HİTİT MEDICAL JOURNAL
HİTİT ÜNİVERSİTESİ TIP FAKÜLTESİ DERGİSİ

e-ISSN: 2687-4717 Cilt|Volume: 7 • Sayı|Issue: 2 - Haziran|June 2025

A Rare Cause of Splenomegaly: Acid Sphingomyelinase Deficiency Type B

Nadir Bir Splenomegali Nedeni: Asit Sfingomiyelinaz Eksikliği Tip B

Havva Demircioğlu[1] | Sinan Demircioğlu[2]

[1]Meram Family Health Center No. 25, Konya, Türkiye
[2]Necmettin Erbakan University, Faculty of Medicine, Department of Hematology, Konya, Türkiye

Sorumlu Yazar | Correspondence Author
Havva Demircioğlu
havvademircioglumd@gmail.com
Address for Correspondence: Meram Family Health Center No. 25, 42090, Konya, Türkiye.

Makale Bilgisi | Article Information
Makale Türü | Article Type: Vaka Sunumu / Case Report
Doi: https://doi.org/10.52827/hititmedj.1624724
Geliş Tarihi | Received: 22.01.2025
Kabul Tarihi | Accepted: 26.03.2025
Yayım Tarihi | Published: 23.06.2025

Atıf | Cite As
Demircioğlu H, Demircioğlu S. A Rare Cause of Splenomegaly: Acid Sphingomyelinase Deficiency Type B. Hitit Medical Journal 2025;7(2):295-300. https://doi.org/10.52827/hititmedj.1624724

Hakem Değerlendirmesi: Alan editörü tarafından atanan en az iki farklı kurumda çalışan bağımsız hakemler tarafından değerlendirilmiştir.
Etik Beyanı: Gerek yoktur.
İntihal Kontrolleri: Evet (iThenticate)
Çıkar Çatışması: Yazarlar çalışma ile ilgili çıkar çatışması beyan etmemiştir.
Şikayetler: hmj@hitit.edu.tr
Katkı Beyanı: Fikir/Hipotez: HD, SD Tasarım: HD Veri Toplama/Veri İşleme: HD, SD Veri Analizi: HD, SD Makalenin Hazırlanması: HD
Hasta Onamı: Hastadan yazılı aydınlatılmış onam ve yayın onamı alınmıştır.
Finansal Destek: Bu çalışma ile ilgili herhangi bir finansal kaynaktan yararlanılmamıştır.

Peer Review: Evaluated by independent reviewers working in the at least two different institutions appointed by the field editor.
Ethical Statement: Not applicable.
Plagiarism Check: Yes (iThenticate)
Conflict of Interest: The authors declared no conflicts of interest
Complaints: hmj@hitit.edu.tr
Authorship Contribution: Idea/Hypothesis: HD, SD Design: HD Data Collection/Data Processing: HD, SD Data Analysis: HD, SD Manuscript Preparation: HD
Informed Consent: Written informed consent and consent for publication was obtained from the patient.
Financial Disclosure: There are no financial funds for this article.

A Rare Cause of Splenomegaly: Acid Sphingomyelinase Deficiency Type B

ABSTRACT

Acid Sphingomyelinase Deficiency is a rare, autosomal recessive inherited metabolic disorder caused by mutations in the SMPD1 gene. It is a pan-ethnic, multisystemic, often progressive, and potentially life-limiting condition, with an age of onset ranging from the first days of life to adulthood. Acid Sphingomyelinase Deficiency results from a deficiency of the enzyme acid sphingomyelinase. In Acid Sphingomyelinase Deficiency type B patients, hepatosplenomegaly and pulmonary pathological changes are frequently observed; however, central nervous system involvement is usually absent. The rarity of the disease and the lack of expertise often lead to misdiagnosis, delayed diagnosis, and limited access to adequate care. In recent years, enzyme replacement therapy with olipudase alfa, which provides an exogenous source of acid sphingomyelinase, has been introduced for children and adults diagnosed with Acid Sphingomyelinase Deficiency without central nervous system involvement, altering the course of the disease. In this case presentation, we aimed to emphasize the consideration of Acid Sphingomyelinase Deficiency in the etiology of splenomegaly.

Keywords: Acid Sphingomyelinase Deficiency, interstitial lung disease, Niemann-Pick disease, splenomegaly, thrombocytopenia.

ÖZET

Asit Sfingomiyelinaz Eksikliği, SMPD1 genindeki mutasyonlardan kaynaklanan nadir bir otozomal resesif geçiş gösteren, başlangıç yaşı yaşamın ilk günlerinden erişkinliğe kadar değişen, pan-etnik, çok nadir, multisistemik, çoğunlukla ilerleyici ve potansiyel olarak yaşamı sınırlayan bir metabolik hastalıktır. Asit Sfingomiyelinaz Eksikliği, asit sfingomiyelinaz enziminin yetersizliğinden kaynaklanır. Asit Sfingomiyelinaz Eksikliği tip-B hastalarda sıklıkla hepatosplenomegali ve akciğerlerde patolojik değişiklikler vardır, ancak genellikle santral sinir sistemi tutulumu yoktur. Hastalığın nadir görülmesi ve uzmanlık eksikliği, yanlış tanıya, teşhisin gecikmesine ve yeterli bakıma erişimin engellenmesine neden olmaktadır. Son yıllarda merkezi sinir sistemi tutulumu olmayan Asit Sfingomiyelinaz Eksikliği tanılı çocuk ve yetişkinlerde, hastalığın seyrini değiştiren, asit sfingomiyelinazın ekzojen bir kaynağını sağlayan bir enzim replasman tedavisi olan olipudaz alfa kullanıma girmiştir. Bu vaka sunumunda splenomegali etyolojisinde Asit Sfingomiyelinaz Eksikliğinin de göz önünde bulundurulmasını vurgulamak istedik.

Anahtar Sözcükler: Asit Sfingomiyelinaz Eksikliği, interstisyel akciğer hastalığı, Niemann-Pick hastalığı, splenomegali, trombositopeni.

Introduction

Acid Sphingomyelinase Deficiency (ASMD) type A and B were previously known as Niemann-Pick disease types A and B, respectively. ASMD-A and ASMD-B are disorders caused by pathogenic variants in the sphingomyelin phosphodiesterase-1 (SMPD1) gene and are characterized primarily by a deficiency in acid sphingomyelinase activity. Niemann-Pick disease type C (NPC) is caused by pathogenic variants in the NPC1 and NPC2 genes, which result in impaired cellular processing and transport of macromolecules, including low-density lipoprotein (LDL) cholesterol and glycosphingolipids (1).

Acid Sphingomyelinase Deficiency Type B typically has a later onset and is less severe than ASMD-A, with a good prognosis in terms of survival into adulthood (1). It is present in all populations worldwide. The overall prevalence of ASMD (types A and B combined) is estimated to be 1 in 250,000 (2). ASMD-B is characterized by the development of hepatosplenomegaly in infancy or childhood. Most affected patients have thrombocytopenia due to hypersplenism. Liver involvement can be severe, with infiltration of foamy histiocytes, ballooning of hepatocytes, and fibrosis observed (3). Other systemic findings include short stature due to delayed skeletal maturation, interstitial lung disease, hyperlipidemia, and ocular abnormalities (macular halos and cherry-red maculas) (4,5). The natural course of the disease is characterized by progressive hypersplenism and a gradual deterioration of lung function (6,7). Most patients with ASMD-B do not have neurological abnormalities. However, a small subset of patients who survive into early childhood may develop varying degrees of central nervous system symptoms, including prolonged nerve conduction velocities, cerebellar signs, cerebrospinal fluid involvement, extrapyramidal involvement, intellectual disability, psychiatric disorders, and peripheral neuropathy (8,9). In this case presentation, we aimed to highlight the importance of considering ASMD in patients with splenomegaly and/or interstitial lung disease.

Case Report

A 54-year-old female patient presented with complaints of shortness of breath, cough, and abdominal distension. It was noted that she had been diagnosed with interstitial lung disease 15 years ago. Ten years ago, splenomegaly was detected following the onset of abdominal swelling and early satiety. The family history revealed that her brother, who also had splenomegaly, passed away in his fifties due to a lung infection. The short-statured patient's physical examination revealed hepatosplenomegaly. When thrombocytopenia was added to these findings, the patient was referred to hematology by her family physician. Her laboratory results showed a leukocyte count of 3300/µL, a neutrophil count of 2340/µL, a lymphocyte count of 700/µL, hemoglobin of 12.6 g/dL, a platelet count of 110,000/µL, total cholesterol of 226.8 mg/dL, triglycerides of 347.8 mg/dL, VLDL cholesterol of 69.56 mg/dL, HDL cholesterol of 12.5 mg/dL, and LDL cholesterol of 144.74 mg/dL. An abdominal ultrasound revealed a liver size of 19.5 cm and a splenic longitudinal axis of 21 cm. High-resolution chest tomography showed increased aeration in the left lower lung, with a 2 cm-diameter thin-walled air cyst observed laterally in the anterobasal segment of the left lower lung. Widespread septal thickening was observed in both lungs. Bronchial wall thickening was noted, along with fibrotic densities extending from the peribronchial area to the pleura. Additionally, consolidation areas were observed in the anterior segment of the left upper lobe and in the basal region of the right lower lobe. Calcification was noted in the anterior segment of the right upper lobe. Sputum cytology revealed lipid-laden macrophages in 10% of all macrophages, with oil red staining, and the lipid load index was 20/400. Prussian blue staining revealed 5% hemosiderin-laden macrophages. Bone marrow biopsy showed PAS (+) benign histiocytic infiltration. These findings suggested a storage disease, prompting enzyme testing. Leukocyte sphingomyelinase enzyme activity was low (0.6 nmol/mg.17s), and plasma chitotriosidase enzyme activity was elevated (352.8 µmol/L.hr). Heterozygous pathogenic variants were identified in the SMPD1 gene. Ocular examination revealed a normal macula. The patient was diagnosed with Acid Sphingomyelinase Deficiency Type B.

Discussion

In the presence of clinical features such as hepatosplenomegaly, thrombocytopenia, interstitial

lung disease, and hyperlipidemia, ASMD-B should be suspected. In ASMD-B patients, central nervous system involvement is typically absent, but hepatosplenomegaly (HSM) and signs of liver failure are commonly observed. Splenomegaly is the most frequent initial finding in ASMD-B, occurring in 78% of patients (10). The enlargement of the spleen is caused by widespread infiltration of lipid-laden macrophages, which gives rise to the "foam cell" appearance, a distinctive pathological feature suggestive of ASMD or other lysosomal storage disorders (11). Other laboratory abnormalities may include liver dysfunction, decreased HDL cholesterol, hypertriglyceridemia, and elevated LDL cholesterol levels (12).

The diagnosis of acid sphingomyelinase deficiency, including ASMD-A or ASMD-B, is confirmed in a clinical context when both alleles of the SMPD1 gene responsible for the disease are identified through molecular genetic testing, or when the residual acid sphingomyelinase activity in peripheral blood leukocytes or cultured skin fibroblasts is less than 10% of the control values (1, 13). ASMD-B is associated with pathogenic variants of the SMPD1 gene. In our patient, an SMPD1 mutation has also been detected. There is some residual activity of the SMPD1 enzyme present in this condition (14). For example, in two studies, acid sphingomyelinase activity in ASMD-B patients was found to be 4% of normal levels, compared to undetectable activity in ASMD-A patients (14, 15). In both ASMD-A and ASMD-B patients, the liver, spleen, lymph nodes, adrenal cortex, airways, and bone marrow are filled with lipid-laden cells. In the bone marrow of ASMD patients, foamy macrophages ("Niemann-Pick" cells) and/or typical "Prussian blue histiocytes" can be observed (16).

In ASMD-B patients, lung involvement can be detected on direct chest radiographs and/or high-resolution computed tomography (HRCT). On HRCT, parenchymal involvement with a reticulonodular pattern, accompanied by interlobular septal thickening, ground-glass opacities, and pulmonary nodules (sometimes calcified) under 1 cm in size, may be observed (17, 18). In our patient's lungs, increased aeration, an air cyst, widespread septal thickening, bronchial wall thickening, fibrotic densities extending from the peribronchial area to the pleura, and calcifications were observed. MRI or CT can be used to calculate liver and spleen volumes. Particularly in splenic imaging, evaluating the accumulated material may benefit from being visible at low resolution on CT or presenting as low echogenicity on ultrasound (USG) (17). In ASMD-B patients, it is important to assess bone age and evaluate for osteopenia/osteoporosis. Dual-energy X-ray absorptiometry (DEXA) is particularly useful in the assessment of osteoporosis (19).

The previously reported case was diagnosed at the age of 41. In this case, the diagnosis was made at the age of 54, which is older compared to the previous case. Similar to the other case, this patient also had splenomegaly, interstitial lung disease, and thrombocytopenia (16).

For patients with ASMD-B, recommended surveillance includes periodic assessments (every 6 to 12 months) of growth and height in children, weight, nutrition, changes in activity levels, bleeding, shortness of breath, abdominal pain, and neurological function in patients of all ages (1). Simultaneously, platelet count, liver enzymes, fasting lipid profile, pulmonary function tests, chest radiography, and skeletal assessment with dual-energy X-ray absorptiometry (DXA) should be monitored (1).

There is currently no curative treatment for patients with ASMD. Experimental therapies, such as bone marrow transplantation, total lung lavage, and amniotic cell transplantation, are being investigated. However, there is insufficient data regarding the short- and long-term outcomes in terms of the risk-benefit ratio (20). Symptomatic pulmonary disease in ASMD-B patients may benefit from supplemental oxygen. Severe bleeding due to thrombocytopenia may require transfusion of blood products. In adults with hyperlipidemia, treatment is recommended to correct elevated total cholesterol levels. In patients with splenomegaly, avoiding contact sports is advised (1).

In acid sphingomyelinase deficiency, enzyme replacement therapy with olipudase alfa, which provides an exogenous source of acid sphingomyelinase, is recommended for both children and adults. Olipudase alfa is a recombinant human acid sphingomyelinase (ASM) being developed to address the symptoms of

ASM deficiency outside the central nervous system. In a placebo-controlled, randomized clinical trial, 36 adult ASMD patients were randomly assigned to receive either olipudase alfa or a placebo in a 1:1 ratio. After one year, olipudase alfa treatment resulted in a greater increase in the predicted mean diffusion capacity of the lungs for carbon monoxide (DLCO) (22% compared to 3% in the placebo group) and a greater reduction in spleen volume (39% decrease compared to a 0.5% increase in the placebo group) and liver volume (28% decrease compared to a 1.5% reduction in the placebo group) (21). In an open-label study involving 20 pediatric ASMD patients, one-year results showed that olipudase alfa treatment was associated with a mean increase of 33% in the expected DLCO (diffusion capacity of the lungs for carbon monoxide) in patients who were able to undergo the test, as well as a reduction in average spleen volume and liver volume, each by more than 40% (22). In August 2022, the U.S. Food and Drug Administration (FDA) approved olipudase alfa for the treatment of symptoms outside the central nervous system in ASMD, the underlying cause of both ASMD-A and ASMD-B.

In conclusion, ASMD-B is one of the rare causes of splenomegaly. Due to its rarity, diagnosis may not be made until later ages, as seen in our patient. Patients with unexplained splenomegaly, interstitial lung disease, short stature, thrombocytopenia, and low HDL levels should be evaluated for ASMD-B. Recent advances in treatment offer hope for reducing disease progression and improving symptoms.

References

1. Wasserstein MP, Schuchman EH. Acid sphingomyelinase deficiency. GeneReviews 2023, Adam MP, Feldman J, Mirzaa GM, et al (Eds.), University of Washington, Seattle. Available at: https://www.ncbi.nlm.nih.gov/books/NBK1370/ (Accessed on March 12, 2024).

2. Meikle PJ: Prevalence of Lysosomal Storage Disorders. JAMA 1999;281:249

3. Takahashi T, Akiyama K, Tomihara M et al. Heterogeneity of liver disorder in type B Niemann-Pick disease. Hum Pathol 1997;28:385–388

4. Wasserstein MP, Larkin AE, Glass RB et al. Growth restriction in children with type B Niemann-Pick disease. J Pediatr 2003;142:424–428

5. Guillemot N, Troadec C, de Villemeur TB et al. Lung disease in Niemann–Pick disease. Pediatr Pulmonol 2007;42:1207–1214

6. Wasserstein MP, Desnick RJ, Schuchman EH et al. The Natural History of Type B Niemann-Pick Disease: Results From a 10-Year Longitudinal Study. Pediatrics 2004; 114:e672–e677

7. von Ranke FM, Pereira Freitas HM, Mançano AD et al. Pulmonary Involvement in Niemann–Pick Disease: A State-of-the-Art Review. Lung 2016;194:511–518

8. Wasserstein MP, Aron A, Brodie SE et al. Acid sphingomyelinase deficiency: Prevalence and characterization of an intermediate phenotype of Niemann-Pick disease. J Pediatr 2006;149:554–559

9. Obenberger J, Seidl Z, Pavlů H, et al. MRI in an unusually protracted neuronopathic variant of acid sphingomyelinase deficiency. Neuroradiology 1999;41:182–184

10. McGovern MM, Wasserstein MP, Giugliani R, et al. A Prospective, Cross-sectional Survey Study of the Natural History of Niemann-Pick Disease Type B. Pediatrics 2008;122:e341–e349

11. Schuchman EH, Desnick RJ Types A and B Niemann-Pick disease. Mol Genet Metab 2017;120:27–33

12. McGovern MM, Pohl-Worgall T, Deckelbaum RJ et al. Lipid abnormalities in children with types A and B Niemann Pick disease. J Pediatr 2004;145:77–81

13. van Diggelen OP, Voznyi Ya V, Keulemans JLM et al. A new fluorimetric enzyme assay for the diagnosis of Niemann–Pick A/B, with specificity of natural sphingomyelinase substrate. J Inherit Metab Dis 2005;28:733–741

14. Graber D, Salvayre R, Levade T Accurate Differentiation of Neuronopathic and Nonneuronopathic Forms of Niemann-Pick Disease by Evaluation of the Effective Residual Lysosomal Sphingomyelinase Activity in Intact Cells. J Neurochem 1994;63:1060–1068

15. Lagerberg JW, Salado-Jimena JA, Löf H et al. Evaluation of the quality of blood components obtained after automated separation of whole blood by a new multiunit processor. Transfusion (Paris) 2013;53:1798–1807

16. Demircioğlu S, Korkmaz C, Akay Çizmecioğlu H et al. Niemann-Pick Disease Type B Diagnosed in the Adulthood. Eastern Journal of Medicine 2018;23:322–324

17. Simpson WL, Mendelson D, Wasserstein MP et al. Imaging Manifestations of Niemann-Pick Disease Type B. American Journal of Roentgenology 2010;194:W12–W19

18. Mendelson DS, Wasserstein MP, Desnick RJ et al. Type B Niemann-Pick Disease: Findings at Chest Radiography, Thin-Section CT, and Pulmonary Function Testing. Radiology 2006;238:339–345

19. Wasserstein M, Godbold J, McGovern MM. Skeletal manifestations in pediatric and adult patients with Niemann

Pick disease type B. J Inherit Metab Dis 2013;36:123–127
20. Schuchman EH, Wasserstein MP. Types A and B Niemann-Pick Disease. Pediatr Endocrinol Rev 2016;13 Suppl 1:674–81
21. Wasserstein M, Lachmann R, Hollak C et al. A randomized, placebo-controlled clinical trial evaluating olipudase alfa enzyme replacement therapy for chronic acid sphingomyelinase deficiency (ASMD) in adults: One-year results. Genetics in Medicine 2022;24:1425–1436
22. Diaz GA, Jones SA, Scarpa M et al. One-year results of a clinical trial of olipudase alfa enzyme replacement therapy in pediatric patients with acid sphingomyelinase deficiency. Genetics in Medicine 2021; 23:1543–1550