CASE REPORT

Neuromyelitis optica spectrum disorder presenting as rhomboencephalitis

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SUMMARY

Rhomboencephalitis, at least in its acute phase, is often a severely disabling syndrome, and can be life threatening. A range of underlying conditions can lead to this clinical syndrome. Rapid diagnosis to initiate treatment early is key to a beneficial outcome. We report the case of a 22 year old Afro-Caribbean woman, who presented with a two -week history of walking difficulties, upper limb incoordination and slurred speech. Her brainstem function deteriorated at pace, and she developed hypersomnia. A broad diagnostic approach led to prophylactic treatment for the most common infectious causes. This did not improve her symptoms. Non-infectious inflammatory causes were therefore considered and plasma exchange treatment was initiated leading to marked improvement within days. Screening for autoimmune conditions confirmed aquaporin-4 positive neuromyelitis optica spectrum disorder (NMOSD) as the underlying cause. Immunotherapy with rituximab was started. So far, no relapse has been observed. While the definition of NMOSD continues to be refined, aquaporin-4 testing should be considered early in patients presenting with rhomboencephalitis who do not respond to antibiotic and antiviral treatment. Vigilance and early intervention are key to limit morbidity and mortality from NMOSD.

BACKGROUND

Neuromyelitis Optica Spectrum Disorders (NMOSD) incorporate a range of rare inflammatory demyelinating central nervous system syndromes that are classically characterised by a combination of severe optic neuritis and transverse myelitis. In the wake of the discovery of aquaporin-4 antibodies as the cause of most cases of NMOSD, clinical presentations other than the combination of optic nerve and spinal cord inflammation have increasingly been recognised, including manifestations that do not involve the optic nerve or spinal cord at all. Rhomboencephalitis is one such manifestation where NMOSD manifests through inflammation of the brainstem and cerebellum. While NMOSD is already a rare condition, rhomboencephalitis is even less common as its presenting syndrome. Early diagnosis can therefore be particularly challenging. Given the significant risk of morbidity and indeed mortality from NMOSD, it is important to make clinicians and medical students aware of the variety of presentations of this autoimmune disease so that effective management can be initiated promptly to (i) treat the acute manifestation and (ii) prevent

relapses. Unlike multiple sclerosis, where disability often emerges as a result of acute relapses and chronic deterioration ('progression'), disability in NMOSD is a consequence of relapses only. Early recognition and effective prevention of relapses, which represent a medical emergency, are therefore key.

CASE PRESENTATION

A 22 year old Afro-Caribbean woman born and raised in the United Kingdom, was diagnosed with vestibular neuronitis preceded by non-specific symptoms including a sore throat and cough lasting 4 weeks. Within 2 weeks of what was initially thought to be dysfunction of the vestibular nerve(s), she developed gait imbalance, upper limb incoordination, slurred speech, dysgeusia, and choking episodes. No hiccups were observed or reported. She denied a recent travel history, and her medical and family history was unremarkable. General physical examination was normal apart from obesity (BMI=44). Neurological examination revealed internuclear ophthalmoplegia indicating damage to the left medial longitudinal fascicle (MLF), multi-directional nystagmus, dysarthria, absence of the gag reflex and bilateral limb ataxia. The signs were suggestive of brainstem and cerebellar dysfunction. On day four of her admission she became unable to walk due to progressive limb ataxia and hypersomnia. Cranial nerve examination at this point revealed gaze palsy towards the left combined with dissociated horizontal ocular movement of the right eye consistent with left sided one-and-a-half syndrome. Downward nystagmus and bilateral incomplete ptosis were observed alongside right-sided peripheral facial weakness and ipsilateral hyperacusis. Oral aphthae were seen at this stage, raising the suspicion of Behçet's syndrome.

INVESTIGATIONS

Investigations were normal for haematology, liver and renal function, electrolytes, c-reactive protein and erythrocyte sedimentation rate. Her autoimmune profile was unremarkable except for aquaporin 4 (AQP4) antibodies, which were positive in a serum sample collected during the first week of admission. Infective causes were ruled out through a comprehensive virology panel, negative blood cultures, and negative serology for syphilis and HIV. Paraneoplastic markers as well as a pathology test were also negative. Cerebrospinal fluid analysis showed three lymphocytes/ μ L, normal protein,

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Figure 1 Five axial slices (at the medullar, ponto-cerebellar, mesencephalic, meso-diencephalic, and thalamic levels) at three time points (at presentation, following deterioration 12 days later, and following treatment and resolution of MRI abnormalities 3 months after presentation) to illustrate the evolution and recovery of the condition.

glucose ratio and slightly increased IgG index (46 mg/L; reference range=0–40 mg/L). Computer tomography of chest, abdomen and pelvis was normal. T₂ weighted MRI head on admission revealed signal abnormalities in the periaqueductal grey matter (figure 1). MRI of the spinal cord was normal. Repeat MRI head 1 week after admission showed progression of signal abnormalities into the medulla and the hypothalamus bilaterally.

DIFFERENTIAL DIAGNOSIS

Symptoms, signs and the pathological changes detected on MRI (figure 1) were suggestive of rhomboencephalitis, also known as ponto-medullary or brainstem encephalitis. Rhomboencephalitis can be caused by bacterial infection, commonly listeria and it can also be caused by viruses such as herpes and enterovirus 71. Autoimmune conditions such as *Behçet's* and paraneoplastic syndromes are other important causes of rhomboencephalitis. In most paraneoplastic cases, small cell lung cancer is the underlying malignancy. Isolated cases of systemic lupus erythematosus causing rhomboencephalitis have also been reported.¹ NMOSD causing rhomboencephalitis is uncommon.

TREATMENT

Due to the biphasic time course with flu-like syndrome followed by brainstem dysfunction, empiric treatment was started using intravenous aciclovir and intravenous ampicillin for possible herpes encephalitis and listeria infection, respectively. Both treatments were continued until microbiological studies became available. Since neither cerebrospinal fluid results nor microbiology were suggestive of an infectious aetiology, and against the backdrop of the significant neurological signs, we started treatment with intravenous steroids (methylprednisolone, 1000mg/day for 3 days) followed by oral prednisolone 1mg/kg, with tapering doses over 4 weeks, for suspected idiopathic inflammatory demyelination. Despite this treatment, the patient rapidly declined further and developed significant hypersomnia requiring transfer to our high dependency unit for monitoring.

In addition, we proceeded to plasma exchange (PE). After two courses of PE, improvement was noted, first by subsiding hypersomnia. Plasma exchange was then performed on alternate days. After finishing her course of plasma exchange, and prior to confirmation of the presence of AQP4 autoantibodies, her neurological function improved, and she started mobilising with a walking frame. She was also found to be myelin oligodendrocyte glycoprotein (MOG) antibody negative. The patient's clinical history and syndrome, underpinned by the lesion pattern detected on MRI and confirmed by AQP4 antibodies led us to conclude that this woman suffered a first manifestation of neuromyelitis optica spectrum disorder (NMOSD) presenting as rhomboencephalitis.

OUTCOME AND FOLLOW-UP

Shortly after tapering off her steroids, and while her neurological status improved, we administered a first course of rituximab (two infusions 300 mg each, 2 weeks apart). The patient also underwent an intensive neuro-rehabilitation programme. On follow-up 8 months after first presenting to our hospital, and 6 months after her first course of rituximab, she had fully recovered. She lives independently and has resumed her studies in media. On examination, all neurological signs, except for subtle tandem gait ataxia, had resolved. She was due to receive as second cycle of rituximab.

DISCUSSION

NMOSD is a group of inflammatory demyelinating disorders of the CNS. Early recognition and treatment are important to prevent disability and, in some cases, avoid a fatal outcome. This case highlights the importance of including NMOSD in the differential diagnosis, and the excellent outcome that can be achieved with rapid treatment escalation.

NMOSD is often associated with the presence of AQP4 antibodies. These antibodies target water channel proteins that are specifically located at the grey matter of the spinal cord,

periaqueductal and periventricular regions and perimicrovessel astrocytic foot processes at the blood brain barrier.² The discovery of the AQP4 antibodies led to a new understanding of NMOSD which was previously considered a syndrome consisting of optic neuritis and transverse myelitis only, with no further central nervous system involvement. In fact, exclusion of inflammatory lesions on brain MRI used to be considered supportive of the diagnosis.³ Kim and co-workers retrospectively analysed brain MRI characteristics in 78 AQP4-Ab seropositive patients.⁴ In 44% of cases the lesions were located in the posterior limb of the internal capsule and the cerebral peduncles. Other radiological characteristics included periventricular confluent white matter abnormalities (lateral, third and fourth ventricles) and periaqueductal grey matter, dorsal pontine and medullary lesions. These findings indicate the significance of detailed characterisation of brain MRI studies in CNS AQP4 autoimmunity as brain involvement with associated clinical manifestations are more common than generally appreciated. Considering the above brain abnormalities, it is postulated that two different pathomechanisms underlie lesion formation in CNS AQP4 autoimmunity. The first is complement mediated inflammation and astrocyte-directed cytotoxicity induced by an attack of target AQP4 that leads to the persistent MRI changes. The second is dysfunction of brain water channels and blood brain barrier hyper-permeability leading to reversible vasogenic oedema. AQP4 allows a bidirectional water flow between the blood and the brain, and has been implicated in both the generation and elimination of cerebral oedema.⁵

The evaluation of suspected NMOSD cases requires a comprehensive history and clinical examination to identify the core clinical syndrome. It requires MRI of brain, orbits and spinal cord with gadolinium, cerebrospinal fluid analysis and the patient's AQP-4 status should be ascertained. The detection of AQP-4 is highly specific for confirming the diagnosis in the appropriate clinical settings.⁶ Serum anti-AQP4 titres seem to correlate with disease activity, drop after immunosuppressive treatment and remain low during remissions. The diagnostic criteria for NMOSD are more demanding in the setting of negative or unknown AQP4-IgG and MOG Ab status. The classical localisation of NMOSD in the brainstem is in the area postrema due to the strong expression of AQP-4. Clinical manifestations include intractable hiccups, nausea and vomiting. Lesions in other areas of the brainstem are rare and can lead to cranial nerve palsies, acute neurogenic respiratory failure and death.⁷

Seronegative NMOSD is managed similarly to seropositive NMOSD. The mainstay of treatment of acute attacks involves high-dose intravenous steroids followed by plasma exchange for refractory or progressive symptoms. For prevention of recurrent attacks, treatment involves systemic immunosuppression. There are, however, no randomised controlled trials evaluating the treatment of NMOSD and recommendations are primarily supported by data from observational studies, case series and expert opinion. There is limited literature on the use of intravenous immunoglobulin (IVIG) in patients with acute NMOSD relapse. In 2014, Elson *et al* conducted a retrospective review of 10 patients treated with IVIG during a relapse, mostly when steroids +/- PE had shown no response. Improvement was noted in 5/11 relapses.⁸ It remains rare for IVIG to be used in this setting. The cornerstone of attack prevention is systemic non-selective or selective immunosuppression using agents including azathioprine, mycophenolate mofetil, methotrexate, mitoxantrone and rituximab. In Bichueti *et al*. 2010, azathioprine as monotherapy or combined with prednisolone reduced the relapse rate, with minor and manageable side effects.⁹ In 2011,

Pellkofer evaluated the long-term efficacy and safety of rituximab as second-line therapy in patients with NMOSD who were treated up to five times. Repeated treatment with rituximab led to sustained clinical stabilisation in most NMOSD patients.¹⁰ Jacob *et al* found, in a retrospective analysis of 25 patients, that rituximab led to significantly lower annualised relapse rate, and disability improved or stabilised in 20/25 patients.¹¹ In a 2015 retrospective study, Zephir *et al* explored the use of rituximab as first line therapy in 32 patients with NMOSD. 27/32 patients were relapse-free at follow-up; reductions in annualised relapse rate and improvements in disability were observed suggesting rituximab as first line treatment is both effective and well tolerated.¹² The early initiation of rituximab may be of paramount importance in preventing relapses and permanent disability in antibody positive NMOSD cases. This concept challenges the current stepwise approach which tends to reserve rituximab for treatment-refractory cases. The low prevalence of NMOSD and consequently small sample size of the studies, as well as the relatively short follow-up, preclude more definitive conclusions. In our patient, the rituximab dose administered (600 mg) may be considered at the lower end of the spectrum given her BMI of 44, though the observed effect in this case appears to justify our choice. Systematic studies into the safety and efficacy of rituximab in NMOSD are warranted. The main predictors of prognosis include the relapse frequency in the first 2 years, the severity of the first attack, older age of onset, a background of other autoimmune disorders and NMO autoantibody status (Aqp4, MOG). A biological response marker closer to the pathomechanism of NMOSD has recently been described in the regular assessment of the CD19⁺/CD27⁺ memory B cell population which is effectively depleted with rituximab.¹³ Larger cohort studies are needed to confirm these prognostic factors.

Learning points

- ▶ Rhomboencephalitis, an inflammatory condition presenting with brainstem and cerebellar symptoms and signs is an uncommon, however potentially life-threatening manifestation of NMOSD.
- ▶ Early recognition, treatment and future prevention of NMOSD relapses with immunotherapy are key to avoid irreversible central nervous system damage.
- ▶ The case presented here was effectively treated using plasma exchange based on strong clinical suspicion and before results of auto-antibody screening confirmed Aqp4 antibodies were available.
- ▶ Though often considered as a second or third line option, targeted B cell depletion is a rational and well tolerated intervention in antibody-mediated autoimmune central nervous system diseases, such as NMOSD. Early use of rituximab should therefore be considered.

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