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Case Report

Adjunct Therapeutic Plasma Exchange For Anti-*N*-methyl-D-aspartate Receptor Antibody Encephalitis: A Case Report and Review of Literature

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Encephalitis associated with autoantibodies directed against the *N*-methyl-D-aspartate receptor (NMDAR) is usually a paraneoplastic syndrome that presents in young females with ovarian teratomas. We report a case of a previously healthy 14-year-old girl with sudden-onset paranoia, hallucinations, hyperactivity, increased speech, decreased sleep, seizures, and violent behavior deteriorating to catatonia. Her cerebrospinal fluid tested positive for anti-NMDAR antibodies. She was treated with five sessions of therapeutic plasma exchange (TPE) after having failed therapy with antibiotics, intravenous steroids, intravenous immunoglobulin (IVIG), one dose of rituximab, and seven sessions of electroconvulsive therapy (ECT). The American Society for Apheresis assigns a Category III (Grade 2C) recommendation for TPE in paraneoplastic neurologic syndromes; however, apheresis specifically for anti-NMDAR encephalitis has not been well studied. Literature review revealed two case reports describing outstanding improvement in patients with anti-NMDAR encephalitis following TPE. We report no improvement in our patient's symptoms after plasma exchange and discuss possible reasons for why it failed along with review of the literature. J. Clin. Apheresis 26:362–365, 2011. © 2011 Wiley Periodicals, Inc.

Key words: anti-*N*-methyl-D-aspartate receptor; encephalitis; catatonia; therapeutic plasma exchange

INTRODUCTION

NMDARs are ligand-gated cation channels localized in post-synaptic membranes that play a role in synaptic transmission [1]. Encephalitis associated with anti-NMDAR antibodies was first described in a cohort of 12 women by Dalmau et al. [2]. This syndrome is considered a paraneoplastic limbic encephalopathy often associated with ovarian teratomas [2] usually presenting with memory deficits, psychiatric symptoms, and seizures [3]. The presence of anti-NMDAR autoantibodies in serum or cerebrospinal fluid is specific for this novel and underdiagnosed disorder [4]. Although central nervous system (CNS) paraneoplastic conditions are considered autoimmune in nature, neither immunosuppressive nor antitumor therapies are beneficial in most cases [5]. However, 65% of patients with anti-NMDAR encephalopathy respond to immunosuppressive therapy and show full or near-full recovery, classifying it as a treatable and potentially reversible paraneoplastic encephalopathy [6].

TPE has been used with varying degrees of success for paraneoplastic neurological syndromes such as paraneoplastic cerebellar degeneration [7], paraneoplastic encephalomyelitis [8], paraneoplastic opsoclonus/myoclonus [9], and cancer-associated retinopathy [10]; for these syndromes, the American Society for Apheresis assigns a category III (Grade 2C) recommendation [5]. The finding of specific autoantibodies in these syndromes has led to the use of TPE in their management. However, despite a specific antibody having been identified in anti-NMDAR antibody encephalitis, there are no guidelines for its management with TPE. A review of the literature revealed two case reports in which adjunct TPE rendered outstanding improvement in anti-NMDAR encephalitis. The first patient was a 22-month-old child

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with the typical clinical symptoms who was treated with 20 cycles of adjunct plasmapheresis (along with immunomodulation) with a recovery to near-normal functioning; the course of her clinical improvement demonstrated a strong temporal relation to TPE [11]. The second patient was a 12-year-old girl, also with typical symptoms, who displayed marked improvement with steroid therapy along with eight sessions of TPE over 13 days, with the apparent benefit of apheresis within the first two days [12]. Although a causal relationship cannot be established in either of these cases, current literature suggests that adjunct TPE would be a reasonable therapeutic consideration for anti-NMDAR encephalitis.

CASE REPORT

A previously healthy 14-year-old female was transferred to our hospital from another facility following a two-month history of sudden-onset paranoia, hallucinations, violent behavior, hyperactivity, increased speech, and decreased sleep. Initial cytological examination of her cerebrospinal fluid revealed pleocytosis (WBC 49 cells/μL range [0–5 cells/μL] with lymphocytes 98% and monocytes 2%, Glucose 61 mg/dL [range, 50–70 mg/dL], protein 30 mg/dL [range, 15–45 mg/dL], for which she was given antimicrobial and long-term antiviral therapy. Her clinical course deteriorated as she became nonverbal, refused to eat, and developed urinary incontinence. Further analysis of her cerebrospinal fluid was significant for anti-NMDAR and Epstein-Barr virus (EBV) antibodies. No anti-NMDAR antibodies were detected in her serum. Full-body imaging including MRI, PET and gallium scans were negative for malignancy. She experienced a seizure, and subsequent electroencephalography revealed frontal slowing with no epilpeptiform activity. She was started on seizure prophylaxis, long-term high-dose intravenous steroid therapy, and a two-day treatment with IVIG for presumed autoimmune encephalitis secondary to the anti-NMDAR antibodies. Her clinical course waxed and waned with no sustained improvement in both medical facilities.

Approximately two months after the onset of symptom, the patient was transferred to our hospital. Testing for Bartonella species, Lyme disease, Mycoplasma, HIV, syphilis, Clostridium species, West Nile virus, cytomegalovirus, arbovirus, and Toxoplasma species was negative. Rheumatological workup was negative for antiglutamic acid decarboxylase antibodies, antivoltage-gated potassium channel antibodies, antinuclear antibodies, rheumatoid factor, Anti Scl-70, Anti-Jo, DNAase B, and anti-centromere antibodies. Her erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were elevated, with values at 120 MM/HR and 163 mg/L, respectively. An endocrine workup was unremarkable. After psychiatric evaluation she was placed on diazepam and risperidone for agitation.

During the first month of her hospitalization, her neurological status waxed, and waned. Physical examination during this time revealed periods of dystonia, dyskinesia, spastic rigidity, cogwheel rigidity, and decreased tone. Administration of intravenous lorazepam resulted in mild improvement of her catatonic state. Following administration of a second round of IVIG, the patient received one rituximab infusion, resulting in hypotension, flushing, diaphoresis, fever, and coarse breath sounds. She was treated for possible serum sickness, and, based on this reaction, was no longer considered a candidate for rituximab.

She declined into malignant catatonia for which electroconvulsive therapy (ECT) was initiated. She underwent 7 ECT sessions on alternate days but experienced continued episodes of agitation, insomnia, and hypersexual behavior. The patient was transferred to the pediatric intensive care unit and underwent five sessions of TPE every other day as a last resort; exchanging 1.5 plasma volumes with 5% albumin (CSL Behring, Kankakee IL) supplemented with calcium gluconate. She tolerated these procedures well but did not improve clinically. Toward the end of her admission, her psychiatric medications were adjusted with minimal improvement. She was started on a regimen of 750 mg cyclophosphamide (the first of four planned doses), after which she demonstrated decreased impulsivity but minimal change in aggression. She was discharged to a rehabilitation center with a recommendation for surveillance imaging for a possible neoplasm every three to six months.

DISCUSSION

Anti-NMDAR-antibody mediated encephalitis is a recently recognized clinical entity. Patients with this syndrome appear to develop a predictable course [3] including continued decompensation, usually leading to intensive care monitoring and mechanical ventilation support. Up to 65% of patients with this type of encephalitis reveal the presence of an ovarian teratoma [6]. The management of anti-NMDAR encephalitis can be very effective with identification and treatment of a tumor (if present); patients with immediate tumor removal are reported to have better outcomes [6]. Mental status changes are seen in most patients either at the onset of the illness or later in the course of disease [6,8]. Immunotherapy and TPE have been touted as beneficial therapeutic considerations [11,12]. Literature review reveals very few case reports of this disease entity. Only a handful claim a beneficial outcome with adjunct use of TPE for anti-NMDAR encephalitis and none to our knowledge report a negative correlation [11,12]. There is a dearth of adequate

data regarding the use of adjunct TPE in this condition, necessitating the description of cases, so as to facilitate the formation of therapeutic guidelines, as have been formulated for various neurologic and non-neurologic syndromes [5,13].

We report the case of a 14-year-old girl with anti-NMDAR positivity and typical signs and symptoms of anti-NMDAR encephalitis with catatonia, that failed to benefit from the use of adjunct TPE. The lack of response to TPE in our case could be attributable to multiple factors. For instance, no malignancy was found in our patient, which may preclude categorization as a paraneoplastic neurologic syndrome. As previously mentioned cases without teratomas constitute only 35% of anti-NMDAR encephalitis and have poorer outcomes as compared with cases in which teratomas can be resected and/or treated [4]. Second, due to initial treatment at a different institution, the initiation of TPE in our patient was approximately three months after the onset of symptoms, when the patient was already catatonic. However, in the two case reports that claim beneficial response to anti-NMDAR encephalitis with plasmapheresis, the institution of therapy was four months [11] and six weeks [12] after clinical onset of symptoms, which is similar to our case. Nevertheless, this delay may have lessened the chance of clinical response, although there are no guidelines regarding the precise timing of therapy. Third, in this case anti-NMDAR antibodies were isolated from the CSF but not from the plasma. However, the absence of serum positivity in our patient may have been an additional factor in the lack of response to TPE. Extensive study has revealed that serum positivity is not needed for benefit from TPE, since antibody-mediated neurologic syndromes where the antibody is not detected in the plasma or in some cases has yet to be discovered (is presumed to be responsible for symptoms) have shown clinical benefit from apheresis therapy [5,13]. One reason for this finding may be the presence of tissue-bound antibodies in this condition. If antibodies are tissue bound and not detectable in the serum, one could argue that successive apheresis runs could help mobilize such antibodies into the circulation and than TPE could result in clinical benefit. Fourth, syndromes of anti-NMDAR have shown excellent response to steroid, IVIG, and/or rituximab therapy with TPE adjunct therapy [11,12], but in our case this kind of synergistic treatment did not yield positive results, and since the patient developed a severe allergic reaction to rituximab, its continued use was limited. It can therefore be argued that synergistic use of TPE and rituximab may be the key to therapeutic success but in our case it was not possible to continue the latter treatment. Yet another factor is the limited number of TPE sessions that were used to treat our case. Literature review of the two cases that showed benefit in symptoms after TPE, reveal a strong temporal association between initiation of treatment and clinical response. In the first case, there were 20 sessions of TPE [11] and in the other 8 sessions were instituted [12] with clinical response being apparent usually within a day or two, warranting sustained apheresis. Lastly, this case was complicated by EBV positivity in the CSF, which may obscured the potential benefit of TPE in our case.

In summary, this report discusses the failure of TPE in a case of anti-NMDAR encephalitis complicated by preexisting catatonia and EBV positivity in the CSF. This outcome brings to light aspects of this newly identified disease and indicates that anti-NMDAR encephalitis may not always respond favorably to TPE. We believe that further case by case analysis is needed before TPE can be established as effective adjunct therapy in anti-NMDAR encephalitis.

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