Efficacies of treatments for anti-NMDA receptor encephalitis

Hsiuying Wang[1]

[1]*Institute of Statistics, National Chiao Tung University, Hsinchu 30010, Taiwan*

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1. ABSTRACT

Treatments for anti-N-methyl-D-aspartate (NMDA) receptor encephalitis include immunotherapy with steroids, intravenous immunoglobulin, plasma exchange, or plasmapheresis as first-line treatments, immunotherapy with rituximab or cyclophosphamide as second-line treatments, and tumor removal. In this systematic review, we evaluated previous studies and examined the association between certain microRNAs and anti-NMDA receptor encephalitis to investigate the performance of different treatment combinations. The efficacies of different combinations of treatments classified into the following four categories were compared: (I) intravenous immunoglobulin administration, (II) plasmapheresis or plasma exchange, (III) treatment with rituximab or cyclophosphamide and (IV) tumor removal. Statistical analyses showed that treatment combinations including at least two of these categories resulted in higher efficacy rates than treatment with a single form of therapy. These findings suggest that if a patient is not recovering, converting to other therapies is more likely to result in early recovery than continuing on the original therapy.

2. INTRODUCTION

Anti-N-methyl-D-aspartate (NMDA) receptor encephalitis is an acute form of encephalitis that has recently been reported as an autoimmune disorder exhibiting a well-defined set of clinical features. This form of encephalitis was described and defined by Dalmau *et al* (1). Thereafter, new cases of anti-NMDA receptor encephalitis have been identified around the world, and many cases have been reported in the literature. A diagnosis of anti-NMDA receptor encephalitis requires the detection of anti-NMDA antibodies in the blood or spinal fluid of an individual in association with symptoms consistent with this disease. Currently, this disease can be diagnosed using a test that was developed at the University of Pennsylvania and that is available worldwide. However, anti-NMDA receptor encephalitis is a rare disease, and patients with this disease may not be diagnosed early. In general, early diagnosis and aggressive treatment improve patient outcomes.

Most patients with anti-NMDA receptor encephalitis develop a multistage illness that progresses from initial psychiatric symptoms to memory disturbances, seizures, dyskinesia and catatonia. In addition to these symptoms, tumors have been detected in a proportion of anti-NMDA receptor encephalitis patients according to previous studies. Therefore, it has been suggested that these patients be screened for tumors.

Steroids, intravenous immunoglobulin (IVIG) or plasma exchange (or plasmapheresis) either alone or in combination constitute the first-line immunotherapies for anti-NMDA receptor encephalitis; rituximab or cyclophosphamide is administered alone or in combination as a second-line immunotherapy. It is suggested that identified tumors be resected from these patients. Most patients are initially treated with steroids. Because steroids are commonly initially administered to encephalitis patients and because their cost is low, we did not consider treatment with steroids in our comparison of treatments. In this study, we compared the effects of different combinations of therapies, including IVIG, plasma exchange (or plasmapheresis), rituximab (or cyclophosphamide) and tumor resection.

Although it has been reported that 79% of patients with anti-NMDA receptor encephalitis achieve a good outcome within 24 months of disease onset (2), some patients largely recover within approximately one year. Because an increasing number of anti-NMDA receptor encephalitis cases are being diagnosed, it is important to identify the factors that may lead to early recovery. The choice of treatments may be a factor that promotes early recovery from anti-NMDA receptor encephalitis, and physicians can more easily control the selection of treatments than other factors, such as the overall health of a patient, which cannot be controlled directly by physicians. As a result, it is difficult for such factors to be of practical use in the development of

strategies to promote early recovery from anti-NMDA receptor encephalitis. Therefore, in this study, we focused on comparing the response to treatments for anti-NMDA receptor encephalitis.

Regarding anti-NMDA receptor encephalitis, it has not been shown whether any particular treatment regimen is superior to another. Moreover, it is difficult to directly compare the effects of different treatments. The possible reasons why it is unknown whether any one set of treatments is more beneficial than another are that (i) no single treatment regimen is superior to the others or (ii) the treatment effects are confounded because each patient may receive different treatments. Therefore, in this study, we collected case reports that clearly described the therapies used to treat patients with anti-NMDA receptor encephalitis and then analyzed the differences in treatment between the patients who recovered early and those who did not. The results of this study showed that combinations of treatments including at least two therapy categories resulted in higher efficacy rates than treatments with a single form of therapy.

In addition to comparing these case reports, we reviewed a previous study of the relationship between the levels of microRNAs (miRNAs) and anti-NMDA receptor encephalitis. miRNAs are single-stranded, non-coding RNAs consisting of 22–24 nucleotides that play important roles in genome expression and that are involved in several biological processes (3-5). Among the several hundred miRNAs expressed in the human brain, let-7 is one of the most abundant (6). Significant down-regulation of let-7a, let-7b, let-7d, and let-7f was demonstrated in anti-NMDA receptor encephalitis patients (7).

It has been revealed that let-7 is closely associated with human cancer and innate immune responses (8); it is often suggested that those with these diseases receive multiple forms of treatment. This recommendation coincides with the suggested therapeutic strategy for anti-NMDA receptor encephalitis, in which let-7 is significantly down-regulated.

3. METHODS

We searched for case reports in the literature and evaluated treatment combinations with respect to the endpoint of complete recovery within approximately one year. We reviewed case reports of 94 anti-NMDA receptor encephalitis patients, including 18 male patients and 76 female patients. The age of the patients ranged between 8 months and 84 years. The treatment regimens administered to these patients were classified into 4 categories: IVIG; plasma exchange or plasmapheresis; rituximab or cyclophosphamide; and tumor resection. Any treatment regimen that included different categories was considered as a treatment combination.

The treatments received by each patient are listed in Table 1. Although 79% of anti-NMDA receptor encephalitis patients completely recovered within 2 years (2), many cases achieved good recovery within approximately one year of symptom onset. To compare the efficacies of different treatment combinations and to identify treatment combinations that may shorten the recovery time, we set one year as a threshold for the recovery time. For each treatment combination, we calculated the efficacy rate as the ratio of the number of patients with a recovery time within approximately one year to the total number of patients who received the given treatment combination. A higher efficacy rate of a given treatment combination indicates that this treatment combination is more likely to result in recovery within one year of symptom onset.

Table 1 presents gender, age, treatments administered, the corresponding references, and the recovery time (within or beyond approximately one year) for the 94 patients included in our analysis. In three cases presented in Table 1, the treatment of the patients requires explanation. Systemic hypotension occurred as a complication during a second plasma exchange session in the patient described in reference (9). Therefore, we recorded only the IVIG treatment administered to this patient. The patient described in (10) began rituximab therapy at 13 months after initial discharge. Because the efficacy rate was computed only for recovery times within approximately one year, we considered only the IVIG treatment that was administered to this patient. Tumor resection was performed on the patient described in (11) more than one year after symptom onset; therefore, we did not consider this treatment in certain analyses.

4. RESULTS

We used the cases listed in Table 1 as a random sample to compare the efficacy rates of different treatment combinations. We separated the treatments into 4 categories, as shown in Table 1: (I) IVIG administration, (II) plasma exchange or plasmapheresis, (III) treatment with rituximab or cyclophosphamide and (IV) tumor resection. We applied a logistic regression model to explore the relationship between the efficacy rate and each form of treatment.

Let x_i, $i = 1,\ldots,4$ denote the indicator function of receiving a treatment in the ith category. That is, let $x_i = 0$ or 1 indicate that a patient did not receive or did receive a treatment in the ith category, respectively. Consider the logistic regression model

$$\log\frac{p}{1-p} = \alpha + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \beta_4 x_4, \qquad (1),$$

where $\beta_i,\ i = 1,..,4$ and α are the coefficients of the regression model and p is the proportion of patients with a recovery time within approximately one year, conditional on x_i. We applied model (1) to the data for the 94 patients analyzed in this study. The estimated values for α and β_i and their corresponding p-values are presented in Table 2. The results showed that the effects of each form of treatment, with the exception of tumor resection, were not significant.

Although the effects of the individual treatments in categories (I)-(III) were not significant, our primary interest was to identify treatment combinations that result in significantly shortened recovery, as many patients receive more than one form of treatment. Because the sample sizes for some treatment combinations were not sufficiently large to draw firm conclusions, we instead focused on the relationship between the efficacy rate and the number of categories of treatments included in a treatment combination. The efficacy rates of the 5 possible treatment categories included in a treatment combination, ranging from no treatment to all 4 treatment categories, are presented in Table 3. A comparison of these rates revealed that the efficacy rates of treatment combinations including more than 1 form of treatment were higher than those including only a single form of treatment. However, most likely because of the insufficient sample sizes for certain treatment combinations, for example, a sample size of 3 for the treatment combination consisting of all 4 forms of treatment, no statistically significant difference was observed between the 5 possible treatment categories. Figure 1 shows a histogram of the treatment combinations including different numbers of treatment categories according to the recovery time.

To determine the relationship between efficacy rates and treatment combinations, we analyzed the data using additional logistic regression models. Significant results were found using the logistic regression model

$$\log\frac{p}{1-p} = a\ s \qquad (2),$$

where $s = 0$, 1 denotes that the treatment included no greater than 1 category of treatment or more than 1 category of treatment, respectively and where p is the proportion of patients experiencing recovery within approximately one year, conditional on s. That is, s=0 represents the treatment combinations consisting of a single form of treatment, and s=1 represents the treatment combinations consisting of at least two forms of treatment.

The estimated value of a for model (2) was $\hat{a} =$ 1.2993, with a p-value of 0.0047. This result showed that the efficacy rates between a single form of treatment and treatment combinations were significantly different. Table 4 shows that the efficacy rates were 0.5 for receiving a single form or no forms of treatment and 0.786 for receiving at least 2 forms of treatment.

Additional statistical analyses were performed to validate this conclusion. Using a method that compares two binomial proportions, we tested whether the efficacy rate of receiving a single form of treatment was equivalent to the efficacy rate of receiving at least 2 treatments; we obtained a p-value of 0.003, which resulted in the rejection of the null hypothesis considering a type 1 error threshold of 0.05. Therefore, we concluded that therapies including at least 2 forms of treatment had a higher efficacy rate than therapy using only one or no forms of treatment. Additionally, the odds ratio was $(19\times12)/(44\times19) = 0.27$; this result showed that patients who received at least 2 forms of treatment were much more likely to recover within one year than patients who received only one or no forms of treatment. We also calculated 95% confidence intervals for both efficacy rates; these intervals were (0.34, 0.66) for the efficacy rate of receiving a single or no forms of treatment and (0.68, 0.89) for the efficacy rate of receiving at least 2 forms of treatment. The upper bound of the formal interval, 0.66, is smaller than the lower bound of the latter interval, 0.68.

The efficacy rates for the male and female patients were 0.389 and 0.727, respectively. Using a method that compares two binomial proportions, we tested whether the efficacy rates for males and females were equivalent; we obtained a p-value of 0.007, which resulted in a rejection of the null hypothesis considering a type 1 error-threshold of 0.05. Thus, we concluded that the efficacy rates were higher in the female patients than in the male patients.

The numbers of patients who received treatments in each of the 4 categories are presented in Table 1. Next, we ranked the probabilities that each treatment category would be used. We considered this analysis as a ranking of the responses to a multiple-response question because each patient could choose any of the treatments, with the exception of tumor resection. Thus, we applied the ranking code “rank.wald” in the R package RankResponse (12) to rank these treatments (12, 13). The ranks of the 4

treatment categories were found to be 1, 4, 4, and 4, corresponding to the first, second, third and fourth categories, respectively. These data showed that IVIG was administered the most frequently.

5. DISCUSSION

The results of this study showed that different treatment combinations result in significantly different outcomes. However, this study contains some limitations. One limitation is that the data analyzed in this study were collected from case reports. Additional factors such as treatment delays and disease severity are known to influence patient outcomes, and we cannot determine whether any of these additional factors varied among the patients analyzed in this study. However, because anti-NMDA receptor encephalitis is a rare disease, even in the context of a carefully designed experiment, it would be difficult to control for the influences of these factors on patient outcomes. Therefore, we believe that any significant results obtained by analyzing different treatment strategies according to case reports can provide useful information about the efficacy of therapies for anti-NMDA receptor encephalitis.

In addition, treatment decisions for the population studied were based on several factors, including treatment decisions by patients, the presence or absence of a tumor, and physician- and institution-specific factors. Potential side effects and the risk of recurrence are additional important factors in treatment decisions. Therefore, we do not recommend any specific treatment based on the results of this study.

6. CONCLUSION

Anti-NMDA receptor encephalitis is an acute encephalitis that presents with psychiatric symptoms in association with other symptoms characteristic of encephalitis. Low-grade fever, headache, common cold-like symptoms, and gastroenteritis are prodromal symptoms that are observed in most cases. A portion of anti-NMDA receptor encephalitis patients who are diagnosed early and treated properly have a good prognosis. The recovery time of the cases experiencing complete recovery ranges from several months to several years. In this study, we compared the cases with a recovery time within approximately one year to the cases with a recovery time of greater than one year. The results revealed that patients who received more than one form of treatment had a significantly shorter recovery time than those who received a single form of treatment. These results suggest that if a patient is not recovering, converting to other therapies is more likely to result in early recovery than continuing on the original therapy. In addition, after steroids, IVIG was most frequently administered to patients with anti-NMDA receptor encephalitis.

7. ACKNOWLEDGMENTS

This study was supported by the Ministry of Science and Technology of Taiwan (103-2118-M-009-001-MY) and was particularly supported by National Chiao Tung University, Taiwan.

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Key Words: Anti-NMDA Receptor Encephalitis, Treatment, Efficacy Rate

Address correspondence to: Hsiuying Wang, Institute of Statistics, National Chiao Tung University, Hsinchu 30010, Taiwan; Tel: 886-3-5712121 ext. 56813; Fax: 886-3-5728745; E-mail: wang@stat.nctu.edu.tw

Table 1. Treatment of ninety-four anti-NMDA receptor encephalitis patients

Gender	Age (years)	Complete recovery within approximately one year	Treatment category				Reference
			I	II	III	IV	
M	45			v	v		(14)
F	30		v	v	v		(15)
F	19	v	v	v		v	(16)
F	23	v	v	v	v	v	(17)
F	25						(18)
F	9						(19)
F	11	v	v		v		(20)
F	17	v	v			v	(21)
F	9	v	v		v		(22)
F	17		v	v	v		(23)
F	3	v	v		v		(24)
M	16		v				(24)
F	35	v	v		v	v	(25)
M	20 months		v		v		(26)
F	26	v				v	(27)
F	23		v				(9)
F	3	v	v				(28)
F	18	v		v		v	(29)
F	16	v	v	v		v	(30)
F	20 months	v	v		v		(31)
M	30	v	v	v			(32)
M	2		v				(10)
F	9	v	v	v	v	v	(33)
M	8 months		v				(34)
F	4	v	v				(35)
M	50	v					(36)
M	8		v				(37)
F	16		v				(38)
M	35				v		(39)
F	3 years 2 months		v	v	v		(40)
F	9	v	v		v		(41)

F	14	v	v				(42)
F	7		v	v	v		(43)
F	8		v				(43)
M	73	v					(44)
F	65			v	v		(45)
M	66	v	v	v	v		(46)
F	4	v	v				(47)
M	8	v	v		v		(47)
F	14		v				(48)
F	5	v	v				(49)
F	21	v	v	v		v	(50)
F	14	v	v		v	v	(51)
F	25	v	v	v			(52)
F	26	v	v				(53)
F	15	v	v		v		(54)
F	15	v	v		v		(54)
F	17	v	v	v	v		(54)
F	31	v		v	v		(55)
M	6	v	v				(56)
F	4		v				(56)
M	17	v	v	v			(57)
F	24	v	v	v		v	(58)
F	21	v	v			v	(59)
F	14	v	v	v	v		(60)
F	29	v	v		v	v	(61)
F	34	v	v	v	v	v	(62)
F	42	v					(63)
F	38	v					(63)
M	13.5		v				(64)
F	29	v		v	v		(65)
M	68						(66)
F	17	v		v		v	(67)
F	41	v					(68)
F	70	v			v		(69)
F	19		v				(70)
F	33	v		v		v	(71)
F	27 months	v	v		v		(72)
F	27 months	v	v	v	v		(72)
F	27	v	v			v	(73)
F	11	v		v		v	(74)
F	20	v				v	(75)
F	21	v	v	v		v	(76)
F	42		v			v	(77)
M	18		v		v		(78)
F	15	v	v			v	(79)
F	21		v	v		v	(80)
F	84		v	v			(80)
M	38		v	v	v		(80)
F	65					v	(81)
F	19	v		v	v	v	(82)
F	21	v	v			v	(83)
F	3 years 9 months	v	v				(84)
F	21						(11)
F	15	v	v			v	(85)
F	20	v	v			v	(86)
F	17		v				(87)
F	33		v				(87)
F	5	v					(88)
F	25	v	v			v	(89)
F	26	v	v			v	(90)
F	17	v				v	(91)
F	28	v					(92)
F	18	v		v		v	(93)
Total		63	67	32	33	32	

(I) IVIG administration; (II) plasma exchange or plasmapheresis; (III) treatment with rituximab or cyclophosphamide; (IV) tumor resection

Table 2. The effect of each treatment

	Estimated value	***p*-value**
α	0.1485	0.7665
$\beta 1$ (treatment in category (I))	-0.2381	0.6563
$\beta 2$ (treatment in category (II))	-0.2602	0.6489
$\beta 3$ (treatment in category (III))	0.7048	0.2021

β4 (treatment in category (IV))	2.2857	0.0011 (< 0.05)

Table 3. Number of patients and efficacy rates for each number of treatment categories included in the therapy

Number of categories of treatments administered	**0**	**1**	**2**	**3**	**4**	**Total**
Complete recovery within approximately one year	7	12	28	13	3	63
Complete recovery beyond one year	4	15	6	6	0	31
Total	11	27	34	19	3	94
Efficacy rate	0.636	0.444	0.824	0.684	1	0.670

Table 4. Number of patients and efficacy rates for therapies including one or no treatment categories and for therapies including least two treatment categories

	One or no treatment categories	**At least two treatment categories**	**Total**
Complete recovery within approximately one year	19	44	63
Complete recovery beyond one year	19	12	31
Total	38	56	94
Efficacy rate	0.5.	0.786	0.67
95% CI of efficacy rate	(0.34, 0.66)	(0.68,0.89)	(0.57,0.77)

Figure 1. Histogram showing the number of patients receiving each number of treatment categories according to the recovery time.

Running title: Efficacies of treatments for anti-NMDA receptor encephalitis