National Commissioning Group
For Highly Specialised Services

Diagnostic and Advisory Service for Neuromyelitis Optica (NMO)

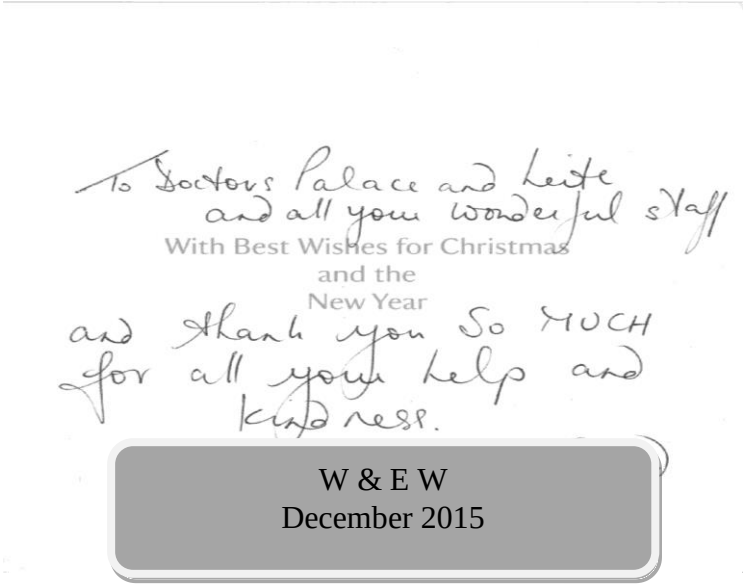
Oxford University Hospitals NHS Trust

Annual Report September 2015

Outcomes that can't be quantified……

NMO Patient Day 2015 – NMO Team photo

"I wanted to thank you for your website on all the information on NMO "Devic's" disease and the exercises are very helpful and just what I was looking for I'm in a wheelchair because of the disease and your website is the best I'm in the United States but if I lived close by I would go to you." sincerely **RS August 2014**



"I can't thank you enough for looking after my mum while she has been in Oxford and for arranging her speedy departure back to her family in Southend. We are very grateful to you and your team." **IS November 2014**

1. Service Overview

The Diagnostic and Advisory Service for NMO at the Oxford Radcliffe Hospital (herein referred to as the "NMO Service") with the Walton Centre in Liverpool, combines a specialist laboratory with a dedicated clinical service to offer a multidisciplinary service for patients across England and Scotland [funded by highly specialised services] and the rest of the UK [directly charged].

The NMO team comprises of:

Clinical team

Dr Jackie Palace	Consultant Neurologist (service lead)
Dr M Isabel Leite	Honorary Consultant Neurologist, Senior Clinical Research Fellow
Dr Saleel Chandratre	Consultant Paediatric Neurologist
Mr John Elston	Consultant Ophthalmic Surgeon
Dr George Tackley	NMO Clinical Fellow
Rosie Gore	NMO Specialist Nurse
Annaliza Rye	NMO Service Coordinator
Kay Day	NMO Occupational Therapist
Nina Eagle	NMO Physiotherapist
Julia Goodgame	Clinical Service Manager, NMO/CMS

Laboratory Team

Prof Angela Vincent	Honorary Consultant in Immunology
Dr Patrick Waters	Senior Postdoctoral Scientist
Dr Mark Woodhall	Postdoctoral Scientist

The service performs around 420 patient activities per year, in a combination of outpatient, inpatient and day case episodes, depending on clinical need. Patients are offered a full multidisciplinary experience when they come to clinic, with assessments from neurologists, ophthalmologists, specialist nurse and a team of therapists. For patients who are unable to attend (possibly due to disability) remote advice from the relevant team specialist is offered to local neurologists and GPs, as well as an advice email and phone line for patients to call with any queries.

To ensure ease of access, the service aims to ensure all appointments and investigations are completed within one visit. All patients are discussed within a multi-disciplinary meeting attended not only by clinicians, but also by laboratory and administrative staff to ensure a holistic and thorough assessment as well as a good communication to patients about appointments.

The service has the ability to admit patients who require urgent review to a dedicated neurosciences unit, with access to specialist therapies such as plasma exchange. A "relapse" (or exacerbation) of NMO can be a medical emergency, so the team liaise closely with bed managers to ensure rapid admission and treatment.

Most patients are on long term oral medication, but the few who need intravenous medication can be admitted as a day case to the neurology investigations unit, where trained nurses can administer medication such as Rituximab. Education links have been developed between the NMO team and the ward staff to ensure continuity of care.

An important part of developing a truly national service is closely linking with our sister NMO team in Liverpool. This is done through a combination of face to face meetings, teleconferences and jointly hosting and attending conferences relevant to the field of NMO. At these meetings, collaboration can be fostered in a supported environment to ensure continual developments in standardised care and evidence based practice for NMO patients.

Our service has an international reputation which means we frequently have doctors from abroad working and learning, which directly improves the service offered to patients at no extra cost.

2. Service Objectives, Outcomes and Performance measures

The purpose and goals of the service are set out in the service specification.

- To make a definitive clinical and laboratory based diagnosis of patients with suspected Neuromyelitis Optica Spectrum Disorder (NMOSD).
- To optimise NMO assay reporting time, this in turn speeds up the diagnostic process.
- To ensure that NMO patients are quickly started on the correct long term immunotherapy to reduce the likelihood of having further relapses. Preventing a relapse is associated with a much better outcome than treating a relapse after it has occurred.
- To involve patients in their own care and allow them to feedback on their own experiences.
- Develop patient / health care professional information.

These are measured using the following outcomes:

Activity levels

- Number of new and follow up outpatient episodes, day cases and inpatient stays.
- Number of AQP4 antibody tests performed in the laboratory.

Performance indicators

- Time to report NMO assay
- Certainty of diagnosis
- Annual relapse rates
- Mortality rate
- < 20% unsatisfactory scoring in patient feedback questionnaires

Miscellaneous

- Geographical access to the service
- Time from the service receiving the referral to being offered a clinical consultation by the service.
- Outreach clinics.
- Service discharge.
- CQUIN.

Activity Levels
The service activity is monitored and recorded on a monthly basis so that the centre can meet the demands of a shifting patient demographic and case load.

Clinical Services Activity:
Basic activities are demonstrated in ***[Appendix 1a and 1b].***

From April 2014 to September 2015 the service received 111 new patient referrals from eligible areas***.*** A large proportion of the patients seen in an outpatient setting are followed up at the centre on an annual basis whilst visiting their local neurologist in between.

Since 2014, the service has increased the number of outpatient clinic slots per year from 184 to 276 per year, to cope with increased demand. This means we now have out-patient clinics every week.

The clinical service activity for 2014-15 was 25% over annual plan for new patients seen, 135% over annual plan for follow up patients seen, 40% under annual plan for day case admissions and inpatient events were 69% under annual plan. This reduction in in-patient admissions is a positive consequence of patients receiving effective medication and management of their condition, resulting in fewer relapse admissions and an increase in patients being managed closer to their home, with advice from our service. Additionally access to NHS beds limit admissions.

The clinical service activity for 2015-2016 is 22.2% over annual plan on new patients seen, 135% over annual plan on follow up appointments and under target for day case admissions and inpatient events to date.

Nurse advice line audit
We have changed the way calls to the nurse advice line are recorded to include a grading of calls, according to complexity, which is similar to that used by the Walton Centre.
This change occurred at the start of 2015, therefore these figures are only for 6 months of the year. Total number of calls to the NMO nurse advice line 1st Feb to 31st July 2015 was 100.
Level 1 = simple admin
Level 2 = simple patient contact/discussion
Level 3 = more complex discussion, e.g. medication or investigations, follow-up required
Level 4 = relapse management, urgent response required, complex care/planning.
Total for Level 1 = 7, Total for Level 2 = 37, Total for Level 3 = 47, Total for Level 4 = 9

Since April 2014 we have dealt with 97 email request and advice. These emails can be broken down into four different groups:
Group 1 = Administration – Patient appointment advice / rebooking.
Group 2 = Administration – Patient referral to service by patients local consultant / GP.
Group 3 = Nursing – Patient medical advice / reporting that is to be dealt with by our Nurse.
Group 4 = Clinicians – Medical advice required by patients Neurologist or GP.
Total for Group 1 = 26, Group 2 = 32, Group 3 = 18, Group 4 = 21

Number of Tele-med appointments from March 2015 to August 2015 was 125. This service was implemented in January 2015. These Tele-med appointments are where the clinician / nurse does an assessment of condition and gives advice i.e. medication changes etc. over the phone.

Laboratory Activity:
A more detailed breakdown of the laboratory activity is shown in ***Appendix 2.***

For the period April 2014 to March 2015 the Laboratory team for the Diagnostic and Advisory Service for NMO (Oxford John Radcliffe Hospital) tested a total of 6346 samples (this is the total of all samples received from eligible and non-eligible countries worldwide) of which 6150 samples were received from the United Kingdom (5549 samples) and other NHS eligible overseas EEA member countries (601 samples) under the testing remit of the service. Of these 6150 samples, 5222 were new patient serum/CSF samples from which 86 (1.6%) were reported positive for AQP4 antibodies ***[Appendix 3]***.

Since the last service year the service has seen a 23.1% increase in the number of NMO tests being performed. During this period April 2014 to March 2015, 99% of all assays completed were reported within 5 days of receiving the sample with the remaining (51/5222) being reported within 10 days ***[Appendix 3]***.

As well as providing the routine AQP4 antibody test the assay service also provides AQP4 titrations on request for individual patients with difficult to manage disease. The team have currently completed serial AQP4 titrations on 135 individual patients either known or on remote advice to the NMO service. Refer to ***Appendix 4*** for a summary of the AQP4 titrations completed over the last service year. Although titrations are labour intensive [6-12 assays for 1 titration], the benefits of being able to follow a patient's AQP4 titres over the course of their disease can be invaluable for assessing the effectiveness of treatment regimes, for example.

Speed of reporting results of NMO antibody test
NMO can be a devastating disease if left undiagnosed and untreated. This can be compounded further by incorrect diagnosis. Therefore the service aims to assess and diagnose patients as rapidly as possible and part of this is a commitment by the assay service to report all samples received within 5 days.

This commitment is highlighted in the turnaround figures for the samples received from April 2015 to date, as even with the additional AQP4 titrations factored in, 100% of all the assays completed were reported within 5 days of receiving the sample ***[Appendix 3]*** with 88% being reported within 3 days.

Diagnosis
The NMO service has access to highly specialist investigations (including the laboratory test for AQP4 antibodies, highly specific for the diagnosis of NMO, and MOG antibodies) as well as review with experienced clinicians to ensure that patients receive an accurate diagnosis of their condition.

Due to the difficulties in differentiating seronegative NMO from other demyelinating and inflammatory disorders, many patients will come to the service with an unclear diagnosis, or in some cases an incorrect diagnosis and we endeavour to clarify or correct the diagnosis where appropriate. Active research undertaken by the service aims to increase the accuracy of diagnosis in uncertain cases (see *Research Developments*).

The service saw 49 new referrals from April 2015 to date. A number of these will have had their diagnoses clarified or changed. Sometimes this is simply because of AQP4 antibody identification confirming the diagnosis. Definitive diagnosis is more difficult in antibody negative patients but we actively pursue evidence to categorise these individuals wherever possible, for it is well recognised, in part because of the work of doctors Palace and Leite in

2008, that multiple sclerosis disease modifying agents (such as beta-interferon), can increase the relapse rate of NMO patients and thus correct diagnosis is crucial.

The following table demonstrates the majority of our current patients have a clear working diagnosis (all AQP4 Ab positives are assumed to have a diagnosis). For antibody negatives at least, a clear working diagnosis is rare at time of referral to our service.

	n	%
Total Active Pts	197	
AQP 4 Positives	74	37.6%
AQP4 Negatives with Diagnosis*	109	55.3%
AQP4 Negatives without Diagnosis*	14	7.1%

* Refers to patients with defined clinical classification

Relapse rates

The following activities ensure that patients are rapidly started on, and remain on immunosuppressive therapies:

- Reaching a correct diagnosis early (see above)
- Providing patient education to increase compliance with treatments and prevention of associated complications
- Facilitating good communication links between the service, patient, GP and other healthcare professionals
- Educating other neurology teams by visiting clinics, talks and email advice.

We focus our inputs on difficult to manage patients but have managed to keep our relapse rates down. Since April 2014 we have had eight definite relapses in our AQP4 antibody positive cohort of 76 patients, giving a favourable annualised relapse rate per patient of 0.11. We have also analysed the severity of relapse on and off Immunosuppressive Treatment (IST) and found that relapse severity is reduced on IST.

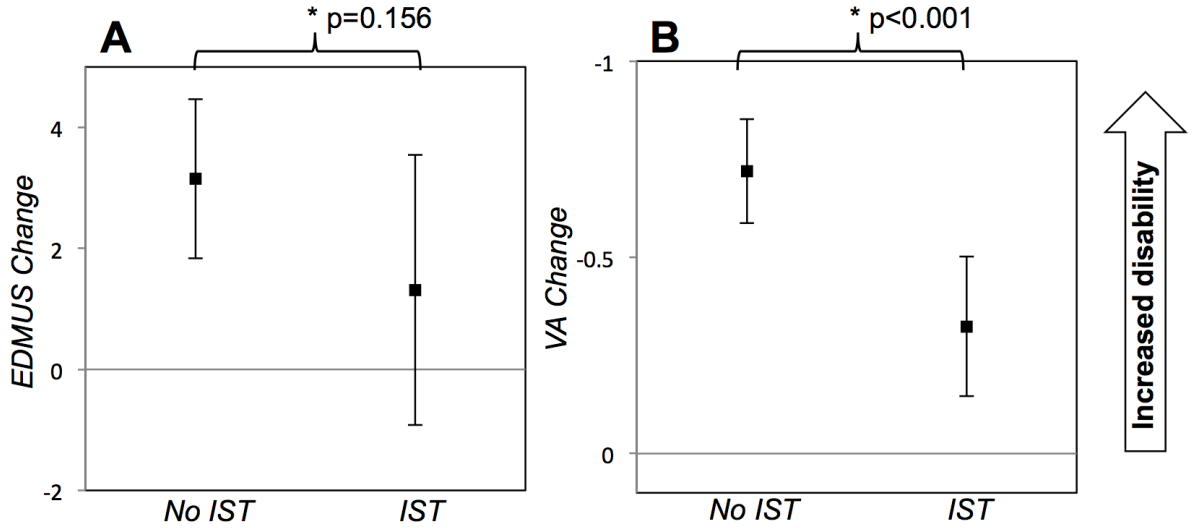


Figure X: Relapse severity differences with and without background immunosuppression.
Change in disability scores with and without established immunosuppressive treatment. **A**. EDMUS changes representing lasting disability of transverse myelitis attacks and **B**. decimal visual acuity (VA) changes for attacks of optic neuritis. Pre-attack EDMUS scores of <6 and pre-attack VA scores of 1 used for analyses (see text). Error bars = 95% confidence intervals. IST, established immunosuppressive treatment, e.g. azathioprine, methotrexate, etc.
NB VA change axis reversed to depict unified direction of increased disability.
* p-value for comparison of least squares means.

	EDMUS mean change after attack (all patients)	VA mean change after attack (all patients)
Off-IST	2.68* (n=24)	-0.72** (n=32)
On-IST	0.05* (n=12)	-0.30** (n=17)

	EDMUS mean change after attack (pre-attack EDMUS <6)	VA mean change after attack (pre-attack VA normal [=1.0])
Off-IST	2.68 (n=23)	-0.72** (n=32)
On-IST	0.05 (n=8)	-0.30** (n=15)

*p<0.05 for comparison of off- and on-IST
**p<0.01 for comparison of off- and on-IST

Mortality rate

There was one patient death during the period April 2014 to March 2015 and two deaths since April 2015:
84 year old lady with AQP4Ab positive monophasic LETM who presented in Feb 2014.This left her immobile and catheterised. She was established on methotrexate. Her cause of death was documented as pyelonephritis. DOD: 19.02.2015.
66 year old lady with AQP4Ab positive NMO (on rituximab), cause of death: Respiratory infection, PMH asthma. DOD: 28.05.2015
64 year old lady with AQP4Ab positive NMO (on azathioprine, prednisolone and for a period eculizumab), cause of death: respiratory, PMH COPD. DOD: 29.05.2015

Patient feedback

The service should be geared towards the needs of the patients and should be sensitive to any suggestions or complaints that are made. To ensure that patients feel they are free to speak freely, they are provided with anonymous questionnaires which focus on their experiences from receiving an appointment through to being seen. This also looks at any remote contact (emails, phone calls) that the patient may have had. An example of this questionnaire is in ***[Appendix 5].*** The feedback questionnaire is currently being reviewed and updated to simplify the format and the same questionnaire will be used by both centres.

April 2014 – March 2015 – data from 69 questionnaires
April 2015 – August 2015 –data from 32 questionnaires ***[Appendix 6]***

The service continues to improve with information regarding appointments and location. There have not been any concerns raised by patients with regard to their appointments, timings or location. Patient choice is adhered to with regard to rescheduling when necessary.

Informing patients of their condition has improved; with all patients who have completed the questionnaire stating they have an understanding of the disease.

The information given to the patients (all booklets) has resulted in 100% positive feedback. The booklets are available in audio format, all blind patients are informed of this and audio discs are sent out to patients on request.

Patient Geographic's

As a national service for NMO Oxford aims to offer equal access to the diagnostic and management expertise at the centre to patients from across the South of England. However, many patients cite transport costs as a limiting factor in their decision to attend the Oxford clinic. In cases where the patients are physically unable to attend an outpatient clinic, a remote advice service is offered to their local clinician regarding diagnosis and management.
Please see ***[Appendix 7]*** for a breakdown of patient Geographic's for patients seen by the NMO Service.

The geographic distribution of email correspondence form April 2014 to date can be seen on the map labelled ***[Appendix 8]***. Please note that each star on the map only represents a place that the assistance was requested from not the frequency of assistance required. In addition to this we also deal with international enquiries as well. This year we have had emails or phone calls from South America, North America, Japan and many European countries.

Referral to consultation time

NMO can be a devastating disease if left undiagnosed and untreated. This can be compounded further by incorrect diagnosis. Therefore the service aims to assess and diagnose patients as rapidly as possible. This is more important in AQP4 antibody positive patients, particularly those not stable on immunosuppression.

To ensure that all relevant correspondence and imaging from the referring centre has been transferred to the NMO service, a timeframe of 8 weeks from receiving referral to assessing the patient was agreed.

Since the 1st April 2013 to date all new patients that have been referred to the service have been offered appointments within 8-9 weeks of their referral being received by the service. Some of the patients however have chosen to be seen at a later date. Urgent appointments, where patients are untreated and immunosuppression is indicated, are offered and the team also liaise with referring clinician in the interim.

Joint/Outreach Clinics

25.07.2014 & 19.06.2015 - Joint clinics are held yearly with Dr Cheryl Hemmingway at Great Ormond Street Hospital (GOSH), members of the National NMO Service and paediatric neurologists with an interest in NMO.
31.03.2015 - Joint clinic was held with Dr Christopher Halfpenny at Southampton General Hospital and the National NMO Service. We wish to continue this on a twice a year basis.
We are in the process of liaising with Kings Cross Hospital about starting a remote clinic there as well.

Service discharge

After NMO clinic assessment and review, those with other demyelinating conditions, such as MS, ADEM or idiopathic transverse myelitis are discharged for local neurology management. The latter two have a significantly lower risk of relapses and often do not require long term immunosuppressant or review from the NMO service. In any case, we ensure that the referring clinician can re-refer the patient if there are any further problems.

CQUIN

Annual CQUIN meetings are held with our sister NMO team in Liverpool. At these meetings, collaboration can be fostered in a supported environment to ensure continual developments in standardised care and evidence based practice for NMO patients. **A meeting was held this year on 25th June 2015 and the next one is scheduled for 24th June 2016 in line with 2013- 2014 CQUIN guidance. *[Appendix 9]*is the minutes from the meeting held on the25th June 2015 and *[Appendix 10] is a* copy of the National CQUIN guidance.**

3. Financial Update

To be presented by the OUH Financial team lead by Carol Ann Gourlay, Neurosciences Finance Manager.

4. Service Developments current and future

Clinical Staffing

NMO Physiotherapist:

The team recruited a new physiotherapist, Nina Eagle, in January 2015, this post has increased hours than the previous position, enabling her to join the team for outreach clinics, attend meetings and contribute to service development.

NMO Nurse:

Funding for an additional nurse post was agreed and the recruitment process is currently underway. This new nurse post, in conjunction with the current NMO nurse, will increase opportunities for home visits, outreach clinics, teaching sessions and service development. The new nurse will help to keep our website updated, contribute to patient information literature, and clinical outcome questionnaires in the clinics.

These developments have been funded from the increased activity.

Review of Clinical Outcome Measures

The NMO nurses from Oxford and Liverpool met to look at the clinical outcome measures used by both centres. The aim, as discussed at the CQUIN meeting in June 2015, was to decide on which measures would be used, how frequently they would be used and how the results would be used. The measures will be used to evaluate patient outcomes; for example, by comparing the baseline measures at the time of initial appointment to one or two years later. Additionally, they could be used to evaluate the impact of an intervention, for example auditing pain or mood before and after an intervention which may impact on that particular problem or need.

The outcome measures were selected where there was evidence of their validity for use in similar long-term neurological conditions, such as Multiple Sclerosis. There is work being undertaken in the USA on establishing clinical outcome measures in NMO but as yet, due to the rarity of the disease, there are none that have been validated specifically in this condition as yet. However, if possible both centres would be keen to explore this or collaborate with other centres.

Measures to be used for 2015-2016:

Self-administered questionnaires:

- Quality of Life – SF36 and self-rated score 0-100 from Euroquol
- Anxiety and Depression –Hospital Anxiety and Depression Scale (HADS)
- Pain –Brief Pain Inventory (BPI)
- Fatigue –Modified Fatigue Impact Scale (MFIS)
- Sexual –Sexual Satisfaction Scale (SSS)
- Bladder –Bladder Control Scale (BLCS)
- Bowel –Bowel Control Scale (BWCS)
- Vision –Impact of Visual Impairment Scale (IVIS)
- Cognition –MS Neuropsychological Screening Questionnaire (MSNQ)

For carers:

- Carer Burden – Zarit Burden Interview

Clinician administered:

- Disability – EDMUS
- Mobility –Timed 25-Foot Walk (T25FW)
- Balance – Tinetti
- Cognition – ACE/MoCA

Self-administered questionnaires will be given to patients at their initial appointment in the NMO service, then annually. Clinical needs will continue to be screened or reviewed at each clinic visit.
Carers will be invited to complete the carer's burden questionnaire to help the team understand and support those directly involved in the patients' care at home. Clinician administered measures will be completed at baseline and annually, except for cognition, which will only be completed if screening indicates cognition is an issue or concern is raised by the patient or their carer. This is because cognition is not commonly associated with NMO but would be important to address if it was an issue for a particular individual. All outcome measures will only be completed with the patient's consent and will be primarily used to measure the patient's progress. These measures may also be used for research projects, with the consent of the patient/carer, to further the understanding NMO and the experience of those living with the condition. We are also looking at the format of the self-administered questionnaires for patients who are visually impaired; either larger print or electronic, so that patients can complete in confidence if they wish.

Physiotherapy Outcomes:
At present, the physiotherapy assessment within the NMO Clinic, includes routine Tinetti Balance assessment, and a 25 foot timed walk.

Other outcome measure have also been looked into. Including the Berg balance assessment, used in MS research and a core stability measure along with measures for non-ambulant patients.

Upon discussion with the Liverpool team and to keep consistency across both services, it was felt that the Tinetti was the best balance assessment to complete with our patient population given the restriction of time and space in both locations. This is the preferred measure as can be done through observation (of when the patient walks into/out of clinic,

transfers in/out of chair) and would only leave a few elements to be assessed subsequently to these.

The 25 foot timed walk will continue to be completed also. Once significant data has been acquired an audit of both outcome measures can be completed.

We have also looked at the outcome measures WISCI II [walking index spinal cord injury version II]- this is a 20 point scale and transverse myelitis can be considered a non-traumatic form of SCI. This would therefore be suitable as it is clinically relevant for this population- it is not always essential to compare to the MS population. It has some limits [such as scores 1-4 require parallel bars] but could easily be assessed at the same time as the timed 10 m walk.

The modified function reach assessment could also be added for the non-ambulant patient population.

In the future, An exercise booklet with specific core stability exercises, strengthening and stretches would be most useful to hand out in clinic.

The Oxford outpatient experience improvement scheme

Kay Day has continued to develop the NMO library section in the Outpatient Department. The library consists of a wide range of patient information leaflets from national charities, healthcare organisations, support groups, publications and magazines of interest to NMO patients. The information can be self selected by patients and is also accessed by the NMO team during clinics. It is hoped to expand the range of NMO patient information booklets in response to the identified needs.

Feedback continues to be incredibly positive:

LH patient “being able to grab leaflets at appointments is so useful – Neurosupport (a neurological support charity) have guided me on employment rights and helped me get back to work”.

Patient information

The existing booklets from the ‘Living with NMO’ series are to be reviewed and updated, these include: Independence in daily life, Movement, mobility and travel, Work and money, From Fatigue to Energy, Staying Active with NMO.

Handouts on pain and psychological well-being, produced for the Patient Information Day 2015, are to be developed into new information booklets. Dr Leite is working on a booklet about pregnancy in NMO. Work is also underway to produce patient information on MOG antibody disease to help patients understand the diagnosis and treatment.

Expertise in NMO is developed by seeing as many patients in our catchment area as possible. It is imperative for the NMO team to share their experiences and observations not only with service users, but also referring clinicians, healthcare professionals and researchers interested in NMO. As NMO is a rare condition, the up-most effort has been made to promote knowledge of NMO and the service to healthcare professionals who may also come into contact with NMO patients.

Web based information

To ensure information is available on as many mediums as possible, the NMO Service has developed a website designed mainly for patients, but with sections for healthcare professionals. This website will hold PDF copies as well as audio files of all written info, up to date news and information about relevant events, trials and research updates as well as

an area for patients to use as a forum. It has been set up in association with the RNIB to ensure easy access for all.
This website is hosted by The Walton Centre NMO Team.

Research Developments

In 2012 we developed an assay to detect antibodies to MOG in patients with clinically-definite AQP4-seronegative NMO and not in patients with multiple sclerosis. We found that these patients initially present with equally severe optic neuritis and/or transverse myelitis, but that they recovered much better than the AQP4 seropositive patients. These patients require less long term immunosuppression.

We have further developed this assay and confirmed a more than 60% increase in sensitivity, while maintaining specificity (i.e. no multiple sclerosis patients identified) based on adult patient cohorts from Oxford, Japan, and two separate cohorts from Korea; and a paediatric cohort from London.

In addition AQP1 antibodies have hit the headlines in NMO after two publications from groups in Greece and Turkey suggesting that some NMO patients also have antibodies to AQP1, another aquaporin present in the brain. We developed an AQP1 cell based assay in collaboration with Dr. Markus Reindl (Innsbruck, Austria) and demonstrated that NMO patients do not have AQP1 antibodies. As AQP1 contains the Colton blood group antigen present on the surface of red blood cells, one might expect patients to suffer from severe anaemia. We don't see this in NMO patients.

Clinically we have demonstrated that pregnant individuals with NMO miscarry more often after disease onset than before (Leite et al. submitted). Miscarriages are more common in patients who demonstrate active disease in the 3 months pre-pregnancy and during pregnancy than those in remission. Based on these observations by Dr. Leite we developed an animal model to show that peripheral injection of NMO-IgG and complement can induce placental inflammation and fetal death in mice, with inflammatory features identical to those seen in human spinal cord and brain lesions. This demonstrates possible AQP4 antibody mediated disease outside the CNS.

We also followed up the initial publication on MOG antibodies (Kitley et al Neurology 2012) to further elucidate the clinical features of these AQP4 seronegative NMO patients in several publications from Oxford and Japan (Waters et al (submitted), Hacohen et al (submitted), Kitley et al. Arch Neurol. 2014, Sato et al, Neurology, 2014). These publications show that patients with MOG antibodies predominantly have optic nerve involvement. When they have myelitis it often involves the conus (lower extremity of the spinal cord); they are mostly oligoclonal band negative (whereas most MS patients are OCB positive), and lack co-existing autoimmunity. Although these MOG positive patients presented with equally, if not more severe disease when compared to AQP4 positive NMO patients, they seem to recover much better and require less long term treatment. In line with these clinical observations we developed a second animal model to compare CNS lesions recovery over 2 weeks in animals that were injected with either AQP4 or MOG antibodies. The animals injected with MOG antibodies recover from the antibody insult much faster than those injected with AQP4 antibodies. They do not fix complement in the same manner or to the same degree and do not have vast lymphocytic cellular infiltrates as is seen in the AQP4 animal model. They do get some alteration in myelin structure and temporary loss of nodal proteins, which recover after 2 weeks.

Clinical research progresses alongside laboratory research. Pain in NMO sufferers is increasingly recognised to be highly prevalent and particularly severe, and in this way distinct from pain in MS. A project in 2011/12 looking at pain characteristics in NMO (presented at ECTRIMS 2012) spearheaded a much larger venture now underway

investigating psychological aspects, impact on quality of life and non-conventional MRI imaging correlates of pain descriptors with the hope of exposing novel treatment targets for NMO related pain. The research has prompted engagement with a pain specialist, who has subsequently developed a clinical interest in NMO, and now regularly reviews patients, offering advice on a case-by-case basis.

Another symptom, fatigue, has also emerged as highly relevant and frequently problematic. We now routinely collect fatigue questionnaires to stratify its characteristics in NMO. Our occupational therapist has created an updated booklet on managing fatigue that has already received much positive feedback. Initial analysis has identified a significant burden of fatigue within our AQP4 antibody positive cohort with the physical-fatigue component coming out as most important. Concurrent depression, anxiety, pain and disability were strong independent predictors of fatigue in NMO.

Through our tissue- and data-bank consent, we have collected a huge body of information on our NMO patients, a process that is on-going. A recent analysis (submitted for publication) has added to existing evidence that immunosuppression reduces relapse rates, but also provided (for the first time) evidence that being on established immunosuppresion likely reduces the disabling impact of an individual relapse.

AQP4Ab negative NMO remains poorly defined and consequently difficult to treat. An externally funded member of our team has begun a multi-modal research project looking into better defining AQP4 negative disease, looking for clinical and investigative differences (including non-conventional MRI) from AQP4 positive NMO, MS and other related conditions, working towards guiding best therapeutic and clinical management.

As a team, we provide the opportunity for medical and scientific trainees to undertake these projects on our behalf with our supervision, which provides them with a unique training experience and us with the manpower to undertake study without a cost implication to the service.

References

Myelin-oligodendrocyte glycoprotein antibodies in adults with a neuromyelitis optica phenotype. Kitley J, Woodhall M, Waters P, Leite MI, Devenney E, Craig J, Palace J, Vincent A. Neurology. 2012 Sep 18;79(12):1273-7

MOG cell-based assay detects non-MS patients with inflammatory neurologic disease. Waters P, Woodhall M, O'Connor KC, Reindl M, Lang B, Sato DK, Juryńczyk M, Tackley G, Rocha J, Takahashi T, Misu T, Nakashima I, Palace J, Fujihara K, Leite MI, Vincent A. Neurol Neuroimmunol Neuroinflamm. 2015 Mar 19;2(3):e89

Myelin oligodendrocyte glycoprotein antibodies are associated with a non-MS course in children. Hacohen Y, Absoud M, Deiva K, Hemingway C, Nytrova P, Woodhall M, Palace J, Wassmer E, Tardieu M, Vincent A, Lim M, Waters P. Neurol Neuroimmunol Neuroinflamm. 2015 Mar 12;2(2):e81.

Neuromyelitis optica spectrum disorders with aquaporin-4 and myelin-oligodendrocyte glycoprotein antibodies: a comparative study. Kitley J, Waters P, Woodhall M, Leite MI, Murchison A, George J, Küker W, Chandratre S, Vincent A, Palace J. JAMA Neurol. 2014 Mar;71(3):276-83.

Distinction between MOG antibody-positive and AQP4 antibody-positive NMO spectrum disorders. Sato DK, Callegaro D, Lana-Peixoto MA, Waters PJ, de Haidar Jorge FM,

Takahashi T, Nakashima I, Apostolos-Pereira SL, Talim N, Simm RF, Lino AM, Misu T, Leite MI, Aoki M, Fujihara K. Neurology. 2014 Feb 11;82(6):474-81.

Antibodies to aquaporin-1 are not present in neuromyelitis optica. Schanda K, Waters P, Holzer H, Aboulenein-Djamshidian F, Leite MI, Palace J, Vukusic S, Marignier R, Berger T, Reindl M. (accepted in Neurol Neuroimmunol Neuroinflamm 2015)

NMO Drug Trials

The team are currently recruiting for two international commercial drug trials:
Chugai - A multicentre, randomized, addition to baseline treatment, double-blind, placebo-controlled, phase 3 study to evaluate the efficacy and safety of SA237 (an anti-IL-6 agent) in patients with NMO and NMOSD.
Alexion - A randomized, double-blind, placebo-controlled, multi-centre trial to evaluate the safety and efficacy of eculizumab in patients with relapsing NMO.

And one national non-commercial drug trial in Transverse myelitis and NMO:
STRIVE - A multicentre randomiSed controlled TRial of IntraVEnous immunoglobulin (IVIg) versus standard therapy for the treatment of transverse myelitis in adults and children.

Meetings/Conferences

NMO Patient Information Day, 9th May 2015

This year's patient information day was held over two days in Birmingham. The first day was more informal with a social event in the evening for patients and carers who wished to stay overnight. The second day consisted of talks by members of the NMO teams and interactive workshops in the afternoon. There was lots of opportunity for participants to meet other people living with NMO as well as discussions with the Oxford and Liverpool teams. The venue was different to last year and the feedback about the venue and the content of the event was very positive. The recently established charity NMO-UK research foundation attended the event and presented awards to fundraisers for their contributions.
Please see ***[Appendix 11]*** for the programme of day two of this meeting.

Fundraiser

A fundraiser/ garden party was held at the home of Dr Jackie Palace this year on the 4th June 2015, to help raise funds for the new NMO charity that just started up this year. Staff supplied foods from around the world as well as supplying entertainment in the form of our Fellows that have their own band, the NMO nurse and Physio sang for everyone and the NMO coordinator taught everyone to line dance. All was a great success and we raised £300.00 for the NMO charity.

All having fun at fundraiser.

NMO scientific/medical publications and presentations
One of the best ways to inform other healthcare providers about work going on within the field of NMO is to publish journal articles. These articles often form the basis of a presentation to other HCP and scientists at various meetings.

NMO Team Presentations for 2014/2015:

Dr Jackie Palace:
1. NMO Patient day - 10th May 2014

2. European NMO Meeting, Gatwick, UK 19th June 2014 to 20th June 2014. (Agenda attached)

3. ACTRIMS - Teaching course NMO treatments - Sept 2014.

4. ACTRIMS : Debate on Placebo in NMO - Sept 2014.

5. Talk in Manchester on the 12th June 2015.

6. Talk at Royal Free Hospital on 31st July 2015

7. ABN – NMO 9th Sept 2015 to 10th Sept 2015

8. MAGNIMS – NMOSD 14th Sept 2015

9. Keeley University in Stoke on Trent on NMO Spectrum 11th Sept 2015.

10. ECTRIMS X2 Talks –Teaching Session on NMO and Satellite symposium on the treatment of NMO - 7th Oct 2015 to 10th Oct 2015

Dr Isabel Leite:
1. NMO Patient day - 10th May 2014

2. TM patient Day – 17th May 2014

3. European NMO Meeting, Gatwick, UK 19th June 2014 to 20th June 2014. (Agenda attached)

4. NMO Round Table on 1st March 2015

Prof Angela Vincent
1. European NMO Meeting, Gatwick, UK 19th June 2014 to 20th June 2014. (Agenda attached)

Dr Patrick Waters
1. International Panel for NMO Diagnosis discussion group.

2. NMO Patient day - 10th May 2014

3. European NMO Meeting, Gatwick, UK 19th June 2014 to 20th June 2014. (Agenda attached)

Dr George Tackley

1. NMO Patient day - 10th May 2014

2. TM patient day - 17th May 2014

3. European NMO Meeting, Gatwick, UK 19th June 2014 to 20th June 2014. (Agenda attached)

Rosie Gore:

1. Guthy Jackson Foundation – Patient Day 4th March 2015: 'Food for Thought': Nutrition for Health "What caregivers are telling their patients today". Panel discussion on nutritional advice and information for people living with NMO.

2. NETS days are teaching sessions at the John Radcliffe Hospital for nurses and health professionals who may come across patients with NMO. The Oxford NMO nurse provides teaching on NMO at these sessions 3-4 times per year.

3. Information about NMO was presented at a regional MS nurse meeting at St George's Hospital, London on 17th June 2015.

5. Appendices

Appendix 1a.	Copy of NMO Monthly stats Mar 14 to Apr 15
Appendix 1b.	Copy of NMO Monthly stats Mar 15 to Sep 15
Appendix 2a.	Monthly activity summary for assay service Mar 14 to Apr 15.
Appendix 2b.	Monthly activity summary for assay service Mar 15 to Sep 15.
Appendix 3a.	Turnaround summary for assay service Mar 14 to Apr 2015.
Appendix 3b.	Turnaround summary for assay service Mar 15 to Sep 15.
Appendix 4a.	Activity summary for AQP4 titrations completed by assay service Apr 14 to Mar 15.
Appendix 4b.	Activity summary for AQP4 titrations completed by assay service Apr 15 to Sep 15.
Appendix 5.	NMO Patient Survey
Appendix 6.	Patient feedback comparison from April 2014 to Mar 2015 and April 2015 to Aug 2015.
Appendix 7.	Map detailing NMO Oxford Patient Demographics
Appendix 8.	Map detailing email advice within the UK since April 2014 to Aug 2015
Appendix 9.	Minutes from CQUIN meeting held on 25th June 2015.
Appendix 10.	Guidance on the implementation of the highly specialised services 2013/14 CQUIN
Appendix 11.	2015 NMO Patient day agenda
Appendix 12.	Publications and presentations of NMO service