

D04/S(HSS)/b

**2013/14 NHS STANDARD CONTRACT
FOR NEUROMYELITIS OPTICA SERVICE (ADULTS AND ADOLESCENTS)**

PARTICULARS, SCHEDULE 2 – THE SERVICES,- SERVICE SPECIFICATIONS

Service Specification No.	D04/S(HSS)/b
Service	Neuromyelitis Optica service (adults and adolescents)
Commissioner Lead	
Provider Lead	
Period	12 months
Date of Review	

1. Population Needs

1.1 National/local context and evidence base

Description of the disease/condition/therapy

Neuromyelitis optica (NMO) is a rare inflammatory demyelinating disorder of the central nervous system with high mortality and morbidity (2-8) when not diagnosed early and treated appropriately. It typically presents as severe optic neuritis and longitudinally extensive myelitis(2) often followed by further severe attacks which usually result in permanent disability (visual loss, limb weakness, respiratory muscle weakness). It is important to note that 23 % of patients (10/41) who were enrolled in a UK wide prospective observational study have died at a median of 3 years from inclusion, indicating the high mortality rate associated with this condition if not diagnosed and treated appropriately.

NMO has recently been associated with the presence of aquaporin-4 antibodies in about 70% of cases (9-12). The discovery that it is an antibody mediated disorder, which responds to immunosuppressive treatments, the difficulty in distinguishing it from multiple sclerosis and acute disseminated encephalomyelitis, and the recognition that the clinical presentation is often atypical means it is frequently misdiagnosed and treated late or incorrectly.

Criteria for diagnosis

There are criteria for diagnosis (Wingerchuk, 1999 and 2006) and serum marker, NMO IgG, assists in the diagnosis(2, 13). The team at Oxford University Hospitals NHS Trust has developed a direct assay for Aquaporin-4 antibodies (AQP-4 Ab), which appears an even more sensitive marker (10, 11). The discovery that NMO is an antibody-mediated disease means it needs treatment with immunosuppressive drugs and sets this disease apart from Multiple Sclerosis, it should be noted that the first line treatment for multiple sclerosis (MS) (Interferon beta) appears to be ineffective or adversely influence disease course in NMO.

Diagnostic criteria for neuromyelitis optica (Wingerchuk et al., 2006):

- Optic neuritis
- Acute myelitis

And at least two of three supportive criteria:

- contiguous spinal cord MRI lesion extending over three vertebral segments
- brain magnetic resonance imaging (MRI) not meeting diagnostic criteria for multiple sclerosis
- NMO-IgG (AQP4-Ab) seropositive status.

However bilateral or relapsing optic neuritis and longitudinally extensive transverse myelitis (LETM) with AQP4-Ab or recurrent LETM are recognised as 'NMO spectrum disorders' often developing typical NMO over time. Additionally, reports identify encephalitic, brainstem and hypothalamic presentations associated with AQP4 antibodies, which are atypical and more difficult to diagnose; these too are appropriate referrals(14-17).

Evidence base

NMO is a rare inflammatory demyelinating disorder of the central nervous system with high mortality and morbidity(2-8) when not diagnosed in time and treated appropriately. It is diagnosed and treated by neurology consultants who, by virtue of its rarity, are often unfamiliar with the disease. As a result it is often misdiagnosed, most frequently as multiple sclerosis, and frequently inadequately or inappropriately treated. It should be noted that in addition to the problem of appropriate immunosuppressive therapy being withheld it appears that MS disease modifying treatments when used in NMO cases may make the disease worse. As NMO is so rare and has only recently been discovered to be antibody mediated there is no good evidence of the clinical effectiveness of a specialist service. The Mayo Clinic is perhaps regarded as the main NMO centre in the world through its research interest, which led to the discovery of the NMO antibody, investigated the specificity and sensitivity of this diagnostic test and recommended that it should be treated differently to MS.

Just over 1% of patients enrolled into an early MS treatment study have subsequently been identified as NMO (18). As NMO is so much rarer than MS

(approx 0.5-1%) this figure suggests many patients do get misdiagnosed as MS and treated with expensive MS drugs. Reports are emerging of NMO patients worsening when MS disease-modifying therapies are used (19-21). Thus misdiagnoses of NMO patients as MS means many patients suffer preventable disability (and death).

The effectiveness of treatments in NMO is assessed from published series and worldwide and UK expert opinion. At five years from onset 50% of untreated patients require a wheelchair or have significant visual loss (registered blind) (20, 22). Aggressive treatment of relapses (steroids, plasma exchange) and prompt immunosuppression (Azathioprine(23), Mitoxantrone(24), Rituximab(25) have now become the standard of care (26). With treatment, reductions in relapse rate of >80% have been reported in case series and long term stabilisation can be achieved (23-25, 27). In the UK series the median annualised relapse rates before initiation of immunosuppressant treatment was 1.6 and post treatment was 0.19 at a median follow up of 2.7(0.04-5.9) years for a subgroup of 33 patients(8). response is as expected for an autoantibody mediated disease. In a recent prospective study of 41 patients with NMO with delayed diagnosis, analysed by the Liverpool group, 10 of the 41 patients enrolled from 2003 to 2009 died: a mortality of 25%. Longer-term follow up showed a 36% mortality (Leite ABN abstract). In those alive disability is often severe (8). It should be noted that the rarity of NMO, the only recent recognition of its antibody aetiology and ethics of withholding treatment has prevented placebo controlled studies for NMO to date.

Evidence of cost effectiveness

NMO leaves severe disability in the wake of its relapses. 50% patients require a wheelchair or are blind at five years from onset if not managed appropriately(2). Early immunosuppression under expert care reduces relapses, hospitalisations (often costly due to the severity of the disability) and sequelae (medical, social and economic).

There is no published evidence specifically addressing cost-effectiveness of treating NMO in terms of cost per quality of life . With the effective preventative immunotherapy that follows from a specialist service, savings in the expense of treating severe relapses requiring inpatient stay, ventilatory and intensive unit (ITU) care are to be expected. There will also be considerable future gains to the NHS, state and society from the prevention of permanent disability (para/quadruplegia and visual impairment). Though no data is available on NMO, extrapolating from European multiple sclerosis data relating to an Expanded Disability Status Score (EDSS) of >8 i.e. wheel chair dependent state, the annual cost to the health service is 51,500 Euros.(28) As stated in the previous section preventing conventional MS drugs from being given to NMO patients due to better diagnosis will in addition to leading to better treatment (and possibly preventing harm by using these drugs) and will save on the high cost of the MS disease modifying treatments (around £8,000 per patient per year).

The suboptimal management of undiagnosed NMO within the health service is not an effective use of resources. Improving diagnostic rates will not only use these

resources appropriately but will improve the quality of life of affected patients. Thus cost savings may exceed the cost of this UK service in addition to the gain in quality of life and reduced mortality.

2. Scope

2.1 Aims and objectives of service

The aim of the service will be to provide a specialist service for patients with Neuromyelitis Optica (NMO) and NMO spectrum disorders.. The NMO service will offer; a rapid access diagnostic service; patient and clinical advice; supervision of clinical management in collaboration with the local referrer and for severe and acute cases provide in-patient treatment.

This multi-disciplinary service will encompass all aspects of diagnosis and treatment recognising the complementary strengths and utilising the specialist clinical and laboratory skills available in conjunction with local services.

The diagnostic skills will include imaging, (the atypical and variable appearances will require expert neuroradiology input), NMO antibody testing at the Oxford unit, and histology (which will require expert neuropathology experience).

Treatment includes :

- advice on immunosuppressive therapy and its monitoring
- delivering aggressive therapies in severe cases where local centres lack experience
- providing paediatric input for children
- physiotherapy input to assess disability and advice on a local rehabilitation programme
- maintaining a phone help line.

Many neurologists do not have experience or the clinical facilities to supervise aggressive immunosuppression. However early diagnosis and appropriate treatment of NMO will prevent irreversible and severe disability. A UK specialist NMO service aims to reduce mis-diagnoses and inappropriate treatment.

The NMO service would thus produce national guidelines for UK neurologists for early referral of potential patients to maximise benefits. Additionally, as with all rare conditions, the added value for patient's lies in being seen by a team of specialists (not only doctors, but specialist nurses, physios etc) who understand their condition and can advise on prognosis and rehabilitation schedules.

Concentrating patients with a rare disorder through a specialist service improves the ability to recruit into clinical trials, which are needed to provide evidence for the most effective and cost-effective treatments.

2.2 Service description/care pathway

Outpatient evaluation

A detailed outpatient clinical evaluation will be undertaken by the multidisciplinary team led by clinicians (assisted by NMO nurses, physiotherapist, and where appropriate occupational therapist, psychologist, and speech and language therapist). The paediatric neurologist will be involved in the treatment of individuals under the age of 16. Clinical investigations that are usually required which include MRI (brain and spinal cord); cerebrospinal fluid examination, evoked potentials and antibody testing will be carried out as soon as possible (either as an outpatient or day case).

Oral immunotherapies will be recommended in most cases. These oral agents (azathioprine, methotrexate and mycophenolate) will continue to be prescribed by the local neurologists or GPs and the funding continue to be within the local Clinical Commissioning Group (CCG) remit. We will produce information sheets on the treatments and monitoring guidelines (many of which already exist for these drugs used for other conditions). Antibody testing will be undertaken in Oxford.

The first 2 courses of Rituximab, i.e. 1st month and 6th month (1 course=2 injections on day 1 and day 14) will be given and funded by NHS England commissioned centres. The central budget for Rituximab is held by The Walton Centre NHS Foundation Trust and that Oxford will cross charge Rituximab to the Walton centre based on use. The centres will assess benefit after the second course of treatment and if ongoing care is needed Rituximab may be given locally as part of a shared care arrangement. On-going drug funding will be the responsibility of the patient's CCG.

Where patient travel to the centre is an issue and there is local appropriate expertise Rituximab can be given locally as part of a shared care arrangement and re-charged to a national budget held in the NMO service.

Patients outside these guidelines will continue to be within the remit of the local CCGs and the service will advise remotely on local in-patient care.

Discharge and Follow Up

Patients will be discharged back to their local services when stable and when a management plan has been instituted for continuing care. The NMO service will produce protocols and guidelines to advise the patients and their local care team. Neurorehabilitation will be provided locally when required, although NHS England NMO multi-disciplinary team will give specific guidance.

Review Visits

Outpatient follow up visits will be arranged at intervals depending on need and may

vary from being within weeks to annually. Magnetic resonance imaging (MRI) scans and AQP-4 Ab testing may be needed to guide ongoing management.

Guidance for Local Services

There will be a clear, streamlined medical management strategies based on current best evidence/experience for each aspect of the illness at the outset of the service and these will be modified with experience, liaison with international colleagues and auditing of data collected on all patients seen within this service. These strategies will be followed by both centres and will form valuable input in developing national and international guidelines on management.

Community visits

When it is impossible for patients to travel to one of the two centres, either because they are severely affected and unstable or because they are too frail to attend, and where remote advice is inappropriate, the NMO nurse and/or clinicians will make community or hospital visits.

Patient feed back through meetings, satisfaction questionnaires, will be useful in planning and modifying services. Detailed information sheets on the disease and its management will be made available through the website.

The provider will work with the to ensure sufficient considerations are given to Communications. Governance issues will be addressed by the provider trusts.

The availability of the service will be communicated through several measures:

- the clinicians within the units will lecture at hospitals
- professional meetings around the country and highlight the availability of the service
- the clinicians will publicise the service at national and international meetings and conferences
- the website will be updated with links to professional websites.

The service will operate within the times needed to deliver the service.

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Paediatric patients will be followed up in the service. Local teams will manage stable patients. Rehabilitation will be done by the patient's local rehabilitation team and appropriate guidelines will be given to the local team.

2.3 Population covered

The service is for adults and children. The provider will monitor postcodes of referred patients. All patients irrespective of sexual orientation, race, religion, disability who are eligible for NHS will be eligible for the service.

The service will be available within this contract to NHS patients registered with a GP within England and Scotland. It will also cover patients from within the EU under Overseas Visitor regulations. Wales and N. Ireland patients are subject to arrangements through their own commissioners.

2.4 Any acceptance and exclusion criteria

Referrals

Healthcare providers across the UK will be informed about the service as outlined below. Referrals will be triaged by the clinicians and appointments offered by one of the centres based on location, wait times and patient convenience. All clinical information will be obtained if possible prior to attendance, from the GP and local physicians/neurologist:

- referrals will be from any NHS consultant or GPs
- self referrals will not be accepted
- patients should have MRIs done in the local hospital. Patients are referred informally through the British Neurological Surveillance Unit, which circulates monthly reminders to all ABN (Association of British Neurologists) neurologists in the UK and will continue to do this. The service will update the UK neurologists of a National specialist service through the ABN and British Paediatric Neurology Association (BPNA) through other professional bodies such as rehabilitationists.

Out-patient:

- all patients with NMO and NMO spectrum disorder for optimisation of management
- any case of suspected NMO or NMO spectrum disorder for diagnosis and management (e.g.: relapsing mellitus).

In-patient :

- rapid clinical worsening of known NMO requiring inpatient treatment or

assessment

- uncertain diagnosis and atypical clinical picture despite local investigations requiring further multimodal investigations (e.g.: requiring brain biopsy, MRI, spinal fluids)
- when multidisciplinary in-patient NMO specialist care is required to improve disability following an acute attack (e.g. for plasma exchange) which are not possible locally
- in cases where parenteral therapy (example: Rituximab or Mitoxantrone) is required.

2.5 Interdependencies with other services

The service will interact with the physicians, GPs, neurologists, patient groups and societies. It will aim to take on the burden of care of complicated NMO patients and guide local teams and GPs to treat simpler cases under guidance. Rehabilitation and associated services, such as wheelchair provision, will be undertaken locally.

Referral and screening criteria are as outlined earlier in section – the NMO assay is also a screening tool and those patients who are positive can also be referred. Networks of MS clinicians, Association of British Neurologists, NMO and MS nurses and charities should be involved and educated to refer appropriately.

3. Applicable Service Standards

3.1 Applicable national standards e.g. NICE, Royal College

All non urgent referrals, where appropriate, will be seen within four weeks from referral within an outpatient setting providing all the information to support the referral is also received:

- patient meetings will be held at least once a year
- a booklet on NMO will be available to all patients
- an NMO website will be maintained and updated as needed
- telephone and email contact with nurses involved will be encouraged
- smaller NMO patient groups across the country will be facilitated as appropriate
- patients will be informed of developments through the NMO Patient Group and the MS Society, who will publish details on their website
- information on NMO will be disseminated through such means as the MS Society patient publication 'MS Matters'.

The provider will work with the commissioner to continually improve the service and react to innovative and dynamic ideas and to continually review and redesign services and consider and act upon requests of the other party. Service improvement will be stimulated through complaints, monitoring, information provider feedback learning from other services needs assessments service user feedback/patient and public involvement research policy/ guidance on best practice

4. Key Service Outcomes

The overall objective of the service is to improve the diagnosis and treatment of patients with NMO.

The purposes and goals of the service, data to be measured against baseline data:

- improve diagnostic rates
- diagnose earlier
- treat early
- treat effectively
- where evidence is not available set up treatment trials.

The expected outcomes of the service to be reported annually are:

- mortality
- relapse rates before & after attending service
- earlier diagnosis & treatment.

5. Location of Provider Premises

The Walton Centre NHS Foundation Trust
Oxford University Hospital NHS Trust