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Clinical analysis of MOG antibody-associated disease overlapped with anti-NMDA receptor encephalitis: a long-term retrospective study

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Abstract

Abstract Objective: To summarize the clinical characteristics, radiological features, treatments, and prognosis of patients with myelin oligodendrocyte glycoprotein (MOG) antibody associated disease (MOGAD) overlapped with NMDA receptor (NMDAR) encephalitis. Methods: We retrospectively analyzed patients who exhibited dual positivity for MOG antibodies and NMDAR antibodies in serum/CSF from Jan 2018 to Jun 2023 Results: Ten patients with MOGAD and NMDAR encephalitis were enrolled. The median age of initial attacks was 23 (range: 10-43) years old. Common symptoms were cortical encephalopathies (8/10), focal neurological deficits (4/10), as well as other presentations including headache, fever, optic neuritis, and transverse myelitis. CSF pleocytosis was general (9/10, median 63.9 cells/μl). Lesions on brain MRI included brainstem (37.5%), cerebral cortex (33.3%), basal ganglia (25.0%), hippocampus (20.8%). The average follow-up duration was 25.4 months. 10/10 patients developed more than one relapse attacks, with MOG positivity before (10%), simultaneous (40%) or after anti-NMDAR encephalitis (50%). Most patients (7/10) had good response to first-line therapy, but experienced next relapse with an average interval of 6.7 (range: 2-14) months. We conducted initial analysis of lymphocyte subsets in these patients, which revealed CD3+ and CD4+ T cells increased after immunosuppressants medication ($p < 0.01$ and $p < 0.05$, respectively). Conclusion: MOGAD overlapping with NMDAR encephalitis presents a distinct clinical phenotype which differs from either MOGAD or NMDAR encephalitis. Brainstem in combination with cortical lesions might be warning signs for this overlapping syndrome. Due to the high recurrent rates, we recommend early diagnosis and timely treatment with high-efficiency immunosuppressants at onset.

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Keyword: myelin oligodendrocyte glycoprotein (MOG), MOG antibody–associated disease, NMDAR encephalitis, MOG antibodies and anti-NMDAR encephalitis overlapping syndrome.

Abstract

Objective: To summarize the clinical characteristics, radiological features, treatments, and prognosis of patients with myelin oligodendrocyte glycoprotein (MOG) antibody associated disease (MOGAD) overlapped with NMDA receptor (NMDAR) encephalitis.

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Conclusion: MOGAD overlapping with NMDAR encephalitis presents a distinct clinical phenotype which differs from either MOGAD or NMDAR encephalitis. Brainstem in combination with cortical lesions might be warning signs for this overlapping syndrome. Due to the high recurrent rates, we recommend early diagnosis and timely treatment with high-efficiency immunosuppressants at onset.

Introduction

Myelin oligodendrocyte glycoprotein (MOG) antibody–associated disease (MOGAD) is an inflammatory demyelinating disease of the central nervous system (CNS) [1]. Following the detection of a distinctive autoantibody against MOG in patients with specific clinical and imaging features, MOGAD was regarded as an isolated disease spectrum differentiating from aquaporin-4 seropositive neuromyelitis optica spectrum disorder (NMOSD) and multiple sclerosis [2]. Optic neuritis (ON) and transverse myelitis (TM) are typical clinical presentations of MOGAD in adults, while acute disseminated encephalomyelitis (ADEM) is common in children [3]. Cerebral cortical encephalitis and brainstem or cerebellar demyelination is less common in MOGAD [4].

The anti-N-methyl-d-aspartate receptor (NMDAR) antibody mainly binds to the GluN1 subunit of the neuronal surface [5], which induces autoimmune encephalitis (AE). The defining features of NMDAR receptor

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encephalitis are abnormal mental behavior, epileptic seizures, altered consciousness, and central hypoventilation [6]. In a cohort study, patients with NMDAR encephalitis were tested for concurrent glial and neuronal surface antibody [7]. Of them, 4% exhibited co-existence with glia-antibodies, among which MOG-antibody was most frequently present. Another study showed that 3.3% of patients with anti-NMDAR encephalitis develop demyelinating disorders, either separately or simultaneously. Among these NMDAR antibody-positive patients, 12 (16.4%) tested positive for MOG antibody [8].

Apart from the phenomena of NMDAR encephalitis in combination with MOG-antibody positivity, an increasing number of cases have recently been reported in MOG antibody positive patients presenting with seizures or cortical and brainstem encephalitis [9, 10], indicating clinical entity distinct from typical MOGAD. These patients have episodes of encephalopathy and demyelination concomitantly or sequentially, in which dual positivity of anti-NMDAR and anti-MOG abs were detected [3, 11]. Other case reports and systematic reviews also revealed that prevalence of the overlapping syndrome may be underestimated [12]. Thus, it is considered important to identify serum MOG-positive patients overlapping with anti-NMDAR antibodies.

Data on the clinical and radiological features of MOGAD overlapping with NMDAR encephalitis are scarce, and the scope of published literature is mainly restricted to case reports [13-15]. Distinct clinical spectra were present in these patients, indicating that the overlapping syndrome is an independent disease entity that differs from patients with single antibody positivity. Hence, this study is aimed to provide a long-term retrospective analysis of MOGAD overlapping with NMDAR encephalitis in the last 5 years by summarizing clinical characteristics, imaging features, and evaluating treatments and prognosis.

2 Methods

2.1 Patients

Patients suspicious of AE were tested for autoimmune antibodies, and patients considered as CNS demyelinating disease were tested for demyelination antibodies. The flow diagram of inclusion criteria was shown in Figure 1A. Exclusion criteria included: (1) follow-up month was less than 3 months; (2) patient information was insufficient; (3) patient was diagnosed as other antibodies positive AE or AQP4-IgG seropositive NMOSD. After data collecting, ten patients fulfilled the criteria and diagnosed as MOGAD overlapping with NMDAR encephalitis between January 2018 and June 2023 at the Second Xiangya Hospital of Central South University.

2.2 Antibody tests

CSF and blood samples were used to test for MOG and NMDAR antibodies. Serum MOG positivity and CSF NMDAR positivity were considered as necessary conditions for diagnosis of the overlapping disease. MOG antibody testing was performed by King Med Center for Clinical Laboratory (Guangzhou, China) using a live cell-based assay (CBA) with cells expressing the full-length human MOG antigen. Endpoint titration was performed as previously describe [16]. AQP4 and MBP antibodies were routinely detected with MOG antibodies to exclude NMOSD and other forms of CNS inflammatory demyelination. The NMDAR antibody was examined using a fixed cell-based assay at the King Med Center for Clinical Laboratory (Guangzhou, China). Additional autoimmune antibodies (AMPA1, AMPA2, LGI1, CASPR2, and GABABR) were tested simultaneously. Five patients were tested for oligoclonal bands to measure intrathecal IgG synthesis.

2.3 MRI images

Brain MRI scans were performed in all patients with sequences including axial T1, axial T2, sagittal T2 fluid-attenuated inversion recovery (FLAIR), diffusion-weighted images, and contrast-enhanced axial T1 images. Optic nerve MRI was performed in five patients (pats 1–2, 4, 9–10), and spinal cord MRI was performed in five patients (pats 3–5, 9–10).

2.4 Laboratory tests

Peripheral blood lymphocyte subsets were tested in three cases at onset and in five cases in the remission period after immunosuppressant treatment. Flow cytometry was used to distinguish CD3+ T, CD4+T,

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CD8+T, CD19+B, and CD56+NK cells. The total number of cells in each subgroup was counted, and the corresponding percentages were calculated as well as CD4+/CD8+ ratio.

2.5 Data collection

The medical records of all patients, including clinical presentations, laboratory results, and MRI findings, were reviewed by two neurologists (TJD and WFY). The severity was measured using the modified Rankin scale (mRS) at admission and discharge in each episode. The patients were followed up at the outpatient department to adjust the dosage regimen.

2.6 Statistical analysis

Skewed data are expressed as the median (interquartile range). Normally, continuous data are expressed as the mean ± SEM. A paired-sample t-test was used to compare antibody endpoint titers in each episode, as well as lymphocyte subsets before and after treatment. Statistical graphs were generated by GraphPad Prism version 9.5.1. software. Differences were considered statistically significant at a two-tailed $p < 0.05$.

2.7 Ethics statement

This study was approved by the Ethics Committee of the Second Xiangya Hospital, Central South University. All participants provided written informed consent.

3 Results

3.1 Demographics and clinical features

In total, 10 patients (8 adults and 2 adolescents) who fulfilled the diagnostic criteria for MOGAD overlapped with NMDAR encephalitis were included. The cohort consisted of 5 female and 5 male patients with a median age at onset of 23 years (range: 10–43). Demographic and clinical data are outlined in Table-1.

In patients with overlapping syndromes, the dominant symptom was encephalopathy (8/10), other manifestations included headache (7/10), fever (temperature range: 38.3–41.0) (6/10), optic neuritis (6/10), focal neurological deficits (4/10), and transverse myelitis (2/10) (frequency of symptoms summarized in Figure 1B). Encephalopathy was defined as a clinic syndrome, including psychiatric symptoms (6/8), seizures (3/8), and disturbance of consciousness (2/8). Common mental symptoms included agitation, hallucinations, slow response, and memory impairment. The focal neurological deficits referred to numbness or weakness of unilateral limb (4/4), verbal disorders (2/4), and ataxia (1/4).

3.2 Laboratory characteristics

Lumbar puncture was performed in all patients. Elevated intracranial pressure (>180 mm H_20) was observed in 7/10 patients with a median of 176.8 mm H_20 (range: 90–280). CSF analysis showed pleocytosis (>8 white cell count/μl) in 9/10 patients with a median white blood cell (WBC) count of 63.9 cells/μl (range: 0–320), and monocytes dominated WBC. CSF protein was elevated in 4/10 patients with a median of 426.1 mg/L (range: 162–1311). Five patients were tested for oligoclonal bands (OCBs), and three (60%) showed positive results, with increasing bands restricted to the CSF (Pattern II).

During the first clinical attack, serum MOG antibody was detected in 5 patients (one was weakly positive in CSF), and anti-NMDAR antibody was detected in the CSF of 9 patients and serum of 4 patients (Table 1). In our study, all 10 patients experienced relapses with new or recurrent symptoms. Thus, we defined a relapse phase based on the following conditions: 1) a clinical attack with symptoms different from previous presentations or similar symptoms recurring; 2) the clinical progression (worsening neurological deficit) was paralleled with serum/CSF autoantibody positivity; and 3) the new episode occurred more than 30 days following the onset of previous attack.

When relapse occurred, the patients with encephalitis or demyelination were tested for both MOG and anti-NMDAR antibodies. We found that five patients showed previous anti-NMDAR-IgG positivity followed

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by anti-MOG-IgG positivity, four patients presented with dual anti-NMDAR and anti-MOG positivity simultaneously, and only one patient presented MOG serum positivity and secondary NMDAR encephalitis. Interestingly, when analyzing clinical relapses with antibody dynamics, we found that MOG-IgG played a dominant pathogenic role in relapse episode with higher antibody titers compared with anti-NMDA-IgG ($p < 0.01$) (Figure 2A), which indicated altering of MOG titers showed more relevant to clinical relapse. In the relapse episodes, the major symptoms included decreased vision (3/10), double vision (3/10), mental symptoms (3/10) (proportion described in Figure 2B).

3.3 MRI findings

Brain lesions were observed in all 10 patients by MRI scan. In a total of 24 episodes of the 10 patients, lesions involved the cortical region (33.3%, 8/24), deep nuclei (basal ganglia and thalamus) (25.0%, 6/24), hippocampus (20.8%, 5/24), juxta white matters (corpus callosum, cingulate gyrus) (12.5%, 3/24), brainstem (midbrain, pons, and medulla) (37.5%, 9/24), and cerebellum (4.2%, 1/24) (lesion distributions summarized in Figure 1C). All 10 patients exhibited hyperintense signals on T2-sequences (Figure 3), and 6 patients showed lesional or meningeal enhancements. In patient-6 who presented as seizures and acute confusion and infected with herpes simplex virus 1 (HSV-1) prior to NMDAR encephalitis, extensive cortical regions and hippocampi involvements were found. After treatment with intravenous acyclovir and methylprednisolone, the brain lesions were clearly adsorbed. However, extensive meningeal enhancement was observed after the contrast agent was administered (Figure 4 D-F).

Abnormal signals in the optic nerve presented in four patients with or without nerve sheath enhancement. Transverse myelitis occurred in only two patients, with one case longitudinally involving both the cervical and thoracic spinal cords (Figure 4 A-C) and one case shortly involving the superior cervical cord.

3.4 Treatment and outcomes

We performed long-term observation for those patients diagnosed with MOGAD overlapping with NMDAR encephalitis. The follow-up duration ranged from 8 to 56 months, with a median time of 25.4 months. Since the initial diagnosis, all patients received first-line immunotherapy, including intravenous methylprednisolone (IVMP, 1000mg/d) (n=8) and intravenous immunoglobulins (IVIG, 0.4kg/mg/d) (n=6). One patient (pat 2) discontinued IVMP owing to side effects (gastrointestinal bleeding) and received rituximab for long-term immunotherapy. Seven patients (70%) remarkably benefited from first-line therapy with improved clinical and radiological outcomes. All patients received normalized long-term immunosuppressive treatments, such as azathioprine (n=9), mycophenolate mofetil (n=1), rituximab (n=1), to avoid relapse (Table-1). However, 10 patients (100%) experienced one or two relapses by follow-up. The median interval between disease onset and the first relapse episode was 6.7 months (range: 2–14). When disease relapsing, the patients underwent a new round of first-line immunotherapy at acute phase, then continuing or changing their immunosuppressants. Four of them increased dosage of azathioprine (pat 1, 3-5), and six of them altered immunosuppressive regimen (pat 2, 6-10). Administration of immunosuppressants and drug dosages were detailed in Table-1. Eventually, the patients did not develop the next relapse at the last follow-up.

3.5 Lymphocyte subsets analysis

Six patients were tested for peripheral blood lymphocyte subsets during the acute onset and/or recovery phase after immunosuppressive treatment. The results related to different medications are summarized in Table-2. The percentages of CD3+ and CD4+ T cells after treatment were significantly higher ($p < 0.01$ and $p < 0.05$, respectively). However, there was no significant difference in the percentage of CD8+ T cells or the CD4+/CD8+ ratio ($p > 0.05$) (Figure 5).

4 Discussion

The dual positivity of anti-MOG and anti-NMDAR overlapping syndrome is an increasingly recognized but rare disease entity that has been reported in only a few cases [12, 14, 15, 17, 18]. In a cohort study by Fan et al., 5 of 42 (11.9%) patients with MOG-antibody disease were identified as NMDAR encephalitis, the frequency of which was higher than that of NMOSD overlapping with NMDAR encephalitis (0.6%) [11].

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However, the number of cases is limited and mainly restricted to children. Furthermore, a large-scale study investigating the co-existence of NMDAR antibodies in 376 MOG-IgG1 patients concluded that testing for MOG-IgG1 and NMDAR-IgG is essential in patients with encephalopathy and demyelinating syndromes [19]. Thus, we realized that the rate of coexisting MOGAD and anti-NMDAR encephalitis was underestimated because of the complex symptoms and heterogeneity of clinical manifestations [12].

Unlike the typical presentation of MOGAD as ON and TM in adults and ADEM in children, common clinical manifestations of the overlapping syndrome include headache, fever, diplopia, vision loss, palsy, aphasia, psychosis, seizures, and confusion. We observed a combination of focal neurological deficits and encephalopathy symptoms in these patients, which may provide clues for recognition of MOGAD overlapped NMDAR encephalitis. As visual impairment and myelopathy are rare in patients with NMDAR encephalitis [5], epilepsy and behavioral disturbance are less frequent in MOGAD [4]; therefore, we suggest that patients suffered from encephalitis and demyelination testing for both NMDAR and MOG antibodies.

Typical MRI findings in overlapping syndromes are differentiated from MOGAD with lesions involved anterior optic nerve bilaterally [2], or from NMDAR encephalitis with lesions involved temporal and hippocampal regions asymmetrically [5]. Brainstem was the most common involvement in our study, followed by lesions in the cortex and deep gray matter. Furthermore, a few patients showed both supratentorial and infratentorial lesions, which may be warning signs of MOGAD overlapping with anti-NMDAR encephalitis. A case report of a psychiatric patient with triple antibodies against anti-NMDAR, anti-CASPR2, and MOG mentioned that bilateral cingulate and hippocampal lesions might be imaging clues suggestive of coexisting antibodies [20]. However, in our study, the involvement of the cingulate gyrus was observed in only one case and that of the hippocampus in two cases, indicating that cingulate gyrus involvement occurred less frequently and could occur unilaterally.

MOGAD can present as either a monophasic or relapsing disease [3]. However, in our cohort, 100% of the patients developed relapse or multiple relapse attacks, indicating a high recurrence risk of the overlapping syndrome. By analyzing the clinical course of each case, we found that MOG positivity occurred before (10%), simultaneously (40%), or after (50%) NMDAR encephalitis, which may indicate pathophysiological differences. Viral infection is considered a precipitating factor for AE [21]. Mariotto et al. reported that 45% of patients with MOGAD had prodromal symptoms or previous infectious processes [22]. In our study, the inducing factors included influenza-like symptoms in one case (pat 1) and viral infections (Herpes S Virus and Epstein–Barr virus) with evidence from CSF next-generation sequencing in three cases (pat 5–7). Brain MRI of Patient 4 showed severe blood-brain barrier (BBB) damage with marked meningeal enhancement after herpes simplex virus infection of the CNS. In addition, our study found that other causes of disease relapse may point to tapering or cessation of steroids, as 60% of patients experienced relapses due to inappropriate glucocorticoid adjustments. When analyzing antibody dynamics in patients, we found that clinical deterioration was associated with increased titers of the responsible antibody. And between these two antibodies, MOG-IgG was more pathogenic than NMDAR-IgG.

The pathogenesis of overlapping autoimmune syndromes remains poorly understood. Based on the observations from our cases and previous reports, we hypothetically propose the possible pathogenesis of MOGAD overlapped with anti-NMADR encephalitis. First, MOG is specifically located on the outer surface of oligodendrocytes in the CNS [23, 24], and NMDAR is expressed on neurons, oligodendrocytes, astrocytes, and excitatory glutamate synapses [25]. This is the biological structural basis of the occurrence of immune cross-reactivity and explains the dual antibody positivity simultaneously in the first episode. Second, viruses can trigger CNS inflammation and immune dysfunction, resulting in NMDAR encephalitis [21]. An excessive inflammatory response leads to BBB breakdown, followed by MOG antigen leakage into the peripheral blood and serum-positive MOG antibody generation. This mechanism reveals an NMDAR-positive course accompanied by or followed by MOGAD, which is the major phenotype of overlapping syndromes. Third, multiple cases showed that the immune system could rebuild and renovate itself when the dosage of immunotherapy is decreased. Meanwhile, the antigenicity of the self-structure could increase, giving rise to immune disorder [26-28]. These theories of immune restitution may account for relapse attacks during steroid tapering or

cessation.

In accordance with previous studies [15, 29], patients with overlapping syndromes had good responses to first-line treatments, such as IVMP, IVIG, PE, and IA, with improved mRS scores and adsorbed lesions on MRI. However, if glucocorticoids are reduced too quickly or discontinued, relapse may occur [15]. However, the optimal timing of immunosuppressant administration remains unclear. In our study, 90% patients were given azathioprine for long-term therapy at their first episode. Then they experienced disease relapse at 6.7 months as median interval. It means the relapse might occur when glucocorticoids tapering, in the meanwhile, immunosuppressants unable to take effects sufficiently. Hence, we recommend adding second-line treatments once diagnosed as MOGAD overlapped with anti-NMADR encephalitis. Moreover, high-efficiency immunosuppressants (rituximab or mycophenolate mofetil) were suggested to reduce further relapse risks. In general, patients recovered well after appropriate first-line treatment with immunosuppressants [30, 31], and our patients showed no significant disability at the final follow-up (average time: 25.4 months). Additionally, we provided lymphocyte subset data for these patients, which is the first report of MOGAD overlapping with anti-NMDAR encephalitis. By comparing the percentage of T cells subtype before and after immunosuppressant treatment, we found that CD3+ and CD4+ T cell counts increased after therapy. However, detailed information on T and B lymphocyte subsets requires further investigation.

There are some limitations in the present study. First, the sample size was limited owing to the low incidence of the disease, although we enrolled all patients diagnosed within the last five years. Second, the retrospective nature of this study determined that some treatments were uncontrollable, which might have caused bias. Third, in real-world clinical practice, data on lymphocyte subsets were not perfect. Only a subset of patients underwent lymphocyte subsets test, and we could not obtain sufficient data to conduct a statistical analysis of T lymphocyte subgroups between different immunosuppressive drugs.

In conclusion, the main clinical feature of MOGAD overlapping with NMDAR encephalitis is encephalopathy symptoms associated with focal neurological deficits. Brainstem lesions combined with cortical involvements on MRI may be warning signs of this overlapping syndrome. Because the relapse rate is high, we believe that early diagnosis and timely treatment with high-efficiency immunosuppressants at onset would be beneficial for these patients.

Conflict of interest

The 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.

Author contributions

TJD write original manuscript and analyzed clinical data; SOY, ZLH and QMZ collected follow-up data; WFY generated concepts, supervised the project, and edited manuscript. All authors reviewed and approved the manuscript.

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Figure legends

Figure 1. Flow chart for patient inclusion and the exclusion criteria. NMDAR-ab, anti-N-methyl-d-aspartate receptor antibody; MOG-ab, myelin oligodendrocyte glycoprotein antibody (A). Graphical summary of clinical symptoms (B) and lesion distributions (C) in patients with MOG antibody-associated disease overlapped with anti-NMDAR encephalitis.

Figure 2. Altering of antibody endpoint titers in each clinical episode (A). Red dots represent serum MOG-ab, blue dots represent CSF NMDAR-ab. Comparison of MOG-ab and NMDAR-ab titers in second episode (first relapse) showed significant difference (** $p < 0.01$). Proportion of dominant symptoms in relapse courses (B).

Figure 3. Characteristic brain lesions of patients with MOG antibody-associated disease overlapped with anti-NMDAR encephalitis. Axial T2 sequence of MRI exhibited patchy or diffusive lesions involving bilateral frontal lobes of pat 7 (A), left basal ganglia and thalamus of pat 3 (B), right deep grey matter and corpus callosum of pat 7 (C), left hippocampus region of pat 3(D), bilateral midbrain of pat 4 (E), right pons and cerebellum of pat 3 (F), and medulla of pat 5 (G). T2-FLAIR hyper-intensity of coronial images (pat 7, pat 2) showed corpus callosum and cingulate gyrus involvements (H-I). Supratentorial and infratentorial lesions (red arrows) in pat 5 on T2-FLAIR indicated a warning sign of the overlapped disease (J).

Figure 4. Lesions of brain and spinal cord presented with contrast-enhancement. Pat 4 with diplopia and paraplegia showed lesions on brainstem, and longitudinal extensive transvers lesions on cervical and thoracic spinal cord (A-B), with multifocal streaky-like Gd-enhancement (C). Brain MRI of pat 6 with seizures and encephalitis after HSV-1 infection revealed large hyperintense lesions of frontal, temporal and insular cortex (not shown). The lesions gradually revolved after acyclovir and steroid treatment (D), but remarkable garland-like contrast enhancement was noted in extensive area of insular cortex, temporal cortex, cingulate gyrus, and juxtacortical white matter (E-F), which indicated BBB damage and vascular leakage.

Figure 5. Comparison of T lymphocyte subgroups before and after treatment of immunosuppressants. Circles represent T cells before treatment, triangles represent T cells after treatment. Comparison of $CD3^+$ T cells (A), $CD4^+$ T cells (B), CD8+ T cells (C) and $CD4^+/CD8^+$ ratio (D) in patients of MOGAD overlapping with NMDAR encephalitis (** $p < 0.01$ and *$p < 0.05$).

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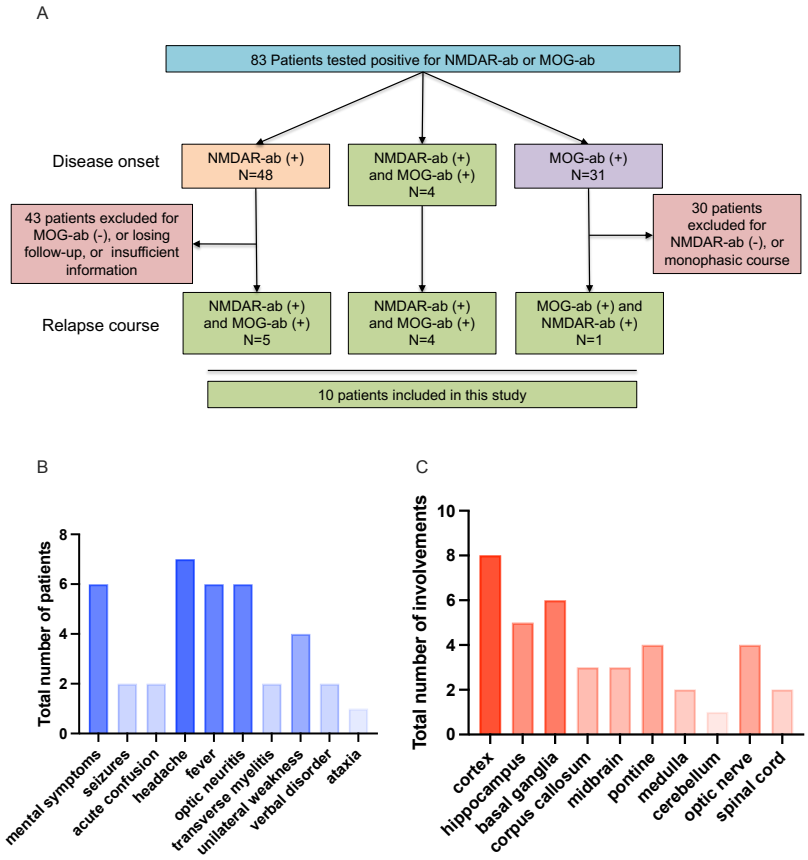

Figure 1

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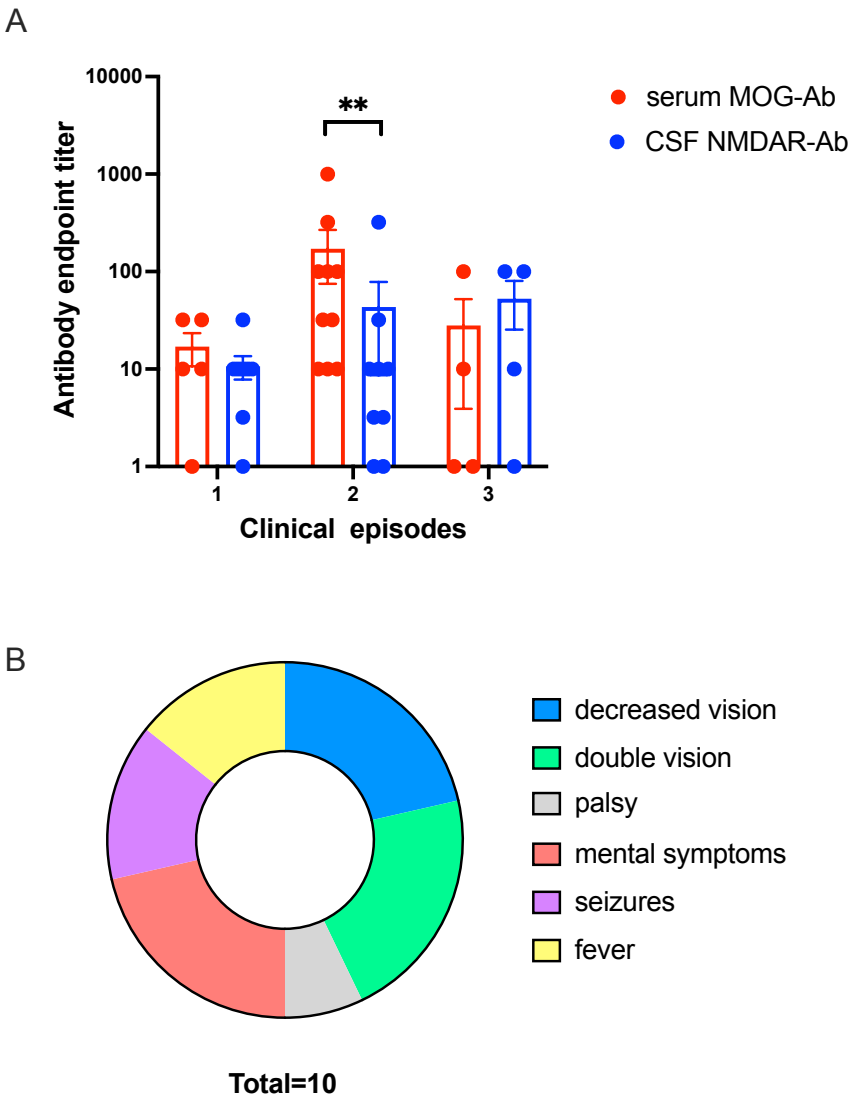

Figure 2

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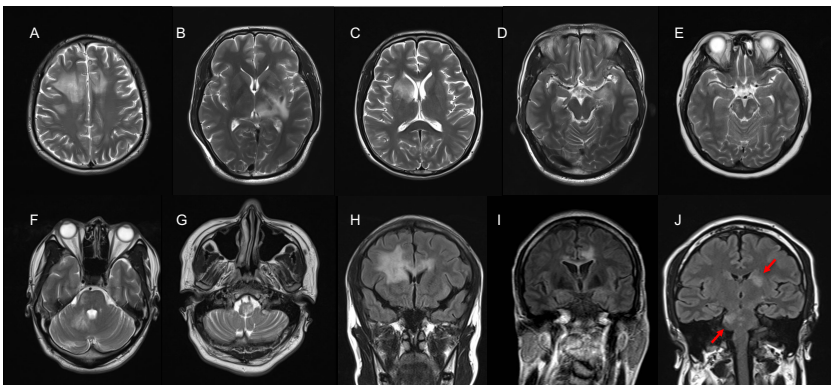

Figure-3

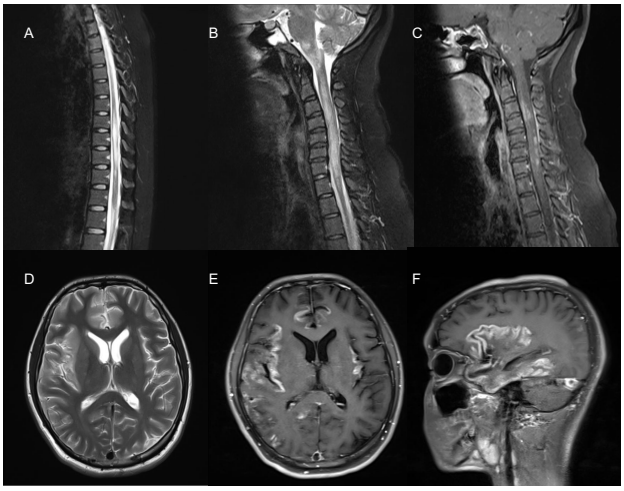

Figure-4

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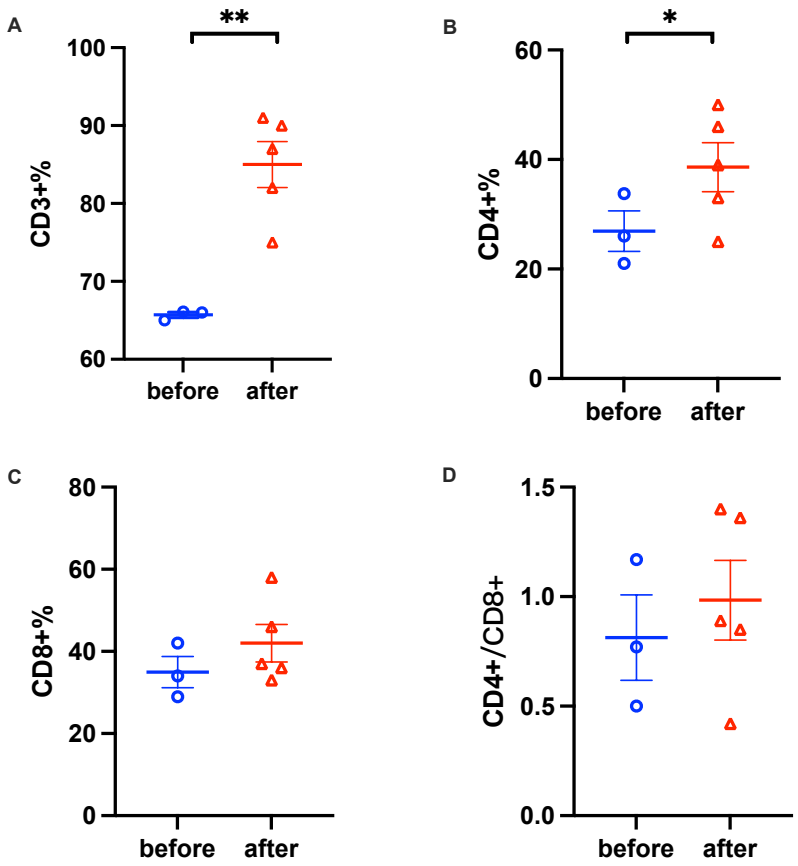

Figure 5

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