orphanaesthesia

Anaesthesia recommendations for

Fabry disease

Disease name: Fabry disease

ICD 10: E75.2

Synonyms: Morbus Fabry, Anderson Fabry disease (AFD), Fabry syndrome, angiosarcoma corporis diffusum, α-galactosidase A deficiency

Disease summary: Fabry disease is a rare lysosomal storage disease of X-linked recessive inheritance, which was first described in Germany and the United Kingdom in 1898 [1,11,50]. Due to mutations in the GLA gene, located on the X chromosome (Xq22.1), patients show a partial or complete deficiency of ceramidtrihexosidase, also referred to as α-galactosidase A (α-Gal A) [3,50]. The biochemical aetiology of this condition was discovered several years later [4,22]. Because of this mutation, sphingolipids accumulate in various tissues. Particularly globotriaosylceramide (Gb3) accumulates in skin, eye, heart, kidney, brain, vascular and nervous systems [50]. Accordingly, Fabry disease is a multisystem disease.

The disease can be divided into a severe, classical phenotype and a generally milder non-classical phenotype. In the severe form, there is typically no residual enzyme activity [3]. The non-classical type, also referred to as late-onset or atypical Fabry disease, often demonstrates a more variable disease severity and progression. Disease manifestations are often limited to a single organ with mainly isolated renal or cardiac manifestation [3]. Males tend to develop greater disease severity than females [50]. Skewed X inactivation might be responsible for the variability of the phenotype in women [3,10].

The overall incidence in new-born children varies between 1/40,000 or 1/117,000 in men up to much higher incidences with about 1/3100 to 1/1000 in high-risk populations, and even 1:875 in male and 1:399 female live births in Taiwan. It seems to differ between various countries [8,18,29,30,42,45].

In a cohort of 98 male patients, the mean age of diagnosis was 21.9 years [27]. The mean median cumulative survival seems to be 50 ± 8 years for males and up to 72 years for females. [5,27,46] The disease may present at any age and generally is progressive [38].

The diagnosis can be difficult, because patients present with nonspecific complaints such as headaches, limb or abdominal pain plus diarrhoea. The definitive diagnosis is most commonly made following severe complications such as stroke, heart and kidney failure [35].

Typical facial features include periorbital fullness, prominent lobules of the ears, bushy eyebrows, recessed forehead, pronounced or prominent nasal angle, generous nose or bulbous nasal tip, prominent supraorbital ridges, shallow midface, full lips, prominent nasal bridge, broad alar base, coarse features, posteriorly rotated ears and prognathism [35]. Other features include short fingers, prominent superficial vessels of hands, 5th digit brachydactyly or clinodactyly [35].

Fabry disease may present with cardiac abnormalities, which occur in up to 60% of male patients with the classical form of Fabry disease [39]. The pre-dominant finding is concentric left-ventricular hypertrophy (LVH). Furthermore, the left-ventricular mass index seems to be inversely correlated with α-Gal activity [49]. Moreover, Fabry patients often present with left-sided valvular dysfunction and conduction disturbances (bradycardia, atrioventricular block, various forms of ventricular and supraventricular arrhythmias, in particular atrial fibrillation) [9,25,39]. However, the right ventricle is occasionally affected, resulting in systolic and diastolic dysfunction [21,26].

End-stage renal disease and cerebrovascular events are not uncommon, largely due to glycolipid deposits in the glomeruli. The chronic kidney disease is characterised by glomerulosclerosis, tubular atrophy and interstitial fibrosis leading to proteinuria and chronic renal insufficiency [2]. The central nervous system has an increased incidence of stroke [39]. Mild cognitive abnormalities are only rarely described [43].

Pulmonary manifestations include obstructive airflow limitation [6,14].

Impaired autonomic and endocrinal function is also common. Gastrointestinal manifestations include abdominal pain or episodic diarrhoea, and are not uncommon. Besides, headaches and fever of unknown origin are frequently reported [37]. Fever of unknown origin as well as reduced saliva and tear formation may occur [7]. Hypohydrosis often leads to decreased exercise tolerance in Fabry patients [38]. Some of these symptoms as well as fatigue, dry skin or vague gastrointestinal complaints are also signs of hypothyroidism, which is a common co-finding in patients with Fabry disease [12,17].
The involvement of the peripheral nervous system leads to neuropathic pain or painful sensations in the extremities and arthralgia and myalgia might result in a decrease in quality of life. These symptoms can be triggered by changes in environmental or body temperature, exercise or emotional stress [37].

Other manifestations of Fabry disease may be corneal opacities (cornea verticillata), angiokeratoma, tinnitus or hearing loss [36,44].

In recent years, enzyme replacement therapy (ERT) has been offered as a treatment for Fabry disease and may halt disease progression [50]. The Mainz Severity Score Index (MSSI) was developed and may help to measure the severity of AFD and to monitor the clinical course of the disease in response to ERT [47].

Medicine is in progress

Perhaps new knowledge

Every patient is unique

Perhaps the diagnosis is wrong

Find more information on the disease, its centres of reference and patient organisations on Orphanet: www.orpha.net

Emergency information

	AIRWAY / ANAESTHETIC TECHNIQUE	prepare for difficult airway (dysmorphic features of head, face and neck) – pulmonary manifestations include obstructive airflow obstruction – no general (dis)advantage for GA (TIVA / balanced) or RA – in patients with severe cardiac, renal or other organ dysfunctions, GA techniques might be the optimal approach whenever applicable
B	**BLOOD PRODUCTS (COAGULATION)**	no specific recommendations
C	**CIRCULATION**	cardiac abnormalities are frequent with predominantly left-sided valvular dysfunction, hypertrophy and conduction disturbances – increased risk for cerebrovascular events – consider IBP and (non-)invasive haemodynamic monitoring
D	**DRUGS**	no risk for MH – consider drug dose adaption in case of renal impairment – continue enzyme replacement therapy – endocarditis prophylaxis (if indicated)
E	**EQUIPMENT**	perioperative availability of dialysis may be necessary – avoid extreme positioning due to haemodynamic impairment and chronic pain – avoid trigger for (neuropathic) pain exacerbation (i.e. emotional stress, changes in body temperature)

Typical surgery

Dermatology: typical vascular skin lesions termed angiokeratoma [16].

Ophthalmology: corneal opacities (cornea verticillata) and other ophthalmological changes [28].

Cardiac surgery: valve repair or replacement, implantation of a pacemaker or internal cardiac defibrillator, cardiac assist devices, resynchronisation therapy and heart transplantation [34,38,39].

Neurology and Neurosurgery: cerebrovascular strokes in small or large vessels [31,32].

Surgery: arteriovenous fistula for haemodialysis, cadaveric renal transplantation [33].

Traumatology: fractures or injuries due to seizures [39].

Type of anaesthesia

General anaesthesia and regional anaesthesia techniques might present potential problems in Fabry patients.

Ideally, these patients require assessment and anaesthesia care by a senior anaesthetist. The involvement of different organs and tissues means that pre-operative assessment needs to be thorough and organ dysfunction should be assessed carefully [24].

General anaesthesia has been described in very few patients. The use of fentanyl, propofol, rocuronium and cisatracurium for induction of general anaesthesia was reported as uneventful [23,40]. There is one case report on a Fabry patient with transient bronchospasm after induction of general anaesthesia using fentanyl, propofol and atracurium. An anaphylaxis was excluded [48]. In case of pre-terminal or terminal renal insufficiency, a relevant prolongation of elimination times must be expected for certain drugs which undergo renal clearance.

For maintenance, sevoflurane, desflurane, propofol as well as remifentanil and fentanyl (boli) were reported as uneventful [24,48].

Post-operative pain management may be difficult due to episodic or chronical pain in the patient's medical history. For analgesia, morphine, metamizole, paracetamol as well as lidocaine were reported as being without incident [24,41].

To minimise post-operative nausea and vomiting, dexamethasone and ondansetron have been described not to cause any problems [24].

Neostigmine and glycopyrrolate were administered to reverse neuromuscular block [24].

In patients with severe cardiac, renal or other organ dysfunctions, regional anaesthesia techniques might be the optimal approach whenever applicable.

Necessary additional pre-operative testing (beside standard care)

There is no general recommendation or protocol for an ideal pre-operative assessment. In consideration of various manifestations and a peculiarity of symptoms, the pre-operative assessment must identify the specific pattern of symptoms present in the individual patient [24]. The assessment should focus on identifying organ dysfunction, particularly with special reference to lung, heart, brain and kidneys [41].

Patients with existing chronic pain require careful consideration of the peri-operative pain treatment plan [24].

Pre-operative evaluation of functional capacity status using an objective tool is likely to be helpful in identifying significant cardiorespiratory disease (e.g. cardiopulmonary exercise testing, 6-minute walk test) [6].

With regard to frequent cardiac involvement in Fabry disease, a 12-lead ECG as well as transthoracic echocardiography may prove useful to identify valvular disease and assess global ventricular function [41]. Some authors recommend a high index of suspicion of occult disease and suggest the use of non-invasive cardiac stress tests in patients over 30 years of age and relevant symptoms [48].

Laboratory analysis is recommended to identify patients with impaired kidney function [41].

Particular preparation for airway management

Airway examination should be performed carefully and with particular attention to the patient‘s anatomic and dysmorphic features, with a focus on head and neck anatomy to evaluate potential airway problems [41]. Difficult airway management should be anticipated and strategies for airway management should be carefully planned in advance. Prognathism or physical features of midface, lips and nose may hinder an optimal mask ventilation. Pulmonary impairment might also aggravate ventilation. Laryngoscopy and intubation may be challenging. [41]

Overall, the evaluation and preparation for airway management in patients with Fabry disease should follow common practice standards for airway management.

Particular preparation for transfusion or administration of blood products

No specific recommendations are given. No typical bleeding disorders were reported for Fabry patients.

Particular preparation for anticoagulation

There are no specific suggestions for Fabry disease. Subject to cardiac and valvular surgery, arrhythmias, strokes or other cardiovascular events in the patient’s anamnesis, anticoagulation should be considered after operation according to current recommendation.

Particular precautions for positioning, transportation and mobilisation

Extreme positioning for specific operations, e.g. a (reverse) Trendelenburg positioning, might lead to haemodynamic impairment if there is severe cardiac involvement. Due to chronic pain disorders in some patients, positioning and mobilisation must be tailored on an individual basis.

Interactions of chronic disease and anaesthesia medications

Not reported. Especially enzyme replacement therapy does not interfere with any of the reported drugs used [24].

Anaesthetic procedure

Pre-operative evaluation: see details above.

Pre-medication: might be performed weighing the benefits and risks in individual patients. Enzyme replacement therapy should be continued following regular prescription when undergoing general anaesthesia.

Prophylaxis for endocarditis: should be performed on patients with an indication for prophylaxis (mainly after cardiac valve surgery) according to current international guidelines and after discussion with the responsible cardiologist [15].

Patient positioning & monitoring: act with caution due to haemodynamic impairment if there is a severe cardiac involvement and long-lasting chronic pain anamnesis.

Vessel cannulation: might be difficult due to vascular impairment or large-area haemangioma [41].

Anaesthesia: induction of anaesthesia should be performed with consideration of patient-specific risk factors and with attention to cardio-pulmonary involvement. With regard to physical features and pulmonary impairment, difficult airway management should be anticipated, particularly bag-mask ventilation, laryngoscopy and intubation. Using established drugs (see details above) for induction and maintenance of anaesthesia has been reported as uneventful. Total intravenous or balanced anaesthesia using volatile anaesthetics appears to be safe. The dosage of used drugs should be adapted to renal function.

There are no reports of regional or neuraxial anaesthesia in patients with Fabry disease. However, the use of regional anaesthesia techniques might be favourable in patients with relevant organ disorders if applicable.

Particular or additional monitoring

A cardiopulmonary evaluation might include invasive blood pressure and non-invasive cardiac output measurement for both intra-operative fluid management as well as blood pressure management as in other patients according to the patient's status and scheduled surgical procedure [41].

Possible complications

Complications in airway management (bronchospasm, laryngoscopy, ventilation) have been reported [41,48]. Post-operative pain management may be challenging and has been reported as such. Haemodynamic instability due to underlying cardiovascular impairment has been reported.

Post-operative care

Post-operative care should be tailored to the individual's disease severity and type of surgery. A stay in intermediate or intensive care unit is not mandatory but might be reasonable if severe organ dysfunctions exist or post-operative dialysis is necessary.

Disease-related acute problems and effect on anaesthesia and recovery

Desaturation and hypoxia: allergic genesis, pulmonary embolism, endotracheal disconnection or other technical problems.

Haemodynamic deviation: anaphylactic genesis, myocardial infarction, bleeding complications.

Ambulatory anaesthesia

Ambulatory anaesthesia is possible and might be performed in institutions with adequate resources and expertise. Depending on pre-existing cardiac, respiratory and renal dysfunction and the procedure itself, this should be discussed on a case-by-case basis. A longer period in the post-anaesthesia care unit (PACU) due to prolongated drug effects may be anticipated. There are no general recommendations regarding outpatient procedures due to the lack of reports in the literature.

Obstetrical anaesthesia

Patients with Fabry disease are fertile. Due to the lack of reports on spinal or epidural anaesthesia in Fabry patients, recommendations cannot be provided. Haemangioma can occur over the medial spine and should be considered [20]. There is one case report of a spontaneous spinal epidural haematoma in a non-pregnant woman with Fabry disease [19]. Although cerebrovascular events are common in Fabry disease, there are no cases of vertebral dissection or spinal cord infarction documented in the literature to date [23]. However, in patients without relevant bleeding anamnesis and with normal coagulation lab results, regional anaesthesia may be considered. Few reports with small cohorts of pregnant women with Fabry disease, who underwent continued or reinitiated enzyme replacement therapy during pregnancy, observed no adverse events either in the mothers or their children [13]. Complications during pregnancy, which led to an emergency Caesarean section, have been reported. They include eclampsia with proteinuria, hypertensive crisis and seizures, pathologic cardiotocographic monitoring or premature birth [13,20].

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