Improving the clinical usefulness of skin biopsy in small fiber neuropathy: examining the intraepidermal nerve fiber density dynamic longitudinally and the importance of adding the proximal/distal ratio

Published: 28-12-2016
Last updated: 17-04-2024

In this study, we will determine the IENFD after at least one year since the first skin biopsy was taken, in patients with the diagnosis of SFN based on the clinical picture and abnormal TTT, but with a normal IENFD at presentation. A biopsy will be...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Peripheral neuropathies
Study type	Observational invasive

Summary

ID

NL-OMON53010

Source
ToetsingOnline

Brief title
Improving the clinical usefulness of skin biopsy in small fiber neuropathy

Condition

- Peripheral neuropathies

Synonym
small fiber neuropathy

Research involving

Human

Sponsors and support

Primary sponsor: Medisch Universitair Ziekenhuis Maastricht
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: IENFD, proximal/distal ratio, skin biopsy, sodiumchannelopathy

Outcome measures

Primary outcome

- Current IENFD at the ankle compared with the IENFD that has been taken during the regular visit, at least one year before. The degree of IENFD decrease or increase over time (corrected for expected age-dependent decline) will be computed. Furthermore, the percentage of IENFD results that turn from normal into abnormal will be calculated.

- Proximal/distal IENFD ratio normative values.

- The proximal/distal IENFD ratio compared between SFN patients and healthy subjects.

Secondary outcome

- Change in number of complaints on the SFN-SIQ related to IENFD alteration.

- Number of complaints on the SFN-SIQ related to proximal/distal IENFD ratio.

- Change in VAS related to IENFD alteration.

- VAS-score related to proximal/distal IENFD ratio.

- Changes on NPS related to IENFD alteration.

- NPS-score related to proximal/distal IENFD ratio.

- The value of abnormal TTT at baseline as predictor of abnormal IENFD in

future.

Study description

Background summary

Small fiber neuropathy (SFN) is a condition in which the smallest nerve fibers are affected, characterized by neuropathic pain and autonomic dysfunction. According to the international criteria, the diagnosis SFN is based on clinical symptoms in combination with abnormal temperature threshold testing (TTT) levels and/or reduced intraepidermal nerve fiber density (IENFD) in skin biopsy. The IENFD reflects the severity of axonal degeneration and is an objective and reliable tool. However, it has a moderate sensitivity to confirm the diagnosis SFN, resulting in false negative findings. It is known that IENFD decreases with age, but only one study has been performed to monitor IENFD during disease course. It is conceivable the decrease of IENFD occurs faster in SFN than in healthy people. Besides, at the moment only the distal IENFD is used to establish the diagnosis SFN. This location is chosen because of the length-dependent general acceptance of its pattern, although non-length dependent forms have been published. To show the length-dependency the proximal/distal IENFD ratio could be used. It is hypothesized that this ratio might be higher in SFN than in healthy subjects. Both follow-up of IENFD and determination of the proximal/distal IENFD ratio may have implications for the diagnostic strategy in patients with possible SFN, because IENFD may be normal at presentation and decrease to abnormal over time, or will remain within the normal range, but might show an increased proximal/distal ratio compared with healthy people.

Study objective

In this study, we will determine the IENFD after at least one year since the first skin biopsy was taken, in patients with the diagnosis of SFN based on the clinical picture and abnormal TTT, but with a normal IENFD at presentation. A biopsy will be taken at the ankle and at the thigh of the same leg. We will differentiate between patients with idiopathic SFN and patients with a sodium channelopathy related SFN. Since no proximal/distal IENFD ratio normative values are present, we will include a healthy age-/gender-stratified control group. Second, we will investigate the relationship between the change of IENFD, proximal/distal IENFD ratio and the amount and severity of SFN complaints (reported with the SFN-symptom inventory questionnaire, visual analogue scale for pain and neuropathic pain scale), and the TTT results. Sensitivity and specificity comparison studies will be performed to determine which technique or combination of findings will yield the highest clinically

applicable method.

Study design

The study is a non-randomized, longitudinal study.

Study burden and risks

The estimated time of duration for the examination is maximal 60 minutes. During this time, the subjects will be asked about their actual complaints and neurological examination will be conducted. Also, the subjects need to fill out questionnaires and will undergo a skin biopsy. Patients also need to travel to/from our hospital.

Contacts

Public
Medisch Universitair Ziekenhuis Maastricht

Oxfordlaan 10 Oxfordlaan 10
AZ 6201
NL
Scientific
Medisch Universitair Ziekenhuis Maastricht

Oxfordlaan 10 Oxfordlaan 10
AZ 6201
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Group 1 (n=40) Idiopathic SFN, with normal IENFD:
a) Male and female subjects of 18 years or older.
b) >=2 positive answers on the SFN-SIQ, not otherwise explained.
c) Normal IENFD and abnormal TTT, according to the international normative values,3,23 during the regular visit in our clinical center at least one year ago.
d) Written informed consent.Group 2 (n = 40) Sodium channelopathy-related SFN, with normal IENFD:
a) Male and female subjects of 18 years or older.
b) >=2 positive answers on the SFN-SIQ, not otherwise explained.
c) Normal IENFD and abnormal TTT, according to the international normative values,3,23 during the regular visit in our clinical center at least one year ago.
d) Possibly pathogenic, probably pathogenic or pathogenic NaV1.7, Nav1.8 and/or NaV1.9 variant
a) Written informed consent.Group 3 (n=140) Healthy subjects (only proximal/distal IENFD ratio study)
a) Male and female subjects of 18 years or older.
b) Written informed consent.Group 4 (n = 20) Idiopathic SFN, with abnormal IENFD (only proximal/distal IENFD ratio study)
a) Male and female subjects of 18 years or older.
b) >=2 positive answers on the SFN-SIQ, not otherwise explained.
c) Abnormal IENFD, according to the international normative values, during the regular visit in our clinical center at least one year ago.
d) Written informed consent.When it appears that the proximal/distal ratio is abnormal in patients with an abnormal TTT, but normal IENFD, the study will be extended with an extra group of patients:Group 5 (n=40) Idiopathic clinical SFN, with both normal IENFD and TTT
a) Male and female subjects of 18 years or older.
b) >=5 positive answers on the SFN-SIQ, not otherwise explained.
c) Patients with a normal IENFD and normal TTT, according to the international normative values, during the regular visit in our clinical center at least one year ago.

Exclusion criteria

All patient groups:
a) Underlying cause of SFN (diabetes, hypothyroidism, renal failure, vitamin B12 deficiency, monoclonal gammopathy, alcohol abuse (more than 5 IU/day), malignancies, drugs that cause neuropathy (e.g. chemotherapy, amiodarone, propafenone)).
b) Large nerve fiber involvement (i.e. weakness, loss of vibration sense,

hypo-/areflexia, abnormal nerve conduction studies).Groups 1, 4 and 5
a) Possibly pathogenic, probably pathogenic or pathogenic NaV1.7, Nav1.8 and/or NaV1.9 variant.Healthy subjects
a) >1 positive answer on the SFN-SIQ.
b) A history of peripheral neuropathy.
c) Signs of peripheral neuropathy in neurological examination.nt claCC

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	26-11-2018
Enrollment:	280
Type:	Actual

Ethics review

Approved WMO

Date:	28-12-2016
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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	NL54704.068.16