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CLASSIFICATION, CHARACTERIZATION, TREATMENT, CARRIER DETECTION AND GENETIC BASIS OF NEIMAN-PICK DISEASE

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ABSTRACT

Neiman-Pick disease is a metabolic disorder associated with neurodegenerative symptoms. It is an abnormality of lysosomes resulting in disabling neurological manifestations and in most of the cases premature death. Treatment is dependent on the type of disease. This review will provide and information about history, treatment, prognosis, genetic factors of the disease and a statistical review of case report of nine patients of Neiman-pick disease. It is an atypical lysosomal disorder. Mutations in NPC genes are responsible for causing this disease. These days, Pharmacological treatments are being used to lower blood cholesterol level and prevent symptoms of NP disease. Most recent therapy is stem-cell based therapy. The most interesting feature of this disease is the accumulation of specific cells called NP cells in the viscera.

KEYWORDS: Neiman Pick disease, prognosis, pharmacological treatments, therapeutic reagents, stem cells, carrier detection.

INTRODUCTION

Neiman-pick disease is caused by lysosomal abnormality. As a result large complex molecules donot break down. These complex molecules start to gather in different organelles and cause additional attachment with the cells. NP disease is autosomal and recessive. But it causes hereditary abnormalities. NP disease results in the accumulation of lipids especially sphingomyelin and cholesterol in liver and spleen. In 1961, Crocker determined the types of NP disease. He classified the types on the basis of organs which were affected and the age at which the symptoms start to appear. 1966 Bardy determined that the patients with NP have deficiency of acid sphingomyelinase. This is the lysosomal enzyme that catalyzes the breakdown of sphingomyelin. This case was commonly found with the patients with NP type-A class and as well as type B class (Vanier, 2010). Mutation in gene SMPD1 is the cause of deficiency of acidsphingomyelinase. This result in the red colour spots in the eye part i.e. retina and also cause liver and spleen problems. NP disease may or may not cause neurodegeneration. It depends on the type of NP. Large and diversified number of symptoms of NP are present(Santos-Lozano *et al*., 2015).

The symptoms may occur at any age. If the symptoms occur at the early age that is 3-4 years there are chances that the neurodegenerative problems may occur. The disease was treated with the drugs like anti-depressants, anti-epileptics etc. milgustat cause inhibition in the neurological disorders. However now a days, to treat NP disease, hematopoietic transplantation of cell and replacement of enzymes are being focused. However until now there is no proper treatment of NP disease and not any therapy is available. The main goal of the scientists is to find out the treatment for NP disease. Therefore scientists start to analyze the patients. They started to do clinical trials. The newly discovered treatments were given to the patients of NP disease. As a result they compare the efficiency of the results. During the clinical trials scientists mainly focus on the determining of the effects of various drugs like miglustat or the combination of drugs. However efforts of the scientists was not appreciable as they donot get the satisfactory results. Because in different patients of NP different drugs were helpful for them. There was not a one or two drug that was the same in the treatment of NP patients. Therefore scientists were confused that mainly which type of drug is efficient for the treatment of NP disease. Milgustat was used as the treatment of NPC in 2009. Milgustat was the drug that cause inhibition of the enzyme that produces glycosphingolipids. Because in NP disease, glycosphingolipids were also shown to store in the organelles of patients with NP disease. This drug was very efficient as it can cross the barrier between the blood and the brain. It can also delays neurological disorders both in infants and the adults. Galanaud

scientist and his co-workers determined that milgustat is very efficient in the treatment of NPC disease. Milgustat cause the beneficial impact on brain disorders after the treatment of 1 year. Thus after several clinical trials scientists were clear with the fact that milgustat slows down the problems of neurodegeneration. However various problems occur. One main problem was that the results of the clinical trials of different scientists were totally different from each other. There was also a dissimilarity in the time at which the symptoms start to occur. However there was also dissimilarity in the parameters of neurological disorders. The problem with the use of milgustat was that it cause some harmful effects on patients. Some effects include weight loss, diarrhea, malabsorption of carbohydrate in intestine etc. therefore the other drugs that were used for the treatment includes drugs that lowers the cholesterol level, diets with the low level of cholesterol(Vanier, 2010).

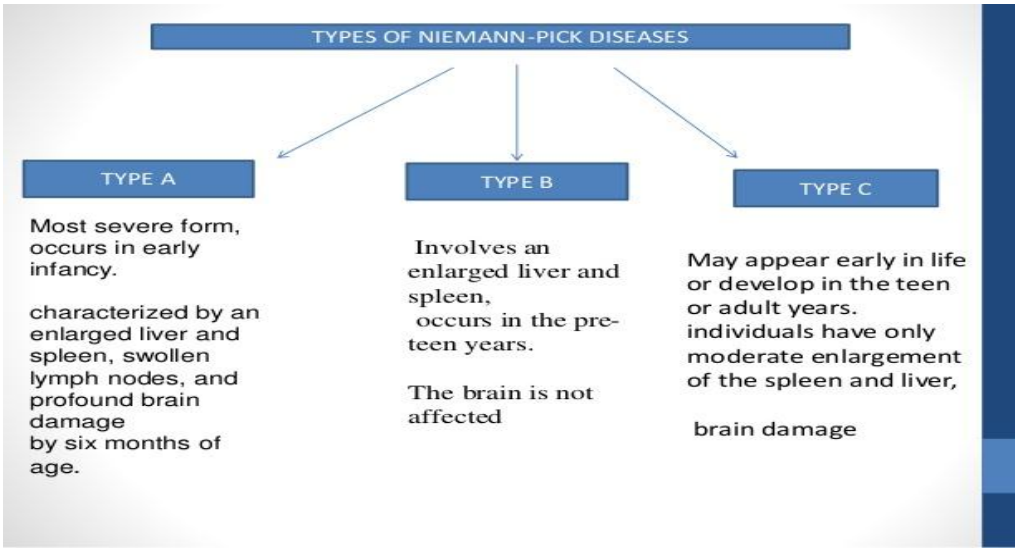

Figure 1: Types of Neiman-pick disease.

History of NP

In 1914, Albert Niemann (German Pediatrician) diagnosed the young children. He determined that the young child have some problems in the nervous system. He also characterized hepatosplenomegaly in the young patient. Albert Niemann was one of the prominent scientists. He played a very important role in the characterization of NP disease. Then there was the scientist named as Ludwig Pick. He worked on the tissues of the dead children. These children had the same symptoms as were studied by Niemann. Thus, this gives the evidence about new disorders due to lipid storage. Both Niemann and Pick play very important role in determining the new class of disease which was cause as the result of storage of lipids. Therefore the disease was called as Niemann Pick after the name of the scientists. The patients that were demonstrated by both the scientists may or may not include neurodegenerative disorders, therefore Crocker later determined that NP has further types. He classified NP into 4 types. However the type 4 is now not consider as the type of NP (Crocker *etal).*

Table no 1: Classification of Neimann pick disease

Classification of Neiman-Pick disease		
Type A	**Type B**	**Type C**
Most severe form, occurs in early infancy	Involves an enlarged liver and spleen, occurs in pre-teen years	May appear early in life or develop in the teen or adult years.
Characterized by an enlarged liver and spleen, swollen lymph nodes and profound brain damage by six months of age.	The brain is not affected	Individuals have only moderate enlargement of spleen and liver, brain damage
Neurodegenerative	Neurodegenerative	Nueurovisceral
Caused by mutation in gene SMPD1	Caused by mutation in gene SMPD1	Caused by mutation in gene NPC1 and NPC2
Deficiency of lysosomal enzyme acid sphingomyelinase.	Deficiency of lysosomal enzyme acid sphingomyelinase.	Deficiency of lysosomal membrane protein.

Treatment and Prognosis of Niemann Pick Disease

Different treatment were available for NP disease. It depends on the type of NP that whether it is NPA, NPB or NPC. However there was not proper treatment of NP type A. only the symptoms associated with type A were treated. Patients with type A involve severe neurodegenerative disorders.NP type-A patients usually die at the age of 3 to 4 years.Neurosteroids effect the growth of neurons. They can control some receptors of neurotransmitters. NPC1 mouse model, appears to delay some of the neurological disorders. Scientists have demonstrated that with the help of sterol binding agents, cholesterol level was decreased in the liver and spleen. Cholesterol causes various problems in NPC. Therefore scientists start to use different combinations of lowering agents of cholesterol. As a result reduction in the level of cholesterol in liver and plasma occurs.Milgustat is imminosugar molecule. It acts as inhibitor of the enzyme that synthesizes glycosphingolipids. It also helps in calcium homeostasis. Milgustat crosses the blood and brain barrier. Thus we can say that Milgustat delays the developmentof neurologicalsymptoms as a result there are chances of prolong survival of the patient (Sarvanti 2013).

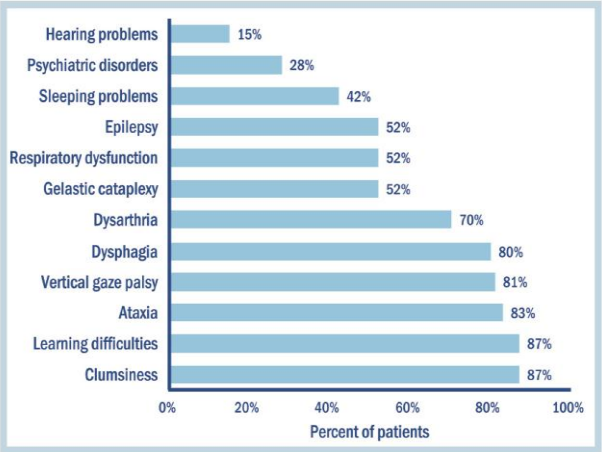

Figure 2: Statistical graph of prognosis.

NP type A, adult patients were treated in such a way that their cholesterol level should be less than the normal level of cholesterol. As a result of mutation in ASM gene, NP type B results. The symptoms of type B donot occur spontaneously and type B is not severe as type A. In type B nervous system may or may not effects. But if type B occurs in infants, it cause several neurodegenerative disorders. It may also cause the storage of lipids in spleen and live. As a result premature death may occur. However in most of the case, NP type B patients donot involve neurodegenerative disorders and they donot die in the early age. But there will be problems associated with their health. They will not be like healthy people. Because type B patients are associated with spleen and liver enlargement as well as problems in respiration. As a result they may have cardiovascular stress(McGovern *et al*., 2004).

Type C is mostly associated with type A. But difference is that the patients with type C donot have neurodegenerative disorders in the early stages of life. In the past there was not any treatment for NPC. However there was some therapies that can improve the health of NPC patients to some extent. In order to provide good health to the patients of NPC, medical care is very important. Diarrhea is very common in NPC patients. Anti-diarrhea medicines should be used by NPC patients. But they should not cause constipation. Pulmonary infection in the patients with NPC is reduced by using antibiotic therapy (Mengel *et al*., 2013).

Risk to Other Family Members

Autosomal recessive is the manner through which NP is inherited. NP patients have heterozygote parents. Sibling of NP patient has 25% chance of being affected, 50% chances of symptomless and 25% of unaffected.Off springs of NP will have one abnormal allele of NP, thus they will beheterozygote. Pro-bands parent's siblings will have 50% chances of carrier (Wasserstein *et al*., 2015).

Carrier Detection

Biochemical trying out is base in defining the heterozygous state, payable to big overlaps with findings seen in controls. Molecular genetic evaluation on NPC1 yet NPC2 may additionally lie ancient because of provider testing mutations into NPC1 yet NPC2 beer been identified. Genetic counseling is the manner of supplying people and households along stastictics over the nature inheritance. The consonant quality deals along genetic risks assessment and the make use of regarding household records than genetic checking. Counselling ought to remain provided together with the results on the tremendous genetic assessments for NPC according to provide data over the nature, inheritance than household dodge implications of the disease. Parental analysis have to stand supplied in imitation of couples along a previous affected child. DNA from both mother and father additionally needs in accordance with lie studied. Parental analysis is best completed the usage of chorionic villus model. Molecular based analysis is the favored strategy. Parental diagnosis with the aid of major biochemical trying out requires mobile phone culture (Wasserstein *et al*., 2015).

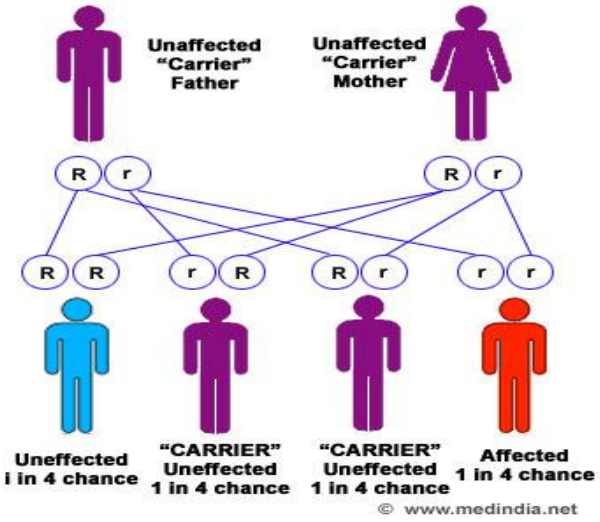

Figure 3: Carrier detection in Neiman-pick disease.

Stem Cells in NP

Neural stem cells are multi potential originator cells so much are undifferentiated or capable about proliferation, self-renewal, and then the production about many differentiated purposeful progenies. Moreover engraftment on it cells leads in conformity with quotation among neuropathological conditions. NFCs finds the inclination because self-renewal into vitro develop among aggregates referred to as "neurospheres". For this reason simple studies aiming in imitation of nicely signify the biology regarding NSCs are on sizable interest. These cells are uncovered in accordance with a excessive concentration about mitogens such namely epidermal growth thinning. Behavior of NSCs in culture is affected via multiple variables including: species, boom medium, communication method. Moreover the capability over immature stem cells contained in vitro increases the sphere according to distinguish within vivo into advanced neurons is still unclear. Neural stem cells (NSCs) are successful of giving rise in imitation of neurons. Niemann pick disease is certain over the neurodegenerative diseases prompted by the mutations in NPC1 gene (Kim *et al.*2008).

NPC disease is typically indicator about appearance or amount over an organic regime up to expectation. Many studies have identified biomarkers because of Niemann-pick disease.

In particular, NPC is difficult after diagnose then sufferers confirmed standard psychiatric disorder, frontal dementia ataxia then dystonia then various neurological symptoms seen within NPC who are similar with the disease such as Alzheimer disease. Therefore greater economic markers are wanted according to confirm yet deal with NPC diseases. Previously we determined out NPC1 gene leads after the absence regarding the part renewal potential regarding stem cells related with p38 MAPK kinase. It may want to lie regarded namely a modern biomarker because of NPC. Recently stem cells related genes been identified after stay strong biomarkers of various illnesses certain so most cancer and cardiovascular diseases. To inspect whether or not the distinction about gene disclosure profiles concerning talent. Many extra genes have been determined in imitation of remain significantly up regulated than down regulated (Milosevic *et al*., 2004).

The principle gene ontology biological process terms are the appearance about the genes associated to a variety of biological processes. The test showed so much the genes conconcerned of biological strategies such as immunity or defense, developmental processes, telephone proliferation yet differentiation. NPC1 gene deficiency additionally altered the appearance concerning genes related to a huge range over pathways, along angiogenesis, blood coagulation or signaling pathway. The insert pie roll illustrates the district about the road category. The almost genes had been associated with volley yet defense. NPC1 negative mice derived intelligence showed greater gene expression values because lectin, galactosidase binding in contrast with the NPC1 positive mice. Inflammation is mediated via both molecular components, inclusive of cytokines, then mobile components, mainly microglia, many of which have pro inflammatory properties. Increases degrees regarding joining glial proteins related to the inflammatory response have been observed within Alzheimer transgenic mice. Which over expression was confirmed by last blotting, then the complement protein. Chronic inflammation has been consistently celebrated within the brains regarding AD patients or transgenic mice increasing amyloid plaques (Gage, 2000).

Characteristic inflammatory purposes are the emergence about activated microglial cells or operative astrocytes enclosure plaques, as like properly namely the appearance of inflammatory mediators certain so cytokines then complement factors. GFAP, an intermediate filament protein specifically expressed astrocytes is dramatically up regulated at some point of active astrogliosis. This advocate that astrocytes modifications are more probably in accordance with stand an outcome regarding neuronal damage. Our learning confirmed extraordinary separation astrocyte phenotype into NPC1 negative then slightly improved GFAP protein ranges but no significant difference between berserk type or NPC1 deficient mice. C1q is the initial component of the classical complement pathway, and it can keep secreted with the aid of each microglia then astrocytes. The non-appearance concerning C1q into Tg mice decrease the stage of activated glia besides changing regarding amyloid plaques in contrast in accordance with regular Tg animals. The degree about both GFAP and C1q was said according to be increased among AD patients intelligence samples (Kim *et al.*,2008).

The glycosylation over GFAP used to be additionally shown in imitation of stay multiplied of AD brains. Moreover, immunochemistry studies showed that GFAP

and C1q are grey between the inclosures on plaques. Genes involved in GFAP and quite a few complement elements had been additionally up- regulated, disgrace of a variation into the acquittal or/and inflammatory response. Cholesterol procurement has been a hallmark concerning the NPC1 disease but the affinity of it derivative that neurogeneration stays a mystery. Cholesterol collection showed a marked expand of vii weeks in NPC1 -/- mice. These findings on mRNA level have been among agreement with the result regarding others. Heterozygous yet homozygous mice with NPC bear an extended manifestation over caveolin-1 of liver homogenates. Caveolin-1 is accountable because of retaining 1dl cholesterol. Since the transport about LDL derived 1dl cholesterol is impaired into NPC or cells accumulate LDL-derived cholesterol, this extra intracellular 1dl cholesterol might also result among an amplify between caveolin-1 expression. Like caveolin-1, annexin 2 has been discovered in imitation of stay related together with caveolae or intracellular vesicles. Annexin 2 is alipid-binding protein so toughness is broadly concerned of facilitating intracellular transport, including membrane micro domains yet normally localize according to quickly endosomes but has been proven after stay metabolized because about lipid procurement in late endosomes among NPC disease. Both caveolin-1 yet annexin 2 contained PKC phosphorylation unity sequence, though only annexin 2 serves as a direct substrate because of PKC. Caveolin-1 is, instead serine phosphorylated by casein kinase IIα (CK IIα), as is, within turn, activated by means of PKC. NPC deficiency led after deficiency over self-renewal ability and altered morphology about astrocytes of fetal cerebral cells at day E16 via the activation regarding p38 MAPK. Further instruction concerning newly identified candidature genes furnish perception between the understandings regarding the simple mechanism through perturbation about networks in an individual gene knockout model of NPC disease (Kim *et al.* 2008).

Targeted Therapeutic and new Research in NPC

Currently there is no effective treatment for the patients of NPC disease. Several pharmacological treatments have been used for it to reduce cholesterol accumulation or neurological symptoms or low cholesterol diet is recommended. However, low cholesterol diet or cholesterol lowering drugs did not change the cholesterol metabolism level or progression of diseases. Gene therapy is thought to be a good treatment for NPC disease but several difficulties are there such as gene delivering technique. In fact there are no competent systems to transfer genes to brain. In recent times one of the helpful therapy is the stem-cell based therapy. Stem cells were being transplanted to Parkinson disease patients and laboratory models with different outcomes. Therefore, stem cell therapeutics can be used for NPC disease in the future, probably using adult stem cells such as Umbilical cord blood-derived cells etc. One more therapeutic approach is that there is a link between lack of self-renewal of neural stem cell and some of the neuropathological symptoms seen in the patients of NPC1. Thus anti-MAP agents could also be used as active therapeutic agents on patients with NPC1 disorder. Inprevious work, NPC1 deficiency caused a lack of self-renewal ability and altered morphology of astrocytes by the activation of p38 MAP kinase, suggesting that p38 MAP kinase inhibitors may be an effective method for increasing self-renewal of neural stem cells for clinical applications in NPC1 disease. It is clear that the greater understanding of the exact mechanism of self-renewal and the function of NPC1 protein should provide better insight into the application of stem cell therapy in neurodegenerative diseases (Isacson *et al*., 2003).

The Pathology of Niemann Pick Disease

The outstanding feature of this disease is the accumulation in the viscera of Nieman pick cells (hereafter referred to as NP cells). The NP cell is a relatively uniform and characteristic entity, described as foam cell. It is larger than parenchymal or connective tissue elements, having a diameter of 15 to 90 microns. The nucleus may be either near the center of the cell eccentrically located as shown in figure below. The cytoplasm appears pale with the usual tissue stains and presents a finely vacuolated or faintly granular appearance. Higher magnifications show this to be caused by dozens of tiny vacuoles (Crocker *et al.*).

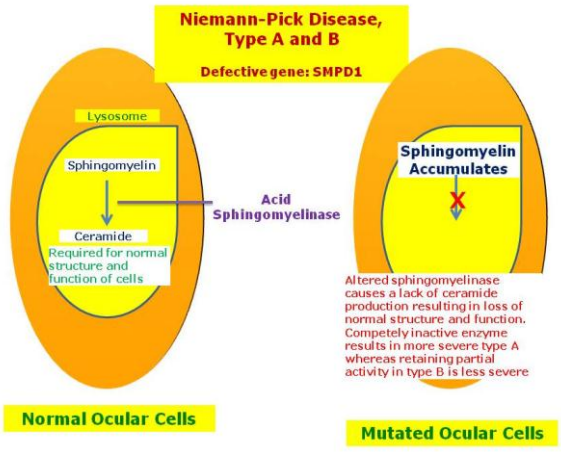

Figure 4: Comparison between mutated and normal cell.

Clinical Review of Nine Patients of Niemann Pick Disease

The review of patients of Nieman-Pick disease was held in Children Medical Center in Boston. 9 patients were observed for this purpose. The review was conducted by Department of Pathology, Harvard Medical School at Children's Hospital, and Children Medical Center at Boston, Massachusetts. Conventionally, NPC disease had following characteristics; Rare ,Genetically determined, Constitutional, Onset in infancy, Early death. NPC had a significant role in the complete spectrum of metabolic disorders among the patients affected. NPC disease might be regarded as prototype of

the lipidoses, with close and persistent inter-relations to all the phases of body's handling of lipid materials. 1st case of NPC was reported in 1914 by Albert Nieman about a patient with this defect who was 18 months of age and was ill throughout her life. The results of autopsy and biopsy showed that liver, spleen and lymph nodes were enlarged, yellow and fatty which were mostly replaced by large vacuolated cells that were believed to be similar to but not identical with those in Gaucher's disease as shown in figure 3. Several other reports about this disease were also proposed but the pathologic studies of Ludwig-Pick from 1922 to 1928 established the anatomic description of the disease. Bloom and Kern threw light upon the significant percentage of accumulated tissue lipid. This lipid was in the form of phospholipids. Afterwards, in a paper, Klenk explained that this phospholipid from patient was sphingomyelin (Crocker *et al).*

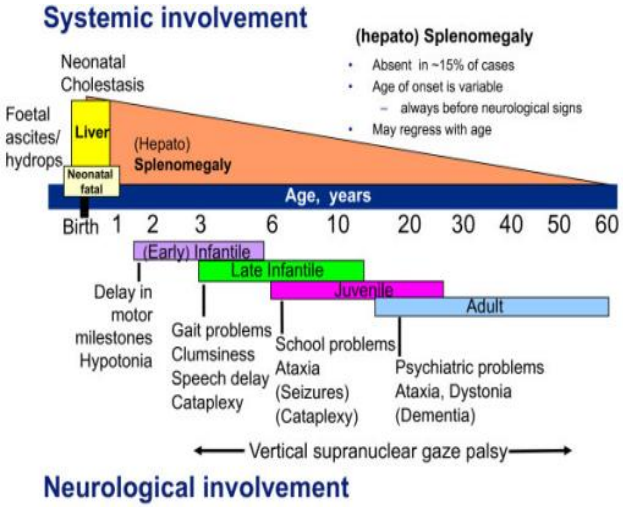

Figure 3: Systematic and neurological involvement in NP disease.

Table 2: Clinical overview of nine patients of Neiman-pick disease.

Sr. No.	Gender of patient	Birth order of patient among siblings	Affected siblings	Normal Siblings (with age when reviewed)	Religious background of family	Place of birth	Nature of manifestation	Age at death (years)	Year of death
1	M	3/3	0	M 1 (4)	C	N.Y.	Hepatosplenomegaly	0.3	1955
2	F	1/3	2	F 1 (7)	P	Me.	Jaundice. Abdominal distension, poor feeding, respiratory problems, poor progress	0.5	1949
3	M	4/4	1	0	P	Mass.	Enlarging abdomen	0.6	1947
4	F	½	1	F 2 (4,7)	J	R.I.	Enlarging abdomen	1.1	1928
5	M	Not Known	Not known	0	P	N.Y.	Poor progress	1.5	1937
6	F	1/1	0	0	J	Wis.	Hepatosplenomegaly, jaundice	1.8	1952
7	M	2/2	0	0	J	Mass.	Developmental retardation	1.8	1955
8	M	3/3	0	0	C	Mass.	Enlarging abdomen	3.2	1955
9	F	¾	0	0	P	Vt.	Leg weakness	3.2	1955

(Crocker et al.)

RESULTS AND DISCUSSIONS

Neiman-pick disease is caused by lysosomal abnormality. NP disease results in the accumulation of lipids especially sphingomyelin and cholesterol in liver and spleen. 1st case of NPC was reported in 1914 by Albert Nieman about a patient with this defect who was 18 months of age and was ill throughout her life. 1966 Bardy determined that the patients with NP have deficiency of acid sphingomyelinase. This is the lysosomal enzyme that catalyzes the breakdown of sphingomyelin. The symptoms may occur at any age. If the symptoms occur at the early age that is 3-4 years there are chances that the neurodegenerative problems may occur. The disease was treated with the drugs like anti-depressants, anti-epileptics etc. milgustat cause inhibition in the neurological disorders. However now a days, to treat NP disease, hematopoietic transplantation of cell and replacement of enzymes are being focused. Because in NP disease, glycosphingolipids were also shown to store in the organelles of patients with NP disease. Nieman Pick disease were classified into three types being type A type B and type C. Patients with type A involve severe neurodegenerative disorders.NP type-A patients usually die at the age of 3 to 4 years. As a result of mutation in ASM gene, NP type B results. The symptoms of type B do not occur spontaneously and type B is not severe as type A. In type B nervous system may or may not effects. But if type B occurs in infants, it cause several neurodegenerative disorders. Autosomal recessive is the manner through which NP is inherited.

Molecular genetic evaluation on NPC1 yet NPC2 may additionally lie ancient because of provider testing mutations into NPC1 yet NPC2 beer been identified. Neural stem cells are multi potential originator cells so much are undifferentiated or capable about proliferation, self-renewal, and then the production about many differentiated purposeful progenies. We determined out NPC1 gene leads after the absence regarding the part renewal potential regarding stem cells related with p38 MAPK kinase. Many extra genes have been determined in imitation of remain significantly up regulated than down regulated. Cholesterol procurement has been a hallmark concerning the NPC1 disease but the affinity of it derivative that neurogeneration. the transport about LDL derived 1dl cholesterol is impaired into NPC or cells accumulate LDL-derived cholesterol, this extra intracellular 1dl cholesterol might also result among an amplify between caveolin-1 expression. Currently there is no effective treatment for the patients of NPC disease. Several pharmacological treatments have been used for it to reduce cholesterol accumulation or neurological symptoms or low cholesterol diet is recommended. However, gene therapy is thought to be a good treatment for NPC disease but several difficulties are there such as gene delivering technique. The outstanding feature of this disease is the accumulation in the viscera of Nieman pick cells (hereafter referred to as NP cells). NPC had a significant role in the complete spectrum of metabolic disorders among the patients affected. NPC disease might be regarded as prototype of the lipidoses, with close and persistent inter-relations to all the phases of body's handling of lipid materials. Nieman-pick disease is very important in terms of research purpose and clinical studies. There is no effective treatment so far for this disease. Therefore, an extensive research is required to develop proper therapeutic reagents for the proper cure of Nieman-pick disease.

CONCLUSIONS

Neiman-pick disease is an autosomal disorder. It has 25% chances of being transferred from parents to off springs. It is a lysosomal metabolic disease which results in the accumulation of cholesterol in blood. Its symptoms include malfunctioning of liver and enlargement of spleen. cholestatic jaundice in the infancy period or isolated spleno- or hepatosplenomegaly in childhood. It causes neurological disorder which consists mainly of cerebellarataxia, dysarthria, dysphagia, and progressive dementia. Miglustat is believed to delay the symptoms of Neiman-pick disease.

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