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ACID SPHINGOMYELINASE DEFICIENCY: A REVIEW

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ABSTRACT

Niemann-Pick disease (NPD)/ Acid Sphingomyelinase Deficiency (ASMD) is caused by deficiency of an enzyme acid sphingomyelinase (ASM) which leads to accumulation of sphingomyelin & other lipids in reticuloendothelial cells of various organs like liver, spleen, bone marrow, lymph node, brain, nerves and kidney. It is a lysosomal storage disease (LSD), caused by an autosomal recessive disorder that causes variation in sphingomyelin phosphodiesterase-1 (SMPD1). Overlap and the lack of some findings make the diagnosis very difficult. Diagnosis is crucial due to the multisystem involvement that this LSD can have. The disease is rare, untreatable with early manifestations and a poor prognosis, with newborns rarely surviving for 2–3 years.

KEYWORDS: Overlap and the lack of some findings make the diagnosis very difficult.

INTRODUCTION

Niemann-Pick disease (NPD) is a lysosomal storage disease (LSD) caused by an autosomal recessive disorder resulting from variants in the sphingomyelin phosphodiesterase-1 (SMPD1) gene[1,2], caused by acid sphingomyelinase deficiency (ASMD) enzyme, which catalyzes the hydrolysis of sphingomyelin (SM) to ceramide and phosphocholine.[3] This disease was described clinically for the first time by the pediatrician Albert Niemann in 1927.

Lysosomal storage diseases are characterized by inherited deficiencies of one or more lysosomal enzymes involved in the degradation of lipids and their products. NPD affects metabolism and the disorder is caused by genetic mutations. When both parents are carriers, there is 25% chance that their child will have the disease and 50% chance that a child will be a carrier.

When both parents are carriers of the abnormal gene, there is.

- a 1 in 4 chance that a child will have the disease
- a 1 in 2 chance that a child will be a carrier
- a 1 in 4 chance that a child will not have the disease and will not be a carrier.[4]

Symptoms may include.

- Ataxia (lack of muscle control during voluntary movements such as walking)
- Loss of muscle tone
- Brain degeneration
- Increased sensitivity to touch
- Spasticity (stiff muscles and awkward movement)
- Slurred speech
- Swallowing and feeding difficulties.[5]

The discovery of disease-specific biomarkers-cholestane-3β,5α,6β-triol (C-triol), trihydroxycholanic acid glycinate (TCG) and N-palmitoyl-O-phosphocholineserine [PPCS, initially referred to as lysosphingomyelin-509 (lysoSM-509)]-has led to development of non-invasive, blood-based diagnoses.[6]

The most common neurologic manifestations of NPD include cognitive or motor developmental delay in childhood-onset cases, vertical supranuclear gaze palsy, ataxia, dysarthria, dysphagia, and dystonia.[7] All types of Niemann-Pick Disease are autosomal recessive, which means that children with the disease have two copies of the abnormal gene. Each parent carries one copy of the abnormal gene without having any signs of the disease themselves. Siblings of the parents may also be carriers of the abnormal gene.[4]

The Niemann–Pick Disease (NPD) community, represented by the International Niemann–Pick Disease Alliance (INPDA), with support from the International Niemann–Pick Disease Registry (INPDR), has initiated and sponsored the development of comprehensive disease management guidelines to provide a resource for the multi-disciplinary team, and to support patients and

their primary professional caregivers on current diagnosis, treatment, monitoring and outcome measures for patients with ASMD.[8]

The NPC1 and NPC2 genes encode proteins that are central for regulation of cellular cholesterol homeostasis. NPC1 is a large transmembrane protein that resides in the limitin lysosome[9], whereas NPC2 is a small soluble lysosomal protein that binds cholesterol within the lysosomal lumen.[10]

Epidemiology

Reported epidemiological data is probably underestimated due to the misdiagnosis of the rare disorder that directly influences the impact of LSDs, such as Gaucher, Fabry, and Niemann Pick, among others in the community.[11] Niemann-Pick disease affects all segments of the population with cases reported in North America, South America, Europe, Africa, Asia, and Australia. However, a higher incidence of NPD has been found in certain populations.[4]

- Ashkenazi Jewish population (NPA and NPB)
- French Canadian population of Nova Scotia (Type D, now considered a variant of Type C or NPC)
- Maghreb region (Tunisia, Morocco, and Algeria) of North Africa (NPB)
- Spanish-American population of southern New Mexico and Colorado (NPC).[4]

Types of Niemann Pick Disease

In 1961 and 1966 the separate works of Allen Crocker and Roscoe Brady classified the disease into four types: A, B, C, and D in which deficiencies of lysosomal proteins cause improper intracellular lipid trafficking causing neurological impairment and death.[1, 2] Type E is a less common variant of NPD that develops in adulthood but this type is very rare.Niemann Pick Disease is classified into four subtypes.[12]

Niemann Pick Disease type A: classic infantile
Niemann Pick Disease type B: visceral
Niemann Pick Disease type C: subacute / juvenile
Niemann Pick Disease type D: Nova Scotian

Type A

People with NPA generally have little or no ASM production (less than 1% of normal) the most severe form, begins in early infancy and occurs most often in Jewish families. Additional symptoms include profound brain damage by six months of age and weakness. Children with this type rarely live beyond 18 months.[5]

Type A is known as infantile neurovisceral form with very low acid sphingomyelinase (ASM) activity and is usually fatal before the age of three. It affects younger children and results in neurological deficits and impaired growth.[7]

It usually presents in first few months of life with abdominal swelling, hepatosplenomegaly, feeding difficulties, loss of early motor skills, recurrent infections and irritability.[2] As age advances progressive loss of motor function, deterioration of intellectual capabilities and in final stage spasticity and rigidity occurs. Blood investigations show pancytopenia.

Type B

While those with NPB have approximately 10% of the normal level of ASM[4] also known as juvenile onset, usually occurs in the preteen years, with symptoms that include ataxia and peripheral neuropathy (nerve damage and disrupted signaling). The brain is generally not affected. In types A and B, insufficient enzyme activity causes the buildup of toxic amounts of sphingomyelin, a fatty substance present in every cell of the body. Children with type B may live a comparatively long time but may require supplemental oxygen because of lung impairment.[5]

Type B is less severe and is characterized by variable visceral symptoms and minimal neurological involvement. The most common visceral symptoms in these phenotypes include hepatosplenomegaly, thrombocytopenia, and interstitial lung disease.[7]

In contrast, NPD type B has variable clinical presentation. Jaundice and hepatosplenomegaly may be detected in early childhood in some patients but may remain barely noticeable in others. In adult life patients may present with pancytopenia & hepatosplenomegaly. Pulmonary involvement may be detected in the form of diffuse reticular or finely nodular lesions. Patients with lung lesions may present with dyspnea, decreased oxygen saturation and repeated life threatening bronchopneumonia or corpulmonale. Rarely involvement of retinal neurons (cherry red spots), CNS and skeletal system are noted. These patients are not affected intellectually. The life expectancy of NPD type B patients is highly variable depending on the severity of their symptoms.[13, 14]

Type C

It appears early in life or develops in the teen or adult years. It is caused by a lack of the NPC1 or NPC2 proteins. Neurological complications may include extensive brain damage that can cause an inability to look up and down, difficulty in walking and swallowing, and progressive loss of vision and hearing. Depending on severity, some individuals die in childhood while others live into adulthood.[5]

Niemann-Pick disease type C (NPC) has a heterogeneous clinical presentation and includes systemic, neurologic, and psychiatric involvement. It usually affects adults but can occur during any phase of life. Early-onset NPC manifests as infantile jaundice, hepatosplenomegaly, or isolated splenomegaly, and usually, these symptoms precede neurological involvement. In about 50% of adult patients, NPC can manifest without or with minimal hepatosplenomegaly, so the presence of isolated

splenomegaly in patients with neurological or psychiatric illnesses favors NPC.[7]

Niemann-Pick Type C (NPC) is very different than Type A or B (ASMD). NPC Patients are not able to metabolize cholesterol and other lipids properly within the cell. Consequently, excessive amounts of cholesterol accumulate within the liver and spleen and excessive amounts of other lipids accumulate in the brain. NPC causes a secondary reduction of ASM activity, which led all three types to be considered forms of the same disease.[4]

TYPE D

It involves a defect that interferes with movement of cholesterol between brain cells. It is now considered as variant of type C. PROGNOSIS: Infants with Type A die in infancy. Type B children live comparatively longer but require supplemental oxygen due to lung impairment (14). In Type C and Type D some patients die in childhood while others less affected may live up to adulthood.

Diagnosis

NPD cases are diagnosed by detection of Niemann Pick cells in aspiration or biopsy of bone marrow, liver and spleen. Diagnosis is confirmed by measuring ASM enzyme activity in peripheral leukocytes, cultured skin fibroblasts, chorionic villi and amniocytes. High performance liquid chromatography (HPLC) using plasma instead of leucocytes is a very reliable and highly sensitive technique to determine ASM activity for accurate diagnosis of NPD patients or carriers.[15]

A blood or bone marrow test can be done to diagnose type A and B. The test can reveal who has the disease, but does not show if one is a carrier then DNA tests can be done to diagnose carriers of type A and B.[16] The child's blood or bone marrow to measure the amount of ASM in white blood cells to diagnose type A and B of Niemann-Pick disease. This type of testing can help them determine whether child has the disease. DNA testing can also determine a carrier of the disease. Type C is usually diagnosed with a skin biopsy stained with a special stain. Once a sample is taken, laboratory scientists will analyze how skin cells grow, as well as how they move and store cholesterol. Doctor may also use DNA testing to look for the genes that cause type C.[17]

A skin biopsy is usually done to diagnose type C and C1. The health care provider watches how the skin cells grow, move, and store cholesterol. DNA tests may also be done to look for the 2 genes that cause this type of the disease.[16]

Other tests might include

- Bone marrow aspiration
- Liver biopsy (usually not needed)
- Slit-lamp eye exam
- Tests to check level of ASM[16]

Sphingomyelinase (nmol/hr/mg)	Remarks
>3	Normal activity
1.5-3	Possibility of carrier state likely
<1.5	Deficient activity

Pathophysiology

ASMD is inherited as an autosomal recessive trait that results from the reduced activity of acid sphingomyelinase due to loss-of-function variants in SMPD1, the gene encoding ASM.[18] To date, over 250 SMPD1 variants have been described in ASMD patients that result in a wide range of clinical phenotypic severity.[19] Carrier individuals who inherit only one pathogenic SMPD1 allele will be clinically normal. If two carrier individuals have children, each offspring has a 1:4 chance of being affected. There is some evidence indicating that SMPD1 may be paternally imprinted (preferentially expressed from the maternal chromosome), but it is not known if this has any impact on the ASMD phenotype.[20]

Niemann-Pick disease types A and B are caused by mutations in the sphingomyelinphosphodiesterase 1 (SMPD1) gene, leading to a strongly decreased activity of acid sphingomyelinase (ASM). The enzyme ASM is mainly present in lysosomes and converts sphingomyelin (SM) to ceramide and phosphocholine. In ASMD, SM and its precursor lipids accumulate in lysosomes and cause cellular damage. There are over 180 mutations of the SMPD1 gene some with residual ASM activity up to 30%. Due to a dramatic reduction of the protein half-life, the condition may phenotypically be type A. Allelic heterogeneity is responsible for most of the variability in severity between types A and B. The mutations can be missense, frameshift, nonsense, and frame deletions. The predominant mutation varies by region.

Niemann-Pick disease type C (NPC) is further classified as type C1 or type C2 based on the pathogenic mutations in the NPC1 or NPC2 genes, respectively. NPC1 is the predominant subtype affecting about 95% of the patient population with over 30 different sequence alterations detected. NPC1 and NPC2 proteins are present in late endosomes and lysosomes and are involved in the transport and intracellular mobilization of cholesterol and sterols. The loss of function of NPC1 and/or NPC2 proteins blocks cholesterol egress from lysosomes, resulting in an excessive build-up of cholesterol in lysosomes. Consequently, toxic cholesterol accumulation results in cellular and organ damage.[21, 22]

Treatment

There are limited available treatments for Niemann–Pick disease, and supportive care through nutrition and physical therapies can improve the quality of life for patients. Additionally, for patients with peripheral organ

pathology, specialists can assist in reducing the severity of symptoms.[23]

As of now, NPD type A/B is not curable. No disease-modifying treatments have been approved by the United States Food and Drug Administration (FDA). However, a multidisciplinary approach can address symptomatic management through supportive measures and palliation.[24]

Niemann-Pick Type A is the most severe form of the disease, with an average life expectancy of 18 months. Type B represents a milder form of disease, and some patients live into late to mid teens, with a few surviving into adulthood. Prognosis for patients with Type C varies between individuals and may range between late childhoods through the mid to late teens, with some patients living into adulthood.[23]

There's no known treatment for type A at this time. Supportive care is helpful for all types of Niemann-Pick disease. In type 2 several treatment options, including bone marrow transplants, enzyme replacement therapy, and gene therapy have been used. Research is ongoing to determine the effectiveness of these treatments. Physical therapy helps with mobility. A medication called miglustat is currently used to treat type C. Miglustat is an enzyme inhibitor. It works by preventing your body from producing fatty substances so that less of it will build up in your body. In this case, the fatty substance is cholesterol.[17]

The guidelines encompass management of patients suspected or diagnosed with ASMD disease at any age. These guidelines should be of value to.
a) Specialist centers, hospital-based medical teams and staff involved with the care of ASMD patients,
b) Family physicians and primary caregivers,
c) Patients and their families
d) Healthcare funders and regulatory agencies. It was developed by experts with extensive experience of European, North and South American healthcare systems and populations.

However, they might equally be applicable to any country that operates similar healthcare services. It is anticipated that implementation of these guidelines will lead to a step change in the quality of care for patients with ASMD.[8]

Recommended multidisciplinary assessment of patients with ASMD.

Discipline	Features of ASMD for which this discipline may be of assistance	Recommended for all ASMD or as needed
Primary care physician	Assist with general medical care; coordinate specialists; provide support for family	All
Metabolic diseases specialist	Diagnosis of ASMD and exclusion of other disorders in the differential diagnosis; Ongoing patient assessment for disease progression and response to therapy. Coordinate the overall care working with primary care physician	All
Neurologist	Assess the possible neurological manifestation of the disease and manage accordingly	All
Hepatologist	Periodic assessments of liver derangements; Manage the impending/existing liver failure	As needed
Haematologist	Assess the risk of bleeding disorder and long term complications	As needed
Pulmonologist	Assess the baseline respiratory functions and periodic assessment for deterioration; manage the pulmonary disease and its complications	As needed
Genetic counselor	To inform affected persons and their families regarding nature and implications of ASMD to facilitate medical and personal decision making; provide counselling for families as to recurrence risk and options for prenatal diagnosis if desired	All
Lipidologist/cardiologist	Manage the mixed dyslipidemia, and perform cardiovascular risk assessment for indicated primary or secondary prevention interventions	As needed
Psychiatrist/clinical psychologist	Assess for behavioral disturbances, depression and manage accordingly	As needed
Speech and language therapist	Assess for dysphagia and aspiration risk; Speech and feeding therapy for children with neuropathic phenotypes	As needed
Occupational and physical therapists/rehabilitation physician	Assess and develop aids and home adjustments as needed for patients with communication and physical challenges	As needed
Nutritionist	Periodic assessments of nutritional status in patients who may be losing weight due to dysphagia or side effects of therapy; gastrostomy tube insertion as indicated	As needed

Social worker	Support of patients and families living with disabilities who require enhanced resources in the community	As needed
Developmental and behavioral pediatrician	Assess for the presence or absence of developmental delays in children; recommend appropriate therapies and educational interventions	As needed

International expert guidelines have been established here to monitor ASMD given the multi-systemic involvement and progressive nature of the disorder. Monitoring goals should be established at diagnosis and reviewed regularly, aimed at identifying and managing disease complications, and enhancing quality of life.[25]

Recently, experimental therapies including stem cell transplantation have been trialed in individuals with Type A and B disease, with varying degrees of success. While transplants have been successful at alleviating disease symptoms in two patients with Type B disease, complications due to the graft itself commonly arise as a consequence of treatment.[23]

- Enzyme replacement therapy (ERT) with recombinant human acid sphingomyelinase (rhASM) is currently being studied as a potentially disease-modifying therapeutic for the treatment of (rhASM).[24, 26]

CONCLUSION

This activity reviews the etiology, epidemiology, and Pathophyiology of Niemann-Pick disease and focuses on the evaluation, management, and complications of the disease, and highlights the inter professional team's role in fostering the best possible outcomes to patients with Niemann-Pick disease. This may help in identify the risk of getting in children of carrier parents. Describe the investigations used in diagnosing, Review the current treatment options available for the management of patients diagnosed, Explain the interprofessional team's role in planning care and highlight the importance of coordinated communication with other professionals in improving clinical outcomes and lowering complications. At present no definite treatment is available however newer treatment modalities like Bone Marrow transplant, enzyme replacement therapy and gene therapy are likely to be useful especially in NPD type B. However such treatment is unlikely to prevent or reverse the major neurological complications of NPD type A. Supportive treatment through nutrition, medication, physical therapy can help to improve quality of life.

REFERENCES

1. Zarco-Román J, Romero-Gómez HE, Carbajal-Rodríguez L: Niemann Pick disease type-A: presentation of 12 cases [Article in Spanish]. ActaPediatr de Mex, 2017; 38: 152-164. 10.18233/apm38no3pp152-1641387.
2. Hu J, Maegawa GH, Zhan X, et al.: Clinical, biochemical, and genotype-phenotype correlations of 118 patients with Niemann-Pick disease types A/B. Hum Mutat, 2021; 42: 614-25. 10.1002/humu.24192.
3. Thurm A, Chlebowski C, Joseph L, Farmer C, Adedipe D, Weiss M, Wiggs E, Farhat N, Bianconi S, Berry-Kravis E, Porter FD. Neurodevelopmental Characterization of Young Children Diagnosed with Niemann-Pick Disease, Type C1. J DevBehavPediatr, 2020 Jun/Jul; 41(5): 388-396.
4. https://nnpdf.org/diseases/
5. https://www.ninds.nih.gov/health-information/disorders/niemann-pick-disease
6. Jiang X, Ory DS. Advancing diagnosis and treatment of Niemann-Pick C disease through biomarker discovery. Exploration of neuroprotective therapy, 2021 Dec 12; 1(3): 146.
7. Eskes ECB, Sjouke B, Vaz FM, Goorden SMI, van Kuilenburg ABP, Aerts JMFG, Hollak CEM. Biochemical and imaging parameters in acid sphingomyelinase deficiency: Potential utility as biomarkers. Mol Genet Metab, 2020 May; 130(1): 16-26.
8. Angeli O, Nagy Z, Schneider M. Felnőttkori B-típusú Niemann–Pick-betegségszemészetimani fesztációja. Orvosi Hetilap, 2023 Nov 19; 164(46): 1838-44.
9. Fuller M, Meikle PJ, Hopwood JJ: Epidemiology of lysosomal storage diseases: an overview .Fabry Disease: Perspectives from 5 Years of FOS. Mehta A, Beck M, Sunder-Plassmann G (ed): Oxford Pharma Genesis, London, UK, 2006; 614-25.
10. Naureckiene S, Sleat DE, Lackland H, Fensom A, Vanier MT, Wattiaux R, et al. Identification of HE1 asthe second gene of Niemann-Pick C disease. Science, 2000; 290.
11. Fuller M, Meikle PJ, Hopwood JJ: Epidemiology of lysosomal storage diseases: an overview. Fabry Disease: Perspectives from 5 Years of FOS. Mehta A, Beck M, Sunder-Plassmann G (ed): Oxford Pharma Genesis, London, UK, 2006; 614-25.
12. International center for type A & type B Niemann Pick disease 2010 The Mount Sinai Medical Center www.mssm.edu/research.
13. National Institute of Neurological Disorders and Stroke.(NINDS). Niemann Pick Disease Information Page www.ninds.nih.gov/disorders/niemann/niemann.htm.
14. Gregory M. Pasteres, Edwin H. Kolodny-Lysosomal Storage Disease. In: Kenneth F. Swaiman, Stephen Ashwal, Donna M. Ferriero editors– Pediatric Neurology: Principle and Practice. Vol I.4th ed. MOSBY Inc, 2006; 673-677.

15. International center for type A & type B Niemann Pick disease 2010 The Mount Sinai Medical Center www.mssm.edu/research
16. https://medlineplus.gov/ency/article/001207.htm
17. https://www.healthline.com/health/niemann-pick-disease#diagnosis
18. Schuchman EH, Levran O, Pereira LV, Desnick RJ. Structural organization and complete nucleotide sequence of the gene encoding human acid sphingomyelinase (SMPD1). Genomics, 1992; 12; 2: 197-205. 1:CAS:528:DyaK3sXhs1ajtrw%3D. 1740330. 10.1016/0888-7543(92)90366-Z.
19. Landrum MJ, Lee JM, Benson M, Brown GR, Chao C, Chitipiralla S, Gu B, Hart J, Hoffman D, Jang W, Karapetyan K, Katz K, Liu C, Maddipatla Z, Malheiro A, McDaniel K, Ovetsky M, Riley G, Zhou G, Holmes JB, Kattman BL, Maglott DR. ClinVar: improving access to variant interpretations and supporting evidence. Nucleic Acids Res, 2018; 46; D1: D1062-D1067. 1:CAS:528:DC%2BC1c XitlGisLfL. 29165669. 10.1093/nar/gkx1153.
20. Li X, Wang J, Coutavas E, Shi H, Hao Q, Blobel G. Structure of human Niemann-Pick C1 protein. Proc Natl Acad Sci U S A, 2016; 113: 821.
21. Pará C, Bose P, Pshezhetsky AV. Neuropathophysiology of Lysosomal Storage Diseases: Synaptic Dysfunction as a Starting Point for Disease Progression. J Clin Med, 2020 Feb 25; 9(3).
22. Cawley NX, Sojka C, Cougnoux A, Lyons AT, Nicoli ER, Wassif CA, Porter FD. Abnormal LAMP1 glycosylation may play a role in Niemann-Pick disease, type C pathology. PLoS One, 2020; 15(1): e0227829.
23. https://brainfoundation.org.au/images/stories/applicant_essays/2012_essays/Niemann-Pick_Disease-_Grubman.pdf
24. 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: 41. 10.1186/s13023-017- 0572-x.
25. Geberhiwot T, Wasserstein M, Wanninayake S, Bolton SC, Dardis A, Lehman A, Lidove O, Dawson C, Giugliani R, Imrie J, Hopkin J. Consensus clinical management guidelines for acid sphingomyelinase deficiency (Niemann–Pick disease types A, B and A/B). Orphanet Journal of Rare Diseases, 2023 Dec; 18(1): 1-28.
26. Acid sphingomyelinase deficiency. (2016). Accessed: July 5, 2022: https://rarediseases.org/rarediseases/acid-sphingomyelinase-deficiency/.