Sodium channel mutations (SCN9A, SCN10A) in anterior cutaneous nerve entrapment syndrome (ACNES)

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

Summary

ID

NL-OMON53262

Source
ToetsingOnline

Brief title
Nav-ACNES

Condition

- Peripheral neuropathies

Synonym
Abdominal wall nerve entrapment, Chronic abdominal wall pain (CAWP)

Research involving
Human

Sponsors and support

Primary sponsor: Maxima Medisch Centrum
Source(s) of monetary or material Support: Stichting SolviMáx Research

Intervention

Keyword: ACNES, Chronic abdominal wall pain, Genetic predisposition, Sodium channel mutations

Outcome measures

Primary outcome

Number of SCN9A and SCN10A mutations. Each mutation will be classified in one

of three classes: unknown pathogenicity, probable pathogenicity and pathogen

variant.

Secondary outcome

To see if there are differences between patients with and without mutations and;

- Known cause of ACNES (surgery, trauma/sport, pregnancy or (viral)infection);

- Mean pain score (NRS 0-10) at start of the treatment;

- Treatment response defined following IMMPACT (the Initiative on Methods,

Measurement, and Pain Assessment in Clinical Trials) recommendations: Treatment

is successful if the patient does not need additional treatment, or has >=50%

pain relief, or >=4 points decrease in NRS score.

Study description

Background summary

Chronic abdominal pain is often due to the anterior cutaneous nerve entrapment syndrome (ACNES). It is theorized that ACNES is caused by a nerve entrapment in the rectus abdominis muscle due to pushing or pulling forces, which cause the pain. This theory is supported by patients who have reported ACNES pain after an increased force on the abdominal wall, such as (laparoscopic) abdominal surgery (20%), trauma/sports (5%) or during/after pregnancy (<10%). However, more than half of patients report a spontaneous onset of pain, which suggests that the pathophysiology is more complex than just an entrapment. The International Association for the Study of Pain (IASP) has defined neuropathic pain as: pain that arises as a direct consequence of a lesion or disease affecting the somatosensory

system. Due to the lesion of the nerve (the entrapment in ACNES) the membrane of the neurons changes, resulting in a hyperexcitable state. Consequently, the nociceptive threshold will be lower and the nerve will start generating spontaneous discharges. This increase in discharges will cause a neuropathic pain signal in the central nervous system. Moreover, these spontaneous discharges will stimulate central sensitization, a phenomenon which magnifies the signals from other non-affected neighboring nerves. Voltage-gated sodium (Nav) channels play an important role in the excitability of the neuron membrane. Therefore, it is believed that the hyperexcitability is caused by an alteration of the different Nav channels, which could be a change in function, density, or redistribution along the neuron membrane. There are three Nav channels present in the dorsal root ganglion (DRG) and the peripheral nervous system: Nav1.7, Nav1.8, and Nav1.9. Of these, Nav1.7 and Nav1.8 are well known to contribute to neuropathic pain, yet the role of Nav 1.9 in neuropathic pain remains less clear. For this reason, only Nav1.7 and Nav1.8 will be investigated in the present study. It is known that the presence of certain Nav channels is genetically encoded in the human genome, and the genes that encode for Nav1.7 and Nav1.8 are SCN9A and SCN10A, respectively. Moreover, gain-of-function mutations of SCN9A and SCN10A are linked to different peripheral neuropathic pain conditions, such as small fibre neuropathy, paroxysmal extreme pain disorder, and inherited erythromelalgia. By contrast, loss-of-function mutations of SCN9A are linked to congenital insensitivity to pain. It is hypothesized that Nav channel mutations act as a risk factor for developing neuropathic pain, as there is no direct causal link between mutation and disease; as not all SFN patients have a mutation and family members with mutations do not always have SFN . In ACNES, it is suspected that some trigger will cause damage to the nerve, such as an increased force on the abdominal wall. People with a gain-of-function mutation are more prone to developing neuropathic pain afterwards, as the membrane is more likely to enter a hyperexcitable state. This gain-of-function mutation could possibly explain why some patients develop ACNES after (laparoscopic) surgery or pregnancy, whereas most patients do not. This study should help understand why some people develop ACNES after surgery and others do not, as well as why some people continue to have recurrences, even at different locations of the abdominal wall. In recent years, an increasing number of relatives with ACNES (mother-daughter, (twin) siblings) have been seen, which could suggest that a hereditary factor contribute to the pathophysiology of ACNES. This possibility has not been investigated before in ACNES. Additionally, the different Nav channels respond differently to lidocaine. For instance, Nav1.7 seems to be four times more sensitive to lidocaine compared to Nav1.8. However, some mutations can also alter the sensitivity to lidocaine. A Nav1.7 N395K mutation (gain-of-function) also decreases the sensitivity of Nav1.7 to lidocaine. For more than twenty years, the present investigators used lidocaine for trigger point injections (TPI) as the first treatment option in ACNES. Most patients have a, at least, temporarily pain relief after TPI with lidocaine and one in three are free of pain after one or more injections. The reason for these differences in treatment response remain unclear. It could be that this study investigating the Nav channel mutations will help shed light on these different treatment responses as well. This exploratory study is designed to gain a better understanding of the pathophysiology of ACNES, but also to give more insight into the treatment responses of individual patients. It is also the first time that Nav channel mutations are being investigated in a local peripheral neuropathy, like ACNES.

Study objective

Our primary objective is to determine if there are (gain-of-function) mutations of Nav1.7 and Nav1.8 in patients with ACNES.

Our secondary objective is to see if there is a difference between patients with and without mutations, and:
- Known underlying cause (surgery, trauma/sport, pregnancy or (viral)infection);
- Average pain score on numeric pain rating scale (NRS) before start of treatment;
- Treatment response to injection regimen, Pulsed RadioFrequency (PRF) and neurectomy.

Study design

A mono-center, exploratory cross-sectional study.

Study burden and risks

Risks of a venepuncture are some pain during the venepuncture and the possibility of a hematoma afterwards. Therefore the risks are negligible.

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

A subject must be 18 years or older, diagnosed with ACNES, and received treatment at SolviMáx Center and fullfilling one of the following criteria:
- Known to have a first-or second-degree relative with ACNES;
- Have more than one recurrence of ACNES after a pain free period or ACNES at multiple locations in the abdominal wall;
- Persistent pain after posterior neurectomy.

Exclusion criteria

- Inability to understand Dutch language.
- Known neuromuscular or neurodegenerative disease.

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	26-10-2023

Enrollment:	50
Type:	Actual

Ethics review

Approved WMO Date:	04-05-2023
Application type:	First submission
Review commission:	METC Maxima Medisch Centrum (Veldhoven)
Approved WMO Date:	26-07-2023
Application type:	Amendment
Review commission:	METC Maxima Medisch Centrum (Veldhoven)
Approved WMO Date:	12-09-2024
Application type:	Amendment
Review commission:	METC Maxima Medisch Centrum (Veldhoven)

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
ClinicalTrials.gov	NCT05877274
CCMO	NL84021.015.23