Relation between human islet amyloid polypeptide (hIAPP) and pain phenotype in chronic idiopathic axonal polyneuropathy (CIAP) and diabetic polyneuropathy (DPN) patients

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

Summary

ID

NL-OMON57344

Source
ToetsingOnline

Brief title
The relation between hIAPP and painful polyneuropathy

Condition

- Peripheral neuropathies

Synonym
diabetic polyneuropathy; nerve pain

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: Argenx

Intervention

Keyword: CIAP, hIAPP, neuropathic pain, polyneuropathy

Outcome measures

Primary outcome

The main study parameters are pathogenic oligomer hIAPP levels in plasma and

skin.

Secondary outcome

Secundary outcome measures are pain and sensory assessments using questionnaire

data, QST, intraepidermal nerve fiber (IENF) density, CPM, sublingual and skin

HVM, and neuroinflammatory markers in plasma.

Study description

Background summary

Polyneuropathy affects approximately 75-125 per 100,000 individuals, with 5-30% classified as chronic idiopathic axonal polyneuropathy (CIAP) and 30 to 50% as diabetic polyneuropathy (DPN). CIAP and DPN lead to progressive damage to peripheral nerves, resulting in diverse symptoms and functional limitations. Neuropathic pain is present in 60% of cases, negatively impacting various quality of life domains. At present disease-modifying treatments are unavailable, leaving patients reliant on symptom-based approaches like anti-neuropathic drugs.
Recent findings, suggest that human islet amyloid polypeptide (hIAPP), which can form pathogenic oligomers, is involved in the pathophysiological process of painful DPN. We found that hIAPP-transgenic mice, which have elevated plasma hIAPP levels without hyperglycaemia, developed peripheral neuropathy as evidenced by pain-associated behaviour and reduced intraepidermal nerve fiber (IENF) density. Type 2 diabetic patients had reduced IENF density and more hIAPP oligomers in the skin compared with non-diabetic controls.

The hIAPP oligomers may also influence the microcirculation as is seen with amyloid deposits in blood vessels in other diseases. By employing hand-held vital microscopy (HVM) we aim to identify potential microcirculatory inflammation and accumulation of hIAPP aggregates.
The exact relation between hIAPP and pain phenotype in DPN patients is unknown. As CIAP has been associated with metabolic syndrome, we hypothesize a common pathophysiological pathway in CIAP and DPN with hIAPP as a potential disease-modifying target. In current study we will further explore this relation between hIAPP levels in plasma and skin and pain and sensory disturbances in CIAP and DPN patients. To investigate whether the pathophysiological pathway involving hIAPP oligomers is specific to CIAP and DPN, we will include a control group with patients with chronic peripheral neuropathic pain after a varicella zoster reactivation, referred to as postherpetic neuralgia (PHN), not associated with changes in hIAPP plasma levels (plasma and skin samples from METC 19-099).

Study objective

The primary objective of phase 1 is to validate a new ELISA measurement that can determine hIAPP oligomers reliably in plasma, and of phase 2 is to correlate pathogenic oligomer hIAPP (in plasma and skin) with pain and sensory disturbances in CIAP and DPN patients. Secondary objectives are 1) to compare hIAPP and pathogenic oligomer hIAPP levels in plasma and skin between CIAP, DPN and PHN patients, 2) to compare hIAPP and pathogenic oligomer hIAPP levels in plasma and skin between CIAP and DPN patients with and without pain, 3) to correlate pathogenic oligomer hIAPP levels with a neuroinflammatory biomarker phenotype in CIAP and DPN patients, and 4) to monitor sublingual and skin microcirculatory inflammation, perfusion and hIAPP oligomers using HVM, and correlate it to a neuroinflammatory biomarker phenotype in CIAP and DPN patients.

Study design

Observational study with invasive measurements and biobanking of residual blood and skin after analyse.

Study burden and risks

Benefit: The obtained knowledge may contribute to more understanding of the pathophysiology of painful polyneuropathy and may lead to the development of a mechanism-based therapy (antibody for hIAPP developed and produced by argenx) in the future. Patients with severe pain are offered to receive health care at the pain clinic of the UMCU. Travel expenses will be compensated for the hospital visit.

Disadvantages:

Patients themselves have no direct benefit from participating in this study.

Risks: The collection of blood and the skin biopsies have negligible risks .
There is no risk involved in the QST, CPM and HVM measurements as they are non-invasive.

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

o Aged 18 years or older
o Diagnosed by a neurologist with CIAP[24] based on the following criteria
o Presence of symmetrical distal sensory or sensorimotor symptoms such as numbness, pins and needles, tightness, coldness, unsteadiness, muscle cramps, and weakness with onset in the lower limbs, compatible with polyneuropathy

o Nerve conduction studies excluding a demyelinating polyneuropathy and confirming large nerve fiber involvement in at least two distinct peripheral nerves
o No identifiable cause for the polyneuropathy after thorough history-taking, clinical examination, and extensive laboratory testing including complete blood count, glucose, HbA1c, insulin, renal function, liver enzymes, creatine kinase, C-reactive protein, vitamin B1, vitamin B6, folic acid, vitamin B12, homocystein, cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, and thyroid-stimulating hormone
o Diagnosed by a physician with DPN based on the following criteria
o Diagnosed with Diabetes Mellitus Type 2 based on the NHG standard
o Presence of symmetrical distal sensory or sensorimotor symptoms such as numbness, pins and needles, tightness, coldness, unsteadiness, muscle cramps, and weakness with onset in the lower limbs, compatible with polyneuropathy.
o A Douleur Neuropathique en 4 (DN4)[25] questionnaire score of 4 or higher
o Able and willing to give written informed consent.

Exclusion criteria

- Patients who have other types of pain, which could confound the assessment of the
neuropathic pain due to CIAP or DPN.
- Patient who received Capsaicin 8% patch treatment in the 3 months before inclusion
- Patients with skin conditions in the area affected by the polyneuropathy that could
alter sensation.
- Patients with major cognitive or psychiatric disorders.
- Problems with communication (language, deafness, aphasia etc.)

Study design

Design

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-03-2025
Enrollment:	100
Type:	Anticipated

Medical products/devices used

Registration:	No

Ethics review

Approved WMO

Date:	05-03-2025
Application type:	First submission
Review commission:	METC NedMec

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	NL88118.041.24