Fabry disease: studies on diagnosis, screening and patients’ perspectives
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SUMMARY

This thesis comprises several studies, aimed at gaining more insight in the pathophysiology of Fabry disease, an improved delineation of phenotypic expression of the disease in heterozygotes and more knowledge on quality of life and psychosocial development of Fabry patients. Finally, our aim was to summarize current screening strategies and to identify issues to be considered in relation to the discussion on population (newborn) screening for Fabry disease.

Chapter 1 presents a concise overview of the history of Fabry disease, its clinical characteristics, pathophysiology, diagnosis and treatment and serves as an introduction to the thesis.

In chapter 2 we studied glycosphingolipid accumulation in placental tissue of two Fabry heterozygotes, one of an unaffected male newborn (placenta A) and one of an affected female newborn (placenta B). Placenta A was completely free of storage, both on the maternal and fetal side. Storage in smooth muscle cells of the umbilical cord of placenta B was found, but not in the placenta itself. These findings combined with those described previously, present a complex and heterogeneous picture. Differences in disease severity in the mothers, the gender of the fetus and the presence of disease in the newborn, may all influence placental pathology in Fabry disease. In addition, the lack of glycosphingolipids storage in placenta B, especially on the maternal side, might be a possible effect of enzyme replacement therapy (ERT), as the mother was treated with ERT during pregnancy.

In chapter 3 we evaluated the diagnostic value of globotriaosylsphingosine (lysoGb3), a relatively new and promising biomarker for Fabry disease. Plasma lysoGb3-values of 37 male and 55 female Fabry patients were measured before treatment with ERT and the association between lysoGb3 and disease severity and disease parameters was determined. Plasma lysoGb3 was found to be increased in all Fabry patients, with the exception of a few young girls. Therefore, lysoGb3 determination can be used for confirmation of the diagnosis of Fabry disease. In patients with atypical Fabry disease, lysoGb3 was within normal values. Plasma lysoGb3 exposure was shown to correlate with disease severity and was found to be an independent risk factor for development of cerebrovascular signs in male patients and left ventricular mass in females.

In chapter 4, the enzymatic, biochemical and molecular characteristics of a young female patient with Fabry disease are described. This girl developed central nervous system involvement (cerebral white matter lesions) due to Fabry disease from the very early age of thirteen years. Despite treatment with ERT, a hemorrhagic infarction occurred at the age of fifteen years. Alpha-Galactosidase A activity, measured in leukocytes, was strongly reduced (1.8 ng/mmol/hr) and plasma lysoGb3 was markedly elevated (99 nmol/ml), which could all be explained by the 100% skewed X-inactivation of the paternal wild-type allele found in leukocytes. Though X inactivation was only assessed in leukocytes, these findings
support the hypothesis that skewed X-inactivation may be one of the contributors of the clinical phenotype in female patients. However, other yet unknown factors will contribute to the remarkably high number of females with clinical signs and symptoms in Fabry disease. Furthermore, these findings support the inclusion of brain imaging by MRI for assessment and follow-up of Fabry patients from an early age, independent of gender.

In order to identify signs and symptoms in females that have not been previously recognized, and to better understand aspecific complaints brought forward by Fabry heterozygotes, a questionnaire for Fabry heterozygotes was developed. In chapter 5, the results of this questionnaire, completed by 63 heterozygotes and 52 aged-matched controls, are reported. Fatigue, palpitations, pains in hands and feet, joint pain, dizziness, loss of libido and proteinuria during pregnancy were found to be significantly more common in Fabry females. Although these symptoms are present in a significant proportion of normal controls, they deserve further attention by treating physicians to better understand their significance in Fabry disease and to study if these symptoms are amendable by ERT or by symptomatic treatment.

Chapter 6 focuses on the psychosocial development and quality of life in 28 young adults with Fabry disease as assessed by the Course of Life questionnaire and the Short Form-36 questionnaires. Compared to an age-matched normative population, social development of Fabry males was affected, as they were less likely to participate in sports and going out to bars and discos. We hypothesized that this difference might be caused by acroparesthesia, which generally aggravate during heat or exercise. This observation strengthens the need for adequate pain management. Furthermore, Fabry adolescents were found to have decreased quality of life in the physical domains of the quality of life assessment. Despite the affected social development and impact of Fabry disease on quality of life, psychosexual and autonomy development, as well as socio-demographic outcomes, were not affected, which is encouraging for families with children with Fabry disease.

The enormous expansion of the availability of information on the internet has resulted in widespread access to this information for both patients and physicians. Regarding rare diseases, the use of internet may provide an important tool in the diagnostic process. In chapter 7 we present two cases in which concerned parents made a correct diagnosis of a lysosomal storage disorder (MPS I and Fabry disease) in their child by searching the internet after a long doctor’s delay. These cases illustrate the utility of publicly available search engines in diagnosing rare disorders and in addition illustrate the lengthy diagnostic odyssey which is common in lysosomal storage disorders.

The results of a study in our cohort on long-term efficacy of treatment with ERT are described in chapter 8. The follow-up of 75 patients, treated during a median of 5.2 (range 0.05-11) years with ERT, of renal function, cardiac mass
and cerebral white matter lesions revealed that there was a substantial disease progression despite ERT in males, as shown by a decline in renal function and an increase in cardiac mass. In females renal function and cardiac mass remained stable. Treatment with ERT did not prevent the occurrence (or progression) of white matter lesions in both males and females. Though the occurrence of major complications, defined as major cardiac events, stroke, end stage renal disease and death did not differ between the treated and untreated cohorts, the odds of developing a first and second complication was favorably influenced by treatment duration. It was concluded that long term treatment with ERT combined with optimal supportive case does not fully prevent disease progression, but may stabilize disease in some. These findings emphasize the need to delineate more precisely who will benefit from ERT and who will not. The possible positive effect of longer treatment strengthens the necessity to study the efficacy of early initiation of treatment.

In chapter 9 the results of a systematic review calculating the overall prevalence of Fabry disease in high risk cohorts are presented. In males on renal dialysis the overall Fabry disease prevalence was found to be 0.33% (95% CI 0.20-0.47) and in females 0.10% (95% CI 0-0.19). Combined prevalence of Fabry disease in patients with a history of renal transplant was 0.38% (95% CI 0.07-0.69) in males and 0% in females. In patients with left ventricular hypertrophy (LVH), selection of study-population and differences in the method of screening hampered the calculation of an overall prevalence (ranging from 0.9-3.9% in males and 1.1-11.8% in females). In premature strokes (N=2 studies) overall prevalence of Fabry disease was 4.2% (95% CI 2.4-6.0) in males and 2.1% (95CI 0.5-3.7) in females.

In chapter 10 the experiences of patients with Fabry disease on the timing of their diagnosis are reported, analyzing semi-structured interviews with 30 Fabry patients. These interviews aimed to identify important patient oriented themes relevant to the discussion on newborn screening of Fabry disease. Six divergent themes were identified as relevant. One was the impact of a delayed diagnosis on severely affected patients, who often felt misunderstood and were frequently misdiagnosed. In contrast, others reported the drawback of a presymptomatic diagnosis, which resulted in stigmatization and medicalization. The ability to anticipate the future was considered as both an advantage and a disadvantage of an early diagnosis. Yet, patients reported that an early diagnosis of Fabry disease would be important to prevent disease progression with timely treatment. The reported divergent themes reflect both the phenotypic heterogeneity of the disease as well as the substantial differences between experiences of patients and bring important nuances to the discussion on newborn screening programs.

Chapter 11 deals with a focus group study aimed at exploring opinions on the issue of newborn screening of Fabry disease of various parties involved: Fabry experts, ethicists and Fabry patients. Several arguments were identified that were considered to be crucial to the discussion on inclusion of Fabry disease in newborn screening programs. This study concluded that the current inability to
predict the severity and course of the disease in asymptomatic patients combined with the lack of knowledge on optimal timing and the efficacy of treatment with ERT, is a strong argument against inclusion of Fabry disease in newborn screening programs. Research should focus on these key questions.

Finally, chapter 12 presents a general discussion on the results of the studies included in this thesis and an outline for further studies aimed at resolving the resulting research questions.