NIEMANN-PICK TYPE C: CLINICAL CHARACTERISTICS, DIAGNOSIS, AND MANAGEMENT. A MINI-REVIEW

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Abstract

Niemann–Pick type C (NPC), is a lysosomal storage disorder and belongs to a group of diseases characterized by defective cholesterol trafficking. It is inherited with the autosomal pattern of inheritance. Early NPC onset is mainly characterized by visceral manifestations, while late NPC onset is characterized by neurological manifestations. The definite diagnosis of NPC is confirmed by the presence of 2 alleles with a known disease-causing mutations in the NPC1 or NPC2 genes. Miglustat is a compound that has been approved for NPC treatment in many countries, while other treatments are also under investigation. Here, we present a brief synopsis regarding the epidemiology, clinical characteristics, biomarkers, genetics, differential diagnosis and management of NPC.

Key words: Niemann-Pick type C, NPC, miglustat, neurogenetics

1. Epidemiology, Genetics, and Pathophysiology

Niemann-Pick type C (NPC), is a lysosomal storage disorder, such as Tay-Sachs and Gaucher's disease [1]. It belongs to a group of diseases characterized by defective cholesterol trafficking [2]. NPC is a genetic disorder, inherited with the autosomal pattern of inheritance [3], while its incidence is estimated to span from 0.61 to 1:100 000 births [2]. Moreover, it accounts for 1 to 2 percent of autosomal recessive cerebellar ataxias (ARCAs) [4].

Mutations in the NPC1 (Chromosome 18: 23,506,184-23,586,506, http://www.ensembl.org/Homo_sapiens/Gene/Summary?g=ENSG00000141458;r=18:23506184-23586506) and the NPC2 (Chromosome 14: 74,476,192-74,494,177, https://www.ensembl.org/Homo_sapiens/Gene/Summary?db=core;g=ENSG00000119655;r=14:74476192-74494177) genes [5-7], have been reported to cause an impaired trafficking of lipids and their consequent accumulation within cells [5-7]. Mutations in NPC1 genes are the commonest accounting for more than 9 out to 10 NPC cases, with more than 30 reported genetic alterations [8].

From pathophysiological aspect, a defective function of NPC1 or NPC2 does not allow the excretion of the cholesterol from lysosomes, leading to the accumulation of toxic cholesterol within them, and therefore leads to an injury of cells and organs, such as the brain, spleen, liver and lungs [9, 10].

2. Clinical features

Phenotypically, NPC is a slowly progressive heterogeneous disorder, with the core manifestations related to the age of onset [11]. More precisely, early onset (perinatal and infancy) is presented mainly with predominantly visceral manifestations, while the NPC with late onset is characterized by neurological manifestations [12]. An earlier onset of the neurological manifestations has been associated with poor prognosis (faster progression, increased morbidity and mortality) [13].

An overview of phenotypic appearance in patients with NPC classified by the age of onset, is presented in Table 1 [12].

3. Diagnostic Assessment

History, neurological examination, laboratory, and genetic testing contribute to the diagnosis of NPC [14]. Physicians should suspect NPC, when visceral and psychiatric/neurological manifestations are pres-

BOX 1

Early NPC onset is mainly characterized by visceral manifestations. Late NPC onset is characterized by neurological manifestations.

Table 1. Commonest phenotypic features of patients with NPC classified by the age of onset.

	Age at NPC onset				
Clinical sign/symptom	**Pre-/peri-natal (<2nd month)**	**Early infantile (<2nd year)**	**Late infantile (2nd - 6th year)**	**Juvenile (6th - 15th year)**	**Adolesence/Adulthood (>15th year)**
Systemic manifestations					
Hepatomegaly	+	+	+	+	
Jaundice	+	+	+		
Hydrops	+				
Foetal ascites	+				
Liver failure	+				
Splenomegaly	+	+	+	+	+
Pulmonary disorder	+				
Thrombocytopenia	+				
Neurological/Psychiatric features					
Hypotonia	+	+			
Motor development delay		+	+		
Speech delay		+	+		
VSGP		+	+	+	+
Spasticity		+	+		
Ataxia			+	+	+
Dystonia			+	+	+
Dysphagia		+	+	+	+
Dysarthia				+	+
Dysmetria				+	
Dyskenisia				+	+
Tremor					+
Clumsiness			+		+
Seizures			+	+	
Cataplexy			+	+	+
Hearing loss			+		
Falls			+	+	
Behavioral				+	
Cognitive decline/ Dementia					+
Psychosis					+
Depression					+

NPC, Niemann-Pick type C; VSGP, vertical supranuclear gaze palsy.

BOX 2

The definite diagnosis of NPC is confirmed by the presence of 2 alleles with a known disease-causing mutations in the NPC1 or the NPC2 genes.

BOX 3

While the Filipin test is no longer considered as the 'gold standard' for the diagnosis of NPC, it is useful in cases suspected for NPC where only one pathogenic mutation in NPC1 and NPC2 genes, is detected.

ent. However, we should bear in mind that atypical also forms exists [15-18], while specific tools are available for estimating disease severity and identifying patients in need of further investigation [12, 14, 19].

3.1. Genetic testing

Following the suspicion of NPC, patients should undergo biochemical and genetic testing. The diagnosis of NPC is confirmed by the mutation analysis of NPC1 and NPC2 genes, in patients with biomarker profile and clinical features suggestive for NPC [12, 14]. The presence of 2 alleles with a known disease-causing mutations in either the NPC1 or the NPC2 genes confirms the diagnosis of NPC [12].

Initial genetic screening for mutations in the NPC1 and NPC2 genes could be performed with Sanger sequencing, which applies polymerase chain reaction (PCR) targeting the 30 coding exons, and intron-exon boundaries, or next-generation sequencing (NGS). Full genomic DNA sequencing with NGS should be spared for patients with clinical and/or biochemical profile compatible with NPC but in which routine sequencing has not identified two known pathogenic mutations, as this methods could identify variants that cannot be interpreted easily [20], and could possibly require mRNA and/or protein studies in specialized laboratories [14].

3.2. Routine laboratory testing.

Results from routine laboratory routine tests (e.g. peripheral blood analyses, levels of lipids in plasma, levels of bilirubin levels, liver function tests, and renal test) are usually unremarkable [12]. However, increased glutamic-pyruvic transaminase (SGPT), and chitotriosidase levels, low high-density lipoprotein (HDL) cholesterol, and low blood platelet count levels can be observed [12, 21-23].

3.3. Biomarkers

Three types of biochemical markers, namely plasma oxysterols (cholesterol oxidation products), plasma lysosphingolipids and urine bale acids, can be used to increase the sensitivity and specificity of the diagnosis of NPC [12, 24, 25]. More precisely, the oxysterols cholestane-3β, 5α, 6β-triol (C-triol) and 7-ketocholesterol (7-KC), the plasma lysosphingolipids [lyso-sphingomyelin (lyso-SM) and lysosphingomyelin-509 (lyso-SM 509], and finally, the specific urine bale acides [3β-sulfooxy-7β-N-acetylglucosaminyl-5-cholen-24-oic acid (SNAG-Δ5-CA) (and itsglycine- and taurine- amides)] appear to be elevated in NPC [12, 24, 25]. However, there are few limitations regarding their applications, such as the fact that they can also be found elevated in other metabolic disorders or in heterozygotes of NPC genes mutations, that some of them can only be measured in specific research institutions at the moment, and there are difficulties in shortage [12]. This, ultimately highlights the genetic screening for mutations in NPC genes as the optimal option for the proof NPC diagnosis.

3.4. The Filipin test

While the Filipin test (a method for detection of accumulated unesterified cholesterol within the lysosomes suggesting impaired intracellular cholesterol transport and homeostasis) was considered as the 'gold standard' for the diagnosis of NPC, it is no longer considered a first line test [12,14, 26, 27].

However, it can be still be useful in the diagnostic process, especially in cases where the genetic analysis and/or biomarkers yielding inconclusive results [12]. The flipping test, is especially useful in cases suspected for NPC and only one pathogenic mutation in NPC1 and NPC2 genes, is detected [12].

3.5. Imaging

Brain imaging of NPC patients usually reveals abnormalities only in late disease stages [28]. However, atrophy (corpus callosum, mild cerebral, cerebellar vermis), demyelination, hypometabolism (in the frontal cortex, in the prefrontal cortex and thalamus), hypermetabolism (in the cerebellum, pons, and the lenticular nucleus of the basal ganglia), have been reported in studies using Magnetic Resonance Imaging (MRI), Magnetic Resonance Spectroscopy (MRS)

Table 2. Differential diagnosis of NPC based the age of disease onset.

Age at NPC onset		
Neonatal/Infatile	**Childhood**	**Adolesence/Adulthood**
Biliary atresia	Hydrocephalus	Alzheimer's Disease
TORCH infections	Brain tumor	FTD/ALS spectrum disorders
Histiocytosis	ADD	PSP
Lymphoma	subacute necrotizing encephalomyelopathy	Pick Disease
Leukemia	HIV encephalopathy	Lysosomal storage disease
Niemann-Pick disease type A	Depression	HIV dementia
Niemann-Pick disease type B	Periodic Paralyses (Hypo-, Hyper-kalemic)	Syphilis dementia
Gaucher disease	Maple syrup urine disease	
Alpha-1-antitrypsin deficiency	Wilson Disease	
Tyrosinemia type I	Neuronal ceroid-lipofuscinosis	
	Tay-Sachs disease	
	Maple syrup urine disease	
	Glutaric acidemia type 1	

NPC, Niemann-Pick type C; TORCH, Toxoplasma gondii, other agents, rubella, cytomegalovirus (CMV), and herpes simplex virus (HSV); FTD, Frontotemporal Dementia; ALS, amyotrophic lateral sclerosis; PSP, Progressive supranuclear palsy; ADD, attention-deficit disorder

and Positron Emission Tomography (PET) imaging techniques [29-32].

4. Differential Diagnosis

Considering the differences in the clinical presentations of the NPC according to the age of onset, the differential diagnosis can include various sets of diseases [33]. The differential diagnosis of NPC based on the age of disease onset is presented in Table 2 (https://www.ncbi.nlm.nih.gov/books/NBK1296/) [34].

5. Follow-up

After the diagnosis of NPC, functional assessments should be performed on regular basis in order to provide an appropriate control and management of clinical features and function. Consequently, physical examination, neuropsychiatric evaluation, calculation of the NPC clinical severity score, hearing examination, swallowing assessment, ophthalmological examination, and developmental or cognitive assessment are usually performed at diagnosis/baseline and then every 6 -12 months [12, 35-38].

6. Management

A causative treatment for NPC has not been developed yet; treatment efforts aim to alleviate symptoms and delay disease progress. Patients are also often encouraged to seek multidisciplinary guidance at large academic centers that can provide better solutions for the multifaceted health issues that arise [12, 14]. Besides the usual symptomatic treatment and frequent medical checks, substrate reduction therapy is also applied in NPC; of note, cholesterol-lowering agents have been long known to be inefficient in NPC [39]. N-butyldeoxynojirimycin (miglustat) inhibits the synthesis of glycosphingolipids and gained approval for the treatment of neurological manifestations in NPC in 2009. It has been shown to stabilize clinical progress and inhibit neurodegeneration [40]. Its commonest side-effects come from the gastrointestinal tract and seem to subside after the first 6 months of treatment [14]. The available guidelines for NPC [12] recommend miglustat -albeit not in the ultimate degree- for patients with neurological manifestations, but not for those with advanced neurological deficits and dementia, or for a concomitant disease that could lead to death within a year. Moving on, acetyl-DL-leucine has been also reported as effective for ataxic symptoms in NPC [41] and will continue to be examined in clinical trials [42]. In this regard, several ongoing clinical trials (clinicaltrials.gov) will assess other therapeutic options in NPC, namely acetyl-DL-leucine (NCT05163288, NCT03759639), arimoclomol (NCT02612129, NCT04316637), human acid sphingomyelinase (NCT01722526), intravenous and intrathecal hydroxypropyl betacyclodextrin (VTS-

270 or adrabetadex) (NCT04958642, NCT02939547, NCT04860960, NCT03471143, NCT03887533, NCT03893071, NCT02912793, NCT02534844, NCT01747135, NCT03879655, NCT03643562), vorinostat (NCT02124083), lithium carbonate (NCT03201627), intrathecal umbilical-cord-blood-derived oligodendrocyte-like cells (NCT02254863), hemopoetic stem cell infusion (NCT01372228) and transplantation of placental-derived human stem-cells (NCT01586455).

7. Conclusions

Niemann-Pick Type C disease is a rare autosomal recessive disease that based on its age of onset can exhibit various symptoms. An early disease onset is associated with visceral manifestations, while a later onset mostly presents neurological manifestations. The diagnosis is primarily set with genetic testing, aided by biochemical marker testing. Treatment-wise, a multi-disciplinary approach is necessary for tackling the heterogeneous symptoms that arise in the course of the disease. One drug, miglustat, is currently approved for NPC patients with neurological manifestations, while many more options are currently under examination.

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