the outflow tract was observed in as many as 90% of cases [11]. Nevertheless, the method is associated with some risk, e.g. of arrhythmias, including complete heart block [12], uncontrolled damage of the myocardium [13], or even sudden death [14]. One may surmise that in patients with Fabry disease, the risk of unforeseen complications may be expected to be higher as compared to other cases of hypertrophic cardiomyopathy; also the effect in late follow-up may be expected to be poorer than in other patients.

A heart transplant, in spite of concerns as to the fate of the transplanted organ, remains an ultimate treatment of choice should conservative and interventional methods of treatment fail.

Using β-blockers in patients with left ventricular hypertrophy is fully justified, regardless of the causes of the phenomenon.

EXPERT'S OPINION

In my opinion, all the theoretically implementable surgical options are invested with risk, although they are still within the limits of feasibility. Surgical alleviation of intraventricular obstruction and increasing the LV lumen is a high-risk procedure and in view of the severe enzymatic error, a surgeon attempting such an operation faces a dilemma of a clinical course that is unpredictable. This is why reports on surgical treatment (muscle excision) in Fabry disease are generally rare [15]. Moreover, the effect of surgery, in view of the diffuse ventricular hypertrophy, may be difficult to predict, although a good hemodynamic effect of myectomy has been described in the condition [16]. Nevertheless, taking into consideration the risk and unpredictable effect of the procedure, I reject this therapeutic method in the initial management stage.

Interventional treatment consisting in inducing controlled myocardial infarction in a well-defined zone of LV muscle mass is not less risky [17]. It is not a standard management method in hypertrophic cardiomyopathy in Fabry disease and experience is lacking in employing the procedure in this genetic syndrome.

Indications for heart transplant should be also considered questionable; qualifying the patient also raises serious doubt-invested questions: in what way the transplant and the necessary subsequent immunosuppression will affect the development of the underlying disease and in what way the enzyme deficiency (as well as the enzyme replacement therapy) will affect the transplanted organ. Literature on the subject is scarce, although there has been reported a heart (and kidneys) transplant in a case of hypertrophic cardiomyopathy in Fabry disease [18].

Having first taken advantage of the opportunities offered by conservative therapy, I would not rigidly observe such contraindications, acting on the assumption that the mean post-transplant survival time in a 50-year-old individual is theoretically the same as the prognosis of life expectancy for the primary disease, assuming there are no serious complications involving other organs (mostly renal), as is the case with the analyzed patient.

CONCLUSION

In my opinion, the treatment of choice in the discussed patient is implementation of conservative treatment with β-blockers, necessarily with continuation of α-galactosidase A enzyme replacement therapy. Blocking the β-adrenergic receptor will result in slowing cardiac rhythm, decreasing heart contractability, decreasing stroke volume, decreasing cardiac oxygen consumption, increasing coronary flow and prolonging diastolic time. All the above-mentioned effects are advantageous for the patient in question. The most expected therapeutic effect is decreasing the left ventricular muscle mass and in consequence eradication of intraventricular gradient and better ventricular filling.

If, however, the therapy does not produce the expected effects, one should – disregarding the afore-mentioned contraindications – consider a cardiological intervention as the second stage of treatment consisting in ethanol-induction of controlled myocardial infarction in the zone that is responsible for obstructing the outflow tract from the left ventricle. Should the result of such treatment modality be unfavorable or no such cardiological intervention be possible, I would still believe qualification for a heart transplant to be justified, since it may ultimately afford the patient the longest survival time. Despite all the problems and reservations associated with the enzyme deficit, the patient should not be disqualified from heart transplant therapy as a treatment modality which is the most preferred in case of persistent hypertrophic cardiomyopathy.

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