Management of Niemann-Pick Type A & B Diseases

(Acid Sphingomyelinase Deficiency)

A Clinical Guideline

Niemann-Pick Guideline Development Group

Project NPDR is supported by the European Commission under the Health Programme Framework

(agreement number 20121201)

version 22 Oct 2015

Introduction

… to Niemann-Pick disease type A and B

Niemann-Pick disease type A (NPA) and B (NPB) are two widely differing phenotypes of a rare genetic disorder resulting from deficient activity of the lysosomal enzyme acid sphingomyelinase, caused by mutations in the *SMPD1* gene. Acid sphingomyelinase deficiencies (ASMD) have an autosomal recessive transmission and a global estimated incidence of 0.4 to 0.6 per 100,000 (Meikle et al., 1999), with large ethnic and geographic differences. The primary enzyme deficiency leads to a progressive accumulation of sphingomyelin in systemic organs of the different phenotypes, and may also involve the central nervous system (CNS) in neuronopathic forms. A prominent secondary accumulation of other glycosphingolipids also occurs. The Niemann-Pick type A phenotype presents in early infancy with hepatosplenomegaly and poor feeding, rapidly followed by severe neurodegeneration and arrest of developmental skills. Patients usually die within the first few years of life. On the contrary, NPB is characterized by a slow, chronic progressive course, with first signs and symptoms manifestation at any age. Hepatosplenomegaly and lung infiltration are disease hallmarks, followed by secondary biochemical signs such as abnormal hepatic enzymes, anemia, thrombocytopenia, leukopenia and an atherogenic lipid profile. Bleeding tendency is frequent as well as failure to thrive and delay puberty. As in other lysosomal storage disorders, ASMD shows a continuum of phenotypes, with intermediate clinical forms between types A and B presenting with a chronic mild CNS involvement. At present no specific disease therapy has been yet available and hence management is still symptomatic, directed particularly to treat disease complications or co-morbidities. Very recently a phase I clinical trial with recombinant ASM was completed with promising results, and phase II/III trials have been commenced in pediatric and adult patients.

… to the Niemann-Pick disease type A and B Guideline Development Project

The guidelines have been developed by an international consortium of clinician, scientist and patient societies involved in the International Niemann-Pick disease registry (INPDR) project, using a robust methodology based on the one utilized by the National Institute of Clinical Excellence (NICE). The method has been adapted to suit rare conditions where the evidence base is limited, and where expert consensus plays a greater role. The members of the guideline development group are listed on page 13.

… to the Niemann-Pick disease type A and B Clinical Management Guidelines

What are the aims of the guidelines?

The guidelines aim to improve the quality of care for ASMD patients by providing clear and wherever possible, evidence-based recommendations for their diagnosis and management.

Who are they aimed at?These guidelines are provided for people with ASMD to use with their primary care and specialist clinicians since many healthcare professionals will not have had personal experience of managing types A or B of Niemann-Pick disease. As it is a multisystem disorder, people with ASMD may require various tests, screening, assessments, referrals and multidisciplinary interventions at different stages of their lives. These guidelines lay out these requirements in a clear format that is accessible to health professionals and parents who are involved in the care of an individual with ASMD.

How are they organised?

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 NPD A & B disease

Age Range	Clinical signs and symptoms	Laboratory	Functional tests and Imaging
Birth-2 yrs	Hepatosplenomegaly/ascites Jaundice Abdominal wall engorged veins Bruising/bleeding tendency Respiratory distress Failure to thrive, vomit, diarrhea Irritability - Pain - Fever Umbilical/inguinal hernia Cherry-red macula Hypo/Hypertonia Spasticity Squint Developmental delay Hydrocephalus	Anemia Thrombocytopenia Leukopenia Increased liver enzymes (AST, ALT, GGT, ALP) Hyperbilirubinemia Hyperlipidemia: increased total and LDL cholesterol, low HDL, increased trygliceride, Hypoalbuminemia Hypergammaglobulinemia Elevated chitotriosidase Reduced leukocyte/fibroblast acid sphingomyelinase (ASM) activity Presence of two SMPD1 deleterious gene mutations	Possible abnormalities at EEG, Auditory Brain Responses (ABR), Evoked Visual Potentials (EVP) Chest X-ray: increased interstitial thickening; ground-glass pattern Abnormal pulmonary High Resolution Computerized Tomography (HRCT): interstitial abnormalities, ground glass appearance, alveolar infiltrates (sometime) Abdominal ultrasound echography (USE) and magnetic resonance imaging (MRI) (liver-spleen volume measurement); portal hypertension Brain atrophy at MRI
3-18 ys	Hepatosplenomegaly Abdominal wall engorged veins Abdominal pain Bruising/Bleeding tendency Increase breath shortness Recurrent pulmonary infections Astenia - Headaches Failure to thrive - Pubertal delay Umbilical/inguinal hernia Cognitive impairment Cherry-red macula Diarrhea Joint/limb pain -Fractures	Anemia Thrombocytopenia Leukopenia Increased liver enzymes (AST, ALT, GGT, ALP) Hyperbilirubinemia Hyperlipidemia: increased total and LDL clolesterol, low HDL, increased trygliceride, Hypoalbuminemia Hypergammaglobulinemia Elevated chitotriosidase Low IGF1 Low GH Reduced leukocyte/fibroblast ASM activity Presence of two SMPD1 deleterious gene mutations.	Reduced pulmonary function (FVC, FEV1, DhLCO) Possible abnormalities at EEG, ABR, EVP ECG abnormalities: arrhythmia, ventricular hypertrophy Chest X-ray: increased interstitial thickening; ground-glass pattern Abnormal pulmonary HRCT: interstitial abnormalities, ground glass appearance, alveolar infiltrates (sometime) Abdominal MRI: liver-spleen volume measurement; portal hypertension Abnormal echocardiography: valves regurgitation, pulmonary hypertension, atherosclerotic plaques. Delayed bone age
Adulthood	Hepatosplenomegaly Abdominal pain Bruising/Bleeding tendency Increased breath shortness Recurrent pulmonary infections Astenia Headaches - Tiredness Cherry-red macula spot Diarrhea Joint/limb pain - Fractures Psychiatric signs (depression/psychosis)	Anemia Thrombocytopenia Leukopenia Increased liver enzymes (AST, ALT, GGT, ALP) Hyperbilirubinemia Hyperlipidemia: increased total and LDL clolesterol, low HDL, increased trygliceride, Hypoalbuminemia Hypergammaglobulinemia Elevated chitotriosidase Reduced leukocyte/fibroblast ASM activity Presence of two SMPD1 deleterious gene mutations.	Reduced pulmonary function (FVC, FEV1, DhLCO) Possible abnormalities at EEG, ABR, EVP ECG abnormalities: arrhythmia, ventricular hypertrophy Chest X-ray: increased interstitial thickening; ground-glass pattern Abnormal pulmonary HRCT: interstitial abnormalities, ground glass appearance, alveolar infiltrates (sometime) Abdominal MRI: liver-spleen volume measurement; portal hypertension Abnormal echocardiography: valves regurgitation, pulmonary hypertension, atherosclerotic plaques.

Recommended Baseline Investigations in Niemann-Pick type A Disease

Management of NPD type A by a multidisciplinary healthcare team

Clinical Features of NPD A	Baseline investigations
Hydrope fetalis/neonatal edema/ascites	Laboratory and imaging tests to discriminate between the different origin: infective, hepatic, cardiovascular, pulmonary, hematologic, syndromic/malformations, metabolic (consider other LSD), immune, neoplastic, maternal causes, umbilical cord/placental malformations, other rare causes.
Neurological involvement during early life (0-2 years)	Neurological examination: generalized hypotonia, failure to achieve milestones and/or progressive loss of previously achieved milestones; deep tendon hyperreflexia; opisthotonus; progression to spasticity and loss of environmental consciousness; irritability end sleep disturbances; crisis of crying; seizures; Presence of cherry red macular spot at fundus examination in about 50% of patients Electrophysiological tests: EEG, ABR, PEV (when indicated)
Nutrition and growth	Progressive feeding difficulty, Failure to thrive; vomits, diarrhea Gastro-esophageal reflux Cachectic status
Biochemical effects of storage process	Hemoglobin, leukocytes, platelets; iron, ferritin Total cholesterol, HDL-cholesterol, LDL-cholesterol Triglycerides Chitotriosidase, CCL18 Myeloma screen
Liver and spleen	Abdominal USE: liver and spleen volumes, signs of portal hypertension MRI (when necessary, considering the risk of sedation): liver-spleen volume measurement and parenchymal abnormalities Fibroscan (liver elastography)
Liver function	a) liver enzymes (AST, ALT, GGT, ALP); b) total and direct bilirubin; c) serum protein, albumin; c) INR, PTT, PT, fibrinogen d) Signs of disseminate intravascular coagulopathy
Pulmonary involvement	Progressive respiratory insufficiency; Oxygen dependency Chest X-ray: diffuse interstitial infiltrate
Skin involvement	Brownish-yellow discoloration; possible presence of xanthomas

Recommended for the Follow-Up Management of Niemann-Pick type A Disease

Laboratory parameters

Management of hepatosplenomegaly by a multidisciplinary healthcare team	
Neurodegeneration	A schedule for the monitoring of the progression of neurodegeneration has to be made on an individual basi depending on the clinical status of the patient and the course of disease progression Provide adequate physiotherapy support and counseling Head circumference/funtanelles should be monitored for signs of hydrocephalus
Liver, spleen and hematological involvement	A schedule for the monitoring of the progression of liver and spleen disease, as well as of hematological abnormalities has to be made on an individual basis, depending on the clinical status of the patient and of disease progression
Nutrition and growth	Provide the needed caloric intake Evaluate the necessity of feeding support (naso-gastric tube, PEG); consider fundoplication for severe gastro-esophageal reflux disease (GERD) Treat possible GERD and malabsorption
Pulmonary involvement	Provide respiratory support (if needed); Prevent or treat appropriately respiratory complications (i.e. ab-ingestis pneumonia, repeated infections)
Palliative care	Provide and support all needed palliative approaches and parent choices in proceeding or not with the tests/interventions

Recommended Baseline Investigations in Niemann-Pick type B Disease

Management of NPD type B by a multidisciplinary healthcare team	
Clinical Features of NPD B	**Baseline investigations**
Hematological effects of storage process	Hemoglobin, leukocytes, platelets; iron, ferritin Total cholesterol, HDL-cholesterol, LDL-cholesterol Triglycerides Chitotriosidase, CCL18 M- protein screen
Liver and spleen storage	Abdominal USE: liver and spleen volumes, signs of portal hypertension MRI: liver-spleen volume measurement and parenchymal abnormalities Fibroscan (liver elastography)
Liver function	a) liver enzymes (AST, ALT, GGT, ALP); b) total and direct bilirubin; c) serum protein, albumin; d) INR, PTT, PT, fibrinogen.
Pulmonary involvement	Functional assessment: Spirometry: FVC, FEV1, DhLCO; 6 - Minute Walking Test Imaging assessment: chest X-ray; pulmonary HRCT
Neurological involvement	Neurological examination with psychomotor developmental and cognitive level Fundus for cherry red macula Electrophysiological tests: EEG, ABR, PEV (when indicated)
Cardiac involvement	Monitoring of arterial pressure, EKG; doppler echocardiograpy; functional tests, cardiac MRI (particularly in juvenile-adult patients)
Endocrine system involvement	Growth evaluation (Tanner percentile curves); wrist X-ray for bone age; pubertal age score (Tanner score) IGF1 and GH level
Skeletal involvement	Bone density (DEXA)
Nutrition	Monitoring of: a. Caloric intake b. nutritional status and laboratory parameters c. presence of intestinal malabsorption Management of food intolerance (i.e. fat)

Recommended for the Follow-Up Management of Niemann-Pick type B disease

Functional tests and Laboratory parameters

Management of NPD type B by a multidisciplinary healthcare team		
Liver and hematological parameters	→	Periodic monitoring (individual based, depending on the clinical status of the patient) of: a. hematological tests b. tests of liver function c. lipid profile d. enhanced liver fibrosis (Fibroscan) ;
Neurological involvement	→	Periodic neurologic assessment (individual based, depending on the clinical status of the patient); when necessary, consider specific electrophysiological tests
Pulmonary involvement	→	Monitoring of imaging and functional tests according with the severity of lung disease (if present). Provide physiotherapy and respiratory support (if needed); Prevent or treat appropriately respiratory complications (i.e. repeated infections)
Cardiac involvement		In juvenile-adult patients, careful monitoring of cardiac complications (timing to be determined in collaboration with referent cardiologist): a. arterial pressure b. basal functional tests (basal ECG and/or dynamic-ECG); doppler echocardiograpy; c. cardiac CT-scan: valvular, coronaric calcifications
Nutrition and growth	→	In case of signs of malnutrition, low BMI: a. Monitoring of caloric intake during growth period or in presence of malnutrition b. Evaluate the presence of malabsorption c. Evaluate the presence of fat intolerance and give an appropriate diet counseling d. Evaluate the presence of an abnormal lipid profile e consider the needing to treat it.
Skeletal involvement	→	In the presence of osteopenia/osteoporosis, consider periodic BMD monitoring (individual based)

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

Immunological system involvement

General immunocompetence	If a history of repeated episode of infections is present, assessment of: complement fractions test of superoxide dismutase; test lymphocyte populations ; IgG, IgA, IgM; study granulocyte functions (NBT test, DHR test, phagocytosis)
Allergic evaluation	An increased allergic diathesis is reported in NPB. If present it is indicated to assess specific tests (i.e. prick tests, IgE level, RAST, etc.)

Recommended for the Follow-Up Management of Niemann-Pick type A & B disease

Genetics

Genetic testing	Testing of ASM activity is available on peripheral blood circulating leukocytes, fibroblasts, amniocytes, corial villi, and dried blood spots. Mutation (SMPD1 gene) analysis in patients and family members. Pedigree testing.
Genetic counseling	Information about recurrence (25%) to adult patients and extended family members.
Prenatal diagnosis	Available only for family with a confirmed patient or in which a disease causing mutation has been identified or both parents identified as carriers
Preimplantation Genetic Diagnosis (PGD)	Available in referral centers (with particular regard for families in which a NPA causing mutation has been identified)

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

Management of Niemann-Pick type A & B disease

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Information for Patients

Sources of information and support

The list below provides useful sources of support and information

INPDA, International Niemann-Pick Disease Association (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 NP

Individual Country-Based Niemann-Pick Associations:

- **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** (www.omim.org)

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 entriescontain copious links to other genetic resources.

- **EURORDIS** (www.eurordis.org)

EURORDIS is a non-governmental patient-driven alliance of patient organisations and individuals active in the field of rare diseases, dedicated to improving the quality of life of all people living with rare diseases in Europe.

Acknowledgements

The development of these guidelines is an outcome of work package 4 of the INPDR project (work package lead dr Bruno Bembi, Academic Medical Center Hospital Santa Maria della Misericordia, Udine, Italy)

The following people kindly contributed to this guideline:

Andria G	Federico II University of Naples, Italy
Brondani G	Academic Medical Center Hospital Santa Maria della Misericordia, Udine, Italy
Coll MJ	Fundació Clínic per a la Recerca Biomèdica, Barcelona, Spain
Dardis A	Academic Medical Center Hospital Santa Maria della Misericordia, Udine, Italy
Hiwot T	University Hospital's Birmingham, UK
Hendriksz C	Manchester Academic Health Science Centre, UK
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