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Short Communication

Gaucher Disease: Therapeutic Agents in the Management of the Disease

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Abstract

Gaucher disease (GD) is the most common lysosomal storage disease. As a lysosomal storage disease, it is a rare autosomal recessive disorder characterized by an accumulation of glucocerebroside due to the defective function of the catabolic enzyme β-glucocerebrosidase.

The clinical signs and symptoms of the disease include bone infarcts and malformations, hepatosplenomegaly, hypersplenism and neurological dysfunctions. Avascular necrosis, chronic pain, fractures, ischemia, lytic lesion, osteonecrosis and osteopenia are some of the complications of Gaucher cells accumulation in bone marrow. Depending on the severity of these complications, the disease progression does vary and does have normal survival. Therapeutic management involves enzyme replacement therapy, substrate reduction therapy and pharmacological chaperone therapy.

Keywords: *Gaucher Disease; Therapeutic Agents*

Introduction

Gaucher disease (GD) is the most common lysosomal storage diseases. Lysosomal storage diseases (Fabry disease, Gaucher disease, Hurler syndrome and Tay-Sachs disease) are heterogeneous group of rare inherited disorders which ultimately leads to cellular dysfunctions and clinical abnormalities due to accumulation of undigested or partially digested macromolecules. In the case of Gaucher disease, glucocerebroside accumulate in lysosomes of macrophages of various tissues of the spleen, liver, bone marrow, bone mineral, lungs, skin, conjunctiva, kidneys, heart including the central nervous system due to absence or reduction of enzymatic activity [1-3].

The mechanism of the pathology of the disease involves inflammatory and apoptotic processes triggered by sphingolipids as well as the activation of macrophages function by glucosylceramide [4,5]. It also entails displacement of the normal adipocytes from the bone marrow compartment by progressive accumulation of Gaucher cells, resulting in abnormal quantities and the distribution of 'dark marrow '(reduced bone marrow signal intensity environ) [6].

As a multisystemic disorder, the disease is classified into three basic clinical forms based on the degree of neurological involvement [7,8]. They include (i) Type 1 Gaucher disease (non-neuropathic)- most frequent form and affects organs such as spleen, liver, bone mar-

row including the kidney and lung in severe cases. Hematological complications such as anemia, thrombocytopenia as well as hepatosplenomegaly might occur if untreated [7,8]. Asthenia, fatigue, nutritional disturbances, postprandial gastric fullness, and stunted growth are also associated with Type 1 clinical form of the disease. (ii) Type 2 Gaucher disease-manifests in early childhood as acute neuronopathy. Neurological deterioration progresses quickly and could lead to death of the child before attending the age of two years, (iii) Type 3 Gaucher disease-manifests in adolescence stage of life as sub-acute neuronopathy with slower neurological deterioration.

The disease is being caused by recessive deficiency of the catabolic lysosomal enzyme β-glucocerebrosidase (acid beta-glucosidase), which is responsible for hydrolysis of glucocerebroside (glucosylceramide) into glucose and ceramide [9,10].

The typical clinical signs and symptoms are hepatomegaly (deposition of Gaucher cells within the liver), splenomegaly (deposition of Gaucher cells within the spleen), hypersplenism (manifests as anemia, cytopenia, thrombocytopenia, and to a lesser degree, leucopenia) and bone disease (chronic bone pain, osteopenia, bone infarct, osteonecrosis, pathologic fractures, lytic lesions, and bone deformities) [11].

The specific diagnosis of Gaucher disease is by (i) measuring the acid beta-glucosidase activity in fresh peripheral blood leukocytes (ii) enzymatic analysis of fibroblasts culture from skin biopsy specimens, (iii) performance of molecular analysis of the acid beta-glucosidase gene which encodes lysosomal acid beta-glucosidase (GBA). However, non-specific tests involve the identification of Gaucher cells on tissue biopsy specimens of bone marrow or liver [12].

Treatment of the disease requires prior confirmation of the diagnosis by enzymatic or molecular tests. The treatment strategy mainly consists of (i) enzyme replacement therapy, (ii) substrate reduction therapy, (iii) pharmacological chaperone therapy, and (iv) induced pluripotent stem cell-derived stem cell transplantation.

The enzyme replacement therapy involves delivering the missing enzyme to the cell to break down accumulated glucosylceramide. Typical examples are elglucerase, imliglucerase (modified form of elglucerase by recombinant DNA technology), velaglucerase alfa and taliglucerase alfa. Imiglucerase is the gold standard for the treatment of type 1 disease [13,14]. The drug is recommended for type 1 and type 3 GD patients (regardless of age) with mild, moderate, or severe clinical symptoms [15].

Substrate reduction therapy entails reversible inhibition of glucosylceramide synthase thereby reducing the synthesis of its substrate (glucosylceramide). Glucosylceramide synthase is an enzyme that catalyses the first step in the synthesis of glycosphingolipids pathway [16]. Typical examples are eliglustat and miglustat. Miglustat, an iminosugar derivative is the drug of choice used orally to treat type 1 Gaucher disease patients for whom enzyme replacement therapy is not an option [17].

Pharmacological chaperone therapy involves induced stabilization of glucocerebrosidase.by stabilizing misfolded mutant proteins, preventing endoplasmic reticulum-associated degradation in proteasomes and allowing trafficking to lysosomes [18]. Typical example is ambroxol hydrochloride [19]. Ambroxol hydrochloride has also been used as a mucolytic agent and in the prophylaxis or treatment (or both) of neonatal respiratory distress syndrome [20].

Although the fourth therapy in the management of Gaucher disease does not involve use of therapeutic agents, its current prospects in the management of the disease demands mentioning it. It involves the use of induced pluripotent stem cell-derived stem cell transplantation that allows monocytes from the peripheral blood to pass across the blood-brain barrier and become central nervous system microglial cells that could affect metabolic processes [21,22].

Conclusion

Gaucher disease is one of inherited metabolic disorders resulting from the inborn errors of metabolism due genetic defects, leading to deficiencies in the production of enzymes or abnormalities in their functions. It is a clinically heterogeneous, progressive disease with high morbidity and mortality rates. It is important that all Gaucher disease patients be regularly monitored from a clinical and laboratory standpoint. Bone disease in children and adults could be confirmed with x-ray and/or magnetic resonance imaging (MRI) examination. To avoid disease progression and onset of serious and irreversible complications, early implementation of adequate therapy after confirmation of diagnosis is very vital. Imiglucerase is the current standard for the treatment of the disease. Substrate reduction therapy is important for patients not treated with enzyme replacement therapy and miglustat is the drug of choice.

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