# High-resolution sonographic visualisation of nerve morphological alterations over time in polyneuropathies: a possible new test for treatment response and prognosis

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| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Peripheral neuropathies |
| **Study type** | Observational non invasive |

## Summary

### ID

NL-OMON47157

**Source**
ToetsingOnline

**Brief title**
HOPE

### Condition

- Peripheral neuropathies

**Synonym**
peripheral nerve damage, polyneuropathy

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Sint Elisabeth Ziekenhuis
**Source(s) of monetary or material Support:** ZON MW

## Intervention

**Keyword:** Polyneuropathy, sonography, treatment, treatment response

## Outcome measures

### Primary outcome

Main study parameters/endpoints: sonographic neural abnormalities (nerve hypertrophy, fascicle enlargement and hypervascularisation), clinical findings (ie pattern and degree of sensory disturbance (Modified INCAT Sensory Sum Score) and muscle weakness (medical research council (MRC) sum-score and Vigorimetry), results of electrodiagnostic studies, laboratory and CSF analysis, treatment response in treated cases, Inflammatory Neuropathy Cause and Treatment (INCAT) Overall Disability Sum Score (ODSS), Rasch-built Overall Disability Scale (R-ODS). (the R-ODS CIDP will be used for patients with CIDP and MIDN, the recently developed R-ODS MMN for patients with MMN; for patients with CIAP the Modified Rankin Scale will be used, because at the moment no R-ODS is available for this type of polyneuropathy.

### Secondary outcome

Not applicable

# Study description

### Background summary

Rationale: Chronic idiopathic axonal neuropathy (CIAP), chronic inflammatory

demyelinating polyneuropathy (CIDP), multifocal inflammatory demyelinating neuropathy (MIDN) and multifocal motor neuropathy (MMN) are chronic peripheral nerve diseases with a high impact on physical functioning. CIDP, MIDN and MMN occur in relatively young people and their resulting clinical deficits have an effect on quality of life and limit work participation. There is no treatment available for CIAP. Corticosteroids are used to treat CIDP and MIDN with varying treatment responses. For treatment of CIDP, MIDN and MMN intravenous immunoglobulins (IVIg) are used, which have less side-effects than chronic corticosteroid use, but this treatment is more expensive. In the Netherlands most patients are treated with IVIg. Standard protocols are used, which are not based on personalised medicine. High-resolution sonography (HRUS) of the peripheral nerves in polyneuropathies is a rapidly evolving field of research. Standardized sonographic protocols allow assessment of multiple morphological alterations. A few studies have demonstrated multifocal enlargement of peripheral nerves in polyneuropathies. However, it is not known what the morphological changes of the peripheral nerves over time are and if HRUS is able to detect those changes in patients with CIDP, CIAP or MMN. Also it is not known if HRUS is of added value to clinical parameters in determining prognosis and treatment response in CIDP and MMN. Such findings might influence future treatment decisions.

**Study objective**

Objectives:
1. The first objective is to determine the nature and spatial distribution of sonographic abnormalities in CIAP and in CIDP, MIDN and MMN.
2. On the basis of the findings in objective 1, we will define a standardized HRUS research protocol. In this protocol only the most common affected nerves will be included for follow-up to assess the highest discriminative value between treatment responders and non-responders and in determining prognosis.
3. To determine whether this standardized HRUS protocol is of additional value to clinical and electrodiagnostic parameters in discriminating treatment responders from non-responders and determining prognosis, consisting of a consecutive group of patients with CIAP and CIDP, MIDN and MMN. If HRUS is of additional value, a prediction rule for determining treatment response and prognosis will be defined.

**Study design**

Study design:
To study objective 1, nerve sonography will be performed in clearly defined, Chronic idiopathic axonal neuropathy (CIAP), chronic inflammatory demyelinating polyneuropathy (CIDP), multifocal inflammatory demyelinating neuropathy (MIDN) and multifocal motor neuropathy (MMN). It will encompass extensive sonographic measurement in multiple nerves in both arms and legs at fixed intervals. Various sonographic parameters will be evaluated (e.g. nerve and fascicle size,

vascularisation). This study results in a description of the nature and distribution of the sonographic abnormalities for each of the investigated polyneuropathies prior to treatment and at follow-up.

To investigate objective 2, the demonstrated temporal distribution of the sonographic abnormalities will be further categorized. By selecting the parameters and nerves with the highest discriminating power between normal and abnormal, the extensive HRUS protocol will be reduced to a standardized HRUS protocol.

Two groups will evaluate objective 3. First, a group of consecutive patients with newly diagnosed CIAP and CIDP, MIDN and MMN will undergo routine clinical and electrodiagnostic evaluation, as well as the extensive HRUS protocol which will be reduced to the standardized protocol depending on the findings of objective 1 and 2. Patients will undergo sonography at fixed intervals. Second, a consecutive group of patients who are already on treatment for CIDP, MIDN or MMN will undergo the extensive HRUS protocol, which might be reduced to standardized protocol as well, at fixed intervals. We will determine whether this standardized HRUS protocol is of additional value to clinical and electrodiagnostic parameters in discriminating treatment responders from non-responders and determining prognosis. We will use the combined information of clinical presentation (MRC-sum score, Modified INCAT Sensory Sum Score and Vigorimetry), electrodiagnostic findings, clinical course and treatment response to assess this question. The Inflammatory Neuropathy Cause and Treatment (INCAT) Overall Disability Sum Score (ODSS) and Rasch-built Overall Disability Scale (R-ODS) will be used as outcome variables (The R-ODS CIDP for patients with CIDP and MIDN, the recently developed R-ODS MMN for patients with MMN; for patients with CIAP the Modified Rankin Scale will be used, because no R-ODS is available for this type of polyneuropathy). If HRUS is of additional value, a prediction rule for determining treatment response and prognosis will be defined.

Validation sub study:
15 participants of the HOPE study will undergo all study procedures and an additional sonogram performed by a different investigator, to determine if the measurements are comparable between investigators (inter-observer variability)
Five patients already participating in the HOPE study at het UMC Utrecht will undergo a second sonogram at the Elisabeth Tweesteden Hospital Tilburg to determine possible variation in sonographic measurements between different sonographic devices.
Five healthy participants at the Elisabeth Tweesteden Hospital en 5 healthy participants at the UMC Utrecht will undergo two sonograms performed by different investigators. Furthermore five heatlhy participants will undergo a sonogram at the UMC Utrecht and a second sonogram on a different device at the Elisabeth Tweesteden Hospital Tilburg.

## Study burden and risks

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Clinical examination, laboratory results and electrodiagnostic studies are part of the standard clinical evaluation of patients clinically suspected for polyneuropathy. The additional burdens that are required for this study are two follow-up visits in which patients will undergo nerve sonography (estimated duration 60 minutes), as well as a nerve sonography during the primary assessment (three nerve sonographic examinations in total). Nerve sonography has proven to be safe, reliable, effective, non-invasive and is usually well tolerated.
In addition patients will undergo a physical examination during follow-up visits and questionnaires will be sent to patients before follow-up visits, which will be collected at the follow-up visit. These procedures are needed to determine several endpoints (Vigorimetry, MRC Sum Score, Modified INCAT Sensory Sum Score, INCAT ODSS, R-ODS and MRS).

Extra sonographic examination after 6 months for patients with newly diagnosed CIDP, MIDN or MMN:
In the group of patients with newly diagnosed CIDP, MIDN or MMN, in addition to the standard sonographic examinations at inclusion, 1 and 2 years follow-up, an extra sonographic examination will be performed at 6 months follow-up. This will be done to evaluate possible early changes in nerve morphology in this specific group of patients with an early stage of a type of polyneuropathy for which treatment is available. These early findings might be relevant for determining the prognostic value of nerve sonography and early treatment response. Those findings might be missed if the standard sonography at 1 year follow-up is performed only.

Optional extra EMG after 2 years
In order to compare EMG and Sonographic data after follow-up participating centres can perform an optional additional EMG at 2 year follow-up. In order to limit burden for participating patients this will be a reduced protocol only investigating the nerves of the most severely impaired arm.

Validation sub study:
Twenty patients already participating in the HOPE study will undergo a second sonogram estimated duration 45 minutes. Furthermore 15 healthy participants will undergo two sonograms estimated duration 90 minutes. In 5 of the HOPE participants and 5 healthy participants sonographies will be performed at different sites (ETZ and UMC Utrecht), therefore study participation for those participants will consume more time. Those patients will receive refunds for their travel expences in order to prevent financial costs for their participation.

# Contacts

**Public**
Sint Elisabeth Ziekenhuis

Hilvarenbeekseweg 60
Tilburg 5000 LC
NL
**Scientific**
Sint Elisabeth Ziekenhuis

Hilvarenbeekseweg 60
Tilburg 5000 LC
NL

# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adults (18-64 years)
Elderly (65 years and older)

## Inclusion criteria

Study objective 1 and 2: 20 patients with CIAP, 20 with CIDP/MIDN and 20 with MMN who are on treatment.
Study objective 3: All newly diagnosed CIAP, CIPD and MMN patients and 70 patients with CIDP/MIDN and 60 patients with MMN who are on treatment will be included.

## Exclusion criteria

Exclusion criteria
A potential subject who meets any of the following criteria will be excluded from participation in this study: age <18 or >80 years, prior history of polyneuropathy other then CIDP, MIDN or MMN, physically unable to undergo electrodiagnostic or HRUS of the peripheral nervous

system (e.g. cast, recent pelvic fracture or prosthetic operation, extensive reconstructive surgery on the extremities).

# Study design

## Design

**Study type:** Observational non invasive

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

## Recruitment

NL

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| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 23-04-2015 |
| Enrollment: | 265 |
| Type: | Actual |

# Ethics review

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| Approved WMO Date: | 09-02-2015 |
| Application type: | First submission |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 18-05-2015 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 28-05-2015 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 16-09-2015 |

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| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 07-04-2016 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 11-05-2016 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 24-05-2018 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |

# 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 | NL50375.028.14 |