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Letter to the Editor

MOG antibody-associated optic neuritis in the setting of acute CMV infection

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Dear Editor,

It has been suggested that cytomegalovirus (CMV) infection can play a significant role in the development of autoimmune diseases. We report the case of a patient with anti-myelin oligodendrocyte glycoprotein (anti-MOG) antibody associated optic neuritis in the setting of acute CMV infection. We discuss the possible role of CMV infection as a trigger for synthesis of anti-MOG antibodies.

1. Case report

A previously healthy 39 year old man was admitted to our hospital with subacute pain and blurred vision in the right eye, in the absence of fever. Physical exam was notable for mydriasis and relative afferent pupillary defect of the right pupil. Visual acuity was 0.5 in the right eye and 1.0 in the left eye. Funduscopic examination of the right eye revealed mild papilledema without concurrent retinitis. Evoked visual potentials were markedly decreased in amplitude on the right side, with P100 latency difficult to assess. Brain MRI revealed longitudinally extensive involvement of the intra-orbital segment of the right optic nerve, as well as one periventricular white matter lesion. Spinal MRI was normal. Cerebrospinal fluid (CSF) analysis disclosed slight dysfunction of the blood-CSF barrier as evidenced by an albumin quotient of 6.9 (age-adjusted upper limit 6.5). CSF cell and protein levels were normal, without oligoclonal bands.

The presence of papillitis prompted the search for an infectious trigger. Positive serum anti-CMV IgM antibodies were found, along with low avidity IgG antibodies (Fig. 1 a,b) and a low CMV viral load (whole blood CMV PCR 300 copies/ml). CSF CMV PCR was negative and there was no evidence of intrathecally produced anti-CMV-antibodies. CSF PCR for HSV, EBV and VZV were negative. HIV, HBV, HCV, EBV, *T. pallidum*, T. gondii, or B. burgdorferi infections as well as an underlying immune deficiency or connective tissue disease were excluded.

The presence of optic neuritis with papillitis in the setting of non-specific brain MRI findings and absent CSF oligoclonal bands also led us to test for the presence of anti-aquaporin-4 and anti-MOG-antibodies. Anti-MOG IgG antibodies were detected in the serum by cell-based assay (CBA) [1]. Their presence was confirmed by a second, independent and blindly analyzed CBA. CSF was negative for anti-MOG-antibodies. Serum and CSF were both negative for anti-aquaporin-4 antibodies (CBA, Euroimmun, Lübeck, Germany).

Antiviral therapy with Ganciclovir 5 mg/kg/12 h IV for 4 days was given in combination with Methylprednisolone 1 g/day IV for 3 days. This was followed by oral antiviral therapy with Valganciclovir 900 mg twice daily for two weeks. There was full recovery of visual acuity and MRI at 6 months follow-up revealed improvement in right optic neuritis.

Longitudinal follow-up of anti-CMV antibodies showed decreasing titers of IgM antibodies with increasing titers of IgG antibodies, paralleled by an increase in anti-CMV IgG avidity (Fig. 1 a,b) and disappearance of CMV viremia. Anti-MOG antibodies were undetectable at 3 and 6 months follow-up (Fig.1 c).

2. Discussion

CMV can affect the optic nerve head by contiguous spread from an adjacent focus of retinitis. CMV-induced optic neuritis in the absence of retinal involvement is considered uncommon. Our patient presented with an acute, longitudinally extensive optic neuritis with papillitis, the combination of which is now recognized to be typical of anti-MOG antibodies associated optic neuritis [2]. These findings led us to consider that the optic neuritis was more likely immune-mediated rather than a direct consequence of CMV infection. We cannot formally distinguish between a primary infection and a reinfection/reactivation. However, given the kinetics of anti-CMV IgM and IgG antibody responses with increasing IgG avidity over time, we think that our patient had a primary infection rather than a reinfection/reactivation.

There is evidence indicating that infectious agents might contribute to the development of autoimmune diseases, most notably by means of molecular mimicry, bystander activation and/or epitope spreading [3]. One publication described a case of neuromyelitis optica (NMO) without

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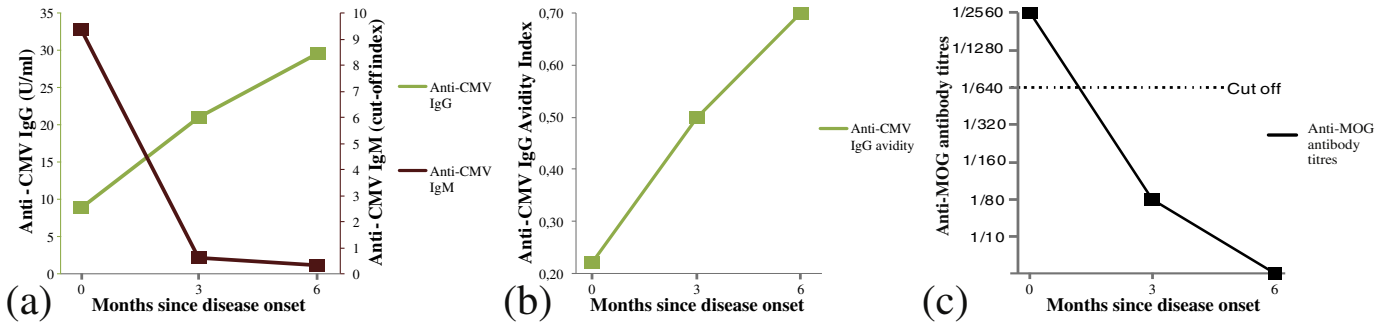

Fig. 1. Evolution of anti-CMV and anti-MOG antibody responses: Measurements of anti-CMV IgM cutoff-index and IgG levels (a), anti-CMV IgG avidity index (b) and titers of anti-MOG antibody (c) at disease onset, 3 months and 6 months follow-up. Anti-CMV IgM and IgG titers were measured with COBAS 6000® analyzers using a standardized method developed by Roche Ltd. CMV IgG avidity index was measured with a VIDAS 30® panel provided by Biomérieux Ltd.; the results were interpreted as follows: CMV IgM: Negative < 0.7cut-off index (COI); indeterminate ≥ 0.7 to < 1.0 COI; positive ≥ 1.0 COI. CMV *IgG*: negative < 0.5 U/mL; indeterminate ≥ 0.5 to < 1.0 U/mL; positive > 1.0 U/mL. IgG CMV avidity: low < 0.40; intermediate ≥ 0.40 to < 0.65; high ≥ 0.65. Anti-MOG antibodies detection was performed using HEK293 cells transfection with full-length MOG and flow cytometry analysis, at the Immunology Laboratory of the University of Lyon, France [1].

anti-aquaporin-4-antibodies in an immunocompetent adult patient with acute CMV infection [4]; MOG antibody status was not mentioned in that particular case report. In another study analyzing a large cohort of MOG IgG positive patients, disease onset was preceded by nonspecific infections in 11 out of 50 patients [2]. No specific infectious agent was mentioned except for one *Yersinia* spp. positive serology. Two other case studies reported preceding EBV and Influenza A virus infections linked to the onset of anti-MOG antibody positive myelitis [5,6].

Cross-reactivity between CMV and MOG peptides was observed in the Lewis rat model of experimental autoimmune encephalomyelitis [7]. Furthermore, immunization of rhesus monkeys with a CMV peptide induced the production of MOG-reactive T cells [8]. These findings provide some indirect evidence for the molecular mimicry hypothesis. In addition, CMV has been shown to drive the expansion of T-cell subpopulations with a cytotoxic and pro-inflammatory phenotype [3]. We acknowledge, however, that the formal link between CMV infection, the production of anti-MOG antibodies and the occurrence of optic neuritis remains speculative.

The transient positivity of anti-MOG antibodies (due to natural disease course and/or treatment effects) has been reported in the literature. One study found that 4 out of 22 patients exhibited a temporary decrease in MOG-IgG titers below the cut-off level [9]. In another study, up to 56% of anti-MOG antibody positive patients had no detectable antibodies during remission [10]. In our case it remains unclear whether or not the prompt initiation of antiviral therapy had an impact on the disappearance of anti-MOG antibodies. Moreover, we cannot ascertain the respective beneficial role of antiviral therapy over immunosuppression. These are important questions that would be best explored in a large prospective cohort.

Currently, there are no established guidelines regarding the treatment of anti-MOG antibody positive patients presenting after a first episode of CNS demyelination. Our patient was not started on long-term immunosuppressive treatment owing to the disappearance of anti-MOG antibodies.

3. Conclusion

To our knowledge, this is the first published case of anti-MOG antibody associated optic neuritis in the setting of acute CMV infection. It is likely that the optic neuritis was virally-triggered, but further research is needed to understand the role of infectious agents in the development of autoimmunity.

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