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Identifying subgroups within a population of chronic non-specific low back pain sufferers, and investigating the role of the immune system in certain subgroups by considering their relationship to chronic primary pain syndromes

Submission date
19/04/2021

Recruitment status
No longer recruiting

Registration date
23/06/2021

Overall study status
Completed

Last Edited
12/07/2021

Condition category
Musculoskeletal Diseases

[X] Prospectively registered
[X] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol
Background and study aims
Non-Specific Low Back Pain (NsLBP) is back pain that does not have an identifiable cause, and will affect around 8 out of 10 people during their lifetime. For some this pain can be significant and long-term, affecting their quality of life, financial circumstances and social interactions. Despite the large number of NsLBP sufferers, we still do not yet fully understand the causes and risks associated with the development of this pain. Current treatment can be beneficial for some but many are left without appropriate symptom control.
Recent research from our group has identified the importance of immune factors in the chronic painful conditions of Complex Regional Pain Syndrome (CRPS – a pain condition that may develop after trauma in a limb) and Fibromyalgia (a widespread pain condition). These conditions are associated with severe pain on light touch/pressure and local skin signs such as increased sweating, or with widespread pain.
Some patients with severe NsLBP present with similar skin signs to CRPS, and NsLBP is a risk factor for the development of Fibromyalgia. We wish to find out whether a specific group of NsLBP sufferers may have similar signs and immune changes as those with CRPS and if sufferers can be identified early as being at particularly high risk for the development of Fibromyalgia. In addition, we wonder whether individuals who may suffer from immune-related pain share similar personal characteristics, such as pain scores or coping mechanisms. This study will provide blood samples for investigations into immune factors and cells, including their function and character related to pain, as well as analysis of DNA for genetic links.
We expect that this study will allow us, for the first time, to identify subgroups of NsLBP with similar immune abnormalities to CRPS or Fibromyalgia, opening new avenues for their future treatment.

Who can participate?
Patients 18 years or older with non-specific LBP without the presence of another condition to explain the pain

What does the study involve?
Participants will be identified at routine physiotherapy appointments, or from previous registration on a local Pain Registry. They will be asked to contact the study team to arrange an initial meeting to discuss involvement in the study. Participants will be asked to complete a series of questionnaires around mental health, social circumstances and pain symptoms prior to attending for the first study visit. At this visit each participant will undergo a routine examination of the lower back and limbs, as well as an assessment of any excess sweating at the back. Tests looking at the sensitivity of the skin at the lower back and arm will be performed, and samples of blood will be taken, up to a maximum of 12 tablespoons, for storage and analysis into immune function and molecules related to pain. These samples will also be used for later DNA analysis into specific genes related to pain.
Ten participants with severe changes in skin sensitivity at the lower back may be invited back for a second study visit, where they will have small blisters formed on the skin of their lower back and arm. These are painless and do not scar. The blister fluid will be analysed for changes in immune function. Another sample of blood will also be taken.
Thirty participants who present with low back pain occurring in worsening ‘flares’ will also be invited back for an additional visit at a time of worsening pain, when they will be re-examined and have another sample of blood taken.
Finally, one year after the first visit, participants will be followed up via telephone and complete a remote questionnaire. In participants who report symptoms of widespread pains we may invite them to return for a further visit to assess the development of Fibromyalgia and take another blood sample.
No participant will be asked to attend every one of the visits mentioned.

What are the possible benefits and risks of participating?
There are no immediate direct benefits to those taking part. However, we hope in the future that the information we discover can be used to improve the lives of everyone with non-specific low back pain. Participants will be asked to donate a sample of blood during the study visit. Blood donation carries a minimal risk related to skin and muscle trauma. All steps will be taken to ensure participant safety and the blood will be taken only by a registered healthcare practitioner. The formation of skin blisters is not a painful procedure, but there is a rare risk of delayed healing of the blister sites and irritation at the site. In the extremely unlikely event that any issues arise we will contact the participants’ GP, with their consent, and they will arrange the necessary follow-up.

Where is the study run from?
University of Liverpool (UK)

When is the study starting and how long is it expected to run for?
January 2019 to December 2023

Who is funding the study?
Pain Relief Foundation (UK)

Who is the main contact?
Dr. Sam Hewitt, Shewitt@liverpool.ac.uk
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Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
CPMS 48956

Study information

Scientific Title
Autoimmunity-informed phenotyping in chronic non-specific low-back pain

Study objectives
There will be distinct subgroups within the study population, who suffer from chronic non-specific low back pain, identifiable through their reported and measured characteristics. Some of these subgroups will show signs and symptoms associated with the pain syndromes of Complex Regional Pain Syndrome (CRPS) and Fibromyalgia (FMS), and that dysregulation of the immune system will play a role in these subgroups.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 10/06/2021, Wales REC 7 (Public Health Wales Meeting Room, Building 1, St. David's Park, Carmarthen, SA31 3HB, UK; +44 (0)2920 230457; Wales.REC7@wales.nhs.uk), ref: 21/WA /0120

Study design
Observational cohort study

Primary study design
Observational

Secondary study design
Cohort study

Study setting(s)
Hospital

Study type(s)
Diagnostic

Participant information sheet
See additional file ISRCTN98833037_PIS_V2.0 (added 23/06/2021)

Health condition(s) or problem(s) studied
Non-specific low back pain

Interventions
We will identify 100 patients from back pain physiotherapist clinics run at the Walton Centre and Aintree Hospital in Liverpool, UK. We have chosen to recruit 100 individuals based on evidence from previous exploratory studies showing that this number is sufficient to allow subgroup identification within a population and appropriate analysis of the genetic basis of extreme pain. Physiotherapists will identify patients with non-specific low back pain who would meet the inclusion criteria of the study. They will inform the patient briefly of the study and provide an information leaflet with contact details to arrange participation. Individuals with back pain may also be identified as potential participants from the Walton Clinical Pain Management Registry

and be informed of the study. Individuals will contact the study team to register interest and arrange a study visit.

Interested individuals will arrange a video meeting with the study team, to reduce COVID transmission risks, during which suitability for the study will be assessed, the study will be explained and informed consent taken. Following consent, the study team will arrange a study visit and mail or email a series of questionnaires aimed at measuring the levels of known factors related to low back pain, such as depressive symptoms and stress levels, to be be completed by each participant and returned at the first study visit. Participants will be seen in the laboratories of the Pain Research Institute where they will then be examined with a focus on non-specific low back pain. The participant will be asked to identify the most painful area at the lower back and this will be examined for evidence of tissue swelling. Quantitative Sensory Testing (QST) uses a number of special tests to investigate the sensory profile of certain nerve fibres and can identify abnormal functioning in these nerves. The use of QST in CRPS, FMS and LBP is well documented and can be used to either support diagnosis of the condition, as in CRPS, or identify subgroups of patients with altered nerve functioning, as in LBP. The full, validated DFNS protocol will be performed on each patient, with the area of maximal pain at the lower back used as the test site and the forearm used as a control site. We will also a starch-iodine solution which, when applied to the skin, changes colour based on the degree of sweating at that site. Sweating is a feature of CRPS and we wonder whether a subgroup of LBP sufferers present with this as well.

We will take sample of blood from each participant and store this for later analysis of immune factors. It is estimated that each visit will require a total of around 2-3 hours. Patient travel and time will be reimbursed to a maximum of £30 per visit.

Within this initial group of 100 participants we will identify 10 participants with the most severe CRPS-like symptoms and invite them back for a single further visit, at a time when their back pain is severe. However if the participant reports that the pain could not get any worse or that they would be unwilling to return during an acute flare due to pain/functional limitation, and they are deemed suitable for a second-visit, the sampling of blister fluid may be conducted at the first study visit. We will use a small device to create painless blisters on the skin over the painful areas and take a small sample of fluid from these blisters for analysis of immune factors. We will take another sample of blood, ideally at a similar time to the first visit, for later analysis of immune factors.

We will also invite 30 participants who do not present with CRPS-like features for a second visit, this time during a pain flare, for blood sampling and storage for analysis. This will allow for comparison with the CRPS-like group to identify important differences in serum factors.

Contact details of those taking part will be kept for one year after involvement in the study and at the end of this year we will arrange a telephone interview to assess the course of pain and any change in symptoms, with particular interest in the development of chronic widespread pain and fibromyalgia (FMS) symptoms. Those people that report these symptoms will be invited back for a final visit where they will be examined with a focus on FMS features, and a final sample of blood taken for later analysis of immune factors. Participants who had been included in the blister-fluid sample population will not be invited back for further consideration in this CWP /FMS population.

Data analysis and interpretation will be performed during the study and following completion of the last visit.

Intervention Type

Other

Primary outcome measure

Participant characteristics, as measured by questionnaire responses and clinical examination findings at baseline:
1. Age and Gender
2. Ethnicity
3. BMI (kg/m²)
4. Past Medical History
5. Past and Current Medications
6. Pain Duration (months)
7. Average Income
8. Highest Educational level achieved
9. Depression severity and risk
10. Markers of life stress exposure
11. Clinical course of pain
12. Tissue swelling in low back pain
13. Alcohol and smoking use
14. Waddell Score
15. Suction blister fluid cytokine levels
16. Anatomical location of most severe pain
17. Presence of widespread, secondary pain
18. Presence and degree of sweating at lower back
19. QST profiles

Questionnaires
1. Present Pain Intensity (0-10 scale)
2. Hospital Anxiety and Depression Scale (HADS)
3. Keele STarT back screening tool
4. Brief Pain Inventory
5. Short-Form McGill Pain Questionnaire
6. Coping Strategies Questionnaire
7. Pain Self-Efficacy Questionnaire
8. Daily Stressors Questionnaire
9. EQ-5D
10. painDETECT Questionnaire
11. Revised Illness Perception Questionnaire (IPQ-R) – timeline questions
12. Touch Experiences and Attitudes Questionnaire (TEAQ)

Secondary outcome measures

1. Somatosensory profiles, as measured by quantitative sensory testing, at baseline
2. Presence of bilateral tissue oedema at the lower back on visual assessment at baseline
3. Presence of excess sweating at the lower back, as measured using the Modified Minors Starch Iodine test at baseline
4. Anatomical site of maximum pain at the lower back, as measured using the painDETECT questionnaire at baseline
5. Local immune mediator levels in non-specific low back pain patients with a CRPS-like presentation, as measured by ELISA analysis at baseline
6. Conversion rate from localised non-specific low back pain to FMS, as measured by the American College of Rheumatology Fibromyalgia criteria, at 12-month follow-up

Overall study start date
01/01/2019

Completion date
01/12/2023

Eligibility

Key inclusion criteria
1. 18 years or older
2. Presence of non-specific LBP without the presence of another condition to explain the pain (ie. cancer, primary musculoskeletal conditions, sciatica)
3. Chronic NsLBP defined as pain persisting for >12 weeks, with pain occurring >4 days/week
4. Non-specific LBP as defined topographically and temporally by the Delphi definition
5. Average weekly pain intensity exceeding 6/10 on VAS scoring
6. LBP that causes severe disability, as defined by the Modified Oswestry Low Back Pain Disability Questionnaire (MODI)
7. Pain may radiate down the buttocks or backs of legs but must not radiate below the knees
8. In patients with features of more widespread, non-specific pain, the low-back pain must be the predominant complaint of pain and the pain intensity of these other pains should not exceed 3 /10 on VAS scoring

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
Planned Sample Size: 100; UK Sample Size: 100

Key exclusion criteria
1. Pregnant or breastfeeding patients
2. Patients with immune deficiency or taking immune modulating drugs
3. Patients with an acute systemic disorder
4. Language other than English as first language

Date of first enrolment
01/08/2021

Date of final enrolment
01/07/2022

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Aintree University Hospital
Lower Lane
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Study participating centre
The Walton Centre NHS Foundation Trust
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Sponsor information

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Sponsor type
University/education

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ROR
https://ror.org/04xs57h96

Funder(s)

Funder type
Charity

Funder Name
Pain Relief Foundation

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer-reviewed journal.

Intention to publish date
01/12/2024

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request. andreasgoebel@rocketmail.com
• Raw data, with patient identification details removed, will be made available.
• Data will be made available immediately following publication and for 10 years following the study, as per University of Liverpool policy.
• Data will be available to investigators who provide methodologically sound and ethically approved proposals.
• All analysis types will be considered on an individual basis.
• Consent from participants will be obtained during the initial study consent process.
• Data will be anonymised, with all identifying patient details removed.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version V2.0		23/06/2021	No	Yes
Protocol file	version V3.0	27/05/2021	23/06/2021	No	No

HRA research summary	28/06/2023	No	No