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Hot topics in Fabry disease

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ABSTRACT

Fabry disease is a rare inborn error of the enzyme α -galactosidase (α -Gal) and results in lysosomal substrate accumulation in tissues with a wide range of clinical presentations. The disease has attracted a lot of interest over the last years, in particular since enzyme replacement therapy (ERT) has become widely available in 2001. With rising awareness and rising numbers of (diagnosed) patients, physicians encounter new challenges. Over 900 α -Gal gene mutations are currently known, some with doubtful clinical significance, posing diagnostic and prognostic difficulties for the clinician and a lot of uncertainty for patients. Another challenge are patients who develop neutralising antibodies to ERT, which possibly leads to reduced therapy effectiveness. In this article, we summarise the latest developments in the science community regarding diagnostics and management of this rare lysosomal storage disorder and offer an outlook to future treatments.

INTRODUCTION

Fabry disease (FD) is of interest to specialties across the spectrum of internal medicine. A range of mutations on the X-chromosome cause a defect in α -galactosidase (α -Gal) enzyme production, resulting in absent or reduced enzyme activity and accumulation of globotriaosylceramide (Gb3) and other sphingolipids in lysosomes in various tissues—mainly cardiac, endothelial, neuronal and renal—resulting in end-organ damage and failure.¹

Newborn screening has now been performed in several countries, yielding a prevalence ranging from 1:1368 to 1:8882.^{2–5} This is in contrast to earlier presumed prevalence of 1:40 000–1:117 000⁶

Clinical variability of different mutations, variable disease severity and symptom onset make the disease notoriously difficult to diagnose. There is huge clinical variability even within the same family mutation^{7,8} as well as large intersex variability. Heterozygote females tend to have higher residual enzyme activity as they are mosaic due to variable X-chromosome inactivation.⁹ Opposed to previous views that women are merely heterozygote carriers with no notable disease activity, we now know that they can display clinical manifestations not dissimilar to males with major organ involvement and associated morbidity/mortality.⁹

A classification of classic phenotype and late-onset phenotype is widely used as the natural disease process and prognosis differ.¹⁰ Typically, classic phenotype patients are null mutant and have no residual enzyme activity, even though due to the method of the enzyme assay they may have reported

enzyme activity of 1%–3%. These patients usually display early onset of symptoms—some already in their early childhood—such as neuropathic pain or anhidrosis. They proceed to major organ complications as early as their 20s or 30s. Late-onset patients—typically females or males with non-classical mutations—may present with only one organ involvement, typically in their 50s.¹⁰ All organ complications can however occur in both classical and late-onset phenotype (see [table 1](#)).

Once suspected, men are diagnosed with FD if enzyme activity is <35% of the mean. The gold standard of diagnosis for females is α -Gal gene sequencing only.¹¹ Genetic analysis is however expensive and only available in specialised laboratories. Moreover, >900 variants of the α -Gal gene have now been identified,¹² many of doubtful pathological significance. In these cases, invasive tissue diagnosis investigating the presence of Gb3 deposits is indicated. Therefore, there is a need for more practical and simple diagnostic tools.

Since 2001 widely available enzyme replacement therapy (ERT) with recombinant agalactosidase alfa and beta has been a game changer for diagnosing and treating FD¹³ and has sparked a lot of interest; the rising awareness resulted in high-risk populations being screened (dialysis, renal transplant, left ventricular hypertrophy, cryptogenic stroke)¹⁴ and whole families started on treatment.

The current challenges of ERT enzyme replacement therapy are many: first, there is relative lack of efficacy with a lack of visible therapy effect. This results in difficulties with standardised disease activity/therapy monitoring. Antibody formation possibly also contributes to reduced therapy effect.

In this article, we review novel biomarkers for diagnosis and therapy monitoring as well as current practice of treating patients who develop antibodies.

We also discuss novel treatment options with oral therapy and gene therapy, raising the possibility of a cure.

Finally, we highlight the need for systematic multidisciplinary approach to assessment of organ involvement and therapy optimisation.

Biomarkers

Many attempts have been made over the years to find a disease-specific marker that would ideally serve as a rapid screening tool as well as indicator of therapy response.

Gb3

As such Gb3—the end product which accumulates in lysosomes and is routinely used to diagnose the disease on tissue biopsy—heart, kidney¹⁵ and most recently skin¹⁶—has so far failed to convince as a



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Table 1 Typical organ involvement in morbus Fabry

Organ system	Complications
Ophthalmological	Cornea verrucillata, tortuous vessels, cataracts ⁵⁸
Dermatological	Angiokeratoma, hypo/anhidrosis, telangiectasia, lymphedema ⁵⁹
Neurological	Neuropathic pain, transient ischaemic attack, stroke, neuropsychiatric complications (depression) ⁶⁰
Cardiac	Conduction abnormalities, left ventricular hypertrophy, sudden cardiac death ⁶¹
Renal	Proteinuria, reduced glomerular filtration rate ⁶²
Gastrointestinal	Diarrhoea, constipation, early satiety, nausea ⁶³
Auditory	Hearing loss, tinnitus, vertigo ⁶⁴
Respiratory	Cough, wheezing, airflow limitation ⁶⁵

suitable plasma or urine marker. A study by Young¹⁷ performed on hemizygotas, heterozygotas and healthy controls failed to reliably detect increased Gb3 levels in plasma and urine in heterozygotas and hemizygotas with non-classical mutation. Additionally, Schiffmann failed to demonstrate a correlation between plasma or urine Gb3 and clinical response to ERT.¹⁸

An interesting approach to detect Gb3 deposits in peripheral blood mononuclear cells (PBMCs)¹⁹ represents a low-cost and simple alternative to invasive biopsies. What is more, the Gb3 load in PBMC decreases with long-term ERT and could potentially be used for disease monitoring. It is important to highlight that this method failed to detect Gb3 deposits in non-classical/missense mutations, in particular in four patients with D313Y mutation, which are known to be non-disease-causing mutations.²⁰

LysoGb3

The Gb3 degradation product, globotriaosylsphingosine (lysoGb3), is currently used in disease screening,^{21,22} but also in the determination of pathogenicity of a mutation for homozygotas as well as heterozygotas. In a prospective evaluation/validation study of 124 patients,²³ lysoGb3 levels were correlated to clinical picture, mutation type as well as biochemical and imaging studies and shown to be a reliable predictor of clinically relevant disease. In another study, a raised level of lysoGb3 could be detected even in females with normal β -Gal activity and subsequently those patients were proved to have clinically significant disease.²⁴

Furthermore, lysoGb3 levels have been shown to decrease with ERT, in particular in patients with classical phenotype.^{25,26} Since these findings, lysoGb3 has been widely accepted as the most accurate marker of disease activity. However, long-term data on clinical outcomes in patients who achieve lysoGb3 reduction are currently not available.

Emerging biomarkers

Several other avenues have been explored but are not yet widely in use due to lack of data. In a pilot study, Cammarata *et al* identified four micro-RNAs specific for Fabry patients²⁷ regardless of mutation, sex or age. However, two of these micro-RNAs were linked with endothelial dysfunction and the number of patients and controls (30 patients and 30 controls respectively) was too small to derive test sensitivity/specificity.

Further attempts to identify Fabry-specific biomarkers include identification of new Gb3 isoforms using metabolomics^{28,29} and quantifying abnormal urinary protein excretion using proteome analyses^{30,31}; however, none were able to validate a clinically useful single parameter.

ERT: pitfalls

As indicated above, intravenous ERT has been the gold standard since 2001.

The therapy efficacy monitoring issue has partially been addressed above. Long-term data over the last 17 years are now available to assess clinical response to therapy,^{32,33} and ERT has been shown to provide the greatest benefit to patients if started early on. On the other hand, during short-term assessments (generally yearly controls), which are relevant to the clinician and patient in standard practice, it can be very difficult to assess progress and make evidence-based decisions on therapy switch or modification, mainly due to slow progression of the disease, coupled with irreversibility of organ damage and poor therapeutic efficacy.

We have already discussed the role of biomarkers measured in plasma and urine and PBMC. A further assessment option is repeated biopsy of affected organs to prove Gb3 deposit reduction,³⁴ which is invasive and impractical. Enzyme activity measurements are equally unsuitable as enzyme activity measured in plasma/leucocytes is sensitive to time after last enzyme infusion.

Therefore, careful clinical assessment, history taking and organ investigations are currently the best tools in the clinician's box in day-to-day practice, alongside standard adjunctive therapy for specific organ involvement.

The next issue around ERT is antibody formation. The main concern in the first trials were immediate infusion-associated reactions which are IgE mediated. Premedication protocols—usually a combination of single-dose paracetamol or a non-steroidal anti-inflammatory drug, antihistamine and steroid, plus increasing infusion duration to prevent such reactions—have been established successfully and are still used.³⁵

IgG seroconversion has been reported in the first clinical trials in approximately 40% patients; however, it was thought not to influence enzyme efficacy.³⁴

Data from the Fabry registry report seroconversion with neutralising antidrug antibodies (ADA) in 73% males as opposed to 12% females treated with agalsidase beta, which is likely due to complete absence of native enzyme in men with classical mutations. This theory is supported in the fact that men with missense mutations were far less likely to develop antibodies, possibly due to residual native enzyme activity.³⁶

Over the years long-term effect of neutralising antibodies has not been studied in detail, in particular their impact on clinical outcomes.

A study by Benichou *et al* observed significantly impaired Gb3 clearance in skin biopsies of patients treated with ERT and high antibody titres.³⁷

A correlation between antibody levels and lysoGb3 has been confirmed in a study of 60 Japanese patients.²⁶ Similarly, when analysing in vitro enzyme inhibition in relation to lysoGb3 levels, disease severity scores and subjective symptoms in a group of 168 patients,³⁸ a study confirmed higher lysoGb3 levels as well as worse disease severity scores in patients with serum-mediated enzyme inhibition. There was no difference for the enzymes used (agalsidase alfa or beta) assuming a cross-reactivity and therefore not advocating for a therapy switch in antibody-positive patients. The theory of cross-reactivity is supported by Linhart *et al*,³⁹ who proved in vitro inhibition to both agalsidase alfa and beta in ADA-positive patients irrespective of which enzyme they were treated with.

In contrast two other studies^{40,41} postulated a reduction in plasma lysoGb3 with switch from agalsidase alfa to agalsidase beta in antibody-positive patients, however, not reaching levels as

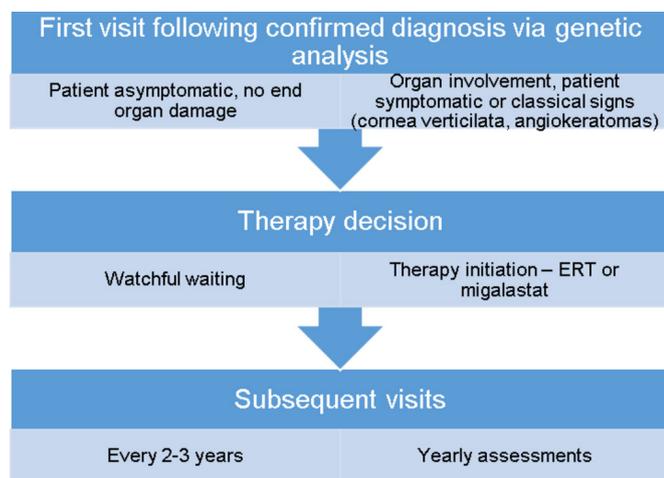


Figure 1 Patient journey in FAZiT. ERT:enzyme replacement therapy.

low as antibody-negative patients. This could be explained by the administration of a higher dose of agalsidase beta with full antibody saturation rather than assumption of non-cross-reactivity. This theory was supported by a study of ADA levels immediately after enzyme infusion, where circulating ADA levels were significantly lower following a higher dose enzyme infusion.⁴²

More recent studies have raised the question of immune modulation therapy in response to antibody formation as experienced in other lysosomal storage disorders eligible for ERT.⁴³ In particular, a study investigating the effect of immunosuppression in transplant patients on antibody formation delivered valuable insights⁴⁴—immunosuppression has been shown to decrease ADAs significantly in therapy naive as well as previously treated patients. Further prospective studies are needed to evaluate clinical impact of lowering ADAs and correlation with biomarkers would be particularly interesting.

To conclude, routine antibody screening is currently not part of clinical practice but may explain why some patients suffer significant disease progression with ERT. Further data are needed to develop strategies for affected patients, be it ERT switch, dose increase, immunomodulation treatment or a switch to a different therapy option.

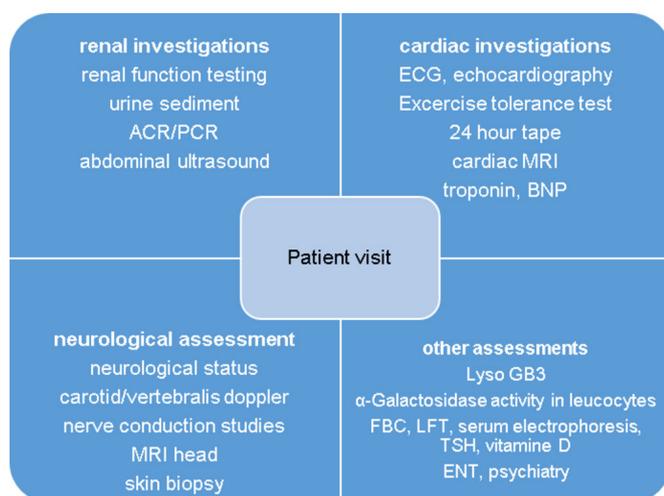


Figure 2 Specialist investigations. ENT, ear, nose and throat; LFT, liver function tests; FBC, full blood count; TSH, thyroid stimulating hormone; BNP, brain natriuretic peptide; MRI, magnetic resonance imaging; ACR, albumin-creatinine-ratio; PCR, protein-creatinine-ratio.

Novel approaches

Migalastat

A new therapy approach with migalastat was established in 2016. Migalastat is a small-molecule chaperone which facilitates enzyme trafficking to lysosomes in certain mutant enzymes.⁴⁵ The advantage for patients is oral administration, thus avoiding the need for biweekly enzyme infusions and possible associated adverse reactions. In theory, migalastat has a higher volume of distribution than ERT⁴⁶ and given consistently may result in better functional enzyme availability. On the downside, migalastat can only be used in suitable mutations—most commonly single missense mutations⁴⁷, which is the case for an estimated 30% of all Fabry patients.⁴⁸ A full updated list of amenable mutations is provided by the manufacturer Amicus Therapeutics. A first randomised controlled trial comparing migalastat with ERT has shown comparable effect on renal function, cardiac and composite outcomes,⁴⁸ first cardiac MRI analyses show a possible positive impact on fibrosis and cardiac hypertrophy.⁴⁹

To date, one phase II study has examined the combination of ERT with migalastat and showed promising results with a 1.2-fold to 5.1-fold increase of enzyme activity compared with ERT alone.⁵⁰ Large co-administration studies are needed to confirm these findings and evaluate long-term clinical outcomes.

Lucerastat

Substrate reduction therapy (SRT) uses yet another approach that was tried in other lysosomal storage disorders such as miglustat in Gaucher disease⁵¹ and offers the advantages of oral therapy irrespective of genotype. A new drug lucerastat—a direct inhibitor of glucosylceramide synthase—is currently in the later stages of clinical trial development. Glucosylceramide synthase catalyses the first step to glycosphingolipid synthesis, therefore by direct inhibition a lower Gb3 load is achieved.⁵² Again, a combination of SRT with ERT and/or chaperone therapy may result in more favourable outcomes for Fabry patients.

Gene therapy

Lastly, first gene therapy clinical trials are under way (<https://clinicaltrials.gov/ct2/show/NCT03454893?cond=Fabry+Disease&draw=3&rank=21>). Animal studies in Fabry knockout mice have succeeded in introducing a working copy of the α -Gal gene via viral vectors (adenovirus or retrovirus), resulting in increased enzymatic activity at 6 months.⁵³ A similar therapeutic approach has been successfully used in human haemophiliacs.⁵⁴ The prospect of a cure with a single infusion of vector gene is exciting; however, there are currently several limitations of vector use—namely vector neutralising antibodies, which in theory can be overcome by emerging non-viral vectors. Other limitations of course include lack of long-term effects data as well as ethical issues of administering genome-modifying treatment to children.

Multidisciplinary team: FAZiT

Because of the rarity and chronicity of the disease, as well as diagnostic and therapeutic uncertainties, we believe that specialist multidisciplinary assessment is of great benefit to our patients, in particular in the setting of lack of national and international guidelines on assessment and management. The first benefits of multidisciplinary work were reported by the oncologists⁵⁵ who are historically champions of comprehensive care of their patients. In the rare diseases community, similar attempts have been successful in treating patients with Gaucher disease.⁵⁶

Our large national centre FAZiT (Fabry Zentrum für interdisziplinäre Therapie – Fabry Centre for Multidisciplinary

Main messages

- ▶ Gold standard diagnosis of Fabry disease is genetic analysis, but distinguishing non-pathogenic variants can still be a challenge.
- ▶ Novel biomarkers such as lyso Gb3 add to establishing diagnosis and treatment monitoring.
- ▶ Relative lack of enzyme replacement therapy efficacy, partly due to antibody formation, may be alleviated by combination with new oral therapy approaches.
- ▶ Multidisciplinary work is key to comprehensive management of Fabry patients.

Current research questions

- ▶ Can we develop a reliable diagnostic tool/score to identify non-pathogenic mutations?
- ▶ Is there a role for immunomodulation in antibody-positive patients on enzyme replacement therapy (ERT)?
- ▶ Will future randomised controlled trials show that combination of ERT and chaperone/substrate reduction therapy add benefit to clinical outcomes?
- ▶ Will gene therapy bypass all current difficulties and deliver a cure?

Therapy), attached to the University Hospital Würzburg, Germany, incorporates the core specialties nephrology, cardiology and neurology, who are involved at each patient visit, with collaboration from other departments - radiology, ear, nose, and throat, ophthalmology, gastroenterology, paediatrics, psychiatry and social services.

For our standard patient journey, see [figures 1 and 2](#).

Putting patient care in the centre of our focus, we are actively involved with patient groups and organise yearly educational meetings with talks by experts in their respective fields. This is a great opportunity for patients to share their experience and support each other.

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Self-assessment questions

Please answer true or false

1. Children—in particular boys—who suffer from Fabry disease can develop neuropathic pain as young as age 3–4.
2. Due to the x-linked nature of the disease, women are carriers but do not develop significant disease.
3. Male patients with Fabry disease always develop angiokeratomas.
4. The main cause of death in classical phenotype patients is end-stage kidney disease.
5. The most reliable biomarker for disease monitoring is lysoGb3.

Lastly, we of course contribute to further research of diagnostic tools and therapies and contribute to international consensus on disease management.⁵⁷

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Answers

1. True.
2. False.
3. False.
4. False.
5. True.