Interdisciplinary Guidelines for the Diagnosis and Treatment of Fabry disease

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Interdisciplinary Guidelines for the Diagnosis and

Treatment of Fabry disease
5. Diagnostics with confirmed Fabry disease ................................................................. 16
  5.1 Kidneys .................................................................................................................. 17
    5.1.1 Initial examination ......................................................................................... 17
  5.1.2 Follow-up ........................................................................................................... 17
  5.2 Heart ....................................................................................................................... 18
    5.2.1 Initial examination ......................................................................................... 18
    5.2.2 Follow-up ........................................................................................................ 18
  5.3 Nervous system ...................................................................................................... 18
    5.3.1 Initial examination ......................................................................................... 18
    5.3.2 Follow-up ........................................................................................................ 18
  5.4 Gastrointestinal tract ............................................................................................ 19
  5.5 Ears ......................................................................................................................... 19
    5.5.1 Initial examination ......................................................................................... 19
    5.5.2 Follow-up ........................................................................................................ 19
  6. Depression and Quality of Life ................................................................................. 19
  7. Treatment and Care ................................................................................................ 19
    7.1 Enzyme replacement therapy .............................................................................. 20
      7.1.1 Status of efficacy data .................................................................................. 20
      7.1.2 Indication and start of treatment .................................................................. 22
      7.1.3 Tolerance ..................................................................................................... 23
      7.1.4 Considerations for treatment in women ...................................................... 23
      7.1.5 Considerations for treatment in children .................................................... 23
      7.1.6 Quality of life .............................................................................................. 23
      7.1.7 Home infusion therapy ............................................................................... 24
    7.2 Concomitant treatments ....................................................................................... 24
      7.2.1 Nephrological add-on therapy ..................................................................... 25
      7.2.2 Cardiological add-on treatment ................................................................... 25
      7.2.3 Neurological add-on treatment .................................................................... 26
  8 Self-Help Organisation ............................................................................................... 26

Literatur .......................................................................................................................... 27
Abbreviations .................................................................................................................. 34
Expert Group Guidelines ............................................................................................... 34
Procedure for consensus-building ................................................................................ 35
Conflicts of interest ....................................................................................................... 35
Period of validity ............................................................................................................ 35
Evidence level ............................................................................................................... 35
What's new – brief outline of the characteristics of the disease

- The classic image of the inherited lysosomal storage disorder Fabry disease, which is carried on the X-chromosome, is that it is observed in the men of the individual families. Women tend to become affected at a later point in time and with a milder form of the disease compared with men
- Fabry disease is progressive. Compared with the average population, patients suffering from Fabry disease have a significantly reduced quality of life in terms of their health
- The first symptoms (acroparesthesias, chronic pain in the joints, gastrointestinal symptoms, sensitivity to heat, tinnitus) usually appear during childhood or adolescence
- Angiokeratomas and non-specific teleangiectasias, disorders of sweat secretion, sensorineural hearing loss and damage to the vestibular organ, are additional manifestations. Obstructive airway diseases, osteopenia and anaemia are also possible. Misdiaisons are frequent – often Fabry disease will not be diagnosed until many years after the appearance of first symptoms
- A frequent ophthalmological characteristic is cornea verticillata: The changes to the cornea are generally easily identified by means of a slit lamp examination
- Up to 18% of children suffering from Fabry disease (below the age of 18 years) may already suffer from proteinuria. Nephropathy is an unfavourable prognosis, regardless of sex
- Cardiac manifestations include cardiomyopathy (LVH) and/or cardiac arrhythmias. Children may already exhibit increased left ventricular mass index and reduced heart rate variability. Ventricular hypertrophy and intramyocardial fibrosis are predictors for malignant cardiac arrhythmias
- In addition to TIA (also reported in children), CNS manifestations include ischemic strokes. Indications for an involvement of the CNS consist of changes to the pulvinar thalami signal intensity in the MRI
- Oligosymptomatic progressions with minor symptoms, frequently with only one organ manifestation, are rarely clinically diagnosed, but have been mainly reported with sufferers who were diagnosed during screening programmes
- For all patients suffering from Fabry disease, the prognosis is highly dependent on early diagnosis and treatment

- If the disease is left untreated, the possible complications for the kidney, heart and CNS significantly reduce the life-expectancy of the sufferers. The main causes of death for patients with Fabry disease are kidney failure, sudden death as a result of cardiac arrhythmias and stroke
- Enzyme replacement therapy (ERT) with Fabry disease can stop the advancement of the disease. Differences between children and adults were not observed in the tolerability profile for ERT
- Two international patient registers have been available since 2001, each of which are supported by one of the two manufacturers of the enzyme replacement preparations: Fabry Outcome Survey (FOS: Shire HGT) and Fabry Registry (Genzyme). An independent national register for patients with Fabry disease was established in Canada by the Canadian Fabry Disease Initiative (CFDI) in 2007

Overview of the most important recommendations

- In male subjects the determination of AGLA activity in blood leukocytes is the method of first choice for diagnosis. The molecular genetic analysis of the α-galactosidase A gene (GLA) together with evidence of a pathogenic mutation is recommended to confirm the diagnosis. If the AGLA activity is within the normal range, Fabry disease is excluded in men, according to the current status of scientific knowledge
- In women, molecular genetic testing is necessary for diagnosis of Fabry disease because the measurement of AGLA activity has only a very limited significance
- If the levels of enzyme activity are reduced and/or the mutation test result is positive, human-genetic counselling should be offered
- Patients with proteinuria or restricted kidney function of unclear origin, particularly younger patients (<55 year old, especially those suffering from basilar ectasia) should be examined for the existence of Fabry disease
- The treatment of Fabry disease requires the close cooperation of various medical specialties
- Following the diagnosis of Fabry disease a clinical baseline assessment of the typically affected organs and organ systems is recommended. This includes the skin, eyes, kidneys, heart, brain, peripheral nervous system (including pain), quality of life, ears and the gastrointestinal tract
The initial examinations and follow-up examinations are the same for men and women
- Organs with life-limiting manifestations or those that reduce the quality of life of the sufferer, such as nephropathy and cerebrovascular diseases, hearing disorders, small-fibre polyneuropathy, should be examined during regular follow-up examinations
- Persons with pathogenic GLA mutations who are asymptomatic should be monitored every 6 months
- Parameters for kidney tests include: Creatinine, creatinine clearance, GFR, excretion of protein in urine, ultrasound, 24-hour blood pressure measurement. Follow-up examinations are recommended at least once per year.
- In the event of proteinuria and/or hypertension an additional treatment must be given, which also applies for other chronic kidney diseases, to delay the progression of kidney failure. ACE inhibitors or angiotensin-II blockers (sartans) are available as a concomitant therapy
- During dialysis and following kidney transplantation, the ERT must be continued as before
- The parameters for the cardiac examination include: ECG, 24-hour ECG, echocardiography, cardio-MRI; Follow-up analyses are recommended every 12 months if cardiological symptoms exist. If cardiological symptoms do not exist and/or there are no pathological findings, follow-up analyses are recommended every 24 months
- The parameters for the examination of the CNS and peripheral nervous system are: Doppler and duplex-sonogram of the vessels supplying blood to the brain (particularly the basilar artery), head MRI, neurography, evaluation of pain intensity and quality of life; follow-up analyses are recommended every 12 months with neurological symptoms, particularly vascular symptoms, if there are no neurological symptoms, every 24 months including a head MRI
- The treatment of Fabry disease comprises ERT as well as concomitant therapies relating to organ manifestations and symptoms
- ERT is currently the only causal treatment for Fabry disease. It is recommended to implement ERT as early as possible for both male and female patients after the diagnosis of Fabry disease has been confirmed and if clinical symptoms exist. The efficacy of ERT is also verified for children
- The treatment goals are to reduce symptoms (particularly alleviation of pain), improve the quality of life, prevent organ malfunction (particularly of kidneys, heart and CNS) and normalise life expectancy
- There is no indication to stop ERT during pregnancy
- Home infusion therapy: if the patient has received approximately six ERT treatments in the clinic and/or practice and has not suffered any infusion reactions, a transfer of the infusions to the home environment can be offered to the patient

Introduction

(Anderson-)Fabry disease is a lysosomal storage disorder and is inherited via the X chromosome. The disease is characterised by a deficiency of the enzyme AGLA, which will typically lead to the accumulation of the sphingolipid globotriaosylceramide (Gb3) in numerous organs of the body. The patients may present with isolated symptoms (e.g. only pain or cerebrovascular disorders) or with multiple symptoms, which can differ in severity. In particular, these include pain (acroparasthesias), sweat secretion disorders, cardiac arrhythmias, dyspnoea, in addition to gastrointestinal symptoms and hearing loss. Important findings include nephropathy, cardiomyopathy, stroke and angiokeratomas. If left untreated, Fabry disease not only impairs the quality of life of the patient, but the life expectancy is also strongly reduced. The main causes for morbidity and mortality are renal, cardiac and cerebrovascular involvement, which result in an early stroke, kidney failure and heart failure. Fabry disease exhibits high clinical variability. A targeted search, which is carried out in cooperation with various specialist doctors, often precedes the diagnosis. Particularly in children, signs of Fabry disease are often left unidentified or are attributed to other disorders.

Aims and field of application

These guidelines summarise the clinical variability of Fabry disease according to the current status of medical knowledge and provide an instruction for the cooperative interdisciplinary diagnosis and treatment of the disease. The main focus is to make the following information and guidelines available for instruction:

- Guidelines for rapid determination of a diagnosis that does not damage patients and resources
• Rational decision-making assistance for the
determination of therapy

These guidelines are designed to be multidisciplinary. It is first and foremost aimed at doctors and patient
organisations that are clinically active.

1 Classification and epidemiology

Fabry disease is a LSD that is inherited via the X
chromosome. Studies relating to the frequency of
Fabry disease, showed prevalences ranging from
1:40,000 to 1:117,000 in live births (Meikle et al.,
1999; Desnick et al., 2001) and that the prevalence
varies considerably between countries. There is
however, evidence that the disease is more common
than previously thought; during screening of
approximately 37,000 male newborn children for
AGLA deficiency, on which Fabry disease is based,
the incidence was around 1:3100 (Spada et al., 2006).

Fabry disease particularly affects men. Women can also suffer from Fabry disease, however, they manifest a modest pathogenesis
and the prognosis can be better.

The mean age of onset in male patients is between
3–10 years of age. In female patients it is between
6–15 years of age (MacDermot et al., 2001 [b];
Ramaswami et al., 2006; Ries et al., 2003). If the
disease is left untreated, kidney insufficiency,
cerebrovascular diseases and cardiomyopathy will
reduce the life expectancy of the patient – by about
20 years in men and by 10 years in women (Germain,
2010; MacDermot et al., 2001 [a]; MacDermot et al.,
2001 [b]).

2 Pathophysiology

Fabry disease is caused by a mutation in the GLA
gene, which codes the lysosomal enzyme AGLA.
Several hundred mutations have been identified in the
GLA gene (Gal et al., 2010).

As a result of the AGLA deficiency, glycosphinolipids – particularly
globotriaosylceramide (Gb3) – are insufficiently
metabolised and accumulate within the lysosomes.
Among others, the cells damaged by
glycosphinolipid deposits are found in:

• Kidneys (mesangial, endothelial and tubular
  epithelial cells, podocytes),
• Heart (myocardial cells, endothelial cells and
  fibrocytes),
• Peripheral nervous system (neurons of the
  dorsal root ganglia and the autonomic nervous
  systems) and
• Blood vessels (endothelial, perithelial and
  smooth muscle cells).

The progressive accumulation of glycosphinolipids
affects numerous organs and tissues, with the patient
often presenting with a wide range of characteristics
and symptoms, which can differ in severity (Peters et
al., 2001).

3 Progression of the disease

The symptoms of Fabry disease vary across different
age groups (see Table 1), and isolated organ
manifestations are frequently in the forefront. Overall
the number of the involved organ systems and the
severity of the symptoms increase with the age of the
patients (Mehta et al., 2004).

The variability of the clinical manifestation is
greater in women than in men, (Deegan et al.,
2006; Wang et al., 2007; Whybra et al., 2001;
Wilcox et al., 2008).
Table 1. Typical characteristics and symptoms of Fabry disease depending on age (adapted according to: Hughes et al., 2005; Mehta et al., 2010).

<table>
<thead>
<tr>
<th>Typical age</th>
<th>Characteristics and symptoms</th>
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| Childhood and adolescence (≤ age 16) | ▪ Neuropathic pain (e.g. acroparasthesias)  
                                              ▪ Chronic pain in the joints  
                                              ▪ Ophthalmological abnormalities (cornea verticillata, tortuous vessels)  
                                              ▪ Hearing loss, tinnitus  
                                              ▪ Vertigo attacks  
                                              ▪ Dyshidrosis (hypohidrosis, rarely hyperhidrosis)  
                                              ▪ Hypersensitivity to heat and cold  
                                              ▪ Gastrointestinal disorders, abdominal pain  
                                              ▪ Lethargy and fatigue  
                                              ▪ Angiokeratomas  
                                              ▪ First renal and cardiac abnormalities (e.g. microalbuminuria, proteinuria, abnormal heart frequency variability) |
| Early adulthood 17–30 years) | In addition to the above symptoms:  
                                              ▪ Further angiokeratomas  
                                              ▪ Lymphoedema in the lower extremities  
                                              ▪ **Kidney**: Proteinuria and advanced kidney failure  
                                              ▪ **Heart**: Hypertrophic cardiomyopathy and  
                                              ▪ LVH, angina pectoris, arrhythmias  
                                              ▪ **CNS**: TIA, stroke  
                                              ▪ Depression |
| Later adulthood (> 30 years) | Deterioration of the above symptoms up to:  
                                              ▪ Heart insufficiency, arrhythmia disorders  
                                              ▪ TIA and stroke relapses  
                                              ▪ Kidney failure, requirement for dialysis |

3.1 Pain

Neuropathic pain is one of the most frequent symptoms of Fabry disease (Evidence level Ib).

Comment: The data on the prevalence of pain in men varies between 33% (Üceyler et al., 2011) and up to 80% (Hoffmann et al., 2005; MacDermot et al., 2001). With women the prevalence data of pain also ranges from 25% (Üceyler et al., 2011) up to 70% (Hoffmann et al., 2005; MacDermot et al., 2001[b]).

Typically the pain occurs in the form of acroparasthesias with burning, tingling or numbness in the extremities. However, stabbing pain and/or burning sensations in the form of so-called ‘painful crises’ are also reported (Hughes et al., 2005). In principle, every other region of the body could also be affected (e.g. neck and/or headaches; Hoffmann et al., 2007 [a]). The trigger for ‘painful crises’ is often physical activity, changes in temperature, psychological stress and/or intercurrent diseases (Burlina et al., 2011).

Neuropathic pain can cause considerable problems during childhood (Evidence level IIa).

Comment: Consistent with the prevalence data in adults, the frequency of pain in children is more than 60% for both sexes. Chronic pain, on the other hand, is only reported in approximately one third of children (Ramaswami et al., 2006).

In a retrospective analysis, the average age for onset of acute pain was 14 years in men and approximately 19 years in women (Hoffmann et al., 2007 [a]). Data from the Fabry register show that the symptoms start even earlier; 9 years in boys and 10 years in girls (Eng et al., 2007).
The pain is caused by damage to the peripheral nerves as a result of Gb3 deposits (Evidence level IIb).

Comment: Histopathological studies have confirmed the involvement of the ganglia in the dorsal spinal marrow stems and an axonal degeneration of smaller unmyelinated nerve fibres, which are responsible for the transmission of pain (Kahn, 1973; Düttsch et al., 2002). The myelin sheaths may protect the nerve fibres from the damaging Gb3 deposits (Düttsch et al., 2002). There is a relationship between the severity of the nerve damage and kidney function (Schiffmann et al., 2006; Üceyler et al., 2011).

3.2 Skin
3.2.1 Angiokeratomas

Angiokeratomas, small dilations of vessels, which mostly occur in groups close to the stem, indicate but do not verify Fabry disease from a diagnostic perspective. Their expansion correlates to the general severity of the disease (Evidence level IV).

Comment: Angiokeratomas are typical of Fabry disease. They are small reddish-brown vascular lesions appearing in clusters, some hyperkeratotic, which are found mainly in the gluteal, periumbilical areas, on the scrotum and on the thighs. Other sites affected by lesions include the hands, feet and the mucous membranes (e.g. oral mucosa). Ultimately however, they can occur on all parts of the skin. The first angiokeratomas are confirmed in childhood and then increase with age. Women generally have fewer angiokeratomas. In an analysis of the skin manifestation in 714 patients, 66% of men and 36% of women (Orten et al., 2007) had angiokeratomas. In addition to angiokeratomas, non-specific telangiectasias are also observed.

3.2.2 Dyshidrosis

Many patients with Fabry disease suffer from reduced sweat secretion, which in a warm environment and with physical activity can lead to fever with peripheral symptoms such as vertigo and vomiting (Evidence level IV).

Comment: Hypohidrosis (reduced) or anhidrosis (absent) is explained by a dysfunction of the peripheral nervous system and the accumulation of Gb3 directly into the sweat glands. Hyperhidrosis can also occur in some cases, which also causes discomfort (Lidove et al., 2006).

3.2.3 Lymphoedema

Another symptom found in some patients is lymphoedema, mainly of the lower extremities. This occurs in approximately 25% of men and 17% of women (Orten et al., 2007).

3.3 Gastrointestinal tract

Approximately half of all patients suffering from Fabry disease will complain of at least one gastrointestinal symptom over the course of the disease (Evidence level II b).

Comment: Numerous case reports have described gastrointestinal complaints in patients with Fabry disease (Anderson, 1898; Fabry, 1898; van Wayjen, 1958; Flynn et al., 1972; Rowe et al., 1974; Bryant et al., 1977; Sheth et al., 1981; O’Brien et al., 1982, Cable et al., 1982; Friedman et al., 1984; Nelis and Jacobs, 1989; Argoff et al., 1998; Hoffmann et al., 2004). MacDermot et al. first reported the symptoms in a large cohort of men with Fabry disease. In this collective the total prevalence for gastroenterological complaints was 69% (MacDermot et al., 2001). The majority of patients complained of abdominal fullness, indigestion and stomach cramps. 40% of the patients reported fluctuating symptoms of diarrhoea and constipation and vomiting was also possible. There was no information on the frequency of isolated symptoms.

An evaluation of gastroenterological symptoms from 342 patients from the Fabry Outcome Survey (FOS) demonstrated a prevalence of 52% (Hoffmann et al., 2007). Independent of age and gender, gastrointestinal pain was most frequently described (32.5%), followed by diarrhoea (20.5%), constipation (13.5%), nausea (12.3%) and vomiting (6.7%). Combinations of such complaints can in certain circumstances also imitate irritable bowel syndrome. Occasionally the patients also report intolerance of certain foods (Hoffmann et al., 2004; Banikazema et al., 2005).

In some circumstances gastrointestinal complaints are the sole or most severe manifestation of Fabry
disease for the patient (Flynn et al., 1972; Rowe et al., 1972; Hoffmann et al., 2004). All previously available data relating to gastroenterological complaints in patients with Fabry disease, which extend beyond the isolated case or series of cases, have a limited significance as they were collected in retrospect. The information is partially based on the information from the relevant patients and has not been confirmed by relevant laboratory, x-ray or endoscopic tests. Isolated cases and series of cases can complement this information as they also describe less frequent manifestations that may be associated with the progression of Fabry disease.

Women may suffer more frequently from gastrointestinal complaints than men (Evidence level IIb).

Comment: Although there is no case report in the literature, which describes gastrointestinal complaints in a woman as the leading symptom, MacDermot et al. established that the total prevalence for gastroenterological symptoms in women suffering from Fabry disease was 60% (MacDermot et al., 2001).

Gastrointestinal complaints with Fabry disease begin in early childhood and in some circumstances be the first or sole symptom of the disease (Evidence level IIb).

Comment: It has been reported that children may be affected considerably by gastrointestinal symptoms during the early stages of Fabry disease through anecdotes by various authors (Sheth et al., 1981; Ries et al., 2003; Ries et al., 2005). In fact, retrospective analyses from larger cohorts showed a prevalence for gastrointestinal symptoms of 60.8% in children (adults: 48.9%). The symptoms are said to start at about 12 years of age (Hoffmann et al., 2007).

Even though the majority of patients with Fabry disease suffer from gastrointestinal symptoms, some with considerable severity, patients suffering from Fabry disease generally do not exhibit signs of malnutrition (Evidence level IIb).

Comment: The BMI of children in the cohorts of the Fabry Outcome Survey was between 50% and 75% (Hoffmann et al., 2007), and there were no differences in the BMI of children with or without gastrointestinal complaints. The average BMI of adult patients with gastrointestinal complaints was even a little higher than that of adults without these symptoms (24.7 vs. 23.9 kg/m²) (Hoffmann et al., 2007).

3.4 Kidney

The significance of a kidney biopsy with regard to the therapeutic consequences has previously not been sufficiently researched. In principle a kidney biopsy can be used to confirm diagnosis; however, it does not deliver any clinically relevant additional information if the diagnosis of Fabry disease has been confirmed by laboratory tests, molecular genetic testing and/or other typical clinical manifestations. The diagnosis of Fabry nephropathy is generally made using light microscopy, preferably via toluidine colouration. An immunohistological or electron microscope examination shows the mostly onion-ring shaped ceramide deposits. In the event of severe damage to the kidney parenchyma and corresponding deterioration of function, interstitial fibrosis and focal sclerosis of the glomerulus will develop with various levels of severity.

The kidney biopsies of 59 patients from 11 centres were used to develop a standardized algorithm based on Fabry-specific as well as general changes, which can be used to estimate the histological severity of the Fabry nephropathy (Fogo et al., 2010). A clinical forecast cannot yet be derived from this and is subject to further tests.

Patients with unresolved microalbuminuria or proteinuria should be examined for evidence of Fabry disease (Evidence level III).

Comment: Chronic kidney disease with a progressive loss of the kidney function, often in combination with proteinuria, is a cardinal symptom of Fabry disease (Ortiz et al., 2008). Fabry nephropathy is a morphological and a clinical-functional term. The diagnosis and progression can be characterised biotopically and by laboratory-chemical parameters of kidney function. The insufficient metabolism of Glb3 results in deposits in various cells of the kidney tissue. This can result in glomerulosclerosis and interstitial fibrosis with proteinuria and kidney failure. In a study of 250,352 US patients with end stage renal disease, Fabry disease was listed as the cause in 42 patients (0.16%) (Thadhani et al., 2002). Compared to screening studies amongst dialysis patients this prevalence may be too low (Linthorst et al., 2010).
Patients with unresolved restriction of kidney function (GFR <60 ml/min/1.73 m²) should be examined for evidence of Fabry disease (Evidence level III).

Comment: A collection of data from 105 male sufferers demonstrated that nephropathy generally starts with proteinuria and after the manifestation of hypertension; chronic kidney failure results in a requirement for dialysis (Branton et al., 2002). On average first clinical signs of nephropathy are observed at age 20, terminal kidney failure occurs on average at the age of 38 (Eng et al., 2007; Ortiz et al., 2010). The age-related variability is high and initial signs of Fabry nephropathy have already been reported for children and adolescents (Tondel et al., 2008). A test from Wanner et al. observed an annual reduction in the eGFR rate of more than 1 ml./min/1.73m² in 71% of men and 39% of women (Wanner et al., 2010).

In a retrospective analysis the average age of men with chronic kidney disease (GFR <60 ml/min/1.73m²) was 42 years of age; the average age of male patients with a GFR of above 60 ml./min/1.73m² was 27. The annual GFR loss was twice as high in the first group than in the group with initially normal kidney function (~3.0 and -6.8 ml/min/year) (Schifflmann, 2009).

In female patients the kidney is normally involved later on and manifests a modest pathogenesis (Ortiz et al., 2008). Nevertheless, the risk for Fabry nephropathy is also considerable for women (Schifflmann, 2009).

The earliest sign of a clinically relevant kidney involvement with Fabry disease is proteinuria, which is verified in 10% of all children under the age of 18 suffering from Fabry disease (Evidence level IIa).

Comment: In isolated cases it can already appear at the age of 2 (Tondel et al., 2008). Kidney failure with Fabry disease is caused by glomerular damage (Tondel et al., 2008; Branton et al., 2002). Kidney biopsies in children have demonstrated glycosphingolipid deposits in podocytes as well as glomerular, tubulointerstitial and/or vascular changes, which obviously appear early on and before clinical impairment of kidney function (Tondel et al., 2008).

In adults the early stages of kidney disease can be detected by histological changes. The severity of kidney function impairment correlates to the extent of sclerosis and to arteriolar and glomerular sclerosis (Fogo et al., 2010).

3.5 Heart

A little more than half of all patients with Fabry disease will develop a typical cardiomyopathy over the course of the disease (Evidence level IIa).

Comment: In principle the metabolic consequence of AGLA deficiency may affect all cardiac structures, including myocardiad, cardiac conduction system and heart valves (Frustaci et al., 2007; Linhart et al., 2007; Mehta A et al., 2004; Weidmann et al., 2009). In a test from Linhart et al, more than 50% of all patients suffering from Fabry disease exhibited cardiac involvement at an average age of 36 (Linhart et al., 2007).

Typical cardiac findings for Fabry disease are:
- Left-ventricular hypertrophy (LVH, mostly in concentric form) (Kampmann et al., 2008; Linhart et al., 2007)
- Intramyocardial fibrosis (Weidmann et al., 2005; Moon et al., 2003; Weidmann et al., 2009)
- Prominent papillary muscle (Niemann et al., 2010)
- ECG changes with short P wave and PR interval, increase in the QRS width and repolarisation disturbances (Namdar et al., 2011)
- Cardiac arrhythmias, the frequency of which increases with age (paroxysmal or permanent atrial fibrillation, non-persistent and persistent ventricular tachycardias (Shah et al., 2005)
- Valve dysfunction (mitral valve, aortic valve) (Weidmann et al., 2009)

Children and adolescents may already be affected by cardiac symptoms (Evidence level IIa).

Comment: In a study with 20 paediatric Fabry patients, Kampmann et al. found evidence of increased left-ventricular mass index (left ventricular heart mass over 75th percentile) and reduced heart frequency variability) in all sufferers (Kampmann et al., 2008).

In a study looking at cardiac manifestations in 8 boys and 12 girls, all children exhibited left-ventricular hypertrophy above 75th percentile in the
Echocardiographic examination. 35% of the children with Fabry disease exhibited classic left-ventricular hypertrophy (Kampmann et al., 2008; Hopkin et al., 2008; Linhart et al., 2007). The enlargement of the heart did not correspond to a systolic or diastolic dysfunction. Using long-term ECG in boys, a restriction in heart frequency variability was observed as a possible first sign of cardiac dysfunction.

**Left-ventricular hypertrophy is the main finding in Fabry cardiomyopathy (Evidence level IIa).**

**Comment:** Left-ventricular hypertrophy (LVH) is observed in more than 50% of men and in approximately 33% of women with Fabry disease (Linhart et al., 2007; Weidemann et al., 2005). Men develop LVH earlier than women (Niemann et al., 2011). Regarding left-ventricular hypertrophy, there is a positive correlation with the frequency of arrhythmia and with diseases of the mitral valve and/or aortic valve (Linhart et al., 2007). If left untreated, left-ventricular hypertrophy is progressive. An obstruction in the left-ventricular outflow tract is extremely rare during hypertrophy. Most patients have concentric LVH (Linhart et al., 2007; Weidemann et al., 2005). Asymmetrical pronounced septal hypertrophy can develop only with advanced cardiomyopathies due to the thinning of the posterolateral wall (Weidemann et al., 2005; Moon et al., 2003; Weidemann et al., 2009 Weidemann et al., 2011, Niemann et al., 2011).

**Intramyocardial fibrosis development is typical of advanced cardiomyopathy (Evidence level IIa).**

**Comment:** In the advanced stages, myocardial fibrosis is typically exhibited in the basal postlateral segments (Weidemann et al., 2005; Moon et al., 2003; Weidemann et al., 2009; Weidemann et al., 2011, Niemann et al., 2011). Evidence of this can be provided in an MRI by means of “late enhancement imaging”.

In the final stage, the thinning of the wall sections are shown with regional wall movement disorders, which can easily be confused with expired myocardial infarction. This so-called replacement fibrosis has a negative effect on the prognosis (Weidemann et al., 2009).

**Complications from cardiac manifestations are among the main causes of death with Fabry disease (Evidence level IIa).**

**Comment:** Patel et al., analysed the natural progression of the disease with regard to cardiovascular events, myocardial infarction, heart failure or death caused by cardiac events in 2,869 Fabry sufferers. A total of 5.8% of men and 3.7% of women had suffered from a cardiovascular event at an average age of 45–54 years. Heart failure was most frequently documented (3.5% of the men and 2.3% of the women). Ventricular hypertrophy proved to be the strongest predictor for cardiovascular events (threshold values: Women septal end diastolic pressure $>10$, Men septal end diastolic pressure $>11$ mm) (Patel et al., 2011). Malignant cardiac arrhythmias appear to be responsible for sudden death in many Fabry patients (Shah et al., 2005).

### 3.6 Central nervous system

**Transient ischemic attack or stroke is one of the most frequent events in patients with Fabry disease (Evidence level IIa).**

**Comment:** In an evaluation of the data of 366 Fabry patients, who were registered in the Fabry Outcome Survey (FOS), Mehta et al. (2004) reported a higher prevalence of stroke in women compared to men (27% vs. 12%). In a review article from 2011, the importance of stroke in the morbidity and mortality of patients with Fabry disease was highlighted (Feldt-Rasmussen, 2011). In an evaluation by Buechnerg et al., almost 25% of the patients suffered a cerebrovascular event over the course of their Fabry disease. The average age at the time of the TIA or stroke for men was 34 and for women was 54 (Buechner et al., 2008; Sims et al., 2009). Other tests have proven that men are on average affected earlier than women and TIA events in children were also reported (Mehta et al., 2004; Ramaswami et al., 2006; Pintos-Morell and Beck, 2009). Patients who has previously not exhibited abnormalities due to a TIA or a stroke, may exhibit a so-called “small vessel disease” in the basal ganglia, thalamus and brain stem as well as in the periventricular region, as Reisin et al. were able to demonstrate in 16 of 36 adult, symptomatic patients with Fabry disease (Reisin et al., 2011).
In isolated cases stroke and/or TIA relapses can be the first manifestation of the disease (Evidence level IIa).

Comment: The cerebrovascular disorder can appear together with renal and cardiac manifestations (Mehta et al., 2005; Schiffmann et al., 2009). A test from Sims et al., shows; however, that a renal or cardiac disease had not been diagnosed before the first stroke in almost 71% of the male and 77% of the female Fabry patients. 50% of the male and 38% of the female patient suffered their first stroke before they were diagnosed with Fabry disease (Sims et al., 2009). Overall stroke and TIA relapses are frequent and associated with a poorer prognosis of the disease (Mitsias et al., 1996; Grewal, 1994; Burlina et al., 2011).

In young patients with a stroke of unknown origin, Fabry disease should always be excluded, in particular with additional symptoms such as ectasia of the basilar artery (Evidence level IIa).

Comment: The prevalence of Fabry disease is higher in certain populations such as with young stroke patients (18–55 years of age) and must be presumed to be pathogenetic for the stroke in at least 1% of these patients (Brouns et al., 2010). Fellgiebel et al. (2011) introduced ectasia of the basilar artery as a potential screening instrument of Fabry disease. Therefore in young stroke patients (aged 18–55) of both sexes with a basilar ectasia, Fabry disease should be excluded (see below). Rolf’s et al. analysed the GLA gene in 721 adults with cryptogenic stroke (aged 18–55). In total 4.9% of the men and 2.4% of the women who suffered strokes exhibited a mutation in the GLA gene. These had mainly developed ischemic strokes in the vertebrobasilar flow region (Rolf’s et al., 2005).

The following CNS changes were observed in MRI examinations in patients with Fabry disease:

- Looped and dilated blood vessels (Fellgiebel et al., 2006; Ginsberg et al., 2005). (Evidence level IIb).
- Atypical indication for CNS involvement with Fabry disease but only verifiable in the MRI T1 weighting in approximately 30% of all cases, are signal changes in the pulvinar thalami (Mehta et al., 2010). (Evidence level IIa).

3.7 Sensory organs
3.7.1 Eyes

The majority of patients with Fabry disease have ocular changes, which can be diagnosed as non-invasive (Evidence level IIb).

Comment: Ophthalmological changes with Fabry disease relate to the cornea, the lens and the conjunctive and retinal vessels. Relevant ophthalmological findings are found in around 60–70% of children with Fabry disease (Ramawami et al., 2006; Pintos-Morell and Beck, 2009). Generally these changes do not lead to a visual impairment (Nguyen et al., 2005).

The most important eye-specific characteristic is cornea verticillata (vertebra shaped, corneal opacity localised below the centre of the cornea), which is observed in 40–90% of the patients (Nguyen et al., 2005; Sodi et al., 2007, Samiy, 2008). The changes in the cornea are generally identified by means of a slit lamp in the ophthalmological test. Histopathological changes in the cornea verticillata were verified in a foetus of the 22nd gestation week (Tsutsumi et al., 1984), on the other hand ocular changes can also be completely absent in children in the first decade (Samiy, 2008). In addition to treatment with amiodarone, rarely chloroquine and/or other amphiphil drugs, Fabry disease is the most frequent cause for this corneal opacity. While a medicinally-induced cornea verticillata is reversible after the discontinuance of the relevant treatment, it also persists in patients with Fabry disease undergoing ERT (Falke et al., 2008; Wasielewa-Poslednik et al., 2011). The so-called “haze” as a diffuse opacity of the corneal stroma is not characterised as strongly. This change appears to be much rarer than cornea verticillata, in some cases it is also overlooked as a discrete manifestation.

Further possible abnormalities include looped (tortuousitas vasorum) retinal and conjunctive
vessels. However, these vessel changes are not pathognomonic; aneurysmal sacks of the vessels are additionally observed in the connective tissue area. The existence of increasingly looped vessels was described in a study as a possible indicator for a more unfavourable cardiac and renal progression of the disease (Sodi et al., 2007). Two different lens opacities are allocated to the symptoms: the anterior as well as posterior subcapsular, so-called Fabry cataract (Sher et al., 1979). Although the latter is considered disease-specific, it is also observed with other lysosomal storage diseases such as mannosidosis. Both cataract forms can only be sufficiently evaluated with medicinally dilated pupils (which is presumably why the prevalence data in the literature is too low). While cornea verticillata is only marginally more frequent in men than in women, the other ocular changes occur at least twice as often in men (Sodi et al., 2007; Samiy, 2008).

In older literature there are a number of case studies on vascular retinal complications (for an overview see Samiy, 2008); interestingly such reports are missing in current publications although with the current large databases one would expect that such complications would be reported more often.

Approximately 30% of the patients with Fabry disease suffer from a subclinical optic neuropathy with discrete and subjectively unnoticed scotoma (Orssaud et al., 2003; Pitz et al., 2009).

The slit lamp microscopic diagnosis of the most frequent eye changes, cornea verticillata is less dependent on the examiner than those of the tortuous vessels and/or the “Fabry cataract”.

3.7.2 Ears

Patients with Fabry disease often suffer from a sensorineural hearing loss, mainly of higher frequencies and tinnitus (Evidence level Ib).

Comment: Tests in smaller (Germain et al., 2002) and larger cohorts showed that the reduction in hearing is generally an advancing process (Hegemann et al., 2006; Ries et al., 2007). In most cases this is largely cochlear hearing loss (Ries et al., 2007). 5–30% of the patients also report acute hearing loss, which develops over a few hours to days (Hegemann et al., 2006; Ries et al., 2007).

Children may already complain about tinnitus and this seems to correlate with the severity of the disease progression (Hegemann et al., 2006; Keilmann et al., 2009).

Regardless of the hearing loss and tinnitus, the vestibular organ is also often damaged in many patients with Fabry disease (Palla et al., 2007; Sergi et al., 2010).

3.8 Quality of life

The quality of life of patients suffering from Fabry disease with non-causal treatment is significantly poorer than that of the normal population. This applies equally to men (Evidence level IIb) as well as women (Evidence level Ib).

Comment: Tests regarding the quality of life in treatment-naive patients suffering from Fabry disease (also without ERT) are available from Great Britain (Miners et al., 2002) and the USA. (Gold et al., 2002) for men. A Phase IIIb study demonstrated that untreated women suffering from Fabry disease also reported a significantly lower quality of life compared to the normal population (Bachner et al., 2003).

In a retrospective analysis of 120 men and women suffering from Fabry disease in the Fabry Outcome Survey, the quality of life was also significantly reduced compared to age and gender matched persons from a standard population from Great Britain (Hoffmann et al., 2005). Various authors have meanwhile clearly verified that this impairment could already be relevant in childhood (Ries et al., 2005; Ramaswami et al., 2006; Hopkin et al., 2008).

3.9 Other manifestations of Fabry disease

Magage et al. (2007) discovered obstructive airway disease in 61% of men and 26% of women suffering from Fabry disease.

Osteopenia in the lumbar spine and femoral neck have been frequently observed in patients suffering from Fabry disease (Germain et al., 2005).

Kleinitz et al. examined the prevalence of anaemia in 345 patients suffering from Fabry disease: 47% of the men and 20% of the women exhibited haemoglobin levels <13 g/dL (men) and/or <12 g/dL (women). The presence of anaemia mainly correlated with an impairment of the kidney
function, heart failure and/or indications for inflammatory processes (elevated CRP levels) (Kleinert et al., 2005).

4 Diagnosis of suspected Fabry disease

With suspected Fabry disease, the diagnosis is made by enzymatic and/or molecular genetic testing. Patients suffering from Fabry disease should be transferred to a centre that is experienced in collecting findings and treating lysosomal storage diseases.

- Basic tests consist of determining AGLA enzyme activity in leukocytes in men, and mutation analysis of the GLA gene in women
- Mutations that are considered pathogenic correlate with pathologically reduced enzyme activity in men – however not necessarily in women
- Fabry disease must be presumed for men with pathologically reduced AGLA activity.
- 20–30% of the women with disease-causing mutations exhibit normal AGLA activity in the blood. Therefore normal enzyme activity in a woman does not preclude Fabry disease. A molecular genetic analysis of the GLA gene must be used to diagnose women.

4.1 Determination of AGLA activity

Costs approximately 60 euros, availability of results within 1–2 weeks

4.1.1 Determination of AGLA activity in men

The method of choice to confirm diagnosis (Evidence level IV) in males is the determination of AGLA activity in blood leukocytes.

Comment: The following are useable as transmittal materials: heparinised blood, EDTA blood. Transport at room temperature, no longer than two days. The enzymatic activity analysis can be performed on blood dried on filter paper. In case of low activity, a second examination in a different material (e.g. EDTA blood) is recommended. Pathologically low AGLA activity shows, as a rule, the presence of Fabry disease. Enzymatic activity lies below the normal range (0–24%) in men with a clinically apparent, but also with a mild ‘oligosymptomatic’ or even symptom-free Fabry disease. Men with an enzymatic activity of 11–24% of the normal range frequently show a milder phenotype.

If the AGLA value lies within the normal range for men, Fabry disease can be ruled out according to the current state of scientific knowledge (Evidence level IVb).

4.1.2 Determination of AGLA activity in women

The determination of AGLA activity in women has no significance (Evidence level IVb).

Comment: Female carriers of Fabry disease have one pathogenic (mutated) and one intact GLA allele. This is the basis for explaining why a portion of the female carriers exhibit an enzymatic activity within the normal range. The measured enzymatic activity is influenced by various genetic and non-genetic factors, and the AGLA value lies within the pathological range in only about 10% of female carriers (≤24% of the normal value). No connection can be observed among women, between the level of enzymatic activity and the clinical syndrome. Except for the cases of genetically confirmed carriers, evidence of a highly probable pathogenic mutation of the GLA gene is necessary for posing the diagnosis in women.

4.2 Molecular genetic testing

Mutations in the GLA gene are usually “private”, family-specific mutations (Evidence level IV).

Comment: The underlying cause of Fabry disease is a mutation in the GLA gene, which codes for AGLA and is localised on the long arm of the X chromosome in band q22. The AGLA precursor protein comprises 429 amino acids, including a 31-base N-terminal signal peptide. The protein-coding fragment (1290 base pairs) of the gene is divided into 7 exons, which in turn are separated from one another by 6 introns.

A large number of different GLA mutations are known (for an overview, see Gal, 2010). Most patients /families (~90%) carry their family-specific
(“private”) mutations. These can be exhibited – according to the heredity – by relatives of the index case. Fabry disease can also be caused by a re-

4.2.1 Disease-causing mutations

The pathogenetic significance of individual GLA mutations can be judged using three categories (Gal et al., 2011). The following classification reflects analytical results of more than 500 different GLA mutations in several thousand patients with Fabry disease.

**Category 1: High-probability disease-causing mutations**

(A) From the group of point mutations

- **Nonsense mutations:** Through the exchange of a nucleotide in one of the 7 GLA exons, a premature stop codon arises. Even if a stable protein is supposed to be synthesised by this GLA allele, the premature break-off of the synthesis of the AGLA protein gives rise to a shortened and not fully functional protein.
- **Splice site mutations:** These alter one of the first (GT) or last (AG) of both nucleotide bases in one of the 6 GLA introns. The GT and AG dinucleotides of the so-called splice consensus sequence represent signal sequences which are essential to the normal splicing of GLA mRNA.
- **Missense mutations:** The enzymatic activity of AGLA can be considerably impacted if, as a consequence of the genetic alteration of one amino acid which plays a critical role in the formation and/or maintenance of the biologically active structure, or which directly participates in the catabolic process, it is interchanged with another amino acid. The assignment of missense variants as disease-triggering causes is problematic in principle for all genes, because they can also be polymorphisms. Currently one uses so-called *in silico* (computer simulation) analyses; i.e. predictive programmes, to arrive at an interpretation. This group of high-probability disease-causing point mutations accounts for about 25% of all GLA mutations.

B) **Rearrangements** This group of mutations includes changes which either alter the number of nucleotide bases or affect two or more consecutive nucleotide bases. Deletions (lack of nucleotides) belong to this category, as do duplications and insertions (excess of nucleotides), inversions (reversed sequence of nucleotides), and combinations of these named changes. Even if a stable protein is synthesised by the mutated GLA alleles named here, it may be nonfunctional. This group accounts for about 29% of all GLA mutations.

**Category 2: Possible disease-causing mutations**

- All *missense mutations* other than those identified in Category 1.
- All *splice site mutations* other than those identified in Category 1.

**Category 3: High-probability non-disease-causing mutations**

GLA mutations which occur in men with normal or borderline low AGLA activity are viewed as non-disease-related. One must note, however, that men with enzymatically confirmed Fabry disease may in rare cases carry two distinct GLA sequence changes, one pathogenic and one non-pathogenic change. We should particularly mention here the definitely non-pathogenic variant p.Asp313Tyr, which is determined by an AGLA activity analysis in serum (but not in leukocytes) on the basis of a pseudodeficiency with lowered values as in classic Fabry disease.

4.2.2 Mutation analysis for diagnostic confirmation in men

A genetic analysis is performed in men if the AGLA enzymatic activity is pathological (Evidence level IV).

**Comment:** Evidence of a disease-related mutation in the GLA gene is recommended for confirmation of the enzymatic finding with a pathological activity of AGLA in men, and for the subsequent analysis of family relatives. With an enzymatically confirmed finding and lack of disease-related GLA mutation in routine molecular genetic diagnostics, Fabry disease should still be assumed.

4.2.3 Mutation analysis to confirm the diagnosis in women

A molecular genetic test of the GLA gene must always be performed in order to obtain evidence of the disease in women (Evidence level III).

**Comment:** Although women are affected in multiple ways by the disease, it is not uncommon to find normal activity of AGLA. A molecular genetic investigation is therefore always required to make the diagnosis. If the mutation is known in the family, the
diagnosis can be confirmed by a targeted mutation analysis. If the family medical history is negative, a molecular genetic analysis of the GLA gene must be performed to make the diagnosis.

4.3 Family investigation and human genetic counselling

DNA findings should be explained to patients in the context of human genetic counselling (Evidence level IV).

Comment: The precondition for a molecular genetic analysis is an appropriate explanation and the patient’s consent, documented in writing. Regardless of gender, the Genetic Diagnostics Act requires that the patient be offered human genetic counselling in case of a positive enzyme diagnosis and/or a positive DNA finding. With asymptomatic persons who are at risk, a genetic consultation by a physician qualified to perform it must be offered at least prior to the genetic analysis and upon communicating its results and an appropriate period for consideration must be observed between the first human genetic consultation and the blood test. The goal is to inform patients and their relatives comprehensively in case of further questions (e.g. X-chromosomal inheritance, evaluation of the DNA findings, prenatal diagnostics). If family members’ findings are used, the applicable data protection regulations must be observed.

A genealogical analysis is always advised. The detailed family medical history is an obligatory part of diagnostics in case of suspicion of Fabry disease (Gal et al., 2012).

4.4 Determination of Gb3 and lyso-Gb3

The determination of Gb3 in urine or in tissue biopsies can in principle supply evidence for the presence of Fabry disease. There is no evidence up to now for an assured diagnosis on the basis of Gb3; however, a newer biomarker, lyso-Gb3, can contribute to improving diagnostic assurance, and above all, contribute to monitoring (Aerts et al., 2008).

4.5 Differential diagnosis

The spectrum of possible differential diagnoses with Fabry disease is broad, and must be considered in connection with the leading clinical symptoms (Evidence level IIa).
5.1 Kidneys
5.1.1 Initial examination

For early diagnosis of Fabry disease, and for prompt recognition of Fabry nephropathy with an unfavourable profile, extensive diagnostics should be performed with each patient.

Comment: Children and adults with Fabry disease should be examined for any renal manifestation (reduced GFR, Fabry nephropathy) at the initial examination. The examinations listed below should be performed for this purpose:

- Creatinine, creatinine clearance, estimation of the GFR by the MDRD formula or Schwartz Formula (estimation of the GFR in children, Schwartz et al., 2009)
- Protein excretion in urine
  - Test strips (microalbuminuria and/or proteinuria)
  - Total protein and albumin/creatinine quotient in spontaneous urine
  - Protein in 24-hour urine
- Ultrasound (vascular lesions)
- 24-hour blood pressure measurement

In cases of confirmed Fabry disease and suspicion of a second disease, a renal histology (biopsy) may be reasonable / necessary for differential diagnosis.

Kidney biopsy for diagnostic assurance and check-up of the course is not recommended, except in controlled clinical trials (ethics committee approval).

5.1.2 Follow-up

Regardless of whether nephrological symptoms exist, all of the 12-month follow-up analyses should be performed.

Comment: The following examinations should be performed with children and adults:

- Creatinine, creatinine clearance, GFR (MDRD formula) or Schwartz Formula (for estimation of GFR in children)
- Protein excretion in urine
  - Test strips (microalbuminuria and/or proteinuria)
  - Total protein/creatinine and albumin/protein quotient in spontaneous urine
  - Protein in 24-hour urine if necessary
- Blood pressure measurement

Ultrasound examination is only required as needed (no Fabry-specific findings). A kidney biopsy (histology) should only be considered (for purposes of prognostication) in cases of progression of the disease in spite of ERT.
5.2 Heart

5.2.1 Initial examination

An extensive cardiac examination should be performed on patients with newly diagnosed Fabry disease.

Comment: At the first appointment with every patient with Fabry disease, cardiac involvement should be investigated and an evaluation of potential cardiomyopathy should be performed on the other. The following diagnostics should be initiated for this purpose:

- ECG
- 24 hour ECG
- Echocardiography
- Cardiac magnetic resonance tomography (with late-enhancement imaging)

These recommendations apply both to children and adults. In the course of the ECG diagnostics, repolarisation defects, signs of hypertrophy and shortened PQ intervals (rest ECG), and malignant heart rhythm disorders (24 hour ECG) should particularly be investigated. A standard data set should be collected in the course of the echocardiography, and in this process the end-diastolic wall strengths of the septum and posterior wall, as well as systolic and diastolic function, should particularly be quantified. Potential occurrence of a replacement fibrosis should be investigated by means of the magnetic resonance tomography.

A coronary angiography and myocard biopsy should be performed only in case of very specific indications: Myocard biopsy allows diagnostic clarification as to whether there is cardiac involvement. It is not indicated by current knowledge, however, if there is evidence of a mutation or, in male patients, with distinctly reduced enzymatic activity.

5.2.2 Follow-up

In the presence of cardiological findings or symptoms, a follow-up examination should be performed every 12 months. In the absence of cardiological symptoms or findings, follow-up examinations every 24 months are sufficient. Essentially the same tests should be carried out as in the initial examination.

5.3 Nervous system

The assessment of organ-specific neurological manifestations of Fabry disease is essentially performed in the context of overall manifestations and of the degree of co-involvement of other organs (especially the heart and kidneys).

5.3.1 Initial examination

In the evaluation of the neurological symptoms of Fabry disease, clinical examinations should be performed with a focus on vascular symptoms and the involvement of the autonomic nervous system.

Comment: The following examinations should be performed with children and adults:

- Doppler and duplex sonography: In Fabry disease, microangiopathic vessels are found only in a small number of cases; intima-media thickening is typically found instead (homogeneously uniform, as a rule no ulcerations of the intima). Ectasia of the Arteria basilis is an important indication.
- MRI of the head
- Evaluation of pain intensity and quality of life: e.g. BPI (pain questionnaire), WHO5 (depression questionnaire), MD10 (enables classification under ICD10), and/or SF-36 (disadvantage: very extensive).

5.3.2 Follow-up

If neurological (especially vascular) symptoms exist, follow-up analyses should be performed every 12 months. With no neurological symptoms, follow-up analyses every 24 months are reasonable.

Comment: The following examinations are recommended for children and adults:

- Doppler and duplex sonography
- SF-36, BPI or alternatively chosen questionnaires
- MRI of the head
- With clinical progression or reappearance of symptoms in spite of ERT:
- Doppler and duplex sonography
- MRI of the head
- SF-36, BPI or alternatively chosen questionnaires

18
5.4 Gastrointestinal tract

Gastrointestinal examination essentially follows the general procedure for abdominal complaints, and will routinely include a transabdominal ultrasound, a gastroscopy (aesophagogastro-duodenoscopy with biopsies), and a colonoscopy (with biopsies). In addition, an H2 respiration test and a capsule videoendoscopy may also be considered where necessary.

Comment: It should be noted that apparative and laboratory chemical investigations may be inconclusive despite pronounced gastrointestinal symptoms (MacDermot et al., 2001).

5.5 Ears
5.5.1 Initial examination

An appointment with an ENT specialist should be made for all Fabry patients at the initial examination, especially if hearing loss, tinnitus, or a balance disorder already exists.

Comment: The following examinations are recommended for children and adults:
- ENT specialist examination with hearing and tinnitus diagnostics
- Testing of the vestibular apparatus

5.5.2 Follow-up

If hearing loss, tinnitus, or balance disorders already exist, follow-up analyses should be done every 12 months; otherwise, follow-up analyses every 24 months are reasonable.

Comment: The following examinations should be performed with children and adults:
- Sound threshold audiometric examinations
- Tinnitus and balance disorder diagnostics as necessary

6. Depression and Quality of Life

Health-related quality of life should be monitored regularly in children and adults, as a supplementary monitoring instrumentality.

Comment: A multi-systemic disease, which is characterised by chronic symptoms (especially pain), a long period of diagnosis, and a shortened life expectancy, suggests an elevated risk for affective disorders: In one examination by Cole and colleagues, almost half of the Fabry patients surveyed suffered clinical depression (Cole et al., 2007).

Investigations of health-related quality of life (physical, psychological, and social condition as well as ability to function) likewise showed corresponding limitations. An enquiry in Great Britain with 38 men with Fabry disease (SF-36 and EQ-5D questionnaire) gave evidence of a significantly lowered quality of life compared to the normal population, in all tested dimensions (Miners et al., 2002). A similar investigation among men with Fabry disease in the U.S.A. confirmed these findings (Gold et al., 2002). A Phase IIIb study from Germany showed a reduced quality of life for women with Fabry disease compared to the normal population, in all dimensions of the SF-36 (Baehner et al. 2003). Other studies among heterozygote women have likewise demonstrated essential limitations on the quality of life (Street et al., 2006; Wang et al., 2007). Another investigation by Hoffmann and colleagues confirmed the significantly lower quality of life (EQ-5D questionnaire) among 120 men and women (Hoffmann et al., 2005).

Even among children with Fabry disease, a reduced quality of life has already been determined in several dimensions of the HRQOL, in comparison to their healthy contemporaries (Hopkin et al., 2008; Ries et al., 2005).

7. Treatment and Care

Treatment of Fabry disease requires close collaboration among different specialist medical disciplines. This includes, in the first instance, personal physician internists, paediatricians, nephrologists, cardiologists, neurologists, gastroenterologists, dermatologists, ophthalmologists, ENT specialists/paediatric audiologists, and human geneticists. Psychiatric or psychosomatic co-therapy is required depending on the individual disease status.

After confirmed diagnosis, the patient should be referred to a centre experienced in the diagnosis and treatment of the disease, for an initial examination and planning of treatment.

Comment: The following treatment goals are aimed at:
- Reduction of symptoms (above all, amelioration of pain)
The currently available treatment for Fabry disease comprises ERT and concomitant therapies for organ manifestations and symptoms.

Most patients with Fabry disease need intensive, expensive, and multi-modal care.

7.1 Enzyme replacement therapy

Since 2001 a causal treatment option has been available with ERT, to compensate for the lack or loss of function of AGLA. The AGLA enzyme manufactured by genetic technology for ERT is infused intravenously every 14 days. Treatment is lifelong. Two enzyme replacement preparations have been approved:

- Agalsidase alpha (Replagal®) is manufactured in a human cell line and applied in a dosage of 0.2 mg/kg of body weight
- Agalsidase beta (Fabrazyme®) is produced recombinantly in CHO cells (CHO = Chinese hamster ovary) and applied in a dosage of 1.0 mg/kg of body weight

The goal of ERT is to maintain normal organ function, or in the ideal case, to cause an existing organ manifestation to regress. ERT currently offers the sole possibility of slowing the progression of the disease and preventing its consequences (Mehta et al., 2010).

7.1.1 Status of efficacy data

Enzyme replacement therapy is clinically effective especially in respect to the improvement of quality of life, pain, kidney and heart function (Evidence level Ib).

Comment: There are only a limited number of randomised, controlled clinical trials for ERT with agalsidase alpha or agalsidase beta (Eng et al., 2001, Schiffmann et al., 2001; Hajjoff et al., 2003; Banikazemi et al., 2007; Hughes et al., 2008). After the approval of both enzyme replacement preparations in 2001, diagnosed patients were, as a rule, put onto ERT. The available data on long-term therapy with agalsidase alpha or agalsidase beta have been generated, as a rule, from open-label extension studies of Phase III investigations, or from the two patient registries, “Fabry Outcome Survey (FOS)” and “Fabry Registry” (see Section 8, “International Patient Registry”). Long-term data with an observation period of up to 5 years have been publicised. Studies of treatment with agalsidase alpha and agalsidase beta have demonstrated the reduction of Gb3 in urine and plasma, as well as a reduction of microvascular endothelial Gb3 accretions in the kidney, heart, and skin (Eng et al., 2001; Schiffmann et al., 2001; Baehner et al., 2003; Wilcox et al., 2004; Eto et al., 2005; Ries et al., 2006; Germain et al., 2007; Hughes et al., 2008; Wraith et al., 2008; Whybra et al., 2009). It was possible to show the lowering of the plasma Gb3 level already after 3 months of treatment (van Bremen et al., 2011).
**Table 2. Evidence for Efficacy of ERT in Patients with Fabry disease – Overview of the Results of Clinical Trials.**

<table>
<thead>
<tr>
<th>Organ system or symptom (Men, women)</th>
<th>Effect</th>
<th>Enzyme</th>
<th>Reference</th>
</tr>
</thead>
</table>
| Kidney                               | Stabilisation of renal function or lengthening of the eGFR reduction (observation period of up to 4.5 years) | Agalsidase alpha | Branton et al., 2002  
Beck et al., 2004  
Schwarting et al., 2006  
Schiffmann et al., 2006  
Feriozzi et al., 2009  
West et al., 2009 |
|                                      |        |        | Wilcox et al., 2004  
Breunig et al., 2006  
Germain et al., 2007  
Banikzemi et al., 2007 |
| Heart                                | Reduction of left ventricular mass (observation period of up to 5 years) | Agalsidase alpha | Bachner et al., 2003  
Beck et al., 2004  
Hughes et al., 2008  
Mehra et al., 2009  
Whybra et al., 2009 |
|                                      |        |        | Weidemann et al., 2003  
Spinelli et al., 2004  
Imbriaco et al., 2009  
Weidemann et al., 2009  
Machann et al., 2011 |
| CNS                                  | Reduction of elevated blood flow velocity | Agalsidase alpha | Moore et al., 2001  
Moore et al., 2002 |
| Gastrointestinal tract               | Reduction of intensity and frequency of gastrointestinal symptoms (abdominal pains, diarrhea) | Agalsidase alpha | Dehout et al., 2004  
Hoffmann et al., 2007 [b] |
|                                      |        |        | Banikzemi et al., 2005 |
| Hearing                              | Stabilisation of hearing ability | Agalsidase alpha | Hajioff et al., 2003  
Hajioff et al., 2006 |
| Pain                                 | Continuous reduction of neuropathic pains and stabilisation (BPI; observation period of up to 5 years) | Agalsidase alpha | Schiffmann et al., 2001  
Beck et al., 2004  
Hoffmann et al., 2005  
Hoffmann et al., 2007 [a]  
Mehra et al., 2009  
Whybra et al., 2009 |
| Peripheral nervous system            | Improvement of peripheral nerve function | Agalsidase beta | Hils et al., 2004 |
| Dyshidrosis                          | Improvement of impaired sweat production | Agalsidase alpha | Schiffmann et al., 2003 |

**Special population**

<table>
<thead>
<tr>
<th>Effect</th>
<th>Enzyme</th>
<th>Reference</th>
</tr>
</thead>
</table>
| Children | Pain reduction (BPI), reduction of the use of analgesic drugs (observation period of up to 4 years) | Agalsidase alpha | Ries et al., 2006  
Ramaswami et al., 2007  
Schiffmann et al., 2010 |
|         | Improvement of heart rate variability (adolescents) (observation period of up to 4 years) | Agalsidase alpha | Ries et al., 2006  
Schiffmann et al., 2010 |
|         | Improvement of impaired sweat production | Agalsidase alpha | Ries et al., 2006 |
|         | Reduction of gastrointestinal symptoms (abdominal pains) | Agalsidase alpha | Hoffmann et al., 2007 [b] |
|         |        | Agalsidase beta | Wraith et al., 2008 |

**Quality of life (men, women, children)**

<table>
<thead>
<tr>
<th>Effect</th>
<th>Enzyme</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Improvement in Euro quality of life (observation period of over 5 years)</td>
<td>Agalsidase alpha</td>
</tr>
</tbody>
</table>
|        | Improvement in EQ-5D | Agalsidase alpha | Beck et al., 2004  
Hoffmann et al., 2005 |
|        | Improvement in the SF-36 | Agalsidase beta | Watt et al., 2010 |
|        | Improvement in pain-related quality of life in children | Agalsidase alpha | Ramaswami et al., 2007 |
In an investigation by Banikazemi and colleagues with patients with mild to moderate renal dysfunction, an ERT significantly delayed the time to first clinical event (renal, cardiac, cerebrovascular, or death) in comparison to a placebo. The mean observation period in this study was 18.5 months (Banikazemi et al., 2007). Other studies on ERT confirm the clinical efficacy, especially with regard to pain, quality of life, and the life-shortening organ manifestations in the kidneys and heart (see Table 2).

The efficacy of ERT was also demonstrated in children (see Table 2).

Both of the available substances show deviations in the glycosylation pattern (Lee, et al., 2003). The state of available data up to this point does not provide any evidence of a clinically relevant distinction in regard to efficacy. An independent study in Canada is currently investigating agalsidase alpha 0.2 mg/kg and agalsidase beta 1.0 mg/kg in a direct comparison – further results from this study are expected in the near future (Sirrs et al. 2010).

**ERT can have the effect of ameliorating neuropathic pain (Evidence level Ib).**

**Comment:** In a Phase I/II study, the infusion of five doses of agalsidase beta (0.3-3.0 mg/kg every two weeks) effected an improvement in the overall sensation of pain and in current pain intensity, in comparison to the start of the investigation (Eng et al., 2001). In addition, in the double-blind, randomised, controlled trial for agalsidase alpha, patients reported significantly fewer pains with ERT, while this was not reported in the placebo group (Schifffmann et al., 2001). A follow-up observation of these patients over 3 years confirmed these results (Schifffmann et al., 2003).

The double-blind, randomised, controlled trial for agalsidase beta also showed a significant improvement of pain sensations after 20 weeks of ERT, in comparison to the start of the investigation; however, this was also the case in the placebo group (Eng et al., 2001).

Also the long-term, retrospective evaluation of larger patient groups allows no uniform assessment of the efficacy of ERT on pain. One retrospective analysis of 752 patients with Fabry disease (393 women, 353 men) from the FOS database showed an improvement of pain after 24 and 36 months (Hoffmann et al., 2007 [b]).

Another evaluation from the FOS database, which only examined women, could not confirm these results (Hughes et al., 2011). The authors concluded that it was possible to obtain an improvement in pain, especially in an early stage of treatment, but this was less pronounced in the long term. This stands in contradiction to Mehta et al., who reported a significant improvement in pain in 181 adults (of whom 126 were men) after 5 years of ERT (Mehta et al., 2010).

Experiences with ERT among children with Fabry disease are also heterogeneous with respect to improvement of pain. The results of a prospective, open-label study on the safety and efficacy of ERT in children showed a sustained, significant improvement of pain intensity in comparison to the start of the investigation (Schifffmann et al., 2010).

By contrast, Ramaswami et al. could find no significant reduction in pain prevalence for the total population, after up to 2 years, in a retrospective FOS analysis of data on 98 children (Ramaswami et al., 2011). However the patients, who at the start of the investigation had complained of pain attacks or chronic pains, reported an improvement in these symptoms after 2 years.

The variety in study approaches and the selection, in part, of very different instruments for measurement of pain, definitely must be taken into account in the assessment of these results. However, ERT in patients with Fabry disease generally shows the ability to effect a regeneration of nerve fibres in the proximal skin regions (Üceyler et al., 2011). The fact that not all patients reported an improvement in pain could be causally connected with already irreversible damage to the nerve fibres, and could serve to recommend the early start of ERT with Fabry disease (Hilz et al., 2004).

In cases of pain, which cannot be controlled by the usual analgesics and also does not respond to ERT, the use of gabapentin (Ries et al., 2003) and carbamazepine (Filling-Katz et al., 1989) can be reasonable.

### 7.1.2 Indication and start of treatment

**ERT is the only treatment for preventing disease progression and its consequences in Fabry disease (Evidence level Ib).**

**Comment:** In order to prevent the primary Gb3 accumulation and the resulting clinical manifestations, ERT should be applied as early as possible after assured diagnosis of Fabry disease and corresponding documentation of the clinical degree of severity and/or progression of symptoms.
Recommendation for male and female patients:

- The indication for ERT is always given by signs of a relevant organ manifestation (heart, kidney, brain, pains), irrespective of the patient’s age. The treatment is required life-long.

7.1.3 Tolerance

ERT is well tolerated, overall, with no difference between men and women, or between children and adults (Evidence level IIb).

Comment: The most frequent adverse events with ERT are infusion reactions. These include primarily headaches, paraesthesias, redness, hot flushes, fever, chills, cold sensations, nausea, vomiting, and fatigue (summary of product characteristics for Fabrazyme® 2010, summary of product characteristics for Replagal® 2010). Most infusion reactions in the treatment studies were mild to moderate. As a rule they occur in the first 3 months after the start of treatment, and decline in frequency over the period of the ERT. After primary treatment of the symptoms (reduction of the infusion rate, application of non-steroidal antiphlogistics, antihistamines and/or glucocorticoids), experience indicates that the infusion can be re-continued after a few weeks/months without these concomitant measures.

Antibody formation

If the efficacy of the ERT declines, an antibody analysis should be performed. In case of a positive finding, a change of preparation can be considered (Evidence level IV).

Comment: One possible cause for infusion reactions is seroconversion with the formation of antibodies (Ab) against human proteins. In clinical studies, the majority (>80%) of treated patients with agalsidase beta developed IgG Ab within the first 3 months of treatment (summary of product characteristics for Fabrazyme® 2010); with agalsidase alpha, this rate was about 24% in the group of male patients, with no antibodies being detectable in female patients (summary of product characteristics for Replagal® 2010). To this point it is unclear what influence the Ab formation has on the efficacy of the treatment. After the infusion of agalsidase beta, IgE antibodies were also detected in a limited number of patients (summary of product characteristics for Fabrazyme® 2010).

7.1.4 Considerations for treatment in women

No indication exists for stopping ERT during pregnancy (Evidence level III).

Comment: The indication for ERT in heterozygote women should be given on the basis of the same criteria as for hemizygote men (Baehner et al., 2003, Mehta et al., 2004). ERT is particularly indicated for women if the following symptoms or organ manifestations exist: proteinuria, renal insufficiency, cardiomyopathy, and/or acroparaesthesias which occur not only transiently and do not, or not adequately, respond to analgesics (Weidemann et al., 2011). The ERT should be continued even in pregnancy, because no damaging influence on mother or child from the enzyme application has been observed in multiple case studies up to this time (Wendt et al., 2005; Germain et al., 2010, Politei et al., 2010); on the other hand, without ERT, there is a proven progression of the disease.

7.1.5 Considerations for treatment in children

Various studies have proven the efficacy of ERT in children as well (Evidence level IIa).

Comment: With treatment, a regression of acroparaesthesias (Ries et al., 2006; Ramaswami et al., 2007; Schiffmann et al., 2010) and abdominal symptoms (Hoffmann et al., 2007 [b]; Wraith et al., 2008) has been shown. A normalisation of heart rate variability (Ries et al., 2006; Schiffmann et al., 2010) and an improvement of impaired sweat production (Ries et al., 2006) was also observed. Regression of the Gb3 concentrations in serum and urine was able to be demonstrated in all studies (see Table 4).

7.1.6 Quality of life

An improvement in quality of life can be obtained with ERT for a large proportion of male and female patients with Fabry disease, regardless of which preparation is used (Evidence level IIa).

Comment: Significant improvement of the quality of life cannot be definitely deduced from the double-blind randomised trials of ERT in Fabry disease, both with agalsidase alpha and with agalsidase beta. Schiffmann et al. have certainly recorded pain-related
quality of life, before and during ERT in men with Fabry disease; however, this was not measured using a dimension in a quality of life instrument, but rather a dimension in the Brief Pain Inventory pain questionnaire (Schiffmann et al., 2001). Nonetheless, the men treated for 24 weeks with agalsidase alpha showed a significant improvement in pain-related quality of life, in comparison to placebo (Evidence level Ib). Eng et al. were able to observe an improvement in two dimensions of the SF-36 (physical and emotional functioning) under treatment with agalsidase beta in their double-blind randomised controlled trial; yet the men with Fabry disease treated with the placebo also reported an improvement of physical functioning and physical pain after 6 months (Eng et al., 2001). Since then, numerous studies have clearly shown the improvement in quality of life of patients with Fabry disease treated with either agalsidase alpha or with agalsidase beta, in both women and men (Baehner et al., 2003; Hoffmann et al., 2005; Eto et al., 2005; Watt et al., 2010).

One 4-year evaluation of the Fabry Outcome Survey showed only a tendency to improved quality of life in men and women under ERT (Hughes et al., 2011). However, it must be considered here that it was likely that the population size was too small to indicate an effect with certainty. One 5-year analysis of the same database was able to demonstrate a significant improvement of quality of life (Mehta et al., 2009).

Additionally, in children, researchers have been able to observe a significant improvement in quality of life – already after an intervention period of 12 to 23 weeks – following the start of ERT (Ramaswami et al., 2007).

Regular data collection on the quality of life among patients with Fabry disease with ERT is desirable and reasonable (Evidence level Ib).

Comment: The use of a standardised questionnaire certainly is no substitute for medical assessments of the well-being of patients and careful monitoring of treatment. But the use of a standardised, validated, age-appropriate questionnaire to ascertain life quality of life can contribute to the objectification of changes under treatment.

7.1.7 Home infusion therapy

When the patient has received approximately 6 ERT treatments in the clinic or practice, and no infusion reactions have occurred, the infusions can be transferred to the patient’s home (Evidence level IIb).

Comment: A shift of the infusions into the home facilitates handling the disease in most cases, and improves compliance. Experiences with home infusion therapy for Fabry disease are now available from various countries (Milligan et al., 2006; Linhorst et al., 2006; Schiffmann et al., 2006; Cousins et al., 2008; Guest et al., 2010). The following preconditions are mandatory for establishing a home therapy:

- Training of the person (e.g., nurse / caregiver) undertaking the treatment at home (knowledge of Fabry disease and ERT, practice in the routine of insertion in a venous aditus). In particular, the person must know the measures to be taken in case of an adverse event.
- Legal questions (e.g. liability of the treating physician) must be clarified prior to the start of home infusion therapy

7.2 Concomitant treatments

Depending on symptoms and organ manifestations, other treatment measures besides ERT may be required or considered (see Table 3).
Table 3. Supplementary Treatment Options with Symptoms or Consequential Damages of Fabry disease (adapted from Hughes et al., 2005; Eng et al., 2006; Mehta et al., 2010; Weidemann et al., 2011).

<table>
<thead>
<tr>
<th>Symptom/Condition</th>
<th>Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>Prevention of trigger mechanisms (physical strain, heat, sudden temperature change, stress, overfatigue); anticonvulsives (e.g. phenytoin, carbamazepine, gabapentin, topiramate), tricyclic anti-depressives</td>
</tr>
<tr>
<td>Renal function impairment, proteinuria</td>
<td>ACE inhibitors, angiotensin-II blockers, anaemia management</td>
</tr>
<tr>
<td>Kidney failure</td>
<td>Dialysis or transplantation</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Anti-hypertensives, e.g. ACE inhibitors (no beta blockers with sinus bradycardia)</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>Anti-arrhythmics, implantation of a defibrillator (ICD)</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>Implantation of a heart pacemaker</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>Diuretics, ACE inhibitors (angiotensin-II blockers if necessary due to ACE inhibitor intolerance), pacemaker or ICD therapy, heart transplantation</td>
</tr>
<tr>
<td>Coronary artery stenosis</td>
<td>PTCA, CABG</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>Stroke prophylaxis (e.g. aspirin or other platelet aggregation inhibitors)</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>Statins</td>
</tr>
<tr>
<td>Breathing passage obstruction</td>
<td>Nicotine abstinence, therapy attempt with bronchodilators</td>
</tr>
<tr>
<td>Sweat secretion disorders</td>
<td>Possible injection of botulinum toxin to inhibit sweat secretion in case of hyperhidrosis</td>
</tr>
<tr>
<td>Delayed emptying of stomach</td>
<td>Small, frequent meals; metcloproamide, H2 blockers</td>
</tr>
<tr>
<td>Pronounced hearing loss</td>
<td>Hearing aids, cochlea implantation</td>
</tr>
<tr>
<td>Depression</td>
<td>Psychiatric / psychological treatment; serotonin-uptake inhibitors</td>
</tr>
</tbody>
</table>

### 7.2.1 Nephrological add-on therapy

As with other chronic kidney diseases, in cases of a proteinuria and/or hypertension, an add-on therapy should be given to delay progression (Evidence level III).

**Comment:** The consistent application of ACE inhibitors or angiotensin-II blockers (sartanes) in combination with ERT in Fabry disease has only been investigated in uncontrolled case series up to now (Tahir et al., 2007). Relatively low blood pressure can be problematic in this regard, affecting compliance with the medication intake schedule. The named concomitant therapy for Fabry disease is not, however, aimed primarily at lowering blood pressure until a predetermined target value is reached. Rather its primary use is for stabilisation of kidney function and reduction of proteinuria.

End-stage kidney disease is treated in exactly the same way as in patients without Fabry disease (Evidence level III).

Comment: In patients with end-stage kidney disease, a haemo- or peritoneal dialysis is indicated. There is no contraindication against kidney transplantation. After kidney transplantation, a recurrence in the transplant on the basis of the normal function of the α-galactosidase in the transplanted organ, has never yet been described. Due to the still existing pathological metabolic situation, ERT should be continued unchanged in order to prevent extra-renal damage. Data on tolerance and efficacy of ERT in patients with kidney transplants have been published (Ojo et al., 2000; Pastores et al., 2007; Mignani et al., 2008; Cybulla et al., 2009).

### 7.2.2 Cardiological add-on treatment

A cardiological add-on treatment should be carried out with patients with Fabry disease and cardiomyopathy (Evidence III).

**Comment:** An add-on treatment is necessary, especially in cases of progressive cardiomyopathy. ACE inhibitors play a central role in this connection,
as they can have a positive effect on hypertrophy regression. It should be noted in this regard, however, that patients with Fabry disease are particularly inclined to hypotension. Good blood pressure monitoring is therefore necessary after introduction of an ACE inhibitor therapy (Weidemann et al., 2010).

All patients with tachycardia rhythm disorders should furthermore receive a β-blocker. This is concurrently effective in protecting against ventricular rhythm disorders. But since many Fabry disease patients also suffer from bradycardia (Shah et al., 2005), especially with such typical symptoms as dizzy spells or syncope, such symptoms should particularly be ruled out in advance by means of a Holter monitor ECG.

In the course of the anti-arrhythmic therapy it should be noted that in patients with Fabry disease, an interaction between amiodarone and the enzyme to be substituted has been described (Whitley et al., 1983). Therefore an amiodarone therapy should be introduced only after very careful consideration.

Patients with progressive cardiomyopathy frequently suffer from symptomatic bradycardias. A pacemaker treatment is therefore indicated for these patients. Before implantation, it is important to rule out malignant ventricular rhythm disorders, which typically appear in the end-stage cardiomyopathy. A defibrillator should be implanted in this case, “according to the general guidelines for ICD implantation in cases of malignant rhythm disorders (ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias”, Weidemann et al., 2010).

In patients with a cardiac involvement, angina pectoris symptoms are common, as a rule not to be traced back to a primary cardiac heart disease, but rather to a small vessel disease. Here, after ruling out coronary heart disease, nitro preparations or low-dose calcium antagonists may be considered.

7.2.3 Neurological add-on treatment

Recurrent TIAs/strokes occur in about 25% of all Fabry patients (Evidence level IIa).

Comment: Patients with Fabry disease have an elevated risk of TIA or stroke (Feldt-Rasmussen, 2011). In these patients, TIAs and strokes frequently occur earlier than in other patients, and the risk of recurrence is greater (Mehta et al., 2010; Viana-Baptista, 2011). Consistent stroke prophylaxis (platelet aggregation inhibition with ASA 75-100 mg and/or 75 mg clopidogrel, and treatment of arterial hypertension) is therefore necessary, along with secondary preventive measures (nicotine abstinence, physical activity, treatment with statins, regulation of metabolic status in case of diabetes mellitus) analogous to the AWMF (Arbeitsgemeinschaft Wissenschaftlich-Medizinischer Fachgesellschaften, Working Group of Scientific-Medical Associations) “Stroke” Guidelines (Registry Number 053-011).

8 Self-Help Organisation

M. Fabry Self-Help Group in Germany

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Literature


29. Fachinformation Fabrazyme®, Stand der Information: 01/2010
30. Fachinformation Replagal®, Stand der Information: 12/2010


94. Nguyen TT, Gin T, Nicholls K, Low M, Galanos J, Crawford A. Ophthalmological manifestations of Fabry disease: a survey of patients at the Royal Melbourne Fabry


Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AGLA</td>
<td>$\alpha$-galactosidase A</td>
</tr>
<tr>
<td>BPI</td>
<td>Brief Pain Inventory, pain questionnaire</td>
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<tr>
<td>CNS</td>
<td>Central Nervous System</td>
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<tr>
<td>ECG</td>
<td>electrocardiogram</td>
</tr>
<tr>
<td>ERT</td>
<td>enzyme replacement therapy</td>
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<tr>
<td>FOS</td>
<td>Fabry Outcome Survey</td>
</tr>
<tr>
<td>Gb3</td>
<td>Globotriaosylceramide</td>
</tr>
<tr>
<td>Lyso-Gb3</td>
<td>Globotriaosylphosphosine</td>
</tr>
<tr>
<td>GFR</td>
<td>glomerular filtration rate</td>
</tr>
<tr>
<td>LVH</td>
<td>left ventricular hypertrophy</td>
</tr>
<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
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<tr>
<td>MDI-0</td>
<td>Major Depression Inventory</td>
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<tr>
<td>SF-36</td>
<td>Short Form 36; health questionnaire for data gathering on quality of life</td>
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<tr>
<td>TIA</td>
<td>transient ischemic attack</td>
</tr>
<tr>
<td>WHO5</td>
<td>questionnaire-quick test</td>
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</table>

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Procedure for consensus-building

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Conflicts of interest

All members of the Guidelines Expert Group have presented their conflicts of interest to AWMF.

Period of validity

These Guidelines apply for 3 years or until revised.

Evidence level

The present guidelines correspond to Development Level S2k+IDA (consensus-based + interdisciplinary harmonisation). The Expert Group are representative of the broader target audience, and have involved the concerned specialist associations in developing the Guidelines. The recommendations of these Guidelines were created on the basis of formal consensus techniques.
The next edition will aim for a guideline at Development Level 3, which takes into consideration all essential elements of systematic guideline development.

**Level Ia:** Evidence on the basis of at least one systematic review (with homogeneity of randomised controlled trials).

**Level Ib:** Evidence on the basis of a single randomised controlled trial (with a narrow confidence interval).

**Level IIa:** Evidence on the basis of systematic review of cohort studies.

**Level IIb:** Evidence on the basis of individual cohort studies. At least one well-planned, controlled trial without randomisation.

**Level III:** Evidence on the basis of systematic review of case-control studies – well-planned, non-experimental descriptive studies (case series, correlation studies).

**Level IV:** Evidence on the basis of reports of expert panels or expert opinions and/or clinical experience of known authorities: descriptive studies, case series.

**Level V:** Case series or one or more expert opinions

Classification of evidence classes according to: Oxford Centre for Evidence-Based Medicine Levels of Evidence (May 2001). Bob Phillips, Chris Ball, Dave Sackett, Doug Badenoch, Sharon Straus, Brian Haynes, Martin Dawes since November 1998.

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