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Pain classification in patients with inflammatory joint and back disease: A cross-sectional DANBIO registry survey

Project supervisor:	Signe Rifbjerg-Madsen[1,2], MD, PhD Student
Clinically responsible physician:	Kirstine Amris[1,2], Consultant, MD
Senior Biostatistician:	Robin Christensen[1], BSc, MSc, PhD

Other collaborators:
Bente Danneskiold-Samsøe[1], Professor, MD, DMSc
Henning Bliddal[1], Professor, MD, DMSc
Anton T. Christensen[1,2], MD, PhD Student
Christian Cato Holm[1], MSc, Database manager

DANBIO collaborators:
Merete Lund Hetland[3] Professor, MD, PhD, DMSc
Niels Steen Krogh[4], MSc, Database manager

Affiliations:
1: The Parker Institute, Department of Rheumatology, Copenhagen University Hospital, Bispebjerg and Frederiksberg, Copenhagen, Denmark.
2: Department of Rheumatology, Frederiksberg Hospital, Copenhagen University Hospital, Bispebjerg & Frederiksberg, Copenhagen F, Denmark.
3: Department of Rheumatology, Glostrup Hospital, Copenhagen University Hospital, Glostrup, Denmark.
4: ZiteLab ApS, Copenhagen, Denmark.

Study site:
The Parker Institute, Department of Rheumatology
Copenhagen University Hospital, Frederiksberg
2000 Copenhagen F
Denmark

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Background

Inflammatory rheumatic disease and pain

Rheumatoid Arthritis (RA), Psoriatic Arthritis (PsA) and Spondylo Arthritis (SpA) are all chronic inflammatory diseases that cause joint destruction, disability and pain. Few studies have examined the role of central pain processing in RA and other inflammatory rheumatic diseases, traditionally considered peripheral inflammatory entities. In RA, pro-inflammatory cytokines, e.g. TNF-alpha and IL-6, are essential co-factors in the inflammatory process in the joints and related to clinical symptoms such as pain (1;2). Also, pressure pain from joints has been shown to resolve in parallel to the treatment response on disease-modifying agents (3;4).

Although peripheral mechanisms of nociception significantly contribute to the generation of pain, the contribution of spinal, as well as supraspinal, thalamocortical mechanisms to pain generation is probably essential. Inflammation sensitizes polymodal nociceptors. This peripheral sensitization induces a hyper excitation of nociceptive neurons in the central nervous system (central sensitization) and the two together generate the features of pathophysiological pain; allodynia and hyperalgesia (5). Furthermore, pro-inflammatory cytokines, such as TNF-alpha and IL-6 not only promote and maintain inflammation, they also contribute to the generation and maintenance of inflammatory pain by acting at nociceptive nerve cells in the central nervous system (6). Thus, both peripheral and central nociceptive mechanisms may contribute to the generation and maintenance of inflammatory pain.

With earlier initiation of disease-modifying therapies and the development of targeted immuno-modulating agents, disease remission or minimal disease activity has become the target of treatment. However, on a population level, mean pain ratings have remained the same for the past 20 years and a substantial subgroup of patients continues to report moderate to severe pain levels (7). In a recent study it was shown that among RA patients in stable DAS28 remission for one year, 12 % continued to report clinically significant pain (8). In these patients, the presence of fatigue, sleep problems, and disability at remission were predictive of pain one year later, while

indices of inflammation and joint damage were not. Further it has been shown that RA leads to widespread pain and pain hypersensitivity in 10-20 % of the patients (9;10) and this phenomenon is associated with worse outcome of the RA (10)The extent to which pain processing is aberrant in RA may, however, occur across a continuum. Application of FMS classification criteria in RA may identify a subgroup of patients with the most abnormal pain processing(11), but also may conceal a larger number of patients in whom central pain mechanisms make an important contribution to more localized pain problems. Supporting this notion, a high tender joint count at baseline have been shown to predict less improvement in pain after 1 year of traditional disease-modifying treatment in early RA, indicating greater contributions of non-inflammatory factors, such as central sensitization in subset of patients (12).

Evaluating pain

The painDETECT Questionnaire (PDQ) is a patient administered screening questionnaire developed and validated to predict the likelihood of a neuropathic pain component being present in individual patients. Originally it was developed by Freynhagen et al. in cooperation with the German Research Network on Neuropathic Pain as a simple screening tool to detect a neuropathic pain component in patients with chronic low back pain (13). The same research group has subsequently compared the somatosensory profiles of the PDQ of 3057 patients with either diabetic neuropathy regarded a prototypical neuropathic pain or fibromyalgia regarded prototypical for central sensitization. They found very similar patterns (14). The PDQ has also been applied on patients with chronic widespread pain and has been shown to correlate with tender point count and pressure-pain thresholds(15) . Rehm et al used PDQ in a cross-sectional survey of 3035 patients with fibromyalgia to subgroup them according to their somatosensory pain profile (16)and Gwilym et al. amongst others found positive correlation between a high painDETECT Score and clinical manifestations of central sensitization in a cohort of osteoarthritis patients (17-20).

The only study to our knowledge that has published data on PDQ in relation to inflammatory joint disease is a small study (N 17) by Wu et al from earlier this year. Their results suggested that back pain in SpA is a mixed pain condition that includes a neuropathic pain component(21).

DANBIO for pain evaluation

The Danish DANBIO-registry is a nationwide rheumatologic registry that was initiated in year 2000 and approved as a clinical quality registry in 2006. DANBIO covers >90% of adults treated with biologics due to rheumatic disease in routine care. Also data on patients treated with disease-modifying antirheumatic drugs, DMARDs, are collected.

Hypotheses

- Implementing painDETECT in national registries facilitate rheumatologists' identification of pain phenotypes in patients with inflammatory joint and back disease.
- painDETECT can be used to determine the prevalence of central sensitization in patients with inflammatory joint and back disease.
    - Peripheral disease: A high painDETECT score is associated with a high disease activity score AND a low Swollen Tender Joint Ratio (STR).

Purpose

The primary aims in this study are to classify pain in patients with inflammatory joint and back disease ; Rheumatoid Arthritis (RA), Psoriatic Arthritis (PsA) and Spondylo Arthritis (SpA) using the painDETECT questionnaire (PDQ) and to detect the prevalence of central pain within the groups. Furthermore the utility of the PDQ as an easily applied screening tool assisting identification of a predominant central pain component will be evaluated. Secondary aim is to investigate the association between PDQ score and disease activity.

Methods

Study design

This study is designed as a cross-sectional survey in the DANBIO registry. The 24 departments of rheumatology in Denmark will be asked to participate which gives a potential of including approximately 20.000 patients. The PDQ will be applied to DANBIO touch screens in parallel to already implemented questionnaires such as HAQ and VAS. Only when giving their consent the patients are directed to the PDQ. It will be applied to DANBIO touch screens for a period of 6 month. The cross sectional data will be based on values from first visit with complete data after application of PDQ. Participant inclusion for this study will begin on December 1st 2013 and continue for a period of 6 month with a test period of one month prior to start on a single location.

Participants

This study includes any patient registered in the DANBIO database as having any form of the following diagnosis: Rheumatoid Arthritis (M05.9 M06.0 M06.9 M13.0), Psoriatic Arthritis (M.07.3A M.07.3B), or Spondylo Arthritis (M45.9 M46.1 M46.8,+M02.9,+M07.2,+M07.3,+M07.4,+M07.5, M46.9), or another “arthritic” condition (M02.9, 13.8).

Variables and data collection

The study will use PDQ score and available data in the DANBIO database, including patient demographics, medicine data and disease activity scores (see Table 1).

Table 1. Patient Characteristics

Demographics:	
Female sex (n (%))	
Age (years)	
Disease duration (years)	
Symptom duration (years)	

DMARDs:	
Hydroxychloroquine yes/no	
Lefl unomide yes/no	
MTX yes/no	
Sulfasalazine yes/no	
Other DMARD yes/no	
> 1 DMARD n	
Number of previous DMARDs , n	
Biologics:	
Abatacept yes/no	
Adalimumab yes/no	
Anakinra yes/no	
Certolizumab yes/no	
Etanercept yes/no	
Golimumab yes/no	
Infl iximab yes/no	
Rituximab yes/no	
Tocilizumab yes/no	
Number of previous biological drugs, n	
Disease activity measures:	
DAS28	
SDAI	
CDAI	
SJC 28	
TJC 68	
SJC 28	
TJC 68	
Provider global assessment mm	

BASDAI (0-100)	
BASDAI sub components (0-100) 1. How would you describe the overall level of fatigue/tiredness you have experienced? 2. How would you describe the overall level of AS neck, back or hip pain you have had? 3. How would you describe the overall level of pain/swelling in joints other than neck, back, hips you have had? 4. How would you describe the overall level of discomfort you have had from any areas tender to touch or pressure? 5. How would you describe the overall level of morning stiffness you have had from the time you wake up? 6. How long does your morning stiffness last from the time you wake up?	
BASFI (0-100)	
BASFI sub components (0-100) 1. Putting on your socks or tights without help or aids (e.g. sock aids)? 2. Bending forward from the waist to pick up a pen from the floor without an aid? 3. Reaching up to a high shelf without help or aids (e.g. helping hand)? 4. Getting up out of an armless dining room chair without using your hands or any other help? 5. Getting up off the floor without any help from lying on your back? 6. Standing unsupported for 10 minutes without discomfort? 7. Climbing 12-15 steps without using a handrail or walking aid (one foot on each step)? 8. Looking over your shoulder without turning your body? 9. Doing physically demanding activities (e.g. physiotherapy exercises, gardening or sports)? 10. Doing a full day activities whether it be at home or work?	

BASMI	
ASDAS	
Thorax excursion cm	
VAS pain mm	
VAS fatigue mm	
VAS global mm	
HAQ	
Biochemistry	
Crp mg/L	
IgM-RF pos/neg	
Anti-CCP pos/neg	
HLA - B27 pos/neg	

painDETECT Questionnaire (PDQ)

The painDETECT questionnaire has been translated into 19 different languages, including Danish. It comprises questions regarding pain intensity (VAS intensity values for current, average, and worst pain), course of pain (selection between four pain course patterns), subjective experience of a radiating quality of the pain (yes/no), and the presence and perceived severity of seven somatosensory symptoms of neuropathic pain rated on a 0–5 verbal rating scale (never, hardly noticed, slightly, moderately, strongly, and very strongly).

A score between 0 and 38 based on the patient's answers in the questionnaire is calculated. For diagnostic purpose a validated algorithm has been developed. A painDETECT score above 18 indicates that a neuropathic pain component could be present, whereas a painDETECT score below 12 indicates that this is unlikely, resulting in three categories of patient pain characteristics.

The painDETECT questionnaire is applicable to touch screens (22;23).

Statistical methods

Potentially up to 10.000 participants can be included during a period of 6 months. Analyses for each PDQ category for each diagnosis will be made. The primary objectives are to detect the prevalence (i.e., proportion) of the 3 different pain phenotypes defined by PDQ and to explore the association between the score on PDQ and the disease activity according to DAS28 and BASDAI/ASDAS. Except for these, all data analyses are exploratory but will be carried out according to pre established statistical analysis plans; all analyses are done applying SAS software (v. 9.3 Service Pack 4; SAS Institute Inc., Cary, NC, USA). All descriptive statistics and tests will be reported in accordance to the recommendations of the "Enhancing the QUAlity and Transparency Of health Research" (EQUATOR) network: the STROBE Statement (24).

Bias

The DANBIO data can be considered of good quality given the premise that it is based on data with a high external validity. According to previous reports, 90% of Danish patients treated with biologic agents are registered in the DANBIO database, probably due to the fact that registration is mandatory irrespective of patient's consent. This is supported by the fact that coverage is much lower in databases using voluntary registration and requiring patient consent. Smoking status, and comorbid disease are other factors that might influence treatment outcomes. These data were only recently introduced in the registry and are still not uniformly available.

Perspectives and dissemination

This study will contribute to the research within central pain sensitization in inflammatory joint and back disease mainly with knowledge about prevalence. For patients diagnosed with RA we expect results in line with earlier published results showing that RA leads to widespread pain and pain hypersensitivity in 10-20 % of the patients (9;10). Within the diagnosis SpA and PsA the frequency of central pain

sensitization remains to be determined(21). Furthermore the study will give insight in relation to defining somato-sensory profiles within the different diagnosis and levels of disease activity. On a greater note this study will be of value in testing the reliability of the painDETECT questionnaire within inflammatory joint and back disease. Finally it is expected that a later follow up study based on data on bio-switchers and –starters from this study will add to determining the value of the PDQ score as a prognostic factor for treatment outcome.

Knowledge about the presence of central pain sensitization in an individual may be useful for rheumatologists when confronted with a patient with a high DAS28 score predominantly due to tender joints and/or persistent pain, since this may help identify those patients with little potential to respond to anti-inflammatory therapy. Increasing our ability to predict the potential for response to treatment is mandatory for several reasons. First of all it can help shift focus to other areas of importance e.g. optimizing analgesic treatment, but it will also spare some patients from unnecessary immuno-suppressive therapy with subsequent risks of side effects. Furthermore, avoiding the unnecessary use of drugs, some of which are very costly, is beneficial for health economic reasons. It is our hope that the results of this study may add to the knowledge of the mechanisms behind persistent pain in inflammatory joint and back disease.

Ethics

Informed consent

The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. The patients can only participate in the questionnaire survey after having given their consent (yes/no) on a touch screen. Questionnaire surveys do not require approval by Ethics Committees.

According to Danish legislation registrations and publications of data from clinical registries do not require patient consent or approval by Ethics Committees.

Data handling

The DANBIO database has been approved by the Danish Board of Health and the Danish Data Registry.

Notification to the Danish Data Protection Agency

As per standard procedure, regarding public health sector research in the capital region, notifications to the data protection agency is done collectively by the capital region. The capital regions information security coordinator is notified about this study and has passed on the notification to the Danish data protection agency. The notification has been approved from 1st of November 2013.

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Publication of results

All results whether positive, negative or inconclusive will be published in international peer reviewed journals. Data will be published consecutively as it is gathered and

analyzed. Authorship will be justified according to ICMJE standards (previously known as the Vancouver declaration) with the chairman of the Scientific Board of the Parker Institute as arbiter.

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