Journal of Neurology (2020) 267:359–368
https://doi.org/10.1007/s00415-019-09586-5

ORIGINAL COMMUNICATION

MOG-IgG-associated demyelination: focus on atypical features, brain histopathology and concomitant autoimmunity

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Received: 31 July 2019 / Revised: 11 October 2019 / Accepted: 14 October 2019 / Published online: 22 October 2019

Abstract

Introduction Antibodies to myelin oligodendrocyte glycoprotein (MOG) have been demonstrated in patients with optic neuritis (ON), encephalitis and myelitis.

Objective To describe the clinical and paraclinical features in patients with MOG-associated demyelination, focusing on unusual cases, brain biopsy and concomitant autoimmunity.

Methods A single centre retrospective observational case series, analysing demographic, clinical, laboratory, histopathology and radiological data from MOG- positive patients.

Results We identified 20 adults. The male/female ratio was 1.5. Mean age at onset was 31.6 years and mean disease duration was 7.5 years. The most frequent presentation was myelitis (45%), followed by ON (30%). One case had simultaneous myelitis and ON. Two patients had a cortical syndrome, 1 patient had an encephalopathic presentation and 1 cryptogenic focal epilepsy. Anti-neutrophil cytoplasmic antibodies (ANCA) were found in 3 cases, while 1 patient had an antibody to glutamic acid decarboxylase (GAD). Brain biopsy was performed in 2 patients. Relapsing course was identified in 60% of patients. We also discuss 3 cases with atypical features, brain histopathology and concomitant autoimmunity.

Conclusion MOG- associated demyelination represents a new disease entity. Unusual cases are reported, expanding the disease spectrum. Elucidating this further should be the focus of prospective studies.

Keywords MOG · Myelin oligodendrocyte glycoprotein · Concomitant autoimmunity · Histopathology

Introduction

Myelin oligodendrocyte glycoprotein (MOG) IgG-antibodies have been associated with multiple sclerosis (MS), aquaporin-4-IgG-negative neuromyelitis optica spectrum disorder (NMOSD) and acute disseminated encephalomyelitis (ADEM) [1, 2]. Recent studies suggest that MOG-associated CNS demyelination is a distinct disease entity [3, 4]. This is based on evidence of pathogenic impact of MOG-IgG, specific histopathological features, lack of aquaporin-4-IgG in almost all MOG positive patients and differences in clinical features, treatment response and prognosis compared to MS and NMOSD [5]. Currently, the clinical spectrum of MOG-IgG-associated demyelination encompasses ADEM, NMOSD and focal cortical disease [4].

The aim of this study was to describe the clinical, laboratory and radiological findings, treatment and outcome in MOG-antibody positive patients, focusing on cases with atypical features, brain biopsy and concomitant autoimmunity.

Methods

We retrospectively studied our patients with MOG-associated demyelination from Nottingham University Hospitals NHS Trust. We recruited all adult patients (age > 16 years old) who tested positive for MOG-IgG between January

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2014 and January 2019. Testing for the presence of serum MOG antibodies was performed in the Autoimmune Neurology Laboratory at John Radcliffe Hospital, Oxford UK, using a live cell-based assay that looks for IgG1 antibodies against the full length human MOG protein, as previously described [6, 7]. Demographic, clinical, serological, cerebrospinal fluid (CSF), magnetic resonance imaging (MRI) and histopathology data were collected from the clinical records. The study was approved by the Quality and Safety Committee of Nottingham University Hospitals NHS Trust.

Results

We identified 20 adult patients with MOG-associated demyelination. Table 1 summarizes the demographic and clinical features of our cohort.

MRI findings were compatible with patient's clinical presentation with or without additional brain MRI lesions. Table 2 demonstrates the brain MRI and laboratory features at presentation.

Brain biopsy results were available from 2 cases, which are discussed separately. Our patients were initially treated with steroids, while 2 patients with longitudinally extensive transverse myelitis (LETM) required plasma exchange (PLEX). All optic neuritis (ON) cases had an excellent initial response to steroids with full recovery, while 1 case with LETM did not respond to steroids and PLEX. 75% (12 out of 16) of our cases that presented with myelitis or/and ON had a good outcome with a current Expanded Disability Status Scale (EDSS) < 3. The 2 myelitis and 2 ON cases with a less favourable outcome had brain MRI lesions at presentation, involving the deep white matter, brainstem and cerebellar peduncle. The 2 cases with cortical syndrome and the ADEM-like case had a full recovery with steroids. However, 1 patient with cortical syndrome subsequently developed moderate disability (EDSS 4), due to further attacks. Immunosuppression has been offered to all relapsing cases.

We will present below 3 individual cases with atypical features, brain histopathology data and concomitant autoimmunity.

Table 1 Demographic and clinical features of MOG-IgG patients

Demographic and clinical features	
Total number of patients	20
Male/Female ratio	1.5 (12 male/8 female)
Mean age at onset in years (range)	31.6 (5–68)
Male mean age in years (range)	35.9 (5–68)
Female mean age in years (range)	25.1 (7–38)
Mean disease duration in years (range)	7.5 (1–29)
Clinical phenotype at onset	
Myelitis, *n* (%)	9 (45%)
LETM, *n*	5
SSTM, *n*	3
LETM + brainstem syndrome, *n*	1
ON, *n* (%)	6 (30%)
BON, *n*	4
UON, *n*	2
LETM + UON, *n* (%)	1 (5%)
ADEM-like, *n* (%)	1 (5%)
Cortical syndrome, *n* (%)	2 (10%)
Focal epilepsy, *n* (%)	1 (5%)
Relapsing course, *n* (%)	12 (60%)
Mean interval between 1st and 2nd attack (range)	5.3 years (1 month-24 years)
Acute phase treatment	
i.v. MTP, *n*	19
PLEX, *n*	2
Chronic therapies, *n*	7
Mean current EDSS score (range)	2.05 (0–8)

n number of cases, *LETM* longitudinally extensive transverse myelitis, *SSTM* short segment transverse myelitis, *ON* optic neuritis, *BON* bilateral optic neuritis, UON unilateral optic neuritis, *ADEM* acute disseminated encephalomyelitis, *i.v. MTP* intravenous methylprednisolone, *PLEX* plasma exchange, *EDSS* expanded disability status scale

Table 2 Laboratory and brain MRI features of MOG-IgG patients at presentation

Laboratory and brain MRI features at presentation	
Concomitant autoimmunity	
ANA, *n*	0/15
ANCA, *n* (%)	3/15 (20%)
P-ANCA with anti-PR3, *n*	1
GAD, *n*	1
Aquaporin-4, *n*	0/19
CSF features	
OCB, *n* (%)	3/14 (21.4%)
Lymphocytosis, *n* (%, mean, range)	5/13 (38.4%, 92.2, 33–140)
Increased protein, *n* (%, mean, range)	9/13 (69.2%, 785.4 mg/L, 468–1146)
Brain MRI at presentation, *n*	20
Normal*, *n*	5
Abnormal, *n*	11
Non specific white matter changes, *n*	4
Topography/characteristics of lesions at presentation	
Gadolinium enhancing lesions, *n*	5
Leptomeningeal enhancement, *n*	3
Deep white matter, *n*	4
Periventricular white matter, *n*	1
Cortical/Juxtacortical, *n*	3
Corpus Callosum, *n*	2
Thalamus, *n*	4
Brainstem, *n*	4
Area postrema, *n*	0
Cerebellar peduncle, *n*	4

n number of cases, *ANA* antinuclear antibodies, *ANCA* antineutrophil cytoplasmic antibodies, *P-ANCA* perinuclear antineutrophil cytoplasmic antibodies, *anti-PR3* proteinase-3 antibodies, *GAD* glutamic acid decarboxylase, *CSF* cerebrospinal fluid, *OCB* oligoclonal band, *normal** does not include optic nerves

Case 1

A 26-year-old male presented in 2012 with complex partial seizures and an isolated secondarily generalised tonic–clonic seizure. His brain MRI scan (performed 3 months after his first generalised seizure) and single electroencephalogram were normal. His voltage gated potassium channel antibodies were negative. He was diagnosed with cryptogenic focal epilepsy and started on Lamotrigine, but due to inadequate seizure control, Levetiracetam was added. A Vagal Nerve Stimulator was implanted in 2017 and his seizure control was improved. On 27th of June 2018 he had a typical complex partial seizure, followed by a right ON. He was treated with 500mg of oral Methylprednisolone for 5 days and his vision returned to normal. He was found to be positive for MOG-IgG antibody. On 31st of July 2018 he had a brain/orbital MRI that revealed a high signal on the right optic nerve, sparing the optic chiasm.

Case 2

A 37-year-old female presented in July 2014 with a 2-week history of expressive dysphasia and right arm weakness. Brain MRI revealed diffuse cortical and leptomeningeal enhancement of the left cerebral hemisphere (Fig. 1a). CSF examination demonstrated 25 lymphocytes/μl, protein at 816 mg/L, normal glucose, negative viral PCR and the presence of oligoclonal bands (OCB). Few days later, she had her first generalised tonic–clonic seizure and started on Levetiracetam. She had a brain biopsy that showed lymphocytic infiltration in the subarachnoid space and around vessels in the cortical tissue (Fig. 2, 3), which extended into the brain parenchyma. There was also a T-cell infiltration in the white matter associated with macrophage aggregation, suggestive of demyelination. She had a full recovery with intravenous steroids and was discharged with oral tapering.

She was re-admitted in November 2014 with progressive left leg weakness. Further brain MRI revealed multifocal

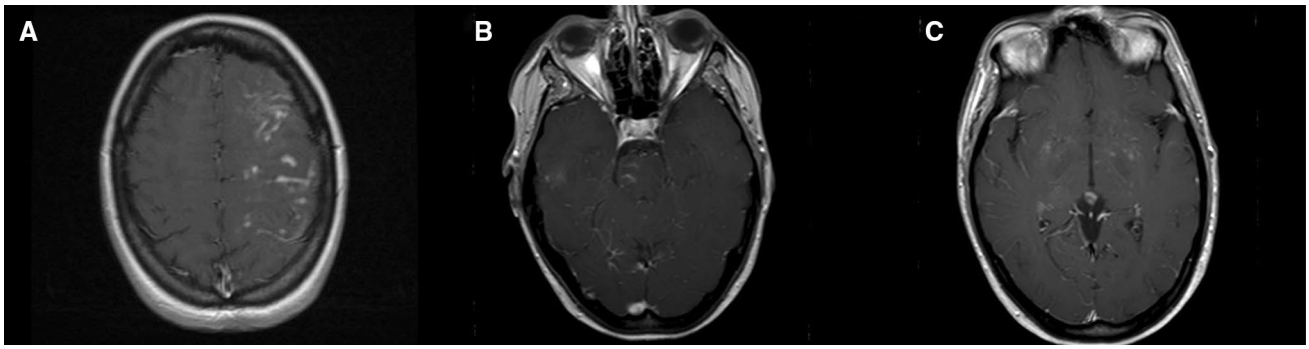

Fig. 1 **a** Axial post contrast T1-weighted magnetic resonance image (MRI) demonstrates diffuse cortical and leptomeningeal enhancement over the left cerebral hemisphere. **b** Axial post contrast T1-weighted MRI shows nodular perivascular enhancement in brainstem. **c** Axial post contrast T1-weighted MRI illustrates perivascular enhancement in basal ganglia

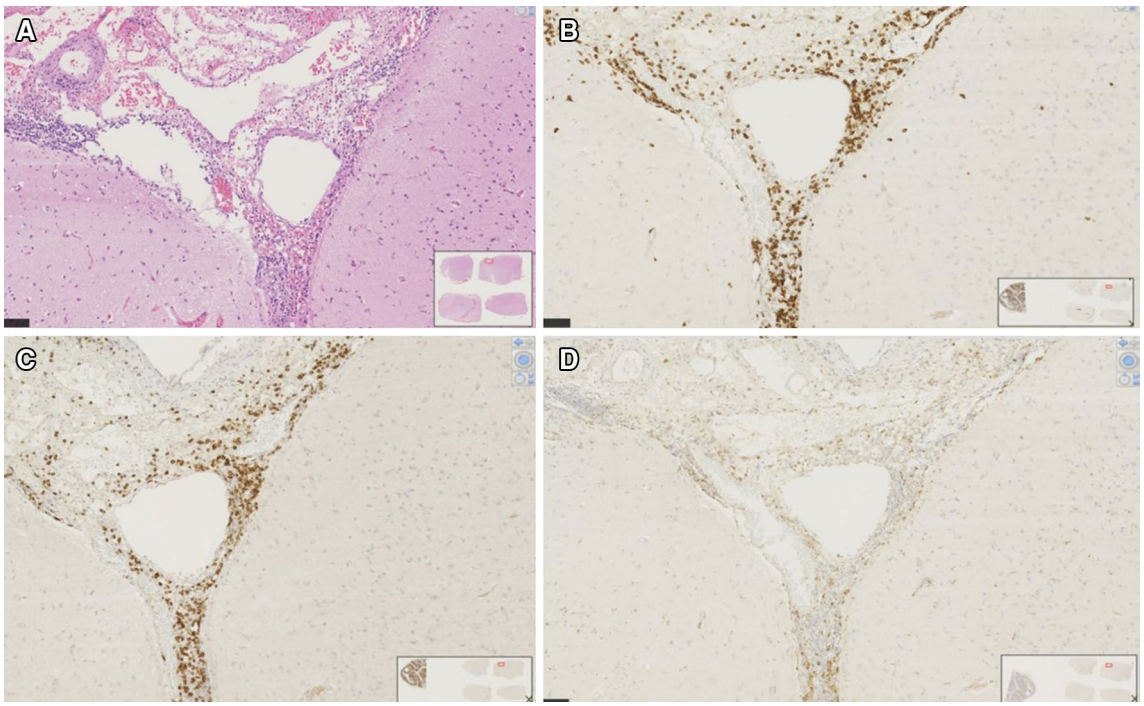

Fig. 2 Representative brain histopathology demonstrates chronic inflammation of the leptomeninges with a predominantly T-cell lymphocytic infiltrate. Hematoxylin–Eosin staining shows infiltration of mononuclear cells (**a**). Immunostaining for CD3 illustrates infiltration of T-lymphocytes (**b**). Immunostaining for CD79a shows B-lymphocytes infiltration (**c**), and immunostaining for CD68 demonstrates macrophage infiltration (**d**)

parenchymal perivascular enhancement (Fig. 1b, c). MRI spine demonstrated abnormal signal from C5 to T2 consistent with inflammatory myelitis. She tested positive for MOG-IgG antibody and was diagnosed with NMOSD [8]. She improved with intravenous Methylprednisolone 1gr for 5 days, followed by a prolonged oral taper. Despite additional immunosuppression (Mycophenolate Mofetil 1gr twice daily), she developed further attacks and was switched to Rituximab. Since then, she is clinically and radiologically stable with EDSS of 4.

Case 3

A 40-year-old male presented in September 2016 with fever, generalised tonic–clonic seizures and altered mental status following a period with significant cocaine exposure. He had a serum white cell count of 22.600/µL (neutrophilia) and CRP of 61 mg/L. CSF examination revealed 450 lymphocytes/µl, protein of 1317 mg/L and glucose of 2.6 mmol/L with serum glucose of 5.4 mmol/L. He

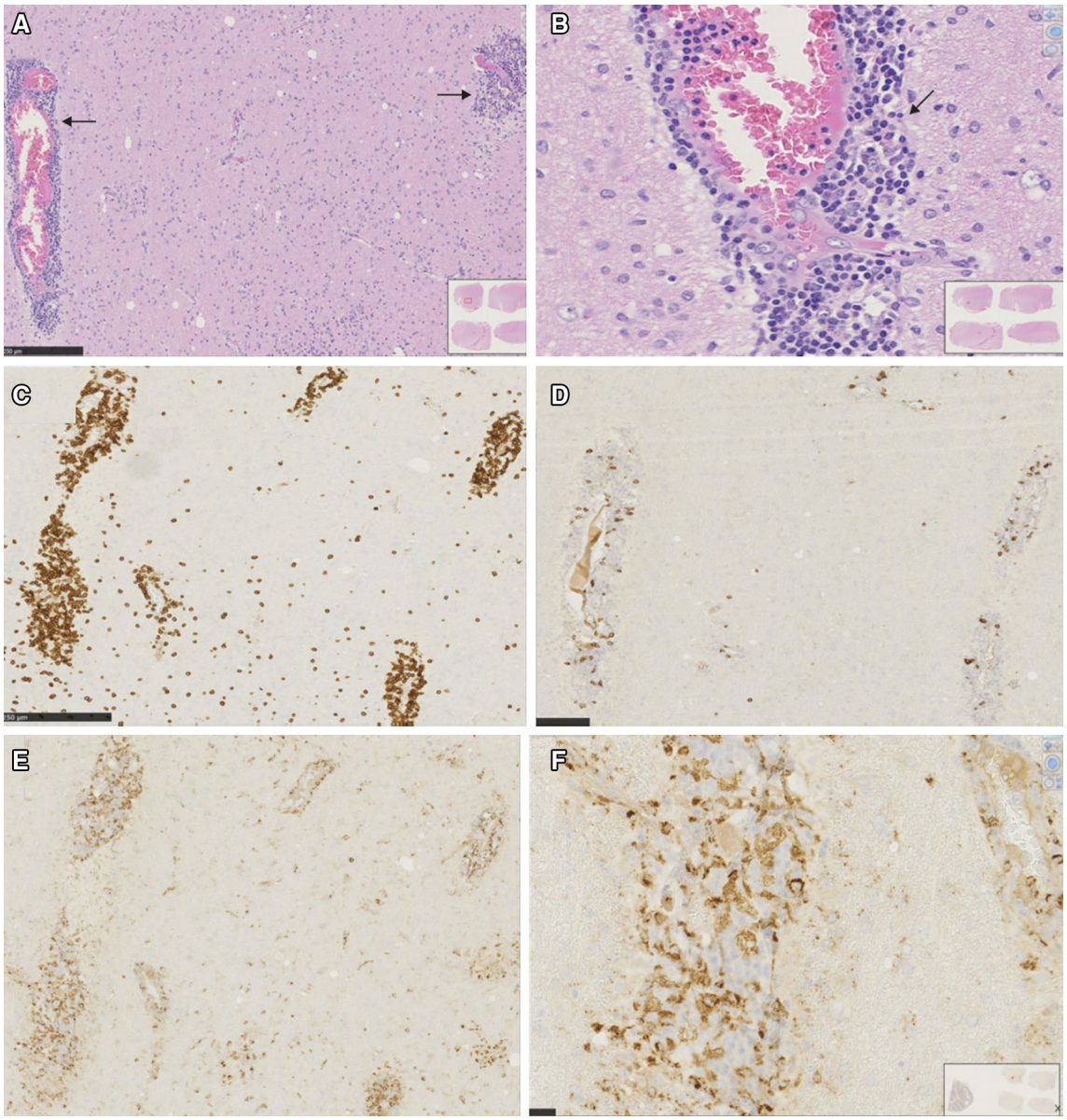

Fig. 3 Representative brain histopathology demonstrates dense perivascular inflammation (arrows) with Hematoxylin–Eosin staining, 10× magnification (**a**), 40× magnification (**b**). Immunostaining for CD3 shows T-lymphocytes infiltration (**c**), and immunostaining for CD79a shows B-lymphocytes infiltration (**d**). Immunostaining for CD68, 10× magnification (**e**), 40× magnification (**f**), illustrates infiltration of macrophages

was treated empirically for possible infectious meningoencephalitis with Ceftriaxone, Acyclovir and Levetiracetam. Extensive infectious screening from serum and CSF was negative. His brain MRI demonstrated diffuse cortical swelling of the left cerebral hemisphere (Fig. 4a).

He subsequently developed mixed aphasia with right sided weakness and had further seizures. Repetition of brain MRI showed multiple new enhancing and non-enhancing lesions (Fig. 4b, c). His autoimmune screening was positive for perinuclear antineutrophil cytoplasmic antibodies (P-ANCA) and proteinase 3 (PR3)-ANCA (22 U/mL). He was also found positive for MOG-IgG-antibody. He had a brain biopsy that revealed marked lymphocytic infiltration in the walls of leptomeningeal and parenchymal vessels in a loose granulomatous pattern (Fig. 5a). There were also areas of parenchymal damage with marked demyelination, including perivascular demyelination (Fig. 5b). Multiple stains for bacteria, fungi and tuberculosis were negative. He was treated with intravenous steroids and showed significant clinical and radiological improvement. He was discharged with oral Prednisolone tapering.

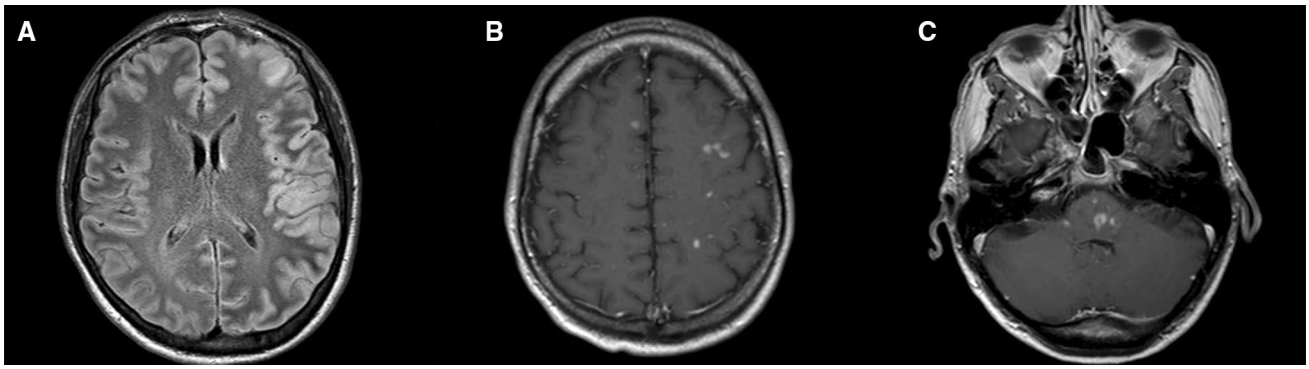

Fig. 4 **a** Axial Fluid Attenuated Inversion Recovery (FLAIR) magnetic resonance image (MRI) demonstrates cortical hyperintense signal of the left cerebral hemisphere. **b** Axial post contrast T1-weighted MRI shows enhancing lesions in subcortical white matter. **c** Axial post contrast T1-weighted MRI shows enhancing lesions in pons

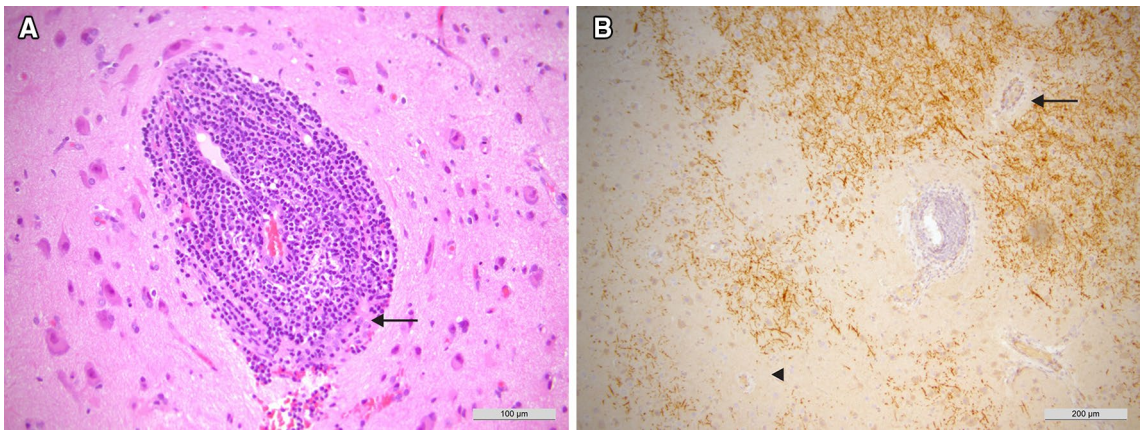

Fig. 5 **a** Representative brain histopathology demonstrates dense lymphocytic (mixed CD3-positive T-cells and CD20-positive B-cells) infiltration in the walls of parenchymal vessels. In some vessels there is a loose granulomatous element to the inflammation (arrow). **b** Myelin Basic Protein immunohistochemistry illustrates marked parenchymal demyelination (arrowhead) with small separate rings of perivascular demyelination (arrow)

His differential diagnosis included cocaine-induced vasculitis, ANCA-associated vasculitis (AAV) and an ADEM-like encephalopathy. However, due to the atypical clinical and radiological presentation, cocaine exposure, the unusual ANCA pattern and histopathological findings, we felt that his diagnosis was probable cocaine induced vasculitis. At that time, the clinical significance of MOG antibodies was uncertain.

He was asymptomatic with a quiet brain MRI and steroids were stopped in May 2017. He was reviewed in clinic in November 2017 with a 2-week history of left sided sensory symptoms. He admitted to using cocaine the previous six months. His brain MRI revealed multifocal new enhancing lesions in the brainstem and cerebellar peduncles. He was re-started on Prednisolone 60mg daily with a slower tapering and he made a full recovery. His relapse was attributed to cocaine re-exposure (MOG-antibody was not retested at this time). He was reviewed again in January 2019 when he was well. His repeat serum MOG-antibody status was negative. He was positive for P-ANCA but PR3 antibodies were negative.

Discussion

In the present study we retrospectively analysed the data of 20 adult patients with MOG-associated demyelination from a single-centre cohort. 60% of our cases were male, while previous studies showed conflicting results regarding sex predominance [9, 10]. MOG-antibody disease can affect children and adults with a broad range of age [4], which was confirmed in our study that had a range from 5 up to 68 years at presentation. Mean age at onset in males (35.9 years) was higher compared to females (25.12 years). Moreover, all our patients with disease onset above the age of 38 (6 cases)

were males, reflecting a possible male preponderance with increasing age.

An ADEM-like encephalopathic presentation was found in 1 patient and focal cortical disease [11, 12] in 2 patients. There was a patient with cryptogenic focal epilepsy as a possible initial manifestation of MOG-associated disease, followed by ON few years later. Although ON is considered the most common presentation [1, 4, 9, 10, 13], in our cohort it was myelitis (45%), followed by ON (30%). One case had simultaneous myelitis and ON. 33% of the myelitis cases had short segment lesions, which is similar to the previously reported 35.3% from a large German study [13], and slightly higher compared to 22.2% from a previous UK study [9]. Regarding ON cases, 3 out of 7 had only one optic nerve affected at presentation which is in accordance with previous findings suggesting that unilateral ON is equally common to bilateral ON [4, 9, 10].

Brain MRI has been shown to be abnormal in up to 45% of MOG patients [10, 13]. In our cohort, 55% (11 out of 20) of the patients had an abnormal brain MRI at presentation, with the deep white matter, thalamus, brainstem and cerebellar peduncle most commonly involved. Like previous reports [10, 13, 14], 15% of our cases had cortical involvement, and 25% had enhancing lesions. However, leptomeningeal enhancement was noted in 15%, which is higher compared to previous findings [10, 13]. Abnormal brain MRI has been associated with increased disability [10], like our 2 myelitis and 2 ON cases with less favourable outcome, that had brain MRI lesions at presentation.

CSF lymphocytosis and increased protein is reported as being present in around 50% of MOG patients [4]. From the CSF results available in our patients, 69% had elevated protein and 38% had lymphocytosis. OCB were found in 21% of our cases, in keeping with previous studies [4].

It is reported that 40–50% of cases with MOG-related disease will have a relapsing course [9, 10]. Our study supports this and suggests it may even be higher, with 60% (12 out of 20) of patients having a relapsing course. Like previous reports [9, 10, 13], ON was the most common relapsing presentation, followed by myelitis.

We have described the general characteristics of our MOG-antibody positive patients. We will discuss below the 3 individual cases, focusing on their atypical features, brain histopathology data and concomitant autoimmunity.

Case 1 with refractory cryptogenic focal epilepsy, developed a MOG-associated ON six years later. Notably, the ON started immediately following one of his typical complex partial seizures. We hypothesize that his focal epilepsy could also be MOG-antibody mediated.

Seizures in MOG-antibody disease have been described in patients during a demyelinating attack, typically with encephalopathy [11, 12, 15]. Brain MRI was abnormal with either a focal cortical hyperintensity, or with more diffuse demyelinating lesions [11, 12]. The cortical hyperintensities were typically present during a demyelinating attack with seizure and were reversible [11, 12]. Unprovoked seizure recurrence (epilepsy) was also noted [11, 12], however it is not clear if ongoing seizures were associated with abnormal brain MRI. In a recent study, 2 patients had cortical lesions on positron emission computed tomography (PET-CT) that were invisible on MRI [15]. In another study, 2 out of 23 patients with seizures or encephalopathy had a normal brain MRI [16]. Our patient's brain MRI was normal however, it was not performed in the acute phase of the seizure disorder and we did not proceed with a PET-CT. There is a previously reported case that developed ON immediately after a seizure [11]. There is also a similar case with focal epilepsy and normal brain MRI that had a NMOSD presentation 5 years later and was found to be positive for aquaporin-4 antibodies [12].

We believe it is very plausible that case 1 had MOG-associated focal epilepsy with normal brain MRI. Clinicians might consider testing for MOG-antibody in cases with refractory cryptogenic focal epilepsy.

Case 2 unusual presentation in 2014 is now well described as part of MOG-associated CNS demyelination [4, 17]. This cortical syndrome was initially thought to be benign and reversible [11], but since then further cases have been described with less favourable outcome [12].

On imaging, apart from the typical MRI cortical abnormalities [12], our patient had diffuse leptomeningeal enhancement which is rare in MOG-associated demyelination. It was found in 3 out of 49 cases in a French nationwide cohort [10], and 1 out of 48 patients in a large multicentre German study [13]. Another unusual MRI characteristic in our case was the brain parenchyma multifocal perivascular enhancement that was recently described for the first time in a MOG-antibody positive case [18]. Perivascular MRI enhancement is likely to represent lymphocytic infiltration around blood vessels, the pathological correlate of which was demonstrated in our brain biopsy.

Histopathological data in MOG cases are very rare. The usual findings are active demyelination with complement deposition in macrophages and the presence of oligodendrocytes and their precursors within the lesions, compatible with MS pattern II lesions [19]. As with our patient, inflammatory infiltration with T cells and macrophages has been shown to be present around the vessels or/and in brain parenchyma [19, 20].

Regarding Case 3, differentiating between cocaine induced ANCA pseudovasculitis or an unrelated idiopathic small/medium vessel AAV is challenging [21–23]. The vasculopathy associated with cocaine is more often localised and is characterised by a discordant ANCA pattern. On the contrary, AAV is usually multi-systemic with a typical ANCA pattern [21, 22]. CNS involvement is quite rare in both conditions [22, 23]. Tissue biopsy is the gold standard

for diagnosis of small vessel vasculitis and can also help differentiate between cocaine induced vasculitis and AAV. In AAV, necrotizing vasculitis affecting small to medium vessels and granulomatosis with inflammatory cell infiltration is typically seen [23]. Significant granulomatosis and extravascular inflammatory changes are typically absent in cocaine induced vasculitis [21]. Our patient's brain biopsy with lymphocytic infiltration in the walls of meningeal and parenchymal vessels in a loose granulomatous pattern favoured cocaine induced vasculopathy. However, the inflammatory changes in the brain parenchyma were suggestive of either AAV and/or ADEM.

Since patient's presentation 3 years ago, the clinical spectrum of MOG-antibody disease has significantly expanded. Cases presenting with fever and meningoencephalitis are currently an important clinical component of MOG-associated demyelination [16, 24, 25]. In retrospect, we believe that the MOG positive result in our patient, tested with a live cell-based assay with high specificity [6, 7], was clinically significant. This is also supported from the characteristic cortical MRI abnormalities and the histopathology finding of marked brain parenchymal demyelination. MOG antibodies were not re-tested at the time of patient's confirmed relapse in November 2017. They were negative in January 2019, while he was clinically stable. Although persistent MOG-IgG positivity has been associated with increased risk of further attacks [3, 26], clinical relapses can occur despite seronegative conversion [27, 28], and have been reported in up to 12% of ADEM relapsed cases with transient seropositivity [26].

Similarly, a case of progressive cognitive decline and behavioural changes manifesting as primary CNS vasculitis with MOG-IgG antibodies has been previously reported [29]. This case had typical vasculitic histopathological findings but no features of demyelination. The patient did not improve on steroids and MOG- antibodies were not subsequently tested. More recently, 2 published cases with fever and meningoencephalitis have been diagnosed as MOG-associated encephalitis despite brain biopsy results suggestive of small vessel vasculitis [30]. One case had histopathology features of demyelination away of the vessel walls, while the other case did not show any evidence of demyelination. MOG serostatus was repeatedly tested in 1 case and finally became negative while the patient was on immunosuppression [30].

We believe that case 3 had MOG-associated disease and concomitant (probable cocaine induced) AAV. It is not clear if the presence of MOG-IgG provoked an AAV or if the ANCA auto-antibodies were primary involved in the pathogenesis and anti-MOG antibody was secondarily generated during the disease course.

To the best of our knowledge, this is the first reported case of concomitant pathogenic autoantibodies (P-ANCA, PR3), other than N-methyl-D-aspartate,-Receptor (NMDA-R) in a MOG-antibody positive patient.

Concomitant auto-antibodies have been found in up to 42.2% of MOG-patients, with antinuclear antibodies being the more frequent, followed by thyroid peroxidase antibodies and ANCA. However, data about PR3 and myeloperoxidase antibodies were not available in previously reported series [10, 13]. MOG-associated demyelination can rarely occur simultaneously or sequentially with anti-NMDA-R encephalitis [31]. In two recent studies, the frequency of this co-existence ranged from 5.7% up to 11.9% regardless of the MOG clinical phenotype and up to 27.8% in MOG-encephalitis cases [15, 32]. It is difficult to clarify whether the clinical phenotype is attributed to MOG, NMDA-R antibodies or both [15].

In our MOG-cohort, we did not find any NMDA-R antibody coexistence. However, 1 patient had concomitant antibodies to glutamic acid decarboxylase (GAD). He is a 23- year-old male who had his first ADEM-like presentation at the age of 8. He developed a relapsing course with mainly ADEM-like attacks. Three years ago, he presented with a brainstem syndrome and cerebellar ataxia. He was tested positive for anti-GAD. A year later, his GAD antibodies were negative, while MOG antibodies were persistently positive. GAD-antibodies-associated neurological syndromes have been thoroughly described [33], however, coexistence with MOG-antibodies has not been reported. We believe that GAD antibodies were probably secondarily generated, although it is unclear (like the cases with NMDA-R antibodies coexistence) if this particular clinical attack with brainstem dysfunction and cerebellar ataxia was (partially or completely) GAD-mediated or not.

Conclusion

The whole spectrum of MOG-associated disease is not yet fully defined. Unusual cases with vasculitis [29, 30], concomitant NMDA-R antibodies [32], MRI negative myelitis [34], and involvement of the nerve roots [35], are reported. Herein, we highlight the atypical features from our MOG-antibody positive cohort, like the patient with cryptogenic focal epilepsy and the cases with concomitant pathogenic autoimmunity (AAV and GAD). We also describe histopathology data that significantly add to the literature on MOG-associated disease.

Further studies examining longitudinal MOG serostatus and concomitant autoimmunity are needed. It is of particular importance that atypical cases are presented and followed, ideally with histopathology data. For such studies, we need a standardization of the MOG-antibody cell-based assays [36].

Acknowledgements We thank the patients who gave consent for us to report their individual cases. We thank Dr N. Evangelou, Dr C. Gilmore and Dr B. Gran, who provided patients for this study. We thank Dr G. Sare for critically reading the manuscript and useful comments.

Funding This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Compliance with ethical standards

Conflicts of interest The authors declare that there is no conflict of interest.

Ethical standards

The study was approved by the Quality and Safety Committee of Nottingham University Hospitals NHS Trust.

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