Ro J Pediatr. 2024;73(4)
DOI: 10.37897/RJP.2024.4.11

Targeted screening for acid sphingomyelinase deficiency – a short guide to early diagnosis of a rare metabolic disease with available treatment

Raluca Maria Vlad

"Grigore Alexandrescu" Emergency Children's Hospital, Bucharest, Romania
UMF "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

ABSTRACT

Acid sphingomyelinase deficiency (ASMD) is a lysosomal storage disorder of sphingomyelin. It is a progressive, potentially fatal disease that affects the liver, spleen, bones, hematological system, and lungs. The incidence is 1 in 250,000 individuals, meaning that statistically, there are 75,900 people with ASMD in Romania. Up until end of November 2024, only 18 patients (15 children and 3 adults) have been diagnosed in our country. Since June 2024, enzyme replacement therapy (ERT) with Olipudase-alfa has been approved in Romania and is now available in accredited centers nationwide. All children diagnosed in Romania are currently undergoing treatment, two of them in the Pediatric Department of "Grigore Alexandrescu" Hospital, accredited within the ASMD subprogram of the National Rare Diseases Program of the Romanian Ministry of Health since November 2024.

Patients with persistent splenomegaly of undetermined etiology, hepato(spleno)megaly with short stature and dyslipidemia, persistent thrombocytopenia of undetermined etiology, recurrent bone pain as well as first- and second-degree relatives of patients diagnosed with sphingolipidoses are good candidates for screening. Dry spot testing can be performed free of charge at our center.

NPD is currently significantly underdiagnosed in Romania. A coherent screening program is essential to enable early diagnosis of a rare disease for which ERT is available in Romania and fully financially covered by the National Health Insurance House. Increasing awareness among clinicians about this rare disease will ensure success in achieving early treatment.

Keywords: acid sphingomyelinase deficiency, Niemann-Pick disease, enzyme replacement therapy, olipudase-alfa

Abbreviations

ASMD – Acid Sphingomyelinase Deficiency
ASM – Acid Sphingomyelinase enzyme
NPD – Niemann-Pick disease
NPA – Niemann-Pick disease type A
NPB – Niemann-Pick disease type B
NPA/B – Niemann-Pick disease type A/B
ERT – Enzyme replacement therapy
ILD – Interstitial lung disease
CNS – central nervous system
DBS – Dried Blood Spot
HSCT – Hematopoietic stem cell transplantation

BACKGROUND

Acid Sphingomyelinase Deficiency (ASMD), also known as Niemann-Pick disease (NPD) types A, A/B, and B is a rare, potentially fatal, inherited lysosomal storage disorder caused by deficiencies in specific enzymes implicated in lipids' metabolism, responsible for sphingomyelin breakdown. Sphingomyelin is a lipid commonly found in cell membranes and nerve cell axons. The disease is caused by pathogenic variants of the SMPD1 gene that encodes production of the enzyme Acid Sphingomyelinase (ASM) thus resulting in the accumulation of sphingomyelin and other lipids in various tissues, leading to progressive organ dysfunction [1-3].

Corresponding author:
Raluca Maria Vlad
E-mail: raluca.vlad@umfcd.ro

Article History:
Received: 2 December 2024
Accepted: 23 December 2024

Niemann-Pick Type A (NPA) results in accumulation of sphingomyelin primarily in the liver, spleen, and central nervous system. It is a severe neurodegenerative disorder that typically presents in infancy with hepatosplenomegaly, developmental regression, and neurologic deterioration, the patients rarely surviving beyond 2-3 years of age. Type B (NPB) involves the same enzyme deficiency, but with a much milder course, primarily affecting the liver and spleen without significant neurological involvement. This is the most prevalent form. Patients with NPB often survive into adulthood and up to 90% have normal mental status [1,2].

There is also NPD type C; Although bearing the same name, this is a different genetic disease which is not related to ASMD, but a deficient esterification of exogenous cholesterol, caused by mutations in the NPC1/NPC2 genes [1,2]. The clinical picture might be similar to NPA: progressive neurodegeneration, psychiatric symptoms, liver dysfunction, but typically presenting later in childhood or adolescence [4]. Type C NPD is not the subject of this article.

ASMD has multisystemic symptoms, the vast majority of patients having hepatosplenomegaly and lung disease. Splenomegaly is the most frequent finding (>90%) [3,5], followed by interstitial lung disease (>80%), hepatomegaly (>70%) [3,5]; more than half of patients exhibit thrombocytopenia, also delayed growth and start of puberty [3,5].

Screening and early diagnosis are vital for initiating therapy and improving long-term outcomes. Advances in genetic testing and biomarker identification have facilitated earlier diagnosis, although awareness among clinicians remains a challenge. Up until three years ago, ASMD had no cure. Enzyme replacement therapy (ERT) developed through recombinant DNA technology is now available [6]. Early detection through screening programs can help in starting ERT at an earlier stage, potentially modifying the disease course.

AIM

The incidence of ASMD is 1 in 250,000 individuals [7], so statistically, there are 75,900 Romanian people with ASMD. Up until end of November 2024, only 18 patients (15 children and 3 adults) have been diagnosed in our country. Since June 2024, ERT with Olipudase-alfa has been approved in Romania and is now available in accredited centers nationwide [8]. All children diagnosed in Romania are currently undergoing treatment, two of them in our Pediatric Department in "Grigore Alexandrescu" Hospital, accredited within the ASMD subprogram of the National Rare Diseases Program of the Romanian Ministry of Health.

This paper aims to provide a short review on a rare disease and to make the most frequent forms of presentation known to the medical community in order to increase awareness. Also the author provides information on our center's screening program through easy access free DBS testing and possibility to treat with ERT, thereby facilitating patient's access to early diagnosis and treatment.

DIAGNOSIS

The phenotype ASMD evolves alongside a large panel of clinical variety: the early-onset form (infantile neuro-visceral ASMD), classically named Niemann-Pick disease type A (NPA) and the later-onset (chronic visceral form of ASMD), Niemann-Pick disease type B (NPB). An intermediate phenotype is also described (chronic neuro-visceral ASMD) termed Niemann-Pick disease type A/B (NPA/B) [7].

Hepatomegaly is a common clinical manifestation and is seen in most ASMD patients. It often occurs alongside splenomegaly and is usually one of the first presenting clinical features [3,9]. Hepatosplenomegaly is obvious by age 2-4 months in untreated NPA; over time liver and spleen volumes become massive [3,7]. In NPA/B and B patients have enlarged and painful abdomen, hepatomegaly and develop liver fibrosis [9]. These patients are at greater risk of portal hypertension, variceal hemorrhage, cirrhosis and liver failure [10,11]. Clinical and imagistic features of hepatosplenomegaly in NPB and NPA/D are presented in figures 1 and 2 respectively. Liver enzymes are typically elevated early in the ASMD disease course (50-75% of patients) [3,11]. Atherogenic lipid profile analyses commonly shows dyslipidemia [9]. Liver disease is one of the leading mortality causes in NPB and NPA/B [12].

A classic cherry-red spot of the retinal macula develops in at least half, up to all patients with NPA [13], up to 25% of patients with NPB [14] and less than one third of patients with NPA/B [15,16]. Ocular cherry red spots are red-colored spots in the macula surrounded by retinal opacifications (macular halo), caused by accumulation of sphingolipid by-products in the cells of the retina [17]. ERT might not have any impact on ophthalmologic findings [7]. Figure 3 presents the cherry-red macular spot in one of the authors patients, NPA/B.

Pulmonary involvement affects a large majority of patients with ASMD. Interstitial lung disease (ILD) caused by sphingomyelin deposits in pulmonary macrophages results in frequent respiratory symptoms (recurrent infections, up to chronic restrrictive respiratory failure). NPB presents respiratory involvement later than NPA, plus the manifestations are less severe: rest or exercise dyspnea and reduced exercise tolerance, pulmonary hypertension [3,7,14,18]. In NPA/B and NPB, impaired O2/CO2

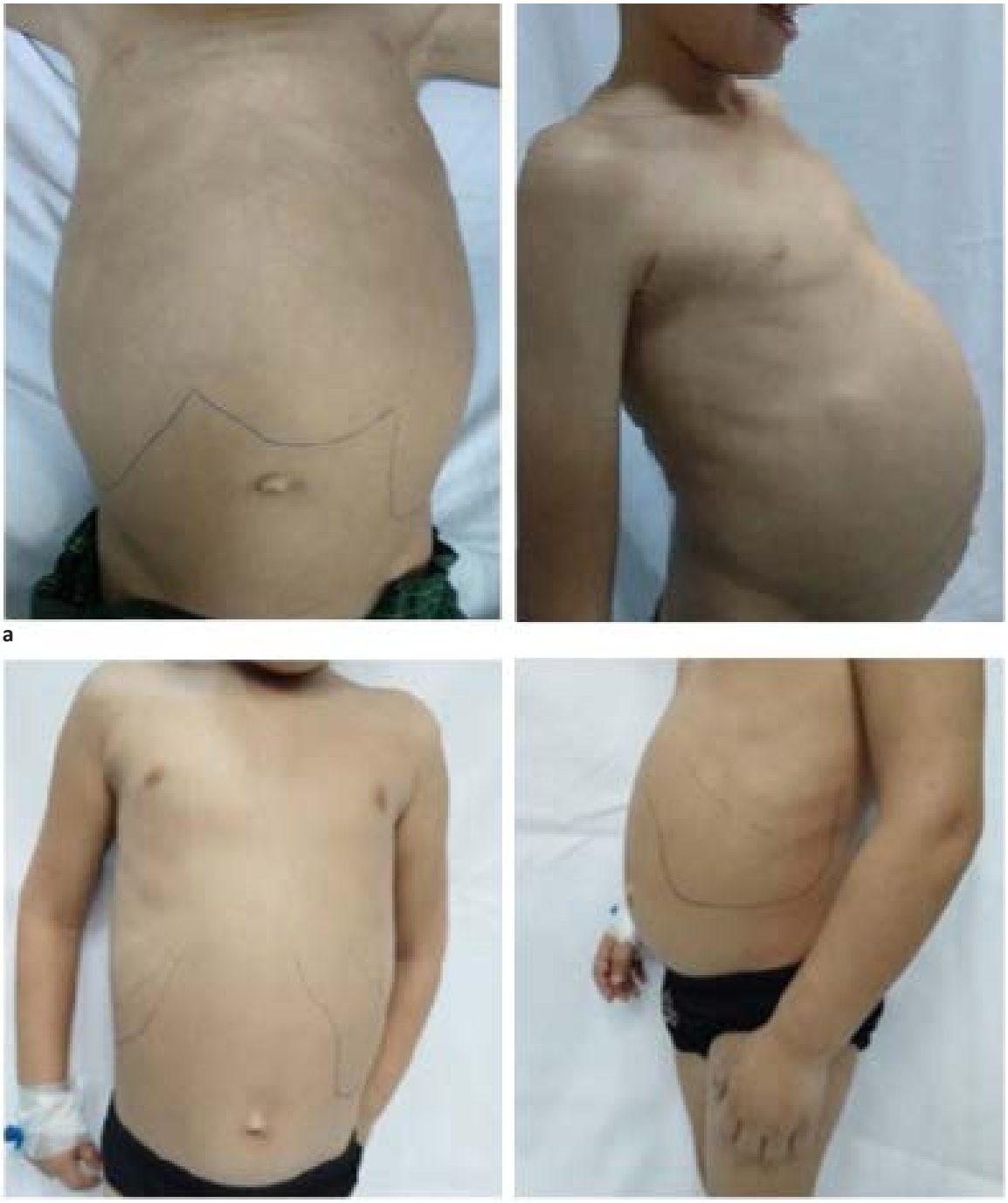
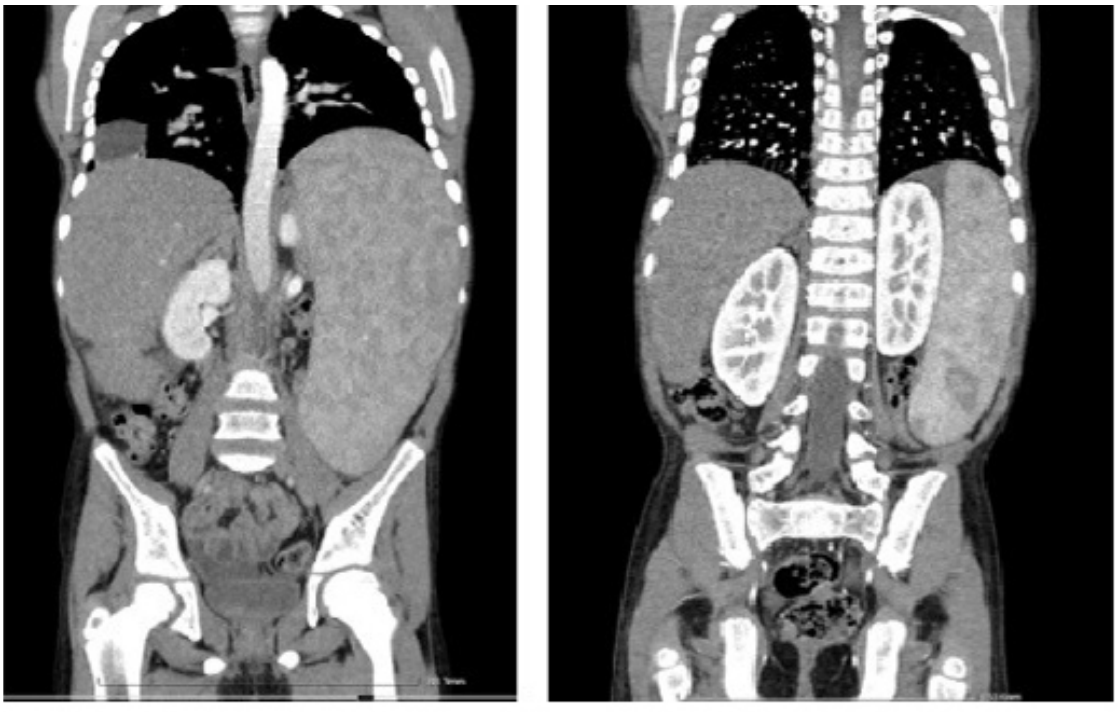


FIGURE 1. Clinical aspects of hepatosplenomegaly in NPD: a) 9 year-old patient with NPA/B presented for massive abdominal distention, fatigue and dyspnea; b) 4 year-old patient with NPB presented for splenomegaly (images from author's personal archive)

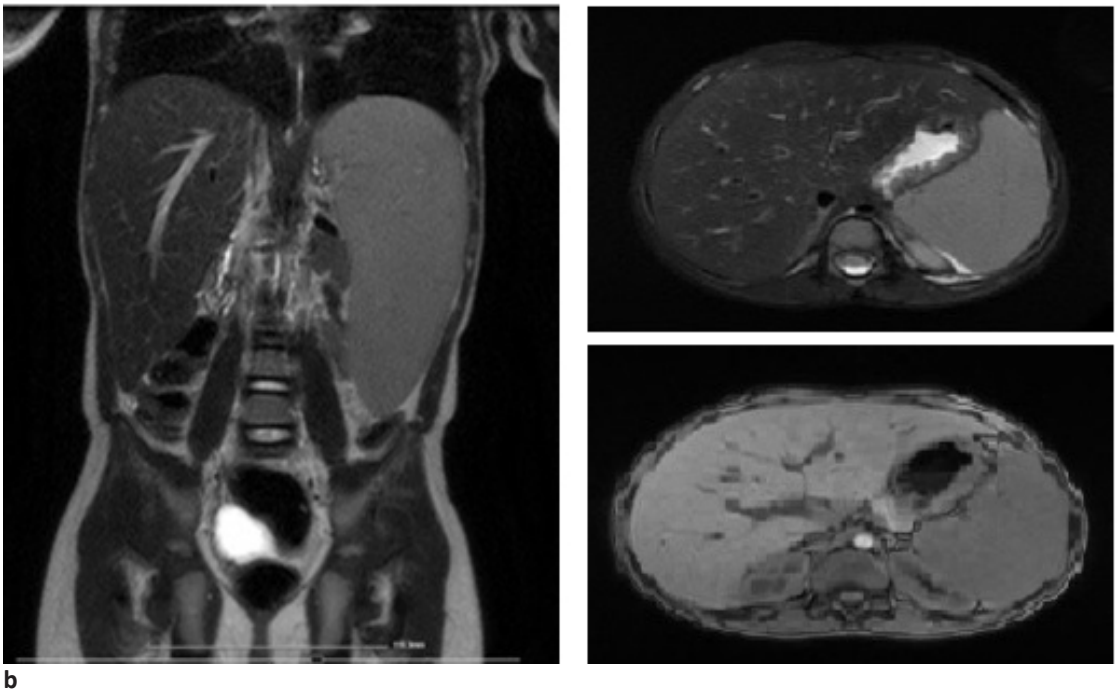
exchange is reflected by severe reductions in diffusion capacity (DLCO). Respiratory diseases are one of the leading mortality causes in ASMD [19]. Figure 4 depicts a representative transverse CT scan of mid-lung segments in an ASMD adolescent showing severe interstitial changes [19].

Hematologic manifestations are reported in nearly half of patients with NPA/B and B. Sphingomyelin-filled foam cells (Figure 5) are present in the bone marrow of NPA and NPB [14,20] and patients present with progressively lower hemoglobin levels, platelet and leukocyte counts [20]. Platelet count progressively decreases over time, especially in pediatric patients leading to bleeding becoming the third most common mortality cause in ASMD patients [21].

Skeletal disease and growth delays are reported in patients with NPA/B and NPB [21]. The numerous bone marrow foam-cells may contribute to the osteologic lesions; bone density [11]. Decreased bone density markers and strong inverse correlation between decreased lumbar spine bone mineral den-



a



b

FIGURE 2. Imagistic aspects of hepatosplenomegaly in NPD: a) Abdominal CT scan showing marked hepatosplenomegaly in a 9 year-old with NPA/B (Hepatic volume 2213 cm^3, splenic volume 2201 cm^3); b) Abdominal IRM revealing hepatosplenomegaly in a 6 years 5 months old patient with NPA/B (Hepatic volume 892,66 cm^3, splenic volume 486,11 cm^3) (images from author's personal archive)

sity and spleen volume has been identified in patients NPB [11]. Short stature and delayed bone age are frequent findings in children and adolescents with NPA/B or B, also joint and limb pain, as osteopenia and osteoporosis is in adults [11,21]. In NPA growth failure is obvious by 2 years [7].

Neurologic deterioration is progressive in NPA patients, infants exhibit hypotonia, muscle weakness and progressive loss of motor abilities from the first six months of life [7,13], psychomotor development stops at the approximate level of one year, after which neurologic deterioration is continuous and relentless; irritability and insomnia adds to the clinical picture [7,22]. Neurologic involvement is highly variable and heterogenous in type A/B: including ataxia, developmental delay, learning disabilities, peripheral neuropathy and psychiatric manifestations. NPB patients have little or no neuro-

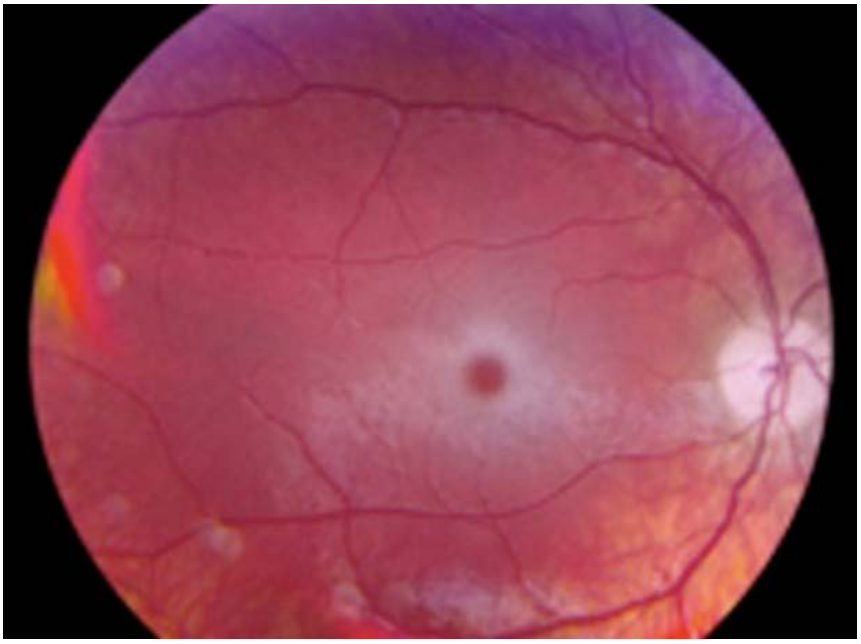


FIGURE 3. Cherry-red spot in 13-year old NPA/B patient (image from author's personal archive)

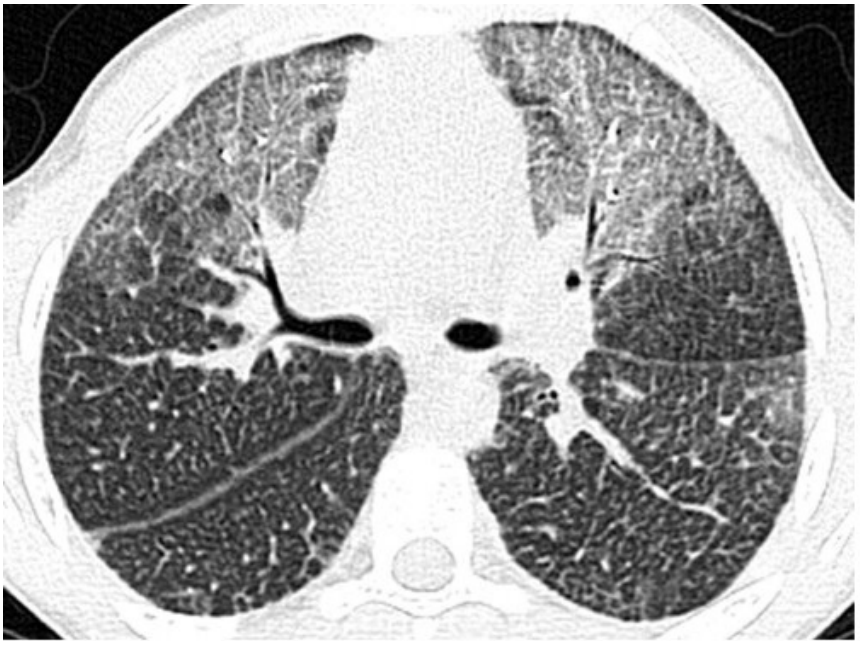


FIGURE 4. Ground-glass opacities, thickened interlobular septa and intralobular lines → "crazy paving" sign in a 16 year-old ASMD patient with normal pulmonary functional tests [19]

logic involvement. This neurologic feature may not be amenable to ERT [3,7].

In conclusion NPA results in hepatosplenomegaly, progressive and severe neurological and pulmonary involvement. In untreated NPB individuals, progressive hepatosplenomegaly results in gradual deterioration in liver function, ILD in gradual decrease of respiratory function tests, patients develop osteopenia and progressive atherogenic lipid profile alterations, but with no central nervous system (CNS) alterations. NPA/B patients have an intermediate clinical picture. The presentation of these individuals varies greatly, although all are characterized by the presence of some CNS symptoms. Survival to adulthood may occur in NPB and NPA/B, even when untreated [7].

The genetic diagnosis of ASMD consists of detecting double alleles pathogenic variants in SMPD1 gene. Molecular genetic testing confirms the diagnosis in patients with residual ASM activity less than 10% (peripheral blood lymphocytes or cultured skin fibroblasts) [6].

Clinical management and surveillance guidelines are published by ASMD expert panels in order to help clinicians develop good practice skills with this rare disease. Periodic assessments of nutritio-

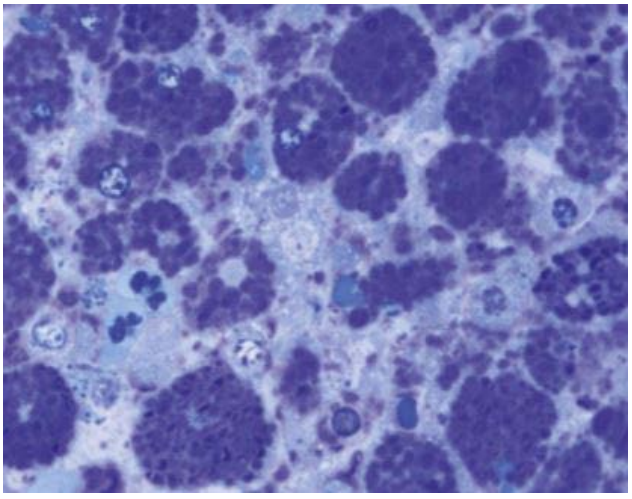


FIGURE 5. Typical "Niemann-Pick' cells (foam-cells due to sphingomyelin accumulation) crowding out the normal hematopoietic elements in the bone marrow of a deceased ASMD type A patient [20]

nal status and developmental milestones are required. Surveillance includes neurologic, hematologic and pulmonary symptoms, cardiac evaluation (electrocardiography (ECG) once every year; echocardiogram every two to four years), liver function tests, albumin levels, coagulation parameters, fasting lipid profile at least annually. Fatigue level, frequency and severity of abdominal pain, and/or frequency of bleeding symptoms should be assessed at least once every year. Ecographic or radiologic measurements of liver and spleen volumes should be done as needed. Clinically assess respiratory symptoms each visit; patients should undertake annual pulmonary function testing, chest radiograph every two to four years and CT scans of the lungs according to the results of the previously mentioned pulmonary clinical, functional and x-ray evaluation. Neurologic function and frequency of headaches shoul be carefully evaluated every year. Assess for limb pain at each visit, but bone mineral density should be evaluated every two to four years. Monitor psychoemotional and educational, occupational and physical therapy needs with every visit; also assess need for family support [7,9,11].

Newborn screening programs might be in the future a good healthcare plan to early diagnosis of ASMD [23].

Diagnosis of ASMD is extremely challenging, often delayed due to disease heterogeneity and frequent misdiagnoses (85%). Patients with NPB or NPA/B typically present with symptoms around 2 years of age. Reaching a diagnosis takes on average 3 years from symptom onset [24]. When the clinical suspicion is high, targeted screening might be the solution. Screening is safe and fast using Dried Blood Spot (DBS) cards. This simple and minimally invasive technique supplies enough sample for biochemical testing (enzyme activity and biomarker) and also genetic confirmation (gene mutation).

All forms of ASMD (NPA, NPA/B, and NPB) are autosomal recessive inherited diseases. When both parents are heterozygous for SMPD1 pathogenic variants, the offspring has a 25% risk of disease, 50% risk of being a carrier, 25% chance of being healthy and non-carrier. SMPD1 pathogenic variants identified in affected family members results in the recommendation of carrier testing for at-risk relatives and prenatal genetic testing. Biochemical prenatal diagnosis is possible by testing ASM activity [7].

Patients with: persistent splenomegaly of undetermined etiology, hepato(spleno)megaly with short stature and dyslipidemia, persistent thrombocytopenia of undetermined etiology, recurrent bone pain and also first- and second-degree relatives of patients diagnosed with sphingolipidoses are good candidates for screening. DBS testing for ASMD ia available free of charge in our center.

Treatment options

Olipudase-alfa is a recombinant human ASM, the first approved enzyme replacement treatment for the non-CNS manifestations of ASMD at any age. The molecule catalyses hydrolysis of sphingomyelin deposits in hepatocytes and macrophages from liver, spleen, lungs and bone marrow [6,9,25]. This drug does not cross the blood-brain barrier [26], it does not treat the neurocognitive issues in NPA or NPA/B, so it is indicated for NPB and NPA/B. As more individuals receive ERT for longer periods of time, the natural history of ASMD is likely to change [7]. ASCEND [27] and ASCEND-Peds [28] clinical trials certified olipudase-alfa efficacy on pulmonary function, spleen/liver volume, platelet number and height and has shown promise in slowing disease progression, especially in pediatric patients. It was approved in Japan under the SAKIGAKE designation on March 2022 for use in adult and pediatric patients with non-CNS manifestations of ASMD and has received a positive Committee for Medicinal Products for Human Use opinion in the European Union in June 2022 [9] and United States (August 2022), marking a significant advancement in managing this condition. Olipudase-alfa received orphan drug, fast track, breakthrough therapy, and priority review designations by the FDA [29]. Therapeutic benefits have not been documented in infantile neuro-visceral ASMD (NPA), the most severe form that is rapidly progressive and uniformly fatal in early childhood [6].

In August 2024, ERT with olipudase-alfa was approved in Romania for NPA/B and B [8]. In our center, two patients diagnosed with NPA/B and B respectively are receiving ERT since july 2024 with very good results and to this day no significant adverse outcomes. Initially Olipudase-alfa was recei-

ved through a humanitarian program and since December 2024 the medication is fully financed by the Romanian Ministry of Health Pediatric Department after accreditation of "Grigore Alexandrescu" Hospital within the ASMD subprogram of the National Rare Diseases Program [30].

Olipudase-alfa is well tolerated; mild infusion-associated reactions are the most common adverse events. A gradual dose escalation, followed by a maintenance phase, is recommended to reduce the risk of toxic sphingomyelin catabolites build up, transient liver cytolysis and infusion-associated reactions [31,32].

Diaz et al. published efficacy and safety results of ERT when former ASCEND-Peds patients completed 2 years of olipudase-alfa treatment. No new safety issues arose; the vast majority of adverse events were mild/moderate. Mean reductions in spleen/liver volumes were 61%/49%, respectively and mean percent-predicted-DLCO increased by 46.6%. Dyslipidemia and liver enzymes improved/normalized by 1 year and maintained a steady course. Height Z-scores improved in all ages (mean change 1.17) [33].

There are still challenges and limitations with Olipudase-alfa treatment at present: ERT is available only in a limited number of accredited centers nationwide, expertise regarding surveillance of treatment, adverse reactions and evolution of symptoms under ERT is limited to a handful of clinicians and last but not least the cost is very high, up to 30 000 euro per dose every fortnight for each patient.

ERT had a sustained positive impact in many domains that are deemed important to patients and families living with ASMD, but, despite the benefits of the enzyme in the management of non-neurological symptoms, there is still the unmet need to treat the neurologic manifestations of the disease [34]. Developing efficient molecules that cross within CNS must be a future goal for research. Hematopoietic stem cell transplantation (HSCT) can correct the metabolic defect, reduce liver and spleen volumes, improve blood counts, but does not stabilize neurologic disease. The morbidity and mortality associated with HSCT limit its use; it is likely to soon become obsolete now that ERT is readily available and efficient [7].

CONCLUSIONS

Acid sphingomyelinase deficiency represents a significant clinical challenge due to its rarity and complexity. However, with advancements in diagnostic tools and therapies, there is hope for better management and improved patient outcomes. There is still room for research on efficient treatments crossing the blood-brain barrier to address the neurological manifestations in the future

ASMD is currently significantly underdiagnosed in Romania. A coherent screening program is essential and will allow for early diagnosis of a rare disease for which efficient and safe enzyme replacement therapy is available in Romania and fully financially covered by the National Health Insurance House. Increasing awareness among clinicians about this rare disease will ensure success in achieving early treatment with better outcomes and increased quality of life and life expectancy.

The author declare that she have no competing interests.

The author declare they have no financial relationships to disclose concerning the content of this work, nor any other conflicts of interest.

REFERENCES

1. Ferreira CR, Gahl WA. Lysosomal storage diseases. *Transl Sci Rare Dis.* 2017;2(1-2):1-71. doi: 10.3233/TRD-160005. PMID: 29152458; PMCID: PMC5685203.
2. Schuchman EH, Desnick RJ. Types A and B Niemann-Pick disease. Mol Genet Metab. 2017;120(1-2):27-33. doi: 10.1016/j.ymgme.2016.12.008. Epub 2016 Dec 16. PMID: 28164782; PMCID: PMC5347465.
3. McGovern MM, Dionisi-Vici C, Giugliani R, Hwu P, Lidove O, Lukacs Z, Eugen Mengel K, Mistry PK, Schuchman EH, Wasserstein MP. Consensus recommendation for a diagnostic guideline for acid sphingomyelinase deficiency. *Genet Med.* 2017;19(9):967-74. doi: 10.1038/gim.2017.7 Epub 2017 Apr 13. PMID: 28406489; PMCID: PMC5589980
4. Vanier MT. Niemann-Pick disease type C. *Orphanet J Rare Dis.* 2010;5:16. doi: 10.1186/1750-1172-5-16. PMID: 20525256; PMCID: PMC2902432
5. Cox GF, Clarke LA, Giugliani R, McGovern MM. Burden of Illness in Acid Sphingomyelinase Deficiency: A Retrospective Chart Review of 100 Patients. *JIMD Rep.* 2018;41:119-29. doi: 10.1007/8904_2018_120. Epub 2018 Jul 12. PMID: 29995201; PMCID: PMC6122055.
6. Penon-Portmann M, Poskanzer SA, Ganesh J, Chang I, ACMG Therapeutics Committee4*documents@acmg.net. Olipudase alfa approved for pediatric and adult patients with acid sphingomyelinase deficiency (ASMD): A therapeutics bulletin of the American College of Medical Genetics and Genomics (ACMG). *Genet Med Open.* 2023;1(1):100780. doi: 10.1016/j.gimo.2023.100780. PMID: 39669258; PMCID: PMC11613600.
7. Wasserstein MP, Schuchman EH. Acid Sphingomyelinase Deficiency. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Amemiya A, eds. GeneReviews® [Internet]. Seattle (WA): University of Washington; 2006. p. 1993-2025. PMID: 20301544.
8. Annex of August 29, 2024, regarding the amendments to Annexes 1 and 2 of Ministerial Order No. 564/499/2021 on therapeutic protocols for medication prescriptions, published in the Monitorul Oficial (Sept. 5, 2024) (romanian).
9. McGovern MM, Avetisyan R, Sanson BJ, Lidove O. Disease manifestations and burden of illness in patients with acid sphingomyelinase deficiency (ASMD). *Orphanet J Rare Dis.* 2017;12(1):41. doi: 10.1186/s13023-017-0572-x. PMID: 28228103; PMCID: PMC5322625.
10. Thurberg BL, Wasserstein MP, Schiano T, O'Brien F, Richards S, Cox GF, McGovern MM. Liver and skin histopathology in adults with acid sphingomyelinase deficiency (Niemann-Pick disease type B). *Am J Surg Pathol.* 2012;36(8):1234-46. doi: 10.1097/PAS.0b013e31825793ff. PMID: 22613999; PMCID: PMC3396757.

11. Wasserstein M., Dionisi-Vici C., Giugliani R., et al. Recommendations for clinical monitoring of patients with acid sphingomyelinase deficiency (ASMD). *Mol Genet Metab.* 2019;126(2):98-105. doi: 10.1016/j.ymgme.2018.11.014
12. Cassiman D, Packman S, Bembi B, Turkia HB, Al-Sayed M, Schiff M, et al. Cause of death in patients with chronic visceral and chronic neurovisceral acid sphingomyelinase deficiency (Niemann-Pick disease type B and B variant): Literature review and report of new cases. *Mol Genet Metab.* 2016;118(3):206-13. doi: 10.1016/j.ymgme.2016.05.001. Epub 2016 May 11. Erratum in: Mol Genet Metab. 2018 Dec;125(4):360. doi: 10.1016/j.ymgme.2017.09.005. PMID: 27198631
13. Schuchman EH, Desnick RJ. Niemann-Pick Disease Types A and B: Acid Sphingomyelinase Deficiencies. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA. eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill Education; 2019. Chap. 144, p. 1-65.
14. McGovern MM, Wasserstein MP, Giugliani R, Bembi B, Vanier MT, Mengel E, et al. A prospective, cross-sectional survey study of the natural history of Niemann-Pick disease type B. *Pediatrics.* 2008;122(2):e341-9. doi: 10.1542/peds.2007-3016. Epub 2008 Jul 14. PMID: 18625664; PMCID: PMC2692309.
15. Pavlů-Pereira H, Asfaw B, Poupctová H, Ledvinová J, Sikora J, Vanier MT, Sandhoff K, Zeman J, Novotná Z, Chudoba D, Elleder M. Acid sphingomyelinase deficiency. Phenotype variability with prevalence of intermediate phenotype in a series of twenty-five Czech and Slovak patients. A multi-approach study. *J Inherit Metab Dis.* 2005;28(2):203-27. doi: 10.1007/s10545-005-5671-5. PMID: 15877209.
16. Hollak CE, de Sonnaville ES, Cassiman D, Linthorst GE, Groener JE, Morava E, Wevers RA, Mannens M, Aerts JM, Meersseman W, Akkerman E, Niezen-Koning KE, Mulder MF, Visser G, Wijburg FA, Lefeber D, Poorthuis BJ. Acid sphingomyelinase (Asm) deficiency patients in The Netherlands and Belgium: disease spectrum and natural course in attenuated patients. *Mol Genet Metab.* 2012;107(3):526-33. doi: 10.1016/j.ymgme.2012.06.015. Epub 2012 Jun 30. PMID: 22818240.
17. Chen H, Chan AY, Stone DU, Mandal NA. Beyond the cherry-red spot: Ocular manifestations of sphingolipid-mediated neurodegenerative and inflammatory disorders. *Surv Ophthalmol.* 2014;59(1):64-76. doi: 10.1016/j.survophthal.2013.02.005. Epub 2013 Sep 5. PMID: 24011710; PMCID: PMC3864975.
18. Faverio P, Stainer A, De Giacomi F, Gasperini S, Motta S, Canonico F, et al. Molecular Pathways and Respiratory Involvement in Lysosomal Storage Diseases. *Int J Mol Sci.* 2019;20(2):327. doi: 10.3390/ijms20020327. PMID: 30650529; PMCID: PMC6359090.
19. Mendelson DS, Wasserstein MP, Desnick RJ, Glass R, Simpson W, Skloot G, et al. Type B Niemann-Pick disease: findings at chest radiography, thin-section CT, and pulmonary function testing. *Radiology.* 2006;238(1):339-45. doi: 10.1148/radiol.2381041696. Epub 2005 Nov 22. PMID: 16304086.
20. Thurberg BL. Autopsy pathology of infantile neurovisceral ASMD (Niemann-Pick Disease type A): Clinicopathologic correlations of a case report. *Mol Genet Metab Rep.* 2020;24:100626. doi: 10.1016/j.ymgmr.2020.100626. PMID: 32714837; PMCID: PMC7371898.
21. McGovern MM, Wasserstein MP, Bembi B et al. Prospective study of the natural history of chronic acid sphingomyelinase deficiency in children and adults: eleven years of observation. *Orphanet J Rare Dis.* 2021;16(1):212. doi: 10.1186/s13023-021-01842-0
22. McGovern MM, Aron A, Brodie SE, Desnick RJ, Wasserstein MP. Natural history of Type A Niemann-Pick disease: possible endpoints for therapeutic trials. *Neurology.* 2006;66(2):228-32. doi: 10.1212/01.wnl.0000194208.08904.0c. PMID: 16434659.
23. Hickey RE, Baker J. Newborn screening for acid sphingomyelinase deficiency in Illinois: A single center's experience. *J Inherit Metab Dis.* 2024 Nov;47(6):1363-70. doi: 10.1002/jimd.12780. Epub 2024 Jul 11. PMID: 38992987; PMCID: PMC11586602
24. Doerr A, Farooq M, Faulkner C, Gould R, Perry K, Pulikottil-Jacob R, Rajasekhar P. Diagnostic odyssey for patients with acid sphingomyelinase deficiency (ASMD): Exploring the potential indicators of diagnosis using quantitative and qualitative data. *Mol Genet Metab Rep.* 2024;38:101052. doi: 10.1016/j.ymgmr.2024.101052. PMID: 38469089; PMCID: PMC10926222.
25. Keam S.J. Olipudase alfa: first approval. *Drugs.* 2022;82(8):941-7. doi: 10.1007/s40265-022-01727-x.
26. Aldosari M.H., de Vries R.P., Rodriguez L.R., et al. Liposome-targeted recombinant human acid sphingomyelinase: production, formulation, and in vitro evaluation. *Eur J Pharm Biopharm.* 2019;137:185-95. doi: 10.1016/j.ejpb.2019.02.019
27. 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. *Genet Med.* 2022;24(7):1425-36. doi: 10.1016/j.gim.2022.03.021
28. 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. *Genet Med.* 2021;23(8):1543-50. doi: 10.1038/s41436-021-01156-3
29. FDA approves first treatment for acid sphingomyelinase deficiency, a rare genetic disease. U.S. Food and Drug Administration. https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-acid-sphingomyelinase-deficiency-rare-genetic-disease
30. Monitorul Oficial, Partea I, numarul 1119 din 8 noiembrie 2024, capitolul IX, articolul 4, punctul 31, litera I; https://monitoruloficial.ro/Monitorul-Oficial--PI--1119--2024.html
31. Syed YY. Olipudase Alfa in Non-CNS Manifestations of Acid Sphingomyelinase Deficiency: A Profile of Its Use. *Clin Drug Investig.* 2023;43(5):369-377. doi: 10.1007/s40261-023-01270-x. Epub 2023 May 3. Erratum in: *Clin Drug Investig.* 2023;43(8):667. doi: 10.1007/s40261-023-01293-4. PMID: 37133675; PMCID: PMC10361862.
32. Wasserstein MP, Jones SA, Soran H, Diaz GA, Lippa N, Thurberg BL. Successful within-patient dose escalation of olipudase alfa in acid sphingomyelinase deficiency. *Mol Genet Metab.* 2015;116(1-2):88-97. doi: 10.1016/j.ymgme.2015.05.013. Epub 2015 May 30. PMID: 26049896; PMCID: PMC4561589.
33. Diaz GA, Giugliani R, Guffon N, Jones SA, Mengel E, Scarpa M, et al. Long-term safety and clinical outcomes of olipudase alfa enzyme replacement therapy in pediatric patients with acid sphingomyelinase deficiency: two-year results. *Orphanet J Rare Dis.* 2022;17(1):437. doi: 10.1186/s13023-022-02587-0. Erratum in: *Orphanet J Rare Dis.* 2023;18(1):55. doi: 10.1186/s13023-023-02647-z. PMID: 36517856; PMCID: PMC9749157.
34. Raebel EM, Wiseman S, Donnelly C, Mathieson T, Pountney J, Crowe J, Hopkin J. Real-life impacts of olipudase alfa: The experience of patients and families taking an enzyme replacement therapy for acid sphingomyelinase deficiency. *Orphanet J Rare Dis.* 2024;19(1):36. doi: 10.1186/s13023-024-03020-4. PMID: 38303068; PMCID: PMC10835881.