

Reference values for peptidergic and non-peptidergic intra-epidermal nerve fiber density in the human hand and distal leg.

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The aim of this study is to provide reference values for peptidergic and non peptidergic intra-epidermal nerve fiber density of the hand and distal leg. Furthermore, we will compare the intra-epidermal nerve fiber density of three biopsy sites of...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Peripheral neuropathies
Study type	Observational invasive

Summary

ID

NL-OMON46631

Source

ToetsingOnline

Brief title

PANPIEF study

Condition

- Peripheral neuropathies

Synonym

not applicable: healthy volunteers

Research involving

Human

Sponsors and support

Primary sponsor: RadboudUMC

Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: human, intra-epidermal nerve fiber density, peptidergic, reference values

Outcome measures

Primary outcome

The primary outcome will be the peptidergic and non-peptidergic intra-epidermal nerve fiber density of the hand and distal leg. Reference values for intra-epidermal nerve fiber density will be stratified for age and for gender and will be provided as the 5th percentile and the mean. Intra-epidermal nerve fiber density will be expressed in fibers/mm.

Secondary outcome

The secondary outcome is the difference in intra-epidermal nerve fiber density between the 3 different biopsy sites of the hand. Furthermore, we will describe adverse events in case they occur.

Study description

Background summary

Neuropathic pain yearly develops in around 1% of the Dutch general population and has a worldwide prevalence estimated between 6.9% and 10%. As neuropathic pain responds poorly to standard pain therapies, patients have a lower health-related quality of life. Treatment specifically for neuropathy and neuropathic pain, like anticonvulsants and anti-depressants, will only be initiated after diagnostic tests have been performed. Skin biopsy for diagnosing peripheral neuropathy in the distal leg by objectively quantifying nerve fibers in the epidermis is a reliable and safe technique and has become a valuable addition to existing neurophysiologic tests. Tests like electromyography and nerve conduction studies focus mainly on large nerve fibers, whereas QST and skin biopsy focus on small nerve fibers. An advantage of the skin biopsy is that it can detect changes in the quantity of nerve

fibers while conventional neurophysiologic tests cannot. Furthermore, the skin biopsy provides a quantitative value, making this technique suitable for follow-up of progression or recovery of neuropathy.⁵ The advantage of skin biopsy over QST is that skin biopsy is completely objective whereas QST is dependent on participation of the patient.

In the skin biopsy the small nerve fibers are counted by using an immunohistochemical staining with the pan-axonal marker anti-protein gene product 9.5 (PGP9.5). Unfortunately, the PGP9.5 staining cannot discriminate between subgroups of small nerve fibers. These fibers detect painful stimuli in the skin and can be divided in peptidergic A-delta and C fibers and in non-peptidergic C fibers. A-delta fibers are thinly myelinated, whereas C fibers are unmyelinated. Peptidergic and non-peptidergic fibers can be further divided by expression of neuropeptides and receptors: Calcitonin gene-related peptide (CGRP) and Substance P (SubP) are predominantly expressed on peptidergic C-fibers but can also be found on A-delta fibers. Neurofilament 200 (NF-200) is expressed on peptidergic A-delta fibers but also on larger myelinated A fibers and can therefore be used as a marker for myelination. Non-peptidergic C-fibers express receptor P2X3. Recent studies in rats have shown that this distinction may be of clinical importance, as regeneration after nerve injury is mostly done by peptidergic fibers. Along with the increase in peptidergic fibers, hypersensitivity develops. Eventually the increase of peptidergic fibers leads to recovery of the total amount of small nerve fibers, but hypersensitivity is still present and the ratio of peptidergic and non-peptidergic fibers is changed as compared to the physiological situation. Furthermore, Schüttenhelm et al. studied the intra-epidermal nerve fiber density in two itch models and one inflammation model of the skin. They found significant changes in peptidergic fibers in all three models and significant changes in non-peptidergic fibers in one model. This shows that peptidergic and non-peptidergic fibers play roles in different pathologies, like the development of neuropathic pain and skin disorders. Therefore, it is important to discriminate between peptidergic and non-peptidergic fibers. As this distinction cannot be made with the PGP9.5 staining, there are no reference values of peptidergic and non-peptidergic fibers in the human skin. Clinically, this could be problematic for patients with complaints of neuropathic pain but skin biopsy with PGP9.5 staining showing a normal nerve fiber density, while the ratio of peptidergic and non-peptidergic fibers is changed. Because they cannot be diagnosed adequately, they might not receive optimal treatment for their neuropathic pain complaints. Previous studies of intra-epidermal nerve fibers density have shown different nerve fiber densities between different biopsy sites all over the human body, thus it is not possible to use the reference values of the distal leg for other parts of the body. No reference values adjusted for age and sex have been provided for the hand, so diagnosing neuropathies in the hand affecting only the small nerve fibers is problematic. As there might be a difference in intra-epidermal nerve fiber density between the innervation territories of the median, ulnar and radial nerve, we will take to biopsies from the palm of the hand and one of the dorsum of the hand respectively. We will compare the intra-epidermal nerve fiber density of the 3

biopsy sites of the hand and if they differ from each other, we will give reference values of all 3 sites. If they do not differ from each other, we will give reference values for only 1 site of the hand.

New information provided by this study will be reference values of the intra-epidermal nerve fiber density for the hand with the distinction between peptidergic and non-peptidergic nerve fibers, which will also be provided for the distal leg. In order to provide these reference values we need healthy volunteers without any signs of neuropathy or risk factors for neuropathy. Since intra-epidermal nerve fiber density is age dependent, we will need to include volunteers of all ages (above 17 years old).

Study objective

The aim of this study is to provide reference values for peptidergic and non-peptidergic intra-epidermal nerve fiber density of the hand and distal leg. Furthermore, we will compare the intra-epidermal nerve fiber density of three biopsy sites of the hand to analyse whether there is a difference.

Study design

The study design is observational with invasive measurements. We will approach volunteers of 18 years or older to participate. All volunteers will have to fill out a questionnaire about their medical history regarding possible neuropathic conditions and will undergo neurological exam. When they do not meet the exclusion criteria, volunteers will be included in the study and get an appointment for taking 4 skin biopsies from the hand and distal leg. One biopsy will be taken from the distal leg, 10cm above the lateral malleolus. The other 3 biopsies will be taken from the hand from areas innervated by the median, ulnar and radial nerve. When we have data on nerve fiber density of the different biopsy sites of 20 volunteers, we will compare them to find out whether there is a difference. If that is the case, we will only take biopsies from the sites that are different from each other. If that is not the case, we will compare the three sites again after 41 volunteers. If we find no difference then, we will only take one biopsy from the hand and the distal leg. After obtaining the skin we will use immunohistochemical stainings to determine the nerve fiber density, which will be expressed in fibers per millimeter. We will use the protocol for the staining and counting as described by Lauria et al.

Reference values will be stratified by age and gender.

Study burden and risks

After volunteers have signed the informed consent form, they will be asked to fill out a questionnaire about their medical history regarding possible neuropathic conditions. If they do not meet any of the exclusion criteria they

will undergo neurological exam. Then, if neurological exam is normal, the volunteer will be included and four skin biopsies will be taken; 3 from the hand and 1 from the distal leg. Skin will be locally anesthetized before taking 3mm circular biopsies. The injection will give physical discomfort and might be painful, especially in the hand. The biopsies will leave 4 small wounds. Volunteers will be advised not to lift heavy things with the biopsied hand until 7 days after the biopsies are taken. The wounds do not need suturing and heal within 7-10 days. Nevertheless, if volunteers wish to get the wounds sutured or if the wounds keep bleeding, we will use sutures. Obtaining a skin biopsy from the distal leg has been shown to be a safe procedure for determining intra-epidermal nerve fiber density, with an incidence of adverse events of 1.9 out of 1000 biopsies and no serious adverse events. There are no numbers of adverse events in the hand, but we estimate these will be comparable to adverse events in the distal leg. Possible adverse events are mild infection and excessive bleeding. Participating in this study will take volunteers approximately 1 hour and the risk for adverse events is very low. With the reference values for peptidergic and non-peptidergic nerve fibers for the leg and hand this study provides new information that can extend the use of the skin biopsy as diagnostic test for neuropathy, therefore we believe that the benefits will outweigh the disadvantages.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age

Adults (18-64 years)

Elderly (65 years and older)

Inclusion criteria

- competent male or female volunteers of 18 years or older, who can speak and understand the Dutch language

Exclusion criteria

- Proven or suspected neuropathy
- Nerve injury and/or neuropathy in one or both hands or legs
- Abnormal neurological exam
- Diabetes mellitus
- Vitamin B12 deficiency
- Hypothyroidism
- Malignancy
- Renal failure
- HIV/AIDS
- skin disorders at the hands or legs
- (history of) chemotherapy
- (history of) chronic alcohol abusis, >4IU/day

Study design

Design

Study type: Observational invasive

Masking: Open (masking not used)

Control: Uncontrolled

Primary purpose: Diagnostic

Recruitment

NL

Recruitment status: Will not start

Enrollment: 120
Type: Anticipated

Ethics review

Approved WMO
Date: 25-07-2018
Application type: First submission
Review commission: CMO regio Arnhem-Nijmegen (Nijmegen)

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	NL62052.091.18