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Fabry disease and the heart

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Fabry disease is induced by a mutation in the alpha-galactosidase A gene, causing a deficiency of the enzyme alpha-galactosidase A. (1) The enzyme defect leads to progressive intracellular accumulation of globotriaosylceramide in lysosomes of various tissues and organs, including heart, kidney and nerve system. Cardiac involvement is common and is presenting as concentric left ventricular hypertrophy. Myocardial replacement fibrosis is a typical feature of more advanced stages of Fabry cardiomyopathy, first limited to the mid-myocardial layers of the basal postero-lateral wall, then spreading to transmural fibrosis. Since 2001, enzyme replacement therapy is available. If therapy is started early, before myocardial fibrosis has developed, a long-term improvement of myocardial morphology, function and exercise capacity can be achieved. In end-stage cardiomyopathy enzyme replacement therapy might prevent further progression of the disease. This review provides an overview of Fabry disease, with a focus on cardiac involvement with its characteristic features, clinical presentation and possible treatment.

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Introduction

Anderson Fabry disease is a rare genetic lysosomal storage disorder with X-chromosomal inheritance [1]. Reported incidence is about 1:40,000 worldwide [2]. However, due to underdiagnosed atypical phenotypes and mutations with limited alpha-galactosidase A activity, the actual incidence is likely to be much higher. The clinical significance of these mutations, however, has not yet been satisfactorily clarified [3]. The disease is induced by a mutation in the alpha-galactosidase A gene (GLA) causing a deficiency of the hydrolase alpha-galactosidase A (alpha-GalA). Absent or reduced enzyme activity leads to the inability to catabolize globotriaosylceramide (Gb3) and related glycosphingolipids, with the result of a progressive intracellular storage of Gb3 in various tissues and organs and an elevated plasma concentration of lyso-Gb3. The most commonly affected organs are heart, vascular endothelium of the kidney, nervous system, eyes, and skin (Fig. 1) [4]. Cardiac manifestations including arrhythmias, chronic heart failure and small vessel disease occur frequently. Of note, malignant arrhythmias [5] are the predominant cause for the substantially increased morbidity and reduced life expectancy [6]. Beside the classical variant of Fabry disease, an atypical variant is also known, characterized by residual alpha-galactosidase A activity. In those cases the clinical manifestation starts later in life, often with single organ involvement, as heart or kidney [7,8].

Anderson Fabry disease is one of the rare lysosomal storage disorders for which a cause-specific therapy is available [9,10]. Enzyme replacement therapy (ERT) has been approved since 2001. Two different enzyme preparations are available: agalsidase alfa and agalsidase beta. Clinical studies have shown that enzyme replacement therapy (ERT) may slow or halt disease progression [9–12]. However, the success of therapy appears to depend heavily on the stage of the disease [12].

Pathophysiology

The malfunction of alpha-Gal A leads to a progressive accumulation of Gb3 in all body cells containing lysosomes, including vascular endothelium and smooth muscle cells [13]. Intracellular accumulation starts *in utero* and is probably the pathogenetic trigger event of the disease [14,15].

Although the clinical presentation of Fabry disease is well explored, the pathomechanism linking the intracellular deposition of Gb3 to the potential cell and tissue dysfunction and finally to the clinical manifestations is still not sufficiently clarified [4]. It has been shown that the storage of Gb3 induces an excessive production of reactive oxygen species in cultured vascular endothelial cells thereby increasing oxidative stress. Gb3 also up-regulates the expression of adherence molecules in vascular endothelium [16]. Other data indicate that Gb3 may cause the release of pro-inflammatory cytokines, especially dendritic cells and monocytes [4]. Thus, it can be hypothesized that Gb3 storage triggers a cascade of pathophysiological processes leading to a structural cellular change, tissue defects, and – over time – to organ failure.

Furthermore, globotriaosylsphingosine (lyso-Gb3), a deacylated metabolite of Gb3, appears to be an additional factor in the pathogenesis of Fabry disease. Lyso-Gb3 is an inhibitor of the enzyme alpha-galactosidase A, thus promoting the storage of Gb3 as well as it stimulates the proliferation of

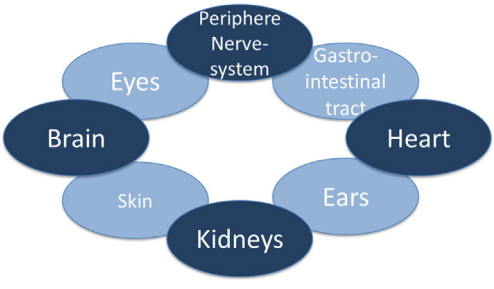

Fig. 1. Overview of the typical organs involved in Fabry disease. The dark fields represent the most important involved organs. Other organs with less effect on life expectancy are marked by a more light-colored circle.

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