The Walton Centre NHS Foundation Trust

Excellence in Neuroscience

Oxford University Hospitals NHS Trust

NMOSD Research Projects

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The Walton Centre NHS
NHS Foundation Trust
Excellence in Neuroscience

Dear All,

Enclosed is a list of the research projects that the NMO team are involved with.

There are 3 sections;

- ◊ **Research that is currently recruiting or on-going**
- ◊ **Research that is closed to recruitment and the results are currently being analysed**
- ◊ **Projects we have planned for the forthcoming year.**

Most of these research projects will not directly benefit participants but all are invaluable to improve the understanding of NMOSD and related conditions and we greatly value your involvement.

Please speak to your NMO nurse if you would like more information.

NMO Service	**NMO Service**
John Radcliffe Hospital	**Walton Centre Foundation Trust**
West Wing	**Lower Lane**
Headley Way	**Fazakerley**
Oxford OX3 9DU	**Liverpool L9 7LJ**
Contact: 01865-2311905	**Contact: 0151-529-8357**

Some of the staff involved in the research and studies:

Dr Jackie Palace

Dr Isabel Leite

Dr Saif Huda

Dr Anu Jacob

Rosie Everett

Dr Paddy Waters

Dr Emily Gibbons

Kerry Mutch

Kay Day

Tricia Kelly

Dr Silvia Messina

Dr Venkat

Sam Linaker

Nina Eagle

Dr Dan Whittam

Dr Mark Woodhall

NMO Studies / Research:

Section One: Currently recruiting

1.1 MRI and Optic Coherence Tomography (OCT) in Neuromyelitis Optica Spectrum Disorders (NMOSD) and Multiple Sclerosis (MS) (VISPRO Project)

Research question:

We aim to compare the characteristics of Optic Neuritis (ON) in people with MOG antibody disease and AQP4 antibody disease and people with MS. We are looking at the visual pathways to determine if there are differences between people with these conditions to help the diagnosis and treatment, and improve the knowledge of visual outcomes.

Study design:

Optic Coherence Tomography (OCT) and MRI scans, where performed already, will be analysed.

Benefit to patients:

Profound and persistent visual loss can occur in NMOSD, but not in MS. Finding out how and why visual loss occurs helps us to discover more effective treatment for this problem.

1.2 A Study of Brain and Spinal Cord MRI in NMOSD and related conditions

Research question:
To compare brain and spinal cord MRIs in patients with AQP4 antibody positive NMOSD, MOG antibody disease and MS patients. To understand what causes neurodegeneration in MOG disease and learn more about this disease.

Study design:
Patients diagnosed with AQP4 antibody positive NMOSD, MOG antibody disease, MS and healthy controls will have brain and spinal cord MRIs and a neurological assessment on two occasions, 1 year apart.

Benefit to patients:
This will assist us in answering questions regarding diagnosis, obtaining more information about how the diseases progresses over time, and help us to better understand the differences between neurodegeneration and inflammation.

1.3 The Oxford Brain Bank (OBB)

Research question:

The research seeks to answer questions that are only possible by direct study of brain tissue. Such as :-

Which parts of the brain look affected by disease under the microscope?

Are there changes that might explain symptoms or severity of a disease and are there any chemical changes in the brain that might help us understand what caused the disease?

Study design:

Tissue, including brain and spinal cord, donated to the OBB will be used for research into various neurological disorders.

Benefit to patients

Brain and spinal cord donation helps to improve understanding and treatment of neurological diseases. Information about the research may be forwarded to you afterwards. People who sign up for this will receive OBB newsletters and invitations to their open days. Funeral arrangements should not be delayed and relatives are supported throughout the process.

1.4 NMO Tissue Bank

Research question:
The study aims to understand more about NMOSD and compare it with other related neurological diseases caused by a problem with the immune system.

Study design:
Using tissue samples (for example blood samples, DNA, urine, spinal fluid and tissue biopsy specimens) that have been collected from patients in the past or need to be collected from patients in the future for diagnosis or medical reasons, as well as clinical details, MRI scans and previous test results for various research studies related to NMOSD.

Benefit to patients:
To improve the understanding of NMOSD, which in turn will help doctors to diagnose, treat and monitor patients with NMOSD more accurately. We have added patient's clinical information (with identifying details anonymised) in a number of different projects around the world to help answer questions about the course of the disease, how it responds to treatment and what influences it's severity.

1.5 Genetic Analysis of NMOSD and MS

Research question:
To identify and study genetic factors important in the demyelinating diseases NMOSD, MOG antibody disease and MS.

Study design:
Patients are asked to donate a blood sample (this may have already been obtained for the NMO Tissue bank) and complete a questionnaire. This is part or an international study with over 1,000 samples already collected (including people without NMO to compare to). The genetic analysis will be performed in Oxford.

Benefit to patients
Studying genetic factors of patients with NMOSD, MOG antibody disease and MS improves our understanding of these conditions including what may influence how likely an individual is to develop the disease, how the disease affects individuals, or how individuals respond to treatment. We believe that identifying these genes and will bring us closer to more effective treatments and preventative measures.

1.6 The meaning of the NMO antibody levels

Research question:
Aquaporin-4 (AQP4) antibodies are present in the blood of a large proportion of patients with NMOSD and the amount of AQP4 antibodies can vary greatly between patients. What is the meaning of the wide range of antibody levels between patients, and in individual patients at certain times? For example, at the time of their first attack compared to when they are stable on treatment. Could antibody levels help to understand how NMOSD starts? Could antibody levels help to predict clinical outcomes?

Study design:
Patients have kindly consented to having blood taken almost every time they come to the clinic; then the AQP4 antibodies are measured in the laboratory. The results are recorded and compared between patients. They are also compared with the previous levels in the individual patient for clinical purposes to help guide treatment dose. Clinical and radiological information regarding each patient, at the onset of disease and during the course of the disease, are also studied.

Benefit to patients
We hope to be able to understand the meaning of the antibody levels particularly in relation to the clinical features of NMOSD. We also hope to be able to advise patients and doctors on whether antibody levels show how a person responds to treatment and if they can predict risk or severity of NMO attacks.

1.7 Immunobiology of antibody mediated diseases of the nervous system

Research question:
We are trying to find out whether aspects of the immune system are imbalanced in patients with NMOSD and other related diseases. We are looking at the cells which make autoantibodies (B cells and plasma cells) and what might affect their function.

Study design:
Patients have kindly consented to having extra blood taken. We are then purifying immune cells from their blood and studying these in the laboratory.

Benefit to patients:
To determine what might cause imbalance in the immune system of patients with NMOSD and hence identify pathways and molecules which can be targeted in their treatments.

1.8 Metabolomics research project

Research question:
Can we use magnetic resonance of blood serum to find out which patients with NMOSD are more likely to relapse?

Study design:
To compare patients with AQP4 antibody positive NMOSD who have a large amount of antibodies to those who have few antibodies. To compare patients with MOG antibody disease who have more attacks with those who have few attacks. Compare episodes of relapse and remission in patients with AQP4 positive NMOSD and MOG antibody disease. Compare episodes of relapse and remission within the same group of patients (MS, AQP4 positive NMOSD and MOG antibody disease patients).

Benefit to patients:
Develop tests that can identify patients who are likely to have more frequent and worse relapses, who may therefore benefit from stronger immunosuppression and closer clinical surveillance. Develop tests that predict relapses, before the relapse occurs, enabling doctors to treat relapses more quickly and effectively, thus improving the outcome for the patient.

1.9 Using magnetic resonance of serum to differentiate between MS and NMOSD, and to diagnose patients who are in-between

Research question:
Can we use magnetic resonance of serum to differentiate patients with NMOSD and MS?

Study design:
Blood samples are assessed using a technique called magnetic resonance spectroscopy to find out more about the chemical compounds that are contained within the blood sample. We are aiming to identify the differences we find between people with MS and NMOSD.

Benefit to patients:
We hope to use this technique to help to diagnose patients who are negative for Aquaporin-4 and MOG antibodies, and those who have overlapping symptoms of NMOSD and MS. This will help us select the best treatment for them.

1.10 NMOSD and pregnancy

Research questions:

Does pregnancy affect NMOSD attacks?

Does NMOSD affect the outcome of pregnancy?

Could a detailed examination of the placenta help us to improve our understanding of potential pregnancy problems?

Study design:

We have been asking patients whether they had attacks during their pregnancy or soon after, and if they were taking any treatment during that period or not. We have also been asking patients to let us know the outcome of all their pregnancies regardless of whether they were pregnant before or after their NMOSD started. Patients are also being asked to kindly donate the placenta, if it is not needed for medical reasons.

Benefit to patients:

We will be able to advise patients regarding the risk of having attacks during pregnancy and whether being on safe treatment prevents NMOSD attacks. We will also be able to advise patients on the potential risk of having pregnancy complications, and hopefully recommend how to prevent them.

1.11 NMOSD and infections

Research questions:
Do NMOSD patients on immunosuppression have common or unusual infections?
Who are the patients more often affected by infections?
Can we identify who is at risk of developing infections?
How can we prevent the infections?

Study design:
We have been recording the occurrence of infections in all patients with NMOSD as well as their clinical and laboratory information about NMOSD and other co-existing illnesses and treatments. We are comparing the characteristics of patients with and without infections to understand what makes some more vulnerable to infections.

Benefit to patients
We will be able to identify patients with a high risk of developing unusual infections and to advise patients and doctors on how to prevent and treat them promptly.

1.12 Assessing weight gain in NMOSD patients who take regular corticosteroids

Research question:
Obesity is a national public health priority. Many of our NMOSD patients put on weight with their steroid treatment.

Study design:
We have been asking patients what their weight was before they started taking steroids, if we have not already measured it. This will be monitored regularly to assess their degree of weight gain. Along with some additional clinical information this will enable us to determine what make someone more at risk of weight gain, for example their gender, ethnicity, age, other illnesses, reduced mobility and their weight prior to NMOSD as well as advising patients in clinic about their weight control.

Benefit to patients:
We will be able to be more proactive in giving dietary and exercise advice.

1.13 Studying the genetic and environmental influences in people with NMOSD

Research question:
Are there environmental influences which alter a person's risk of getting NMOSD and how severely they are affected, particularly if they migrate?

Study design:
We collected clinical and demographic data from Asian and Afro-Caribbean patients in the country in which they were born and in countries they have migrated to.

Benefit to patients:
This collaborative research can help us to understand the genetic and environmental factors that may affect the disease.

1.14 Association of fatigue with pain, Quality of Life (QoL), and mood.

Research question:

What is the association between fatigue and various factors related to quality of life, including pain and mood?

Study design:

We collected questionnaires on fatigue, mood, pain and quality of life, which were completed by patients with NMOSD. We plan to look at the association between these different factors.

Benefit to patients:

We hope to understand how people with NMOSD are affected by fatigue and what the relationship is with other aspects of quality of life.

1.15 Antibody production in lymph nodes despite circulating B-cell depletion of Rituximab in NMOSD

Research question:

Rituximab is a very effective drug for most patients with NMOSD, but why do some patients continue to relapse? Is it because the aquaporin-4 antibody is being produced by B-cells in lymph nodes, which aren't killed by rituximab?

Study design: .

Patients treated with rituximab, who continue to have high aquaporin-4 antibody levels, are being recruited for a lymph node aspiration. This is a minor procedure, taking only a couple of minutes, in which a small needle is passed into a lymph node under the chin, using an ultra-sound scan for guidance.

Benefit to patients:

This is an early study but it could contribute to the development of new medications to treat patients who don't respond to rituximab.

1.16 Predictors of prognosis and treatment response in MOG antibody disease

Research question:

How can we predict, which people with MOG antibodies will go on to have further relapses and accrue disability?
Who do we treat and with which medications?

Study design: .

In this study we are using both the clinical information of our MOG positive patients (e.g. age, ethnicity, type of first attack, response to treatment) and stored blood samples, to look at antibody levels, and presence of other proteins, which are associated with either a good or a poor prognosis.

Benefit to patients:

There is a huge variety of disease patterns seen in people with MOG antibodies; many have only one attack and make an excellent recovery but some have lots of attacks. We need accurate and early ways to predict this, so we know which people to treat with immunosuppressive medications.

1.17 A study of long-term steroid usage and side-effects in aquaporin-4 antibody positive NMOSD

Research question:
We think that taking low dose Prednisolone along with other immunosuppressant medications gives people with NMOSD more protection from relapses. But how much protection does it really add? And at what cost?

Study design:
Retrospective study of steroid use and clinical outcomes in our group of aquaporin-4 antibody positive patients. Outcomes include relapse rates, disability and possible complications from steroid therapy, e.g. fractures, diabetes, weight gain, high blood pressure, strokes.

Benefit to patients:
This study will help people with NMOSD to make more of an informed choice about whether they want to take prednisolone and how long for.

1.18 Developing a patient-reported outcome measure (PROM) for NMOSD

Research question:
When designing clinical trials in NMOSD and evaluating clinical services for patients with NMOSD, it is vital to be able to measure quality of life—not just traditional outcomes standard measures like relapse rates, which are not always meaningful to patients. In order to do this we need to understand what is important to patients with NMOSD.

Study design:
Following on from earlier work, we have now developed a preliminary questionnaire, or 'PROM'. We are now in the process of validating and refining this questionnaire, to ensure that it truly reflects what is important to people living with NMOSD.

Benefit to patients:
A well designed and validated PROM would allow our patients to provide meaningful, measurable and efficient feedback, which can be used to improve the quality of our treatments and overall care.

1.19 An international expert survey of treatment approaches to MOG antibody disorders.

Research question:
There are no established guidelines on how to treat MOG antibody disorder. We wanted to find out how experts around the world treat this rare condition.

Study design:
We sent out a survey to 50 international experts, asking about their treatment strategies for treating relapses, preventing future relapses and monitoring the disease.

Benefit to patients:
This survey will provide insights on how treatment strategies differ between experts and which important questions need answering with prospective studies and clinical trials.

Section Two: Closed to recruitment; results are being analysed

2.1 Pain Project (Abide)

Research question:
To determine the effectiveness and side-effects of this new drug in the treatment of pain associated with NMOSD, MS and transverse myelitis.

Study design:
Patients receive this new drug and their pain levels are assessed using pain scores.

Benefit to patients:
More than 80% of patients with NMO experience pain due to their condition, which severely affects their quality of life. Pain medications currently used do not produce satisfactory relief. Therefore finding a drug that can help people carry on with their lives free of pain would be an invaluable advance in the treatment of neuropathic pain.

2.2 Comparison of brain changes in MS and NMO using ultra-high field MRI

Research question:
Are there differences between the chemicals found in NMOSD lesions and MS lesions?

Study design:
NMOSD and MS patients were asked to undergo a high power MRI scan. The high power of the research scanner allows us to use a technique to determine the differences in chemicals at specific sites in the brain. Two sites of the body for each person are looked at; one that has been altered by the underlying condition (MS or NMOSD) and one that has not been affected.

Benefit to patients:
This helps us to learn about the process that causes NMOSD lesions and the differences between how this happens in NMOSD and MS. Results from this study could also help to distinguish MS and NMOSD more accurately.

2.3 Separating NMOSD from MS to guide treatment

Research question:

Is it possible to separate patients with overlapping symptoms of NMOSD and MS into distinct disease groups?

Study design:

We are now running an MRI study where we look at the brains and spinal cords of such patients to look for the presence of MRI features which would be typical for either MS or NMOSD. We also use other information from the clinical notes such as results of tests including OCT, Visual Evoked Potential (VEP) or lumbar puncture.

Benefit to patients:

Patients who have overlapping symptoms of NMOSD and MS are challenging to diagnose. This study will help group and classify such patients with the aim to choose suitable therapy for them. This is crucial as treatment for NMOSD and MS differs and might be ineffective or even harmful if used inappropriately.

2.4 Looking for blood markers that predict pain in NMO

Research question:
Are there chemicals in the blood that differ between AQP4 antibody positive NMOSD sufferers with pain and those without?

Study design:
Using magnetic resonance spectroscopy allows us to take research bloods samples and characterise a huge number of the various chemicals they contain. Using a complex statistical method, we are able to find out which chemical components make one subject more likely to be in a high-pain group or a low-pain group.

Benefit to patients:
This project seeks to understand the cause of pain in NMOSD and possibly identify new treatment options. The results might also be used to help predict who is likely to develop pain in NMOSD.

2.5 Immunosuppression in MOG antibody disease

Research question:
Does chronic immunosuppression influence the severity of relapse in MOG antibody disease?

Study design:
We collected clinical and demographic information of patients with MOG antibody disease who were treated with immunosuppressant medication and those who were not treated with immunosuppressants. We plan to look at the severity of relapse that occurs in both groups of patients.

Benefit to patients:
Studying the effects of immunosuppression on relapses can help the doctors to better manage this condition and to have more information regarding how well the treatment works in this condition.

2.6 The use of visual evoked potentials (VEP) in MOG antibody disease

Research questions:

Do the results of VEP tests in patients with MOG antibody disease correspond with the severity of ON? Are the VEP results able to predict the recovery from ON?

Study design:

We will collect all the VEP reports of MOG antibody patients. We plan to describe the VEP results and to look at the relationship of the results with the severity of ON and the recovery from ON.

Benefit to patients:

The aim of this study is to improve our understanding of how this visual test helps to give us information regarding ON in patients with MOG antibody disease.

2.7 Seasonality of attacks in MOG antibody disease and AQP4 antibody NMOSD

Research question:
Do the attacks of patients with AQP4 antibody positive NMOSD and MOG antibody disease occur during a specific time of the year?

Study design:
We collected all the clinical and demographic information about relapses for these two groups of patients. Using a complex statistical analysis we aim to look at when the attack occurs in a specific period of time (taking into account geographical differences).

Benefit to patients:
This project will help us to understand if there are specific environmental factors that can trigger the occurrence of relapses (i.e. infections) and potentially to avoid them.

2.8 Smoking in patients with AQP4 antibody positive NMOSD

Research question:

Can smoking worsen the occurrence of relapse and disability in patients with AQP4 antibody positive NMOSD?

Study design:

We collected clinical, demographic data and smoking history for patients with AQP4 antibody positive NMOSD and patients with MS. We plan to compare the time interval between attacks/relapses, the number of relapses and the recovery from relapses between smokers and non-smokers for these patients.

Benefit to patients:

It is well known that smoking can worsen MS. The aim of our study is to show the effects of smoking in patients with AQP4 antibody positive NMOSD and to help the patients to understand the importance of a healthy lifestyle when living with disability.

2.9 Comparison of fixed versus variable dosing of rituximab in NMOSD

Research question:

Rituximab kills B-cells in the bloodstream and is an effective treatment for NMOSD, but the ideal dosing regime is not known. We compared a standard fixed high dose regime (2grams every 6 months) versus a lower dosing regime with B-cell monitoring—patient have monthly blood tests and are retreated with 1gram of rituximab when B-cell re-appear.

Study design:

Retrospective review of outcomes in all our patients treated with rituximab. We numbers of relapses and number of infusions in patients on fixed high dosing versus those on variable lower dosing.

Benefit to patients:

Variable lower dosing of rituximab with B-cell monitoring appeared equally effective to fixed dosing, but patients needed few infusions. This approach reduced cost, increased patient convenience and has the potential for reducing side effects.

2.10 How effective is rituximab in MOG antibody disorder?

Research question:

We know that rituximab works well for aquaporin-4 antibody NMOSD, but there are only small numbers of MOG antibody positive patients treated with rituximab, and the benefit is not clear.

Study design: .

This is an international study, looking retrospectively at the effect of rituximab on relapses in over 100 people with MOG antibodies. We found that overall, there was a reduction in relapses after starting rituximab treatment. However, the benefit is less marked than with aquaporin-4 antibody NMOSD.

Benefit to patients:

This study highlights that some MOG antibody positive patients will not respond fully to rituximab. It provides insight into possible underlying disease mechanism and will stimulate exploration of alternative treatments.

Section Three: Planned for 2018/19:

3.1 MOG & preceding headache

We noticed several patients with MOG antibody disease had a severe headache just before an attack of optic neuritis. We plan to explore if this is this a feature of MOG antibody disease that can help identify cases earlier?

On a scale of 1 to 5 (1= not useful and 5= very useful), how useful do you think this study is to you.

1	2	3	4	5

3.2 Hearing loss in NMOSD

A few cases of hearing loss in patients with NMOSD have been noted. We plan to explore the underlying cause for the hearing loss and if it related to NMOSD and AQP4 antibodies.

On a scale of 1 to 5 (1= not useful and 5= very useful), how useful do you think this study is to you.

1	2	3	4	5

3.3 Optic Neuritis in older adults with AQP4 antibody positive NMOSD

It is thought to be more common for older patients to have transverse myelitis as their first attack of AQP4 antibody positive NMOSD. We plan to explore the occurrence of optic neuritis in older people to learn more about the condition and ensure visual problems in older patients are not being missed.

On a scale of 1 to 5 (1= not useful and 5= very useful), how useful do you think this study is to you.

1	2	3	4	5

3.4 Steroids management in AQP4 antibody positive NMOSD and MOG antibody disease patients

Steroids are the most effective treatment to prevent the occurrence of relapses, in autoimmune diseases that are caused by antibodies. Currently there are no clear guidelines regarding the most effective dosage, the length of time treatment should be given and the risk related to a rapid reduction of steroids. We plan to explore the role of the morning cortisol level (the body's natural steroid hormone) to help doctors to manage the use of steroids and their risks in these diseases.

On a scale of 1 to 5 (1= not useful and 5= very useful), how useful do you think this study is to you.

1	2	3	4	5

3.5 Steroid-induced avascular necrosis

We have had a few cases of patients with avascular necrosis (damage to bone tissue due to a lack of blood supply), which is thought to be related to long-term steroid use. We plan to explore what the risks are for NMOSD patients and what can be done to help to prevent this occurring.

On a scale of 1 to 5 (1= not useful and 5= very useful), how useful do you think this study is to you.

1	2	3	4	5

3.6 Cardiac disease in patients with NMOSD

We are exploring the risk factors associated with cardiac disease in patients with NMOSD. We are looking at clinical information that may affect the heart, including other health conditions, family history, medications, weight and lifestyle factors and reduced mobility. We hope to be able to offer advice to help prevent heart problems in patients with NMOSD.

On a scale of 1 to 5 (1= not useful and 5= very useful), how useful do you think this study is to you.

1	2	3	4	5

Thank you for your help.

If you are interested in any Research Projects Please contact the NMO service