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Short Communication

Thrombocytopenia and Unexplained Splenomegaly; The Role of Hematologists in the Early Diagnosis of Gaucher Disease

Abstract

Hematologists should consider the diagnosis of Gaucher disease; when they look for the cause of unexplained splenomegaly and thrombocytopenia. In countries which consanguineous marriage is prevalent, autosomal recessive disorders like Gaucher Disease may be seen frequently. The diagnosis can be done today by a simple blood test, so liver biopsy is not necessary. BM aspiration and biopsy may be needed for exclusion of other diagnoses and can be deferred until report of enzyme assay. Genetic study is needed for definite diagnosis.

Splenomegaly is a clinical hallmark of Gaucher disease, and it is often associated with relative thrombocytopenia; although anemia and leukopenia are late findings [1]. Most patients with splenomegaly and thrombocytopenia are referred to hematologists during the diagnostic workup; and thus, hematologists should be familiar with Gaucher disease and should consider this diagnosis when they look for the cause of unexplained splenomegaly or thrombocytopenia. Gaucher disease was first described more than a century ago by Phillippe Charles Ernest Gaucher in Paris, and he made a misdiagnosis by stating that the first patient described with this disease had a lymphoma [2]. Later it was understood a genetic defect leading to a reduction of an enzyme called glucocerebrosidase [or acid beta glucosidase] is the cause of this disease. It leads to the storage of a nonmetabolised substrate called glucocerebroside. The prevalence of type 1 Gaucher disease is 1 in 40,000 in many countries, but may be as high as 1 in 1,000 in Ashkenazy Jews [1]. Patients with type 2 and 3 Gaucher disease are very infrequent, with a prevalence of less than 1 in 100,000 [3]. Because patients with type 2 and 3 Gaucher disease usually present with severe symptoms in early childhood; they are referred by pediatricians, to pediatric neurologist, pediatric endocrinologist or pediatric gastroenterologist. Patients with type 2 and 3 Gaucher disease always have neurological complications including regression of mental function also, whereas type 1 patients do not. In type 1 Gaucher disease the non-metabolized substrates accumulate in macrophages; so in all organs where macrophages are prevalent, such as spleen, liver, and bone the disease may cause symptoms. But macrophages,

of course, are all over the body, and manifestations of Gaucher disease in many other organs may be seen, too. Splenomegaly will be seen in almost all of the patients. Hepatomegaly is also prevalent, and thrombocytopenia is more prevalent than anemia, so this diagnosis should be kept in mind in patients who have thrombocytopenia and splenomegaly without signs of liver disease or portal hypertension. Bone complications, such as femoral head necrosis and pathological fractures, may be present in about one third of the patients, and most patients have some kind of fatigue. Bone complications is detectable by X-Ray in two third of them; but may be detected by magnetic resonance imaging in >90% of the patients. The symptoms and signs of Gaucher disease are extremely heterogeneous, and in some ways are quite unspecific, so they can be easily mistaken or considered symptoms for other hematological disorders. For example, bone pain, one of the important signs in Gaucher disease, is common in the majority of hematological oncologic disorders such as acute leukemia, chronic myeloid leukemia, and non-Hodgkin lymphoma. Bruising and bleeding are common abnormalities observed in hematological disorders. Fatigue is a very common symptom which can be attributed to many disorders, not only hematological; so that is very misleading. Hepatomegaly and splenomegaly can be common in other disorders. Due to the challenges in diagnosis, there is almost in all patients a relatively long delay between the first symptoms and the definite diagnosis, up to 10 years or even more. Mistry et al reported the diagnostic delay in 136 patients with Gaucher disease, and have been consulted a mean number of eight physicians before the diagnosis: that means internists,



pediatricians, hematologists, gastroenterologists, geneticists, neurologists, gynecologists, orthopedists, rheumatologists, and so on [4]. But finally hematologists were contacted at some point prior to diagnosis by almost 90% of the patients. Even most hematologists considered bone marrow (BM) aspiration and biopsy before enzyme study in order to rule out other differential diagnoses such as leukemia, lymphoma and myelodysplastic syndrome. Because usually Gaucher disease is a progressive disease the consequence of this diagnostic delay, may be bone fractures, progressive liver disease, chronic bone pain, growth retardation in children, life-threatening bleedings, or severe sepsis. So it should be emphasized that early diagnosis and timely therapy are crucial, because an effective and safe enzyme replacement therapy for Gaucher disease is available. Treatment is most beneficial in early stages of the disease, and thus timely diagnosis and therapy can prevent disease progression, ameliorate visceral and hematological abnormalities, prevent bone disease, and provide a better quality of life. Of course, some bone and joint complications may be irreversible, when diagnosis and treatment are too late. Note that elevated serum ferritin level is a sign of disease severity and will become normal after enzyme replacement therapy [2]; so should not be misleading to other impressions like Hemophagocytic Lympho-Histiocytosis (HLH). Of great importance in the management of cases of hyper-splenism is consideration of Gaucher disease in the list of differential diagnosis; because total splenectomy in this situation may cause progressive mental dysfunction due to accumulation of glucocerebrosides in the brain, so enzyme study and then

enzyme replacement therapy is the best management of hyper-splenism. Partial splenectomy in some cases of severe abdominal discomfort and pancytopenia may be suggested.

For example, recently four cases of unexplained splenomegaly and thrombocytopenia or anemia for whom enzyme study was requested, finally was diagnosed as Gaucher disease and had prompt response to enzyme replacement therapy. One of these cases was referred by a Pediatric Surgeon for pre-operation evaluation (the case was scheduled for total splenectomy due to hyper-splenism); the other cases were referred by Pediatricians due to workup of relative thrombocytopenia and splenomegaly with or without anemia.

References

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