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# Neimann-Pick Diseases: Beyond Lipid Accumulation - Genetic, Diagnostics, and Therapeutic Strategies

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## Abstract

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Rare genetic disorders are the group of disorders/diseases that occur in such a low count that they are not considered much active market for therapeutics unless encouraged by appropriate incentives and support. They are too rare to be fully investigated and managed by health professionals. Genetic disorders are caused by change in genes and are often serious and complex. Around the world, most affected individuals are found to be children. They can be progressive and might get worse as children grow older. Niemann-Pick diseases (NPD) is one such group of rare genetic diseases that are characterized by unwanted and abnormal accumulation of lipids within the cells. In this review, we discuss the history, genetic basis, clinical manifestations and diagnostic approaches for NPD. We further discuss the pathophysiology of accumulation of lipids and their impact on cellular functions and organ systems and various management strategies.



## Introduction

There are certain groups of rare genetic disorders that disrupt the lysosomal storage inside the human body resulting in disrupted molecular and cellular mechanisms. Niemann-Pick disease (NPD) is one example of such disorder that is caused by mutations in genes crucial for processing and transport of lipids (sphingomyelin and cholesterol) [1,2]. Lipid metabolism is severely affected in all three types of NPD [3,4]. It fatally affects various tissues and organs leading to progressive degeneration of crucial organs of the body [5,6]. There are three types of Nieman-Pick disease [7] (Table 1). Niemann-Pick type A (NPA) is caused by a deficiency of acid sphingomyelinase [8]. It is present in early infancy with rapid disease progression and characterized by hepatosplenomegaly, developmental delays, and a shortened lifespan. Type B (NPB) is also caused by a deficiency of the same enzyme, and it can occur in either childhood or later in life. NPB often exhibits milder symptoms affecting mainly visceral function such as hepatosplenomegaly. In hepatosplenomegaly, both liver and spleen get enlarged beyond their normal sizes. On the other hand, NPC (type C of NPD) is caused by the mutations in the genes that are crucial to cholesterol trafficking. NPC1 and NPC2 are the primarily affected genes in this case [9]. NPC constitutes a wide range of symptoms including neurological abnormalities, liver dysfunction and splenomegaly as well in some cases. It is the most dangerous type of NPD as it can show anytime from infancy to adulthood. It is quite a challenging task to diagnose NPD due to their rarity and complexity in clinical context [6]. Based on a recent study of 602 patients over 15 years, global distribution and prevalence of NPC is shown in Figure 1 [10].

However, the rarity of NPDs contributes to the diagnostic challenges [11]. Clinical presentations may mimic other more common conditions necessitating specialized testing such as genetic analysis and lipid profiling for the accurate diagnosis. As of now, therapeutic interventions remain limited, often focusing on symptomatic management. Effective treatment is hindered by the complexity of the underlying molecular mechanisms and the rarity of these conditions. Moreover, the rarity of these diseases seeks a need for increased awareness, innovative research and collaborative efforts.

Research in the NPD field has significantly progressed after the researchers could elucidate the genetic basis and molecular mechanism involved in lipid metabolism, especially sphingomyelin and cholesterol processing. Further, the specific gene mutations were identified which are linked to each subtype, paving the way for refined diagnostic methods and emerging therapeutic strategies. The devastating

factor about this rare disease is that it manifests itself as multi-systemic disorders affecting vital organs of the body including liver, spleen and nervous system.

NPD bring about life-altering consequences for affected individuals and their families. The progression of symptoms, especially in the severe forms, can significantly compromise the quality of life, leading to physical abilities, cognitive decline and emotional distress. NPD follows an autosomal recessive inheritance pattern, meaning that both parents must carry a mutated gene for the disorder to manifest in their child [12]. Due to this reason, parents often become apprehensive of family planning emphasizing the importance of genetic counseling. Further, the smaller patient population poses challenges to advocacy and fund-raising efforts.

The review aims to provide a holistic and up-to-date understanding of NPD, contributing to the ongoing dialogue in research, clinical practice, and public awareness. The multifaceted approach encompasses genetic, clinical, and psychosocial dimensions, fostering a comprehensive resource for healthcare professionals, researchers, policymakers, and the broader community.

## Methods

### Literature search and selection criteria

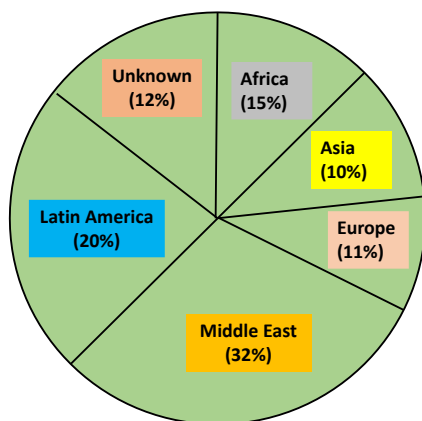
Google scholar, Pubmed, Scifinder and google web were used to obtain data for this review paper. Various keywords were used to retrieve the required information from different published research and review articles. Published papers consulted for this review were taken from year 2017-2024.

## Discussion

### Genetic basis of Niemann-Pick disease and pathophysiology

Niemann-Pick diseases (NPD) are a group of rare inherited metabolic disorders characterized by the abnormal accumulation of lipids, particularly sphingolipids, within various tissues [13]. There are three primary types of Niemann-Pick disease: Type A, Type B, Type C. Each type has distinct genetic and clinical characteristics, and they are caused by mutations in different genes. Niemann-Pick Type A (NPA) is a rare and severe genetic disorder characterized by a deficiency of acid sphingomyelinase (ASM) enzyme activity [14]. NPA is primarily caused by mutations in the SMPD1 gene, located on chromosome 11p15.1 (Figure 2) [15]. This particular gene encodes ASM which plays a crucial role in lipid metabolism by hydrolyzing sphingomyelin into ceramide and phosphocholine [16]. That ceramide is involved in many cellular processes including cell death, differentiation, apoptosis, inflammation and

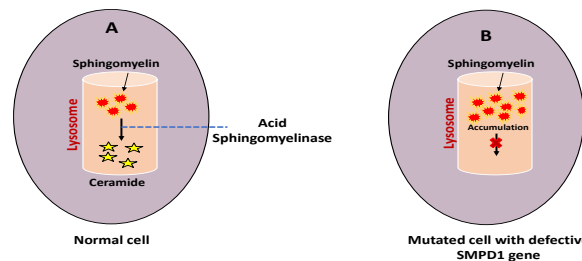
senescence. Various types of mutations are responsible for affecting the ASM's activity. Among them, missense mutation is a common type in NPA that involves single-nucleotide substitutions leading to amino acid changes in ASM enzyme [15], impairing its catalytic activity and affecting its ability to breakdown sphingomyelin. Nonsense mutations, another type of mutation, introduce premature stop codons in the SMPD1 gene that results in a non-functional ASM. Nonsense mutations often lead to a more severe form of NPD type A. A deficiency of normal ASM can also occur due to genetic mutations in NPA blocking normal degradation of sphingomyelin. Undegraded sphingomyelin then accumulates within lysosomes disrupting the normal turnover of cellular components and resulting in the overstuffed lysosomes and the formation of foam cells.



**Figure 1:** Pie chart illustrating the percentage prevalence of NPDs [10].

The presence of lipid-laden foam cells contributes to tissue damage, particularly in organs with high lipid turnover such as the liver, spleen and lungs. The molecular consequences extend to lysosomal dysfunction, impacting cellular homeostasis and contributing to the characteristic lipid storage seen in Niemann-Pick diseases. Specific mutations in the SPMD1 gene contribute to a spectrum severity in NPA [17]. Certain mutations may result in a more severe phenotype with an earlier onset and rapid disease progression, while others may lead to a milder form of disorder.

NPB is primarily associated with mutations in the SMPD1 gene, which is located on chromosome 11p15.1 [18]. In individuals with NPB, mutations in the SMPD1 gene results in a deficiency or dysfunction of ASM enzyme. The genetic basis of NPB exhibits heterogeneity with different mutations leading to variations in the severity of the disorder, age of onset and the extent of organ involvement.



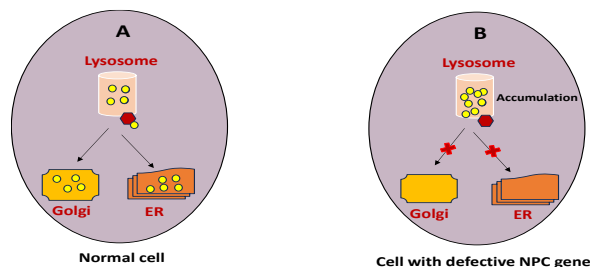
**Figure 2:** (A) Normal cell (B) Inactive or altered enzyme results in sphingomyelin accumulation and lack of ceramide, causing loss of normal cell structure and function leading to NPA and NPB.

NPC is distinguished by distinguished by the buildup of cholesterol and glycosphingolipids within the late endocytic pathway [19]. It occurs primarily due to mutations in two genes- NPC1 and NPC2. The diverse spectrum of mutations including missense, nonsense, and splice site mutations, influences the severity and age of onset of NPC. These genetic mutations result in defective cholesterol metabolism causing the hallmark lysosomal lipid storage bodies. The NPC1 gene is located on chromosome 18q11-q12 and it encodes a transmembrane protein crucial for intracellular cholesterol transport, while the NPC2 gene, located on chromosome 14q24.3 and encodes a soluble lysosomal protein involved in lipid metabolism [20, 21]. Mutations in NPC1 disrupt the process and cause the abnormal accumulation of cholesterol within lysosomes forming characteristic storage bodies (Figure 3). Similarly, mutations in NPC2 contribute to impaired cholesterol trafficking and lysosomal storage causing altered endocytic pathways. Cholesterol accumulation in endolysosomal system also impacts autophagy- a crucial cellular process for recycling damaged cellular components. Moreover, Cholesterol is vital for cellular membranes, and its abnormal accumulation in Niemann-Pick disease type C affects membrane fluidity and signalling, contributing to neurodegeneration. Lipid accumulation disrupts cellular communication and signalling pathways. Sphingolipids like ceramide and sphingosine-1-phosphate are crucial for cell signalling, and their dysregulation in Niemann-Pick diseases interferes with pathways involved in apoptosis, cell survival, and inflammation [22]. This disruption likely contributes to neurodegeneration in Niemann-Pick disease type C and other systemic issues in types A and B.

### Impact on neurological functions

The impact of NPDs on neurological function is a central and often devastating aspect of these disorders. NPA an NPB are characterized by a rapid and severe neurological deterioration. The accumulation of sphingomyelin in neurons leads to progressive damage causing ataxia, muscle weakness and cognitive decline.

Children affected by NPA typically experience a regression of developmental milestones and fail to achieve normal neurological maturation [23]. The severity of neurological involvement contributes significantly to the limited life expectancy in this case. On the other hand, NPC presents with a more varied and protracted neurological course. The effect on neurological function is multifaceted and include ataxia, dysarthria, dysphagia and cognitive decline [24]. VSGP, a specific oculomotor abnormality is a characteristic feature. Seizures and psychiatric symptoms such as mood disorders and psychosis may also occur. The central nervous system's vulnerability to lipid accumulation is particularly evident in NPDs. The accumulation of sphingolipids and cholesterol within neurons impact membrane integrity, intracellular trafficking and cellular signalling pathways. These alterations contribute to the degeneration of neurons and the progressive loss of neurological functions. The cerebellum, brainstem and other regions crucial for motor coordination and cognitive processes are particularly affected leading to the observed neurological symptoms.



**Figure 3:** (A) Normal cell (B) Defective NPC1 gene prevents the cholesterol transport leading to accumulation of cholesterol in lysosome resulting in NPC.

### Advancements in understanding enzymatic deficiencies – targeted interventions

NPDs are characterized by enzymatic deficiencies that results in the abnormal accumulation of lipids within cells. Mutations disrupt cholesterol egress from lysosomes, leading to its abnormal accumulation which can affect multiple organs. Advancements in understanding the enzymatic deficiencies of Niemann-Pick diseases have paved the way for therapeutic exploration. Enzyme replacement therapy (ERT) involves replacing the deficient or malfunctioning enzyme, acid sphingomyelinase, in individuals with Niemann-Pick disease. ERT involves the production of therapeutic enzymes primarily in mammalian cells, with some also produced in plant and yeast cells. These enzymes undergo extensive processing to ensure their activity, high bioavailability and lesser susceptibility to the degradation. Despite the success of ERT, however, several factors pose challenges to its efficacy enhancement. These challenges involve optimizing the

interaction of the enzymes with cell membranes and improving their internalization into target cells, reducing the immunogenic response to the enzymes and overcoming the blood brain barrier when targeting neuronal cells [25]. Nevertheless, ERT stands a highly successful example of targeted biologic therapies, proved to be both effective and safe in treating various genetic rare diseases, saving the lives of newborns and significantly improving the quality of patients' life. Recent research has focused on developing ERT with olipudase alfa, a recombinant human ASM to treat NPA and NPB. One study evaluated the effects of ERT on lipid parameters and inflammatory markers in five adults with NPA over 26 weeks. The patient showed higher levels of triglycerides, PCSK9, apoB48, oxidized LDL, and TNF- $\alpha$ , and lower levels of HDL-C and apoA1 compared to a reference group. ERT led to improvements in total cholesterol, triglycerides, LDL-C, small dense LDL-C, oxidized LDL, and apoB100. Despite a slight reduction in HDL-C, apoA1 levels increased, and TNF- $\alpha$  levels decreased. The study suggests that ERT improves dyslipidemia in NPD-B patients, potentially through reductions in TNF- $\alpha$  and PCSK9 [26]. The interplay of enzymes and lipid metabolism in these disorders remains a subject of ongoing investigation, offering hope for future therapeutic advancements.

Moreover, NPDs share overlapping clinical features with various metabolic and neurodegenerative disorders making the differential diagnosis challenging. Conditions such as Gaucher disease and Tay-Sachs disease exhibit similarities in terms of sphingolipid accumulation [27], but specific enzyme assays and genetic testing help distinguish each type. Additionally, mucopolysaccharidoses (MPS), Wilson disease, and mitochondrial disorders may present with hepatomegaly, neurological symptoms or systematic involvement requiring specific biochemical and genetic tests for accurate differentiation [28]. Rett syndrome, characterized by neurological regression also shares features with NPDs but specific clinical criteria and genetic testing for MECP2 mutations aid in distinguishing the two [29].

### Diagnostic approaches for NPD

#### Genetic testing

Genetic testing plays a significant role in the diagnosis and management of NPD. Since these disorders are quite heterogenous genetically, identifying the specific genetic mutations is essential for accurate diagnosis and classification into type A, B and C of Niemann-Pick diseases [30]. DNA sequencing and mutation analysis are the common methods employed to identify pathogenic variants in genes SPMD1, NPC1 and NPC2 [31]. Molecular genetic testing is quite helpful in

identification of specific mutations as it not only confirms the diagnosis but also give insight into the potential severity of the disease. Its further aids in prognostication process. For instance, certain mutations in NPC1 or NPC2 genes may be associated with a severe or milder form of NPC [32]. Genetic testing is also significant for carrier identifications in families helpful for family planning decisions and genetic counselling [33]. Further advancements in genetic testing technologies such as next-generation sequencing (NGS), targeted gene panels, whole exome sequencing and microarrays have facilitated more comprehensive screening of affected genes [34, 35]. One study has discovered and assessed the pathogenicity of three mutations which were previously unidentified on one known mutation in NPC1 gene through whole exome sequencing [36]. Such studies are helpful for the genetic and prenatal diagnosis of the disease.

Moreover, as research progresses and new genetic variations linked to these conditions are uncovered, the accuracy and precision of genetic testing methods are being enhanced. This advancement plays a role, in improving how these disorders are clinically managed and in exploring treatment options. With the development of medicine genetic testing will continue to play a central role in the comprehensive approach to comprehending diagnosing and addressing NPD.

#### **Biochemical testing**

Biochemical testing plays a role, in assessing individuals suspected of having NPD. One important test involves checking sphingomyelin levels in tissues in blood samples [37]. High sphingomyelin levels indicate issues with sphingomyelinase activity which are common in NPA and NPB. Enzyme tests that measure acid sphingomyelinase activity, are useful for confirming these subtypes diagnosis. For example, a study showed that lower acid sphingomyelinase activity in leukocytes and higher plasma 7 ketocholesterol levels were closely linked to the disease's onset and severity [38]. In the case of NPC, testing typically includes examining oxysterols like cholestane  $3\beta,5\alpha,6\beta$  triol, which can build up due to cholesterol trafficking problems [39]. Increased levels of oxysterols in blood or cerebrospinal fluid may indicate NPC presence. Additionally using filipin staining on fibroblasts is a method that reveals abnormal cholesterol storage patterns specific, to NPC.

#### **Imaging modalities**

In individuals with NPC, magnetic resonance imaging (MRI) is often used to detect brain abnormalities because it provides detailed images of the nervous system. A recent study found that patients with NPC had a thalamus volume and higher quantitative

susceptibility mapping in the pulvinar nuclei compared to the control group [40]. A correlation was also noted with the help of MRI between increased quantitative susceptibility mapping in the pulvinar nuclei clusters which was associated with severe disease symptoms. MRI imaging technique support the idea that iron levels play a significant role in neurodegeneration process in NPC [41].

There are several other functional imaging techniques that are used to study metabolic and physiological changes associated with NPD [42]. Examples include positron emission tomography and photon emission computed tomography. These methods are helpful in deep analysis of how the disease affects the brain function. Another method is ultrasound that is used to check a clinical sign of NPD i.e. hepatosplenomegaly, in which organ size can be monitored [43]. Fundoscopy is another imaging method that is used for eye examination in case of cherry red spot which is a clinical feature in certain type of NPD [44]. Despite all the imaging modalities, diagnosis of NPD has many challenges. Even among the affected individuals of the same family, a range of clinical symptoms can be observed within each subtype [45].

#### **Approaches for management and treatment of NPD**

##### **Symptomatic management**

The treatment of NPD symptoms plays a role, in caring for patients given the range of symptoms that impact different parts of the body [46]. A collaborative approach is taken to manage the signs and enhance the quality of life for those affected. Liver and spleen enlargement are common in NPA and NPB. Managing symptoms involves monitoring organ sizes and providing support to ease associated issues. Regular imaging and assessments help evaluate the effectiveness of treatments like enzyme replacement therapy or substrate reduction therapy which aim to reduce buildup in organs. NPC often shows signs like ataxia, dysarthria and cognitive decline. Managing these symptoms requires a team effort involving neurologists, physical therapists and occupational therapists. Treatments focus on preserving mobility improving communication skills and offering assistance. New pharmacological methods like miglustat aim to slow down decline and enhance function [47]. Certain forms of NPD, type C can lead to breathing problems. Symptomatic care includes support measures such as assisted ventilation when needed. Regular monitoring of breathing function along with intervention is crucial to manage issues like pneumonia and ensure lung health [48]. NPC may also present symptoms such, as mood disorders and psychosis [49].

Treating these symptoms involves teamwork, between brain specialists and mental health experts. Using medications and therapies that offer support can help ease health issues and enhance the quality of life for those affected. The distinctive cherry red spot seen in the eye's macula might appear in forms of NPD. Although it acts as a clue its effect on eyesight is usually minor. Routine eye checkups are done to keep an eye, on eye health and deal with any vision related worries.

### **Enzyme Replacement Therapy**

Enzyme Replacement Therapy (ERT) has shown promise as a treatment approach, for managing aspects of NPD, particularly type A and B [50]. Acid sphingomyelinase plays a crucial role in breaking down sphingomyelin and when it's lacking this lipid accumulates in lysosomes. ERT entails administering acid sphingomyelinase to supplement the enzyme function and aid in breaking down the accumulated sphingomyelin. The impact of ERT on NPD type A and B has been most notable in addressing hepatosplenomegaly, a symptom [51]. By reducing the sphingomyelin stored in the liver and spleen ERT helps diminish organ enlargement and alleviate related symptoms. Significant enhancements in organ enlargement have been observed in studies indicating that ERT is effective in slowing disease progression enhancing quality of life and increasing survival rates for those affected [52]. However, challenges remain when it comes to tackling the symptoms of NPD through ERT. While enzyme replacement therapy has proven effective in animal studies by reducing sphingomyelin accumulation in the system overcoming the blood brain barrier to ensure sufficient enzyme penetration remains a hurdle [53]. The limited spread of enzymes, to the brain complicates the management of issues that often significantly influence patient prognosis and quality of life.

### **Substrate Reduction Therapy (SRT)**

SRT is a treatment strategy that aims to lessen the effects of NPA and NPB by decreasing the buildup of sphingomyelin. It works by inhibiting the production of sphingolipids which reduces the amount, for storage and slows down disease progression [54]. The use of SRT has been particularly effective in managing hepatosplenomegaly in Niemann Pick diseases A and B where it helps reduce the accumulation of sphingomyelin in the liver and spleen. Clinical studies have shown that SRT can improve organ enlargement and related symptoms leading to a quality of life for those affected. This treatment method involves taking an administered molecule that blocks the first step in glycosphingolipid synthesis. The goal is to lower the production rate of glycosphingolipids to counteract

issues with their breakdown thereby restoring a balance between their creation and breakdown rates. Ketogenic dietary therapies (KDT) have been successful in managing seizures in patients with metabolic disorders including those with seizure disorders. Since individuals with Niemann Pick type C often face drug seizures and nerve cell degeneration KDT could offer advantages. For instance, there's a documented case involving a 17-year girl, with NPC who received both miglustat medication and KDT over three years [26].

Despite the patient's neurodegeneration, there was a decrease, in seizure occurrences fewer hospital visits due to worsened seizures and an improvement in alertness. This indicates that KDT could be a beneficial treatment option for individuals with NPC. It has demonstrated effectiveness in reducing seizure frequency decreasing medication needs and offering neuroprotection for those with epilepsy and IMD. However, due to concerns about cholesterol metabolism in NPC patients it is important to be cautious, about their intake of lipids [55].

### **Emerging therapy and clinical trial cases**

The field of NPD is changing as new treatments are being explored and people are actively taking part in studies. Rare metabolic conditions, like types A, B and C have always been difficult to treat. Recent progress in understanding how they work has opened up possibilities for treatment. One exciting option is gene therapy, which aims to fix the underlying issues by giving working copies of the genes that are missing [56, 57]. Researchers are currently studying gene therapy methods, in animals and small clinical trials to see how safe and effective they are with the hope that this could lead to a treatment that offers lasting benefits [58].

Challenges include ensuring effective delivery of therapeutic genes to target cells, addressing immune responses, and optimizing vector design. Small molecule therapies, including pharmacological chaperones and modulators, are being explored for their potential to correct enzyme function or enhance the cellular response to the underlying metabolic defects [59]. These compounds aim to restore proper cellular function and reduce the accumulation of lipid substrates. Several small molecule therapies are currently in preclinical and clinical development, with ongoing trials assessing their safety and efficacy. Researchers are actively working on optimizing SRT approaches, aiming to enhance drug delivery to the central nervous system. Strategies include developing more brain-penetrant compounds and exploring alternative administration routes. SRT, which has shown efficacy in addressing hepatosplenomegaly, remains an essential component of emerging therapeutic strategies, especially for types A and B.

Type	Age of onset	Gene mutation	Hepatosplenomegaly	Neurological involvement	Cholesterol metabolism	Cherry-red spot in macula	Respiratory complications	Life expectancy
Niemann-Pick Disease Type A (NPA)	typically presents in infancy	mutations in the SMPD1 gene, leading to a deficiency of acid sphingomyelinase (ASM) enzyme	Yes	Rapid or severe neurodegeneration	Elevated cholesterol and sphingomyelin in tissues	Common	Respiratory difficulties may occur	significantly shortened, often resulting in death during early childhood
Niemann-Pick Disease Type B (NPB)	can occur at any age	mutations in the SMPD1 gene, leading to deficient ASM activity	Yes	Milder or absent	Elevated cholesterol and sphingomyelin in tissues	Absent	Respiratory difficulties may occur	may survive into adulthood
Niemann-Pick Disease Type C (NPC)	can manifest at any age	mutations in either the NPC1 or NPC2 genes, affecting intracellular cholesterol trafficking	Yes	progressive neurological decline, ataxia, and psychiatric symptoms.	Variable cholesterol metabolism, systemic manifestation	May be present in some cases	Respiratory complications, interstitial lung disease	may survive into adulthood

**Table 1:** Types of Neimann-Pick disease.

S. No.	Biomarker	Sensitivity	Specificity	Relevance for diagnosis and monitoring	Reference
1	Acid Sphingomyelinase	High	Moderate	Essential for confirming Niemann-Pick diseases, particularly NPD-A and NPD-B.	[70]
2	N-Palmitoyl-O-phosphocholine serine (PPCS)	Moderate	High	Emerging biomarker showing promise in reflecting disease severity and progression.	[10]
3	Chitotriosidase	Moderate	High	Elevated levels indicative of macrophage activation; useful for NPD-C.	[77]
4	Oxysterols	High	High	Reflects disrupted cholesterol metabolism; relevant in NPD-C.	[78]
6	GM2 gangliosides	Moderate	High	Accumulation in tissues; indicative of lysosomal storage, observed in NPD-B.	[28]
7	Lyso-sphingomyelin	Moderate	Moderate	Elevated levels associated with sphingomyelinase deficiency, seen in NPD-A and NPD-B.	[64]
8	Glucosylceramide	Moderate	High	Elevated levels in NPD-B; useful in differentiating subtypes.	[70]
9	Cholesterol	High	Moderate	Altered levels reflecting disruptions in cholesterol trafficking in NPD-C	[80]

**Table 2:** Exploring biomarkers linked to Niemann Pick diseases.

ERT continues to be a focus of research, with efforts to improve enzyme formulations, increase efficacy, and enhance targeting. Novel ERT approaches seek to overcome challenges related to blood-brain barrier penetration, aiming to provide more comprehensive treatment for neurological manifestations, particularly in NPC. Novel nanotechnology-driven enzymes replacement strategies have been explored for such lysosomal storage disorders [53]. The emerging trend in Niemann-Pick disease research involves exploring combination therapies that target multiple aspects of the disease simultaneously [61]. Combining different modalities, such as gene therapy with small molecule treatments or ERT with SRT, aims to synergistically address the complexities of organ involvement and improve overall outcomes [62, 63]. Genetic testing can comprise specific examination of NPC1/NPC2 genes or specialized gene panels, and it can be complemented by conducting enzymatic assay tests for acidic sphingomyelinase and evaluating the biomarker N-palmitoyl-O-phosphocholine serine (PPCS). Study has suggested that beyond its role in variant classification, the biomarker PPCS could potentially function as an indicator of the severity or progression of the disease [10].

### Identification of biomarkers

The identification of reliable biomarkers for the diagnosis and prognosis of NPDs has become a crucial focus in advancing clinical management and therapeutic interventions [64]. Biomarkers play a pivotal role in facilitating early and accurate diagnosis, enabling timely interventions and improved patient outcomes (Table 2) [65]. Several potential biomarkers associated with various aspects of NPDs are under investigation, reflecting the complex and heterogeneous nature of these disorders. Genetic testing remains a cornerstone in the diagnosis of Niemann-Pick diseases, providing definitive confirmation of the underlying genetic mutations associated with each subtype [64, 66]. Advanced technologies such as NGS, has paved the way for the identification of particular pathogenic variants, enhancing the accuracy and efficiency of genetic testing [67]. Genetic biomarkers not only aid in diagnostic certainty but also contribute to family planning decisions and genetic counselling. Assessing biochemical markers associated with sphingolipid metabolism is fundamental in diagnosing and monitoring NPDs [68]. Elevated levels of sphingomyelin and other sphingolipids in blood or

tissues serve as indicative biomarkers. Furthermore, the analysis of oxysterols, which're byproducts of cholesterol breakdown has become a potential tool, for diagnosis especially in NPC. Different imaging techniques like MRI offer indicators for evaluating organ involvement and disease progression [69]. Hepatosplenomegaly, cerebellar atrophy and other structural irregularities detected through imaging play a role in the process and continuous monitoring. The presence of a cherry spot in the macula is an observation in certain types of NPDs and acts as a significant indicator during eye examinations. Recognizing this sign helps with diagnosis. Provides insights into the overall impact of the disease on the body. Studies have also examined blood markers related to processes in NPC1 patients [71]. Optical coherence tomography (OCT) presents an opportunity to study retinal changes in systemic neurological disorders affecting both adults and children [72]. These OCT characteristics, such as. Spots on the retina, SND (subfoveal neuroretinal detachment) changes in retinal layer thicknesses and alterations in inner and outer retinal layer integrity serve as indicators, for neuroinflammation or neurodegeneration. For example, OCT angiography was utilized to assess deposit patterns in layers of NPB patients underlining the importance of combining imaging techniques for identifying deposit patterns and diagnosing NPA patients [73].

The evaluation of these OCT biomarkers plays a role, in monitoring the status of the nervous system allowing for a comprehensive approach necessary for accurate diagnosis and effective management of these conditions. Researchers are increasingly exploring biomarkers found in cerebrospinal fluid (CSF) to understand their potential in reflecting involvement of the nervous system [74]. Analysis of CSF, which includes studying proteins or metabolites can provide insights into the neurodegenerative aspects of Niemann Pick diseases aiding both in diagnosis and prognosis. Recent research has validated proteins in CSF from NPC1 patients that warrant further investigation [75]. Additionally, a recent study highlights the use of neurofilament light chain in CSF as a novel biomarker for evaluating both the severity of symptoms and treatment response in NPC1 [76]. As new therapies advance through research and early clinical trials there is optimism within the Niemann Pick community regarding potentially transformative treatments. However, challenges such as selection, long term safety concerns and addressing the nature of these diseases continue to persist. Ongoing collaboration and active participation in trials are crucial for propelling these therapies towards wider availability and improved outcomes, for patients.

## Conclusion

In summary, this detailed review provides an examination of the rare genetic condition, NPD. It discusses background, genetic basis, clinical features and current research findings in the field of NPD research. In such condition, early detection through enzyme and genetic testing is crucial to prevent the premature mortality. There is always a chance that healthcare professionals miss or delay the proper diagnosis due to the overlapping symptoms, owing to its rarity and diversity. The present study helps understand the complexity, disease management, psychological, social and economic aspects in dealing with NPD.

## Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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