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Determining the accuracy of changes in the nerves in the cornea using a method called corneal confocal microscopy to identify small nerve fibre damage in patients with fibromyalgia

Submission date
18/01/2021

Recruitment status
No longer recruiting

Registration date
07/06/2021

Overall study status
Completed

Last Edited
08/07/2021

Condition category
Musculoskeletal Diseases

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

Plain English summary of protocol

Background and study aims
Fibromyalgia is a common type of arthritis which affects around 5-6% of the general population. It is characterised by debilitating widespread body pain. Fibromyalgia has traditionally been considered to be a disturbance in the way the brain processes pain and sensation. However, the type of pain experienced is increasingly recognised to overlap with nerve-related pain (neuropathic pain). There has been a recent interest in the role of small nerve fibres (which are the pain transmission nerves) and their role in fibromyalgia. Indeed, studies have shown that small nerve fibre damage occurs in ~50% of people with fibromyalgia.
In this study, we will determine the accuracy of changes in the nerves in the cornea (known as the corneal sub-basal nerve plexus) using a method called corneal confocal microscopy to identify small nerve fibre damage in fibromyalgia syndrome (referred to as fibromyalgia in the lay application) compared to the current reference standard, skin biopsy. We will then explore the relationship between small nerve fibre damage (small fibre neuropathy), its function through a method called microneurography and characteristics (phenotype) of pain.
Corneal confocal microscopy is an eye test which allows direct visualisation of the small nerve fibres in the cornea in an area called the corneal sub-basal. These are the same type of nerves involved in nerve-related pain (neuropathic pain) and are present in skin. This technique is non–invasive, real–time, rapid (taking about 10 minutes) and readily repeatable. In a range of disorders, such as diabetes, corneal confocal microscopy is as accurate as skin biopsy in detecting and stratifying the severity (classifying the amount) of small nerve fibre damage.

Who can participate?
Healthy volunteers and people with fibromyalgia, aged 18 years or above.

What does the study involve?
Fifty healthy-volunteers and seventy-seven people with fibromyalgia will have detailed

assessment of pain and a comprehensive evaluation of small nerve fibres by corneal confocal microscopy and skin biopsy. In addition, microneurography will be undertaken in 14 healthy-volunteers, 14 people with fibromyalgia and no small nerve fibre damage and 14 people with fibromyalgia with small nerve fibre damage. These 28 people with fibromyalgia will be followed up at 1 year with corneal confocal microscopy and skin biopsy.

What are the possible benefits and risks of participating?
Possible benefits of taking part - There are no direct benefits from undertaking this study. During the study your condition will be assessed in detail. The knowledge gained from this study may affect the tests employed in the future to diagnose nerve damage. In the event of identifying any abnormal results which require attention, we will write to inform you and your GP (with your consent).
Possible risks of taking part - There may be bleeding and some discomfort at the skin biopsy site. Occasionally, there may be some slight discolouration at the site of the skin biopsy after it is healed. There is a rare possibility of an infection or poor healing at the biopsy site. A biopsy site check will be undertaken at 1 week to ensure there are no complications. There may be some minor bruising at the site of the routine blood tests. There are no recognised risks of the other procedures proposed for this study.

Where is the study run from?
Aintree Hospital Clinical Sciences Centre (UK)

When is the study starting and how long is it expected to run for?
January 2020 to October 2022

Who is funding the study?
Versus Arthritis (UK)

Who is the main contact?
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Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
234270

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
IRAS 234270, Sponsor reference UoL001532

Study information

Scientific Title
Diagnosing and dEtermining the contribution of small FIbre NEuropathy to pain in FibroMyalgia Syndrome

Acronym
DEFINE-FMS

Study objectives
In people with fibromyalgia syndrome (FMS), the presence of small fibre neuropathy can be detected by the corneal sub-basal nerve plexus imaged with CCM with similar accuracy to intra-epidermal nerves in skin biopsy.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 04/11/2020, South West - Frenchay Research Ethics Committee (Level 3, Block B, Whitefriars, Lewins Mead, Bristol, BS1 2NT, UK; +44 (0)207 104 8379; frenchay.rec@hra.nhs.uk), ref: 20/SW/0138

Study design
Single centre cross-sectional and nested longitudinal non-Interventional study

Primary study design
Observational

Study type(s)
Diagnostic

Health condition(s) or problem(s) studied
Fibromyalgia

Interventions
Participants with fibromyalgia will be requested to provide details of their medical history, current and past use of pain medication and a record of their height, weight and blood pressure will be collected. A blood sample of approximately 20mls (equivalent to 4 teaspoons) will be

taken and a neurological examination of nerve function (nerve conduction studies) and ankle reflexes will be completed. Sensory testing to determine the types and quantity of pain perceived during a protocol of temperature changes, pressure and pinprick through a number of devices using a standardised internationally recognised protocol. Corneal confocal microscopy will also be undertaken. This is using a special camera, we will look at the nerves in the of your eye (cornea). There is usually no or only slight/minimal discomfort to this procedure. A drop of local anaesthetic will be applied to the front of the eye to numb this part to reduce your blinking during the test period. Some jelly (artificial tears) will be applied to the eye. A red light is seen which does not harm the eyes in any way and images of the nerves in the cornea will be captured. Additionally, three skin biopsies will be undertaken, one from the lower leg and two from the side of the thigh (1 upper thigh and 1 lower thigh). A 3mm area of skin will be removed from each area. This is performed using a local anaesthetic (numbing medicine) so that no pain or only minimal discomfort is felt. A pencil-like instrument is used to remove a small, thin cylinder of tissue. The small area in the skin will heal over in a few days. These assessments will take approximately 3 hours.
A check of the biopsy sites will be undertaken after 1 week to ensure the biopsy sites are healing well.
We will ask some people (in total 28 of 77 people with fibromyalgia) to re-attend for a test called microneurography. This assessment is used to visualise and record the normal traffic of nerve impulses that are conducted in the nerves of people. To study nerve impulses, a very fine tungsten needle electrode (similar to a hair) will be inserted into the nerve in the lower leg and connected to an amplifier. This will require an additional visit of between 2-3 hours depending on the ability to record the impulses. People who are invited to have microneurography will be asked to be followed up at 12 months to have repeat set of selected tests (corneal confocal microscopy, neurological examination and blood test) which will take approximately 1 hour.

Intervention Type
Other

Primary outcome(s)
Corneal nerve fibre pathology measured using corneal nerve fibre density (CNFD) at baseline and additionally at 12 months in a sub-group of participants

Key secondary outcome(s))
1. Corneal nerve fibre pathology measured using corneal nerve fibre length (CNFL) and corneal nerve branch density (CNBD) at baseline and additionally at 12 months in a sub-group of participants.
2. Intraepidermal nerve fibre density (IENFD) determined using skin biopsy at baseline and small fibre dysfunction determined by microneurography (assessed once during an 18-month window post visit 1).
3. Small and large nerve fibre function determined using thermal, mechanical, vibration and pressure detection and pain thresholds (quantitative sensory testing protocol) at baseline and additionally at 12 months in a sub-group of participants.

Completion date
30/10/2022

Eligibility

Key inclusion criteria

1. Aged 18 years and over
2. Fibromyalgia patients (diagnosis of FMS defined by one of the current guidelines criteria)
3. Healthy volunteers (no history of FMS, diabetes, metabolic, neurological disorders or small fibre neuropathy or conditions which may cause small fibre neuropathy)

Participant type(s)
Mixed

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
1. People will be excluded if they have a positive history of diabetes, high risk susceptibility to complications of COVID-19 as defined by current UK government guidelines, malignancy, connective tissue, autoimmune diseases, poorly controlled hypothyroidism, Addison's disease, vitiligo, current systemic, infectious disease, autoimmune disorder, chronic renal failure, liver failure, any other rheumatological disease i.e. rheumatoid arthritis, Sjorgren's syndrome, etc, history of peripheral neuropathy, current or previous history of alcohol abuse, current psychosis or psychiatric disorder which does not allow for the completion of the scientific protocol*
2. Any contraindication to skin biopsy i.e history of blood dyscrasias, coagulopathy, use of warfarin or a novel anti-coagulant agent (dual anti-platelet therapy is permitted for skin biopsy), previous non-healing limb ulcers, active infection at biopsy sites, recurrent cellulitis, active dermatological disorder at the biopsy site, peripheral vascular disease
3. Any contraindication to microneurography i.e. use of warfarin or a novel anti-coagulant agent, permanent pacemaker, any implanted electronic device (in the microneurography group only)
4. Any contraindication to nerve conduction studies i.e. use of warfarin or a novel anti-coagulant agent, permanent pacemaker, any implanted electronic device. If there is a contraindication to nerve conduction studies then participants can continue with the rest of the protocol (VPT is <15 volts and NDS is <4 will be defined as no definitive large fibre involvement)
5. Abnormal nerve conduction studies (using age-matched normative cut-offs) or VPT (>15 volts) signifying large fibre neuropathy
6. Systemic or localised neurological conditions causing pathology of corneal nerves i.e. cluster headaches, trigeminal neuralgia, previous severe traumatic head injury
7. Concurrent ocular disease, infection or inflammation
8. People with moderate-severe dry eye based on the Schirmer's test (<8 mm wetting of the paper after 5 minutes)
9. Any corneal pathology due to hereditary, trauma or infection (including current infection)
10. Unable to complete the experimental protocol at initial assessment
11. Inability to undertake corneal confocal microscopy or skin biopsy for any reason

12. Participating in any other interventional (CTIMP) research trial
13. Inability to safely walk to the research centres
14. Inability to provide informed consent

*Solid organ transplant recipients, people with severe respiratory conditions including all cystic fibrosis, severe asthma and severe chronic obstructive pulmonary (COPD), people with rare diseases and inborn errors of metabolism that significantly increase the risk of infections (such as Severe combined immunodeficiency (SCID), homozygous sickle cell), people on immunosuppression therapies sufficient to significantly increase risk of infection and women who are pregnant with significant heart disease, congenital or acquired.

Date of first enrolment
11/01/2021

Date of final enrolment
30/10/2022

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Aintree Hospital
Liverpool University Hospitals NHS Foundation Trust
Clinical Sciences Centre
Lower Lane
Liverpool
United Kingdom
L9 7AL

Study participating centre
Royal Liverpool Hospital
Liverpool Hospitals NHS Foundation Trust
Prescot Street
Liverpool
United Kingdom
L7 8XP

Study participating centre
The Walton Centre
Lower Lane
Liverpool

United Kingdom
L9 7LJ

Sponsor information

Organisation
University of Liverpool

ROR
https://ror.org/04xs57h96

Funder(s)

Funder type
Charity

Funder Name
Versus Arthritis

Alternative Name(s)
Arthritis UK

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
All data generated or analysed during this study will be included in the subsequent results publication.

IPD sharing plan summary
Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?

HRA research summary			28/06/2023	No	No
Participant information sheet	version v2	05/10/2020	08/07/2021	No	Yes
Participant information sheet	version v2	05/10/2020	08/07/2021	No	Yes
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes