Journal of Clinical Apheresis 26:320–325 (2011)

Therapeutic Plasma Exchange for the Treatment of Anti-NMDA Receptor Encephalitis

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Anti-*N*-methyl-D-aspartate receptor (NMDA-R) encephalitis is thought to be one of the common paraneoplastic-associated encephalitides. Between February 2001 and February 2011, nine patients were diagnosed with this disorder at Columbia University Medical Center: eight females (mean age 23 years) and one male (3 years of age). Four female patients had ovarian teratomas, which were removed as part of their treatment. Therapeutic plasma exchange (TPE) was used as one of the treatment modalities in addition to immunosuppressive therapy, including corticosteroids, intravenous immunoglobulin (IVIG), and/or rituximab. A total of 56 TPE procedures were performed in these patients on alternate days (range, 5–14 procedures/patient). Approximately 1 plasma volume (PV) was processed for all patients; 5% albumin and 0.9% normal saline were used as replacement fluid. Complications occurred in 20% of TPE procedures; 9% were possibly due to underlying disease. The remaining 11% of complications were hypotensive episodes that rapidly responded to either a fluid bolus or a vasopressor treatment. One patient demonstrated immediate clinical improvement after three TPE treatments, and four patients had significant improvement at time of discharge from the hospital. Long-term follow-up showed that early initiation of TPE appears to be beneficial, and patients who received IVIG after TPE did better than those who received IVIG before TPE. However, the number of patients in this series is too small to provide statistically significant conclusions. Overall, TPE is a relatively safe treatment option in patients with anti-NMDA-R encephalitis. Further studies are needed to elucidate the benefit of TPE in this disease. J. Clin. Apheresis 26:320–325, 2011.

Key words: NMDA receptor antibodies; encephalitis; plasma exchange

INTRODUCTION

Encephalitis associated with antibodies directed against the NMDA-R was initially described as occurring predominantly in young women with ovarian teratomas [1,2]. Further investigation revealed that anti-NMDA-R encephalitis occurs in both sexes, with or without an associated tumor [3,4]. The exact incidence of this disease is unknown; however, it is thought to occur more frequently than other known paraneoplastic-associated encephalitides [5]. The pathogenesis and clinical syndrome of this disease are related to the antibodies directed against the NR1 subunit of the NMDA-R, all of which are of the IgG1 and/or IgG3 subclasses [5,6]. The antibodies cause a decrease in NMDA-R expression, which leads to inactivation of the γ-aminobutyric acid receptor, resulting in disinhibition of excitatory pathways. This clinical presentation of this disease includes psychiatric symptoms, seizures, dyskinesias, and autonomic instability [5]. Early recognition and prompt treatment with immunosuppressive therapy, and tumor removal in paraneoplastic cases, is essential for recovery [5,7,8]. Dalmau et al. [5] proposed a treatment algorithm, which includes TPE and corticosteroids pharmacotherapy as first line therapy in cases with and without an associated ovarian teratoma. The evidence for the efficacy of TPE in this setting is very limited, mostly derived from case reports [9,10]. Therefore, we retrospectively reviewed our institution's experience with the use of TPE in the management of patients with anti-NMDA-R encephalitis.

MATERIALS AND METHODS

Study Design

This is a retrospective observational review of TPE in the management of patients with anti-NMDA-R encephalitis who presented for care at the New York-Presbyterian Hospital—Columbia University Medical Center (CUMC) between February 2001 and February 2011. TPE was part of the treatment plan for all patients with anti-NMDA-R encephalitis at CUMC. These patients were identified using a natural language

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Received 19 April 2011; Accepted 2 August 2011

Published online 5 September 2011 in Wiley Online Library (wileyonlinelibrary.com).
DOI: 10.1002/jca.20311

TABLE I. Patients Demographics

Patient	Age (years)	Initial symptoms	Symptoms duration before admission (days)	Ovarian teratoma	Duration between admit date and initiation of TPE (days)
1	21	HA, AMS	180	No	28
2	29	PSY	35	No	56
3	18	HA, AMS	8	Yes	2
4	20	HA	46	Yes	6
5	20	PSY	38	No	15
6	17	PSY	53	Yes	21
7	27	HA, AMS	30	Yes	13
8[a]	30	HA, AMS, PSY	30[a]	No	8
9[a]	3	AMS	34[a]	No	1

AMS, altered mental status; HA, headache; PSY, psychiatric symptoms.
[a]These patients were peviously diagnosed with anti-NMDA-R encephalitis. The duration of symptoms indicates the duration before the initial admission which led to the diagnosis.

search with the terms ''encephalitis'' or ''NMDA receptor'' in the final diagnosis field of the pathology information system database, the CoPath Informatic System (Cerner, Kansas City, MO). Medical records were reviewed for each patient to assess the procedures and complications as well as the clinical presentation and response to TPE.

TPE Procedures

All patients underwent TPE on alternate days either on the medical floor or in the intensive care unit. All TPE procedures were performed using the COBE Spectra (CaridianBCT, Lakewood, CO). Citrate was used as the only anticoagulant for all the procedures. All patients received ~1 PV exchange per procedure, using both 5% albumin and 0.9% normal saline as replacement fluid.

Outcomes

Patients were assessed for clinical improvement during the course of TPE and immediately after completion of the last TPE. Each patient's clinical status was also assessed at the time of hospital discharge, and they were followed long-term until their last visit to CUMC up to February 15, 2011. The criteria used to assess clinical improvement were similar to those of Florance et al. [4] in their case series: patients were considered to have ''full neurologic improvement'' if they were able to return to most or all of their baseline activities; ''substantial improvement'' if they returned home or went to a rehabilitation center with mild deficits and were improving; and ''limited improvement'' if they were at home, in the hospital, or a rehabilitation center with minimal change in the neurologic status. A physician reviewed the medical records and categorized the patients, as outlined earlier.

RESULTS

Demographics

Nine patients with anti-NMDA-R encephalitis were treated with TPE between February 2001 and February 2011 (Table I). The diagnosis was confirmed by the presence of plasma anti-NMDA-R antibodies (all tests were performed in the laboratory of Dr. Josep Dalmau, University of Pennsylvania, Philadelphia, PA). Eight patients were female with an average age of 23 years (range, 17–30 years) and one patient was male (Patient 9; age 3 years). All patients had clinical symptoms consistent with a clinical diagnosis of anti-NMDA-R encephalitis. The duration from the onset of symptoms to clinical presentation ranged from 8 to 180 days, with a median of 35 days.

Four of the 8 female patients had ovarian teratomas, which were surgically resected in a median of 10 days (range, 7–29 days) from the time of admission. Of the seven patients treated for the initial presentation, TPE was started within a median of 15 days from admission (range, 2–56 days). Two patients were re-admitted to CUMC for TPE trials for relapse, after initial treatment and discharge from prior hospitalization(s) (Patients 8 and 9). These two patients were discharged immediately on completion of the course of TPE. The treatment schemes for all patients were very heterogenous, which consisted of corticosteroids, TPE, IVIG, and/or rituximab (Table II).

TPE Procedures and Adverse Events

A total of 56 TPE procedures were performed on these nine patients on alternate days. The number of TPE procedures was determined in agreement with the neurology team caring for the patients. Seven patients, including the pediatric patient, each received five procedures. Patient 1 received seven procedures and

TABLE II. Treatment Plans

Patient	First treatment	Second treatment	Third treatment	Fourth treatment	Fifth treatment
1	Corticosteroids	TPE	IVIG		
2	Corticosteroids	TPE	IVIG	IVIG	
3	Corticosteroids + TPE	Teratoma removal	IVIG	Rituximab	
4	TPE	IVIG	Teratoma removal	Rituximab	
5	Corticosteroids	TPE	IVIG		
6	Teratoma removal	IVIG	Corticosteroids	TPE	
7	Corticosteroids	IVIG	Teratoma removal	TPE	TPE
8[a]	Corticosteroids + IVIG	Corticosteroids + TPE	Rituximab		
9[a]	Corticosteroids	IVIG	TPE	Rituximab	

[a]Patient with previous diagnosis of anti-NMDA-R encephalitis, who was admitted to CUMC specifically for TPE.

Patient 7 received a total of 14 in two separate courses, 39 days apart from each other (eight procedures in the first course and six in the second). The average replacement fluid used on eight female patients was 60% of 5% albumin and 40% of 0.9% normal saline. The male pediatric patient received 75% of 5% albumin and 25% of 0.9% saline as his replacement fluid for each procedure.

Of the 56 TPE procedures, there were 11 documented adverse events (20%), which happened in five adult patients. Six adverse events, all hypotension, occurred in four patients; of these, one patient had three episodes (Patient 2), and the remaining three patients each experienced one episode (Patients 3, 6, and 7). The hypotension was successfully treated with either a 0.9% normal saline bolus (five of the six episodes treated this way) or norepinephrine (given to Patient 7 for a blood pressure drop to 94/34 with subsequent increase to 145/84 after treatment). Of note, Patient 7 was already receiving this medication before TPE due to her inability to maintain her mean arterial pressure above 60 mmHg. The remaining five events all happened in one patient (Patient 1). This patient experienced agitation during her TPE procedures, which improved after treatment with diphenhydramine. Agitation was also one of her presenting clinical symptoms, and it was unclear if this agitation was due to her underlying disease or to the procedure itself. All patients completed each TPE after treatment of the adverse event.

Outcomes

The clinical outcomes for all patients were variable (Table III). All patients had limited improvement during and immediately after TPE except for one patient, who had substantial improvement during her course of TPE (Patient 5). Similar outcomes were noticed in seven patients who received TPE as one of the treatment modalities for their initial hospitalization in comparison with two patients who were admitted for TPE treatment for relapse of the disease. Regarding seven patients with initial hospitalization for anti-NMDA-R encephalitis, two of three patients without ovarian tumor and two of four patients with ovarian tumor had substantial improvement at the time of discharge from the hospital. Furthermore, substantial improvement at discharge appears to be a good prognostic predictor for good outcome in long-term follow-up in patients presenting for initial treatment; however, the number of patients is too small to show statistical significance.

Excluding two patients admitted for relapse of the disease, four patients who had, at least, substantial improvement at discharge received TPE as either the first or second line of treatment. The median time between admission and the start of TPE for the patients who had significant improvement was 11 days (range, 2–28 days), whereas the median for patients with limited improvement was 21 days (range, 13–56 days). The patients who improved also received TPE before IVIG. Furthermore, two patients who had TPE as first line treatment had good outcomes, with one eventually attaining full recovery. Although the number of patients is too small to show statistical significance between the order of treatment (i.e., TPE before vs. after IVIG) and outcome, this limited data suggest that early initiation of TPE may be beneficial.

DISCUSSION

TPE is currently recommended as a first-line therapy for several neurologic diseases caused by identifiable autoantibodies, such as myasthenia gravis and acute inflammatory demyelinating polyneuropathy [11]. In these immune-mediated neurologic disorders, TPE removes the disease-causing antibodies [12]. However, in paraneoplastic-associated neurologic syndromes, it is difficult to quantify the effect of TPE on outcome, because many patients also receive concurrent immunotherapy; therefore, there are conflicting data regarding the success of TPE [11]. Anti-NMDA-R encephalitis is thought to be due to immune-mediated neuronal dysfunction caused by IgG1 and IgG3 anti-NMDA-R antibodies. The definitive diagnosis requires demonstration of these antibodies in patient plasma or cerebrospinal fluid (CSF) [5]. Therefore, therapeutic modalities for this disease include TPE for removing the offending

TABLE III. Treatment Outcomes

Patient	Number of TPE procedures	Outcome during and immediately after TPE	Duration between last TPE and discharge (days)	Discharge outcome summary (discharge location)	Long-term outcome [duration between last tpe and last follow-up (days)]
1[a]	7	LI	17	SI—improved in mental status, decreased in muscle contraction and agitation (RC)	SI—able to perform daily activities at home (296)
2[a]	5	LI	78	LI—remained ventilator dependent and was not able to interact (NH)	LI/DNR—was not able to interact (1300)
3[b]	5	LI	72	SI—was able to follow verbal commands and stand with assistance (RC)	N/A
4[b]	5	LI	96	SI—ceased seizing and was able to participate in physical therapy (RC)	FI—returned to baseline function (827)
5[a]	5	SI after TPE #3—improved in verbal and social skills	9	SI—improved in language and mental status (RC)	N/A
6[b]	5	LI	4	LI—did not improve in seizure control and delirium (NH)	N/A
7[b]	14	LI	246	LI—remained ventilator dependent and nonresponsive (NH)	LI / DNR—remained nonresponsive (272)
8[a,c]	5	LI	1	LI—discharged immediately after completion of TPE (H)	LI—remained global aphasic (30)
9[a,c]	5	LI	1	LI—discharged immediately after completion of TPE (H)	SI—improved in social interactions and motor skills (85)

SI, substantial improvement; FI, full improvement; LI, limited improvement; DNR, do not resuscitate; RC, Rehabilitation Center; NH, nursing home; H, home; N/A, not available data (i.e., last time patient seen was at discharge).
[a]Patient without an ovarian tumor.
[b]Patient with an ovarian tumor.
[c]Patient with relapse, admitted to CUMC specifically for TPE.

antibody in adjunct to immunotherapy for suppressing antibody production, and teratoma excision, if present, for removing the possible antibody stimulus. Isolated case reports regarding the use of TPE in treating anti-NMDA-R encephalitis described conflicting results [9,10]. Schimmel et al. [10] described a successful TPE treatment of anti-NMDA-R encephalitis in a 12-year-old girl—she was treated with TPE for eight procedures ~6 weeks from her admission. She showed improvement only after two TPE procedures and was able to achieve full recovery afterward [10]. However, TPE could only help to control seizures in a 42-year-old woman and she only achieved full recovery after intensive treatment with rituximab [9]. Both patients failed corticosteroids treatment before TPE, and IVIG was not used in any of these two patients [9,10]. To the best of our knowledge, our case series is the first one to describe the use of TPE as a possible treatment modality in this disease entity.

IgG antibodies have a long half-life as well as a large volume of distribution in the body; therefore, it will take approximately five to six TPE treatments to reduce the blood level substantially [12]. Because of the distribution of IgG in the intravascular and extravascular spaces, there is a suggestion that TPE should be scheduled every 24–48 h to allow for equilibration of the antibody between these spaces [13]. Furthermore, the antibody needs to equilibrate between the plasma and CSF, because the antibody titer in the CSF (but not in plasma) appears to correspond best with prognosis [5]. Therefore, optimized therapy would include five to six TPE procedures on alternate days. This was the approach used for the patients in this series. Recovery has been reported to be a gradual process with patients often requiring a long period of hospitalization [8]. Hence, it is not surprising that the majority of patients (89%) in this series did not improve during or shortly after the completion of TPE therapy.

Although there is no standard treatment regimen for anti-NMDA-R encephalitis, Dalmau et al. [5] proposed a treatment plan consisting of teratoma removal (if present), corticosteroids and IVIG or TPE as the first line of treatment, and rituximab and cyclophosphamide as the second line of treatment, if patients did not respond initially. The exact order of the treatments (i.e., corticosteroids, IVIG, and TPE) was not defined [5]. The treatment regimen for our patients was similar to this proposal. Interestingly, in our series, all four patients who had substantial improvement at discharge received TPE before IVIG. Furthermore, all of them

had TPE as either the first or second treatment option after diagnosis. Although the number of cases was small and the difference was not statistically significant, this observation suggested that early initiation of TPE could be beneficial.

Many patients with anti-NMDA-R encephalitis have autonomic instability that may lead to difficulty in administering TPE [5]. In our series, 6 of 11 adverse events were due to hypotension and were treated successfully with either fluid bolus or vasopressors. The remaining five adverse events occurred in one patient and were described as episodes of agitation. It was not possible to distinguish these events from her underlying disease. If these five events are excluded from the analysis, the incidence of adverse events was 11%, which is comparable to the incidence of complications reported in all TPE procedures done for all indications (5–12%) [12]. Therefore, TPE is a relatively safe treatment option in this group of patients, although they need to be observed closely for the development of hypotension and autonomic instability. It is the standard of care at CUMC to use 5% albumin and 0.9% normal saline as the replacement fluid in TPE for neurologic diseases, unless there is an indication to use plasma (e.g., to correct a coagulopathy). In patients with autonomic instability, increasing the ratio of 5% albumin to 0.9% saline in the replacement fluid could help prevent episodes of hypotension due to hypovolemia because of the difference in distribution of 5% albumin (only intravascular) to 0.9% normal saline (both intra- and extravascular).

All patients in this series had symptoms consistent with the known manifestations of anti-NMDA-R encephalitis [5,8]. Furthermore, they all had anti-NMDA-R antibodies. In addition to early diagnosis and initiation of treatment, the antibody titer has been associated with clinical outcome, especially the CSF titer [5,8]. Unfortunately, titer results were not available pre- and post-TPE procedures or at long-term follow-up, because the assay was routinely performed qualitatively. Moreover, the titer was often not performed because of the cost and the complexity of the assay (personal email from Josep Dalmau, March 10, 2011, unreferenced) as well as the difficulty and inconvenience in regularly obtaining CSF samples.

Regarding long-term morbidity, three of six patients available for long-term follow-up had substantial or full neurologic improvement. Two of the four patients with ovarian teratoma had improvement at the time of discharge and/or at long-term follow-up. This rate is low compared to the reported average of 75% of patients recovering completely or having mild sequelae [5]. Spontaneous neurologic recovery has also been reported without treatment [14]. Eight of nine patients in our series were diagnosed and treated within 4 months of the presenting symptoms, which places them in a good prognosis category [3]. Therefore, it is unclear why our patients had a lower rate of recovery than that reported in the literature; nonetheless, this might be due to the complexity of this disease and that many aspects and prognostic factors are still unknown.

There are several limitations to this study, including its retrospective observational nature. For example, there were only nine patients and their treatment plans were somewhat heterogeneous. Therefore, it is difficult to isolate the effect of TPE on the clinical outcome as well as to elucidate the role of TPE on modifying the course of the disease. Furthermore, the optimal treatment plan, as well as the time to start TPE with respect to the other immunosuppressive therapies, cannot be determined from these few cases. It has been suggested that this disease might be more common than what was originally thought [5]; thus, a randomized, controlled, multicenter, prospective trial (RCT) to determine the optimal treatment plan might be possible. Teratoma resection to remove the presumed stimulant for autoantibody production, immunosuppressive therapy (e.g., corticosteroids, IVIG, and rituximab) to inhibit antibody production and TPE to remove the plasma autoantibodies; all have a role in treating this disease. Although the risk of adverse events associated with TPE for treating this disease is similar to that associated with other diseases treated by TPE, RCTs should be designed to identify the role and safety of TPE in the treatment plan. One example would be a RCT consisting of corticosteroids and IVIG in one treatment arm and corticosteroids and TPE followed by IVIG in the other arm, assuming that teratomas are resected when appropriate. The type of replacement fluid(s), duration, and frequency of TPE as well as the order of TPE relative to other immunosuppressive therapies should also be explored.

CONCLUSIONS

TPE may have a role in treating anti-NMDA-R encephalitis. In our small patient series, early initiation of TPE, and TPE followed by IVIG, provided better outcomes. Furthermore, TPE appears to be a relatively safe treatment option. Further studies should be performed to identify the time, frequency, duration, and type of replacement fluid(s) used in TPE as well as the order of TPE relative to surgery and to other immunosuppressive therapies, such as IVIG and corticosteroids.

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