National Commissioning Group
For Highly Specialised Services

Diagnostic and Advisory Service for Neuromyelitis Optica (NMO)

Oxford University Hospitals NHS Trust

Annual Report September 2016

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Outcomes that can't be quantified……

May 2016

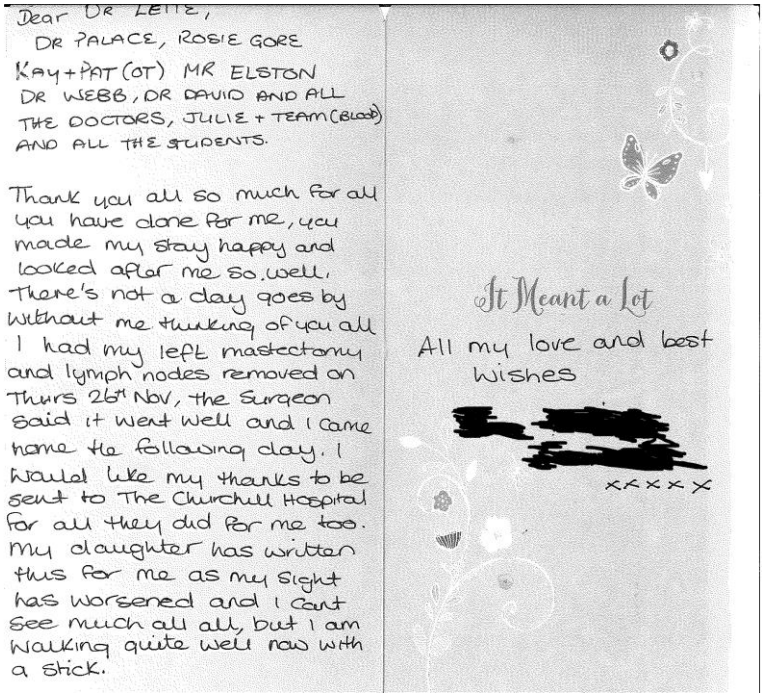
To Annaliza and the N.M.O Team,

Please accept our grateful thanks for all the hard work that went into the N.M.O Conference. We feel so much better being well informed and thankful for all the research being done. Meeting other patients and their families was inspiring and moving.

We are your biggest fans!

With best regards

NMO Patient Day 2016 – NMO Team photo and Thank you card



Dear Dr Leite,

Dr Palace, Rosie Gore

Kay + Pat (OT) Mr Elston

Dr Webb, Dr David and all the Doctors, Julie + Team (Blood) and all the students.

Thank you all so much for all you have done for me, you made my stay happy and looked after me so well. There's not a day goes by without me thinking of you all. I had my left mastectomy and lymph nodes removed on Thurs 26th Nov, the Surgeon said it went well and I came home the following day. I would like my thanks to be sent to The Churchill Hospital for all they did for me too. My daughter has written this for me as my sight has worsened and I can't see much all all, but I am walking quite well now with a stick.

It Meant a Lot

All my love and best wishes

[redacted]

xxxxx

Inpatient referred to the NMO Team for diagnosis

Positive feedback from patients seen in 2016

1. All staff were notably efficient, courteous and highly professional. Excellent impression that Dr Palace and her team were keen to provide a total service, requiring utmost detail + immediate retests of previous spurious results.
2. *Felt very invested in! * Everyone was very approachable / Friendly! *Questions answered well - Thank you!
3. I found my first visit to the NMO Clinic positive and helpful. Very efficient and caring staff. Thanks to all.

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
Miss Srilakshmi Sharma	Consultant Medical Ophthalmologist
Dr George Tackley	NMO Clinical Fellow
Rosie Gore	NMO Specialist Nurse
Sandra Reeve	NMO Specialist Nurse
Annaliza Rye	NMO Service Coordinator
James Moore	NMO Admin Assistant
Kay Day	NMO Occupational Therapist
Nina Eagle	NMO Physiotherapist
Julia Goodgame	Clinical Service Manager

Laboratory Team

Dr Patrick Waters	Senior Postdoctoral Scientist/Co-director of the Laboratory
Dr Sarosh Irani	Associate Professor/Co-director of the Laboratory
Dr Mark Woodhall	Postdoctoral Scientist

The service performs around 450 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.
- Scoring in patient feedback questionnaires.
- Time from referral to first clinic appointment.

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 2015 to 1st September 2016 the service received 113 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.

For financial year 01/04/2015 to 31/03/2016, the service has increased the number of outpatient clinic slots per year from 276 to 353 per year, to cope with increased demand. This means we now have out-patient clinics every week, which often extend into the afternoon.

The clinical service activity for 2015-16 was 40% over annual plan for new patients seen, 95% over annual plan for follow up patients seen, 23% under annual plan for day case admissions and inpatient events were 55% 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 in-patient beds limit admissions.

The clinical service activity for 2015-2016 is 64% over annual plan on new patients seen, 102% over annual plan on follow up appointments and under target for day case admissions and inpatient events to date.

Nurse advice line audit

Remote advice	Calls 2016 (4 months) 01.04.16 - 31.07.16	Calls 2015/16 (12 months) 01.04.15 – 31.03.2016	Calls 2015 (6 months) 01.02.15 – 31.07.15
Patient/carers	182 (546)	341	100 (200 in 12 months)
Professionals	20 (60)	29	Not recorded
Total	202 (606)	370	

There was 70.5% increase in annual patient calls from 2015 to 2016. The calls measured for 4 months in 2016 represent a further increase of 60%. So far there has been 106% increase in calls to professionals from 2015/16 figures.

Patient call categories

	Calls 2016 (4 months) 01.04.16 - 31.07.16	Calls 2015/16 (12 months) 01.04.15 – 31.03.2016	Calls 2015 (6 months) 01.02.15 – 31.07.15
Level 1	1 (3 in 12 months)	19	7 (14 in 12 months)
Level 2	71 (213)	59	37 (74)
Level 3	92 (276)	179	47 (94)
Level 4	18 (54)	84	9 (18)
Total	182 (546)	341	100 (200)

Call grading:
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.

There was 35% increase in calls at Level 1 from 2015 to 2015/16 and 84% reduction so far this year. Level 2 calls dropped by 20% in 2015/16 but have increased by 261% this year. This increase is due to the introduction of routine pre-clinic telephone calls. There was 90% increase in

Level 3 calls in 2015/16 and a further increase of 54% so far this year. Level 4 calls increased by 366% in 2015/16 but have reduced by 35% so far this year.

Being able to contact the NMO nurses is greatly valued by our patients, who receive prompt response and follow-up.

Remote support (email)
Apr 2015 – Mar 2016

Existing Patients	**183** emails
Potential Patients	**44** emails which include external countries e.g. Poland, Croatia and Switzerland.
Professional Queries	**135** emails
Total Emails	**362**

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

For the period April 2015 to March 2016 the Laboratory team for the Diagnostic and Advisory Service for NMO (Oxford John Radcliffe Hospital) tested a total of 6515 samples (this is the total of all samples received from eligible and non-eligible countries worldwide) of which 6254 samples were received from the United Kingdom (6126 samples) and other NHS eligible overseas EEA member countries (128 samples) under the testing remit of the service. Of these 6254 samples, 5249 were new patient serum/CSF samples from which 103 (2.0%) were reported positive for AQP4 antibodies ***[Appendix 3]***.

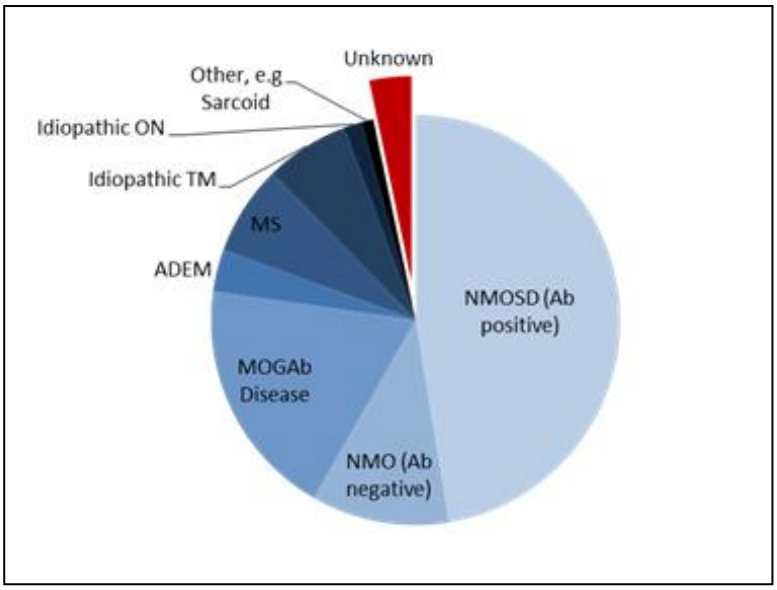
Turnaround times
We aim to report all samples within 5 days and even though the number of samples tested have increased by 0.5% this year our turnaround times have reduced. During April 2015 to March 2016, 97.8% of all assays were reported within 5 days with the remaining (117/5249) being reported within 9 days ***[Appendix 3]***. This year the turnaround time has improved with 100% of the assays reported within 3 days ***[Appendix 3]*** and 91% reported within 2 days from April 2016 to August 2016.

End-point titres to follow serum antibody levels
As well as providing the routine AQP4 antibody test we also provide AQP4 titrations on request for individual patients. Dr. Woodhall has completed serial AQP4 titrations on 264 patients who are either seen within the service or are receiving remote advice from the 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 regimens for example. An important use of the AQP4 titres was highlighted earlier this year when a patient accidentally stopped taking their mediation. This resulted in an increase in their AQP4 titres that alerted the Oxford medical team to investigate.

Diagnosis
% definitive diagnosis made
Of our follow-up NMO patients and of the recently seen mimics, only 3.3% remain with an uncertain diagnosis.

Diagnosis	*No (%)*
NMOSD (Ab positive)	*100 (47.4)*
NMO (Ab negative)	*23 (10.9)*
MOGAb Disease	*40 (19)*
ADEM	*7 (3.3)*
MS	*15 (7.1)*
Idiopathic TM	*14 (6.6)*
Idiopathic ON	*3 (1.4)*
Other, e.g. Sarcoid	*2 (0.9)*
Unknown	*7 (3.3)*



Relapse rates

Relapse rates pre & post Rx.

Note: Patients are more likely to be kept under our care if their disease is active.

Table 1. *Pre- and post- NMO service relapse rates for new patients.*

	No of patients	*47*
Post NMO Service	*Follow-up, yrs.*	*0.66*
	No Relapses	*3*
	Average relapse n (per pt.)	*0.06383*
	Annualized Relapse Rate	*0.09723*
Pre NMO Service	*Follow-up, yrs.*	*5.753402*
	No Relapses	*89*
	Average relapse n (per pt.)	*1.893617*
	Annualized Relapse Rate	*0.32913*

Table 2*. Number of relapses over last financial year.*

For 01/04/2015 - 31/03/2016	
Total Active Patients:	*216*
Total Relapses:	*29*
n pts who relapsed:	*25*
Overall ARR:	*0.13*
Overall % who relapsed:	***11.57***
n AQP4:	*85*
AQP4 Relapses:	*13*
n AQP4 pts who relapsed:	*12*
AQP4 ARR:	*0.15*
AQP4 % who relapsed:	***14.12***

n MOG:	*36*
MOG Relapses:	*6*
n MOG pts who relapsed:	*4*
MOG ARR:	*0.17*
MOG % who relapsed:	***11.11***

Mortality rate

May 2015: TE – 66 y/o, AQP4Ab positive NMO (on rituximab), cause of death: Respiratory infection, PMH asthma. Disease onset with ON in 2005, followed by 7 attacks of TM up to 2009, resulting in severe disability, one further attack of ON in 2013.

May 2015: PG – 64 y/o, AQP4Ab positive NMO (on azathioprine, prednisolone and for a period eculizumab), cause of death: respiratory, PMH COPD. Disease onset with ON in 2010, another ON in 2013 resulted in bilateral blindness, referred to service in 2014 after TM resulted in paraplegia.

March 2016: MJ – 66 y/o, AQP4 positive NMO (on Azathioprine), cause of death: rapid onset malignant brain tumour, PMH obesity, type 2 diabetes. Disease onset in 1994, 3 attacks of ON and 2 TM by 2010 resulted in severe disability and compounded by pain.

July 2016: MM – 55 y/o, AQP4Ab positive NMO (on cyclosporine and prednisolone), cause of death: sepsis. Disease onset in 2003, 2 attacks of ON and 4 attacks of TM by 2010 resulted in severe disability, one further attack of TM in 2012.

Births:
Mother: AMC – 41 y/o AQP4Ab positive gave birth to 2nd child Nov 2015 with no complications.
Mother JR – 21 y/o Ab negative TM aged 10 y/o gave birth to first child with no complications.

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 can be seen 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 2015 – March 2016 – Please see *[Appendix 6]*
April 2016 – Sept 2016 – Please see *[Appendix 7]*

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 8]*** for a breakdown of patient Geographic's for patients seen by the NMO Service in clinics, our Telemed patients and our email advice given for the financial year 2015 - 2016.

Please see ***[Appendix 9]*** for a breakdown of patient Geographic's for patients seen by the NMO Service in clinics, our Telemed patients and our email advice given from April 2016 to August 2016.
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 2015 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 are offered, where patients are untreated and immunosuppression is indicated, and the team also liaise with referring clinician in the interim.

Joint/Outreach Clinics
Current:
- Joint clinic with Dr Cheryl Hemmingway at Great Ormond Street Hospital (GOSH) twice per year
- Joint clinic with Dr Peter Brex at Kings College Hospital four times per year
- Joint clinic with Dr Christopher Halfpenny at Southampton General Hospital every year
- Joint clinic with Dr Arani Nitkunan at St Georges Hospital twice per year
- Joint clinic with Dr Leonora Fisniku at the Princess Royal Hospital, Brighton twice per year

Planned:
- Gloucester
- Plymouth

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.

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 24th June 2016 and the next one is scheduled for 23rd June 2017 in line with 2013- 2014 CQUIN guidance. Minutes from the meeting held on the 24th June 2016 *[Appendix 10]* and copy of the National CQUIN guidance *[Appendix 11]*.**

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 Nurse:
The team recruited a new nurse, Sandra Reeve, in January 2016.
This new nurse post, in conjunction with the current NMO nurse, will increase opportunities for outreach clinics, teaching sessions and service development.
The new nurse will be actively involved in all aspects of clinical care of NMO patients and support Rosie to keep our website updated, update and produce new patient information literature, and audit clinical outcome questionnaires.

NMO Occupational therapist has increased hours to 10 hours per week, this helps her to attend outreach clinics, CQUIN and patient day meetings and contribute to service developments.

NMO Admin Assistant:
The team recruited a new admin assistant, James Moore, in November 2015 to replace the previous assistant to aid in the ever growing NMO Service.

These developments have been funded from the increased activity.

Review of Clinical Outcome Measures

Rosie Gore and Kerry Mutch met to discuss patient reported outcome measures. The aim being to have consistency across both services. Oxford currently use:

- Quality of Life – Euroqol EQ-5D
- Anxiety and Depression – Hospital Anxiety and Depression Scale (HADS)
- Pain – Brief Pain Inventory (BPI)
- Fatigue – Modified Fatigue Impact Scale (MFIS)

Completed at initial appointment and at least once/year thereafter
Plan to include bladder and bowel control scales. Other questionnaires have been explored including an alternative quality of life (SF-36), which is more thorough but requires more analysis to calculate result. Suitable questionnaires for measuring the impact of visual problems and sexual problems are being sought.

- Quality of life audit (QoL/pain/mood/fatigue) RG
  Quality of life outcomes are being collated for individual patients to show how their self-reported scores have changed over time, since they have been receiving support from the service. Pain and mood scores are being assessed before and after seeing the pain specialist. Quality of life scales are now being measured in older ages of paediatric patients.

- Diet SR
  Project: Monitor the weight of patients on steroid medications (Prednisolone).
  Aim: To provide nutritional and exercise support and information for patients on long term steroid medication (Prednisolone).
  Rationale: Patients diagnosed with NMO are treated with steroids which is a long term treatment to reduce the risk of potential NMO relapses. Some of the associated side effect of Prednisolone are weight gain, osteoporosis, high blood sugar, mood and behaviour changes.
  Monitoring and helping patients to minimise some of these side effects can also contribute to improving their sense of well-being and general health.
  Supporting people to self -manage their weight and exercise may also contribute to reducing other associated symptoms of NMO such as Pain, Fatigue, loss of movement and muscle tone.

- Alert card pilot trial SR
  An alert system is being piloted for 11 patients who have AQP4 antibodies. Patients often contact the NMO patient helpline with concerns about relapse symptoms. As relapses are difficult to determine over the phone and some patients are unable to travel to oxford for an assessment. The aim is for patients to present the Alert card to their on call GP or the A&E department

should they develop a possible relapse symptoms. It will enable the urgent assessment and referral to the local neurology service for urgent immunosuppression treatment if required. The patients will also have a paper summary sheet to carry with their latest details to aid the local neurologist.

Physiotherapy Outcomes:

Evaluation of the Tinetti Balance score in patients that attend the NMO clinic.

Details and Objectives of the Audit:
This Project is a service evaluation which will explore Tinetti Balance scores in Neuromyelitis Optica Patient within the clinical setting. This standardised measure allows the therapist to look at a patients balance and gait and measure their risk of falls. This is important when referring to other therapists who can then improve function.

Objectives:
The evaluator wishes to consider the use of an outcome measure within the NMO group to identify if outcome measures improved after coming to clinic. This could include,

- Advice
- Medication
- Equipment
- Physiotherapy
- Natural recovery

The ultimate aim of this project is to encourage service development with this condition.

Criteria:
Adults who attend the NMO clinic over 18 years. Patients who were wheelchair based were excluded due to the nature of this test. This assessment would be performed as part of routine assessment by Physiotherapist during the NMO clinic.
17 patients were measured and the results were as follows.

Tinetti score
Balance (16), Gait (12) Total (28)
Between 04/2015 and 03/2016

1st assessment

	Tinetti Balance Audit	Average
Age Range	27 -79	53
Total Tinetti Score	15-28	23
Total 25 ft timed walk	4-16	8.6

Falls Risk		
<18	3	High
19-23	5	Med
>24	9	Low

2nd assessment (following physio/ drug management/ natural recovery)

	Tinetti Balance Audit	Average
Age Range	27 -79	53
Total Tinetti Score	19-28	24.6
Total 25 ft timed walk	4-14	7.69

Falls Risk		
<18	0	High
19-23	7	Med
>24	10	Low

	Pre intervention	Post intervention	%

					improvement
Total Tinetti Score	15-28	Av. 23 82%	19-28	Av. 24.6 87.8%	5.8%

This is only a small study but it demonstrates that even with a small number of patients a change can be noted when they have come to clinic and received the advice, therapy and medication needed.
To make this more specific to physiotherapy, triage would be as a first measure then hands on Physiotherapy exercise, followed by re-measure and monitoring.

The NMO physiotherapist is considering how best to record physio outcomes for the range of NMO patients we see and how to assess the effectiveness of interventions when patients are seen infrequently, compared to a regular community physiotherapy programme.

Future plans include:

- Auditing results under diagnosis category; those with poor vision may score highly due to poor vision and not poor balance comparing those with NMO only and/ or NMOSD/ unclear diagnosis / those with no residual deficit.
- Assess and reassess patients identified with NMO/ NMOSD/ MOG with specific guided exercises given to the patient and telephone call follow up before the next clinic visit.

Patient information

Patient Information Booklets KD, RG, AR

- A series of x4 medication information leaflets on Methotrexate, Mycophenolate, Prednisolone, Azathioprine produced by Kerry Mutch , NMO nurse specialist Walton Centre
- Therapy and blood Monitoring Record Booklet produced by Kerry Mutch
- Feb 2016 small increase in Occupational Therapy hours enabled Kay Day NMO OT, Oxford to begin reviewing/updating existing NMO booklets, decision made to incorporate patient experiences into revised versions as per From Fatigue To Energy Booklet. NMO patient study day utilised for patient experiences and continues via weekly clinic currently.
- MOG information booklet currently in draft, almost ready for printers
- The NMO new patient booklet has been updated to reflect the new staff members and new information regarding the NMO Service – see [Appendix 12].
- The Advice line pamphlet has been redesigned, trust approved and is now available with the option of interpretation, Easy Read, another language, Large print, Braille or audio version – see ***[Appendix 13].***

Plans:

1. To complete update of existing booklets with patient experiences.
2. To produce new booklets on mood & pain and pregnancy
3. To produce a selection of Physiotherapy Exercise information sheets

Web based information

a) **NMO Website** www.nmouk.nhs.uk
Approximately 800-1000 hits per month.

b) **Charity NMO-UK research foundation**
Website: www.nmo-ukresearchfoundation.org
The NMO charity NMO-UK is a non-profit charitable organisation which aims to raise awareness of NMO, support people living with the condition, provide financial support and legal advice. This was set up from the annual patient days, and the NMO services work closely with the charity to raise awareness of the condition, run fundraising events, to set the program for the patient days and to distribute NMO patient publications.

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. The papers have now been published and further advanced world-wide understanding of the clinical features of MOG disease (Sato et al 2014; Kitley et al 2014). A world-wide study led by Patrick Waters and Markus Reindl (Innsbruck, Austria) to compare MOG assays is planned for 2017.

We also followed up the initial publication on MOG antibodies to further elucidate the clinical features of these AQP4 seronegative NMO patients (Kim et al 2015; Symmonds et al 2015; Piccolo et al 2016; Woodhall et al 2015), pediatric patients (Hacohen et al 2014, 2015) and the biology of the disease (Horellou et al 2015; Saadoun et al 2015; Kaneko et al 2015) in several publications. 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 (Saadoun et al 2015).

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. Dr. Markus Reindl (Innsbruck, Austria) developed an AQP1 cell based assay in collaboration with Patrick Waters and demonstrated that NMO patients do not have AQP1 antibodies (Schanda et al 2015). 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 (Nour et al. 2016). 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 (Saadoun et al 2015).

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.

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NMO Drug Trials

Commercial drug trials:

We currently have on active patient (the only one thus far in the UK) participating in the Chugai trial: 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.

We remain open to recruitment but have active patients for the Alexion trial: a randomized, double-blind, placebo-controlled, multi-centre trial to evaluate the safety and efficacy of eculizumab in patients with relapsing NMO.

Coming soon:

Abide Project: Assessment of the safety and efficacy of a new therapy administered orally in patients with pain associated with neuromyelitis optica spectrum disorders (NMOSD)

Full list of research project at Oxford – see ***[Appendix 14]***

Hand-out given to patients regarding research at Oxford – see ***[Appendix 15]***

Meetings/Conferences

NMO Patient Information Day, 20th May 2016 & 21st May 2016

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 16]*** for the programme of day two of this 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. For publications please see ***[Appendix 17]***

NMO Team Presentations for 2015/2016:

Dr Jackie Palace:

1. Norwegian Muscular Interest Group, Oslo 11 March 2015. "Congenital Myasthenic Syndromes"
2. NMO Patient day - 9th May 2015
3. Manchester Neurology Grand Round 12th June 2015 'The role of antibodies in MS and related disorders'
4. Royal Free 31 July 2015 "NMO Spectrum Disorders"
5. Magnims 2nd September 2015 "Predicting Treatment Response in Using Clinical Measures"
6. ABN autumn meeting invited lecture on NMO 10th September 2015 "NMO Spectrum Disorder"
7. Keele University Neuroinflammatory meeting invited lecture 11 September 2015 "NMO Spectrum Disorders"
8. ECTRIMS X2 Talks –Teaching Session on NMO and Satellite symposium on the treatment of NMO - 7th Oct 2015 to 10th Oct 2015
9. Milan advanced course on MRI in MS 17th March 2016. Anti-MOG and anti-aquaporin 4 antibodies in children: pathogenesis, clinical manifestations, imaging features"

Dr Isabel Leite:

1. NMO Patient day - 9th May 2015
2. Lavia Neuroimmunology meeting – September 2015
3. ECTRIMS – one platform presentation - October 2015
4. Guthy-Jackson Charitable Foundation - Neuromyelitis optica - Los Angeles, USA - February 2015
5. Teaching session for Neurology specialist registrars London – March 2016

Dr Patrick Waters

1. NMO Patient day - 9th May 2015.
2. 2016 March, Oxford Immunology Group meeting, JR, Oxford.
3. 2016 March, Mastering Immunity, St. Hugh's College, Oxford.
4. 2016 March, Oxford Neurosciences meeting, Mathematical Institute, Oxford.
5. 2016 April, B-cell group meeting at CCVTM.
6. 2015 September Dresden, Germany: Symposium on autoantibodies: gave a talk on antibody assays.
7. 2016 February Los Angeles, USA: Guthy-Jackson Charitable Foundation - Neuromyelitis optica

Dr Mark Woodhall

1. Video presentation NMO Patient day - 9th May 2015- Journey from your blood to your antibody result

Dr George Tackley

1. NMO Patient day - 9th May 2015

Rosie Gore:

1. Information about NMO was presented at a regional MS nurse meeting at St George's Hospital, London on 17th June 2015.
2. 02.03.2016 Guthy Jackson Foundation Patient Day – Neuropathic Pain in NMO (with Dr Tackley).
3. 12.05.2016 John Radcliffe Hospital Neurology Ward training – Managing complex neurological conditions.
4. 21.05.2016 NMO Patient Day – workshop on managing anxiety and complementary therapies.
5. 24.05.2016 John Radcliffe Hospital Neurology Ward training – Spinal day 'NMO and TM'.
6. 09.07.2016 – 10.07.2016 Transverse Myelitis Society family weekend – Discussion/workshops about NMO & TM with parents and children affected by NMO/TM

3. Appendices

Appendix 1a.	Copy of NMO Monthly stats Mar 15 to Apr 16
Appendix 1b.	Copy of NMO Monthly stats Mar 16 to Aug 16
Appendix 2a.	Monthly activity summary for assay service Apr 15 to Mar 16.
Appendix 2b.	Monthly activity summary for assay service Apr 16 to Aug 16.
Appendix 3a.	Turnaround summary for assay service Apr 15 to Mar 16.
Appendix 3b.	Turnaround summary for assay service Apr 16 to Aug 16.
Appendix 4a.	Activity summary for AQP4 titrations completed by assay service Apr 15 to Mar 16.
Appendix 4b.	Activity summary for AQP4 titrations completed by assay service Apr 16 to Aug 16.
Appendix 5.	NMO Patient Survey Form
Appendix 6.	Patient feedback from April 2015 to Mar 2016.
Appendix 7.	Patient feedback from April 2016 to August 2016.
Appendix 8.	NMO Oxford Patient Demographics breakdown including clinics, Telemed and email advice April 2015 to Mar 2016.
Appendix 9.	NMO Oxford Patient Demographics breakdown including clinics, Telemed and email advice April 2016 to Aug 2016.
Appendix 10.	Minutes from CQUIN meeting held on 24th June 2016.
Appendix 11.	Guidance on the implementation of the highly specialised services 2013/14 CQUIN
Appendix 12	NMO New patient introduction booklet
Appendix 13	Advice line pamphlet
Appendix 14.	Full list of research projects being done in Oxford.
Appendix 15.	Hand-out given to patients regarding research being done in Oxford.
Appendix 16.	NMO Patient day agenda 21st May 2016
Appendix 18.	Publications of NMO service April 2015 to Aug 2016