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Intravenous Methylprednisolone Versus Therapeutic Plasma Exchange for Treatment of Anti-N-Methyl-D-Aspartate Receptor Antibody Encephalitis: A Retrospective Review

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Introduction: Anti-N-methyl-D-aspartate (NMDA) receptor antibody encephalitis is an increasingly recognized form of autoimmune encephalitis. Conventional treatments include therapies such as corticosteroids, intravenous immunoglobulin (IVIg), and/or therapeutic plasma exchange (TPE). Although TPE is regularly used for treatment of anti-NMDA receptor antibody encephalitis, the American Society for Apheresis has given it a category III recommendation only. Earlier administered immunotherapies in tumor-negative patients may facilitate faster recoveries, but it remains unclear whether or not TPE is superior to steroids and/or IVIG.

Methods: We retrospectively evaluated 10 of 14 patients that received steroids and TPE with modified Rankin scores and subjectively assessed the point of largest sustained improvement in all 14 patients.

Results: In the patients that received both steroids and TPE at our institution during the same hospitalization (only 10 of 14 patients), 7/10 patients after TPE had improved with the modified Rankin score versus 3/10 patients after steroids. The average modified Rankin score improvement after steroids in this group was −0.1 as compared with 0.4 after TPE. Based on subjective chart review analysis during which all 14 patients were assessed, the largest sustained improvement occurred immediately following the third–fifth exchange in 9/14 patients, whereas only 2/14 patients appeared to have had significant benefit immediately following steroids.

Conclusions: This is compelling preliminary data that suggests that corticosteroids may not be as effective compared to steroids followed by TPE. Given the importance of time-sensitive treatment, more formal studies may illuminate the ideal first-line treatment for anti-NMDA receptor antibody encephalitis. J. Clin. Apheresis 00:000–000, 2015.

Key words: apheresis; NMDA encephalitis; plasma exchange

INTRODUCTION

Anti-N-methyl-D-aspartate (NMDA) receptor antibody encephalitis is an increasingly recognized form of autoimmune encephalitis characterized by encephalopathy, a movement disorder, seizures, and, often, behavioral/psychiatric changes [1–3]. First characterized in young females with benign teratomas less than 10 years ago, it has been recently recognized as one of the most common non-infectious causes of presumed encephalitis and it was responsible for up to 1% of intensive care unit admissions of unexplained encephalitis [4,5]. Typically, patients present with subacute new-onset seizures with variable rates and degrees of neurologic deterioration. By convention, patients are typically given high-dose intravenous steroids (such as methylprednisolone) for 3–5 days followed by intravenous immunoglobulin (typically dosed at 2 gm/kg over 3–5 days) and/or therapeutic plasma exchange (TPE) [2,6,7]. Collectively, these three treatments are considered "first-line" therapies in several large reviews of treatments and clinical courses, however the American Society for Apheresis (ASFA) has noted that there is a paucity of data to support TPE for routine use in anti-NMDA receptor antibody encephalitis [2,8,9].

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Following these options, some patients are treated with the "second-line" therapies, intravenous rituximab (with variable dosing regimens, including 375 mg/m^2 or a 1000 mg fixed dose) and/or intravenous cyclophosphamide (dosed typically at 750–1000 mg/m^2) [8]. Studies have shown that aggressive treatments, such as cyclophosphamide or rituximab, in poorly responding cases corresponded to improved recovery rates [2]. In patients with tumors at onset, removal of the tumor portends a good prognosis, however, especially in children, populations with low tumor rates tend to not respond as well to immunotherapies [8]. In addition, there are few studies comparing the relative impact of "first and/or second-line" therapies to one another.

Although TPE is not considered standard therapy for anti-NMDA receptor antibody encephalitis, recent published evidence demonstrates favorable response to this treatment modality. Current ASFA guidelines assign category III to paraneoplastic neurological syndromes, which includes anti-NMDA receptor antibody encephalitis [9]. There is a paucity of published reports on the role of TPE in the management of anti-NMDA receptor antibody encephalitis, and there are no published studies comparing TPE to other treatment modalities in the management of NMDA-R antibody encephalitis [10–12]. At our center, we have not clinically appreciated significant responses to intravenous steroids, and we performed a retrospective assessment of patients who have received both steroids and TPE at our center to determine if there was clear superiority of either therapy.

METHODS

After approval of the institutional IRB, all cases of anti-NMDA receptor antibody encephalitis were retrospectively assessed from January 1, 2009 through the end of 2013. Patients with known anti-NMDA receptor antibody encephalitis, confirmed by laboratory assessment of the serum and/or CSF performed by either ARUP, Athena labs, or Mayo, were identified from our adult and pediatric clinic populations. In addition, we retrospectively assessed their documented exam assessments by neurology, psychiatry (where applicable), and/or general pediatric or general internal medicine teams and scored their overall functionality and physical exam status with a modified Rankin score at admission and every five days thereafter throughout their hospitalization. The modified Rankin scale is a 6 item scale assessing level of disability ranging from 0 (no disability) to 6 (death), and although it is typically used in stroke patients, recent papers have noted some utility in other neurological conditions [13]. Three reviewers performed these assessments, one who was not blinded and was part of the patients' treatment teams, either inpatient and/or in the clinic, and two reviewers who were completely blinded to any treatments the patients had received. Medical records were printed and redacted to remove any information in regards to treatment courses in an attempt to remove the potential bias on the Rankin scores. Both immunotherapies and symptomatic therapies, such as benzodiazepines or antipsychotic medications, were redacted for the blinded reviewers. One of the reviewers had some knowledge of one of the adult patients, so she was asked not to score that patient. In addition to the modified Rankin scores, the reviewers were asked to make a subjective assessment based on the chart review of a day or several day span for which the most significant improvement was noted that was then sustained. An intraclass correlation coefficient assessing interrater reliability for the modified Rankin scores across the three reviewers was calculated to be 0.7395, thus confirming reliability across the non-blinded and two blinded reviewers [14]. All TPE procedures were performed using COBE Spectra and Spectra Optia cell separators (TerumoBCT, Lakewood, CO).

Adult Patients

One (patient 1) to 1.2 (patients 2,3) plasma-volume exchanges were performed. Replacement fluid was 5% albumin. Generally, first 2 procedures were performed daily, with the remainder on every other day schedule. Two patients (patients 1,2) received a course of 5 procedures each. One of them (patient 1) had an additional course of 5 TPE three weeks later. One patient (patient 3) started the TPE course at an outside institution receiving 2 daily procedures on days 1 and 2, and received additional 5 procedures at our facility every other day, for a total of 7 procedures. Citrate (ACDA) was used as the anticoagulant for all procedures with standard IV calcium chloride repletion.

Pediatric Patients

All children received 1.1 plasma volume TPE, performed every other day, for a total of 5 (one patient) or 7 (10 patients) treatments. Replacement fluid was 5% albumin unless pre-procedure fibrinogen was $<$140 mg/dL. Coagulopathic pediatric patients received one unit cryoprecipitated anti-hemophilic factor per 5 kg body weight as the final portion of fluid replacement. Citrate (ACDA) was used as the anticoagulant for all procedures with standard IV calcium chloride repletion. Calcium gluconate would have been preferred (due to lower side effect profile especially IV infiltration), but was not readily available due to local shortage.

RESULTS

There were a total of 14 patients, 3 adults and 11 pediatric age-range (defined as age $<$18 years) patients,

TABLE I. Mean and Change in Modified Rankin Scores at Admission and Precompletion and Postcompletion of Steroids and TPE

Patient	Mean admission Rankin score	Presteroids Rankin score	Pre-TPE Rankin score	Δ in mean Rankin score poststeroids	Δ in mean Rankin score post-TPE
1	5	5	5	0	0
2	3.3	3.3	3.7	0	0.4
3[a]	4	N/A	N/A	N/A	N/A
4[b]	5	N/A	N/A	N/A	N/A
5	4	4	3.7	0.7	1.4
6	3	4	4.3	−0.3	0.6
7	3.7	4.3	3.3	1	−0.7
8	4.7	4.7	5	−0.3	0.3
9	3	3	3	0	1
10	2.7	2.7	4.7	−1.6	−0.3
11	3	3	3.3	−0.3	1
12[c]	2	N/A	N/A	N/A	N/A
13[d]	4.7	N/A	N/A	N/A	N/A
14	4	4	4.3	0.3	0.3

[a]This patient received initial part of her care at an outside facility, including 2 rounds of TPE, and she completed the remainder of her TPE at our institution and, thus, she was not included in analysis.
[b]This patient also received initial part of her care, including steroids, IVIg, rituximab at an outside institution before being transferred to our facility.
[c]This patient was an infant and did not receive steroids due to a prior herpetic infection, he received IVIg and TPE.
[d]This patient went initially undiagnosed and only received TPE during his second (of two) hospitalizations.

who were treated at our institution. All 14 patients received TPE, but only 10 of 14 patients received both steroids and TPE at our institution during the same hospitalization – 4 patients were excluded from Rankin score analysis either because they did not receive steroids at all or received them prior to admission to our institution from an outside facility (see Table I). The ages of the patients ranged from 10 months to 46 years. Of the adults, two were male and one was female. Five of the pediatric patients were female, and six were male. None of the patients had tumors on initial presentation, although one of the pediatric patients was subsequently found on surveillance imaging to have a benign testicular tumor approximately four years after the anti-NMDA receptor antibody encephalitis diagnosis. Patients 1–3 and 11 were confirmed anti-NMDA receptor antibody positive in the CSF only, and the remainder of the patients were confirmed anti-NMDA receptor antibody positive in the serum.

Of the 14 patients that were retrospectively assessed subjectively, 10 patients had received both intravenous steroids and plasma exchange at our institution, although all 14 patients received TPE at some point during their treatment course. In the other 4 patients, 2 patients did not receive steroids at all, 1 patient received steroids at an outside facility prior to her admission and 1 patient received steroids during a prior hospitalization several months before diagnosis was established. All patients tolerated TPE well. One pediatric patient had a mal-positioned catheter, which resulted in an aborted TPE, a hydrothorax, catheter removal and replacement with a new central line. No other serious adverse events or side effects were observed. In addition, one patient (patient 3) developed dilutional hypofibrinogenemia following the first and fourth procedures that had not recovered by the following procedure, and received two units of fresh frozen plasma supplemented with the second and fifth procedure. One patient (patient 3) developed an episode of transient mild hypotension during TPE.

For the analysis, as noted above, the intraclass correlation coefficient for the interrater reliability of the modified Rankin scores was 0.7395. The average modified Rankin either pre-treatment or at admission score for the 10 patients that received both steroids and TPE was 4.2. For the 4 excluded patients from this analysis, the average modified Rankin score pre-treatment or at admission was 4.6. Scores for response to steroids or plasma exchange was based on the most immediate pre-intervention average Rankin score or the worst average pre-treatment score prior to completion of the therapy (as some patients had worsening during first 1–2 days of either therapy – see Table I). According to this assessment, of the 10 patients that had received both steroids and TPE, 3/10 patients had no clear improvement based on the modified Rankin scores with intravenous steroids; 4/10 patients worsened in their average modified Rankin scores, and 3/10 patients had clear improvement in the average Rankin scores following steroid treatment. For plasma exchange, only one of the patients had no change in the average Rankin scores, two patients worsened in their average Rankin scores and 7/10 patients improved. The average modified Rankin score improvement after steroid treatment in the 10 patients that had received both therapies was −0.1, whereas the average modified Rankin score

TABLE II. Timing of Treatments and Periods of Recovery for Adult and Pediatric Patients with Anti-NMDA Receptor Antibody Encephalitis

Pt \ Day	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 39 39 40 41 42 43 44 45 46 47 48 49 50 56 61 73 76 112 116 139 170
1	>>> S S S S S >>> SPSPS SP S P >>> P C >>> P P >>> P >>> P >>> P >>> R **>>>** >>> D
2	S S S S SPP >>> P >>> P >>> P **>>> P >>>** >>> C >>> D
3	>>> P >>> P >>> **P** >>> P >>> P >>> R D
4	>>> P >>> P >>> P >>> P >>> P >>> P >>> P >>> C >>> M >>> **M** D
5	S SP >>> P >>> P >>> **P >>> P** >>> P >>> P >>> D
6	>>> S S S S S P >>> P >>> **P >>> P >>> P >>> P >>> P >>>** D
7	>>> I I I I I >>> S S **S S S P >>> P >>> P >>> P >>> P >>> C >>>** >>> D[a]
8	>>> SPS SPS SP >>> P >>> P >>> **P R P >>> I I I I I >>> R >>>** C >>> D
9	>>> S S SPS SP >>> P >>> P >>> **P >>> P** >>> P D
10	>>> SPS SPS P >>> P >>> P >>> P >>> P I I I I I R >>> **R >>> C >>>** >>> D[b]
11	>>> S S S S S P >>> **>>>** P >>> P >>> P >>> P >>> D
12	>>> I I I I I >>> P >>> P >>> P >>> **P >>> P >>>** P >>> P >>> D[c]
13	>>> P >>> P >>> P >>> P **>>> P >>> P >>> P >>>** D
14	>>> S S S S S P >>> P >>> P >>> P **>>> P >>>** >>> C >>> D

[a]Discharge date approximate, patient 7 discharged on day 51.
[b]Discharge date approximate, patient 10 discharged on day 54.
[c]Discharge date approximate, patient 12 discharged on day 53.
C: cyclophosphamide; I: intravenous immunoglobulin; S: steroids (methylprednisolone); P: plasma exchange; M: intravenous methotrexate; R: rituximab; D: day of discharge; Shaded areas: areas of sustained improvement.

improvement after TPE in those same 10 patients was 0.4. These overall numbers were not sufficient for statistical analysis. With regards to the retrospective assessment of improvement, reviewers were asked to determine the day at which (if applicable as some patients did not have days of clear sustained improvement) there subjectively appeared to be the largest and most sustained improvement (see Table II). The "largest" improvement was defined as the biggest subjective neurologic improvement based on chart review, and "sustained" improvement was defined as improvement not followed by neurologic regression or deterioration as assessed on chart review. All 14 patients had received TPE and were assessed in this manner, although 4 of the patients had received steroids prior to admission at an outside facility or had not received steroids during the same hospitalization. In 9/14 patients, this was identified as occurring at or near the completion of 3 or more plasma exchanges; 3/14 patients had identified improvement later in their courses after chemotherapy interventions were required, not clearly temporally linked to either intravenous steroids or plasma exchange. Finally, 2/14 patients had their first identified largest and most sustained improvement near the completion or immediately following the completion of steroids. Although there was some variability between reviewers, assessment of the time period of the largest sustained improvement varied by five days or less in 50% of patients and varied by fourteen days or less in 85% of patients (See Table II). Of note, in our most severe adult patient, both reviewers (one of the blinded reviewers was unable to retrospectively assess patient due to prior knowledge of the patient) felt that the patient had the most improvement on the same hospitalization day. In our most severe pediatric case, only one of the reviewers was able to identify a day retrospectively where a clear sustained improvement began.

DISCUSSION

In this retrospective chart review, we note fewer patients showed improvements as assessed using modified Rankin scores following corticosteroids as compared immediately following TPE. Furthermore, when the charts were assessed with two reviewers blinded to the treatments and one unblinded reviewer, there was agreement that the point at which there was the largest sustained improvement was at a point in which TPE should have reached peak efficacy, between the third–fifth exchange. Of concern with respect to steroids was that the average Rankin score improvement was −0.1 when immediate (or admission) Rankin score was compared with the post-steroids Rankin score, and just as many patients worsened after steroids, (4 patients), as improved (3 patients).

There were significant limitations to this study. First, steroids were given prior to TPE in all 10 patients that received both treatments at our institutions, and we cannot necessarily attribute all the perceived benefits to only the TPE that was noted in the Rankin score analysis. All patients did receive TPE, and in 9/14 patients as assessed subjectively on chart review, there appeared to be a clear temporal link between TPE and clinical improvement. In addition, our numbers are too small for formal statistical analysis. Despite the data being retrospective, we did feel that using blinded reviewers to both subjectively assess the clinical courses and assign Rankin scores suggests that this preliminary data is compelling.

In anti-NMDA receptor antibody encephalitis, although there is evidence to suggest that earlier immunotherapy is superior, the lack of data from head-to-head treatment trials may be, at least in part, contributing to the small but significant minority of patients that poorly respond to therapies [8]. Furthermore, it should be noted that 8/14 of our patients required more intensive immunotherapy, which included cyclophosphamide, rituximab, or intravenous methotrexate, so the role for more aggressive therapies beyond TPE, steroids, or IVIg cannot be stressed enough at this point. In addition, because TPE is not available at all medical centers, unlike steroids or IVIg, which are more widely available, superiority of this therapy is important to establish as it has impact on where these patients need to be treated.

CONCLUSION

We have found preliminary compelling data to suggest that TPE after steroids might be more efficacious than corticosteroids alone in the early stages of anti-NMDA receptor antibody encephalitis. Although our study has limitations, with respect to the small numbers and that TPE was administered after steroids, we feel that the blinded assessments add to the potential impact of this chart review. Further head-to-head studies are warranted, as successful treatment of this condition is known to be time-sensitive with respect to immunotherapy [2,8].

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