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Review

Anderson-Fabry Disease in Females

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Abstract

Anderson-Fabry disease (AFD) is the second most common lysosomal storage disease. This is an X-linked disorder due to lysosomal enzyme deficiency of α-galactosidasae A, that results in accumulation of globotriaosylceramide in various tissues leading to organ damage, and resulting in a variety of cardiovascular, renal, neural, dermatological, psychological signs and symptoms. Despite being X-linked, heterozygous females can suffer from symptoms equally severe as male hemizygotes. This paper presents signs, symptoms, specific diagnostic approach and treatment possibilities of AFD in female patients.

Key words: Anderson-Fabry disease, α-galactosidasae A, female patients

Introduction

Anderson-Fabry disease (AFD) is an X-linked disorder due to lysosomal enzyme deficiency of α-galactosidasae A (GLA). After Gaucher's disease, it has been reported to be the second most common liposomal storage disease. Meikle, *et al*. reported the incidence of Fabry hemizygotes in Australia to be 1 in 117 000. No data on heterozygotes have been obtained, but the incidence determined in hemizygotes could be extrapolated to give a combined incidence of 1 in 58 000 [1]. In the UK, based on notifications of patients with low GLA activity the prevalence of Fabry disease was reported to be 1 in 366 000 [2]. The prevalence in Netherlands was estimated at 1 in 476 000 [3]. As it can be seen, the data on AFD incidence and prevalence are diverse [2-4]. AFD results from mutations in the GLA gene. More than 400 mutations have been indentified (mainly missense mutations but also nonsense and single amino acid deletions and insertions). The majority of these mutations have been identified only in individual families, while mutations of CpG dinucleotides account for most of the recurrent point mutations found in unrelated families with AFD [5].

Patients with this disorder are unable to effectively degrade membrane glycosphingolipids containing a terminal α-glycosidic galactose, especially globotriaosylceramide (Gb3). Gb3 accumulates in various tissues as the primary insult, followed by secondary cellular dysfunction, ischemia and fibrosis, which eventually lead to tissue damage and finally organ dysfunction [6]. The process of Gb3 accumulation, starting in the unborn child, can be subclinical until organ dysfunction appears. Anderson-Fabry disease affects all major organ systems in the human body, resulting in a variety of cardiovascular, renal, neural, dermatological, psychological signs and symptoms. In untreated patients death occurs typically in the late fifth to early sixth decade due to kidney failure, strokes and cardiac events [7,8]. As AFD is an X- linked disorder most females were thought to be asymptomatic through a normal life span or to develop only minor manifestation of the disease. Several studies have shown a severe and aggressive presentation indistinguishable from that seen in males [9]. Diversity of AFD clinical manifestations in female patients was demonstrated by Lukas, *et al.* in an extended Spanish family where related female AFD patients presented with severe neurological, cardiac and renal symptoms to only acroparesthesia [10]. Here we present a review of literature on clinical presentation, diagnostic specifics and treatment of Anderson-Fabry disease in women.

Clinical manifestations

The wide variability in clinical presentation is thought to be partly due to lionization [11], a process that occurs in embryos where one copy of the X-chromosome is randomly inactivated in all of its cells. This process happens in females that have essentially a "mosaic" of normal and mutant cells in varying proportions.
According to Fabry Registry (global clinical database that records longitudinal data on AFD), out of 1077 enrolled females in the registry, 69.4% had symptoms and signs of AFD. The median age at symptom onset among females was 13 years, which was significantly later in life than in male patients (9.0 years). Family history was positive in 84.1% of female patients, but

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the diagnosis was made at the median age of 31 years, with males being diagnosed at median age of 24 years. Twenty percent of female AFD patients experienced major cerebrovascular, cardiac or renal events at the median age of 46 years [7]. Signs and symptoms of AFD, as well as time of onset are shown in Table 1.

Table 1. Signs and symptoms of Fabry disease

Typical time at onset	Signs and symptoms
Childhood and adolescence (≤16 years)	Neuropathic pain
	Ophthalmological abnormalities (cornea verticillata and tortuous retinal blood vessels)
	Hearing impairment
	Dyshidrosis (hypohidrosis and hyperhidrosis)
	Gastrointestinal disturbances and abdominal pain
	Lethargy and tiredness
	Angiokeratomas
	Onset of renal and cardiac signs, e.g. microalbuminuria, proteinuria, abnormal heart rate variability
	Extension of any of the above
	Proteinuria and progressive renal failure
Early adulthood (17–30 years)	Cardiomyopathy
	Transient ischaemic attacks, strokes
	Facial dysmorphism
	Worsening of any of the above
Later adulthood (age >30 years)	Heart disease (e.g. left ventricular hypertrophy, angina, arrhythmia and dyspnoea)
	Stroke and transient ischaemic attacks
	Osteopenia and osteoporosis

Signs and symptoms of Fabry disease according to age (adapted from Mehta, *et al*. *Q J Med* 2010; 103:641-659 [5])

Cardiovascular manifestations

Cardiac manifestations of AFD may be due to the involvement of any of the cardiac structures, including myocardium, conduction system and valves [12-14]. Data in the Fabry Registry showed that cardiovascular disease was the most common cause of death [15]. In both female and male AFD patients arrhythmia is common and its frequency increases with age [16]. Left ventricular hypertrophy (LVH) is detected in ~ 50% of patients but is less frequent and occurs nearly 10 years later in life among females than in males. In female patients ejection fraction is preserved, and in the absence of myocardial infarction, or arrhythmia, with only palpitations being more common in female FD patients [17], they can have silent but progressive cardiac disease [18,19].

Renal disease

Among all AFD patients renal injury is reported in approximately 50% of patients, proteinuria being the most common renal symptom [20,21]. Data in the Fabry registry show that female patients exhibit significant kidney involvement as manifested by proteinuria and reduced estimated glomerular filtration rate (eGFR). Among female patients with eligible eGFR data 62.5% had eGFR<90ml/min/1.73m2, and 19% had eGFR<60 mL/min/1.73m2. Proteinuria ≥300 mg/day was present in 39.0% of females [7]. Also, female AFD patients have high proteinuria during pregnancy, and a slightly increased prevalence of hypertension and pre-eclampsia in comparison to non-AFD females [17]. Renal biopsy studies have shown that glomerular and vascular changes are present before progression to overt proteinu-

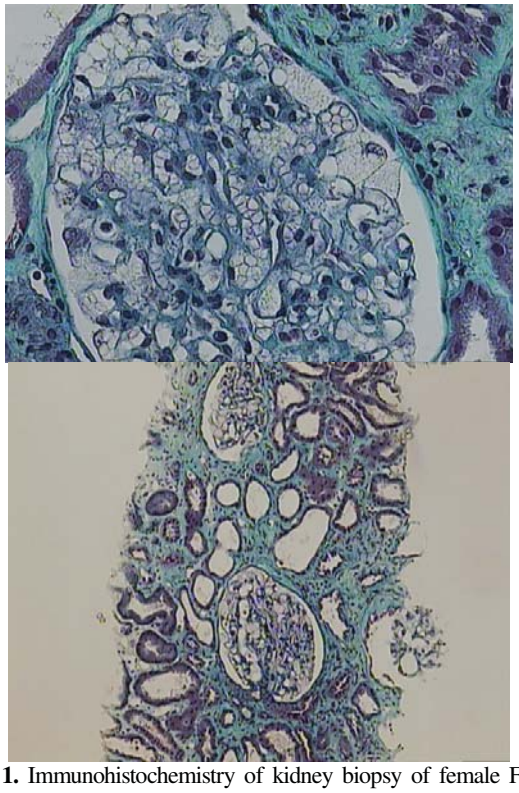

Fig. 1. Immunohistochemistry of kidney biopsy of female Fabry patient. Kidney was used for transplantation as described previously [22]

ria, which makes renal biopsy a potential useful tool for early detection of renal disease. Due to the late onset of renal involvement in female patients and proteinuria being present in less than a quarter of patients, it has been reported in literature that kidneys from a deceased female donor with undiagnosed Fabry disease were used for transplantation [22]. The histological changes from this transplanted Fabry graft are shown in Figure 1. End-stage renal disease (ESRD) is less common in females with AFD than in males. However, female patients develop ESRD approximately at the same age (median 38 years) as male patients [7].

Cerebrovascular and neurological manifestations

Transient ischemic attack (TIA) and stroke are frequently observed in Fabry disease [12,23]. Onset in female patients is later in life than in males. Stroke, mostly ischemic type, occurred in 4.2% of the females in the Fabry Registry, at a median age of 43.5 years. Fabry Outcomes Survey (FOS) registry data indicate that female Fabry patients have higher prevalence of stroke or TIAs of 16% compared to 11% in males [24]. According to Sims, *et al*. most patients (76.9% females and 70.9% males) did not experience renal or cardiac disease before their first stroke and 38.3% of females had their first stroke before being diagnosed with Fabry disease [25]. Isolated hyperintensity in the pulvinar on MRI T1 weighed images, the so-called "pulvinar sign" was shown as a characteristic manifestation of Fabry disease [26,27]. This sign was not found in any female patients [27]. The importance of the pulvinar sign was challenged by Fellgiebel, *et al*. whose study showed that basilary artery diameters were superior to all other MR measures for separating Fabry disease from control with the accuracy of 87% [28].
Neurological symptoms are the most frequently reported symptoms in Fabry disease (occurring in ~ 80% of patients). Pain in hands and feet, acroparesthesia, is a common symptom in AFD females, as well as joint pain [7,17]. Neuropathic pain usually occurs at a mean age of 16-20 years in females [12,29]. Overall prevalence of acroparesthesia is approximately 60% [17]. Hypohidrosis is considered to be a classic feature of Fabry disease; it was present in 29% of female AFD patients and was significantly more common than in control female patients [17]. Data from the Fabry Outcome Survey showed that hyperhidrosis was more prevalent among females than males (11.9% of females vs. 6.4% of males), and is an increasingly recognized feature of AFD [30].

Gastrointestinal symptoms

High prevalence of gastrointestinal symptoms was found in 82% of Fabry females in comparison to 51% controls in a case control survey that was performed in the Netherlands [17]. However, none of the individual symptoms were significantly more prevalent in AFD group in comparison to control group, which was also observed by Wilcox in the Fabry Registry data [17]. Nevertheless, nausea, swallowing difficulties, abdominal pain, diarrhea and constipation were more common in AFD females ($p<0.05$, OR 3 to 5) than in control patients in the case control survey published by Bouwman, *et al.* [17].

Other symptoms

Skin manifestations in AFD include angiokeratomas, teleangiectasias and abnormal sweating which have been previously elaborated. Angiokeratomas are a hallmark of Fabry disease (but are not specific for Fabry disease), 36% of female patients have angiokeratomas [8,31,32]. Angiokeratomas are usually diffuse and located in the lower part of the abdomen, but can also be discrete patches that are evident only by careful clinical examination.
Cornea verticillata is the most common ocular symptom in AFD, which occurs in over 70% of males and females [33].
According to Hegemann, *et al*. hearing in AFD patients is significantly impaired with respect to age-matched general population and this leads to clinically relevant hearing impairment in 16% of cases. Hearing loss is mostly sensorineuronal. Women are affected later in life and less severely than men [34]. There is also evidence in the literature of a positive association between hearing loss and the degree of peripheral neuropathy and cerebrovascular and renal damage [35].
In the case control study published by Bouwamn, *et al*. AFD female patients reported fatigue as the most common symptom (9%), which was in agreement with previous reports [8], although a substantial proportion of normal controls also experienced chronic fatigue (57%), which was significantly prevalent in the AFD females [17].

Diagnosis

A general algorithm for diagnosis of AFD in females is shown in Figure 2. In literature, serum and urine Gb3 concentrations, as well as globotriaosylsphingosine (lyso-Gb3) have been proposed as potential biomarkers [36-38]. By some authors only detection of elevated plasma lyso-Gb3 levels is a reliable biomarker for diagnosis of AFD in female patients [10]. Female patients with a positive family history or with clinical suspicion of AFD should be genetically tested for GLA gene mutations. Sequencing of the entire GLA gene including exon-intron boundaries is considered as the method of choice in detecting GLA mutations by some authors [39,40]. According to Lukas, *et al.* mere sequencing of GLA gene is insufficient in finding some gene mutations, and should be rounded up or replaced with multiplex ligation-dependent probe amplification (MPLA) [10].

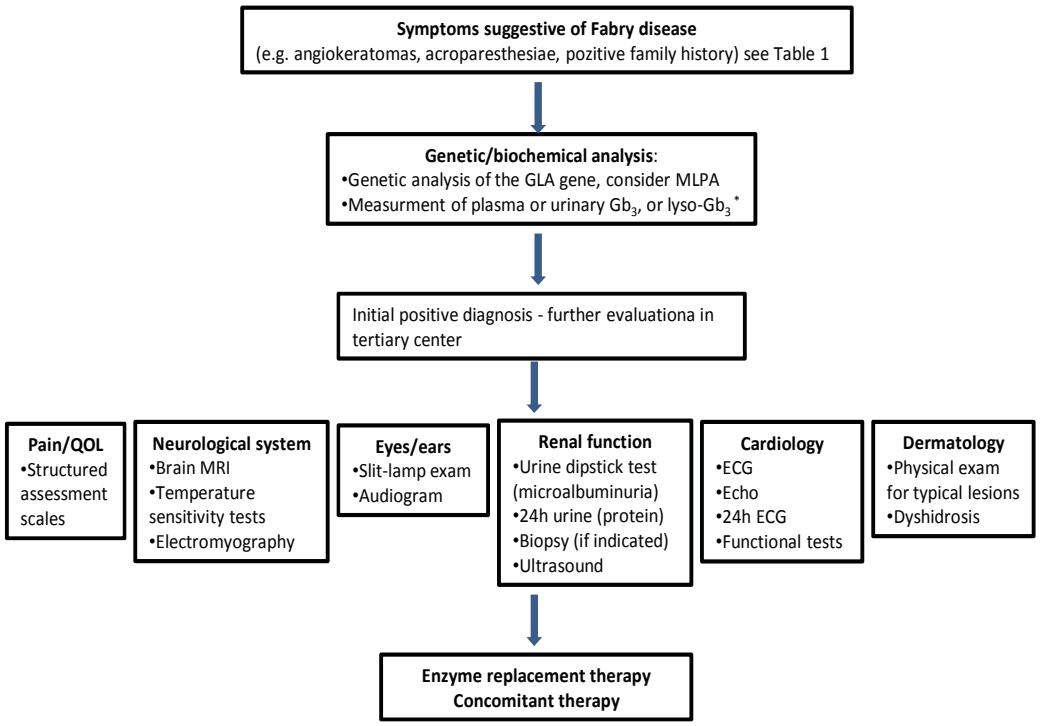

Fig. 2. Algorithm for the diagnosis and assessment of female patients with Fabry disease *some authors do not consider this to be specific for female patients, see text for further details. MLPA multiplex ligation-dependent probe amplification, QOL-quality of life; Adapted from Mehta, *et al. Q J Med* 2010; 103: 641-659

Enzyme replacement therapy (ERT)

Introduction of enzyme replacement therapy in 2001 marked a turning point in clinical management of AFD patients as this was a disease-specific treatment. Before ERT era clinical management was symptomatic and consisted in treatment of pain, cardiac and cerebrovascular complications and ESRD [6].

Two types of ERT are available. Agalasidase beta is produced in Chinese hamster ovary cells and was infused at a dose of 1.0 mg/kg every 2 weeks [41,42]. Agalasidase alfa is purified from a stably transfected human cell line and was infused at a dose of 0.2 mg/kg every 2 weeks. No differences in clinical outcomes could be determined between the two forms of agalasidase in a 24-month treatment [43]. ERT normalizes Gb3 in many different organs in most patients and may be associated with symptomatic benefit.

Treatment should be initiated early, as soon as clinical symptoms and signs are observed [44-46]. United Kingdom and USA guidelines have proposed the following criteria for initiation of ERT, based on evidence of renal disease: persistent proteinuria (>300 mg/24h), and clinically relevant reduction in eGFR (to <90 ml/min/1.73m2) [47,48].

Prospective trials show that initiation of ERT for mild Fabry nephropathy in which GFR is still normal or slightly impaired stabilizes GRF [45,49]. In patients whose GFR was already been compromised, the goal of treatment is stabilization or reduction of GFR rate decline. Observational reports of 8 stage 3 CKD patients (including 4 females) treated with agalasidase alfa showed stabilization of kidney function after 1-2 years of treatment, but in year 3 and 4 GFE decreased by more than 5 ml/min/1.73 m^2 per year in male patients [50]. A prospective, randomized, placebo controlled clinical trial showed no reduction in overt proteinuria with agalasidase beta ERT in patients with advanced Fabry nephropathy (stage 3 CKD) with overt proteinuria and continued decline eGFR [44,45]. Also in men with LVH at base line, it has been reduced after ERT treatment [51,52].

The largest and longest examination of agalasidase alfa therapy on women was described by Whybra, *et al*. They performed a longitudinal study of 36 female Fabry patients treated with agalasidase alpha for four years. This study showed that in female patients "pain at its worst" described by Brief Pain Inventory was significantly reduced after 12 months of therapy and remained reduced through 4 years. Mean left ventricular mass decreased from 89.4±29.3 g/m2 at baseline to 66.5±29.3 g/m2 after 12 months and remained reduced through 4 years. Average kidney function (eGFR and proteinuria) remained constant during the study [51].

Adjuvant therapy

Renal disease

Patients that develop chronic kidney injury require blood pressure, anemia and proteinuria management. Angiotensin converting enzyme (ACE) inhibitors and angiotensin

receptor blockers (ARB) are recognized as mainstay in the therapy of all forms of proteinuric kidney disease. The use of ACE inhibitors and ARBs has been associated with improved outcomes in Fabry disease [53]. Patients that develop end-stage renal disease require renal replacement therapy. Renal transplantation is therapy of choice. Ojo, *et al*. showed that patients with AFD demonstrated equivalent 5-year patient and graft survival compared with controls [54].

Cardiovascular and cerebrovascular disease

Patients with systolic impairment due to cardiovascular manifestations of AFD should be treated with conventional therapy (ACE inhibitors, or ARBs, diuretics). In advanced stages of the disease many patients may require pacemaker implantation due to conduction abnormalities. Those with malignant ventricular arrhythmias may benefit from implantable cardioverter- defibrillator implantation. Patients with advanced heart failure may be candidates for heart transplantation [55].
In primary prevention of stroke along with lifestyle changes, lipid control and blood pressure control, acetylsalicylic acid and other antiplatelet drugs are used.

Neuropathic pain control

Patients should change their lifestyle and take preventive measures to avoid exposure to individual provocateurs of pain. According to available data, there is no randomized controlled trial of analgesic for the treatment of painful peripheral neuropathy in Fabry disease. The treatment of other types of painful neuropathy may serve as a guide for treating the AFD patients. Multiple medications targeting different aspects of the complex pathways might be considered in patients with advanced disease. One should start pain medication(s) at low dose, and evaluate the tolerability and effectiveness of a change in medication(s) after 2-3 weeks. Carbamazepine alone or in combination with pregabalin is recommended as the first-line treatment in Fabry neuropathic pain [56].

Gastrointestinal symptoms

Delayed gastric emptying and dyspeptic symptoms in patients with AFD should be managed with metoclopramide and histamine 2 receptor blockers [47,57].

Prognosis

Without treatment, lifespan is typically reduced by 15 years in women with Fabry disease [2]. Surprisingly according to Fabry Registry data only 53.1% of females with LVH and 46.7% of females with stage 3 CKD or greater are treated with ERT [7].

Conclusions

Clinical presentation in female Fabry patients may range from minor manifestations to a major aggressive form very similar to clinical presentation in male patients. The cardiovascular and renal symptoms are less frequent in female FD patients than in males and they develop later in life. Interestingly, female patients have a greater prevalence of TIA and stroke than male patients, and many of these patients are not diagnosed with Fabry disease at the time of their first stroke. Early diagnosis of Fabry disease is essential. The diagnosis of the disease in female patients is based on genetic analysis of the GLA gene. Screening for Fabry disease should include unexplained end-stage renal disease, hyperthrophic cardiomyopathy and cryptogenic stroke in women. Enzyme replacement therapy and other adjunctive therapy is beneficial for female patients and should be started timely and in a large number of female FD patients.

Conflict of interest statement. None declared.

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