Fulminant demyelinating encephalomyelitis

Insights from antibody studies and neuropathology

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ABSTRACT

Objectives: Antibodies to myelin oligodendrocyte glycoprotein (MOG) are detectable in inflammatory demyelinating CNS diseases, and MOG antibody–associated diseases seem to have a better prognosis despite occasionally severe presentations.

Methods: We report the case of a 71-year-old patient with acute visual and gait disturbance that dramatically worsened to bilateral amaurosis, tetraplegia, and respiratory insufficiency within a few days.

Results: MRI showed multiple progressive cerebral and spinal lesions with diffusion restriction (including both optic nerves) and marginal contrast enhancement. Routine blood and CSF measures including oligoclonal bands were normal. At disease onset, MOG immunoglobulin G was detected (serum titer 1:1,280, corresponding CSF titer was 1:20) and remained positive in patient serum. Aquaporin-4 antibodies were absent at disease onset but seroconverted to positive at week 9. In addition, CSF glial fibrillary acid protein and myelin basic protein levels were very high at onset but decreased during disease course. After 4 months, the patient died despite immunomodulatory treatment. Postmortem neuropathologic examination revealed an acute multiple sclerosis (MS) defined by multiple demyelinating lesions with a pronounced destructive component and loss of astrocytes. Lesion pattern of optic chiasm met MS pattern II characterized by antibody and complement-mediated demyelination.

Conclusion: The case with the clinical presentation of an acute demyelinating encephalomyelitis with predominant optic and spinal involvement, absent oligoclonal bands, a histopathology of acute MS pattern II and development of aquaporin-4 antibodies extends the spectrum of MOG antibody–associated encephalomyelitis. Although, MOG antibodies are suspected to indicate a favorable prognosis, fulminant disease courses are possible and warrant an aggressive immunotherapy.
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GLOSSARY

ADEM = acute disseminated encephalomyelitis; **AQP4** = aquaporin-4; **GFAP** = glial fibrillary acid protein; **Ig** = immunoglobulin; **MBP** = myelin basic protein; **MOG** = myelin oligodendrocyte glycoprotein; **MS** = multiple sclerosis; **NMO** = neuromyelitis optica.

Acute inflammatory demyelinating syndromes of the CNS comprise heterogeneous diseases such as multiple sclerosis (MS), neuromyelitis optica (NMO), and acute disseminated encephalomyelitis (ADEM) with different pathogenesis, severity, prognosis, disease course, and treatment options.[1] Diagnosis, based on clinical examination, neuroimaging, as well as CSF examination[2] might be challenging, and reliable biomarkers are—except for NMO[3]—still missing. Although biopsy is only rarely performed to exclude other treatable differential diagnoses, neuropathologic characteristics of different MS patterns, ADEM, and NMO are well known[4] and facilitate the diagnosis of different demyelinating CNS diseases.[5] However, since the initial clinical assessment does not always correlate with the final diagnosis, less invasive markers are necessary to identify different diseases or disease patterns.

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In addition to antibodies to aquaporin-4 (AQP4) in NMO, myelin oligodendrocyte glycoprotein (MOG), a cell surface protein of myelin sheaths and oligodendrocytes in the CNS, is an important and extensively studied target structure of immunoreactivity in CNS demyelinating diseases.[6] Measured by cell-based assay, MOG antibodies are predominately found in children with CNS demyelinating diseases.[7–11] However, MOG antibodies have also been described in adults with ADEM, in anti-AQP4 antibody–negative NMO cases,[12,13] and in patients with anti-NMDA receptor encephalitis with demyelination.[14]

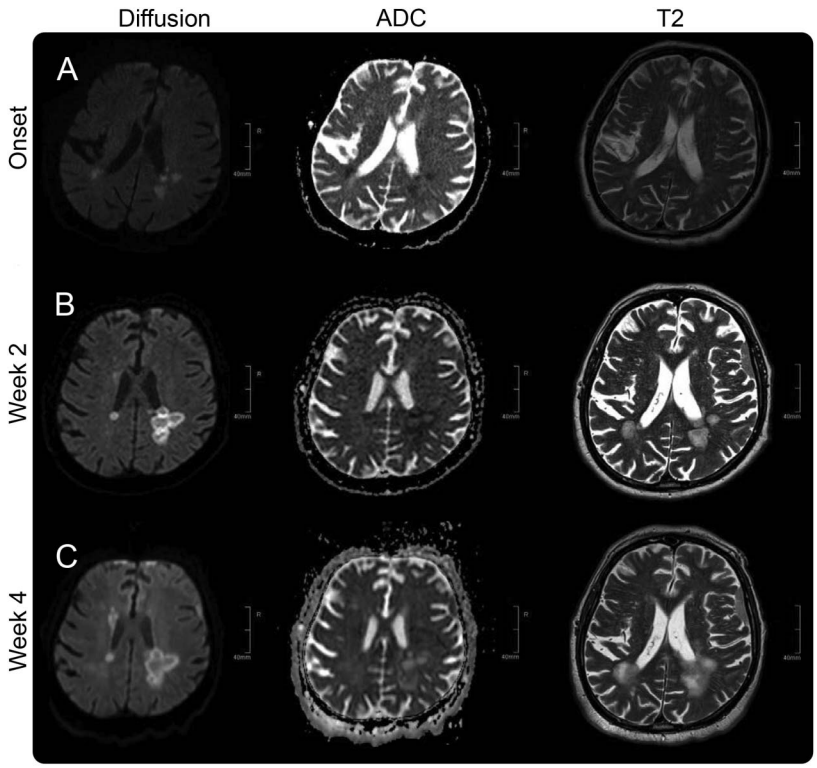
Herein, we report the postmortem neuropathologic examination of a patient with an acute demyelinating fatal CNS disease and antibodies against MOG.

CASE REPORT **Clinical course.** A 71-year-old male patient with a current history of bronchial asthma and arterial hypertension complained of acute bilateral vision and gait disturbance in August 2013. Initial assessment, performed at an external hospital, included cerebral MRI and lumbar puncture. CSF analysis including oligoclonal bands was normal. Cerebral and spinal MRI showed multiple supra- and infratentorial lesions with marked diffusion restriction, only slight hyperintensity on T2-weighted images (figures 1A, 2, A and D), and intramedullary lesions (figure 2B). Lesions marginally enhanced contrast (figure 2C). After admission, the patient's condition worsened dramatically to bilateral amaurosis within 2 days and tetraplegia within 5 days.

Subsequently, the patient was referred to our neurologic intensive care unit for further diagnostics and treatment. Within 1 day, the patient's condition deteriorated again, and acute respiratory insufficiency necessitated mechanical ventilation.

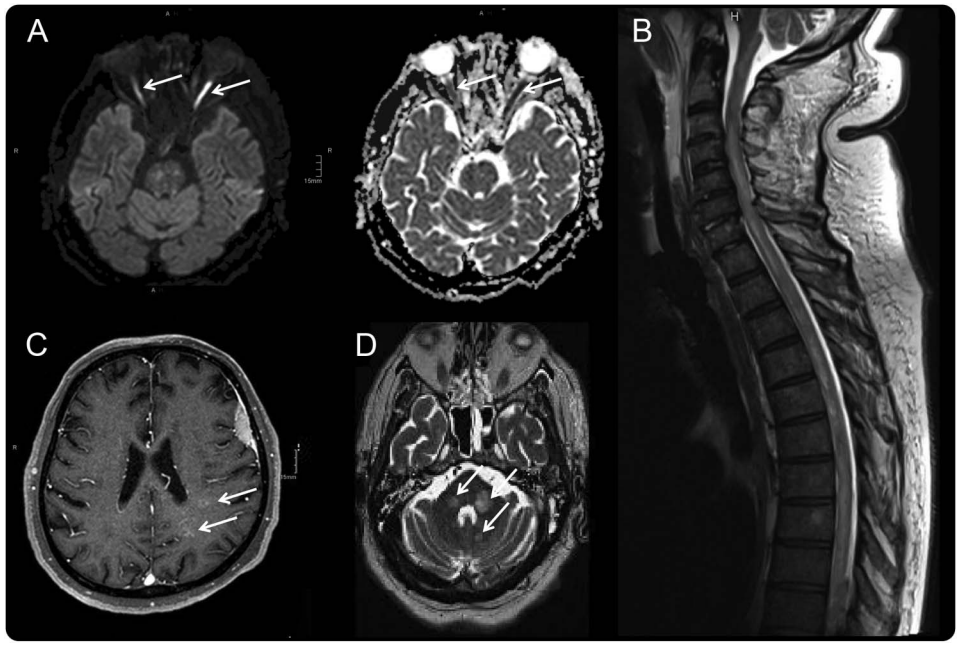
The cerebral and spinal MRI showed progressive multiple cerebral supra- and infratentorial and spinal lesions. The lesions were now clearly hyperintense on T2-weighted images and were predominantly localized periventricular, in the brainstem and intramedullary. The MRI also demonstrated a restricted diffusion of both optic nerves (figure 2A). There was no evidence of any vascular pathology. Incidental findings were a frontotemporal meningioma and vertebrostenosis due to degenerative changes of spinal column (figure 2, B and C).

Figure 1 **Cerebral MRI during the disease course**



Cerebral MRI with multiple cerebral supratentorial lesions during the disease course: periventricular lesions with diffusion restriction, only slight hyperintensity on T2-weighted images (A). Progressive diffusion restriction and now clearly hyperintense lesions on T2-weighted images 2 weeks after disease onset (B) and 4 weeks after disease onset (C). ADC = apparent diffusion coefficient.

Figure 2 Cerebral and spinal MRI



(A) Restricted diffusion of both optic nerves (arrows) on diffusion-weighted and apparent diffusion coefficient imaging. (B) Intramedullary lesions. (C) Marginal contrast enhancement at disease onset (arrows). (D) Brainstem lesions (arrows).

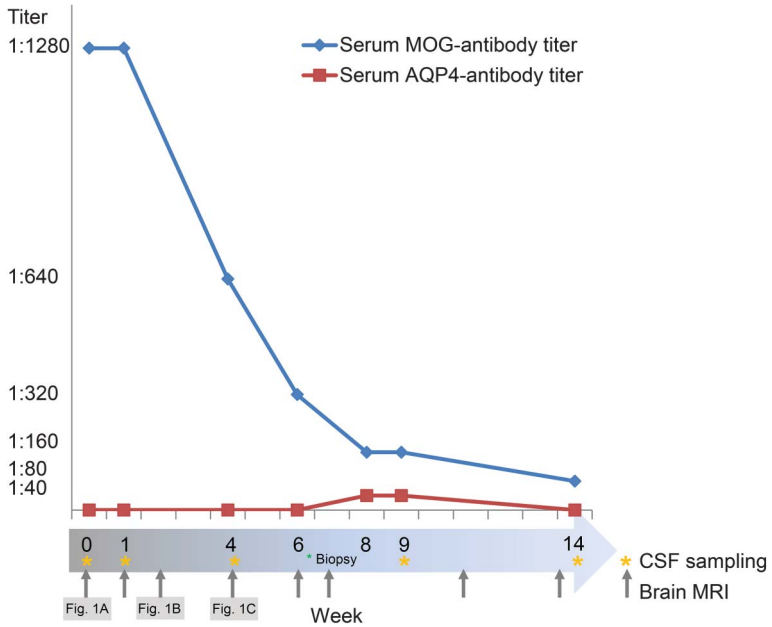
A second CSF sample taken 1 week after disease onset now revealed inflammation with pleocytosis composed of lymphocytes and neutrophilic granulocytes, and increased permeability of the blood–brain barrier. Oligoclonal bands were absent. Routine laboratory findings including cell count of peripheral blood and inflammatory measures were normal. Further detailed laboratory investigations such as serologic analyses for potential infectious agents (including culture and PCR in blood and CSF) and several autoantibodies (such as anti-ganglioside and onconeural antibodies, thyroid antibodies, PR3 and MPO antineutrophil cytoplasmic antibodies, antiphospholipid antibodies) were negative. However, immunoglobulin G (IgG) MOG antibodies were positive in serum with a titer of 1:1,280 (IgG1 only with a titer of 1:640) and in CSF (titer 1:20), whereas AQP4 antibodies were absent at disease onset (figure 3). MOG and AQP4 antibodies were measured using a recombinant live cell-based immunofluorescence assay and an optimized tissue-based immunohistochemistry antibody assay as described before.[12,13]

An empiric antimicrobial combination therapy was initiated because of the differential diagnostic suspicion of an infectious cause. However, no treatment response was observed, and another cerebral MRI showed progressive findings 2 weeks after disease onset (figure 1B). Simultaneously, an immunomodulatory therapy with corticosteroids and IV immunoglobulins was started. Because the patient did not respond to the immune treatment as evidenced by repeated neuroimaging, a brain biopsy was performed. Corticosteroids were discontinued 3 weeks before biopsy. Histopathology showed small fragments of an actively demyelinating lesion with inflammatory infiltrates consisting of macrophages and CD3- and CD8-positive T cells (figure 4, A–C). There was no evidence of CD20-positive B cells (data not shown). One vessel in the periplaque white matter revealed perivascular complement deposition (figure 4D).

The diagnostic findings suggested an acute demyelinating encephalomyelitis with predominantly optic and spinal involvement associated with MOG antibodies.

In the following 3 months of continuous hospitalization, repeated MRI, CSF, and laboratory analyses were performed. All MRI controls (from September to December 2013) showed a stable lesion load without any contrast enhancement (MRI 4 weeks after disease onset, figure 1C). CSF cell counts continuously decreased to normal ranges in December 2013. Serial serum MOG antibody testing was conducted at weeks 1, 4, 6, 8, 9, and 14 after disease onset. At 4 weeks, serum MOG antibody titer had decreased to 1:640 and at 14 weeks to 1:80 (figure 3). CSF MOG antibodies (available at disease onset and at weeks 1, 4, 9, and 14) were detectable at onset with a titer of 1:20, at week 1 (1:20), and week 4 (1:4) and were negative at weeks 9 and 14. Subclass analyses of IgG 1–4 revealed that the antibodies belonged to the IgG1 subgroup. Furthermore, only at disease onset, IgM MOG antibodies were present at a titer of 1:160.

Figure 3 Antibody titers during the disease course



Temporal dynamic of MOG and AQP4 antibodies and time points of MRI and CSF sampling. AQP4 = aquaporin-4; MOG = myelin oligodendrocyte glycoprotein.

Serum AQP4 antibodies were absent at disease onset but seroconverted to low-titer positive at week 9 (titer 1:40; IgG1 subclass only; figure 3) by cell-based immunofluorescence assay and were negative using tissue immunohistochemistry. CSF AQP4 antibodies were negative at all time points. The patient was negative for AQP1 antibodies at all time points.

CSF glial fibrillary acid protein (GFAP) and myelin basic protein (MBP) levels were retrospectively analyzed by Sato and colleagues at disease onset, week 4, and week 9 as described before.[15] Initial levels of GFAP and MBP were very high at 152,492 and 3,709 ng/mL, respectively; CSF GFAP levels decreased in week 4 to 709 ng/mL, whereas CSF MBP levels firstly increased to 7,224 ng/mL. In week 9, both CSF GFAP and MBP levels clearly declined to 12 and 291 ng/mL, respectively.

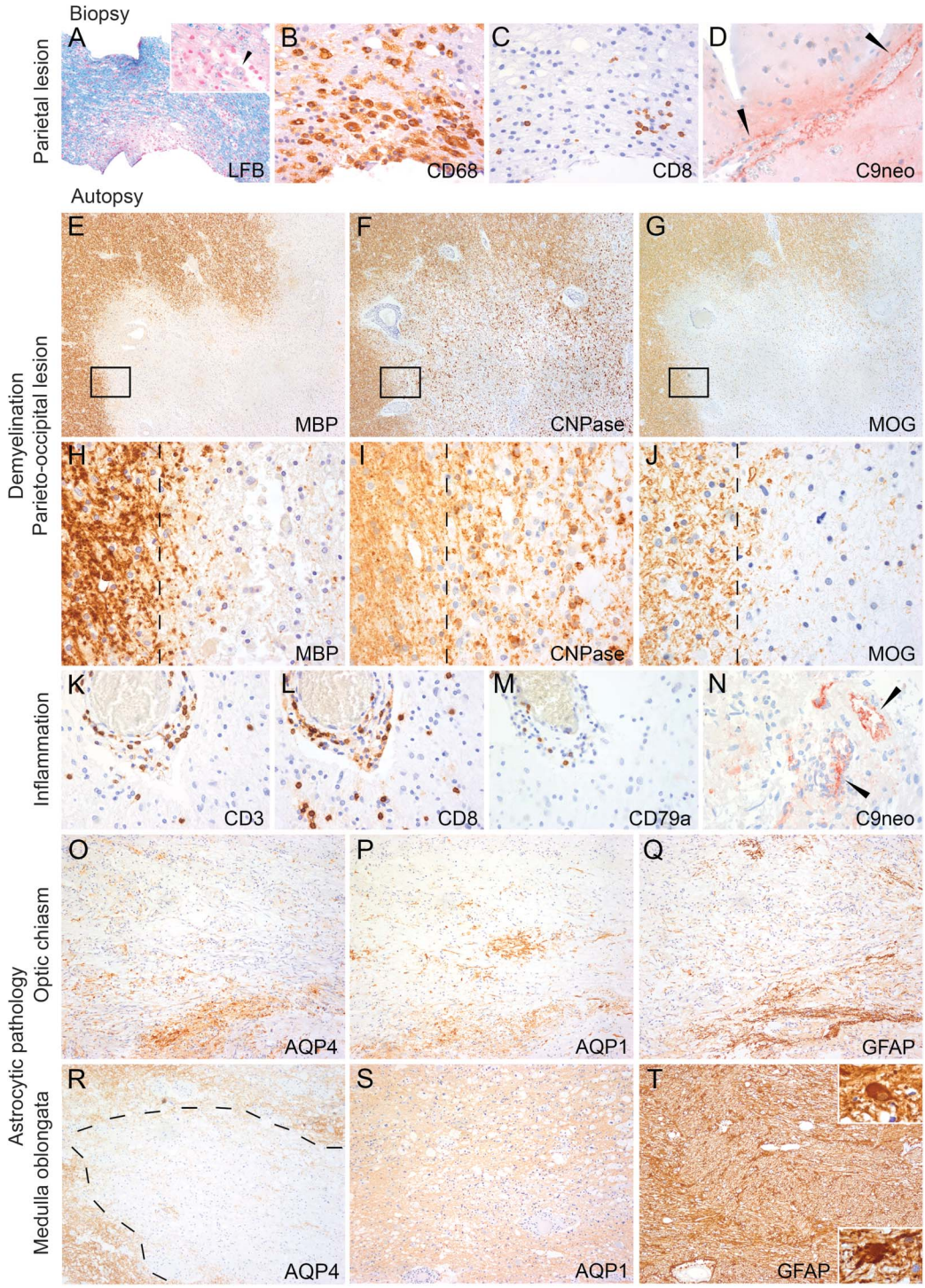
Apart from stable or even improved laboratory and imaging findings, the clinical condition of the patient with amaurosis and tetraplegia was unchanged and required continuous mechanical ventilation. Because of the prolonged clinical course without any functional improvements, treatment was switched to comfort therapy according to the patient's living will. The patient died at the end of December, 2013, and an autopsy was performed.

Neuropathology. Postmortem examination of the brain revealed multiple demyelinating lesions in optic chiasm, cerebrum, and brainstem. The cerebrum showed multiple confluent chronic inactive demyelinated plaques with well-demarcated lesion borders (figure 4, E–G) and relatively better preserved axons (data not shown). The plaques were characterized by an absence of myelin in the Luxol fast blue, anti-PLP (data not shown), and anti-MBP staining (figure 4H) but contained abundant large preoligodendrocytes that strongly labeled for CNPase (figure 4I) while MOG was almost negative (figure 4J). Cortical plaques were not visible. The inflammatory infiltrates mainly contained CD3- and CD8-positive T cells (figure 4, K and L), and perivascular CD20- and CD79a-positive B cells (figure 4M). The optic chiasm showed demyelination with residual lesion activity with perivascular complement deposition (figure 4N) and was characterized by destructive tissue injury with tissue rarefaction and severe loss of astrocytes in the anti-AQP4, AQP1, and GFAP staining (figure 4, O–Q). One plaque in the medulla oblongata was characterized by selective loss of AQP4 (figure 4R) while AQP1 and GFAP were still preserved (figure 4, S–T). The astrocytes in this lesion showed clasmatodendrosis with beading or loss of cellular processes resulting in rounded astrocytes (figure 4T, magnified sections). Activated complement deposition was not found in these areas.

DISCUSSION We report the case of an acute fatal CNS demyelinating disease with MOG antibodies and postmortem neuropathologic examination. The case shared clinical, imaging, and laboratory features of different demyelinating diseases. Clinically, the patient had an acute inflammatory demyelinating disease with predominant involvement of optic nerves and spinal cord. The older age of the patient is unusual. However, several cases with acute CNS demyelinating diseases in this age group were described before.[16,17] Cerebral and spinal MRI showed lesions of both optic nerves and a longitudinally extensive transverse myelitis compatible with the diagnosis of NMO. However, since there were additional multiple brain lesions with gadolinium enhancement and a negative AQP4 antibody status at disease onset, the 2013 criteria as well as the new, recently published diagnostic criteria of NMO were not met.[18,19] Other potential differential diagnoses of our case were ADEM and MS. In children, diagnostic criteria for ADEM require a demyelinating polyfocal CNS event accompanied by encephalopathy and typical MRI alterations,[20] whereas widely accepted ADEM diagnostic criteria in adults are lacking.[21] In our case, the presence of periventricular T1 hypointense lesions, which are useful to distinguish ADEM from MS,[22,23] argued against diagnosis of ADEM.

Fulminant clinical course, imaging findings, and absence of oligoclonal bands are also not typical for MS and current diagnostic criteria of a relapsing remitting or primary progressive MS were not met.[2]

Figure 4 Neuropathology of MOG and AQP4 antibody-associated demyelinating lesions in the brain



The biopsy specimen revealed a small actively demyelinating lesion (A, arrow in the magnified section indicates macrophages containing LFB-positive myelin degradation products) and inflammatory infiltrates composed of CD68-positive macrophages (B), and CD8-positive T cells (C). One vessel showed perivascular deposits of activated complement complex C9neo (D, arrows). The autopsy tissue showed confluent demyelinating lesions in the brain that were immunohistochemically characterized by loss of MBP (E, rectangle enlarged in H) but contained large preoligodendrocytes that strongly labeled for CNPase (F, rectangle enlarged in I) while MOG was almost negative (G, rectangle enlarged in J; lesion borders highlighted with dotted lines). The inflammatory infiltrates mainly contained CD3-positive (K) and CD8-positive (L) T cells and perivascular CD79a-positive B cells (M). The lesion in the optic chiasm showed perivascular deposits of activated complement complex C9neo (N, arrows) and was characterized by a destructive tissue injury with loss of astrocytes in the anti-AQP4 (O), AQP1 (P), and GFAP staining (Q). One plaque in the medulla oblongata showed a selective loss of AQP4 (R; lesion border highlighted with dotted lines) while AQP1 (S) and GFAP (T) were still preserved. The astrocytes in this lesion showed clasmatodendrosis with beading or loss of processes resulting in rounded astrocytes (T, magnified sections). Magnification: E–G: ×40; A and O–T: ×100; B–D: 200×; H–N and magnified section in T: 400×; magnified section in A: 600×. AQP = aquaporin; CNPase = 2′,3′-cyclic-nucleotide 3′-phosphodiesterase; GFAP = glial fibrillary acid protein; LFB = Luxol fast blue; MBP = myelin basic protein; MOG = myelin oligodendrocyte glycoprotein.

However, neuropathology revealed features of acute MS characterized by destructive lesions with typical hallmarks of pattern II demyelination[24]: well-demarcated demyelinating lesions were characterized by T cell–mediated inflammation, absence of myelin, preserved axons, and complement deposits. Similar to our case, the clinical presentation may lead to the misdiagnosis of ADEM, as it has been shown that 9% of patients with a clinical diagnosis of ADEM had in contrast to ADEM with typical perivenous demyelination, confluent demyelination in histopathology and revealed clinically definite MS in the follow-up.[25]

In our case, inflammatory infiltrates were composed of CD68-positive macrophages and CD3- and CD8-positive T cells in accordance with pattern II demyelination.[24] In contrast to pattern I, the presence of immunoglobulins and complement is a typical finding and indicates the important role of the humoral immune response. The diagnosis of the case presented here was complicated by the fact that both early MOG and late AQP4 antibodies were detected. MOG antibodies were recently shown to be present in a subgroup of AQP4 antibody–negative NMO cases.[12,26] In addition, they have been found in different CNS demyelinating diseases such as ADEM,[7,11,27,28] optic neuritis, transverse myelitis, recurrent optic neuritis,[29,30] and a subgroup of anti-NMDA receptor encephalitis with signs of demyelination.[14] In MOG antibody–positive ADEM cases, NMO typical sites of demyelination (such as longitudinally extensive transverse myelitis/recurrent optic neuritis) seem to be involved more often than in MOG antibody–negative cases.[31,32] The disease course of this patient was fulminant without any signs of improvement and finally fatal. In other studies, MOG antibodies were associated with a more favorable disease outcome,[13,26,33] although patients with antibodies occasionally have severe acute presentations.[9] Because of the possible differential diagnosis of an infectious disease, start of immunomodulatory treatment was delayed and no treatment escalation was induced. These factors in combination with the older age of the patient may have been relevant for the poor outcome.

MOG antibody–positive patients with demyelinating diseases in whom histopathologic results of a biopsy were available are rare,[34,35] and in accordance with our case, pathology showed MS findings of pattern II. Furthermore, in the present case and another case,[34] antibodies mainly belong to the IgG1 subclass with the capability to bind complement. Since MOG was identified as a potential target of antibodies in MS and experimental autoimmune encephalomyelitis,[36] a MOG-specific immunoreactivity in the group of MOG antibody–associated encephalomyelitis seems likely. Although bystander activation cannot be completely excluded, the high immunoreactivity at disease onset and histopathologic evidence of an antibody-mediated disease mechanism supports the hypothesis of a primary involvement of MOG antibodies in disease pathogenesis.

Besides MOG antibodies, our patient also developed AQP4 antibodies and lesions with complement activation and AQP4 loss, indicating AQP4-mediated NMO pathology.[37] Coexistence of AQP4 and MOG antibodies is very rare; only single cases are described in literature.[12,13,33,38] The temporal dynamics of antibodies to AQP4 (first detectable after 9 weeks) and MOG (high titer at disease onset) might indicate that the immune response to AQP4 developed secondary to the release of a new antigen(s). However, severe loss of astrocytes in optic chiasm and selective loss of AQP4 in one brainstem lesion suggests, in addition to the loss of myelin per se, a pathogenic relevant immunoreaction against astrocytes, although typical pathologic findings of NMO were missing. Furthermore, the initial elevation of GFAP as well as MBP levels, markers for astrocyte and myelin damage, respectively, supports a coexisting injury of myelin and astrocytes early at disease onset. A possible explanation for the high GFAP levels at disease onset instead of negative AQP4 antibodies is that AQP4 antibodies were bound to sites of inflammation and not detectable in serum, as described in a patient with very large and fulminant NMO lesions in whom serum AQP4 antibody titers decreased and accumulated in the corresponding CNS lesion.[39] Finally, it is also possible that 2 different pathogenic processes associated with MOG and AQP4 antibodies overlapped in a single patient as has been demonstrated in a subgroup of patients with anti-NMDA receptor encephalitis and demyelinating syndromes with MOG or AQP4 antibodies[14] or the co-occurrence of antibodies to MOG and the glycine receptor α1 subunit in patients with isolated optic neuritis.[40]

In different clinical presentations, MOG antibodies are detectable and MOG antibody–associated diseases seem to be related to an MS pattern II pathology. These findings elucidate the upcoming spectrum of MOG antibody–associated diseases and importantly contribute to the understanding of their pathogenic mechanism.

AUTHOR CONTRIBUTIONS

Case analysis: F.D.P., R.B., E.S., T.B. Neuropathology: R.H., H.L. Antibody analysis: M.R., K.S. MRI: P.R. GFAP and MBP measurements: D.S., K.F. Wrote the manuscript: F.D.P., M.R.

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