

ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

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Gaucher Disease: Hematologic and Oncologic Implications

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H&O What is Gaucher disease?

DH Gaucher disease is a rare, genetic, lysosomal storage disorder. In patients with this disease, the lysosomal enzyme glucocerebrosidase is missing or reduced in activity, which results in accumulation of the substrate glucosylceramide. This accumulation causes disruptions in various cells and organs, particularly the macrophages, resulting in enlargement of the liver and spleen, reductions in blood counts because of infiltration in the bone marrow, and problems with the bones themselves. More rarely, patients develop malignancies, such as multiple myeloma.

The exact causal relationship between the accumulation of glucocerebroside and the pathology of Gaucher disease is not entirely clear. In some patients, bulk accumulation of the substrate causes enlargement of the spleen and the liver. In other patients, the pathology is related to downstream events, such as production of cytokines, immunologic activation of cells, and fibrosis of the organs.

The prevalence varies with different populations. It is most common among Ashkenazi Jews. In the general population, the prevalence is about 1 in 40,000.

H&O What are the hematologic implications of Gaucher disease?

DH The hematologic sequelae are caused by the accumulation of glucocerebroside in macrophages within both the bone marrow and the spleen. Gaucher patients with progressive splenic enlargement usually first develop a decrease in the platelet count that is followed by a decrease in the hemoglobin, a reflection of bone marrow infiltration. Gaucher patients develop abnormalities in terms of bleeding and bruising, and they can develop anemia. Rarely, there is also a reduction in the white cell

count, although unsplenectomized patients do not appear to be at increased risk of infection. Some patients may develop clotting abnormalities, such as abnormal clotting factors and changes in platelet function, but these reports are less well documented. Patients with Gaucher disease can have problems with bleeding and bruising, even when their platelet count is normal, suggesting that other parts of the coagulation cascade are also affected.

H&O How is Gaucher disease associated with malignancy?

DH Several years ago, the first small studies suggested an increased risk of malignancy in Gaucher disease based on data from postmortem patients. They showed that a larger proportion of patients than would be expected had a malignancy at postmortem, including patients who died of other causes. Larger studies have shown that there is an increased risk of hematologic malignancy, especially of multiple myeloma. In some series, patients with Gaucher disease have an increased risk of multiple myeloma that is up to 50 times greater than in people without the disease. There are also case reports of cancers, such as lymphomas, chronic lymphocytic leukemia, and acute myeloid leukemia, although these reports do not reflect a definite increase. A recent study examined the number of patients who developed multiple carcinomas; quite a few patients developed 1 or 2 or even more malignancies. Overall, the risk of malignancies seems to be highest in patients who had undergone splenectomy—the historical treatment for these patients. A large study of patients from the Netherlands and Germany detected an increased risk of hepatocellular carcinoma, an association that makes logical sense considering the background of the changes that occur within the liver.

H&O What are the current treatment approaches?

DH Until about 15–20 years ago, patients with Gaucher disease were treated palliatively with pain medications, transfusions of blood and platelets, and splenectomy to improve blood counts. Enzyme replacement therapy was then developed, initially using an enzyme made from the human placenta. In 1994, the US Food and Drug Administration (FDA) approved the recombinant agent imiglucerase (Cerezyme, Genzyme) for the treatment of Gaucher disease. Patients receive an infusion of this agent every 2 weeks. This therapy had been associated with reduction of spleen and liver volumes and improvement in hematologic function. In 2003, the FDA approved the oral agent miglustat (Zavesca, Actelion), which works through the mechanism of substrate reduction. Instead of contributing the deficient enzyme, miglustat prevents the build-up of substrates by inhibiting glucocerebrosidase synthetase. It has also been shown to improve hemoglobin and platelets and to reduce organ volumes. It is approved for patients with mild to moderate Gaucher disease who are not able to tolerate enzyme replacement therapy. Another enzyme therapy is velaglucerase alfa (VPRIV, Shire), which was approved by the FDA in 2010.

There are many more options for these patients than there were a few years ago. These agents have had positive effects on the hematologic consequences of Gaucher disease. However, we do not know whether they will impact the risk of malignancy.

H&O What are the novel approaches to treatment?

DH An enzyme also in phase III development is taliglucerase alfa (Protalix Biotherapeutics). This enzyme is made from a plant recombinant system. Rather than being made in cells from Chinese hamster ovaries, as is imiglucerase, or in human cells, as is velaglucerase alfa, taliglucerase alfa is made in carrot cells. A new version of

substrate reduction therapy, eliglustat (Genzyme), is also in development.

H&O What are some areas of future research in Gaucher disease?

DH It is important to understand the pathogenesis of Gaucher disease, so that treatments can be used in a rational way, especially with respect to the less well understood complications—such as multiple myeloma or other malignancies—that can occur in patients later in life. Another challenge is the long-term effects on the bones. Although bones show some response to treatment, on the whole, established bone disease is not as easy to treat as the hematologic sequelae. Recent reports have recognized an association between Gaucher disease and Parkinson's disease; a higher risk of Parkinson's disease has even been seen in people who carry the genes for Gaucher disease. That is an important area of future research that might provide insight into some of the more common conditions that are associated with Gaucher disease as well as the disease itself.

Suggested Readings

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