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REVIEW

Diagnosis and Screening of Patients with Fabry Disease

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Abstract: Fabry disease (FD) is an X-linked lysosomal storage disorder caused by absence or deficient activity of α-galactosidase A (α-Gal A) due to mutations in the α-galactosidase A gene (*GLA*), leading to progressive accumulation of globotriaosylceramide (Gb3) in tissues and organs including heart, kidney, the eyes, vascular endothelium, the nervous system and the skin. Cardiac involvement is leading to fatal complications and reduced life expectancy. FD is treatable with disease-specific treatment (enzyme replacement therapy (ERT) or with chaperone therapy). Therefore, the early diagnosis of FD is crucial for reducing the morbidity and mortality. Screening of high-risk populations (eg, patients with unexplained left ventricular hypertrophy (LVH), young patients with unexplained stroke, and patients with unexplained renal failure proteinuria or microalbuminuria) yields good results. The diagnostic algorithm is gender-specific. Initially, the measurement of α-Gal A activity is recommended in males, and optionally in females. In males with non-diagnostic residual activity (5–10%) activity, genetic testing is afterwards done for confirming the diagnosis. In fact, diagnosis of FD is not possible without genetic testing for both males and females. Globotriaosysphingosine (lyso-Gb3) for identification of atypical FD variants and high-sensitive troponin T (hsTNT) for identification of cardiac involvement are also important diagnostic biomarkers. The aim of this review was to provide an update on diagnosis and screening of patients with FD.

Keywords: metabolic disease, genetics, hypertrophic cardiomyopathy, proteinuria, algorithm, heart failure

Introduction

Fabry disease (FD) is an X-linked rare multisystemic lysosomal storage disorder resulting from α-galactosidase A (α-Gal A) deficiency and is disease-specific, but not curatively treatable with enzyme replacement therapy (ERT) since 2001 and chaperone therapy with Migalastat (Galafold®, Amicus Therapeutics, Cranbury, NJ, USA) since 2016.[1–4] The recombinant enzyme is available as agalsidase-alpha (Replagal®, Shire Human Genetic Therapies AB, Stockholm, Sweden) and agalsidase-beta (Fabrazyme®, Sanofi Genzyme, Cambridge, MA, USA).[5] However, early diagnosis of FD is crucial to reduce morbidity and mortality. Cardiovascular complications are the major cause of death in patients with FD.[6,7]

Epidemiology and Pathogenesis of Fabry Disease

The prevalence of FD has been estimated between 1:40,000 and 1:117,000 individuals.[8] However, this prevalence is underestimated. In newborn screenings, higher prevalence values were described, for example in Spain, where the

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prevalence of FD in males was estimated at 1:7575 (0.013%).[9] In genetic screening studies of high-risk populations, the overall prevalence of individuals with α-galactosidase A (GLA) gene variants, including genetic variants of unknown significance (GVUS), was 0.62%; prevalence of definitive FD diagnosis was 0.12%.[10] In patients (male and female) receiving hemodialysis treatment in Brazil, the estimated prevalence for FD was 0.87%, close to that reported in other trials.[11–14] In young patients with stroke a prevalence of 0–4% was found.[15–19] In patients with unexplained hypertrophic cardiomyopathy (HCM) FD should be considered. In two cohorts of men with unexplained LVH (≥ 13mm) the prevalence of decreased α-gal A activity was 6.3% and 3.0%, respectively.[20,21] In a cohort of females with unexplained HCM, up to 12% of these patients were affected by FD.[22] In large cohorts of patients with unexplained LVH, α-gal A mutations were described in 0.5% and 1.0%, respectively.[23,24] Doheny et al reanalyzed all published screening studies for FD from 1995 through 2017 and provided more valid prevalence estimates of previously unrecognized FD in high-risk cohorts, ranging from 0% in female renal transplant patients to about 0.9% among both male and female cardiac cohorts.[25] Previous prevalence values from 1.6-fold in male renal transplant patients to 33-fold and 15-fold in male and female patients with stroke, respectively, may be due to benign variants.[25] Capuano et al reanalyzed the prevalence of GLA mutations in dialysis patients in FD screening studies published between 1995 and 2019 after assigning their correct phenotype. They found an overall prevalence recalculated on the basis of only pathogenetic mutations of 0.14%.[26]

FD is caused by a deficiency or absence of α-Gal A activity due to mutations in the GLA gene (located on Xq22.1), resulting in intracellular accumulation of globotriaosylceramide (Gb3) and multiorgan damage.[27,28] Heterozygous female may have clinical manifestations of FD, too, but usually on average 10 years later than male patients. Phenotypic expression and penetrance varies among families with the same variant and, also, within the same family. There are various phenotypes, with early severe classic presentations, and the later, milder presentation.[28] Two phenotypes of FD are relevant: classic FD and variant FD. Males with the classic FD develop early signs and symptoms in childhood or adolescence (e.g., periodic crisis of severe pain in the extremities (acroparesthesias), neuropathic pain, telangiectasias and vascular lesions called angiokeratomas (in the groin, hip and periumbilical areas), sweating abnormalities (anhidrosis and hypohidrosis), gastrointestinal symptoms, corneal (cornea verticillate) and lenticular opacities).[29–31] Vascular complications, renal failure with unknown etiology, including unexplained proteinuria or microalbuminuria, unexplained LVH mimicking sarcomeric HCM, or neurological manifestations (e.g., cryptogenic stroke, transient ischemic attack [TIA], sensoneuronal hearing loss, migraine) may be clinical features in adults.[10,30,32–34] Patients with atypical variants may develop late-onset renal failure, LVH, cerebrovascular disease, or a combination thereof.[30,35] Symptoms in female subjects vary. Presentation ranges from asymptomatic to severely affected, but subjects are typically older compared to male subjects.[30,34–36] Gb3-deposition and its deacylated metabolite globotriaosysphingosine (lyso-Gb3) are associated with the cellular involvement.[37] This may lead to alterations of tissue (interstitial fibrosis and replacement fibrosis, inflammation, apoptosis, hypertrophy).[38] The cellular damage is multifactorial and partly caused by cellular signaling or microvascular ischemia via affected endothelial cells or both, leading to organ dysfunction, renal and heart failure, for example.[39] Plasma lyso-Gb3 concentrations appear to correlate with disease stages, the mutation severity and decreasing during ERT.[37] There is still debate about which patients or variants really do show correlation of LysoGb3 levels as treatment response (or both ERT and chaperone).[5,40]

Diagnosis of Fabry Disease

Diagnosis of classic FD in males may be straightforward, whereas in females and in individuals with genetic variants the diagnosis can be challenging.[41]

A diagnostic approach involving a detailed history, family history, physical examination, clinical and biochemical findings, genetic testing, various imaging procedures, and expert opinion is recommended.[10,42,43] Some clinical findings and signs, e.g., acroparesthesia, angiokeratomas and cornea verticillate may have a high specificity.[10]

In males suspected to have FD, α-Gal A activity should be measured. Alpha Gal A activity < 1% is highly suggestive for the diagnosis of classic FD.[44] Even in the presence of clinical signs, the α-Gal A activity is variable and can be within the normal range in females.[45,46] Most of these females develop clinically significant disease.[27,47]

Genetic confirmatory testing is mandatory in males and females.[10] Mutations in the *GLA* gene may be associated with the classic FD, a variant phenotype or a GVUS.[10] We present an updated diagnostic algorithm in Figure 1.[10,27,31,43,48,49] At the diagnosis of FD, determination of amenability for pharmacological chaperone therapy with migalastat is possible with good laboratory practice (GLP)-validated human embryogenic kidney cell-based in vitro assay.[50,51] This in vitro assay is currently the only approved method for this evaluation.[52]

Lyso-Gb3 has also clinical relevance and emerged a powerful biomarker for FD, particularly the variable α-Gal A activity and mutations.[37,48] In patients with GVUS, to determine if the mutation is possibly clinically significant, and if the diagnosis of FD should be made, the lyso-Gb3 test can be used. Lyso-Gb3 can be used for stratifying patients as classic and variant phenotypes, even before clinical manifestation is present.[48] Lyso-Gb3 is especially helpful as a phenotype discriminative marker because of phenotypic variability, most prominently in females.[42]

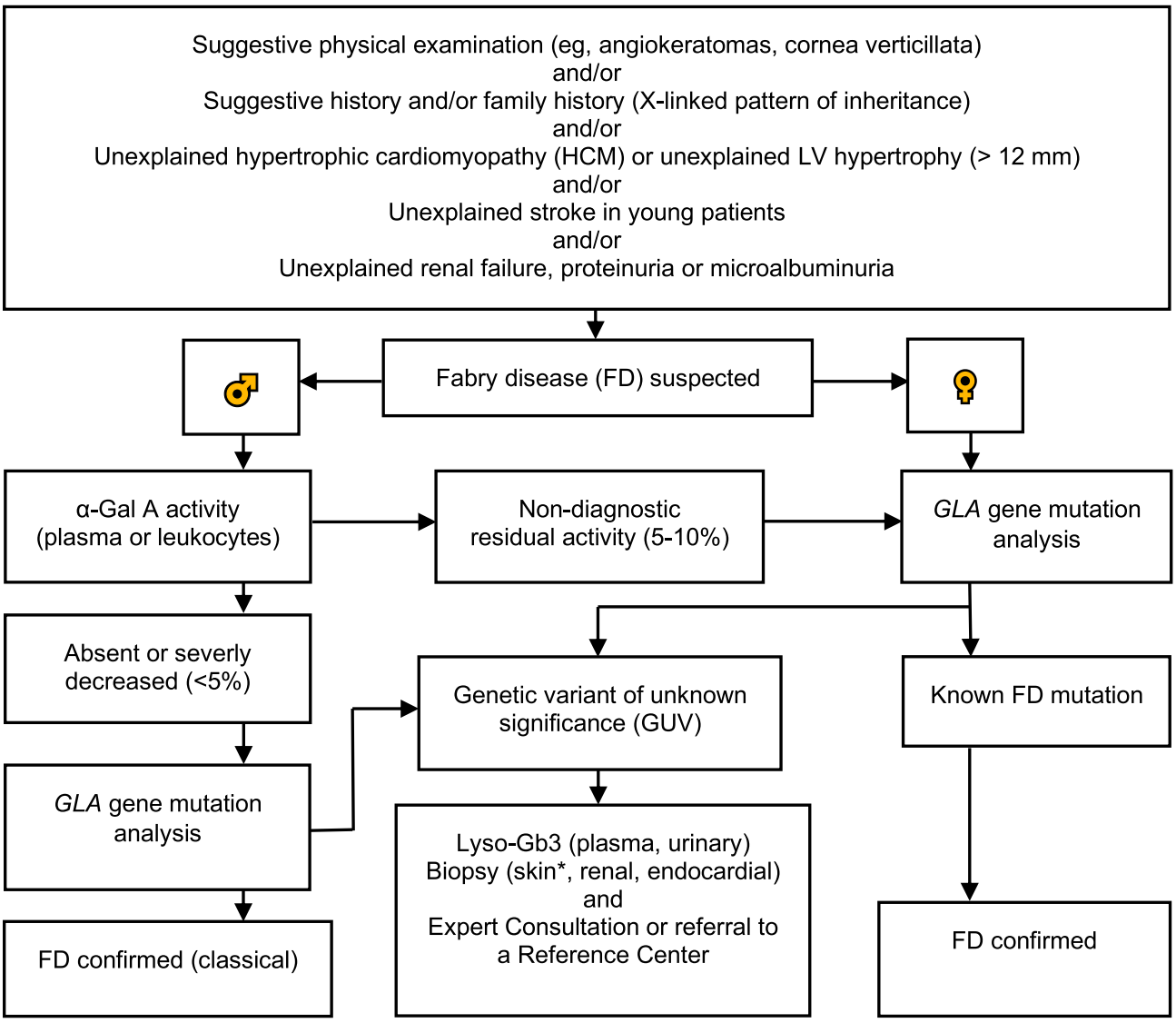

Figure 1 Updated diagnostic algorithm for FD. Adapted with permission from van der Tol L, Smid BE, Poorthuis BJ, et al. A systematic review on screening for Fabry disease: prevalence of individuals with genetic variants of unknown significance. *J Med Genet*. 2014;51:1–9. Copyright © 2014, BMJ Publishing Group Ltd.[10] Adapted with permission from Yogasundaram H, Kim D, Oudit O, Thompson RB, Weidemann F, Oudit GY. Clinical Features, Diagnosis, and Management of Patients With Anderson-Fabry Cardiomyopathy. *Can J Cardiol*. 2017;33:883–897. © 2017 Canadian Cardiovascular Society.[27] Adapted with permission from Putko BN, Wen K, Thompson RB, et al. Anderson-Fabry cardiomyopathy: prevalence, pathophysiology, diagnosis and treatment. *Heart Fail Rev*. 2015;20:179–191. Copyright © 2014, Springer Nature.[49] Adapted with permission from Laney DA, Bennett RL, Clarke V, et al. Fabry disease practice guidelines: recommendations of the National Society of Genetic Counselors. *J Genet Couns*. 2013;22:555–564. © 2013 National Society of Genetic Counselors, Inc.[43] Data from Niemann et al [48] and Putko et al.[49] α-Galactosidase A (α-Gal A), α-galactosidase A gene (GLA gene), globotriaosysphingosine (Lyso-Gb3), left ventricular (LV). *Punch biopsy, taken from proximal (thigh: 15 cm above the patella) and distal (leg: 10 cm above the lateral malleolus) hairy skin sites or from other lesions to evaluate Gb3 deposits, and for other histopathological evaluations.[31]

Diagnosis of Cardiac Involvement

The first step to assess the Fabry cardiomyopathy is transthoracic echocardiography.[53,54] Typical signs for FD are concentric LVH and a prominent papillary muscle. In addition, most patients show signs of diastolic dysfunction. Global left ventricular function assessed by ejection fraction (EF) during echocardiography is only reduced in end-stage patients.[53,54]

Patients with FD suspected to have cardiac involvement should undergo cardiac magnetic resonance imaging (CMR) imaging, echocardiography, a 24-h Holter ECG to assess cardiac structure and function, as early as possible.[55]

The diagnostic gold standard for cardiac fibrosis in cardiomyopathy patients with FD is CMR imaging examination with late gadolinium enhancement (LGE-CMR).[55] In cases of patients with contraindications, e.g., in patients with an implanted cardioverter or pacemaker, or with end-stage renal disease, echocardiographic modalities (e.g., speckle-tracking echocardiography [STE]), are available for indirect evaluation of cardiac involvement.[56,57] Starting ERT is recommended as soon as clinical signs of organ involvement are seen, e.g., when detection of LGE first becomes apparent.[42,55] T1-MRI mapping has been proposed to discriminate FD from other causes of LVH.[58] In FD patients with LVH, abnormal native myocardial T1 values are highly prevalent.[59,60] Cardiac MRI-derived myocardial mapping may have a high sensitivity and specificity to discriminate FD patients.[58,59] Nappi et al showed the feasibility of PET-MR imaging for the early detection of cardiac involvement, even in patients with non-hypertrophic stage.[61] PET-MR examinations can provide unique and simultaneous results to detect myocardial inflammation.[58]

In cardiology, high-sensitive Troponin T (hsTNT) is established to detect myocardial tissue damage. However, for Fabry cardiomyopathy only few data are available regarding biomarkers to detect cardiac involvement.

Seydelmann et al showed, that hsTNT is the most promising biomarker for cardiac involvement in FD, with Values >14ng/mL, suggesting pathological late enhancement in MRI.[62] This biomarker was correlated with the progression of FD, and patients with elevation of hsTNT during observation showed the progress of myocardial fibrosis, and a decrease of EF.[62] Elevation of hsTNT can predict an increment in the magnitude of fibrosis.[63]

In patients with FD and cardiac involvement, assessed by echocardiographic findings, NT-proBNP levels are elevated and correlate with electrocardiographic findings, but not with myocardial fibrosis.[62,64] However, NT-proBNP levels are not correlated with disease progression.[64,65] The evaluation of myocardial fibrosis defines the stage of the cardiomyopathy and is associated with a poor prognosis.[53,66]

The noninvasive biochemical markers, imaging strategies and genetic tests for the diagnosis of FD are sufficient, therefore the place value for endocardial biopsy has diminished.[27]

Diagnosis of Renal Involvement

General diagnostic tools for the baseline assessment of renal function, e.g., serum creatinine, calculated GFR and urine protein diagnostics (24 hour collection would be ideal, but spot urine total protein/creatinine and albumin/creatinine ratios has been established) can be used initially in FD patients.[67] Additionally, the creatinine and cystatin C based GFR-calculation is recommended for the assessment of renal function.[63] Serum cystatin C concentration is a more sensitive marker than creatinine to detect early renal dysfunction.[65] Urine lyso-GB3 showed no correlation to renal involvement in FD.[68,69] Proteinuria and albuminuria is the most important indicator for early renal involvement in FD; regular measurement is essential.[70] Measurement of albumin-creatinine ratio in spot urine is highly recommended for early detection of microalbuminuria. Glomerular hyperfiltration (age-corrected eGFR > 130 mL/min/1.73/m2 corrected for age) may be an early marker for renal involvement.[69] Furthermore, a kidney ultrasound should be carried out.[71]

In FD patients with persistent albuminuria and/or proteinuria a renal biopsy should be performed.[72]

Diagnosis of Neurologic Involvement

Unfortunately there are no specific blood biomarkers available for the assessment of neurological signs in FD patients. In cases of suggestive physical examination and/or history (and/or) family history (e.g., paresthesias/dysesthesias, hypohidrosis/anhidrosis, chronic burning pain, attacks of excruciating pain, sensory losses, tinnitus, hearing loss, nausea, dizziness, abdominal cramp, [post-prandial] diarrhea, bloating) further neurological diagnostics should be initiated.[73–75] Neurological involvement is usually assessed by brain MRI, audiometry, etc. White matter hyperintensities, dolichoectasia, and infarcts are characteristic signs found on brain MR imaging in classic FD.[76,77]

Screening Strategies for Fabry Disease

In epidemiology, screening is defined

> as the examination of asymptomatic people in order to classify them as likely or unlikely to have the disease that is the object of screening. People who appear likely to have the disease are investigated further to arrive at a final diagnosis. Those people who are then found to have the disease are treated.[78]

To be suitable for general use, a procedure for early detection and treatment should meet many criteria in addition to reducing morbidity or mortality.[78] For cost-effectiveness, a high positive predictive value (PVP) is required in the population screened.[78] Therefore, screening for FD is currently only recommended in high-risk populations and in families of index patients.[11,79] Due to various reasons, systematic newborn screening for FD was not introduced.[9] Several screening strategies are possible. For males, initially, biomarker-based screening methods (α-Gal A or lyso-Gb3) are used.[49,80] Enzyme-based screening methods are not appropriate for females.[19] Vascular lesions, especially the retinal vessel diameter can help during screening for FD.[81]

High-Risk Screening

Screening of the following high-risk populations could increase the diagnostic rate of FD:[82] 1) Patients with unexplained HCM or with unexplained LVH (>12 mm);[20,23] 2) Patients with end-stage renal disease (receiving hemodialysis treatment), patients after kidney transplantation or patients with unexplained proteinuria or microalbuminuria;[80] 3) Individuals (aged 15–55 years) with unexplained stroke.[15,16,18,19]

Many screening studies in high-risk populations revealed an unexpectedly large number of mutations or GVUS in the galactosidase alpha gene (*GLA*) and/or impaired α-gal A activity.[10] In contrast to the absent or near absent α-gal A activity in classically affected males, most male patients with GVUS have residual activity of α-gal A.[10]

The diagnostic algorithm (Figure 1) may also be adapted for screening for FD.

Family Screening

Pedigree analysis and genetic counseling is crucial for patients with FD, relatives may need to be genetically tested.[43]

Conclusion

FD is a rare, progressive multi-system disease with a reduction in life expectancy. Therefore, early diagnosis of FD is essential, using diagnostic and screening procedures adapted to consensus guidelines, which we present in this review.

Disclosure

Dr. Vardarli and Dr. Rischpler report no conflicts of interest in this work. Dr. Herrmann reports personal fees from Bayer, stock options (less than 1%) from Sofie Biosciences, personal fees from SIRTEX, non-financial support from ABX, personal fees from Adacap, personal fees from Curium, personal fees from Endocyte, grants and personal fees from BTG, personal fees from IPSEN, personal fees from Siemens Healthineers, personal fees from GE Healthcare, personal fees from Amgen, personal fees from Novartis, personal fees from Y-mAbs, outside the submitted work. Dr. Weidemann has received research grants from Genzyme and Shire and speaker honoraria from Amicus, Genzyme, and Shire.

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