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Fabry Disease: A Review

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ABSTRACT

Fabry disease (FD) is a X-linked lysosomal storage disorder caused by pathogenic variants in GLA. Deficiency of an enzyme leads to the buildup of glycosphingolipids in various cell types, including vascular endothelial cells, podocytes, cardiomyocytes, neurons and others. Symptoms like hypohidrosis, neuropathic pain, hypertrophic cardiomyopathy, angiokeratomas, arrhythmias and progressive chronic kidney disease (CKD) to end-stage renal disease (ESRD) were considered as organ manifestations. Early diagnosis enables disease modifying therapy that can prevent or slow organ damage. This review article mainly focusses on genotype-phenotype spectrum, molecular pathology & diagnostic biomarkers, diagnostic approach & screening recommendations, treatment & established therapies, supportive & organ-directed care, treatment evidence & outcomes, special diagnostic & management issues, newborn & popular screening challenges, bio-markers use in monitoring & treatment decisions, safety & adverse effects of the treatment, gaps in evidence & research priorities and practical clinical recommendations of FD. In male with early CKD or cryptogenic stroke, with neuropathic pain, corneal verticillata, angiokeratomas or with un-explained LV hypertrophy FD is suspected, so the tests must be done promptly. Diagnostic algorithm for both males and females must be monitored. In males, α-galactosidase A activity must be measured and GLA genetic testing must be performed, whereas, in case of females, GLA genetic test must be performed regardless of enzyme level and measure plasma lyso-Gb3 for baseline monitoring. After multi-disciplinary evaluation patients who were diagnosed with ERT or Migalastat for amenable mutations must be initiated to disease-modifying therapy at earliest. Cardiac, neurological status and renal activities must be monitored regularly. With promising results emerging gene-therapies and substrate reduction strategies can be helpful in treating yet, long term evaluation is required. Vigorous genotype interpretation, multi-disciplinary care and careful counseling must be considered as critical clinical priorities.

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Introduction

Fabry disease (FD) is a X-linked lysosomal storage disorder caused by pathogenic variants in GLA. Deficiency of an enzyme leads to the buildup of glycosphingolipids in various cell types, including vascular endothelial cells, podocytes, cardiomyocytes, neurons and others. These glycosphingolipids include mainly globotriaos. The prevalence among white males is thought to be between 1:17,000 to 1:117,000 cases of Fabry disease. There are 1:22,000 to 1:40,000 classic Fabry disease cases among males while the number of males with the atypical variants is 1:1000 to 1:3000. Females with this condition make up 1:6000 to 1:40,000 cases. Symptoms like hypohidrosis, neuropathic pain, hypertrophic cardiomyopathy, angiokeratomas, arrhythmias and progressive chronic kidney disease (CKD) to end-stage renal disease (ESRD) were considered as organ manifestations. Early diagnosis enables disease modifying therapy that can prevent or slow down the organ damage [1-3].

Genotype-Phenotype Spectrum

New born screening and targeted screening of high-risk populations like hyperptrophic cardiomyopathy, early CKD, cryptogenic stroke, unexplained left ventricular hypertrophy has revealed a higher prevalence of later-onset GLA variants. New born screening conducted in Taiwan, reported a high frequency of a later-onset cardiac variant, illustrating population differences and detection of later-onset phenotypes.

In males with <1-3% of residual enzyme activity is present in adolescence with neuropathic pain, corneal verticillata, hypohidrosis, angiokeratomas and progressive involvement of heart, kidney and CNS were treated as classic phenotype. In case of males in middle-to-older age where the residual enzyme activity is higher the later onset (attenuated) phenotypes often manifest predominantly as cardiac hypertrophy or late renal disease.

Due to random X-chromosome inactivation in heterozygous females the FD shows a broad clinical spectrum. Therefore, to assess and prevent the risks, testing and clinical assessment is required for all the at-risk relatives [4].

Molecular Pathology and Biomarkers

In men with classic disease where levels correlate with disease burden in many, but not in all contexts, Lyso-Gb3 has emerged as a useful diagnostic and pharmacodynamic biomarker. Pathophysiology of organ damage involves endothelial dysfunction, podocyte injury, inflammation and progressive fibrosis [5].

Diagnostic Biomarkers

Enzyme activity assay: Low α-galactosidase A activity in plasma or leukocytes is a reliable diagnostic approach in males, whereas it is unreliable in many heterozygous females due to normal or near-normal activity may be present.

Genetic testing: In both males and females and for family cascade testing GLA sequencing is required to confirm diagnosis. For variant pathogenicity and genotype-phenotype correlations, attention is required in interpretation.

Lyso -Gb3: In many patients elevated plasma lyso-Gb3 supports the diagnosis and can be used to monitor therapy response [6].

Diagnostic Approach and Screening Recommendations

Females with suggestive features or family history and males with early neuropathic pain, unexplained early CKD or cryptogenic stroke, unexplained LV hypertrophy, characteristic ophthalmic signs must undergo genetic testing irrespective of enzyme activity. For later-onset variants; programs must be planed for variant interpretation and long- term follow-up, the method newborn screening is essential. α-galactosidase A, enzyme assay (males), GLA gene sequencing, baseline organ assessment, plasma lyso Gb3, ECG and in case of neurological issues brain MRI are considered as core-diagnostic tests [7].

Treatment and Established Therapies

Enzyme Replacement Therapy (ERT): Medication like Agalsidase α and Agalsidase β can be used for every 2 weeks in a dosage of 0.2 mg/kg and 1.0 mg/kg respectively. In early initiation, long term registry and observational follow-up proves that ERT can stabilize or slow organ damage and reduce plasma Gb3/lyso-Gb3. It has also been a historic standard disease-modifying therapy.

In many patients, the outcomes from the past decade for agalsidase beta shows better benefits. In some patients, infusion burden, infusion-related reactions can be manageable. In some others antibody formation (neutralizing) anti-bodies can attenuate whereas for some others the need for life-long infusion is required. In some regions, the dosing difference between products and supply issues have been clinically considered [8].

Oral Pharmacological Chaperone- Migalastat

Migalastat binds and stabilizes certain misfolded α-galactosidase A proteins encoded by "amenable" GLA variants, enhancing trafficking to lysosomes and increasing residual activity. Adults who were diagnosed with FD and amenable GLA variant Migalastat is prescribed. Variant amenability should be interpreted with validated assays and in consultation with genetics. Migalastat offers an oral alternative to life-long intravenous ERT for eligible patients [9].

Substrate Reduction and Other Small-Molecule Approaches

Substrate Reduction Therapy (SRT): As monotherapy or adjunct and data are evolving, agents that reduce the formation of glycosphingolipids are under investigation. Recent reviews summarize the progress and challenges of SRT in FD.

Supportive and Organ-Directed Care

Renal: ARBS/ACE inhibitors for proteinuria, dialysis, nephrology follow-up and kidney transplantation were indicated.

Neurologic: Neuropathic pain agents, stroke prevention and rehabilitation.

Cardiac: Antiarrhythmics, devices (like pace makers/ICDs) as per cardiology guidance, heart failure management, specialized cardiac imaging (MRI with LGE) for fibrosis assessment.

Multi-disciplinary follow-up: With monitoring of eGFR, urine protein, lyso-gb3, ECG/echo and periodic cardiac MRI are required [10].

Treatment Evidence and Outcomes

ERT evidence base: Due to the ethics of placebo use in progressive diseases, randomized controlled trails in FD are limited by sample size. However, long-term observational and registry data shows reduction in plasma Gb3, stabilization of renal function in many patients and reduced major clinical events in some cohorts. In association with attenuated benefits the late initiation and neutralization of antibodies is common. Comparison of the effectiveness between alfa and beta is always debatable due to the differences in dose and product [11].

Migalastat evidence: With ongoing post-marketing surveillance and guidance on variant testing, clinical trials showed pharmacodynamic and organ level, effects on patients with amenable variants which reflects in evidence due to the regulatory approvals [9].

Gene-therapy land scape: Multiple approaches like AAV-based liver directed gene transfer, lentiviral ex-vivo hematopoietic stem-cell gene therapy trails have progressed from phase 1-2. To assess the durability and benefits of organ there are ongoing trials that can last longer. Recently there has been data reported on early safety/tolerability and biochemical effects. The other gene-therapy programs along with STAAR (Studies of Therapy for AAr-related Renopathy) are still active. Even though gene-therapy offers the potential with one-time durable increase in α-galactosidase A, it raises concerns regarding the vector durability, long -term safety and immune response require careful evaluation [12].

Special Diagnostic and Management Issues

The scope for development of clinically significant FD in heterozygous females is high, so the full evaluation, genetic testing and individualized treatment decisions are essential. Even when the enzyme assays are normal they can't be excluded. The management of organ-based indications is similar to males [7].

Newborn and popular screening challenges

With certain uncertainty, in clinical manifestations and timings Newborn screening detects, many later-onset or VUS-GLA variants which raises the need of counseling and follow up ethical considerations and complexity. Tiwan's experience with cardiac variant stands as an example highlighting both value and complexity of screening. To avoid further over-or-under treatment, programs must be planned for long-term follow up and counseling for specific genotype [13].

Bio-Marker Use in Monitoring and Treatment Decisions

Even though plasma lyso-Gb3 is helpful in monitoring and diagnosis in many patients, it is not perfect for predicting individual organic progression. Consensus documents, recommend sex-informed monitoring strategies and genotype placing regular organ-specific monitoring as priority [14].

Safety and Adverse Effects

Gene therapy: Early trials report on infusion reactions, potential off-target or insertional risks in integrating vectors and vector related immunogenicity suggesting a careful surveillance for a long- term. Whereas, in case of recent gene therapy developments focuses on regulatory oversight in other diseases.

Migalastat: Rather than for amenable variants, drug interactions and renal function limitations, Migalastat is generally well tolerated.

ERT: In some patients, monitoring is advised where there is development of anti-drug antibodies. With the help of pre-medication, the infusion reactions can be manageable, however, long-term infusion logistics and infection control must also be considered.

Health System, Access and Real-world Considerations

Treatment access and cost: All patients can't have Migalastat as oral option as it can be prescribed only to selected patients. New treatments like gene-therapy may be a one-time process yet they are expensive with requirement of specialized centers. ERT is costly which requires life IV infusions. Care has been affected due to the regional differences between ERT products and genetic-testing.

Gaps in Evidence and Research Priorities

The head-to-head trials or vigorous registry based comparative studies of ERT (Enzyme Replacement Therapy) products vs migalastat vs substrate reduction are limited. Long-term gene therapy out comes such as organ level benefits, durability and recent safety data are required. Especially in newborn- detected individuals, natural

history of later-onset variants and optimal timing of therapy initiation must be prioritized. Improved predictive bio-markers for organ progression and therapy response beyond lyso-Gb3 must be discovered. For standardized newborn screening, pathways with genotype specific follow up algorithms are required.

Practical Clinical Recommendations

In male with early CKD or cryptogenic stroke, with neuropathic pain, corneal verticillata, angiokeratomas or with un-explained LV hypertrophy FD is suspected, so the tests must be done promptly. Diagnostic algorithm for both males and females must be monitored. In males, α-galactosidase A activity must be measured and GLA genetic testing must be performed, whereas, in case of females, GLA genetic test must be performed regardless of enzyme level and measure plasma lyso-Gb3 for baseline monitoring. After multi-disciplinary evaluation patients who were diagnosed with ERT or Migalastat for amenable mutations must be initiated to disease-modifying therapy at earliest. Cardiac, neurological status and renal activities must be monitored regularly. For all confirmed cases genetic counselling and family cascade testing must be offered. Enrollment in registries and clinical trials must be considered where appropriate [7,9,11,12,14].

Conclusion

Fabry disease is a heterogenous, X-linked lysosomal disorder with well-defined molecular pathology and a growing therapeutic armory. Early diagnosis, individualized therapy combined with organ-directed care can improve patient outcomes. With promising results emerging gene-therapies and substrate reduction strategies can be helpful in treating yet, long term evaluation is required. Vigorous genotype interpretation, multi-disciplinary care and careful counseling must be considered as critical clinical priorities.

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