PERSPECTIVE

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Gaucher Disease for Hematologists

Hematologlar için Gaucher Hastalığı

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Abstract

Gaucher disease (GD) is a rare hereditary lysosomal storage disease that arises due to deficiency of glucocerebrosidase. Early diagnosis is very important for starting proper treatment and preventing complications. Splenomegaly, anemia, and thrombocytopenia are the most common findings in GD and so most patients are initially referred to hematologists. The Turkish Society of Hematology established its Rare Hematological Diseases Subcommittee in 2015. One of the main topics of this subcommittee was to increase and improve awareness and education of rare diseases among hematologists in Turkey. This review presents GD with an overview of its clinical features, pathophysiology, and treatment options for hematologists.

Keywords: Gaucher disease, Anemia, Thrombocytopenia, Splenomegaly

Öz

Gaucher hastalığı (GH) nadir görülen kalıtsal bir lizozomal depo hastalığıdır. Gaucher hastaları sıklıkla geç tanı alırlar. Erken teşhis; uygun tedaviye başlamak, komplikasyonları ve hastalığın ilerlemesini önlemek için önemlidir. Splenomegali, anemi ve trombositopeni GH'de en sık görülen bulgulardır, bu nedenle çoğu hasta başlangıçta hematologlara sevk edilir. Türk Hematoloji Derneği 2015 yılında "Nadir hematolojik hastalıklar alt komitesini" kurmuştur. Alt komitenin ana amaçlarında biri Türkiye'deki hematologların nadir görülen hastalıklar konusunda bilinçlendirilmesi ve eğitimlerinin artırılması olmuştur. Bu derleme, hematologlar için GH'nin klinik özellikleri, patofizyolojisi ve tedavi seçeneklerine bir bakış sunmaktadır.

Anahtar Sözcükler: Gaucher hastalığı, Anemi, Trombositopeni, Splenomegali

Introduction

Gaucher disease (GD) is a rare hereditary lysosomal storage disease [1]. It occurs due to deficiency of the lysosomal enzyme glucocerebrosidase and the results of several compounds related to the substrate accumulating in cell lysosomes. The glucocerebrosidase 1 *(GBA1)* gene encoding glucocerebrosidase is located on chromosome 1. This disease has traditionally been classified into subtypes according to clinical findings, course, and the patient's ethnic origin. Type 1 GD (GD1, adult type) is the most prevalent form. Visceral findings such as hepatosplenomegaly, cytopenia, and bone disease are observed. While cases of GD1 lack involvement of the central nervous system, recent studies have shown that Parkinson disease and peripheral neuropathy are more common in these cases [2]. Type 2 GD (GD2, infantile) is the most severe form and begins within the first 6 months of life with a life expectancy of <2 years [3]. In addition to enlargement of the spleen and liver, progressive neurological findings are observed. In type 3 GD (GD3, juvenile), patients have both visceral and neurological findings with longer survival. Recently, however, this classification according to subtypes is being abandoned. The three subtypes are now thought to be continuations of each other within the spectrum of the same disease, rather than disorders with different phenotypes.

Patients with GD often have delays in diagnosis of up to 10 years [4]. Early diagnosis is important for starting proper treatment and preventing complications as well as disease progression. Splenomegaly, anemia, and thrombocytopenia are the most common findings in GD so most patients are initially referred to hematologists with a differential diagnosis of leukemia, lymphoma, or immune thrombocytopenia [5,6]. The Turkish Society of Hematology established a Rare Hematological Diseases Subcommittee in 2015. One of the main tasks of the subcommittee was to increase and improve awareness and education of rare diseases among hematologists in Turkey and GD was selected as one of the target diseases within this project.

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Weekend courses, online educational meetings, and guidelines for the diagnosis and treatment of GD were organized. This review presents GD with an overview of its clinical features, pathophysiology, and treatment options for hematologists.

Clinical Findings

There is a distinct phenotypic diversity in GD that cannot be fully explained by the genotype [7,8,9]. The clinical findings are shown in Table 1 [7]. The visceral organs, bone marrow (Figure 1), and bones are affected in almost all cases. The most common finding is splenomegaly [10]. Isolated thrombocytopenia alone is the most common cytopenia. Anemia and rarely leukopenia may be seen. Bone findings may present as diffuse bone pain and pain attacks associated with osteonecrosis. Osteolytic lesions, pathological fractures, and compression fractures are more common in patients who have undergone splenectomy. Many patients have growth retardation and delayed puberty [11]. Interstitial lung disease may be detected in rare cases [12].

Diagnosis

Laboratory and radiological findings are summarized in Table 2 and Table 3. Serum angiotensin-converting enzyme and particularly its tartrate-resistant isoenzymes may be increased [13]. Levels of chitotriosidase, an enzyme secreted from lipid-laden macrophages, are elevated [14]. Hyperferritinemia is frequently encountered in GD [15]. Lyso-GL1 (glucosylsphingosine), which is a downstream metabolic product of glucosylceramide, has been identified as a promising biomarker for the diagnosis and monitoring of patients with GD in recent years [16]. The definitive diagnosis of GD is made with glucocerebrosidase enzyme detection and genetic mutation analysis. Glucocerebrosidase can be examined in peripheral leukocytes or skin fibroblasts. For this, it is necessary to take a dry blood sample on filter papers [17]. Genetic analysis provides additional confirmation of the diagnosis and is also helpful for genetic counseling and the detection of carriers [18]. *GBA1* is the only gene known to mutate in GD and the most common mutation is the N370S mutation [7]. Lipid-loaded macrophages can be seen in the bone marrow in GD, but that is not a specific finding. Pseudo-Gaucher cells can be seen in other diseases [20]. Bone marrow aspiration/biopsy is not required for the definitive diagnosis but may be performed to rule out other diseases.

Table 1. Signs and symptoms of Gaucher disease.

Splenomegaly	85%
Hepatomegaly	63%
Thrombocytopenia	68%
Anemia	34%
Bleeding	Frequent (no percentage reported)
Osteopenia	55%
Bone pain	33%
Pathological fractures	7%
Bone crises	7%
Growth retardation	36%

Treatment

The goals of treatment are the elimination of symptoms, prevention of complications, and improvement of quality of life [21]. Due to the heterogeneity of the disease and the uncertainty of disease progression, the management should be individualized. Enzyme replacement therapy ameliorates most of the manifestations of GD1 and improves quality of life [22]. Treatment is not recommended for GD2 patients as it does not stop the clinical course. Enzyme replacement therapy may be beneficial for GD3 patients who have chronic visceral manifestations. Indications for starting treatment in cases of GD1 are considered according to the severity of the disease at the initial evaluation or according to the progression of

Table 2. Laboratory findings in cases of Gaucher disease.

- Cytopenia
  - * Anemia
  - * Thrombocytopenia
  - * Leukopenia
  - * Bicytopenia/pancytopenia
- Coagulation disorders
- Elevated liver enzymes
- Increase in serum ACE level (especially tartrate-resistant isoenzymes)
- Increase in acid phosphatase activity
- Hyperferritinemia
- Increase in chitotriosidase
- Poly- and monoclonal gammopathy
- Lipid-loaded macrophages in tissues (bone marrow, liver, spleen)

Table 3. Radiological findings in cases of Gaucher disease.

- Bone radiography
  - ° Erlenmeyer flask deformity
  - ° Bone fractures and lytic lesions
- Bone magnetic resonance imaging (MRI)
  - ° Bone marrow involvement
  - ° Bone infarcts
  - ° Osteonecrosis
- Dual-energy X-ray absorptiometry (DEXA)
  - ° Osteopenia
- Abdominal ultrasonography (USG)
  - ° Hepatomegaly
  - ° Splenomegaly
- Echocardiography
  - ° Pulmonary hypertension
- Chest X-ray/thorax computed tomography (CT)
  - ° Lung involvement

the disease. The severity of the disease can be evaluated with scoring systems [23]. Enzyme replacement therapy for GD1 may include imiglucerase, velaglucerase alfa, and taliglucerase alfa [24,25,26]. There is no consensus on the optimal dose or frequency in the administration of recombinant enzymes. The recommended dose for imiglucerase is 15-60 units of enzyme/kg every 2 weeks intravenously. The ideal dose has been set at 60 units/kg in most studies, but good response was also shown at lower doses [27]. Treatment is life-long and interruptions are not recommended. A small percentage of patients may develop antibodies (15%) [28]. Glucosylceramide synthase inhibitors (miglustat and eliglustat) are used for substrate reduction therapy [29,30]. They reduce the amount of substrate and prevent the symptoms that develop accordingly. Miglustat is approved for patients with mild to moderate GD1 who cannot undergo enzyme therapy and also for the small group of patients for whom enzyme therapy is unsuitable due to adverse events or venous access problems [31]. The role of splenectomy has decreased with the availability of enzyme replacement therapy. Some studies have shown that total splenectomy worsens bone findings in GD [32]. Bone marrow transplantation offer the potential of cure, but no clinical trials to date have assessed its safety and efficacy in comparison to enzyme replacement therapy or substrate reduction therapy [33].

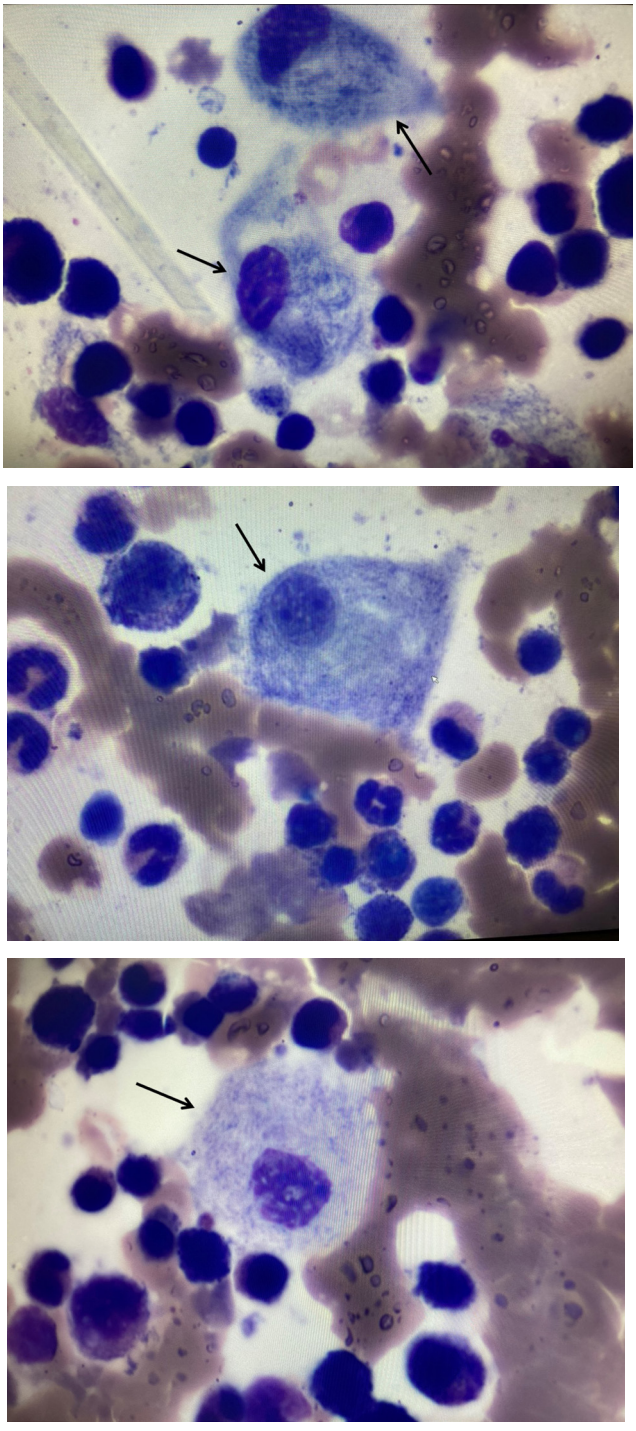

Figure 1. Bone marrow aspirate showing a number of large macrophages laden with cerebrosides (arrows: Gaucher cells) in a patient with Gaucher disease.

Conclusion

Gaucher disease is a rare but treatable metabolic disease. High levels of suspicion are necessary for early diagnosis as this disease may present with different clinical findings. Early treatment will be beneficial in preventing irreversible complications.

Authorship Contributions

Concept: G.N.Ö.; Design: G.N.Ö., E.G.; Literature Search: E.G.; Writing: G.N.Ö.

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