Natural course of Niemann-Pick disease type C in the Netherlands

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Ethical review	Approved WMO
Status	Pending
Health condition type	Metabolism disorders NEC
Study type	Observational non invasive

Summary

ID

NL-OMON34986

Source
ToetsingOnline

Brief title
Niemann-Pick type C

Condition

- Metabolism disorders NEC

Synonym
Niemann-Pick Disease type C, NP-C

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W,Actelion Pharmaceuticals,zie G2

Intervention

Keyword: Lysosomal storage disorder, Mutations, natural course, Niemann-Pick disease type C

Outcome measures

Primary outcome

Outcome of the study will be an increased knowledge on the natural course of

Niemann Pick disease type C, more knowledge on symptoms and life expectancy. In

addition, there will be more knowledge on the geno- phenotype relation in NPC.

Secondary outcome

Not applicable

Study description

Background summary

NPC is a rare neurodegenerative disease with an approximated minimal incidence of 1:150.000 births. The primary defect Niemann-Pick type C (NPC) lies in mutations of the genes NPC1 (found in approximately 95% of NPC patients) and on NPC2 (found in about 4% of patients). In healthy individuals, NPC1 and NPC2 cooperate smoothly in realizing outbalanced intracellular lipid transport. In NPC the intracellular transport of unesterified cholesterol, glycosphingolipids and sphingosine is impaired, leading to the accumulation of unesterified cholesterol, sphingomyelin, bis (monoacylglycero)phosphate, glycoshingolipids and sphingosine in liver and spleen. In the central nervous system, levels of glucosylceramide, lactosylceramide, GM2 and GM3 gangliosides are markedly increased.

Due to structural damage to (neuro)visceral tissue, clinical features of NPC involve a broad range of aspecific systemic, neurological and psychiatric symptoms. Considering this extreme heterogeneous clinical presentation, recognising NPC in patients can be a challenging task for physicians and therefore may lead to underdetection and even misdiagnosis of NPC.

Although the onset of clinical signs and symptoms of NPC can occur at any age, mostly children and adolescents are affected. Systemic manifestions such as fetal hydrops, hepatosplenomegaly, prolonged cholestasis, respiratory failure

and hepatic failure mostly arise early in life, whereas psychiatric symptoms including schizophrenia and depression are generally found in adolescent and adult NPC patients. The neurological signs and symptoms of NPC include central hypotonia, hearing loss, seizures, cataplexy, vertical supranuclear gaze palsy, progressive ataxia, dystonia, dysphagia and dysarthria. These neurological findings have a dramatic influence on disease prognosis. The younger the age at onset of neurological symptoms, the faster will be the rate of deterioration, consequently increasing the risk of premature death.

The recent EU-commission approval of *Miglustat* as a disease-modifying drug for NPC, entails significant benefits for NPC patients, as the drug delays the onset of neurological symptoms and prolongs the survival during pre-clinical studies.

NPC patients need regular follow up by their physicians in order to measure respons to therapy and the disease course. Unfortunately, there is a lack of biochemical markers for monitoring follow up.

Study objective

The first aim of this study is to extend clinical knowledge on NPC. This has several reasons:

1) The heterogeneous clinical presentation of NPC makes extensive clinical knowledge amongst physicians a prerequisite in preventing diagnostic delay. Considering the acceleration of disease progression after the onset of neurological signs and symptoms, recognising patients as early as possible is crucial for the treatment and prognosis of NPC patients.
2) Given the chronic and in general invalidating nature of the disease, clinical knowledge is essential in counselling and supporting parents and other care-providers of NPC patients.
3) Because NPC is an inheritable disease, not only NPC patients, but also their families need accurate and up-to-date information that requires extensive knowledge of the physician.
4) With the recent developments in therapeutic options, extensive clinical knowledge can play a key role in improving not only the disease outcomes, but also the compliance in NPC patients.

The second aim of this study is to expand knowledge the genetic aspects on NP-C. This has several reasons:

1) Genetic testing provides essential information about treatment modalities and prenatal diagnostic measurements. Diagnostic measurements for NPC require time-consuming tests that need to be performed in specialized laboratories and need accurate interpretation by specialists. Increasing the rate of sequencing the NPC1 and NPC2 genes can shorten the diagnostic delay, and help the

physician to treat patients according to their specific genetic defect more rapidly. Expanding knowledge on the relation between genotype and phenotype will help.
2) Very little is known about the different genotypes in the Netherlands. Collecting information of the genetic mutations in Dutch NPC patients, increases knowledge on the relation between genotype and the course of the disease with or without treatment of Miglustat.

Study design

In deceased NPC patients, treating physicians will be asked their permission for medical records to be retrieved and studied on follow-up data of

In living NPC patients, parents or legal representatives will be asked to fill out seven questionnaires:
1) A questionnaire on medical history
2) A questionnaire to evaluate behaviour.
3) Functional adaptive behaviour as measured by the Vineland Adaptive Behavioral Scales, Second Edition (VABS-II).
4) A questionnaire to assess the functional ability of the patients. The validated *NPC functional disability rating scale* will be used.
5) A questionnaire to screen general cognitive impairment. The *Minimal Minds State Examination* will be used.
6) A questionnaire to evaluate cognitive domains that are commonly affected in NPC. The *Frontal Assessment Battery Scale* will be used.
7) A special short test for retrieval of non-specific information will be used.

Patients will be examined once in the outpatient clinic by a medical practitioner. The physical examination includes:
* General appearance
* Skin
* Head and neck
* Lymph nodes
* Eyes
* Ears nose and throat
* Heart
* Lungs
* Abdomen
* Extremities, joints and back
* Neurological and mental status

All patients will be photographed and filmed for clinical assessment of NPC.

With the permission of parents or legal representatives of patients, genetic sequencing of NPC1 and NPC2 will be performed if initial biochemical testing results were dubious or difficult to interpret. This will be assessed by sampling 2-10 ml EDTA blood of the patients. Mutational analysis will be performed in the laboratory of the Academic Medical Center in Amsterdam.

Study burden and risks

There are no risks associated with participation in the study, except for the risk of a hematoma after drawing blood. The extend of the burden for the patients participating in the study is relatively low. Patients are once seen in the out patient clinic and a developmental test is done in the home environment. Blood is only drawn if genetic sequencing showed inconclusive results.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

The patient should have undergone a filipin staining test that showed impaired intracellulair cholesterol transport and homeostasis and/ or has documented mutations in the genes NPC1 or NPC2.

Exclusion criteria

The patient, parent or legal representative of the patient is unwilling to participate or no clinical information is available.

Study design

Design

Study type: Observational non invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-03-2010
Enrollment:	45
Type:	Anticipated

Ethics review

Approved WMO
Application type: First submission

Review commission: METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL31000.018.10