



Diagnostic and Advisory Service for Neuromyelitis Optica (NMO)

Oxford University Hospitals NHS Trust

Annual Report October 2014

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Outcomes that can't be quantified.....



Last summer we bought N a dog that we are training for a guide dog .



DA: "I am proud daddy" - she is already 1 year old.

"I just wanted to say 'Thank you' for all your ongoing help and support. It is so reassuring and good to know there is such a dedicated and committed team working for the NMO cause. It is really appreciated" – **LH card of thanks 2013**



It's so important to keep living your dreams.

"I am very happy with all my visits, they listen to what I want to say, and help in any way they can however small my question is. Always made to feel welcome." **(From anonymous "patient experience questionnaire" feedback, 2013 - 2014)**

"I thought the balance of clinical expertise and personal care was excellent." **(From anonymous "patient experience questionnaire" feedback, 2013 -2014)**

"The team at the NMO unit were all very nice, helpful and thoughtful. They made me feel very welcome and had empathy and understanding of my difficulties. It was my 1st visit and there was a lot to do in a small space of time. I look forward to my next visit." **(From anonymous "patient experience questionnaire" feedback, 2013 - 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 the England, 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
Kay Day	Occupational Therapist
Kate Browne	NMO Physiotherapist
Julia Goodgame	Clinical Service Manager, NMO/CMS
Annaliza Rye	NMO Service Coordinator
Nabeela Ahmad	NMO Admin Assistant

Laboratory Team

Prof Angela Vincent	Honorary Consultant in Immunology
Dr Patrick Waters	Senior Postdoctoral Scientist
Dr Mark Woodhall	Postdoctoral Scientist
Miss Sian Peach	Laboratory Technician

The service performs around 375 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 have frequent 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 replies 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.

Basic Activity:

Basic activities are demonstrated in **[Appendix 1a and 1b]**.

Laboratory Activity:

A more detailed breakdown is shown **[Appendix 2]**.

For the period April 2013 to March 2014 the Laboratory team for the Diagnostic and Advisory Service for NMO (Oxford John Radcliffe Hospital) tested a total of 5074 samples (this is the total of all samples received from eligible and non-eligible countries worldwide) of which 4879 samples were received from the United Kingdom (4674 samples) and other NHS eligible overseas EEA member countries (205 samples) under the testing remit of the service. Of these 4879 samples, 4192 were new patient serum/CSF samples from which 82 (2.0%) were reported positive for AQP4 antibodies **[Appendix 3]**.

Since the last service year the service has seen a 6.1% increase in the number of NMO tests being performed. During this period April 2013 to March 2014, 92.7% of all assays completed were reported within 5 days of receiving the sample **[Appendix 3]** with the remaining being reported within 10 days.

These figures include the routine antibody testing and provide AQP4 titrations on request for individual patients with difficult to manage disease. The team have currently completed serial AQP4 titrations on over 100 individual patients either known or on remote advice to the NMO service **[Appendix 4]**. Although titrations are labour intensive 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.

Clinical Services Activity:

In the April 2013 to August 2014 the service received 90 new patients 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 have increased our clinics to weekly.

The clinical service activity for 2013-14 was 15% over annual plan on new patients seen, 72% over annual plan on follow up patients seen, 20% under annual plan for day case admissions and inpatient events were 48% under annual plan.

The clinical service activity for 2014-2015 has been set at an expected forecast for the year and this equates to 11.5% over annual plan on new patients to be seen, 98% over annual plan on follow up patients to be seen, 100% on target for day case admissions and under for inpatient events.

Remote advice for patients and clinicians is incredibly important, especially for those unable to attend clinic due to disability or current illness. An audit of remote advice provided by the NMO Nurse in one month is summarised in Table 1 below. The reasons for the calls

are indicated along the top row, with the number of calls, time taken (in minutes), and any follow-up undertaken by the nurse below.

	Symptom management	Medication Advice	Clinical Event	Follow-up from clinic	Clinical Advice	Admin/ Lab	Total
Calls	4	3	5	7	1	2	24
Time	60	45	75	120	30	30	360
Follow-up	3	2	5	6	0	0	16
Time	60	60	105	120	0	0	345

Table 1:

The NMO email advice activity distribution from April 2013 to date can be seen on the map labelled **[Appendix 5]**. 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.

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.

Samples received from April 2013 to date, with the additional AQP4 titrations factored in, 92.7% of all assays completed were reported within 5 days of receiving the sample with the remaining being reported within 10 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.

The service saw 90 new referrals between April 2013 to date¹¹ and many of these patients will have had their diagnoses clarified or changed. It is now 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.

Of the 90 new referrals seen in the NMO service, a snapshot of the time to diagnosis of the new patients has been calculated and can be seen in **[Appendix 6]**.

Relapse rates

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

- Reaching a correct diagnosis;
- 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 2013, we have had 43 relapses in 172 patients (AQP4 Ab positive and negative). This equates to an annualised patient relapse rate of 0.16. [pre service rate was 0.87].

Mortality rate

Deaths since April 2013 have amounted to 3 patients, the cause of death were listed as:

1. Pneumonia (this patient was already bedbound); this patient also had Myasthenia Gravis and was 70years old.
2. GI Bleeding and shock this patient was 65 years old
3. Acute severe NMO attack of the brain stem this patient was 48 years old but refused treatment as she thought the disease was caused by witchcraft.

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 7]**.

April 2013 – March 2014 – data from 70 questionnaires

April 2014 – August 2014 – data from 23 questionnaires

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.

Please see **[Appendix 7a]** for further outcomes from the questionnaires.

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 outpatient clinic a remote advice service is offered to their local clinician regarding diagnosis and management.

Please see **[Appendix 8]** for a breakdown of patient Geographic's for patients seen by the NMO Service.

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.

To ensure that all relevant correspondence and imaging from the referring centre has been transferred to the NMO service, a figure 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 weeks of their referral being received by the service. Some of the patients however have chosen to be seen at a later date.

Joint/Outreach Clinics

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. We also have two Southampton clinics scheduled for next year.

Service discharge

After NMO clinic review and work-up, 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

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. **A meeting was held last year on 19th December 2013 and one is scheduled with the NMO team on 30th October 2014 in line with 2013- 2014 CQUIN guidance.** **[Appendix 9]**

3. Financial Update

To be presented by the ORH Financial team lead by Rachael Raven, NTSS – Assistant Business Partner, Oxford.

4. Service Developments current and future

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 initial information booklets developed have now been expanded to include two new booklets on fatigue and staying active.

The booklets were written in response to further information needs highlighted at the 2013 NMO Patient Information Day. Patient’s own experiences and thoughts have been included with kind permission.

- Living with NMO – Independence in daily life,
- Living with NMO – Movement, mobility and travel,
- Living with NMO – Work and money,
- Living with NMO – From Fatigue to Energy,
- Living with NMO – Staying Active with NMO.

Feedback:

RS Patient – USA “I wanted to thank you for your website with all the information on NMO Devic’s Disease, 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 there”.

Expertise in NMO is developed by seeing as many patients in our catchment area as possible. It is imperative 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.

Increase in clinical staffing

We are currently arranging to increase the time for occupational therapy (OT) and physiotherapy (Physio) to allow the OT and Physio time to attend all clinics and allow them to attend three therapist outreach clinics per year.

We aim to appoint a new Healthcare Professional in combination with our CMS service to help keep updated our website, patient information literature, and performance outcome questionnaires in the clinics. This person will lead on analysis of patient services and implement improvement projects where needed.

These developments will be funded from the increased activity.

Research Developments

Following the successful demonstration of the high level of sensitivity and specificity in our routine diagnostic cell based assay for AQP4, run by Dr Mark Woodhall and Dr Patrick Waters, when compared with indirect immunohistochemistry, ELISA and immunohistochemistry (Waters et al 2012), we have now led a European-wide study to compare diagnostic assays in 17 dedicated European centres (Waters et al. in preparation). This study demonstrates again that the cell based assays are the most sensitive and specific, but the results from centres using flow cytometry are not consistent. These methodologies need more work. Individual groups have improved indirect immunohistochemistry techniques. It also showed that commercial slides from Euroimmun AG, were 100% specific when done in-house, and almost as sensitive as live cell based assays that are carried out at research institutes only.

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. A junior doctor is currently collating his analyses of our fatigue scores ready for publication.

Through our tissue- and data-bank consent, we have collected a huge body of information on our NMO patients. We have recently queried our database to analyse relapses, their rates and severity, with relation to treatment and other clinical and demographic information. This has added to existing evidence that immunosuppression reduces relapse rates, but also provided (for the first time) evidence that being on established immunosuppression likely reduces the disabling impact of an individual relapse (presented at ACTRIMS/ECTRIMS 2014).

AQP4Ab negative NMO remains poorly defined and consequently difficult to treat. A member of our team has begun a multi-modal research project looking into better defining AQP4 negative disease, looking for clinical and investigative differences 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.

International NMO Drug Trials

The team are engaged in two NMO drug trials but we have declined placebo designed trials.

Excitingly, this September (2014) we recruited our first NMO patient into the double-blind, placebo add-on, randomised control trial of eculizumab, a complement-inhibitor with promising preliminary data in NMO. Recruitment for this and another NMO trial (testing an anti-IL-6 agent) are on-going.

Meetings/Conferences

NMO Patient information day, May 2014.

To follow on from last year's patient information day in Birmingham, the Oxford and Liverpool NMO services jointly organised two day of talks which changed the dynamics of the meeting and interactive sessions for patients, friend and families of those affected by NMO. The feedback from the meeting was excellent. Although the majority of attendees

were known to the 2 services, a few patients and families who were unknown also came along, after seeing advertising on the MS society, and other websites. This led to new referrals to the NMO service at the John Radcliffe Hospital.

Please see **[Appendix 10]** for the programme of day two of this meeting.

People attending were encouraged to network, which led to patients setting up support groups on social sites, such as Face book as well as a section on the NMO UK website for web forums and local support groups.

European NMO Meeting, Gatwick, 19th – 20th June 2014.

The European NMO Meeting 2014 took place in London (Crown Hotel, Croydon) on the 19th & 20th June 2014. The meeting was organised by Drs Jackie Palace (UK), Romain Marignier (F), M Isabel Leite (UK) and Prof Angela Vincent (UK), with the administrative support of Annaliza Rye (NMO coordinator in Oxford). It was partially supported by Pharma.

The meeting was attended by over 65 clinicians and or researchers from 15 European countries, all with specialist interest and experience on NMO.

There were two non-European invited speakers - Dr Brian Weinshenker (USA) and Dr Kazuo Fujihara (JP) – who are internationally recognised as great experts on NMO. The meeting focused on a range of topics with clinical relevance and they included diagnosis of NMO, syndromes that mimic NMO, genetic aspects of the disease, paediatric NMO, imaging aspects of the disease, clinical outcomes (motor and visual) and treatments, including clinical trials. The meeting was very interactive and there was opportunity for all participants to exchange ideas, experiences and to plan collaborative studies on NMO across Europe and internationally.

Please see **[Appendix 11]** for the programme of this two day meeting.

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. See **[Appendix 12]** for a full list of publications, presentations and posters produced by the team.

5. Appendices

Appendix 1a.	Copy of NMO Monthly stats Mar 13 to Apr 14
Appendix 1b.	Copy of NMO Monthly stats Mar 14 to Aug 14
Appendix 2.	Monthly activity summary for assay service 2013-2014
Appendix 3.	Turnaround summary for assay service 2013-2014
Appendix 4.	Activity summary for Titres done by assay service 2013-2014.
Appendix 5.	Map detailing email advice within the UK since April 2013 to Aug 2014
Appendix 6.	Snapshot of time to diagnosis of patients seen from April 2013 to Aug 2014
Appendix 7.	NMO Patient Survey Final version
Appendix 7a.	Patient feedback comparison from 2013 to 2014 and 2014 to Aug 2014.
Appendix 8.	Map detailing NMO Oxford Patient Demographics
Appendix 9.	Guidance on the implementation of the highly specialised services 2013/14 CQUIN
Appendix 10.	2014 NMO Patient day agenda
Appendix 11.	2014 European NMO Meeting, Gatwick, Agenda
Appendix 12.	Publications and presentations of NMO service