Fabry disease/Anderson-Fabry disease

It is an X-linked lysosomal disorder that leads to excessive deposition of neutral glycosphingolipids in the vascular endothelium of several organs and in epithelial and smooth muscle cells. Progressive endothelial accumulation of glycosphingolipids accounts for the associated clinical abnormalities of skin, eye, kidney, heart, brain, and peripheral nervous system. Screening in subjects with LVH reveals a high prevalence of Fabry disease. Often, a diagnosis is uncertain because characteristic clinical features are absent and genetic variants of unknown significance (GVUS) in the α-galactosidase A (GLA) gene are identified. This carries a risk of misdiagnosis, inappropriate counselling and extremely expensive treatment (Smid et al., 2014). LVH is a key feature and occurs in up to 50% of males and one-third of females (Kampmann et al., 2008). In most cases, LVH is concentric; however, an asymmetrical variety with septal thickening and basal inferior wall fibrotic thinning may be present in an advanced stage. Mild left ventricular diastolic dysfunction is seen early in the disease process and progresses to severe forms in later stages. Right ventricular hypertrophy is also common and may progress to right ventricular dilatation (Niemann et al., 2010). The fibrotic process in Fabry cardiomyopathy starts with intramural and later transmural, involvement that is invariably present in the inferobasal lateral segments (Yousef et al., 2013). However, although myocardial accumulation of Gb3 begins very early in life, LVH most commonly manifests itself only decades later, at an average age of 32 years in men and 40 years in women (Linhart et al., 2007). LVH is a key feature in Fabry disease and is reported in up to 50% of males and one-third of females().[10] Conversely, among individuals with uncharacterized LVH, the Fabry gene has been identified in up to 4% of cases (Linthorst et al., 2010). In most cases the LVH is concentric; however, an asymmetrical variety with septal thickening and posterior wall fibrotic thinning may present in severe cases. RVH is also common and may progress to RV dilation. The fibrotic process in Fabry cardiomyopathy starts with intramural involvement with later transmural involvement. Fibrosis is invariably present in the basal posterolateral segments (Weidemann et al., 2010).

CMR is the imaging modality of choice in these cases. Typical ECG findings include PR interval shortening due to shortening of the P-wave duration. Later abnormalities include PR interval prolongation, voltage signs of LVH, repolarization abnormalities, and atrioventricular block. Longitudinal studies suggest that arrhythmias occur in 27–42% of

male and 27% of female patients (Linhart et al., 2007). Management of arrhythmias (including device therapies) should follow standard guidelines (Weidemann et al., 2010).

Early signs and symptoms of Fabry disease

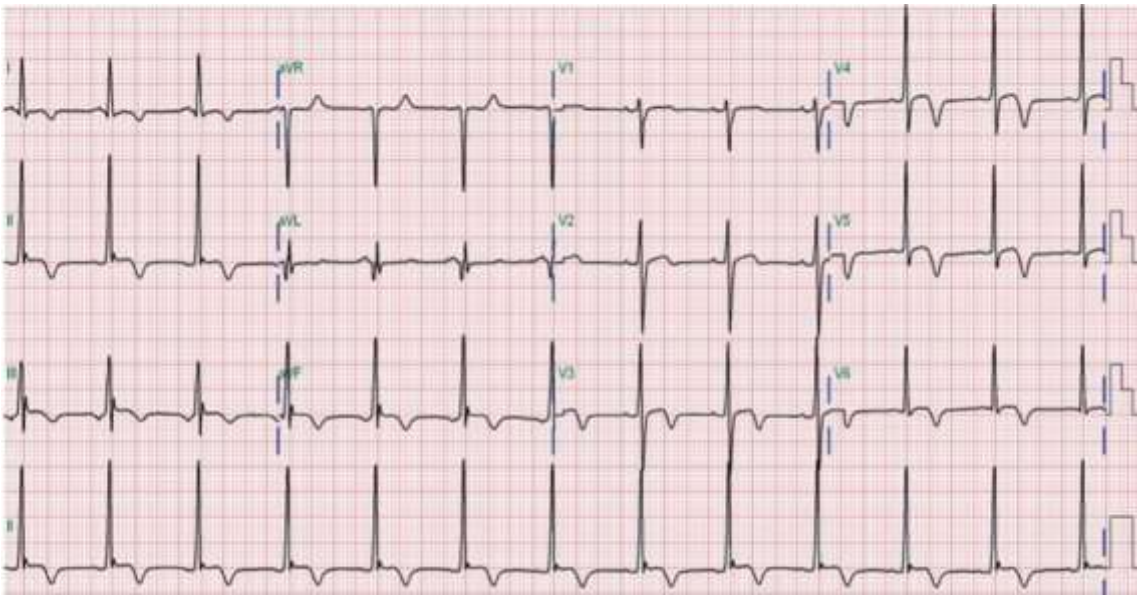
Acroparesthesias Nerve deafness Heat intolerance Hearing loss, tinnitus, nausea, vomiting, diarrhea postprandial bloating and pain, early satiety difficulty gaining weight skin angiokeratomas, hyperhidrosis eyes corneal and lenticular opacities vasculopathy (retina, conjunctiva) Kidneys: Microalbuminuria, proteinuria Impaired concentration ability, hyperfiltration Increased urinary Gb3 excretion.

Heart: Impaired heart rate variability, arrhythmias ECG shortened PR interval, mild valvular insufficiency. ECG parameters are not suitable to stage Fabry cardiomyopathy. Most ECG parameters were normal, the absence of ST or T alterations seems to almost exclude late enhancement on CMR in these patients (**Niemann M1, Hartmann T, Namdar M, Breunig F, Beer M, Machann W, Herrmann S, Ertl G, Wanner C, Weidemann F.Cross-sectional baseline analysis of electrocardiography in a large cohort of patients with untreated Fabry disease.J Inherit Metab Dis. 2013;36(5):873-9**.).

Value of ECG for early recognition of cardiac disease

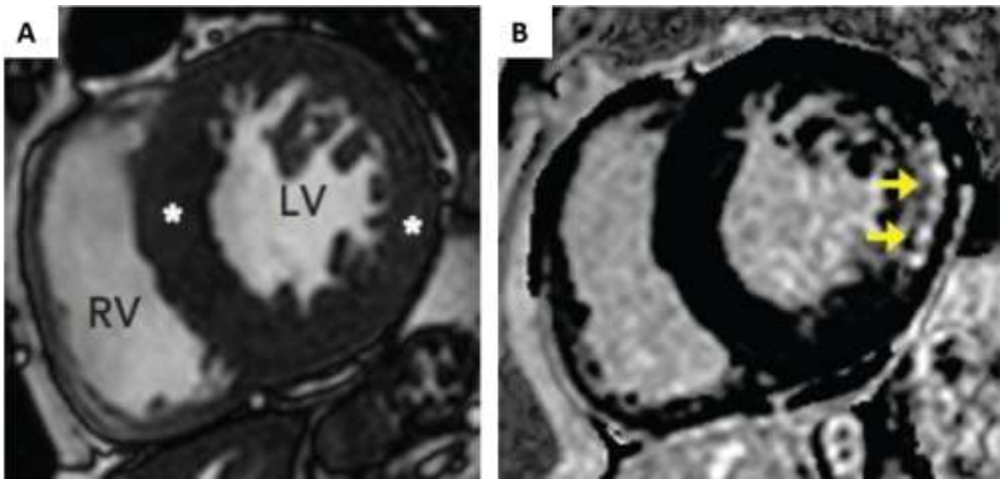
Macroscopic structural cardiac manifestations of FD may be preceded, eventually accompanied or even diagnosed by specific ECG signs, as is the case with shortened P-wave and PR intervals, various indices for LVH or repolarisation abnormalities in FD. Repolarization abnormalities in particular—if absent —have been reported to play an important role in exclusion of myocardial replacement fibrosis (**Niemann M, Hartmann T, Namdar M, et al. Cross-sectional baseline analysis of electrocardiography in a large cohort of patients with untreated Fabry disease. J Inherit Metab Dis 2013;36:873–9**.). This observation gains much importance since long-term data suggest that treatment should be started before myocardial fibrosis has developed to achieve long-term stabilization or improvement in myocardial morphology and exercise capacity. Patients with Fabry disease, particularly those with hypertension and/or LVH, have a high risk of experiencing HF and MI at a relatively young age. Many patients also experience various types of arrhythmias. The cardiac manifestations of Fabry disease are consistent with other forms of CV disease, which makes it difficult to identify the disease solely on the basis of cardiac assessments. Cardiologists should be aware of Fabry disease as a possible cause of cardiac dysfunction. Earlier diagnosis of these patients, before the onset of end organ failure, will allow for prompt initiation of appropriate treatment.

Example of ECG in Fabry´s disease (**Germain DP. Fabry disease. Orphanet J Rare Dis. 2010;5:30**.)



ECG showing LVH with strain pattern Deep narrow q wave in aVL.

Example of typical CMR in Fabry´s disease



Fabry's disease confirmed by genetic testing (pathogenic mutation in the galactosidase αgene). A: Pre-contrast short-axis CMR image in a 44-year-old woman with increased LV wall thickness in both IVS and lateral wall (maximum wall thickness of 16 mm in septum and 13 mm in the lateral wall). B: Post-contrast images in the same patient demonstrate LGE confined to the basal inferolateral wall leading to concern for Fabry's disease.