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Niemann-Pick Disease

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Abstract: **Niemann-Pick disease is an inherited condition involving lipid metabolism, which is the breakdown, transport, and use of fats and cholesterol in the body. In people with this condition, abnormal lipid metabolism causes harmful amounts of lipids to accumulate in the spleen, liver, lungs, bone marrow, and brain. Niemann-Pick disease type A appears during infancy and is characterized by an enlarged liver and spleen (hepatosplenomegaly), failure to gain weight and grow at the expected rate (failure to thrive), and progressive deterioration of the nervous system. Niemann-Pick disease type B has a range of features that may include hepatosplenomegaly, growth retardation, and problems with lung function including frequent lung infections. Signs of Niemann-Pick disease type C include severe liver disease, breathing difficulties, developmental delay, seizures, poor muscle tone (dystonia), lack of coordination, problems with feeding, and an inability to move the eyes vertically. Niemann-Pick disease type C is further subdivided into types C1 and C2, each caused by a different gene mutation. Prognosis for NPC patients vary depending on the type and supportive therapies includes neurosteroids, sterol binding agents and cholesterol lowering agents variably effective as far as manifestations are concerned and improves patent's quality of life. Mode of inheritance is autosomal recessive manner. Carrier detection and genetic counselling can further decrease risk to other family members of future generation.**

Keyword: **Niemann pick disease, molecular biology and genetics, symptoms and diagnosis, treatment and prognosis, risk to other family members.**

I. INTRODUCTION

Niemann-Pick is an autosomal recessive genetic disorder resulting in abnormal lipid metabolism. It can result from a deficiency of the acid sphingomyelinase enzyme, leading to type A or B disease, or the NPC1 or NPC2 (also called HE1) proteins involved in cholesterol and fatty acid metabolism in lysosomes resulting in type C disease. The severity of the disease and age of onset vary, but it is always fatal. Neonates can present with ascites and severe liver disease from infiltration of the liver and/or respiratory failure from infiltration of the lungs. Other infants, without liver or pulmonary disease, have hypotonia and developmental delay. The classic presentation occurs in mid-to-late childhood with the insidious onset of ataxia, vertical supranuclear gaze palsy (VSGP), and dementia. Adults are more likely to present with dementia or psychiatric symptoms, severe metabolic disorders that allow sphingomyelin to accumulate in lysosomes, which are organelles in animal cells. The severe form is fatal in toddlerhood; people with milder forms may live into their teens or young adulthood [1]. This disease involves dysfunctional metabolism of sphingolipids, which are fats found in cell membranes, so it is a kind of sphingolipidosis. Sphingolipidosis, in turn, are included in the larger family of lysosomal storage diseases (LSDs).

II. Molecular Biology and Genetics

Lipids like sphingomyelin and cholesterol are present in all cell membranes and are metabolized in lysosomes. Sphingomyelin appears to be involved in signaling cascades [1]. Exogenous cholesterol, in the form of cholesterol esters, is taken up from the bloodstream as LDL via endocytosis, creating endosomes in the cell. Acid sphingomyelinase, which breaks down sphingomyelin, also found in lysosomes. Once the cholesterol esters are broken down to free cholesterol and fatty acids, free cholesterol diffuses out of the lysosomes to the plasma membrane and endoplasmic reticulum. Free cholesterol in the cell activates mechanisms that downregulate LDL receptors, decreasing the amount of cholesterol taken up by the cells and excess cholesterol is present in the cell, is stored as cholesterol ester. In Niemann-Pick, these processes are disrupted [2,3]. Genetic mutations in the SMPD1 gene cause Niemann–Pick disease types A and B. This gene provides instructions for producing an enzyme called acid sphingomyelinase. This enzyme is found in the lysosomes (compartments that digest and recycle materials in the cell), where it processes lipids such as sphingomyelin. Mutations in this gene lead to a deficiency of acid sphingomyelinase and the accumulation of sphingomyelin, cholesterol, and other kinds of lipids within the cells and tissues of affected individuals. They stop the body from making an enzyme, acid sphingomyelinase, that breaks down lipids. ASM deficiency results in an accumulation of sphingomyelin-containing

lysosomes-like storage organelles. These lysosomes build up forming lysosomal inclusions, giving the cells a characteristic foamy appearance and eventually causes cell death.

Niemann-Pick Type C disease (NPC) is a lysosomal storage disorder due to defect in intracellular cholesterol trafficking and consequent accumulation and sequestration resulting in neuro-visceral complications. Niemann-Pick Type C disease is a rare inherited metabolic disorder characterized by lipid accumulation and systemic manifestations due to multiple organ involvement. Mutations in NPC1 or NPC2 cause Niemann–Pick disease type C is caused by mutations to NPC1 gene on chromosome 18 or NPC2 gene on chromosome 14. NPC1 gene provides instructions for producing a protein that is involved in the movement of cholesterol and lipids within cells encodes a large protein that resides in the limiting membrane of endosomes and lysosomes and mediates intracellular cholesterol trafficking via binding of cholesterol to its N-terminal domain. It is predicted to have a cytoplasmic C-terminus, 13 transmembrane domains, and 3 large loops in the lumen of the endosome -the last loop being at the N-terminus. This protein transports low-density lipoproteins to late endosomal/lysosomal compartments where they are hydrolized and released as free cholesterol. Defects in this gene cause Niemann-Pick type C disease, a rare autosomal recessive neurodegenerative disorder caused by over accumulation of cholesterol and glycosphingolipids in late endosomal/lysosomal compartments.

NPC2 gene provides instructions to produce a protein that binds and transports cholesterol. Reduced or absent levels of this protein lead to the abnormal accumulation of lipids and cholesterol in the cells as seen in people with Niemann-Pick disease type C2. The exact functions of the NPC1 and NPC2 proteins are not fully understood. About 95% of type C disease is due to NPC1 mutations, which affects a protein used to transport lipids [4]. NPC1 is a transmembrane protein that spans the lysosomal membrane. Intracellular cholesterol transporter which acts in concert with NPC2 and plays an important role in the egress of cholesterol from the endosomal/lysosomal compartment. The *NPC2* gene provides instructions for producing a protein that is located mainly inside lysosomes, compartments in the cell that digest and recycle materials. The NPC2 protein binds to cholesterol. Both NPC1 and NPC2 function as the cellular 'tag team duo' (TTD) to catalyze the mobilization of cholesterol within the multivesicular environment of the late endosome (LE) to effect egress through the limiting bilayer of the LE. NPC2 binds unesterified cholesterol that has been released from LDLs in the lumen of the late endosomes/lysosomes and transfers it to the cholesterol-binding pocket of the N-terminal domain of NPC1 [5]. Cholesterol binds to NPC1 with the hydroxyl group buried in the binding pocket and is exported from the limiting membrane of late endosomes/ lysosomes to the ER and plasma membrane by an unknown mechanism and NPC2 binds oxysterol with higher affinity than cholesterol. May play a role in vesicular trafficking in glia, a process that may be crucial for maintaining the structural and functional integrity of nerve terminals but the exact function of the NPC2 protein is unknown.

III. Symptoms and Diagnosis

Type A and B are diagnosed by measuring the level of activity of an enzyme called acid sphingomylinase (ASM) in white blood cells while this test will identify persons with Type B (as well as Type A), it is not very reliable for detecting persons who are carriers (who have only one non-functional copy of the ASM gene). Further, the test will show decreased activity of ASM, but it cannot always predict whether the individual will have type A or Type B or an intermediate variant of the disease; that requires clinical evaluation of the individual. Molecular genetic testing is now available commercially for Niemann-Pick disease, type B (or ASM Deficiency) at several laboratories. Once an affected individual has been tested and his or her mutations have been identified, it is then possible to diagnose Type B carriers by DNA testing within the individual's family. An initial diagnosis is confirmed through biochemical or genetic testing. This test will not determine carrier status, as ASM activity appears to be normal in heterozygotes. NP-C is a neurovisceral condition; clinical features that indicate a possible diagnosis of NP-C involve systemic, neurological and psychiatric symptoms. Neonates with ascites or fluid in the abdomen and severe liver disease from infiltration of the liver and respiratory failure from infiltration of the lungs. Other infants, without liver or pulmonary disease, have hypotonia and developmental delay. The classic presentation occurs in mid-to-late childhood with the insidious onset of ataxia, vertical supranuclear gaze palsy (VSGP), and dementia. Dystonia, ataxia and seizures are common. Dysarthria and dysphagia eventually become disabling, making oral feeding impossible; death usually occurs in the late second or third decade from aspiration pneumonia. Adults with the disease most often experience depression, bipolar disease, or schizophrenia [6,7]. Niemann-Pick Type C (NPC) is a rare and extremely variable condition can be determined by taking a small piece of skin ("skin biopsy"), growing the cells ("fibroblasts") in the laboratory, and studying their ability to transport and store cholesterol. The transport of cholesterol in the cells is studied by measuring conversion of the cholesterol from one form to another ‘’esterification’’. The storage of cholesterol is assessed by staining the cells with a chemical ‘’filipin’’ that

glows under ultraviolet light. This can show whether the cholesterol is being stored inappropriately in lysosomes, the recycling centers of the cell [8]. It is important that both the transport and storage tests be performed, since reliance on one or the other may lead to an incorrect diagnosis or a missed diagnosis of a variant form of NPC. Biopsies of bone marrow, spleen, and liver tissue were, until recently, commonly used diagnostic tools.

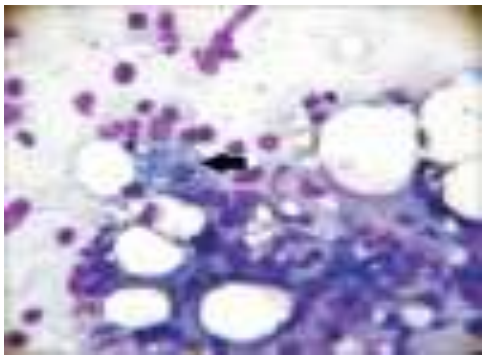

Fig. 1High power view of bone marrow aspirate smear, showing normal cellularity with normoblastic maturation and presence of sea blue histiocyte (marked with arrow) which is characteristic of Niemann - Pick disease Bone marrow aspiration cytology demonstrated sea blue histiocytes implying lysosomal storage disorder.

IV. Treatment and Prognosis

Clinical prognosis for patients with Niemann Pick Disease varies depending on the type that they have and is very different. There is no specific treatment for Type A but symptoms are treated. In adult patients with Type B, doctors try to keep cholesterol levels down to normal levels Type A has a very rapid, progressive onset of neurological symptoms. Patients with Type A will generally die by the second or third year of life. Since Type B is associated with a more mild mutation of the ASM gene that does not completely impair its function, the symptoms do not occur as rapidly or as severely. However, during early adulthood, the central nervous system may begin to be affected, and the accumulation of lipids, particularly foam cells, in the liver spleen and lungs leads to a premature death. Patients with NPB generally have little or no neurologic involvement and may survive into adulthood, though there may be health complications. Type B individuals usually have enlarged livers and spleens, and respiratory problems are common. The enlargement of organs and the respiratory problems can cause cardiovascular stress and can lead to heart disease. The progression of Type C is more similar to that of Type A, although the neurological symptoms do not appear as immediately, and early development can proceed normally [6]. Until recently, there was no disease-modifying treatment for NP-C. Supportive therapies are variably effective for the alleviation of clinical manifestations of NP-C, and can improve patients' quality of life. High-quality general pediatric and medical care is essential to maximize quality of life in patients with NP-C. Palliative pharmacotherapy is available for dystonia, cataplexy, seizures, sleep disorders, gastrointestinal symptoms. Gastrointestinal signs are often seen in NP-C, and diarrhoea can be frequent in both treated and non-treated patients. Anti-diarrhoea medications and dietary modification can help, and monitoring program should be maintained to prevent constipation. Secondary lung involvement due to aspiration frequently complicates dysphagia. Prophylactic antibiotic therapy may avoid pulmonary infection in these patients. Primary lung involvement directly related to NP-C disease is rare, but can be treated with aggressive broncho dilation and, in some cases, chest physical therapy. There are no controlled data from clinical trials to support the use of these interventions.

Neurosteroids: Neurosteroids can affect neuronal growth and differentiation and can modulate a variety of neurotransmitter receptors. NPC1 mouse model, early intraperitoneal infusion of allopregnanolonein b-cyclodextrin appeared to delay some of the neuropathological signs of disease progression and neurological symptom onset, and to prolong survival [9].

***Sterol-binding agents*:** Recent data show that early treatment of NPC1-mutant mice with 2-hydroxy-b-cyclodextrin resulted in strikingly reduced cholesterol concentrations in liver and spleen, ameliorated liver dysfunction and neurodegeneration, and notably prolonged survival [10].

***Cholesterol-lowering agents*:** Strategies to reduce intracellular cholesterol storage have been tested, based on the hypothesis that cholesterol is an offending metabolite in NP-C. Although combinations of cholesterol-lowering agents reduce hepatic and plasma cholesterol levels, there has been no reported evidence of amelioration of neurological disease during clinical use [11].

***Miglustat*:** Miglustat is a small iminosugar molecule that acts as a competitive inhibitor of the enzyme, glucosylceramide synthase, which catalyses the first committed step in glycosphingolipid (GSL) synthesis. Miglustat might also indirectly modulate intracellular calcium homeostasis through its effects on glucosylceramide levels]. Impaired calcium homeostasis related to sphingosine storage may be an initiating factor in the pathogenesis of NPC1 .Miglustat is able to cross the blood–brain barrier, and was shown to reduce GSL accumulation and cellular pathology in the brain, delay onset of neurological symptoms, and prolong survival during pre-clinical studies [12].

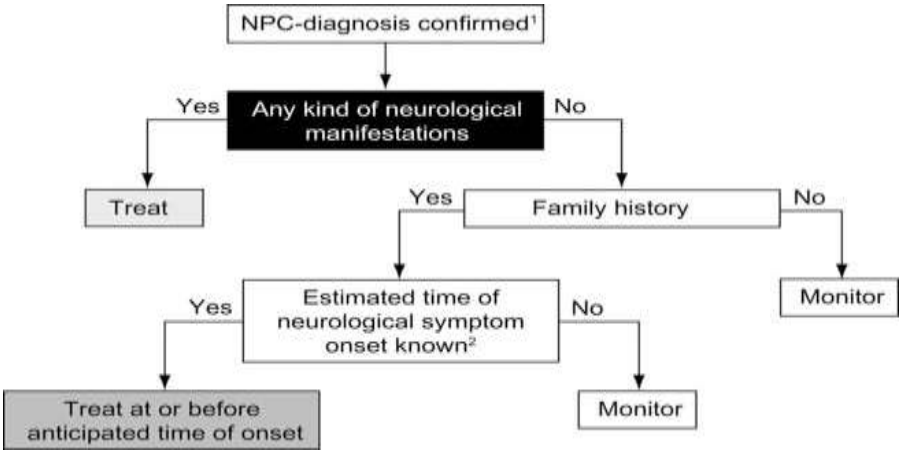

Fig.2: Protocol for initiation of miglustat treatment in NP-C. 1 Biochemical and/or molecular-genetic diagnosis, with or without systemic or other clinical signs and symptoms. 2 Patients asymptomatic or with isolated splenomegaly, and with one or more older siblings in whom the time of neurological symptom onset and rate of progression are known.

V. Risk to other family members

***Mode of Inheritance*:** Niemann-Pick disease is inherited in an autosomal recessive manner.
***Parents of a proband*:** Parents of children with NPC are obligate heterozygotes.
***Sibs of a proband*:** At conception each sib of affected individual has 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. The phenotype usually runs true in families; that is, if the proband has early-onset disease, subsequent affected individuals will have a similar clinical course. In rare cases, a proband and subsequent offspring have had different clinical presentations.
***Offspring of a proband*:** The offspring of an individual with NPC will inherit one abnormal *NPC* allele from the affected parent and are thus obligate heterozygotes.
***Other family members of a proband*:** Each sib of a proband's parents is at a 50% risk of being a carrier.

VI. Carrier Detection

Biochemical testing is unreliable in defining the heterozygous state, owing to significant overlaps with findings seen in controls. Molecular genetic analysis of *NPC1* or *NPC2* may be used for carrier testing if mutations in *NPC1* or *NPC2* have been identified. Once mutations have been identified in the index case of a family, a parental study should be performed to ensure allele segregation. This also allows reliable detection of heterozygote carriers in family members. Genetic counselling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. Counselling should be provided with the results of positive genetic tests for NP-C to provide information on the nature, inheritance and family planning implications of the disease. Prenatal diagnosis should be offered to couples with a previous affected child. Identification of mutations in every new NP-C case for which parents may request prenatal diagnosis should be a priority. DNA from both parents also needs to be studied, ideally before final genetic counselling. Prenatal diagnosis is best achieved using chorionic villus sampling (CVS) at 10–12 weeks. Molecular genetic analysis is the preferred strategy, and can be applied to uncultured CVS. Prenatal diagnosis by primary biochemical testing requires cell culture, and is only reliable if the affected individual in the family has a 'classic biochemical phenotype' [13,14].

VII. Discussion

Niemann-Pick Disease are inherited in an autosomal recessive manner is a rare neurodegenerative disease with variable systemic manifestations. The primary biochemical defect is severely impaired intracellular lipid transport [15], and is caused by mutations in either one of the two genes NPC1 (in 95% of cases) or NPC2 (in around 4% of cases); undetected causal gene mutations may also exist [16,17]. NP-C has an extremely heterogeneous clinical presentation. Symptoms, disease progression rates and life expectancy vary greatly and are strongly influenced by age at onset of neurological symptoms. Until recently, there were no available disease-specific therapies for the treatment of NPC. With the recent approval of miglustat, and the possible development of additional disease specific therapies, treatment can be aimed toward stabilizing neurological disease. Supportive therapies are variably effective for the alleviation of numerous clinical problems associated with the disease. This is the first guideline proposed for the management of this rare inherited disease, and it is intended that it will be updated in the future as new data become available. Intensive research into the epidemiology, pathophysiology, diagnosis, and treatment of NP-C is ongoing at a number of expert centres. Further important findings on disease screening and the use of monitoring techniques in NP-C are expected over the coming year. The sophisticated diagnostic techniques and recently approved treatment being unavailable in India, increased knowledge and better understanding of clinical profile might help in early diagnosis and secondary prevention of complications.

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