ISSN: 2690- 909X

Case Report

Advances in Neurology and Neuroscience

Acute-onset bilateral visual loss in the context of longstanding myasthenia gravis: don't forget anti-aquaporin-4 antibodies!

Fan Cheng[1], Wen Wang[1*]

[1]*Department of Neurology, The Emergency General Hospital, Beijing, China.*

[*]Corresponding author
Wen Wang, The Emergency General Hospital, Beijing, China.

Submitted: 13 Jun 2022; **Accepted**: 20 Jun 2022; **Published**: 30 Jun 2022

Citation: *Fan Cheng and Wen Wang (2022). Acute-onset bilateral visual loss in the context of longstanding myasthenia gravis: don't forget anti-aquaporin-4 antibodies!. Adv Neur Neur Sci. 5(2), 102-107.*

Abstract

Acute-onset visual loss is a medical emergency necessitating prompt and timely intervention to preserve vision and prevent further deterioration. Besides ocular pathologies, neurological conditions account for a significant proportion of cases of visual loss, particularly optic nerve pathologies including demyelinating or inflammatory optic neuritis. Inflammatory optic neuritis may cause unilateral or bilateral acute visual loss in isolation, as the first presentation of multiple sclerosis or neuromyelitis optica spectrum disorder, or in association with systemic autoimmune conditions. We hereby present a case of sequential bilateral anti-aquaporin-4 autoantibody-positive optic neuritis presenting as acute bilateral visual loss and initially diagnosed as temporal arteritis in a patient with longstanding myasthenia gravis. Our case highlights the importance of timely recognition of the possibility of optic neuritis when assessing acute visual loss, and the need for prompt initiation of corticosteroid therapy for residual vision preservation. It also illustrates the importance of maintaining awareness of possible neuromyelitis optica spectrum disorders and diligently testing for anti-aquaporin-4 antibodies in patients presenting with ocular symptoms in the context of co-existing autoimmune pathology and no other obviously attributable ophthalmological pathologies.

Keywords: Acute-Onset Visual Loss, Aquaporin-4 Antibodies, Neuromyelitis Optica Spectrum Disorder, Optic Neuritis, Giant Cell Arteritis.

Introduction

Acute-onset visual loss is a serious, emergency clinical presentation with significant morbidity, disability and socioeconomic burden, warranting prompt diagnosis and timely intervention to preserve vision and preclude further deterioration [1, 2]. Besides ocular causes, neurological conditions account for a significant proportion of cases of visual loss, particularly optic neuropathy due to demyelinating, inflammatory, vasculitic, ischaemic, toxic, metabolic, traumatic, and other aetiologies [3]. Amongst these pathological entities, inflammatory optic neuritis (ON) is a frequent cause of acute unilateral or bilateral optic nerve injury with potential to cause visual loss in patients of all ages, with protean causes encompassing demyelinating, autoimmune, granulomatous, infectious and paraneoplastic disorders [4]. Of particular relevance, ON may represent the first presentation of demyelinating conditions including multiple sclerosis (MS) or neuromyelitis optica spectrum disorder (NMOSD). In particular, NMOSD tends to be relapsing, is associated with pathogenic immunoglobulin G1 (IgG1)-complement activating autoantibodies against astrocytic aquaporin-4 channels (AQP4 Ab) in 80% of patients, and typically presents with core clinical features of ON, longitudinally extensive transverse myelitis (LETM), area postrema syndrome, acute brainstem syndrome, and acute diencephalic or cerebral syndromes with typical NMOSD-type brain magnetic resonance imaging (MRI) lesions, as defined by the international consensus NMOSD diagnostic criteria [5, 6]. Moreover, AQP4 Ab titre may correlate with disease activity during the attack phase [7]. However, ON in NMOSD is often bilateral with significantly higher risk of visual loss and long-term residual visual disability than that of MS, whilst NMOSD also requires distinct and more aggressive treatment strategies compared to MS [8]. Therefore, rapid determination of the causative aetiology of visual loss and recognition of ON as a possible diagnosis is critical for initiating targeted, appropriate, timely and effective therapeutics to ameliorate visual prognosis.

Myasthenia gravis (MG) is an autoimmune neuromuscular junction disorder with typical pathognomic IgG autoantibodies targeting nicotinic acetylcholine receptor (nAChR), muscle-specific kinase (MuSK), low density lipoprotein receptor-related protein 4 (LRP4) and others, resulting in skeletal muscle weakness and fatigability [9]. However, MG patients also demonstrate increased incidence of other autoimmune conditions, including Hashimoto thyroiditis, Graves' disease, rheumatoid arthritis, systemic lupus erythematosus and pernicious anaemia [10, 11]. Moreover, recent research has demonstrated an association between MG and

NMOSD, particular in Caucasian patients [12, 13]. We present a case of sequential bilateral ON due to AQP4 Ab-positive NMOSD, presenting as acute bilateral visual loss and initially diagnosed as temporal arteritis in a patient with longstanding MG.

Case Report

A 74 year-old Chinese man with a stable background diagnosis of MG presented to hospital following rapid deterioration of vision in his right eye. He had a history of coryzal symptoms with sinusitis 7 weeks prior to presentation and 3 weeks previously had developed sudden-onset, painless blurring of vision in his right eye associated with photopsia, which gradually worsened over 10 days to no vision. Additionally, he reported feeling fatigued with aches in his shoulders and knees, although there was no history of temporal pain, headache, weight loss, fevers or history of traumatic injuries to his eyes or head. He was diagnosed with nAChR-positive MG at the age of 48 following 3 years of diplopia, eyelid droop and mild bilateral leg weakness when ascending stairs. He was commenced on long-term pyridostigmine without subsequent recourse to immunosuppressive therapy and underwent thymectomy aged 57. He reported no other previous visual symptoms except diplopia in the context of his MG. He was taking regular pyridostigmine 120mg four times daily as his only regular medication. He is a retired factory worker, lived with his wife, is a non-smoker and consumed no alcohol. Following initial onset of symptoms, he had presented to another institution, where examination was reported to show no perception of light in his right eye at all, whilst left eye visual acuity was 6/9 and improved to 6/6–2 with pin-hole assessment. Fundoscopy demonstrated a pale right optic disc and normal left optic disc. A right afferent pupillary defect was noted. Blood results were normal. Based on this presentation, the differential diagnosis was felt to be right optic nerve compression or temporal arteritis, and urgent outpatient MRI brain and temporal artery biopsy were promptly arranged. Although ON was also queried at the time as a possible cause of his symptoms, importantly, no corticosteroid treatment was commenced at this stage.

4 days after this clinical encounter and whilst awaiting the planned MRI and biopsy, he developed further painless left eye visual acuity deterioration. Again, there was no associated headache, temporal discomfort or jaw claudication. On assessment, there was left eye visual blurring. He was able to see hand movements in his right eye with profound blurring, but was unable to finger-count. Examination demonstrated visual acuity of 6/60 in the right and deterioration to 4/36 in the left eye, improving to 6/60 with pinhole assessment. Colour vision was 0/17 in both eyes on the Ishihara test, and pupillary reflex was absent in the right eye and very modest in the left eye. Visual fields testing demonstrated loss of temporal visual field in the left eye. Fundoscopy demonstrated atrophied right optic disc and bilateral pale discs, but healthy retina with no evidence of intraocular infections. There was no ophthalmoplegia and no other cranial nerve abnormalities. Investigations included blood tests for full blood count, renal function, liver function, complement-reactive protein (CRP), erythrocyte sedimentation rate (ESR), coagulation profile, anti-nuclear antibodies (ANA), nAChR autoantibodies and thyroid function tests; urinalysis and urine microscopy, culture and sensitivities (MC&S); chest X-ray to exclude concomitant infections; and an urgent computed tomography (CT) brain [Table 1, Figure 1].

Table 1: Initial Investigation Results

Blood results:	
- Haemoglobin	15.1 g/dL
- White blood cell count	7.73 x 109/L
- Platelet count	176 x 109/L
- Sodium (Na+)	143 mmol/L
- Potassium (K+)	3.9 mmol/L
- Urea	5.1 mmol/L
- Creatinine	62 µmol/L
- Estimated glomerular filtration rate (eGFR)	>90 ml/min/1.73m2
- Bilirubin	7 µmol/L
- Alanine aminotransferase (ALT)	17 IU/L
- Alkaline phosphatase (ALP)	143 IU/L
- Albumin	38 g/L
- Calcium (adjusted)	2.53 mmol/L
- Thyroid stimulating hormone (TSH)	1.2 mU/L
- Free T3	5.9 pmol/L
- Free T4	15 pmol/L
- Complement-reactive protein (CRP)	3.6 mg/L
- Erythrocyte sedimentation rate (ESR)	5 mm/hour
Urine investigations:	
- Urinalysis	Trace leukocytes, ++ blood
- Urine microscopy, culture and sensitivities (MC&S)	No cells. No bacterial growth
Chest X-ray:	Normal appearances of lung, mediastinum and pleura

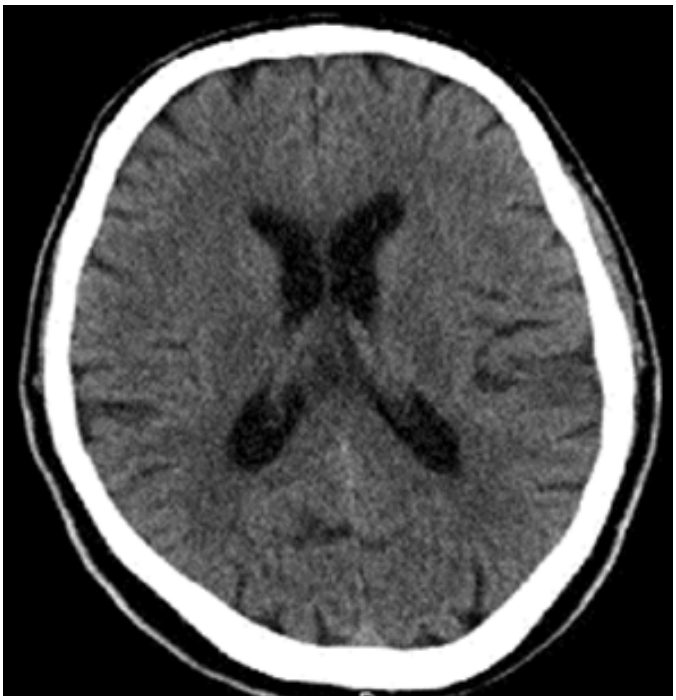


Figure 1: CT brain. This showed no space-occupying lesion, macroscopic abnormality along the visual pathways to account for visual loss, with normal appearance of globes, recti and retro-orbital fat bilaterally and no orbital apex or cavernous sinus masses.

Blood results demonstrated no signs of infection. CXR was clear and CT brain demonstrated no intracranial pathologies to account for his visual loss. He was reviewed urgently by Ophthalmology, who again felt the likely diagnosis to be temporal arteritis, and commenced intravenous methylprednisolone pulse at 1gram daily for 5 days with regular monitoring of visual acuity, blood pressure and blood glucose, before switching to oral prednisolone 60mg daily. He was additionally commenced on daily omeprazole and calcium and vitamin D supplementations as prophylaxis against the gastric and osteoporotic side-effects of prolonged glucocorticoid therapy.

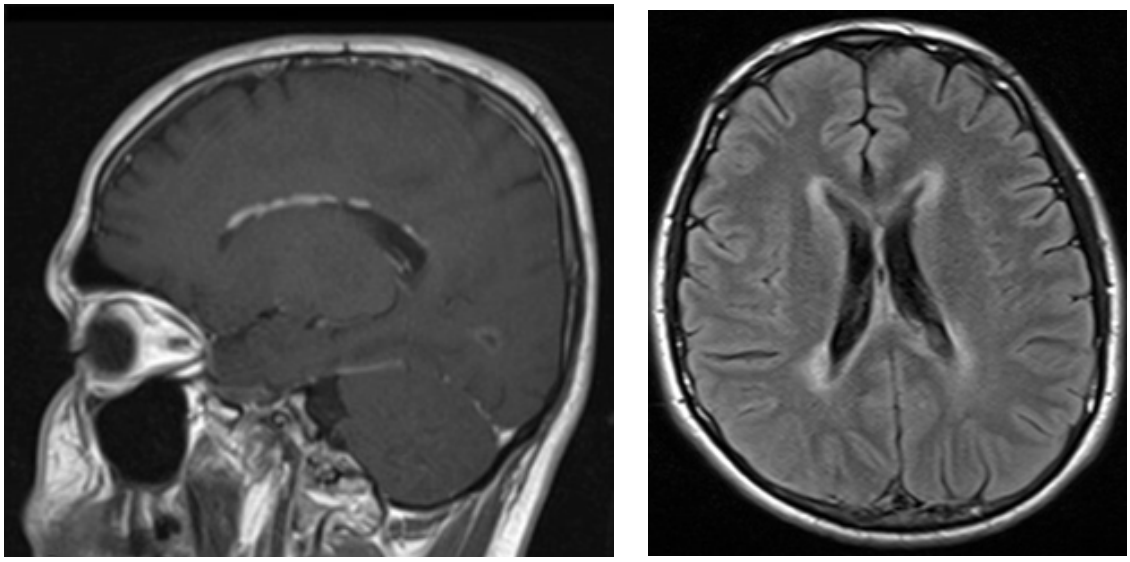
Although intravenous methylprednisolone treatment was commenced for a presumed diagnosis of temporal arteritis, the many atypical features of his presentation, including absence of temporal pain, headache, jaw claudication or symptoms identifiable and consistent with polymyalgia rheumatica, reduces the likelihood of a giant cell arteritis as the underlying diagnosis. Therefore, further tests were arranged to elucidate the cause of his visual loss, in addition to the pending temporal artery biopsy. These included connective tissue autoantibody profile, AQP4 Ab level, anti-myelin oligodendrocyte glycoprotein (MOG) Ab level, microbial serologies, MRI brain and orbit and cerebrospinal fluid (CSF) analysis via lumbar puncture [Table 2, Table 3 and Figure 2]. In particular, AQP4 Ab is the predominant autoantibody present in most NMOSD patients and, given the patient already has a background of MG that itself can co-exist with NMOSD, it was therefore critical to investigate this possibility and investigate for AQP4 presence in both serum and CSF.

Table 2: Extended Autoimmune Profile

Autoantibodies:	
- Anti-aquaporin 4 antibody (AQP4 Ab)	Positive (titre 1:320)
- Anti-myelin oligodendrocyte antibody (MOG Ab))	Negative (0 – 5 x 10-10/ml)
- Anti-nicotinic acetylcholine receptor (nAChR Ab)	8 (<0.5nmol/L)
- ANA	Positive: 1:320
- Anti-double stranded DNA (dsDNA)	Negative
- Anti-Smith	Negative
- Anti-ribonucleoprotein 1 (RNP1)	Negative
- Anti-Ro	Positive: 12 (<1 IU/ml))
- Anti-La	Negative
- Anti-centromere	Negative
- Anti-Scl 70	Negative
- Anti-thyroperoxidase (anti-TPO))	< 35 (0 – 60 IU/ml)
- Anti-cardiolipin	1 (0 – 10 GPL-U/ml)
- Anti-β2 glycoprotein	9 (<20 IU/ml)
Microbial serologies:	
- Human immunodeficiency virus (HIV) 1 and 2	Negative
- Human T cell lymphotrophic virus (HTLV) 1, 2, 3 and 4	Negative
- Hepatitis B	Negative
- Hepatitis C	Negative
- Syphilis	Negative
- Lyme	Negative
Cryoglobulins	Negative
Serum ACE	23 (18 – 55 units/L)

Table 3: Lumbar Puncture Results

Cerebrospinal fluid:	
- Appearance	Clear colourless fluid
- Protein	389 mg/L (0 – 400 mg/L)
- Glucose	4.2 mmol/L
- IgG	4.13 mg/dL
- Albumin	29.7 mg/dL
- CSF IgG:albumin ratio	13.9% (0 – 22%)
- Oligoclonal bands (OCB)	Positive
- Leukocytes	4/μL (lymphocytes 3/μL, polymorphs 1/μL)
- Erythrocytes	13/μL
- Gram Stain	No organisms
- Microbial culture	No growth after 2 days
- Cytology	Mild to moderate lymphocytic pleiocytosis with occasional macrophages. No evidence of lymphomatous cells
- AQP4 Ab	Positive (titre 1:640)
Serum:	
- Glucose	5.3 mmol/L
- OCB	Negative



(a) (b)

Figure 2: MRI brain and orbits with gadolinium contrast

Figure 2: MRI brain and orbits with contrast (selected images). This demonstrated multiple white matter hyperintensities including in the corpus callosum with contrast enhancement (a) and periventricular lesions (b). There were also multiple small hyperintensities within deep grey nuclei with no evidence of micro-haemorrhage, no signal abnormality in either optic nerves, and no compressive lesions within orbit or intracranially (not shown).

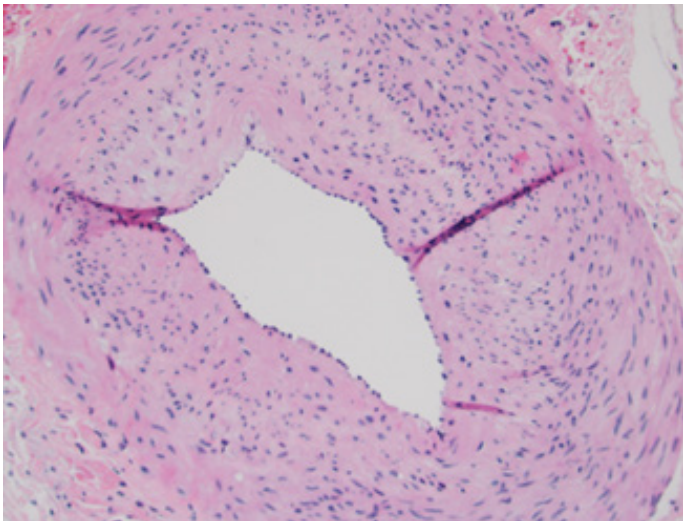


Figure 3: Left superficial temporal artery biopsy

Figure 3: Left superficial temporal artery biopsy. Multiple transversely orientated tissue sections through an elastic artery of average calibre were obtained. The segment of artery biopsied showed no evidence of active giant cell arteritis nor other arteritic processes (above).

The most prominent results above are the strongly positive AQP4 Ab titres in both serum and CSF [Table 2, Table 3]. Moreover, lumbar puncture demonstrated positive oligoclonal bands in the CSF but not serum, thereby confirming intrathecal-specific immunoglobulin synthesis consistent with central nervous system inflammation [Table 3]. MRI showed periventricular and multiple corpus callosal white matter hyperintensities with contrast enhancement, but no evidence of orbital or optic nerve signal abnormalities [Figure 2]. Temporal artery biopsy was negative [Figure 3]. Serum and CSF AQP4 Ab-positivity and supportive CSF analysis, coupled with the negative temporal artery biopsy, confirm that the most likely pathological process underlying the cause of the patient's bilateral visual loss is an autoimmune, inflammation-driven bilateral sequential ON, rather than an ischaemic vasculitis. Therefore, the most accurate diagnosis is that of ON secondary to AQP4-positive NMOSD. He was commenced on immunosuppressive therapy with uptitration of azathioprine and a tapering regime of oral prednisolone. Visual acuity in his right eye subsequently stabilised at 6/60, and colour vision in his left eye has subsequently demonstrated a degree of subjective improvement.

Discussion

We describe a case from a rare but important patient cohort with co-existing MG and AQP4 Ab-positive NMOSD, who developed bilateral visual loss secondary to severe ON that was initially diagnosed as temporal arteritis, but without prompt initiation of corticosteroid therapy. Whilst previously under-appreciated, the co-incidence of AQP4 Ab-mediated NMOSD with nAChR-positive MG has become increasingly well-recognised recently [12, 13]. In a seminal study, Leite et al characterised 16 predominantly Caucasian patients with MG and NMOSD from 9 international centres, 15 of whom were female [12]. Association between NMOSD and MG were significantly greater than expected by chance. All patients had early onset MG, mostly with mild generalised disease. MG predated NMOSD onset in >80% patients, by a median of 16 years. Initial NMOSD symptoms were ON and LETM in 8 patients each, including one case of bilateral ON, with 13 patients subsequently developing a relapsing course and 10 patients developing blindness in at least one eye or inability to walk. Furthermore, 13 patients demonstrated laboratory features of autoimmune comorbidities, including 7 patients with clinical manifestations (autoimmune thyroid disease, systemic lupus erythematosus and voltage-gated potassium channel antibody-induced limbic encephalitis) and 6 patients with additional autoantibodies including ANA, anti-dsDNA, anti-TPO and anti-cardiolipin antibodies. A second study confirmed that co-existence of MG and NMOSD was more prevalent in females, with early onset of typically mild MG, which precedes NMOSD onset by over 10 years on average [13]. Both studies noted a history of thymectomy for MG before NMOSD onset in the majority of patients, suggesting prior thymectomy as a potential risk factor for subsequent NMOSD development. As autoimmune antibody-mediated channelopathies affecting the central and peripheral nervous systems respectively, recent molecular analyses have delineated similar pathophysiological mechanisms for NMOSD and MG, including reduction in circulating regulatory T cells, abundance and overactivity of CD4 and C-X-C motif chemokine receptor 5 (CXCR5)-expressing follicular B helper T cells, which correlates with pathogenic nAChR and AQP4 antibody titres in both conditions, and depletion of regulatory B cells in both conditions, which correlates with clinical severity in MG [14, 15].

Consistent with those in the reported literature, our patient had longstanding, relatively well-controlled mild MG, whilst our patient also demonstrated additional autoantibodies including ANA and anti-Ro. Moreover, our patient underwent prior thymectomy more than 10 years before NMOSD onset, supporting the hypothesis that thymectomy in MG may be a risk factor for subsequent NMOSD development. However, unlike most patients in the literature, our patient is male, non-Caucasian and older, and developed AQP4-positive NMOSD after a longer-than-average period of time from MG onset compared to the literature. Our case highlights the importance of always considering ON as a possible diagnosis for sudden onset visual loss, particularly in a patient with longstanding co-existing autoimmune neurological pathologies, in whom the risk of an autoimmune ON is elevated. Furthermore, it also illustrates the vital importance of testing for the presence of AQP4 Ab in any patient, regardless of age, who present with ocular symptoms superimposed on a background of co-existing autoimmune pathology and with no other obviously attributable ophthalmological pathologies to account for their symptoms, particularly considering the highly relapsing nature of NMOSD and its significant disability burden. Moreover, the unfortunate delay in commencing corticosteroid therapy and resultant profound loss of vision in this patient further underline the necessity for urgent and prompt initiation of corticosteroid therapy in a patient suspected to have ON or temporal arteritis, in order to maximise the probability of preserving residual vision.

Conclusion

We present a case of severe bilateral sequential ON due to AQP4-positive NMOSD in a male patient with longstanding MG, which was initially diagnosed as temporal arteritis without prompt corticosteroid initiation. Our case highlights the need for timely recognition of the possibility of ON, thorough diagnostic work-up to correctly identify the causative aetiology, and prompt commencement of corticosteroid therapy to preserve vision. It also illustrates the importance of maintaining vigilance for possible NMOSD and diligently testing for AQP4 Abs in patients with co-existing autoimmune pathologies presenting with ocular symptoms and no other obviously attributable ophthalmological pathologies.

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