Overlapping Autoimmune Neurological Syndrome: A Case Report of Triple-Positive Antibody

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Introduction

The co-existence of several autoimmune conditions has been reported with neuromyelitis optica (NMO) spectrum disorders (NMOSD) [1]. While a rare disorder, there have been documented cases of concurrent N-methyl-D-aspartate (NMDA) receptor (NMDAR) encephalitis, and myasthenia gravis (MG). Hence, the patient manifested both central and peripheral nervous system immune-mediated neurological syndromes. A middle-aged female with a history of seropositive aquaporin-4 (AQP4) NMOSD on mycophenolate 1 g twice daily presented with severe fatigue and right eye ptosis (three months since NMOSD diagnosis) and tested positive for acetylcholine receptor (AChR) binding antibody, consistent with MG. Six months after the patient’s NMOSD diagnosis, she began to experience subacute progressive cognitive decline, behavioral changes, imbalance, anxiety/panic attacks, and paranoid delusions. NMDAR encephalitis was suspected, and she tested positive for cerebrospinal fluid NMDAR antibodies. After treatment with steroids failed, she was given two doses of rituximab 1 g, two weeks apart, and reported improvement in her symptoms shortly after the second dose.

Case Presentation

A 44-year-old previously healthy female presented to an outside hospital emergency department with a headache followed by imbalance, right upper and lower extremity numbness, and weakness. Her examination findings on admission were notable for 3/5 strength of her right upper and lower extremities. She also had a loss of sensation in her right upper extremity. The rest of her examination was unremarkable. She had a head computed tomography (CT) performed, which was unremarkable. Magnetic resonance imaging (MRI) of the brain showed T2 hyperintensities in the bilateral hypotalamic regions and pontomedullary junction, prominent on the left side without associated diffusion restriction and enhancement (Figure 1A-1C). The patient refused a lumbar puncture and was told to follow up with a neurology outpatient. At her three-month follow-up, she reported that her symptoms have gradually improved with physical therapy and now only has residual right-handed numbness. As a demyelinating process was suspected, she had an extensive neurological workup over the next three months. She underwent a lumbar puncture with an opening pressure of 12 cm H2O, a protein count of 35 mg/dl, and a
cell count of 1/mm³. Serum studies showed negative cell-based assay serology for AQP4 immunoglobulin (Ig) G and MOG-IgG and mildly elevated ribonuclear protein (RNP) and Sjogren’s antibody for soluble substance A/ Ro (SS-Ro) (Table 1). Workup for sarcoidosis was negative with normal angiotensin-converting enzyme levels and normal chest CT without mediastinal and hilar lymphadenopathy. MRI of the cervical spine revealed T2 signal changes from the cervicomedullary junction to C3 level with faint enhancement (Figure 1D, 1E). MRI of the thoracic spine was normal without signal changes. Cerebrospinal fluid analysis and paraneoplastic panel were negative except for mildly elevated N-type calcium channel antibodies of 0.04 and mildly elevated IgG index of 0.8 (Table 2).

**FIGURE 1: Magnetic resonance imaging (MRI) of the brain and cervical spine**

MRI of the brain fluid-attenuated inversion recovery axially showing T2 hyperintensities in the bilateral hypothalamic regions (A, B) and pontomedullary junction (C), with interval resolution imaging after a year (F-H). MRI of the cervical spine showing T2 signal changes from cervicomedullary junction to C3 level (D) with faint gadolinium enhancement (E). Repeat MRI of the brain, interval of two years, showing new T2 hyperintensities in the bilateral thalami (I, J). Repeat MRI of the cervical spine, interval of 18 months, showing improved T2 hyperintensities within cervical medullary junction (K), without enhancement (L).
| Laboratories                                      | Values      | Reference range and units                        |
|--------------------------------------------------|-------------|--------------------------------------------------|
| ANA screen and titer                            | Negative    | Negative, <1:80 titer                           |
| *Borrelia burgdorferi* total IgG/IgM Ab          | 0.23        | <0.90 index value                                |
| C-reactive protein                               | 0.1         | <0.5 mg/dl                                       |
| Erythrocyte sedimentation rate                   | 19          | <20 mm/hour                                      |
| HBsAg                                           | Negative    | Negative                                         |
| HBc Ab IgM                                       | Negative    | Negative                                         |
| Hepatitis C Ab                                   | Negative    | Negative                                         |
| Hepatitis A Ab IgM                               | Negative    | Negative                                         |
| International normalized ratio                   | 0.94        | 1                                                |
| Myelin oligodendrocyte glycoprotein-IgG1         | Negative    | Negative                                         |
| Neuromyelitis optica/aquaporin-4 IgG            | Negative    | Negative                                         |
| N-Methyl-D-aspartate receptor Ab, IgG            | <1:10       | <1:10                                            |
| Acetylcholine receptor Ab                        | 0.53        | <0.3 nmo/L                                       |
| B2 glycoprotein IgG Ab                           | <9          | <20 SGU                                          |
| B2 glycoprotein IgM Ab                           | <9          | <20 SMU                                          |
| B2 glycoprotein IgA Ab                           | <9          | <20 SMU                                          |
| Angiotensin-converting enzyme                    | 39          | 8-52 U/L                                         |
| Methylmalonic acid                               | 0.13        | <0.40 umol/L                                     |
| Quantiferon TB Plus                              | Negative    | Negative                                         |
| IgG                                              | 1939        | 700-1600 mg/dl                                   |
| Albumin                                          | 3963        | 3848-5304 mg/dl                                  |
| Ribonuclear protein Ab                           | 1.8         | <1.0 ELISA units                                  |
| SM Ab                                            | 0.2         | <1.0 ELISA units                                  |
| SS A/Ro Ab                                       | 3.0         | <1.0 ELISA units                                  |
| SS B/La Ab                                       | <0.2        | <1.0 ELISA units                                  |
| Treponemal IgG/IgM                               | Nonreactive | Nonreactive                                      |
| C-ANCA                                           | <1:20       | <1:20 titer                                      |
| P-ANCA                                           | <1:20       | <1:20 titer                                      |
| PT                                               | 12.7        | 12.1-14.5 seconds                                |
| PTT                                              | 34          | 22-36 seconds                                    |
| DRVVT                                            | 31          | 27-45 seconds                                    |
| Lupus anticoagulant                              | 37.5 seconds| 30.3-43.2 seconds                                |
| DNA Ab (ds) Crithidia, IFA                       | Negative    | Negative                                         |
| TPMT enzyme activity                             | 26.2        | >21 EU                                           |
| Cardiolipin Ab IgA                               | 42.9        | <12 APL                                          |
| Cardiolipin Ab IgG                               | <9.0        | <15 GPL                                          |
| Cardiolipin Ab IgM                               | <9.0        | <12.5 MPL                                        |
| Vitamin B1, whole blood                          | 50          | 38-122 ug/L                                      |
| Varicella IgG Ab                                 | 2.6         | <1.0 units                                       |
| Test Description                                      | Initial Values | Repeat (18 months) Values | Reference Range and Units |
|------------------------------------------------------|----------------|---------------------------|---------------------------|
| N-Methyl-D-aspartate receptor Ab IgG serum with reflex to titer | 1:5            | 1:5                       | <1:1                      |
| West Nile IgG Abs                                    | -              | <1.3                      | <1.30 antibody not detected, 1.30-1.49 equivocal, and >1.49 antibody detected |
| West Nile IgM Abs                                    | -              | <0.9                      | <0.90 antibody not detected, 0.90-1.10 equivocal, and >1.10 antibody detected |
| Varicella zoster, PCR                                | Not detected   | Not detected              | Not detected              |
| Cytomegalovirus PCR, qualitative                      | Not detected   | Not detected              | Not detected              |
| EBV DNA, PCR CSF                                     | Not detected   | Not detected              | Not detected              |
| HSV 1 DNA                                            | Not detected   | Not detected              | Not detected              |
| HSV 2 DNA                                            | Not detected   | Not detected              | Not detected              |
| VDRL                                                 | Nonreactive    | Nonreactive               | Nonreactive               |
| Protein                                              | 34.9           | 50                        | 15-55 mg/dl               |
| Lactic acid                                          | -              | 1.4                       | 1.2-2.4 mmol/L            |

**TABLE 1**: Patient initial serum laboratory results with reference values

Ab: antibody; AchR: acetylcholine receptor; AGNA-1: anti-gliial nuclear antibody type 1; ANA: antinuclear antibody; ANCA: antineutrophil cytoplasmic antibodies; ANNA: antineuronal nuclear antibody; C-ANCA: antineutrophil cytoplasmic autoantibody, cytoplasmic; CRMP-5: collapsin response-mediator protein-5; ds: double-stranded; DRVVT: dilute Russell viper venom time; GAD: glutamic acid decarboxylase; HB: hepatitis B; Ig: immunoglobulin; P-ANCA: perinuclear anti-neutrophil cytoplasmic antibodies; PCA: Purkinje cytoplasmic antibody; PCA-Tr: Purkinje cytoplasmic antibody titer; PT: prothrombin time; PTT: partial thromboplastin time; S: serum; SM: smooth muscle; SS: Sjogren’s syndrome; TPMT: thiopurine S-methyltransferase; ELISA: enzyme-linked immunosorbent assay; HBsAg: hepatitis B surface antigen; HBC: hepatitis B core; IFA: immunofluorescent assay.
The patient was recommended clinical observation and a repeat MRI of the brain and NMO IgG in six months. She had a repeat MRI of the brain a year later (delayed due to the COVID-19 pandemic), which showed complete resolution of the initially reported T2 signal changes in the bilateral hypothalamus and pontomedullary junction (Figure 1F-1H). Re-imaging of the cervical and thoracic spine was not performed at this time. NMO IgG serology was repeated and was positive with a titer of 1:100 one year after she initially tested negative (Table 1). To prevent future attacks, the patient was started on mycophenolate mofetil 1 g twice daily for AQP4-positive NMOSD. A few months later, the patient presented with severe fatigue, diplopia, anorexia, generalized weakness, and an unintentional 30 lb weight loss. Neurological examination was normal except for mild right fatigable ptosis. Laboratory testing showed normal complete blood count; comprehensive metabolic panel, thyroid profile, folate level, iron profile, and monoclonal protein evaluation; and low normal vitamin B12 level of 189 pg/ml with normal methylmalonic acid. She had normal glycated hemoglobin, parathyroid hormone, and vitamin D levels. Repeat antinuclear antigen was positive with a titer of 1:320 homogenous. Due to her constellation of symptoms, she was tested for acetylcholine receptor (AchR) binding antibodies, which were positive at 0.53 nmol/L, consistent with the diagnosis of MG. The patient declined neurophysiological testing at that time. She underwent a chest/abdomen/pelvis CT for evaluation of a thymoma, which was negative for malignancy. She was started on pyridostigmine 30 mg three times/day for MG-related fatigue and generalized weakness.

Eighteen months after her NMOSD diagnosis, the patient presented with subacute progressive cognitive decline, imbalance, and behavioral problems. She was accompanied by her sister, who reported that the
patient was having severe panic attacks, bizarre behavior, paranoid delusions, and short-term memory problems. Neither the patient nor her sister reported a history of anxiety. Neurological examination showed mild cognitive impairment and impaired tandem gait. On the Montreal Cognitive Assessment, she scored 24/30 and showed difficulty with executive, visuospatial functioning, recall, and fluency. Given the subacute progressive cognitive decline, there was a high suspicion of encephalitis and vasculitis. A repeat MRI of the brain/cervical/thoracic spine was performed and showed new areas of T2 hyperintense foci within the bilateral posterior thalami without associated enhancement (Figure 1I, 1J). In the cervical spine, there was improvement in the previously reported T2 signal changes without new lesions (Figure 1K, 1L). The thoracic spine showed only mild degenerative changes and was negative for any demyelinating lesions.

Repeat lumbar puncture showed normal cell count, glucose, and protein (Table 2). Cerebrospinal fluid viral polymerase chain reactions were negative. Cerebrospinal fluid was positive for anti-NMDAR IgG at 1:5, indicative of NMDAR encephalitis. Serum anti-NMDAR IgG was negative (Table 1). She was given a three-day course of intravenous methylprednisolone 1 g without improvement. She had chest/abdomen/pelvis CT, which showed a right ovarian cyst but was negative for malignancy. Transvaginal ultrasound was performed and negative for a possible teratoma. The patient received rituximab 1 g, two doses, two weeks apart, and her anxiety, behavioral symptoms, and cognition significantly improved.

The patient was seen most recently eight months after her first rituximab infusion. She has received two rounds of infusions so far per her maintenance therapy plan. Her cognition and focal neurological deficits have remained stable. She has not had a relapse of her NMOSD or MG symptoms. She continues to suffer from anxiety and depression, which is being treated with clonazepam 0.5 mg at bedtime. Additionally, she reported a new sugar craving and weight gain, which is thought to be possibly related to limbic involvement of her NMDAR encephalitis. She was referred to behavior health for assistance in treating the symptoms, and the patient will follow up before each infusion (every six months).

Discussion

While these three conditions are rare, there have been documented cases of concurrent NMOSD-NMDAR encephalitis and NMOSD-MG [3-8]. We could not find any literature related to a patient who exhibited the symptoms of these disorders while testing positive for all three antibodies (AQP4, AchR, and NMDAR) on different occasions.

The clinical significance of patients with overlapping NMOSD-NMDA encephalitis remains unclear. However, overlapping cases typically presented with more severe symptoms and required high-efficacy treatment [3]. In prior documented cases, there does not appear to be a pattern of one condition preceding the other. Patients who develop these disorders may test positive for only one antibody at the time of diagnosis and later develop detectable levels of the other antibodies [2,3]. It is thought that the immune upregulation involved in the pathogenesis of these syndromes may increase one’s susceptibility to other autoimmune disorders. These two conditions have very different clinical manifestations. Clinicians treating patients with NMOSD who later develop psychiatric symptoms, such as bizarre behavior, delusions, or hallucinations, should consider testing for anti-NMDAR.

While there are no published cases of patients with NMDA encephalitis and MG, there have been reports of concurrent MG and leucine-rich glioma-inactivated 1 (LGI1) protein antibody-associated encephalitis. This disease process presents with characteristic faciobrachial seizures and the same psychiatric symptoms as NMDA encephalitis [9]. The patient has not been tested for anti-LGI1 IgG at the time of writing. However, the patient’s lack of seizures and negative limbic involvement on imaging made LGI1 encephalitis unlikely. However, the association between these disorders should prompt anti-LGI1 IgG testing when patients with MG present with symptoms of encephalitis.

In patients with concurrent MG and anti-AQP4 NMOSD, MG typically presented several years before NMOSD, and the presentation of NMOSD did not correlate with cessation of MG immunosuppressive therapy [4,8,10]. Patients typically tested positive for the anti-AQP4 antibody at the time of MG presentation but did not show symptoms until years later [8]. Concurrent MG was not related to a worse prognosis in patients with AQP4-NMOSD [10]. While thymic hyperplasia is a well-known source of anti-AchR, new evidence suggests that the thymus could be a source of anti-AQP4 [7]. This could explain the increased incidence of these disorders occurring together compared to chance. Although the patient’s imaging was negative for a thymoma, CT is only 55% sensitive for thymic hyperplasia and 20% sensitive for a focal thymic mass [11]. Therefore, the thymic origin of these disorders cannot be excluded. Individuals diagnosed with MG should be tested for anti-AQP4 and counseled on the possibility of developing NMOSD in the future.

The subsequent manifestations of these rare disorders are likely a consequence of coexisting autoimmunity. NMDA encephalitis has been associated with concomitant demyelinating syndromes [5]. The mechanism behind this phenomenon remains unclear. Malignancies and their associated paraneoplastic syndromes often cause new-onset autoimmune disorders, including those seen in this patient. However, the patient’s workup has been negative for malignancy thus far.
Rituximab is a monoclonal antibody against the CD20 B-cell surface receptor. The binding of the antibody to this receptor triggers B-cell death and has a powerful systemic immunosuppressive effect [12,13]. Conveniently, rituximab has been shown to be an efficacious treatment for all three disorders [14-16]. A systematic review found that 30% of AChR+ patients saw decreased posttreatment antibody titers [14]. Response to rituximab is strong, with the majority of patients having some or all of their encephalitis symptoms reversed posttreatment [16]. We believe the benefit of treating these three conditions with a single drug will provide the best possible outcome for the patient with the least amount of side effects.

Conclusions

Over the course of two years, this patient developed the clinical manifestations of three rare neurological autoimmune disorders at subsequent points in time. Not only did the symptoms of each disease overlap, but also the patient had positive serology for all three conditions simultaneously. After failing first-line therapy with glucocorticoids, she continues to respond well to rituximab. It is essential to address poor response to first-line immunosuppressive therapies early on, as the continuation of these therapies may not be effective in some cases. Additionally, central (NMOSD and NMDAR encephalitis) and peripheral (MG) neurological syndromes can occur simultaneously and even present at distant points in time. Clinicians need to be vigilant about the overlap of neurological syndromes affecting the central and peripheral nervous systems to avoid delays in the diagnosis and treatment to prevent poor clinical outcomes.

Additional Information

Disclosures

Human subjects: Consent was obtained or waived by all participants in this study. Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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