Management of Niemann-Pick type C Disease

A Clinical Guideline

Niemann-Pick Guideline Development Group

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Introduction

… to Niemann-Pick type C disease

Niemann–Pick C disease (NP-C) is an autosomal recessive lysosomal lipid storage disorder associated with mutations of two different genes: NPC1 (95% of patients) and NPC2 (5% of patients). The disease is pan-ethnic, and its incidence is estimated at less than 1:100000 live births (Vanier et al., 2010) while its prevalence in Western Europe has been calculated to be approximately 1:150.000. Owing to its phenotypic heterogeneity, these numbers may well be underestimates. Recently, Wassif et al. suggested adult onset NP-C could be as high as 1:20.000. Whether or not the disease results from the defects in the NPC1 or NPC2 genes, the metabolic consequences are similar and involve a unique impairment in processing and utilization of endocytosed cholesterol, as well as the storage of a broad range of sphingolipids. The disease is often described as a cellular cholesterol trafficking defect, but the situation is more complex in the brain, where neurons accumulate mostly GM2 and GM3 gangliosides and much less cholesterol. There is also a defect in lysosomal calcium homeostasis that may play a role in the pathogenetic cascade (Lloyd Evans et al 2008). The main features of the neuropathology include neuronal storage, prominent neuronal loss (especially of Purkinje cells), ectopic dendrites, neuroaxonal dystrophy, and Alzheimer-like changes.

In neonates and infants, systemic features predominate, including prolonged neonatal jaundice and varying degrees of visceral involvement with hepatosplenomegaly with or without signs of liver failure. Some patients have pulmonary infiltrates (NPC2). Neurological manifestations dominate the picture at the beginning of late infancy. Children may manifest developmental delay and hypotonia in the second year if life; vertical supranuclear gaze palsy (VSGP) is usually not recognized in this group. Later in childhood and beyond, VSGP is frequently the earliest neurologic manifestation of NP-C, although it can easily be missed. Clumsiness evolving into overt ataxia, dysarthria, dysphagia, learning difficulties as the precursor of dementia, a variety of movement disorders (dystonia), changes in muscle tone (spasticity), and paroxysmal disorders, including gelastic cataplexy and epileptic seizures, round out the picture. Psychiatric presentations (depression, hallucinations, mood instability, aggressive or bipolar behavior), with masked or subtle neurological signs, are prominent in adolescence or adulthood, as is early onset dementia.

… to the NPC guidelines project

These guidelines have been developed by referring physicians and geneticists involved in the INPDR project (www.inpdr.org).

The experts who participate in the guidelines development are listed on the page 15.

… to the Niemann-Pick C clinical management guidelines

What are the aims of the guidelines?

These guidelines aim to provide recommendations for the diagnosis, management and follow-up of Niemann Pick type C patients. They are directed to guarantee a high quality resource for patients and families and to support professionals involved in the diagnostic and clinical management of the disease. The guidelines consider particularly the age related clinical signs and symptoms to optimize the care effort and to promote attention to transition needs.

The guidelines are divided into:

- Clinical features and diagnostic criteria.
- Baseline investigations.
- Any recommended tests, which are listed and organized into specific groups corresponding to the different symptoms and affected organs.
- Any recommendations that are specifically addressed either to children or to adult patients are specified.

A list of references organized according to the different sections of the guidelines can be found on page 11.

Additionally, a list of useful contacts for patients and families affected can be found at: www.inpdr.org/contact

Diagnosis and clinical features for Niemann-Pick type C disease

Age Range/ classification	Clinical Signs and synptoms	Laboratory	Functional tests and Imaging
Neonatal	**Visceral signs:** Prolonged neonatal jaundice Hepatosplenomegaly Signs of hepatic failure Pulmonary insufficiency **Neurological signs:** developmental delay, hypotonia	**Initial assessment:** Anemia, thrombocytopenia; abnormal liver enzymes (AST, ALT, GGT, ALP); abnormal coagulation tests (INR, PTT, PT, fibrinogen); reduced albumin. **Diagnostic tests:** Increased Chitotriosidase and plasma oxysterols; positive filipin test on skin fibroblast; NPC1 or NPC2 gene mutations	**Abdominal magnetic resonance imaging (MRI) and /or ultrasound echography (USE)**: increased volume of liver and spleen and abnormal parenchymal pattern **Chest X-ray**: interstitial thickening **EEG**: May be normal, or show slowing and/or epileptiform discharges; often evolves over time **MRI Brain**: Often normal early. Some infants show delayed or abnormal myelination. Cerebellar atrophy is usually first to appear; Thinning of the corpus callosum, appears in late stages of the illness.
Early infantile (<2 years)	**Neurological signs:** developmental delay, hypotonia **Visceral signs:** hepatosplenomegaly Signs of hepatic failure Pulmonary insufficiency	**Initial assessment:** Anemia, thrombocytopenia; abnormal liver enzymes (AST, ALT, GGT, ALP); abnormal coagulation tests (INR, PTT, PT, fibrinogen); reduced albumin. **Diagnostic tests:** Increased Chitotriosidase and plasma oxysterols; positive filipin test; NPC1 or NPC2 gene mutations	**Abdominal MRI and USE:** increased volume of liver and and spleen and abnormal parenchymal pattern **Chest X-ray**: abnormal interstitial pattern **EEG**: May be normal, or show slowing and/or epileptiform discharges; often evolves over time **MRI Brain**: Often normal early. Some infants show delayed or abnormal myelination. Cerebellar atrophy is usually first to appear; Thinning of the corpus callosum, appears in late stages of the illness.
Late infantile (2-6 years)	**Neurological signs:** developmental delay abnormal muscle tone, seizures **Visceral signs:** hepatosplenomegaly	**Initial assessment:** Anemia, thrombocytopenia; abnormal liver enzymes values (AST, ALT, GGT, ALP); abnormal coagulation tests (INR, PTT, PT, fibrinogen); reduced albumin. **Diagnostic tests:** Increased Chitotriosidase and plasma oxysterols; positive filipin test; NPC1 or NPC2 gene mutations	**Abdominal MRI and USE**: increased volume of liver and and spleen and abnormal parenchymal pattern **Chest X-ray**: abnormal interstitial pattern **EEG**: May be normal, or show slowing and/or epileptiform discharges; often evolves over time **MRI Brain**: Often normal early. Some infants show delayed or abnormal myelination. Cerebellar atrophy is usually first to appear. Thinning of the corpus callosum appears in late stages of the illness. Elevated severity score index

Juvenile (6-15 years)	**Neurological signs:** developmental delay abnormal muscle tone, seizures **Visceral signs:** (hepato)splenomegaly	**Initial assessment:** Anemia, thrombocytopenia; abnormal liver enzymes values (AST, ALT, GGT, ALP); abnormal coagulation tests (INR, PTT, PT, fibrinogen); reduced albumin. **Diagnostic tests:** Increased Chitotriosidase and plasma oxysterols; positive filipin test; NPC1 or NPC2 gene mutations	**Abdominal MRI and USE**: increased volume of liver and and spleen and abnormal parenchymal pattern **Chest X-ray**: abnormal interstitial pattern **EEG**: May be normal, or show slowing and/or epileptiform discharges; often evolves over time **MRI Brain**: Often normal early. Some infants show delayed or abnormal myelination. Cerebellar atrophy is usually first to appear. Thinning of the corpus callosum appears in late stages of the illness. Elevated severity score index
Adult (>15 years)	**Neurological signs:** developmental delay abnormal muscle tone, seizures **Psychiatric manifestations:** Psychosis, depression, hallucinations, dementia……. **Visceral signs:** (hepato)splenomegaly	**Initial assessment:** Anemia, thrombocytopenia; abnormal liver enzymes values (AST, ALT, GGT, ALP); abnormal coagulation tests (INR, PTT, PT, fibrinogen); reduced albumin. **Diagnostic tests:** Increased Chitotriosidase and plasma oxysterols; positive filipin test; NPC1 or NPC2 gene mutations	**Abdominal MRI and USE**: increased volume of liver and and spleen and abnormal parenchymal pattern **Chest X-ray**: abnormal interstitial pattern **EEG**: May be normal, or show slowing and/or epileptiform discharges; often evolves over time **MRI Brain**: Often normal early. Some infants show delayed or abnormal myelination. Cerebellar atrophy is usually first to appear. Thinning of the corpus callosum appears in late stages of the illness. Elevated severity score index
Visceral symptoms only	Hepatosplenomegaly, with or without liver failure Pulmonary infiltrates with impaired gas exchange	**Initial assessment:** Anemia, thrombocytopenia; abnormal liver enzymes values (AST, ALT, GGT, ALP); abnormal coagulation tests (INR, PTT, PT, fibrinogen); reduced albumin. **Diagnostic tests:** Increased Chitotriosidase and plasma oxysterols; positive filipin test; NPC1 or NPC2 gene mutations	**Abdominal MRI and USE**: increased volume of liver and and spleen and abnormal parenchymal pattern **Chest X-ray**: abnormal interstitial pattern **EEG**: May be normal, or show slowing and/or epileptiform discharges; often evolves over time **MRI Brain**: Often normal early. Some infants show delayed or abnormal myelination. Cerebellar atrophy is usually first to appear. Thinning of the corpus callosum appears in late stages of the illness. Elevated severity score index

Diagnosis an clinical features for Niemann-ick P type C disease

Recommended Baseline assessment /investigations in Niemann-Pick type C Disease	
Clinical Features of NP C	**Baseline investigations/assessment**
Visceral signs (liver and spleen involvement): …. biochemical parameters	- liver enzymes (AST, ALT, GGT, ALP); - total and direct bilirubin; serum protein, albumin; - INR, PTT, PT, fibrinogen. - FBC,
…. imaging tests	- Abdominal MRI and US: increased volume of liver and and spleen and abnormal parenchymal pattern
Pulmonary involvement … Imaging assessment	Chest X-ray Pulmonary HRCT
Neurological involvement: …. general neurologic examination	- cognitive delay; - movement abnormalities: ataxic gait, clumsiness, coordination state, dystonia; - abnormal muscle tone; - cataplexy; - eye movements: vertical supranuclear gaze paly; horizontal supranuclear gaze palsy later
…. auditory evaluation	- Audiometry
…. electrophysiological tests	- EEG, Auditory Brain Responses (ABR)
…. evaluation of neurological progression	- NPC Disability Scale: Ambulation – Manipulation – Speech – Swallowing - Seizures
Psychiatric involvement	Evaluate signs of suspected psychiatric involvement: hallucinations, delusions, depression, mood instability, aggressive behavior.

Recommended for the follow-up management of Niemann-Pick type C disease

I. Neonatal form laboratory parameters

Management of visceral involvement in neonatal form by a multidisciplinary healthcare team		
Laboratory differential diagnosis with other causes of neonatal hepatosplenomegaly (sepsis, hepatitis, biliary atresia, other metabolic diseases, etc)	→	a. FBC; Protein C, blood culture, b. Infection screen- TORCH, HBV, HCV, HIV, Ig; c. liver enzymes (AST, ALT, GGT, ALP); d. INR, PTT, PT, fibrinogen; e. glucose, total and direct bilirubin; serum protein, albumin; f. Total cholesterol, HDL-cholesterol, LDL-cholesterol, Triglycerides g. Galactosemia, Alpha1-antitrypsin, thyroxine, G-6-PD, other specific enzymes; h. Chitotriosidase; i. Oxysterols. j. Filipin staining
Liver imaging	→	Organ parenchymal assessment, biliary tract exam, organ size measurement by abdominal US and/or MRI
Lung involvement	→	Presence of clinical signs of respiratory distress Chest X-ray Pulmonary gas exchange monitoring

II. Early infantile (<2 years)

Management of Early Infantile NPC by a multidisciplinary healthcare team		
Differential diagnosis with other causes of early hepatosplenomegaly	→	Assessment of: FBC, Protein C, blood culture, a. Infection screen- TORCH, HBV, HCV, HIV, Ig; b. liver enzymes (AST, ALT, GGT, ALP); c. INR, PTT, PT, fibrinogen; d. glucosemia, total and direct bilirubin; serum protein, albumin; e. Total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides f. alpha1-antitrypsin, thyroxine, G-6-PD g. eventually lysosomal enzymes and enzymes whose deficiency could be responsible of protracted jaundice h. specific biomarkers: Chitotriosidase, Oxysterols
Imaging studies: …. abdominal …. lungs	→ →	Liver and spleen parenchymal assessment, biliary tract exam, organ sizes measurement by US and/or MRI Lung study for interstitial thickening
Neurological evaluation	→	a. Evaluate the presence of relevant clinical signs that could indicate the presence of neurological and cognitive deterioration b. If indicated, perform electrophysiological tests: EEG, ABR to evaluate the presence of pathological electric patterns and hearing level. c. When possible, use NPC Disability Scale d. If indicated, perform brain MRI study
Diet/feeding necessities	→	Evaluate the presence of nutritional needs, caloric intakes and support necessities (i.e. special foods, naso-gastric tube, PEG)
Pain	→	If pain present, consider the possible causes: teeth, gastric reflux, intra-tracheal gastric reflux.
Prevent infective complications	→	Consider the necessity of specific antibiotic therapy to prevent pneumonia or other infective complications.
Supportive treatments	→	Consider specific physiotherapeutic programs to sustain general motor skills

III. Late Infantile (2-6 years)

Diagnosis an clinical features for Niemann-ick P type C disease

Management of Late Infantile NPC by a multidisciplinary healthcare team		
Visceral involvement: …. hepatosplenomegaly …. lungs	→	Monitoring of hematological parameters (FBC), liver function, coagulation tests, lipid profile and oxysterols. Evaluate the presence of clinical signs of pulmonary deficiency and the necessity of imaging study Consider the necessity of respiratory support
Neurological evaluation	→	- Evaluate the presence of and history of gait abnormalities or frequent falls; - Evaluate the presence of signs of cognitive delay - If indicated, perform electrophysiological tests: EEG, ABR to evaluate the presence of pathological electric patterns and hearing level. - Use the NPC Disability Scale - If indicated, perform brain MRI study
Diet/feeding necessities	→	Evaluate the presence of nutritional problems, caloric intakes and support necessities (i.e. special foods, naso-gastric tube, PEG)
Pain	→	If pain present, consider the possible causes: dental, gastric reflux, intra-tracheal gastric reflux.
Prevent infective complications	→	Consider the necessity of specific antibiotic therapy to prevent pneumonia or other infective complications.
Supportive treatments	→	Consider specific physical therapy programs to sustain general motor skills

IV. Juvenile (6-15 years)

Diagnosis an clinical features for Niemann-ick P type C disease

Management of Juvenile NPC by a multidisciplinary healthcare team	
Visceral involvement: …. hepatosplenomegaly …. lungs	Monitoring of hematological parameters (FBC), liver function, coagulation tests, lipid profile and oxysterols. Evaluate the presence of clinical signs of pulmonary deficiency and the necessity of imaging study Consider the necessity of respiratory support Consider the prevention of aspiration pneumonia
Neurological evaluation	- Evaluate the presence of ataxic gait, clumsiness, dystonia, abnormal muscular tone, falls, ambulation support, cataplexy, seizures; - Evaluate the presence of signs of cognitive delay, speech capacity; - Use the NPC Disability Scale - If indicated, perform electrophysiological tests: EEG, ABR to evaluate the presence of pathological electric patterns and hearing level. - If indicated, perform brain MRI study
Psychiatric evaluation	Evaluate the presence of psychiatric signs: depression, hallucinations, impulsivity, agitation, sleep disorders, mood instability, other psychiatric signs Consider specific psychotropic drug treatment.
Diet/feeding necessities	Evaluate the presence of nutritional problems, caloric intakes and support necessities (i.e. special foods, nous-gastric tube, PEG)
Pain	If pain present, consider the possible causes: teeth, gastric reflux, intra-tracheal gastric reflux.
Prevent infective complications	Consider the necessity of specific antibiotic therapy to prevent pneumonia or other infective complications.
Supportive treatments	Consider specific physiotherapeutic programs to sustain general motor skills

V. Adult (>15 years)

Diagnosis an clinical features for Niemann-ick P type C disease

Management of Adult NPC by a multidisciplinary healthcare team	
Visceral involvement: …. hepatosplenomegaly	Monitoring of hematological parameters (FBC), liver function, coagulation tests, lipid profile and oxysterols.
…. lungs	Evaluate the presence of clinical signs of pulmonary deficiency and the necessity of imaging study Consider the necessity of respiratory support
Neurological evaluation	- Evaluate the presence of and history of gait abnormalities or frequent falls; - Evaluate the presence of signs of cognitive delay - If indicated, perform electrophysiological tests: EEG, ABR to evaluate the presence of pathological electric patterns and hearing level. - Use the NPC Disability Scale - If indicated, perform brain MRI study
Psychiatric evaluation	Evaluate the presence of psychiatric signs: depression, hallucinations, impulsivity, agitation, sleep disorders, mood instability, others psychiatric signs Consider specific psychotropic drug treatment.
Diet/feeding necessities	Evaluate the presence of nutritional problems, caloric intakes and support necessities (i.e. special foods, naso-gastric tube, PEG)
Pain	If pain present, consider the possible causes: dental, gastric reflux, intra-tracheal gastric reflux.
Prevent infective complications	Consider the necessity of specific antibiotic therapy to prevent pneumonia or other infective complications.
Supportive treatments	Consider specific physiotherapeutic programs to sustain general motor skills Consider the presence of bone decalcification and needing of specific therapy.

Genetics

Genetic testing	Mutation analysis in patients, and family members.
Genetic counseling	Counsel regarding the recurrence risk of 25% for each conception to parents with an affected child; counsel relatives regarding risk of carrier status and frequency of carriers in the general population.
Prenatal diagnosis	Available only for family with an index case or in which disease causing mutations have been identified.
Preimplantation Genetic Diagnosis (PGD)	Available in referral centers

You may wish to add general assessment such as:

1. ***Pain- using abbreviated pain score***
2. ***Quality of life- using SF-36 or simpler version***

INFORMATION FOR PATIENTS

Sources of information and support

The following sites contain are useful and reliable information for families and professionals:

INPDA, National Niemann-Pick Associations (www.inpda.org).
The International Niemann Pick Disease Alliance (INPDA) is a global network of non-profit patient support groups, associated with a group of rare genetic conditions known as Niemann Pick Diseases (NPD). The alliance was formed in 2009 to provide a forum for patient groups and professionals working in the field of NPD.

Gene Reviews (http://www.ncbi.nlm.nih.gov/books/NBK1296/**).**

Gene reviews is an NIH funded website based at the University of Washington, Seattle, WA, USA, that currently contains regularly updated, systematic descriptions of 639 genetic disorders. The reviews comprise clinically relevant and medically actionable information on the diagnosis, management, and genetic counseling of patients and families with specific inherited conditions.

Orphanet (www.orpha.net**)**
Orphanet is an online database and related services provided though Europe. It contains information on more than 5000 rare diseases and lists reference centers, specialists, diagnostic laboratories, patient's organizations, research projects and clinical trials.

OMIM (http://www.omim.org) (http://www.omim.org/entry/257220?search=nieman-pick%20disease%20type%20c&highlight=c%20nieman%20disease%20pick%20niemanpick%20type)
OMIM is a comprehensive, authoritative compendium of human genes and genetic phenotypes that is freely available and updated daily. The full-text, referenced overviews in OMIM contain information on all known mendelian disorders and over 12.000 genes. OMIM focuses on the relationship between phenotype and the entries contain copious links to other genetic resources.

RareConnect (www.rareconnect.org) (https://www.rareconnect.org/en/community/niemann-pick-disease-type-c)

Management of Niemann-Pick type C disease

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Clinical features

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