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Agalsidase Alpha and Agalsidase Beta Effect in Fabry Disease

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Abstract

Rare diseases are a group of diseases caused by genetic mutations. Fabry disease is a lysosomal storage disease with a low incidence in society and is caused by the mutation of the *GLA gene* above the X chromosome. Enzyme replacement therapy and oral chaperone therapy constitute the treatment of the disease. The management of Fabry disease requires the collaboration of various multidisciplinary health professionals. Because Fabry disease is chronic and progressive, the primary role of the nurse is to provide management of symptoms and help the patient and family manage the disease, as well as administer and follow up treatment.

Keywords: Rare diseases, Fabry disease, enzyme replacement therapy (ERT), oral chaperone, nursing care

Introduction

Rare diseases are a group of diseases that have a low incidence in society and are caused by genetic mutations.[1] Fabry disease (FD) is one of the rare diseases and its incidence occurs between 1 : 40 000 and 1 : 117 000 worldwide. Moreover, it is a lysosomal storage disease (LSD) that occurs due to the mutation of the *GLA gene* located on the X chromosome.[2] It is one of the diseases whose diagnosis is confused especially in the pediatric group in terms of multiple system complications such as cardiac, respiratory, renal, and neurological.[3] Orphan drugs are used in the treatment of rare diseases and the use of these drugs in health care is increasing, and also the trend toward biotechnological drugs is showing a rapid rise nowadays.[4] Enzyme replacement therapy (ERT) and oral chaperone therapy are used to treat the disease. Fabry disease can be treated with agalsidase alfa and agalsidase beta enzymes.[5] Migalastat is also used in oral chaperone treatment.

Including FD in newborn screening (NBS) is the most effective way to detect the disease before symptoms appear. With the help of this approach, FD screening has been initiated in NBSs in Taiwan, the United States, Europe, and Turkey.[6]

Definition of the Rare Disease

Diseases defined as rare diseases, which are also called orphan diseases, are classified as chronic and progressive diseases with a prevalence of less than 1/2000 in the population. These diseases generally affect more than one system, and it is stated that 80% of them are caused by genetics and 20% by environmental or idiopathic causes. Worldwide, more than 6000 rare diseases have been defined. Although these diseases affect a limited number of people, most of them can be diagnosed in childhood.[1] According to Online Mendelian Inheritance in Men, 5081 of these diseases have known phenotype definitions and molecular basis. In addition, 1597 of them have unknown phenotype or locus.[7]

Fabry Disease

Fabry disease is a rare LSD inherited by the X chromosome and results in the accumulation of globotriaosylceramide (Gb3) in many tissues such as nerves, kidneys, heart, and skin as a result of α-galactosidase enzyme deficiency.[3] Fabry disease causes inflammation and fibrosis as a result of the accumulation of neutral glycosphingolipids, galactosylceramide, and globotriaosylcerebroside (Gb3) in various tissues due to the deficiency of alpha-galactosidase A enzyme, which functions in sphingolipid metabolism and also

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impairs multiple organ and system functions. Consequently, it causes renal, cardiac, neural, and skin pathological symptoms.[8] A large number of missense mutations were detected in patients with FD and it leads to the production of misfolded gene products and the accumulation of Gb3 in the endoplasmic reticulum, resulting in the stimulation of various cascade systems within the cell.[9]

The etiology basis of FD is genetic mutations, and it has been shown that there are more than 550 mutations of the *GLA gene* that causes the disease. Many of these are specific to the genotype of the patient and their family members. It has been determined that approximately 3% and 10% of the patients have novo mutations (mutations not found in the patient's family).[10]

Pathophysiology

Sphingolipids are important components of eukaryotic cells, many of which act as bioactive signaling molecules. Ceramide, one of them, is a central metabolite and plays an important role in various cellular regulations including cell growth, viability, differentiation, and aging regulation.[11] Lysosomes that contain lysosomal hydrolases and sphingolipids are responsible for the degradation of structurally different metabolites such as protein, glycosaminoglycan, glycogen, nucleic acid, oligosaccharide, and complex lipids. Due to changes in lysosomal hydrolases and lysosomal membrane proteins that lead to dysfunction or loss, they cause the accumulation of non-metabolizable substrates in the cell and the formation of LSDs.[12]

The etiopathogenesis of lysosomal diseases is divided into 2 main groups. In the first group, there is a deficiency of the lysosomal enzyme, damage to the cell, and deterioration of its function due to the accumulation of substrate specific to that enzyme. In the second group, pathological accumulation is observed due to transport protein disorders that enable the hydrolyzed molecules to be transported out of the cell in lysosomes. Clinical findings in LSD differ according to the stored substance and their distribution in the organism.[13]

Fabry disease is inherited as an X-linked disorder in the lysosomal storage glycosphingolipid metabolic pathway, which is the second most common after Gaucher disease.[14] In the lysosome, the enzyme alpha-galactosidase A hydrolyzes GB3 in the ceramide pathway, resulting in the release of galactose and ceramide dihexose. Neutral glycosphingolipids, galactosylceramide, and Gb3 that accumulate due to alpha-galactosidase A enzyme deficiency resulting from mutations cause symptoms involving various systems.[8] The first signs and symptoms of FD appear in childhood, but diagnosis is often delayed because it is confused with other diseases. The disease is classically characterized by angiokeratomas, acroparesthesias, and gastrointestinal tracts in childhood and adolescence period. Data for FD shows that the average onset of symptoms in males is 6 years and in females is 9 years. Acroparesthesia, which is characterized by numbness in the fingers and toes, is one of the first clinical manifestations in children. Recurrent gastrointestinal symptoms were the second most common feature with a rate of 27%. Hypohidrosis and heat intolerance are also common symptoms in the early phase of the disease.[15] Pathological GB3 accumulation causes progressive neurological, cutaneous, renal, cardiovascular, cochleovestibular, and cerebrovasular signs and symptoms that shorten life expectancy by 10-20 years in male and female patients in the long term.[9]

Incidence Frequency

Fabry disease can occur in all ethnic, racial, and demographic groups. In males, the estimated incidence is 1:50 000, and recent population estimates range from 1:40 000 to 1:117 000.[10] As a result, FD is a rare, life-threatening disease that is often misdiagnosed, and its accurate incidence and prevalence are unknown because of its different forms.

A pilot study for FD screening was conducted in Japan and measurement of GLA activity was performed from dried blood stains. In this study, in which 21 170 newborns participated in total, it was found that 7 of them (5 males and 2 females) had low GLA levels, the prevalence of babies with the positive test was 1/3024, while the rate of those with pathogenic mutations was 1/7057.[2] According to the study by Colon et al, 14 600 dry blood samples (7575 boys and 7025 girls) were collected and 1 patient had a GLA mutation, 10 had genetic variants of uncertain diagnosis, 1 girl had non-characterized variant F18Y, 25 patients had polymorphisms. Nucleotide substitutions described were determined. The estimated prevalence for FD in North-West Hispanic men was 0.013%.[16]

Studies on FD have also started in Turkey, and Turkmen et al examined the prevalence of FD in chronic kidney patients in 2016. Diagnosis was confirmed by α-galactosidase activity and *GLA gene* mutation analyses in dry blood samples. Three male patients out of 313 patients were diagnosed with FD and its prevalence was determined as 1.80%. Family screening was also performed and 8 patients were shown to have FD.[26] In another study conducted on dialysis patients in Turkey, 130 of 1527 patients had low α-Gal activity. Diagnosis of 5 patients with low α-Gal A was confirmed by GLA genotyping.[27] In addition, case studies show that the prevalence of the disease is quite wide in Turkey.[3,8] Patients usually go to the health facility with symptomatic findings and when evaluated in a detailed examination, they appear to have FD.

Studies show that the prevalence of this disease in the community is not to be underestimated, so this shows that FD should be taken seriously.[1,3,6,7] Considering each disease individually, the number may seem low, but considering the numerical excess of rare diseases and in addition to many unknown cases that cannot be diagnosed, the high number of affected people in European countries such as Turkey, Italy, and the United States makes this situation a global phenomenon.[7]

New Born Screening

Congenital metabolic diseases are hereditary diseases, mostly inherited, resulting from disorders in the biochemical functions of the body. These congenital diseases, which are generally caused by the primary deficiency or ineffectiveness of an enzyme or transport protein, cause physical and mental health problems and may adversely affect the health of a newborn.[17] Metabolic diseases within the scope of NBS program in Turkey contain phenylketonuria (PKU), congenital hypothyroidism, biotinidase deficiency, and cystic fibrosis.[18] In Turkey, NBS does not include LSDs such as Pompe, Gaucher, Fabry, NiemanPick A/B, and Krabbe disease.

Worldwide, whole NBS for LSDs is performed as a first-line test by measuring lysosomal enzymatic activities in dried blood stains. Two current methodologies currently used for the measurement of enzymatic activities are tandem mass spectrometry and digital microfluidic fluorimetry.[19]

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Treatment

Enzyme Replacement Therapy

Biological therapeutic agent, which is a large molecule drug form in polypeptide or protein structure compared to normal drugs, is obtained by living microorganisms using recombinant DNA technology and hybridoma.[20] Biotechnologically produced drugs are used in the treatment of FD. Enzyme replacement therapy is a treatment to replace the missing enzyme in the cell. For this purpose, agalsidase alfa and agalsidase beta are used in the treatment of disease.

Replagal (Agalsidase Alfa)

After Johnson and Brady showed that α-Gal obtained from the placenta decreased the GB3 level in 1973, the studies in this area gained momentum, and after 2001, the production of α-Gal was carried out using recombinant DNA technology. It is a drug used in long-term ERT for FD. Treatment with the enzyme has been shown to reduce GB3 accumulation in many cell types, including endothelial and parenchymal cells. It is produced by the replacement of the α-galactosidase A gene in cells. Then, the enzyme is separated from the cells and the sterile concentrated solution is prepared for infusion.[21]

Replagal is administered by intravenous infusion over 40 minutes at a dose of 0.2 mg/kg body weight every 2 weeks. There is no different dose recommendation in hepatic insufficiency, renal insufficiency, pediatric population, geriatric patients, lactation period, and pregnancy. According to the studies conducted in pediatrics, it is recommended to be used in children between the ages of 7 and 18.[22]

Weight × 0.2=... mg (1 mg of Replagal is contained in 1 mL)=... mL/3.5 (vials contain 3.5 mL of solution)= ... Number of vials

The dose calculation for a 60-kg patient is as follows:

60 × 0.2=12 mg=12 mL (If 1 mL is 1 mg, 12 mg is 12 mL)=12 mL/3.5= 3.4 ~ 4 vial.[17]

In a study by Rawaswami et al evaluating the efficacy of agalsidase alfa in 11 children (age range 3.5–18) with FD, children were infused with 0.2 mg/kg for 40 minutes every 2 weeks for 23 weeks. No side effects were observed, infusion reactions occurred in 4 boys, 8 mild and 3 moderate, throughout the infusion; also increased plasma Gb3 concentrations were observed. As a result, it was determined that children tolerated agalsidase alfa well in the short term and the pain associated with the disease decreased.[28] In addition, Schiffmann et al conducted the first randomized study on FD. The patients received 12 doses of agalsidase alfa treatment for a period of 22 weeks, and the improvements in neuropathic pain, creatinine clearance levels, and cardiac conduction were the most important results of the study and increased the reliability of the therapeutic effect of the drug.[30]

According to the study of Weidemann et al, it was found that there was a decrease in glomerular filtration rate in the dose-reduced group, and an increase in albumin-creatinine levels in patients who switched to agalsidase alfa. However, since renal biopsy was not performed in these patients, a definite conclusion could not be reached about whether there was any renal damage.[31]

Fabrazyme (Agalsidase Beta)

Agalsidase beta is a recombinant human alpha-galactosidase indicated to treat FD, a genetic deficiency in the enzyme that leads to the accumulation of Gb3. Agalsidase beta is a recombinant human α-galactosidase A similar to agalsidase alfa. While patients generally do not experience a clinically significant difference between the 2 drugs, some patients may benefit more from agalsidase beta.[4,5] The use of agalsidase beta in Europe has decreased in favor of agalsidase alfa after a contamination event.[16] In an observational study conducted by Tsuboi and Yamamoto in 2012, it was observed that there was no change in renal functions, cardiac volume, and quality of life for 1 year in patients who switched from 1 mg/kg/every other week's agalsidase beta to 0.2 mg/kg/every other week's agalsidase alfa.[2]

Comparison of Agalsidase Alpha and Agalsidase Beta

Agalsidase alpha and agalsidase beta contain the same active ingredient (alpha-galactosidase A), but they have been produced using different protein expression systems. Both have the same glycosylation structure. Agalsidase beta has a higher level of sialylated oligosaccharides and phosphorylation. Biodistribution studies in animal models have shown similar organ uptake. Antigenicity studies showed no difference in antibody cross-reactivity between the 2 drugs.[23] Two recombinant α-Gal enzymes are administered biweekly by intravenous infusion, but there is a dose difference. Agalsidase alfa is used as 0.2 mg/kg and agalsidase beta is used as 1.0 mg/kg.[16]

Viral contamination in the agalsidase beta production process led to a global agalsidase beta deficiency in June 2009. It was suggested by the European Medicines Agency to reduce the dose of agalsidase beta, but due to the serious side effects observed in the patients, it was recommended to use agalsidase beta again as a full dose or it was decided to switch to agalsidase alfa within the determined dose limits. Switching to agalsidase alfa in those using reduced-dose agalsidase beta provided the opportunity to compare the 2 drugs.[17]

According to the studies that evaluated the efficacy of ERT, it has been shown that there is no significant difference between agalsidase alfa and agalsidase beta in terms of any side effects such as dyspnea and hypertension, and adverse effects are more significant in agalsidase beta compared to placebo. In addition, there was no significant difference in side effects between patients receiving agalsidase alfa and beta; when doses were compared among patients receiving agalsidase alfa, 3 doses (0.2 mg/kg for 2 weeks, 0.1 mg/kg per week, and 0.2 mg/kg per week) in 1 group were followed by 2 more doses in the other group (0.4 mg/kg per week), and it was found that there was no difference in Gb3 levels when the treatment was carried out in other weeks.[29]

In a cohort study of 387 patients, of which 192 were women, 248 patients were given agalsidase alfa and the risk of developing antibodies was higher for patients treated with agalsidase beta. It was found that there was a higher decrease in the left ventricular volume index after the first year of agalsidase beta treatment, and the eGFR slopes were similar.[32] According to a retrospective observational study conducted in Latin America (33 patients) switched from agalsidase beta to agalsidase alpha, it was observed that glomerular filtration rates did not change, and there were no significant changes in the left ventricular mass index, the interventricular septum, and the left ventricular posterior wall.

According to the final results of the studies, there were no changes in renal and cardiac functions, quality of life, pain, disease severity scoring, and safety at least 2 years after switching from agalsidase

Figure 1. Mechanism of Germain, D.P.Fabry disease. Germain Orphanet Journal of Rare Diseases 2010.5:30.

beta to agalsidase alpha.[33] GB3 level was also studied with pediatric groups, and it was reported that boys had higher levels of GB3 in plasma and urine compared to girls. Moreover, GB3 decreased to normal after 12 and 23 weeks of treatment with agalsidase alfa.[5]

Oral Chaperone Therapy (Migalastat)

Although agalsidase alpha and agalsidase beta treatment prevent the progression of the disease, there are some limitations due to factors such as treatment-related reactions and high cost. Therefore, Migalastat as an oral chaperone therapy, as an alternative to ERT, has been started to be used in the treatment of FD. The main molecule increases lysosomal activity by stabilizing the transport of appropriate mutant forms of the α-galactosidase A enzyme from the endoplasmic reticulum to the lysosomes.[18,24]

In clinical studies, oral chaperone therapy has been shown to significantly reduce cardiac mass compared to ERT. It was also observed that it was well tolerated by patients.[34]

Nursing Care in Fabry Disease

Managing FD requires team collaboration. Because FD is chronic and progressive, the nurse's primary task is to manage symptoms and help the patient and family manage the disease. For this reason, it is the basis of nursing care to take the patient and his family as a whole, to help them understand FD, to strengthen their coping mechanisms, to help them cope with chronic symptoms, to control and manage pain, and to take part in education and counseling processes.

At the same time, during the ERT treatment, its management and patient follow-up in terms of complications constitute one of the primary responsibilities of the nurse. In addition, since FD is caused by genetic mutations, a detailed evaluation including genetic information should be made for each patient. In this way, the genetic background of the disease is determined by identifying family members who are potentially affected or likely to be affected.[25]

Conclusion and Recommendations

Enzyme replacement therapy can prevent disease progression before irreversible organ damage begins. Therefore, early diagnosis and treatment are important in FD. Pilot studies comparing ERT and oral chaperone therapy and related to FD should be increased, genetic counseling should be provided to families at genetic risk as a nursing intervention, the patient and family should be educated about the management of the disease by nurses after diagnosis, and resources should be expanded.

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