Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disease and Varicella Zoster Virus Infection - Frequency of an Association

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To determine whether there is a correlation between myelin oligodendrocyte glycoprotein (MOG) antibody-associated diseases and varicella zoster virus (VZV) infection. We provide a case report and performed a study to determine the frequency of MOG antibodies (MOG-IgG) in neurological VZV infections. Patients admitted to the Medical University of Innsbruck from 2008–2020 with a diagnosis of a neurological manifestation of VZV infection (n=59) were included in this study; patients with neuroborreliosis (n=34) served as control group. MOG-IgG was detected using live cell-based assays. In addition, we performed a literature review focusing on MOG and aquaporin-4 (AQP4) antibodies and their association with VZV infection. Our case presented with VZV-associated longitudinally extensive transverse myelitis and had MOG-IgG at a titer of 1:1280. In the study, we did not detect MOG-IgG in any other patient neither in the VZV group (including 15 with VZV encephalitis/myelitis) nor in the neuroborreliosis group. In the review of the literature, 3 cases with MOG-IgG and additional 9 cases with AQP4 IgG associated disorders in association with a VZV infection were identified. MOG-IgG are rarely detected in patients with VZV infections associated with neurological diseases.

Keywords: AQP-4-IgG, MOG-IgG, MOG antibody associated diseases, longitudinally extensive transverse myelitis, varicella zoster virus infection, neuromyelitis optica spectrum disorder

1 INTRODUCTION

Varicella zoster virus (VZV) is an exclusively human neurotropic herpes virus, presents with chickenpox (varicella) as inaugural infection, and remains latent in the dorsal root ganglions, cranial nerves, and the autonomic nervous system, and upon reactivation, results in rash and pain in one or more dermatomes, known as shingles (herpes zoster). This would occur often decades after the primary infection, particularly in susceptible immunocompromised patients, and older patients due to immunosenescence (1).
Typical VZV neurological complications include postherpetic neuralgia, VZV vasculopathy, cranial nerve neuropathy, and radiculopathy (2). Central nervous system (CNS) demyelinating-inflammatory diseases, such as myelitis and encephalitis, are rare complications in primary VZV infection and VZV reactivation (3, 4). It has been suggested that VZV myelitis is caused by direct viral invasion of the spinal cord and cell lysis (5). However, there is mounting evidence for an immune-mediated mechanism, as there are several case reports of aquaporin-4 antibody (AQP4-IgG) positive neuromyelitis optica spectrum disorder (NMOSD) following VZV infection (6–13). Recently, in addition to AQP4-IgG associated NMOSD, the identification of myelin oligodendrocyte glycoprotein (MOG) antibodies has broadened the spectrum of antibody-associated CNS demyelinating-inflammatory diseases that are distinct from classical multiple sclerosis (1-4). Similar to the identification of AQP4-IgG following VZV infection, some case reports described MOG-IgG antibody-associated disease (MOGAD) following VZV, influenza A, or herpes simplex virus infection (15-18).

However, until now, there has been no systematic analysis about the association of MOG-IgG and neurological manifestations of VZV infection. Here, we describe a patient with MOG-IgG positive VZV-associated longitudinally extensive transverse myelitis (LETM), perform a study to determine the MOG-IgG frequencies in patients with VZV infection and neurological involvement and present the results of a literature review.

2. MATERIALS AND METHODS

2.1 Patients and Samples

The retrospective study included 59 patients who were admitted to the Medical University of Innsbruck between 2008 and 2020 with the diagnosis of a neurological manifestation due to VZV infection and had an available serum sample of at least 500 µl. Diagnosis of VZV infection with neurological involvement (i.e., meningitis, encephalitis, myelitis, encephalomyelitis, cranial nerve or/and segmental zoster paresis) was based on the presence of typical dermatomal rash followed by neurological symptoms and supported by laboratory findings (elevated CSF cell count, positive VZV DNA in the cerebrospinal fluid (CSF)) as determined by polymerase chain reaction (PCR), or increased CSF VZV-IgG) (19, 20). CNS involvement was defined as encephalitis or myelitis or a combination of both. In the absence of a typical rash, diagnosis was always based on a positive CSF VZV DNA and CSF pleocytosis.

Patients with neuroborreliosis [previously published (21)] were included as control group (n=34), as this is also a disease entity of infectious origin that might affect the CNS as well as the PNS, and also typically shows elevated CSF cell count and disrupted blood-CSF-barrier as indicated by elevated Qalb. In addition, there is no known association of neuroborreliosis with AQP4 or MOG antibodies. Briefly, these patients were admitted to Medical University of Innsbruck between 2009 and 2016 and received diagnosis of neuroborreliosis according to EFNS criteria (22). Diagnosis was based on typical neurological symptoms, appropriate routine CSF findings (pleocytosis, blood-CSF barrier impairment, and/or intrathecal synthesis of immunoglobulins), and intrathecal synthesis of borrelia-specific IgG antibodies [antibody specificity index (ASI) >1.5] (22).

Results of routine diagnostic procedures, clinical, magnetic resonance imaging (MRI), and CSF data were collected. Routine CSF work-up comprised red blood cell (RBC) and white blood cell (WBC) count, CSF total protein concentration, CSF/serum albumin quotient, and CSF and serum IgG, IgM, and IgA concentrations. Intrathecal synthesis of IgG, IgM and IgA were calculated by the Auer and Hegen formula (23) and expressed as percentage intrathecal fraction. IgG index was calculated as [CSF IgG/serum IgG]/[CSF albumin/serum albumin]. CSF was collected by lumbar puncture and blood by simultaneously peripheral venous puncture. Serum was isolated from blood by centrifugation after the blood samples were allowed to clot for ≥30 min. All samples were centrifuged at 2000 g for 10 min at room temperature.

2.2 MOG-IgG Assay

The presence of MOG-IgG was determined by live cell-based immunofluorescence assay with HEK293 cells transfected with full-length human MOG (alpha-1 isoform), as previously described (24). Screening for serum antibodies was performed at 1:20 and 1:40 dilutions by two independent investigators blinded for the clinical diagnosis. An isolated IgM reactivity was excluded by the use of heavy chain-specific secondary antibodies against IgG (Dianova, Hamburg, Germany) (24).

2.3 Ethics

The study was approved by the Ethics Committee of the Medical University of Innsbruck (approval number AM3041A). Written informed consent was obtained from all patients. Authorization has been obtained for disclosure (consent to disclose) from the index case patient.

2.4 Statistics

Statistical analysis was performed using SPSS 26.0 (SPSS Inc, Chicago, IL, USA). Non-parametric data were displayed as median and interquartile range. Categorical variables were reported as frequency and percentage. For group comparisons, Mann-Whitney-U and χ2 tests were applied, as appropriate. Two-sided P-values <0.05 were considered statistically significant.

2.5 Literature Review

We conducted a literature search in MEDLINE and Google Scholar. Search terms were: VZV AND MOG or AQP4 or NMOSD or LETM; herpes zoster AND MOG or AQP4 or NMOSD or LETM. Abstracts that primarily did not deal with VZV infection and MOGAD or NMOSD or LETM were excluded. In addition, articles identified in reference lists of the individual papers were selected if considered appropriate.

3 RESULTS

3.1 Index Case

A 30-year-old, previously healthy man presented in 2019 with sensomotor paralytic syndrome (sensory level below T6),
subsequent gait ataxia and neurogenic bladder disturbance requiring catheterization at our emergency department. Six days before the first neurological symptoms, the patient had developed herpes zoster infection (dermatome T6 right side) treated by his general practitioner with oral acyclovir (5 days, 3 x 1000 mg per day orally). There was no history of constitutional symptoms or a recent vaccination. A MRI of the spinal cord showed a T2 hyperintense lesion extending from T1 to conus medullaris confined to gray matter (Figure 1) with only a very faint contrast enhancement, whereas brain MRI was normal. CSF analysis revealed lymphocytic pleocytosis with a WBC count of 101 cells/μl, and oligoclonal bands were negative. Despite the VZV DNA PCR results being negative, the CSF VZV antibody-specific index (ASI) was highly elevated (9.4). However, in addition, MOG-IgG in serum were positive at high titer (1:1280), while AQP4-IgG were absent. Further diagnostic work-up to determine immune deficiency or a malignancy was negative (including a whole body 18F-fluorodeoxyglucose positron emission tomography-computed tomography, human immunodeficiency virus screening, serum immunoglobulin levels, flow cytometry of peripheral blood). MOG-IgG associated LETM following VZV infection was diagnosed, and the patient was treated with a combination of high-dose methylprednisolone (10 days: 1,000 mg for 3 days, 500 mg for 4 days, 250 mg for 3 days) followed by oral tapering and intravenous acyclovir (3 x 750 mg for 10 days, 3 x 500 mg for 8 days followed by oral acyclovir 3 x 1000 mg for 5 days). Thereafter, no further disease-modifying or immunosuppressive therapy was started. After three months, the MOG-IgG titer had decreased to 1:320, and MOG-IgG was undetectable after another five months. Except for mild neurogenic bladder dysfunction, there was complete clinical and imaging remission without further relapses after an 18-month follow-up. EDSS improved from an initial score of 3.5 to 1.0 at 18-month follow-up.

3.2 Retrospective Study
3.2.1 Demographic, Clinical, and Main Cerebrospinal Fluid Characteristics
A total of 59 patients with neurological involvement due to VZV infection and 34 patients with neuroborreliosis were included into this study (Figure 2). Demographic and main clinical...
characteristics of patients with VZV infection and CNS involvement are shown in Table 1, those of patients with neuroborreliosis elsewhere (21). Fifteen patients with a VZV infection (25.4%) presented with either myelitis (n=6; one patient with a LETM), encephalomyelitis (n=1), or encephalitis (n=8). Parenchymal CNS involvement occurred in three (8.8%) of the patients with neuroborreliosis. Patients with neuroborreliosis (median age 46 years, interquartile range [IQR] 10.4–65.6) were younger than patients with VZV infection (median age 63 years, IQR 45.5–76, p<0.001), while males and females were equally distributed in both disease groups (p=0.610). The average interval between typical VZV-associated rashes and neurological symptoms was 7 days (range 2–12). In Table 2, the main CSF findings of VZV infection with CNS involvement and neuroborreliosis are shown. In both diseases, the WBC count was increased, although the WBC count was significantly higher in patients with neuroborreliosis. Intrathecal IgG and IgM fraction (%) was significantly elevated in patients with neuroborreliosis compared to patients with VZV infection.

3.2.2 MOG-IgG in VZV Infection With CNS Involvement

All patients – those with VZV infection with CNS involvement and those with neuroborreliosis – were negative for serum MOG-IgG. One patient with VZV infection and radiculitis had a borderline MOG-IgG positive titer of 1:160. This result was not confirmed by using heavy chain–specific secondary antibodies and was therefore regarded as negative.

3.3 Literature Review

We identified 2 case reports (15, 25) and 1/10 patients in a case series (20) with MOG antibody-associated myelitis in association with a VZV infection; in addition, there are 9 reports of AQP4 antibody-associated CNS disorders in patients with VZV infections (6–13, 20) (Table 3).

4 DISCUSSION

Here, we present a case with MOG-IgG associated LETM triggered by VZV infection. In a subsequent retrospective study of 59 patients with VZV infection and neurological involvement; however, we did not found MOG-IgG in any patient (including 15 with VZV encephalitis/myelitis).

MOG-IgG are more often present in children than in adults and are associated with a variable clinical spectrum. Typical clinical presentation of MOGAD, particularly in children, is an acute disseminated encephalomyelitis (approximately 50%), whereas in adults myelitis (up to 30%) or optic neuritis (up to 50%) are more common (14, 26–28). Similar to our case, MOG-IgG associated myelitis is characterized in the MRI by longitudinally extensive T2 hyperintense lesions affecting mainly the grey matter and lack of contrast enhancement (29). MOG-IgG case reports showing an association between MOGAD and VZV infection are rare. Two case reports

**TABLE 1** | Demographic and clinical data of patients with varicella zoster virus infection with central nervous system involvement.

|                          | Number (Percentage) |
|--------------------------|---------------------|
| **Sex (female), n (%)**   | 28 (47.5%)          |
| **Age (years), median (IQR)** | 63 (45.5–76)       |
| **Clinical presentation, n (%)** | 32 (54.2%)     |
| - Poly/radiculitis or cranial neuritis | 32 (54.2%)     |
| - Isolated meningitis     | 12 (20.3%)          |
| - Myelitis, encephalomyelitis, or encephalitis | 12 (20.3%)     |
| - Combination radiculitis or cranial neuritis with myelitis/encephalitis or encephalomyelitis | 3 (5.1%)      |
| **Days between rash and neurological symptoms, median (IQR)** | 7 (2–12)        |
| **Typical VZV associated rash, n (%)** | 53 (89.8%)       |
| **Diagnosis based on, n (%)** | 44 (74.6%)       |
| - Positive VZV DNA PCR   | 44 (74.6%)          |
| - Typical clinical features and elevated CSF cell count | 3 (5.1%)        |
| - Increased CSF VZV IgG  | 12 (20.3%)          |

VZV, varicella zoster virus; IQR, interquartile range; n, number.

**FIGURE 2** | Inclusion flowchart VZV infection with neurological involvement. * Negative CSF VZV specific antibody index, VZV DNA PCR and normal CSF cell count.

CSF, cerebrospinal fluid; VZV, varicella zoster virus.
described the occurrence of LETM after herpes zoster and chicken pox, respectively (15, 25) (Table 3). In only one patient, the VZV DNA PCR result was available and reported as positive. In our case, the VZV DNA PCR result was negative, which may have been due to the preceding acyclovir therapy (6 days). However, elevated WBC count and a highly increased CSF/serum albumin ratio in herpes zoster (31). As CSF analysis of MOG-IgG improve the sensitivity by 7%, parenchymal involvement were negative for MOG-IgG (n=44). A possible hypothesis for MOG and AQP4 antigens (30). A possible hypothesis for MOG and AQP4 association in the two relapsing patients, no VZV reactivity was observed. Given the rising number of cases with the presence of MOG-IgG or AQP4-IgG and the typically delayed onset of neurological symptoms (Table 3) after the rash, immune-mediated genesis seems likely. The mechanisms suspected to be involved in triggering autoimmunity after infection are molecular mimicry, bystander activation, epitope spreading, and the release of cryptic antigens (30). A possible hypothesis for MOG and AQP4 antibody-associated autoimmunity triggered by a VZV infection is that the VZV infection causes a breakdown of the blood-brain barrier, as indicated by the common finding of an elevated CSF/serum albumin ratio in herpes zoster (31). Subsequently, CNS antigen is released into the periphery, which induces an immune reaction against self-antigens by autoreactive B and T cells.

A limitation of our study is the retrospective design and small number (n=15) of patients with myelitis, encephalomyelitis, or encephalitis. However, data specifically excluded a nonspecific bystander reaction, as patients with VZV infection without parenchymal involvement were negative for MOG-IgG (n=44). As CSF analysis of MOG-IgG improve the sensitivity by 7%, another limitation is that MOG-IgG was only tested in patient sera (32).

Overall, we showed that the presence of MOG-IgG is a rare finding in patients with a VZV infection complicated by CNS demyelinating-inflammatory diseases. Nevertheless, due to

### Table 2 | Cerebrospinal fluid characteristics of patients with varicella zoster virus infection and neuroborreliosis.

|                         | VZV infection | Neuroborreliosis | p-value*
|-------------------------|--------------|-----------------|--------
| RBC count (cells/μL)    | 2 (0–21)     | 4 (0–7)         | 0.719  |
| WBC count (cells/μL)    | 99 (18–274)  | 154 (105–216)   | 0.037  |
| CSF/serum glucose ratio | 0.55 (0.48–0.67) | 0.53 (0.44–0.65) | 0.227  |
| CSF total protein (mg/dL) | 67 (46–102)  | 102 (46–179)    | 0.132  |
| IgG index, median (IQR) | 0.58 (0.51–0.66) | 0.79 (0.62–1.01) | <0.001* |
| Intrathecal IgA synthesis, median (IQR) | 0 (0–0) | 2.02 (0–25.56) | <0.001* |
| Intrathecal IgG synthesis, median (IQR) | 0 (0–0) | 0 (0–6.39) | 0.059 |
| Intrathecal IgM synthesis, median (IQR) | 0 (0–0) | 42.54 (0–66.4) | <0.001* |
| VZV antibody index, median (IQR) | 2.1 (0.6–3.1) | na | na |
| Borrelia antibody index, median (IQR) | na | 23.6 (7.5–43.8) | na |

Data from: 1 90 cases, 2 85 cases, 3 31 cases (18 cases>1.5). CSF WBC and RBC were counted within the Fuchs-Rosenthal chamber (volume of 3.2 μL). Counts are reported as “cells/μL.” (correction for a standard volume of 1 μL, was achieved by dividing by 3.2), CSF, cerebrospinal fluid; IQR, interquartile range; n, number; na, not applicable; PCR, polymerase chain reaction; RBC, red blood cell; WBC, white blood cell; Qalb, CSF/serum albumin quotient; VZV, varicella zoster virus.

*calculated by Mann-Whitney U test, uncorrected p-values are shown, after Bonferroni correction still significant at a level of 0.05.
| Case   | Clinical phenotype                      | Neurological symptoms                                                                 | Presence of rash | Time of onset after Rash in days | Level rash | VZV DNA PCR | Presence/absence of VZV-IgG/IgM elevation | Imaging findings                                                                 | Antibody status                  | Follow-up                                                                 | Reference |
|--------|-----------------------------------------|---------------------------------------------------------------------------------------|------------------|---------------------------------|------------|-------------|------------------------------------------|--------------------------------------------------------------------------------|----------------------------------|--------------------------------------------------|-----------|
| Cases with MOG IgG |                                        |                                                                                       |                  |                                 |            |             |                                          |                                                                               |                                   |         |
| Male, 69 a | LETM                                  | Paraparesis                                                                            | +                | 10                              | Left L2-3 dermatome | +            | nK                                      | Lesion from the bottom of the medulla oblongata to the upper (T2) thoracic region | MOG-IgG +, cell-based-assay |                  | (15)       |
| Female, 34 a | Myelitis                              | Paraparesis, loss of pain and temperature sensation below her groin, absent vibration sense in both lower limbs | primary VZV infection | 21 | na | nd | nd |                      |                                                                               | MOG-IgG +                        |                  | (25)       |
| Female, 42 a | LETM                                  | nk                                                                                    | +                | 1                               | C dermatome | nK            | Increased VZV IgM                        | Leptomeningeal contrast enhancement | MOG-IgG +                    | (20)       |
| Male, 30 a | LETM                                  | Sensomotor paralytic syndrome (sensory level below T6), subsequent gait ataxia, neurogenic bladder disturbance | +                | 6                               | Right T6 dermatome | –            | CSF VZV ASI increased (9-4) | Lesion: T1 to the conus medullaris with only a very faint                       | MOG-IgG +, (1:1280), cell-based assay |                  | Present case |
| Cases with AQP4 IgG |                                        |                                                                                       |                  |                                 |             |             |                                          |                                                                               |                                   |         |
| Female, 63 a | LETM                                  | Paraparesis (3-4/5) and mild hypesthesia of the left leg, sensory impairment for temperature and pain of the right leg and the trunk below level T10, urine incontinence | +                | 14                              | Along the lumbar spine | –            | CSF VZV ASI normal                        | Lesion from C7 to Th9 with marked oedema and moderate gadoilin enhancement    | AQP4-IgG +, tissue-based indirect immunofluorescence assays |                  | (7)        |
| Female, 51 a | LETM                                  | Decreased power (3/5), hyperreflexia along with sensory loss in the right upper and lower extremity, hypesthesia in the entire left lower extremity | +                | 49                              | Right C5 dermatome | –            | nK                                      | Enhancing intramedullary lesion C2 -4, centrally into the right of the midline with signal changes at the T1 level without enhancement or expansive appearance | AQP4-IgG first attack (nd, relapse + (>1:160) |                  | (6)        |
| Female, 59 a | LETM                                  | nk                                                                                    | +                | 15                              | C dermatome | nK            | Increased VZV IgM                        | Myelitis: C1-6                        | AQP4-IgG +                    | (20)       |
| Female, 29 a | LETM                                  | Acute quadriplegia                                                                    | +                | 7                               | Left T4-6 dermatomes | –            | Increased VZV IgM                        |                                                                               | AQP4-IgG first attack (nd, relapse + (1:180), tissue-based indirect immunofluorescence assays |                  | (9)        |
| Female, 77 a | LETM                                  | Paraparesis, sensory level by L4, urine retention                                      | +                | 2                               | Left L4-S1 dermatomes | +            | nK                                      | Lesion extending from C2-C3 to T12 with no gadolinium enhancement              | AQP4-IgG first attack (nd, relapse + indirect immunofluorescence serum assay (1:10) |                  | (10)       |
| Female, 48 a | LETM                                  | Right arm abduction paraparesis, brisk reflexes in the lower limbs, diminished reflexes in the upper limbs, extensor plantar response bilaterally | +                | 14                              | Right C6 dermatome | –            | nK                                      | Cervical LETM                        | AQP4-IgG positive, cell-based assay |                  | (11)       |

(Continued)
therapeutic implications, antibody screening is a useful tool, particularly in patients with a higher pre-test probability, e.g. with LETM. Further prospective larger studies, including children, are required to analyze the frequency of neurological antibody-associated diseases triggered by VZV infection.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Medical University Innsbruck. Written informed consent to participate in this study was provided by the participants’ legal guardian/next of kin. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

FDP conceptualized the study, collected data, case analysis, statistical analysis, drafted the manuscript, and revised the manuscript for intellectual content. PM collected data and revised the manuscript for intellectual content. KB collected data and revised the manuscript for intellectual content. MA collected data and revised the manuscript for intellectual content. AB collected data and revised the manuscript for intellectual content. TB case analysis and revised the manuscript for intellectual content. GB collected data and revised the manuscript for intellectual content. PR MRI analysis and revised the manuscript for intellectual content. KS collected data and revised the manuscript for intellectual content. AZ collected data and revised the manuscript for intellectual content. FDe case analysis, conceptualized the study, and revised the manuscript for intellectual content. MR conceptualized the study, and revised the manuscript for intellectual content. HH conceptualized the study, collected data, case analysis, statistical analysis, drafted the manuscript, and revised the manuscript for intellectual content. All authors contributed to the article and approved the submitted version.

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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