Diagnosis and Treatment of Fabry Disease – A Review

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ABSTRACT

Fabry disease is a rare lysosomal storage disease that is caused by the irregular degradation of a fatty acid. This disease causes a multisystem disorder affecting mainly the heart and kidneys due to the accumulation of the fatty acid Gb3. There is a classical presentation of Fabry, where patients show symptoms in childhood or early adolescence as well as late onset where patients show symptoms later in life in the third or fourth decade. Early diagnosis is imperative for the success of treatment. This review focuses on symptoms, diagnostic steps, treatment, and future research of Fabry disease.

Introduction

Lysosomal storage disorders (LSD) as a whole affect 1 in 5,000 live births, but with over 40 different kinds of disorders, individually, they are considered to be rare diseases (Platt et al., 2018). These disorders are caused by mutations in genes that affect proteins that aid in lysosomal formation and function (Myerowitz et al., 2020). The lysosome is an organelle in which cellular material is recycled and the material is recycled through a process called autophagy. Autophagy has three different pathways all which end with the lysosome and in LSD these pathways are flawed due to a mutation which disrupts it (Myerowitz et al., 2020). The issue with these different LSD's stems from the fact that each disorder has a different mutation, which affects different autophagy, and each disorder stores a different material incorrectly. The difference in what storage material is being held in the lysosome is what affects metabolism and how it affects organs and the general pathology of the disease (Gieselmann et al., 2006). All of these factors create unique disorders that have different effects on the pathology of the disease.

Fabry disease is one of the 40 plus lysosomal storage disorders and is caused by mutations in alpha-galactosidase A gene (GLA gene) located on the X chromosome (Eng et al., 1994). This gene affects the activity of the enzyme alpha-gal which leads to the irregular accumulation of two fatty acids, globotriaosylceramide (Gb3) and globotriaosylsphingosine (lysoGb3) (Kok et al., 2021). The accumulation of these compounds causes a cascade of cellular issues which in turn affects the functioning of organs as well as with the quality of the person's life. The brain, heart and kidneys are the organs that experience the most issues associated with this disease. Strokes, kidney damage, heart attacks and decreased life expectancy can be expected with Fabry (Fabry Disease, 2021). Men who have Fabry have a life expectancy of 58.2 years opposed to the average 74.7 years and women with the disease have the life expectancy of 75.4 instead of the average 80 years (Waldek et al., 2009). Since this is a rare disease, its reported incidences are about 1 in 476,000 to 1 in 117,000 (Germain, 2010). The variance in numbers is due to the fact this disease is underdiagnosed as symptoms are common such as abdominal pain, anemia, and malabsorption (Fabry Disease, 2021). There are ways to test for the disease yet there is no cure for it. A few different types of therapies are offered to patients with this disease such as gene therapy, enzyme replacement therapy, and chaperone mediate therapies, but none completely cure the disease and the effectiveness of each is dependent on how early the disease is found (van der Veen, 2020). Understanding more about the pathology of the disease after flawed lysosomal storage could lead to finding a better treatment for this disease.

Genetics

There are over 900 variants of mutations that occur on the GLA gene that can lead to Fabry disease (Nowak et al., 2021). Mutations in this gene cause loss of function which is what leads to the accumulation of the fatty acids in the lysosome. The types of mutation variants lead to different phenotypes of Fabry (Nowak et al., 2021). The different types of mutations lead to variability in the activity levels of the enzyme alpha-gal which will lead to either late onset Fabry or classical Fabry disease. When alpha-gal enzyme activity is 3% or less this will lead to the classical phenotypic presentation of the disease. When the enzyme is 3%-15% of normal activity it is considered to be late onset presentation of Fabry (Fabry Disease- Symptoms, Causes, 2019). Late onset is ten times more likely to occur than classical Fabry disease and the symptoms are usually lessened. The symptoms will not occur until 30-70 years of age and organ damage can be less severe while patients with the classical presentation of the disease experience symptoms in childhood and have more severe organ damage ((Fabry Disease- Symptoms, Causes, 2019). There are five different types of mutations that occur on the GLA gene: missense, nonsense, deletions, insertions, and splicing issues. The frameshift variants such as nonsense mutations usually lead to the classical phenotype as there is little to no enzyme activity associated with these mutations. Missense mutations usually lead to late onset phenotype as there is some enzyme activity (Nowak et al., 2021). An issue that presents itself when testing for this disease is that there are other types of mutations, less common than what was mentioned, that are missed by sanger sequencing. These mutations consist of mosaics, deep intronic variants and copy number variants (Nowak et al., 2021). With many different types of mutations this causes high variability in the phenotypes of Fabry disease.

Since the mutation that occurs in Fabry is associated with the X chromosome, women are known to be carriers of the disease. This does not mean that men or women are more likely to get the disease as there is no consensus on whether the disease is dominant or recessive since there is a spectrum of ways the disease presents itself (Ries et al., 2006). Along with the variants of the disease males and females have different medical presentations of the disease. Men tend to have a higher chance of having the classical phenotype while women tend to present the disease as late onset (Bernardes et al., 2020)). The theory behind men and women being affected differently is that women have one functioning X chromosome and one mutated X chromosome while men only have the defective X and a functioning Y (Bernardes et al., 2020). The disease is passed onto 50% of all offspring of a person with Fabry. If a woman has Fabry there is a 50% chance all of her children will have it, if a man has Fabry all of his daughters will have it but none of his sons will (Fabry Disease, 2021). Another interesting aspect of Fabry is that each family tends to have their own unique mutation that is passed down through generations (Ries et al., 2006). Even with family members sharing the same mutation, the disease itself will still express variability in its symptoms. The variability in family members may be due to non-genetic factors such as an accumulation of misfolded proteins (Ries et al., 2006). Overall, Fabry is a complicated disease as the same mutations within the disease do not always present the same phenotypes.

Diagnosis

With the disease not being presented in a straightforward way, early diagnosis is sometimes difficult as symptoms are overlooked. Some of the more frequent symptoms consist of pain episodes in the extremities, whorls in the eyes, decreased ability to sweat, stomach pains and eventually organ failure (Fabry Disease, 2021). An easy way to diagnose this disease is for newborn screenings to take place. This helps to catch the disease early on which can allow for more effective treatment later in life and improve the patients' overall standard of living (Colon et al., 2017). With common symptoms and the disease being underdiagnosed, increasing newborn screenings would help to reveal a more accurate prevalence of the disease. The testing is relatively simple, all that is needed is a dry blood spot and then an enzymatic test is performed to see what levels of alpha-gal are present in the blood (Colon et al., 2017). For females more genetic testing may be necessary as there is usually increased enzymatic activity in heterozygous fe-

males with the disease (Colon et al., 2017). Having a genetic diagnosis is also important for males as specific family mutations will present themselves in different ways (Nowak 2021). Having newborn screenings and genetic testing increases detection rate and helps to increase future quality of life.

Once diagnosed with Fabry there are a variety of symptoms a person will experience. Due to the mutated GLA gene alpha gal enzymatic activity is severely decreased which leads to the accumulation of the glycosphingolipid Gb3 (Desnick et al., 2003). This accumulation affects the vascular endothelium which is the inner most layer of cells that coats the arteries, capillaries, and veins (Krüger-Genge et al., 2019). The lysosomes with the improper degradation accumulate in the vascular endothelium which leads to ischemia and infarction (Desnick et al., 2003). Ischemia is the restriction in blood supply to tissues, muscles and organs and infarction is the result of prolonged ischemia and leads to tissue death (Desnick et al., 2003). The restriction in blood supply can be the cause of organ damage. Kidney damage and kidney failure are the main issues in Fabry disease. The increased deposition of Gb3 causes renal lesions in the kidneys which eventually leads to renal failure in the third to fifth decade of a patient's life (Germain 2010). One way that the kidneys compensate for these lesions and accumulation is they will hyper filtrate which can be a symptom and early sign of Fabry (Germain 2010). Another symptom of Fabry is stomach pains and malabsorption of nutrients and this is because of the accumulation of lyso-Gb3 which disrupts the homeostasis of microbes in the stomach (Aguilera-Correa et al., 2019). Another main symptom of Fabry is neuropathy, or pain episodes in the extremities, sometimes known as a Fabry crisis. These pain episodes are caused by the loss of thin myelinated and unmyelinated fibers (Politei et al., 2022). These pain episodes occur in early childhood and are brought on by overheating or extreme temperature changes. Another unique aspect of Fabry and a good symptom to look out for is the lack of sweating in patients with Fabry. This symptom, like most other symptoms in Fabry, is due to the deposition of Gb3 and in this case the deposition of Gb3 in eccrine sweat glands which decreases one's ability to sweat (Kokotis et al.,2018). There is also some evidence to suggest that nerve damage is partially responsible for the decreased ability to sweat (Kokotis et al., 2018). Finally, the last symptom unique to Fabry is cornea verticillata which is whorls in the cornea of the eye (Sodi et al., 2006). This symptom is easily identified at an optometrist. While Fabry is underdiagnosed there are a multitude of symptoms that are unique to Fabry that require slightly more attention to detect but make them good markers for the disease.

The next step after being diagnosed with Fabry disease is to determine if it is classical or late onset. As mentioned in the introduction, classical is when alpha-gal is 3% or less of normal activity and late onset is when alpha-gal is 3%-15% of normal activity. While looking at the enzyme activity level is important, there are a few other biomarkers that have the potential to indicate the severity of the disease. A new biomarker that seems to help determine the severity in males with Fabry is sphingosine-1-phosphate (S1P). In a study done on male patients with Fabry it was seen the S1P levels were higher in males with the non-classical phenotype (Mauhin et al., 2022). This new finding could suggest that there are distinct pathways between the two phenotypes of this disease. S1P has been associated with cardiomyopathy and immune regulation, so future treatments could be directed at this S1P pathway for non-classical presenting males (Mauhin et al., 2022). Another biomarker that has been looked at is the compound of Gb3 called lysoGb3. There has been debate on whether this is a reliable biomarker for the disease that fully encompasses the patient's disease therapy. The overall consensus of lysoGb3 is that it is effective in the initial diagnosis of the phenotype but does not reflect the severity of it or accurately depict the phenotype after treatment (Liu et al., 2014). Another way to determine whether it is classical or late onset is to look at the different symptoms. Usually, neuropathic pain and cornea verticillata will be seen in classical but not late onset (Mauhin et al., 2020). In conclusion an effective diagnosis will be a multistep process, beginning with newborn screening, genetic testing and measuring multiple biomarker levels in order to create a comprehensive picture of what the disease entails for each person.

Treatments

After diagnosis, a treatment plan will be necessary to determine the correct time and treatment for each patient. This is where a thorough and early diagnosis is imperative because treatments available may not be effective if the disease is caught too late and organ damage is too severe (Arends et al., 2018). While there is no cure for the disease there are treatment options that can lessen organ damage and overall symptoms of Fabry disease.

Enzyme replacement therapy (ERT) is the most common treatment Fabry patients receive. There are two types that are available: agalsidase alpha and agalsidase beta. Both are very similar biochemically and structurally speaking (Arends et al., 2018). The difference between the two types is that the beta treatment's dosage is about five times higher than that of alpha. The alpha treatment is about .2mg/kg while the beta treatment is about 1mg/kg. As of right now, only agalsidase beta (Fabrazyme) is licensed in the US while agalsidase alpha is offered in Europe and Canada (Arends et al., 2018). The drug is administered through an IV about every two weeks and treatments can last from 3 hours to 8 hours each session depending on the reaction and dosage that is being received and patients will receive treatment for multiple years (Danapilis, 2021). The drug is available through specialty pharmacies only. It is possible to get Fabrazyme covered by insurance, but the patient's insurance agency and doctor will come up with a plan (Danapilis, 2021). According to Drugs.com the cost of 35mg is $7,267.78, so for a person weighing 170lbs or 77kgs the cost of one treatment would be almost $20,000. The manufacturer Genzyme provides assistance with insurance policies to help lower the cost of treatment.

ERT is the standard treatment so far and has many clinical trials to demonstrate its effects. In one study done there were no clinical event rate differences between the two treatments but agalsidase beta seemed to decrease lysoGb3 levels more than agalsidase alpha did (Arends et al., 2018). Along with decreasing the lysoGb3 storage, agalsidase beta had a more positive effect on left ventricular mass as Fabry patients tend to have enlarged left heart ventricles which can cause heart issues (Fabry Disease, 2021). On the other hand, patients had fewer allergic reactions to agalsidase alpha, most likely because it was given at a much lower dosage (Arends et al., 2018). In a ten-year study done on agalsidase, beta seemed to decrease the number of severe adverse effects in patients although it did not completely prevent these severe events (Germain et al., 2015). This ten-year study also confirmed that if treated later in life some damage was not able to be undone and organ damage was irreversible. A different four-year study done on just women with agalsidase alpha found that there was a clinical benefit of using this treatment (Catharina et al., 2009). The clinical benefits consisted of stability in kidney function, reduction in the left ventricular mass, improvement of heart failure classification and the overall pain severity of the disease decreased as well. While Fabrazyme is affective there are some symptoms that patients can experience when on this treatment. According to Fabrazyme 59% of patients experienced infusion related reactions while on treatment. Some of these symptoms consisted of headache, fever, dizziness and burning sensation. According to Fabrazyme these symptoms usually occur in patients who have antibodies for the drug. Treatment can continue but usually with an antihistamine and a slower treatment. Only 1% of patients on Fabrazyme experience severe allergic reactions, and these reactions usually cannot continue treatment. Overall, both ERT's offer patients some solutions to the effects of the disease as long as the disease is treated early enough, before major organ damage occurs.

Another treatment that is becoming available for Fabry patients is chaperone mediated therapies. These therapies focus on using a chaperone called a migalastat that stabilizes the mutant enzyme in order to correct its function (Hughes et al., 2019). There are some benefits to using chaperone mediated therapy as it can be taken orally and avoids antibody formation against the treatment like ERT sometimes does (Germain et al., 2016). It is less invasive than ERT because a pill is taken every other day at the same time on an empty stomach (Fitting Galafold, n.d.). The side effects seem to be less than ERT as they consist of headaches, runny nose, and urinary tract infections (Fitting Galafold, n.d.). According to drugs.com the pricing for galafold is $2,073.96 for one pill or $29,035.45 for 14 pills which would last one month. The manufacturer of this drug, Amicus Assist, offers a program to provide insurance assistance to patients prescribed to migalastat so they are not paying close to $30,000 a month. This is a relatively new treatment and has some interesting clinical trials. A 6-month double blind, phase 2 clinical trial with

50 patients found that there were no statistical differences between the placebo group and the chaperone migalastat group (Germain, 2016). Another study done on 57 patients tested the effectiveness of the migalastat chaperone. Researchers found it had similar effects to ERT (Hughes et al., 2019). These findings differ from the first study because all of the patients were on ERT before taking the chaperone therapy for 18 months. This difference might have allowed the patients to maintain levels around the ERT patients, but it does not seem conclusive as to whether or not the chaperone would have worked the same way on its own. Another issue that presents itself when working with chaperone therapies is that the mutation has to be compatible with the chaperone for the enzyme to bind with the chaperone (Hughes et al., 2019). While chaperone mediated therapies offer a less invasive and more manageable treatment form, it does not seem to be a catch all solution. It may be worth looking into using it more as combination therapy as it seems to be able to maintain ERT levels after ERT has taken place.

A third option available to patients with Fabry is gene therapy. Gene therapy would offer patients a one-time treatment that would deliver a functional alpha-gal enzyme and bring activity to normal levels (Khan et al., 2019). The delivery of the functional enzyme would be through stem cells. Limited studies have been done on the safety and reliability of this therapy. In one study done on five patients over the course of 33 months, researchers found that there were no serious safety concerns (Khan et al., 2019). In this study three patients have not needed to continue ERT but one patient was still showing signs of chronic kidney disease. Currently there are three different gene therapies in Phase 1 or 2 clinical trials that could be future options for patients with Fabry. ST-920 is a US gene therapy, FLT190 is a European gene therapy and AVR-RD-01 is in the US, Canada, and Australia (Tan, 2020). Overall, more studies need to be conducted before gene therapy can be a viable option for treatment.

These three options are the most widely used treatment options for Fabry today but there are other possible future options for treatment as well. Second generation enzyme replacement therapies could be an option. The second generation ERT is a plant-based therapy thought to have a different more widely spread biodistribution of the enzyme alpha-gal (van der Veen et al., 2020). In current ERT the enzyme distributes itself unevenly with most ending up in the liver while these second-generation therapies offer a more even distribution so the more severely affected cell types such as cardiomyocytes podocytes take up the enzyme (Yim et a., 2021). Substrate reduction therapy is another up-and-coming therapy that would limit the formation of the metabolites (lysoGb3 and Gb3) that cannot be degraded due to irregular lysosomal function (van der Veen et al., 2020). With many options available and how versatile the disease is there most likely will not be a catch all solution but rather combination therapies specific to each person with the disease.

Conclusions

Even with many treatment options available there is no current cure for the disease. With the variabilities in phenotypes and the numerous mutations that can happen on the alpha-gal gene there is probably not one treatment that will cure the disease. Possibilities of combination therapy and having multiple options for treatment are promising as it does not limit a patient with only one option. New research in gene therapy offers patients the exciting possibility of a one-time treatment, but more research on safety and efficacy is needed. Even with the ample information on the issues with lysosomal fusion, what gene is mutated, and how the accumulation of fatty acids will affect the body regarding Fabry, there is still much unknown about the disease. Areas of focus that seem to be lacking are the flawed pathways after the accumulation in the lysosome that lead to a multisystem disorder. Being able to identify the flaws in the pathways may allow new avenues for treatments and a better understanding of the disease. While there is a general understanding of what mutations can cause either the classic presentation or late onset presentation of the disease, more research could be done on the correlations between mutations and severity of the disease. Furthering research in the genetics area of Fabry could make diagnosis easier and more accurate in the severity levels. As families seem to have the same mutations, knowing their symptoms, type of mutation, and how each individual presents the disease is vital information for further defining and comprehending the disease. These topics may offer more insight into Fabry and more effective treatments in the future.

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