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Case report

Transient MOG antibody seroconversion associated with immunomodulating therapy

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A B S T R A C T

Immunoglobulin G (IgG) autoantibodies targeting myelin oligodendrocyte glycoprotein (MOG) have recently been associated with autoimmune CNS demyelination. We present the case of a 35-year-old patient who was seronegative for MOG-IgG (as confirmed by means of three independent immunoassays) during two corticosteroid-responsive attacks of brainstem encephalitis and optic neuritis, respectively, but turned positive for MOG-IgG under treatment with interferon-beta (IFN-beta), which was commenced 6 months after onset of the first attack. MOG-IgG serum levels declined after therapy was switched to glatiramer acetate. The fact that seroconversion was first observed under treatment with IFN-beta is in accordance with previous evidence suggesting a role of IFN-beta in disease exacerbation in antibody-mediated disorders.

1. Introduction

Recently a robust association of immunoglobulin G (IgG) antibodies to full-length human myelin oligodendrocyte glycoprotein (MOG) with optic neuritis (ON), myelitis, brainstem encephalitis, and acute disseminated encephalomyelitis has been demonstrated (Palace et al., 2010), MOG-IgG-positive encephalomyelitis (MOG-EM) shows a substantial phenotypical overlap with both anti-aquaporin-4 (AQP4)-IgG-positive neuromyelitis optica spectrum disorders (NMOSD) and multiple sclerosis (MS) (Höftberger et al., 2015). However, based on differences in immunopathology, clinicoradiological presentation, optimum treatment and prognosis, MOG-EM is now regarded an independent disease entity. Empirically and based on case series patients with MOG-EM are treated with intravenous steroids and plasma exchange for acute attacks and with B-cell-depleting and other immunosuppressive treatments for attack prevention (Jarius et al., 2016). In AQP4-positive NMOSD, treatment with a number of MS-approved drugs, including interferon-beta (IFN-beta), seems to be associated with increased relapse probability (Palace et al., 2010). Preliminary data suggest that IFN-beta might have detrimental effects also in MOG-EM (Jarius et al., 2016).

Here, we describe the case of a patient with relapsing-remitting demyelinating disease of the brain stem and optic nerve who was negative at onset but turned positive for MOG-IgG after commencement of IFN-beta treatment, as confirmed by means of three independent cell-based assays utilizing HEK293 cells transfected with full-length human MOG.

2. Case presentation

In July 2015, a 35-year-old patient first presented with acute horizontal, binocular diplopia due to abducens nerve palsy on the left side. Magnetic resonance imaging (MRI) of the brain and spinal cord showed a singular, contrast-enhanced lesion within the left ventral

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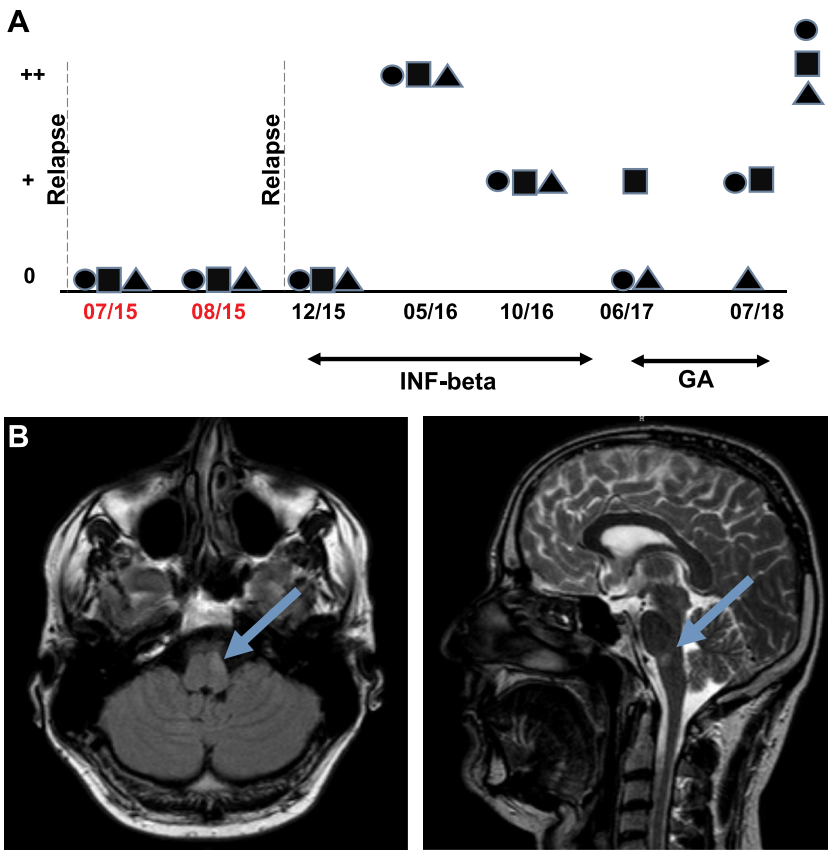

Fig. 1. A: Chart shows the course of MOG-IgG analysis in three different laboratories over time (0: negative, +: positive, + +: highly positive); At the times marked in red, additional analyses of MOG-IgG were performed in cerebrospinal fluid, all were negative. Bars present immunomodulatory treatments regimes (INF-beta: Interferon-beta, GA: glatiramer acetate). Laboratory 1 = Neuroimmunology, Institute of Clinical Chemistry, University Hospital Schleswig-Holstein, Kiel, Germany; Laboratory 2 = Neuroimmunology Group, Department of Neurology, University of Heidelberg, Germany; Laboratory 3 = Clinical Department of Neurology, Medical University of Innsbruck, Innsbruck, Austria **B:** Panel displays MRI (T2-FLAIR) examination during first relapse, indicating the infratentorial lesion.

pontomedullary junction without additional focal abnormalities (Fig. 1). Cerebrospinal fluid (CSF) analysis demonstrated pleocytosis (25 cells/µl) and CSF-restricted oligoclonal bands indicating intrathecal IgG production. Antibody indices for Borrelia burgdorferi and neurotropic viruses, in particular the MRZ (measles virus, rubella virus and varicella zoster virus) reaction, a highly specific marker of MS, were negative. Serum and CSF MOG-IgG were negative when tested by means of a live cell-based assay (CBA) (University of Kiel, Germany) (Fig. 1) (Höftberger et al., 2015); AQP4-IgG were negative as well. Symptoms remitted completely after intravenous pulse therapy of high dose methylprednisolone (1000 mg/d over 5 days). A control examination of CSF and serum two weeks later again showed negative results for MOG-IgG and AQP4-IgG. After 6 months, the patient developed corticosteroid-responsive left retrobulbar ON without signs of additional demyelinating MRI lesions. Once more, we documented pleocytosis (20 cells/µl), CSF-restricted oligoclonal bands, negative MRZ reaction and an absence of serum anti-MOG ab. A diagnosis of relapsing-remitting MS was made and treatment with IFN-beta1a was initiated in December 2015. MOG-IgG testing was repeated at a follow-up visit during clinical remission in May 2016 and was for the first time positive. Testing of a further sample obtained in October of 2016 confirmed MOG-IgG seroconversion. The positive test results were retrospectively confirmed in two further laboratories (University of Heidelberg, Germany; Medical University Innsbruck, Austria) by means of two methodologically different CBAs (2 x live CBA, 1 x fixed CBA; 1 x H + L chain-specific secondary antibody; 1 x Fc receptor-specific secondary antibody), as were the negative results obtained in July, August and December 2015 (Fig. 1). The initial serum samples were retrospectively found to be negative also for MOG-IgG1, MOG-IgG2, MOG-IgG3, MOG-IgG4, MOG-IgA and MOG-IgM MOG-IgG, -IgA and -IgM were retrospectively also absent in two CSF samples taken at disease onset. We suspected IFN-beta-induced, increased autoantibody production and switched the disease modifying therapy to glatiramer acetate. At repeat testing in June and July 2017 MOG titers had declined (still weakly positive in two assays and slightly below cut-off in one). Under either immunomodulating therapy, no clinical evidence of disease activity could be detected. The therapy was not switched again, because the patient showed no worsening (last follow up: 01.07.2019).

3. Discussion

The late seroconversion observed in this patient is highly unusual. In typical MOG-EM, MOG-IgG is detectable already at disease onset (Di Pauli et al., 2011; Spadaro et al., 2016), although MOG-IgG titres may decline during remission and under treatment (Jarius et al., 2016). By contrast, MOG-IgG was negative in samples obtained during two acute attacks and prior to steroid or immunosuppressive treatment but turned positive during remission. Seroconversion was confirmed by use of three methodologically independent assays. Moreover, a further sample, which was obtained during acute ON, was tested in all three assays and was negative in all of them.

It is difficult to interpret these findings. The patient's symptoms as well as MRI and CSF findings were compatible with MOG-EM (ON and brainstem encephalitis; MRI otherwise normal, in particular no Dawson's finger lesions, no ovoid periventricular lesions, no lesions in the inferior temporal lobe, no juxtacortical U fibre lesions; negative MRZ reaction; MOG-IgG-positive serostatus). It is therefore at least possible that the patient's disease was caused by MOG-IgG. This would imply that MOG-IgG may be pathogenic at levels below the detection levels of the currently used cell-based assay. Alternatively, however, the initially negative MOG-IgG results may reflect genuine absence of MOG-IgG at onset. In that case, two scenarios are conceivable: 1.) The immune response was targeted at MOG from the beginning, but was initially mainly driven by T cells, with antibodies to MOG occurring only later. 2.) ON and brainstem encephalitis were not at all caused by autoimmunity to MOG, but MOG-IgG occurred as a secondary phenomenon not directly related but triggered by intralesional exposure and release of MOG protein or, less likely, as a result of cross reactivity

due to epitope spreading. The fact that the patient did not develop any new signs or symptoms of MOG-EM after seroconversion argues in favour of (but by no ways proves) the latter hypothesis. In both cases, it would be tantalizing to speculate that IFN-beta was involved in seroconversion: IFN-beta is thought to cause a so-called Th1/Th2 shift in cytokine levels, which promotes autoantibody synthesis (Wandinger et al., 2001). Moreover, it could be shown that IFN-beta treatment induces upregulation of B-cell activating factor (BAFF), a crucial survival factor for B cells, and thus may facilitate the production of autoantibodies (Krumbholz et al., 2008). In patients with AQP4-IgG-positive NMOSD as well as in patients with MOG-EM, an increase in autoantibody levels as well as disease exacerbation has been reported following treatment with IFN-beta (Palace et al., 2010).

This case is not only of immunopathophysiological interest but has potentially important diagnostic implications. As we cannot rule out that the patient's disease was caused by autoimmunity to MOG, we have to acknowledge that, in a subset of patients, MOG-EM may possibly only develop in the later course of the disease. With increasing evidence for differences in the optimum treatment of MS on the one hand and NMOSD and MOG-EM on the other hand (Jarius et al., 2016) careful selection of treatment regiments becomes increasingly important. As highlighted in a recent consensus paper on MOG-EM (Jarius et al., 2018), repeat testing of patients seronegative for MOG-IgG should thus be considered in patients with clinical and/or paraclinical features suggestive of MOG-EM but initially negative MOG-IgG serostatus to solidify diagnostic classification. As patients with MOG-EM often meet the clinicoradiological criteria for MS, repeat testing should be taken into consideration not only in patients with unclassified demyelinating disease of the CNS, but also in patients with an established diagnosis of MS. An extensive list of clinical and paraclinical features that are suggestive of MOG-EM and which should thus prompt testing for MOG-IgG in patients presenting with acute CNS demyelination of putative autoimmune aetiology can be found in reference (Jarius et al., 2018).

Ethical publication statement

We confirm that we have read the journal's position on issues regarding publication ethics and that this report is consistent with those guidelines.

Declaration of Competing Interest

MP received speaker honoraria from Roche, Genzyme and Novartis as well as travel/accommodation/meeting expenses from Novartis, Biogen Idec, Genzyme and Merck Serono. CC reports no conflict of interest. LR received travel reimbursements from Merck Serono and Sanofi Genzyme. HH reports no conflict of interest. FL received speaker honoraria and travel/accommodation/meeting expenses from Biogen, Grifols, Teva, Roche, Fresenius and Merck and is working in an institute in which studies on antineuronal antibodies are performed. KPW is working in an institute in which studies on antineuronal antibodies are performed. The University Hospital and Medical University of Innsbruck (Austria, employer of MR) receive payments for antibody assays (MOG, AQP4, and other autoantibodies) and for MOG and AQP4 antibody validation experiments organized by Euroimmun (Lübeck, Germany). BW has received research grants and/or honoria from Merck Serono, Biogen, Teva, Novartis, Sanofi Genzyme, and Bayer Healthcare, and research grants from the Dietmar Hopp Foundation, the Klaus Tschira Foundation, the German Federal Ministry of Education and Research (BMBF; FKZ 01GI1602A), and Deutsche Forschungsgemeinschaft (DFG). The work of SJ was indirectly supported by research grants from the Dietmar Hopp Stiftung (to BW) and Merck Serono, Germany (to BW). PK reports no conflict of interest.

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