Identification of inflammatory mediators in spinal liquor in relation to synovial nerve sprouting and pain in osteoarthritis

Published: 07-06-2017
Last updated: 17-04-2024

Our key objective of this proposal is to elucidate potential peripheral and central mechanisms of chronic pain in humans with OA. Primary Objective: Identify if specific inflammatory mediators are different in the spinal liquor of knee OA patients...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Joint disorders
Study type	Observational non invasive

Summary

ID

NL-OMON46137

Source
ToetsingOnline

Brief title
Cerebrospinal fluid and osteoarthritis pain

Condition

- Joint disorders

Synonym
osteoarthitis

Research involving
Human

Sponsors and support

Primary sponsor: LTI

Source(s) of monetary or material Support: REUMAFONDS

Intervention

Keyword: cerebrospinal fluid, nerve, osteoarthritis, pain

Outcome measures

Primary outcome

Cytokines and chemokines and growthfactors in spinal cerebral fluid measured by LUMINEX.

- Patients will be selected based on the clinical parameter knee pain VAS (visual analog scale) specifically for the affected knee.

The primary outcome is a normally distributed continuous variable and will be the the level of inflammatory mediators in the spinal cerebral fluid. Knee OA patients will be selected either of having severe pain , defined by as knee VAS>60 or limited clinical pain (knee VAS<40).
We will determine an broad panel of cytokine/chemokines and growth factors (up to 100) with validated assays and available at the LUMINEX core facilities of the laboratory of translational immunology. The panel will at least include, IL1, TNF, IL6, IL10, IL4, IL13, TGF, IL17, VEGF, CCL2, CXCL4, BDNF, NGF, Cathepsin S, M-CSF, IL34, GFAP, S100

Secondary outcome

To asses different aspects of pain we will include additional pain questionnaires. These include:

- Intermittent and constant osteoarthritis pain (ICOAP).

-The Knee injury and Osteoarthritis Outcome Score (KOOS) score to dichotomize

the knee OA patients.

- PAINDETECT questionnaire

We will also evaluate differences in the following determinants:

2. nerve innervation of the synovium measured by immunohistochemistry of

tyrosine hydroxylase (sympathetic nerves) and PGP9.5 (sensory neurons).

3. nerve innervation of the subchondrial junction measured.

Study description

Background summary

Osteoarthritis (OA) is a progressing degenerative joint disorder, characterized by joint pain and functional impairment, leading to disability. Pain is the most important defining clinical presentation of OA. This persistent pain has a major impact of the quality of life, but is difficult to treat. Current treatment provides modest relief at best and inadequately controlled pain is a major reason for total joint replacement. Moreover, in approximately 20% of patient that have had total joint replacement pain remains. The efficacy of 'first-line' agents such as paracetamol is hard to distinguish from placebo, and our most common effective therapies, NSAIDs and opioids have very small effect sizes on OA pain. Therefore, better understanding of the mechanisms driving persistent OA pain is required to develop new therapeutic approaches that specifically target deteriorating pain conditions in OA.
Local joint inflammation,altered cartilage and bone turnover in OA have been implicated to lead to a range of molecular mediators that mediate OA pain. However, clinically there is disparity between the degree of pain perception and the extent of joint damage in subjects with OA. It remains largely unknown why a relatively poor correlation exists in OA between the radiologic signs of OA (eg, joint-space narrowing, erosive changes) and the severity of pain as well as the specific mechanisms that drive spontaneous (at rest) versus movement (at activity)-evoked joint pain in OA. Research with animals has expanded our understanding of these potential mechanisms that might drive OA pain independently of joint damage. However, translation of these findings to

humans with OA is very limited and void the development of novel analgesics to treat pain in OA.

Pain can arise as a result from changes in the sensory nervous system at several levels: 1) central mechanism including activation of spinal cord glial cells to produce pro-inflammatory cytokines and neuronal plasticity in spinal cord and brain circuits processing sensory signals; 2) ongoing generation of peripheral stimuli due to damage or inflammatory reactions in the joint leading to long-lasting changes in primary sensory neurons that detect sensory stimuli. A growing body of research involving pain mechanisms in OA indicate involvement of central pain mechanisms, including neuroinflammation6. Microglia, the resident macrophages (macrophages of the central nervous system) and astrocytes modulate chronic pain in different rodent models for chronic pain induced by inflammation or damage. In these chronic pain models, including models for OA pain, resident microglia and astrocytes in the spinal cord switch from a quiescent inactive state to an activated phenotype associated with inflammatory mediator production and hypersensitivity of the pain system. In a rodent model of OA, induced by intra-articular injection of mono-iodoacetate (MIA), spinal cord microglia and astrocyte are activated. Moreover, in this rodent model of OA multiple pro-inflammatory cytokines and chemokines such as IL-1, CCL5, CINC 2*/*, IL-13, IL-17, TNF*, and VEGF are increased in the spinal cord, whilst the anti-inflammatory cytokines IL4 and IL10, the chemokine CX3CL1 (fractalkine) and growth factor GM-CSF are reduced11. The fact that neuro-inflammation plays an important role in rodent models for chronic pain and is a potential target for treating OA pain is highlighted by the fact that inhibition of anti-inflammatory IL-10 signalling in the spinal cord using a neutralising IL-10 antibody strongly prolongs inflammatory pain. In addition, anti-inflammatory cytokines can dampen chronic pain. In the Laboratory for Translational Immunology (LTI) and department of rheumatology & clinical immunology we have developed a fusion protein of the anti-inflammatory cytokine IL-4 and IL-10, called IL4-10 synerkine. Intriguingly, intrathecal injection of IL4-10 completely blocks hyperalgesia in rodent models of chronic pain induced by peripheral paw inflammation or nerve damage whilst combined IL-4 and IL-10 treatment is only partially effective. Similarly, local administration of IL4-10 synerkine in the knee joint attenuates pain in a dog model of OA. Whether spinal neuro-inflammation plays a role in human subjects with OA pain is unknown.
One other potential mechanism that may explain the dissociation between disease progression and pain in OA is active and ectopic sprouting of sensory and sympathetic neurons in synovial tissue drivingchronic pain. Inappropriate remodelling of sensory and sympathetic nerve fibers in peripheral tissues is associated with chronic pain such as in patients suffering from endometriosis and irritable bowel syndrome and in rodent models for rheumatoid arthritis and bone cancer pain. Most importantly, in a mouse model of OA, pain is associated with increased sensory and sympathetic sprouting in the affected joint. Until now it remains to be determined if similar changes in sympathetic and sensory neuron innervation of the knee synovium occur in patients with OA pain.

There is clear evidence of an important role of spinal cord neuro-inflammation and peripheral neuron sprouting in the development of chronic pain in rodent models for chronic pain and those specifically for OA. However, until now it is not known whether such mechanisms truly translate to the human situation. This knowledge is crucial to consolidate the next step to identify therapeutic possibilities to specifically treat OA pain.

Study objective

Our key objective of this proposal is to elucidate potential peripheral and central mechanisms of chronic pain in humans with OA.

Primary Objective:
Identify if specific inflammatory mediators are different in the spinal liquor of knee OA patients with severe pain compared to those with relatively little pain.

Secondary Objective(s):
Asses different aspects of pain (intermittent/constant aspects of pain, neuropathic component, severity) in knee OA patients and elucidate whether these aspects are associated with ectopic sprouting of sensory or sympathetic nerve fibers in the knee and or specific profiles of inflammatory mediators in spinal liquor of OA knee patients.

Determine if a relation exists between these inflammatory mediators in the spinal cord and extent of peripheral nerve innervation in the knee: Do they have a seperate or combined effect on pain perception?

Study design

Design: This is a multicenter observational study, with invasive (spinal cerebral fluid sampling) measurements and collection of knee tissues that have been removed during total knee replacement in regular practice.

Setting: Collection of spinal cerebral fluid and knee synovial, bone, and cartilage tissues will be performed at the St Antonius Ziekenhuis. Fluid and tissue analyses will be performed at the University Medical Center Utrecht.

Duration: Inclusion is estimated to take 12 months.

After informed consent (see 9.1 for exact detail on recruitment and consent), patients are asked to fill out the ICOAP (intermittent and Constant Osteoarthritis Pain), KOOS (pain stiffness and physical function) and PAINDETECT (neuropathic pain components) questionnaires to Asses the extent of different elements of pain before the day of surgery.

On the day of surgery, spinal cerebral fluid(300 uL) will be collected prior to the spinal anesthesia that is part of the standard operation procedures for total knee replacement. Knee tissue consisting of bone, cartilage and synovial tissue, that has been removed during total knee replacement will be collected, fixed and stored for further analysis.
The spinal cerebral fluid will be used to measure several factors (see 8.1.1) associated with spinal cord neuroinflammation. Knee synovial tissue will be used to assess the extent of infiltration of inflammatory cells and innervation. Cartilage tissue will be used to assess the actual cartilage degeneration in the knee joint.

Study burden and risks

Benefit: Patients have no direct benefit of participating in this study.
Results will elucidate the underlying mechanisms of osteoarthritis pain and may provide insights for novel pain treatment strategies.
Burden: Prior to spinal anaesthesia, 300 ul cerebral spinal fluid will be obtained in a syringe. Since the aspiration can be performed with the same needle as injection of the epidural anaesthesia requires no additional burden is introduced. The aspiration will take approximately maximum 5 minutes.
Risks: Postdural headache or infection is negligible

Contacts

Public
Selecteer

lundlaan 6
Utrecht 3584 EA
NL
Scientific
Selecteer

lundlaan 6
Utrecht 3584 EA
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet the following criteria:;* At least 18 years of age
* In regular practice eligible for surgery under spinal anesthesia for
o knee joint replacement as treatment for knee OA
o A knee VAS pain score (on a scale of 100) either lower than 40 or higher than 60.
* Able and willing to give written informed consent

Exclusion criteria

Other (auto) immune disease or diabetes mellitus.
Use of (pain) medication other than NSAIDS

Study design

Design

Study type: Observational non invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	28-08-2017
Enrollment:	42
Type:	Actual

Ethics review

Approved WMO Date:	07-06-2017
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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	NL56782.041.16