Introduction

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

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.
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.

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 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% |

| 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- and monoclonal gammopathy                       |

| 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].

**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.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

**References**

1. Grabowski GA. Gaucher disease: gene frequencies and genotype/phenotype correlations. Genet Test 1997;1:5-12.
2. Biegstraaten M, van Schaik IN, Aerts JM, Hollak CE. 'Non-neuronopathic' Gaucher disease reconsidered. Prevalence of neurological manifestations in a Dutch cohort of type I Gaucher disease patients and a systematic review of the literature. J Inherit Metab Dis 2008;31:337-349.
3. Sidransky E. New perspectives in type 2 Gaucher disease. Adv Pediatr 1997;44:73-107.
4. Mistry PK, Sadan S, Yang R, Yee J, Yang M. Consequences of diagnostic delays in type 1 Gaucher disease: the need for greater awareness among hematologists-oncologists and an opportunity for early diagnosis and intervention. Am J Hematol 2007;82:697-701.
5. Thomas AS, Mehta A, Hughes DA. Gaucher disease: haematological presentations and complications. Br J Haematol 2014;165:427-440.
6. Linari S, Castaman G. Hematological manifestations and complications of Gaucher disease. Expert Rev Hematol 2016;9:51-58.
7. Charrow J, Andersson HC, Kaplan P, Kolodny EH, Mistry P, Pastores G, Rosenbloom BE, Scott CR, Wappner RS, Weinreb NJ, Zimran A. The Gaucher
1. Alfonso F, Aznarez S, Giralt M, Pocovi M, Giraldo P; Spanish Gaucher's Disease Registry. Mutation analysis and genotype/phenotype relationships of Gaucher disease patients in Spain. J Hum Genet 2007;52:391-396.

2. Alpan O, Tayebi N, Gayfullin NM, Schwartz DE, Samokhodskaya LM, Kost A, Özdemir G.N., and Gündüz E.: Gaucher Disease. Turk J Hematol 2022;39:136-139.

3. Baris HN, Cohen UJ, Mistry PK. Gaucher disease: the metabolic defect, pathophysiology, phenotypes and natural history. Pediatr Endocrinol Rev 2014;12(Suppl 1):72-81.

4. Miller A, Brown LK, Pastores GM, Desnick RJ. Pulmonary involvement in type 1 Gaucher disease: functional and exercise findings in patients with and without clinical interstitial lung disease. Clin Genet 2003;63:368-376.

5. Danilov SM, Tikhomirova VE, Metzger R, Naperova IA, Bukina TM, Goker-Alpan O, Tayebi N, Gayfullin NM, Schwartz DE, Samokhodskaya LM, Kost OA, Sidsinsky E. ACE phenotyping in Gaucher disease. Mol Genet Metab 2018;123:501-510.

6. van Dussen L, Hendriks EJ, Groenew JJ, Boot RG, Hollak CE. Plasma lipids in Gaucher disease: potential pathophysiological implications. Blood Rev 2016;30:431-437.

7. Elstein D, Mellgard B, Dinh Q, Lan L, Qiu Y, Cozma C, Böttcher T, Zimran A. Reductions in glycosylphosphatidylinositol (glyco-Gb1) in treatment naïve and previously treated patients receiving velaglucerase alfa for type 1 Gaucher disease: data from phase 3 clinical trials. Mol Genet Metab 2017;122:113-120.

8. Herrera D, Monaga M, Campos D, Pampín Y, González EC, Lavaut K. Ultramicro-fluorimetric assay for the diagnosis of Gaucher disease in dried blood spots on filter paper. J Neonatal Perinatal Med 2013;6:61-67.

9. Yoshida S, Kido J, Matsumoto S, Momosaki K, Mitsuhashi H, Shimazu T, Sugawara K, Endo F, Nakamura K. Prenatal diagnosis of Gaucher disease using next-generation sequencing. Pediatr Int 2016;58:946-949.

10. Dahl N, Lagerström M, Erikson A, Pettersson U. Gaucher disease type III (Norrbottnian type) is caused by a single mutation in exon 10 of the glucocerebrosidase gene. Am J Hum Genet 1990;47:275-278.