My spine is on fire: neuroinflammation in spinal radiculopathy and physiotherapy on it.

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Spinal cord and nerve root disorders
Study type	Interventional

Summary

ID

NL-OMON55329

Source
ToetsingOnline

Brief title
NOTICE (NeurOinflammaTion In Cervical radiculopathy)

Condition

- Spinal cord and nerve root disorders

Synonym
Nerve pinched in the neck; neural impingement

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Exercise, Glia, Neural mobilisation, Neuroinflammation

Outcome measures

Primary outcome

1) [11C]-R-DPA713 BPnd in the spinal cord and neuroforamina

Secondary outcome

2) Δ [11C]-R-DPA713 BPnd in the spinal cord and neuroforamina between a) joint-

and neural mobilisations and b) therapeutic exercise, compared to c) a soft

collar

3) Intraclass correlation coefficient (ICC2.1), Standard Error of Measurement

(SEM) and Smallest Detectable Change (SDC)

Study description

Background summary

Cervical radiculopathy is a specific type of neck pain in which a cervical nerve root is pinched by intervertebral discus material or osteophytes which causes inflammation of the nerve. Neuroinflammation can be visualised in vivo using the [11C]-R-DPA713 tracer combined with a positron emission tomography - computed tomography (PET-CT) scan. [11C]-R-DPA713 is a second-generation tracer which binds to the translocator protein (TSPO) which is upregulated in glial cells within the nervous system during neuroinflammation and is therefore a marker of neuroinflammation in vivo. In lumbar radiculopathy patients, an increased tracer uptake within the spinal cord and neuroforamina is found. Moreover, the tracer uptake was associated with the experienced pain intensity. Results from preclinical studies show that joint- and neural mobilisation and therapeutic exercise are able to reduce neuroinflammation in neuropathic pain models and it is assumed that these findings can be transferred to patients. There is lack of knowledge if neuroinflammation is also present in patients with cervical radiculopathy and whether this neuroinflammation (if present) can be reduced by conservative treatment. Increased knowledge about the pathophysiological mechanism behind cervical radiculopathy could lead to better conservative treatment, which is the first and preferred treatment option for

these patients. Conservative treatment targeting at the present neuroinflammation can contribute to increased recovery. Therefore, in this study patients with cervical radiculopathy having neuroinflammation will be randomised into three groups and treated with 1) joint- and neural mobilisations, 2) therapeutic exercise, or 3) a soft collar. After four weeks of intervention, potential changes in neuroinflammatio and the correlation with patient reported outcomes will be assessed. Joint- and neural mobilisation and therapeutic exercise will be compared to the control intervention: a soft collar. Six additional cervical radiculopathy patients will be recruited and will be scanned for neuroinflammation twice with one week between to provide information regarding test-retest reliability.

Study objective

The overall aim of this study is to gain insight into the pathophysiological mechanisms behind cervical radiculopathy and determine if conservative treatment targets these processes. Different research questions are formulated:
1) Is there any neuroinflammation present in patients with cervical radiculopathy compared to healthy control measured in vivo using [11C]-R-DPA713 PET imaging?
2) If present, does 4 weeks treatment with a) joint- and neural mobilisations or b) therapeutic exercise, reduce the present neuroinflammation compared to c) a soft collar?
3) What is the test-retest reliability of [11C]-R-DPA713 in measuring [11C]-R-DPA713 binding potential non-displaceable (BPnd) in the neuroforamina and spinal cord in cervical radiculopathy patients?

Study design

The study is a *proof of principle* study with a:
1) Cross-sectional design assessing baseline neuroinflammation between patients with cervical radiculopathy and healthy control.
2) Randomised controlled design (RCT) with three arms, block randomization with block sizes of 3, and an 1:1:1 allocation ratio with four weeks treatment follow up measurement.
3) Test-retest design with one week follow- up.

Intervention

In the RCT patients will be treated with a) joint- and neural mobilisations, b) therapeutic exercise, or c) a soft collar (control intervention)

Study burden and risks

Patients and healthy control will undergo one MRI session of maximum sixty minutes. Before treatment and after four weeks, for all patients with evident

neuroinflammation and for the healthy controls, a [^{11}C]-R-DPA713 PET-CT scan will be obtained, which takes maximally 60 minutes. PET-CT scans involve exposure to a small amount of radiation, as well as venous blood sampling (7 x 5ml) to measure [^{11}C]-R-DPA713 input function. Both visits include examination of symptomatology. Blood sampling during imaging, MRI and PET-CT are all safe procedures; standard procedures are followed, which will be performed by appropriately trained (medical) staff to minimise risks. Maximum total radiation dose is 4.6 millisievert (mSv) for the cervical radiculopathy patients, which is of the same order of magnitude as the annual natural background radiation in the Netherlands for two years. The healthy control will receive a maximun total radiation dose of 2.3 mSv. This research fits the radiation-risk 2b conform the NCS-26 (2016) guidelines: 1) new imaging techniques, 2) provides insight in the pathophysiology of a severe condition. Before and after four weeks, in total three vacutainer tubes (5ml each) will be collected for the screening parameters and immune blood markers. The healthy control will provide two vacutainer tubes (5ml each) during the whole study. Participation in this study may be of therapeutic benefit to patients since joint- and neural mobilisations, therapeutic exercise, and a soft collar been associated with both clinical and functional improvement.
To use BPnd as an outcome measure for the PET signal, a 60 minutes in duration dynamic scan will be necessary. In part because blood radioactivity can be calculated and used for the input function.

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Cervical radiculopathy patients
Inclusion
• Age between 30-65 years.
• Minimal score of 4 on the Numeric Pain Rating Scale (0-10).
• Cervical radiculopathy based on the clinical diagnosis confirmed by the Magnetic Resonance Imaging (MRI through a medical specialist). The compression must be caused by a discus protrusion or herniation.
• Written informed consent of the patient.
• Referral by a medical specialist
• High and mixed affinity binders for second generation TSPO radiotracers
• Evident [11C]-DPA713 binding in the neuroforamina and/or spinal cord. Only applicable for research question 2 and 3.

Healthy control
Inclusion
• Age between 30-65 years.
• Asymptomatic for neck or shoulder pain and other musculoskeletal conditions in the past 3 months.
• Written informed consent of the healthy control.
Referral by a medical specialist
• High and mixed affinity binders for second generation TSPO radiotracers

Exclusion criteria

Cervical radiculopathy patients and healthy control
A potential participant who meets any of the following criteria will be excluded from participation in this study:
• Pregnancy or postpartum for 9 months
• Contra-indications for venipuncture (e.g. phlebitis)
• Underwent treatment for current complaints for the last 2 weeks (e.g.

physiotherapy, manual therapy, general practitioner etc.)
• Taken one of the following medications for the last 6 weeks: corticosteroids (e.g. prednisone), immunomodulatory medication (e.g. methotrexate, infliximab etc.) and the use of botox for the last 3 months.
• Taken one of the following medication: NSAID*s (e.g. diclofenac, ibuprofen, naproxen etc.), Aspirin, Simvastatin (29) for the last week.
• Benzodiazepine (30) use for the last six weeks.
• MRI contraindications, (e.g. claustrophobia, inability to lie still in the scanner or metal objects in or around the body)
• Inability to undergo PET-CT with administration of radioligand [^{11}C]-R-DP713.
• Significant radiation exposure such that inclusion in this study will take the total dose >10mSv within the preceding 12 months.
• Current participation in another clinical trial.
• Previous participation in a PET-CT study in the last 12 months.
• Having a medical disease with immune system involvement (e.g. MS, Spondylitis Ankylpoetica)

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Single blinded (masking used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-11-2021
Enrollment:	30
Type:	Actual

Medical products/devices used

Generic name:	soft collar
Registration:	No

Ethics review

Approved WMO Date:	14-09-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-01-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	NL71697.029.20
Other	NL8060