CASE REPORT

Neuromyelitis optica and myasthenia gravis in a young Nigerian girl

Salisu Abdullahi Balarabe,¹ Mohammad Dantani Adamu,² Musa Mamman Watila,³ Nma Jiya⁴

¹Usmanu Danfodio University Teaching Hospital, Sokoto, Sokoto, Nigeria

²Department of Ophthalmology, Usmanu Danfodiyo University Teaching Hospital, Sokoto, Sokoto, Nigeria

³Department of Medicine, University of Maiduguri Teaching Hospital, Maiduguri, Borno, Nigeria

⁴Department of Paediatrics, Usmanu Danfodiyo University Teaching Hospital, Sokoto, Sokoto, Nigeria

Correspondence to
Dr Salisu Abdullahi Balarabe,
sabalara3@yahoo.com

Accepted 23 April 2015

SUMMARY

Neuromyelitis optica (NMO) and myasthenia gravis (MG) are rare autoimmune disorders. The coexistence of the two disorders, although rare, has been documented. This is a case report of a 16-year-old student who presented with recurrent episodes of transverse myelitis and optic neuritis, 8 years after diagnosis of MG. She presented with visual impairment, relapsing and remitting weakness, numbness and paraesthesia of her lower limbs, with bladder and bowel incontinence. Her examination revealed bilateral optic atrophy, spastic paraparesis of the lower limbs and patchy sensory loss up to thoracic level (T4-5). She had a positive acetylcholine receptor antibody, a positive aquaporin-4 antibody and chest CT finding of thymic enlargement. We therefore confirmed the previous diagnosis of MG and performed a recent diagnosis of background NMO. A high index of suspicion is needed to make a diagnosis of this rare coexistence of NMO and MG in resource-limited settings such as Nigeria.

BACKGROUND

Myasthenia gravis (MG) and neuromyelitis optica (NMO) are rare autoimmune disorders, with an estimated prevalence of 15/100 000 and 5/100 000, respectively.^{1 2} MG is an autoimmune disease that is mediated by autoantibodies against acetylcholine receptors (AChR) on the postsynaptic membrane of the neuromuscular junction, with features of fatigable muscle weakness and ptosis.³ NMO is an inflammatory disorder that is characterised by one or more attacks of optic neuritis (ON) and myelitis, with specific diagnostic criteria developed to distinguish it from multiple sclerosis (MS).⁴ The majority of patients with NMO have antibodies to aquaporin 4 (AQP4-Ab), a water channel protein expressed in foot processes of astrocytes.⁵ MG appears to be prevalent in patients with a diagnosis of NMO, with studies reporting a 2% prevalence of MG and presence of AChR-Ab in 11% of patients with NMO; suggesting that the coexistence of MG and NMO is not merely a coincidence.⁶

Patients with NMO and MG are associated with other coexisting autoimmune disorders and over the years there have been case reports of patients having NMO with MG coexisting suggesting a shared immunogenicity between the two disorders.⁷⁻¹⁴ Although uncertain, AQP4 may be expressed in the human thymus, suggesting that the thymus may play a role in the immunopathogenic mechanisms triggering the two conditions. IgG1

antibodies that activate complementally predominantly mediate both diseases.^{5 8} Antibodies in NMO might possibly be produced as a paraneoplastic response in patients with MG with thymoma. An alteration in the immune system functioning caused by thymectomy and immunosuppressive treatment for MG may lead to the development of NMO.^{8 9 14}

To the best of our knowledge, an association between these two diseases has not been previously reported in this region. We therefore report a case

Figure 1 Cervical MRI shows gadolinium enhancing patchy lesions in the cervical spinal cord

To cite: Balarabe SA, Adamu MD, Watila MM, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2014-207362

of a 16-year-old Nigerian girl with AChR-Ab positive MG and AQP4-Ab positive NMO.

CASE PRESENTATION

A 16-year-old Fulani girl presented with a 3-week history of sudden weakness of her lower limbs that was preceded by numbness and paraesthesias. A week later, she developed urinary and faecal incontinence. She had a dull-aching back pain, with no history of trauma to the back. She had a history of two episodes of sudden weakness of the lower limbs 2 years and 1 year prior to presentation, for which she was admitted and managed with methylprednisolone as a case of transverse myelitis. She was diagnosed with bilateral optic atrophy in the ophthalmology unit when she presented with history of bilateral visual loss about 2 years prior to presentation. She was diagnosed with MG at the age of 8 years, based on a clinical history of fatigable weakness, ptosis and ophthalmoplegia, and a positive tensilon test when she presented at the paediatric unit. Her family history is unremarkable. Examination revealed visual acuity in both eyes that was down to hand-movement only. On ophthalmoscopy, there was bilateral pallor of the optic discs (cup-disk ratio of 0.2). She had features of spastic paraparesis of the lower limbs, with patchy sensory loss up to thoracic (T4–5) level.

INVESTIGATIONS

MRI of the whole spine taken 6 weeks after the onset of her symptoms revealed patchy areas of T2-weighted hyperintensity extending over three or more segments of the cervical and upper thoracic cord with enhancement on postcontrast study (figure 1). Although the MRI revealed non-longitudinally extensive patchy lesions that are atypical, this finding may rarely occur in AQP4-IgG-positive NMO (about 7%). Depending on timing issues, short lesions may be present if the MRI is performed very early after attack onset or very late during partial remission.

The patchy nature in this case may be explained by the 6-week delay.

MRI of the brain revealed normal signal intensity of the cerebral grey and white matter, normal cerebellum and brain stem. Cerebrospinal fluid analysis was negative for oligoclonal band. CT of the chest with contrast findings showed bilateral enlargement of the thymus gland. Serum autoantibody for AQP4 and AChR-Ab were positive using an ELISA (ElisaRSRM AQP4 Ab V2 AQP4 autoantibody ELISA V2 kit) with a value of 6.1 units (positive value is >4 units).^{15 16} Haematological profile and serum biochemistry assay were essentially normal. The visual evoked potential was delayed and suggestive of visual pathway dysfunction bilaterally (left more than right). The somatosensory evoked potential showed prolonged latencies.

The patient's clinical features met Wingerchuk's^{4 10} criteria for NMO (box 1); she is currently being managed for NMO.

DIFFERENTIAL DIAGNOSIS

Other differentials considered in our patient included MS, infectious transverse myelitis, tuberculous myelitis, neurosarcoidosis and paraneoplastic neurological syndromes.^{17 18} Many patients with NMO were wrongly diagnosed as MS in the past;^{2 19} NMO is now diagnosed based on an established set criteria (box 1).¹⁰ AQP4-IgG testing is also used to rule out MS and to confirm NMO in these cases.^{15 19}

Box 1 Revised criteria for diagnosis of neuromyelitis optica

Absolute criteria

- ▶ Optic neuritis
- ▶ Acute myelitis

Supportive criteria

- ▶ Normal brain MRI at disease onset, or not meeting diagnostic criteria for myasthenia gravis
- ▶ Spinal cord MRI with T2 signal abnormality extending over three or more vertebral segments
- ▶ Neuromyelitis optica (NMO)-IgG aquaporin 4 (AQP4-IgG) seropositive status

Diagnosis of definite NMO requires two absolute criteria plus at least two of three supportive criteria.¹⁰

TREATMENT

The patient's initial diagnosis of MG was treated with anticholinesterase (pyridostigmine tablets at 30 mg six hourly), she improved remarkably well with very few complaints. During her first and second episodes of lower limb weakness, she was treated as a case of transverse myelitis with methylprednisolone and physiotherapy. She was counselled for a thymectomy, but the patient and her next of kin objected due to financial constraints.

In the index presentation, the patient was treated with intravenous Solumedrol (methylprednisolone sodium succinate) at a daily dosage of 1.0 g for 3 days, followed by a gradual decrement dose of oral prednisolone of 2 mg daily.

OUTCOME AND FOLLOW-UP

The patient made significant improvement in her motor functioning over the course of her treatments. Her vision, however, has not improved significantly.

DISCUSSION

The clinical features of our patient are in keeping with the diagnosis of MG coexisting with NMO. This is the first reported case in our region; however, other cases may not have been reported due to failure of diagnostic acumen and unavailability of diagnostic facilities. The findings in this patient are in keeping with other previous reports of most patients being women and with almost all cases having features of MG predating the development of NMO.^{8 9 11–14 20} The age of our patient was younger than those mostly reported. The age of onset of NMO is most common around the fourth decade of life, with the first attack occurring earlier or later than this age. The female predominance in NMO has been observed, especially in AQP4-Ab positive patients.¹⁹ NMO is also more likely to occur in people of African descent.^{12–14} Our patient had mild MG, which was observed in the case series by Jarius *et al*,¹⁴ who reported that MG often presents with relatively mild symptoms and presents years earlier than NMO, and the median lag between the two diseases may be up to 16 years. Ogaki *et al*²⁰ reported a similar patient with NMO developing in MG, who had thymectomy. Most of the cases of NMO developing in patients with MG had had a thymectomy done^{7 20}; our patient did not have a thymectomy. Kay *et al*¹³ reported a case similar to ours, in which a patient with MG developed NMO without a thymectomy having been done. The report by Kay *et al*¹³

proposed that a thymectomy is not necessarily a prerequisite of NMO occurrence in patients with MG.

The association between NMO and MG is unclear, since antibodies produced in these conditions target different and specific substrates.^{5 21} Antibodies produced in NMO target AQP4, the major water channel protein expressed in the foot processes of astrocytic cells, playing an important role in water homeostasis and maintaining the functional integrity of the blood brain barrier,^{22 23} while AchR-Ab in MG targets AchR on the postsynaptic membrane of neuromuscular junction. Despite this difference, the association may not necessarily be coincidental but rather aetiological. This is suggested by the evidence that patients with either MG or NMO have a higher risk of developing other autoimmune disorders such as systemic lupus erythematosus, Sjögren's syndrome, coeliac disease and sarcoidosis.^{17 24–26} The occurrence of these autoimmune diseases is increased not only in patients but also in their relatives.^{27 28} Autoantibodies with other targets may occur in MG and NMO, however, an antibody with common targets in these conditions has yet to be found. Wakayama *et al*²⁹ reported that AQP4 is also expressed at the neuromuscular junction, which may represent a common target in autoimmune disorders affecting both sites, however, these findings are inconclusive. Recently, autoantibodies against myelin oligodendrocyte glycoprotein (MOG) were found in an AQP4 seronegative NMO patient, and suggested that there is a possibility of other undiscovered autoantibodies with dual pathomechanisms existing in patients with NMO with MG.³⁰

The exact mechanism for the coexistence of the two conditions is not fully known, but may be due to possible shared autoimmune predisposition.^{9 22} This theory is supported by the fact that IgG1 antibodies activate complementally to mediate both diseases, indicating that MG and NMO are both T-helper (Th2)-dominant disorders.²³ It has also been proposed that the thymus may play a role in the coexistence of these two conditions. Patients with MG produce AQP4 autoreactive T-cells in the thymus.^{13 22} Thymoma cells of patients with or without MG express AQP4, this is proved by the fact that AQP4-Ab from the serum of patients with NMO binds to AQP4 expressed on thymoma cell membrane.^{14 22} In addition, NMO in patients with MG may be a paraneoplastic phenomenon associated with thymoma,²² raising the possibility that immunological response may be initiated against AQP4 expressed on thymoma cell membrane.^{12 22} Thymectomy on the other hand has been found to lead to immune dysregulation, interrupting self-tolerance and predisposing patients to future development of NMO; AQP4 autoreactive T-cells could be exported out of the thymoma to reside in other lymphopoietic organs and trigger NMO years following a thymectomy.^{9 12 22}

Treatment of acute attacks is usually with high-dose intravenous methylprednisolone (1 g/day for five consecutive days). Plasma exchange (five to seven cycles) and intravenous immunoglobulin in NMO has been demonstrated to be useful in patients with acute attacks and in those with respiratory involvement. Long-term immunosuppressive treatment is strongly recommended, as NMO usually takes a relapsing course in most. First-line long-term treatment options include azathioprine (2.5–3 mg/kg body weight/day orally with monitoring of haematological parameters and liver enzymes; target lymphocyte count: 600–1000/ μ L target mean erythrocyte volume increase: ~5% from baseline), combined with oral steroids at a dose of 1 mg/kg body weight/day during the first 3–6 months due to a delay in therapeutic effect. A B-cell depleting drug such as rituximab can also be used.⁵ Second-line treatments believed to be

effective in NMO include methotrexate, mitoxantrone (the use of which is limited by the risk of cardiotoxicity and acute leukaemia) and mycophenolate mofetil. Third-line treatments include tocilizumab and combination treatments. Cyclophosphamide has failed to show efficacy in two recent studies and should only be used when other immunosuppressive therapies fail or are not available. Intravenous immunoglobulins are potentially useful in NMO and may be used especially in patients with contraindication to other treatments or, particularly, in children.⁵ Interferon- β , natalizumab and fingolimod are of no proven effect in NMO and have even been shown to cause disease exacerbation in NMO so, accordingly, must not be used in this condition.⁵

Our patient had a good response to corticosteroids, since both conditions respond to prompt corticosteroid therapy.¹⁴

Learning points

- ▶ Although rare, neuromyelitis optica and myasthenia gravis can coexist.
- ▶ The association between the two conditions is still unclear, but might possibly be due to a shared immunopathogenic mechanism mediated by the thymus.
- ▶ This case has shown that a high index of suspicion and good clinical acumen is needed in diagnosis, especially in resource-limited settings such as Nigeria.

Contributors SAB, MDA and NJ were involved in the management of the patient at various times. SAB and MMW were involved in writing the manuscript. All authors read and approved the final manuscript.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Robertson NP, Deans J, Compston DA. Myasthenia gravis: a population based epidemiological study in Cambridgeshire, England. *J Neurol Neurosurg Psychiatry* 1998;65:492–6.
- 2 Mealy MA, Wingerchuk DM, Greenberg BM, *et al*. Epidemiology of neuromyelitis optica in the United States: a multicenter analysis. *Arch Neurol* 2012;69:1176–80.
- 3 Carr AS, Cardwell CR, McCarron PO, *et al*. A systematic review of population based epidemiological studies in Myasthenia Gravis. *BMC Neurol* 2010;10:46.
- 4 Wingerchuk DM, Lennon VA, Pittock SJ, *et al*. Revised diagnostic criteria for neuromyelitis optica. *Neurology* 2006;66:1485–9.
- 5 Trebst C, Jarius S, Berthele A, *et al*. Update on the diagnosis and treatment of neuromyelitis optica: recommendations of the Neuromyelitis Optica Study Group (NEMOS). *J Neurol* 2014;261:1–16.
- 6 McKeon A, Lennon VA, Jacob A, *et al*. Coexistence of myasthenia gravis and serological markers of neurological autoimmunity in neuromyelitis optica. *Muscle Nerve* 2009;39:87–90.
- 7 Furukawa Y, Yoshikawa H, Yachie A, *et al*. Neuromyelitis optica associated with myasthenia gravis: characteristic phenotype in Japanese population. *Eur J Neurol* 2006;13:655–8.
- 8 Leite MI, Coutinho E, Lana-Peixoto M, *et al*. Myasthenia gravis and neuromyelitis optica spectrum disorder: a multicenter study of 16 patients. *Neurology* 2012;78:1601–7.
- 9 Uzawa A, Mori M, Iwai Y, *et al*. Association of anti-aquaporin-4 antibody-positive neuromyelitis optica with myasthenia gravis. *J Neurol Sci* 2009;287:105–7.
- 10 Wingerchuk DM, Lennon VA, Lucchinetti CF, *et al*. The spectrum of neuromyelitis optica. *Lancet Neurol* 2007;6:805–15.
- 11 Vaknin-Dembinsky A, Abramsky O, Petrou P, *et al*. Myasthenia gravis-associated neuromyelitis optica-like disease: an immunological link between the central nervous system and muscle? *Arch Neurol* 2011;68:1557–61.
- 12 Kister I, Gulati S, Boz C, *et al*. Neuromyelitis optica in patients with myasthenia gravis who underwent thymectomy. *Arch Neurol* 2006;63:851–6.

- 13 Kay CSK, Scola RH, Lorenzoni PJ, *et al.* NMO-IgG positive neuromyelitis optica in a patient with myasthenia gravis but no thymectomy. *J Neurol Sci* 2008;275:148–50.
- 14 Jarius S, Paul F, Franciotta D, *et al.* Neuromyelitis optica spectrum disorders in patients with myasthenia gravis: ten new aquaporin-4 antibody positive cases and a review of the literature. *Mult Scler* 2012;18:1135–43.
- 15 Jarius S, Wildemann B. Aquaporin-4 antibodies (NMO-IgG) as a serological marker of neuromyelitis optica: a critical review of the literature. *Brain Pathol* 2013;23:661–83.
- 16 Jarius S, Franciotta D, Paul F, *et al.* Testing for antibodies to human aquaporin-4 by ELISA: sensitivity, specificity, and direct comparison with immunohistochemistry. *J Neurol Sci* 2012;320:32–7.
- 17 Trebst C, Raab P, Voss EV, *et al.* Longitudinal extensive transverse myelitis—it's not all neuromyelitis optica. *Nat Rev Neurol* 2011;7:688–98.
- 18 Jarius S, Wandinger KP, Borowski K, *et al.* Antibodies to CV2/CRMP5 in neuromyelitis optica-like disease: case report and review of the literature. *Clin Neurol Neurosurg* 2012;114:331–5.
- 19 Jarius S, Ruprecht K, Wildemann B, *et al.* Contrasting disease patterns in seropositive and seronegative neuromyelitis optica: a multicentre study of 175 patients. *J Neuroinflammation* 2012;9:14.
- 20 Ogaki K, Hirayama T, Chijiwa K, *et al.* Anti-aquaporin-4 antibody-positive definite neuromyelitis optica in a patient with thymectomy for myasthenia gravis. *Neurologist* 2012;18:76–9.
- 21 Vincent A, Waters P, Leite MI, *et al.* Antibodies identified by cell-based assays in myasthenia gravis and associated diseases. *Ann N Y Acad Sci* 2012;1274:92–8.
- 22 Chan KH, Kwan JSC, Ho PWL, *et al.* Aquaporin-4 water channel expression by thymoma of patients with and without myasthenia gravis. *J Neuroimmunol* 2010;227:178–84.
- 23 Jarius S, Wildemann B. AQP4 antibodies in neuromyelitis optica: diagnostic and pathogenetic relevance. *Nat Rev Neurol* 2010;6:383–92.
- 24 Jarius S, Jacobi C, de Seze J, *et al.* Frequency and syndrome specificity of antibodies to aquaporin-4 in neurological patients with rheumatic disorders. *Mult Scler* 2011;17:1067–73.
- 25 Bergamaschi R, Jarius S, Robotti M, *et al.* Two cases of benign neuromyelitis optica in patients with celiac disease. *J Neurol* 2009;256:2097–9.
- 26 Jarius S, Jacob S, Waters P, *et al.* Neuromyelitis optica in patients with gluten sensitivity associated with antibodies to aquaporin-4. *J Neurol Neurosurg Psychiatry* 2008;79:1084.
- 27 Klein R, Marx A, Ströbel P, *et al.* Autoimmune associations and autoantibody screening show focused recognition in patient subgroups with generalized myasthenia gravis. *Hum Immunol* 2013;74:1184–93.
- 28 Carvalho DC, Tironi TS, Freitas DS, *et al.* Sjögren syndrome and neuromyelitis optica spectrum disorder co-exist in a common autoimmune milieu. *Arq Neuropsiquiatr* 2014;72:619–24.
- 29 Wakayama Y. Aquaporin expression in normal and pathological skeletal muscles: a brief review with focus on AQP4. *J Biomed Biotechnol* 2010;2010:731569.
- 30 Sato DK, Callegaro D, Lana-Peixoto MA, *et al.* Distinction between MOG antibody-positive and AQP4 antibody-positive NMO spectrum disorders. *Neurology* 2014;82:474–81.

Copyright 2015 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- Submit as many cases as you like
- Enjoy fast sympathetic peer review and rapid publication of accepted articles
- Access all the published articles
- Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow