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Thrombocytopenia associated with galsulfase treatment

Murat Doğan[1], Yasar Cesur[2], Erdal Peker[3], Ahmet F Oner[4] and Sekibe Zehra Dogan[3]

Abstract

Mucopolysaccharidosis type VI (MPS VI), or Maroteaux-Lamy syndrome, is a lysosomal storage disorder that results from a deficiency of the enzyme *N*-acetylgalactosamine-4-sulfatase or arylsulfatase B (ASB). It is a relatively rare disorder, with an estimated incidence of 1 in 248,000 to 1 in 300,000. The diagnosis is made on the basis of findings of elevated urine glycosaminoglycans and a deficiency of ASB activity in leukocytes or cultured fibroblasts. In treatment of MPS VI, enzyme replacement therapy (galsulfase; human recombinant ASB enzyme) became available. Infusions of galsulfase were generally well tolerated. But in some patients, infusion-associated reactions including rash, urticaria, headache, hypotension, nausea, and vomiting were documented and were managed successfully by interrupting or slowing the rate of infusion and/or by the administration of antihistamines, antipyretics, corticosteroids, or oxygen. Here, we report a case with MPS VI who developed thrombocytopenia after third dose of therapy. To the best of our knowledge, this is the first report about thrombocytopenia associated with galsulfase therapy in the literature. Additionally, with this report, we want to share our approach for this case.

Keywords

mucopolysaccharidosis type VI, galsulfase therapy, thrombocytopenia

Introduction

Mucopolysaccharidosis type VI (MPS VI; Maroteaux-Lamy syndrome) is a lysosomal storage disorder that results from a deficiency of the enzyme *N*-acetylgalactosamine-4-sulfatase or arylsulfatase B (ASB). It is a relatively rare disorder, with an estimated incidence of 1 in 248,000 to 1 in 300,000.[1] The diagnosis is made on the basis of findings of elevated urine glycosaminoglycans and a deficiency of ASB activity in leukocytes or cultured fibroblasts.[2,3] The majority of patients present in childhood with hepatosplenomegaly, coarse facial features, corneal clouding, and dysostosis multiplex.[3] Until recently, treatment for MPS VI has mainly involved symptom management. In May 2005, enzyme replacement therapy (ERT) became available for the treatment of MPS VI with the approval of the human recombinant ASB enzyme (galsulfase [Naglazyme, BioMarin Pharmaceutical Inc, Novato, California]) by the US Food and Drug Administration). Infusions of galsulfase were generally well tolerated. But in some patients, infusion-associated reactions including rash, urticaria, headache, hypotension, nausea, and vomiting were determined and were managed successfully by interrupting or slowing the rate of infusion and/or by the administration of antihistamines, antipyretics, corticosteroids, or oxygen.[1,3]

Here, we report a case with MPS VI who developed thrombocytopenia after third dose of therapy. To the best of our knowledge, this is the first report about

[1] Department of Pediatrics, Division of Pediatric Endocrinology, School of Medicine, Yuzuncu Yil University, Van, Turkey
[2] Department of Pediatrics, Division Pediatric Endocrinology and Metabolism, School of Medicine, Yuzuncu Yil University, Van, Turkey
[3] Department of Pediatrics, School of Medicine, Yuzuncu Yil University, Van, Turkey
[4] Department of Pediatrics, Division Pediatric Hematology, School of Medicine, Yuzuncu Yil University, Van, Turkey

Corresponding author:
Murat Doğan, Hafiziye Mahallesi, K Karabekir Caddesi, Araştırma Hastanesi Arkası, Uğur Sitesi, D blok 4, kat No 9, 65100 Van, Turkey
Email: doganmurat.md@gmail.com

thrombocytopenia associated with galsulfase therapy in the literature.

Case report

A 5-year-old boy was admitted to our pediatric endocrinology and metabolism outpatient clinic due to macroglossia, growth failure, and difficulty on respiration. The patient was a term, normal-sized male infant, born to a no consanguineous Turkish couple after an uncomplicated pregnancy. In his history, thoracal kyphosis had been observed by his family when 7 months old. He had begun to sit at 1 year, to walk at 18 months, and to talk at 4 years. He could eat only liquid or mashed food. In family history, it was learnt that he had a cousin who had similar symptoms and signs like him. On physical examination, he was noted to have coarse facial features, abundant scalp hair, posteriorly rotated ears, a prominent nose, congestion with noisy breathing, a short neck, a liver edge palpable 4 to 5 cm below the right costal margin, a spleen edge palpable 4 cm below the left costal margin, spade-like hands and feet, thoracal gibbous deformity, and restricted joint mobility. His weight and height was 15 kg (between 3 and 10 percentile) and 89.7 cm (−4.4 standard deviation score (SDS)), respectively. Blood chromosome analysis revealed a normal 46,XY karyotype. He was cruising and walking independently and reportedly saying 10 clear words. The findings were suggestive of an MPS disorder, and the diagnosis of MPS VI was confirmed by demonstration of a deficiency of ASB activity in leukocytes (Arylsulfatase B: zero μmol/hour), an elevated urine glycosaminoglycans level, and dysostosis multiplex on skeletal survey. He had normal echocardiogram examination. Corneal clouding was noted during detailed ophthalmology examination. At 5 years 5 months of age, the patient began ERT with weekly infusions of galsulfase. He received the recommended dose of 1 mg/kg and premedication with diphenhydramine (1 mg/kg) 1 hour before the infusion. The initial infusion rates were those recommended by the manufacturer, with the typical infusion lasting 4 hours. The patient experienced no side effect during the first 3 weeks of treatment. The patient was routinely evaluated in detail before each dose infusion. Prior to third dose of treatment, the patient had no infection finding and the complete blood count examination revealed the following: hemoglobin, 14.2 g/dL; white blood cell, 10 $\times 10^9$ L^{-1}, Platelet, 325 $\times 10^9$ L^{-1}. During the third dose infusion, no adverse event was recorded. After his third infusion, thrombocytopenia (platelet count was measured as $50x10^9L^{-1}$) was recorded. Before and during thrombocytopenia, no infection and no drug-taking history except ERT were determined. Erythrocyte sedimentation rate was 12 mm/h and C-reactive protein was negative. Salmonella, brucella, hepatitis (hepatitis A, B, and C), and Ebstein-Bare virus, cytomegalovirus' serologies were negative. Additionally, lupus anticoagulants, antinuclear antibody, and anticardiolipin antibody immunoglobulin G (IgG) and immunoglobulin M (IgM) serologies were also negative. The examinations of parasitism in serum and gaita samples were performed in our patient, but we did not find any parasitic infection. On bone marrow examination, mildly increased megakaryocytic cells were observed. Antibody examination against thrombocyte or galsulfase was not performed due to lack of laboratory difficulties. The infusion dose was decreased to 0.5 mg/kg and given for 1 week. On follow up, thrombocyte count was getting to resolve and it was measured as 72 $\times 10^9$ L^{-1} 1 day after fourth dose, 92 $\times 10^9$ L^{-1} 3 days after, and 325 $\times 10^9$ L^{-1} 1 week after. The thrombocytopenia resolved 1 week after and the normal infusion dose (1 mg/kg/week) was restarted. The patient was 6 years old at the time of submission of this report and on the 24th week of follow up. There was no thrombocytopenic event.

Discussion

MPS VI, also known as Maroteaux-Lamy syndrome, is caused by the deficiency of *N*-acetylgalactosamine-4-sulfatase (arylsulfatase B, ASB). Clinical manifestations include distinctive facial features, skeletal dysplasia leading to short stature, joint contractures, and cardiopulmonary involvement. Patients have reduced exercise capacity and endurance, and limitations in joint range of motion.[1] Efficacy of galsulfase was demonstrated in the clinical trials by improved endurance in patients.[4-6] Very few serious adverse events occurred during the clinical trials.[3,5] The typical adverse events observed during infusion included rash, urticaria, headache, hypotension, nausea, and vomiting.[4-6] The other adverse reactions that were reported were confusional state, increased blood pressure, anemia, hypertension, conjunctivitis, pruritus, face edema, exanthema, abdominal pain, respiratory distress, cough, bronchos-

pasm, apnea, dyspnea, myalgia, pain, malaise, localized edema, infusion site pain, chest pain, and pyrexia.[1,3] In our patient, thrombocytopenia associated with enzyme therapy was determined after third dose of infusion. To the best of our knowledge, this is the first report about thrombocytopenia related to ERT.

Naglazyme is intended to provide an exogenous enzyme that will be taken up into lysosomes and increase the catabolism of GAG. Galsulfase uptake by cells into lysosomes is most likely mediated by the binding of mannose-6-phosphate-terminated oligosaccharide chains of galsulfase to specific mannose-6-phosphate receptors. Nearly all patients who receive treatment with Naglazyme develop antibodies to galsulfase.[7] The observed adverse events were noted as consistent with immune reactions expected with infused recombinant proteins.[1,3] The reactions were manageable and responded to interruption of the infusion and adjustment of the rate of infusion as well as to the administration of supplemental antihistamines and antiinflammatory agents such as ibuprofen and corticosteroids.[1] We think that thrombocytopenia associated with ERT can be related with immune reactions expected with infused recombinant proteins. In our patient, bone marrow examinations revealed normal heterogenic cellular screening except increased megakaryocytic cells. These findings support our hypothesis about immune-related thrombocytopenia. In our case report, the patients did not discontinue the therapy and was not given any additional therapy (intravenous immunoglobulin, steroid, or other therapies) for thrombocytopenia. However, ERT was given to them as half-dose (0.5 mg/kg/week) for only 1 week. After that, normal thrombocyte account was achieved. Although normal dose (1 mg/kg/week) was given to them afterwards, no thrombocytopenia has been recorded.

The laboratory findings of patients who had side effect associated with Galsulfase treatment revealed that anemia was the most common event reported; a total of four episodes were reported for 3 of 36 ERT patients. Two episodes of increased INR (blood clotting time) were reported for one patient. Single instances of decreased serum albumin, increased alkaline phosphatase, increased phosphorus, decreased potassium, decreased hemoglobin, decreased complement factor, abnormal INR, hyponatremia, hematuria, and proteinuria were also reported. None of these events were severe or serious adverse events.[8] All of the side effects associated with Galsulfase treatment, especially infusion-related reactions, complement depletion, proteinuria, hematuria or anemia was thought some immune related reactions. As well, in our case, we observed thrombocytopenia as a side effect, and no other cause that explains thrombocytopenia was found. Additionally, on bone marrow examination, increased megakaryocytic cell was seen. Therefore, we speculated that the cause of thrombocytopenia may be a result of immune-related reactions due to destruction of platelets. We did not give the patient steroid due to mild thrombocytopenia, which was measured as 50×10^9 L^{-1}. Immune-related thrombocytopenia is a common, acquired bleeding disorder in childhood period and it is a benign disease characterized by increased destruction of the circulating platelets and diagnosed by excluding the other thrombocytopenia reasons.[9,10]

In conclusion, we suggest that complete blood count examination should be performed in patients who received ERT because of thrombocytopenia, which can be observed during therapy, and when seen, giving the drug as half-dose can resolve this problem without needing any other therapies, like our case that had mild thrombocyteopenia.

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