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Frequent rhabdomyolysis in anti-NMDA receptor encephalitis

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ABSTRACT

The aim of this study was to analyze the clinical presentation and provocation factors of rhabdomyolysis in anti-NMDAR encephalitis. Among the 16 patients with anti-NMDAR encephalitis in our institutional cohort, nine patients had elevated CK enzyme levels and clinical evidence of rhabdomyolysis. Rhabdomyolysis was more frequent after immunotherapy. The use of dopamine receptor blocker (DRB) increased the risk of rhabdomyolysis. None of the patients without rhabdomyolysis received DRBs. Rhabdomyolysis is a frequent complication in anti-NMDAR encephalitis and more common after immunotherapy and the use of DRBs increases the risk. Therefore, DRBs should be administered carefully in patients with anti-NMDAR encephalitis.

1. Introduction

Anti-*N*-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is the most common autoimmune encephalitis. In this condition, IgG antibodies against the NR1 subunit of *N*-methyl-D-aspartate receptor (NMDAR) induce subsets of symptoms (Dalmau et al., 2008; Titulaer et al., 2013). Treatment includes immunotherapy and tumor removal.(Dalmau et al., 2008; Titulaer et al., 2013) While approximately 80% of patients have good outcomes, still many experience life-threatening illnesses because of intractable seizure, ventilator care, or rhabdomyolysis.

Rhabdomyolysis is a critical syndrome in which damaged muscle fibers degrade, and muscle components leak into blood. It is often a major cause of morbidity and mortality and results in acute renal failure (Bosch et al., 2009). Rhabdomyolysis often worsens general health conditions of patients and results in admission into intensive care units. While status epilepticus and neuroleptic malignant syndrome (NMS) cause rhabdomyolysis, patients with anti-NMDAR encephalitis also experience rhabdomyolysis because of severe dyskinesia and dystonia (Chapman and Vause, 2011). In addition, because dopamine receptor blockers (DRBs) are frequently administered to patients to control psychiatric symptoms or bowel immobility, they could serve as a risk of rhabdomyolysis.

In this study, we observed a high frequency of rhabdomyolysis in the anti-NMDAR encephalitis population. To identify the possibility of any prevention, here we analyzed the clinical characteristics and precipitating factors for rhabdomyolysis in anti-NMDAR encephalitis.

2. Methods

2.1. Study population

We used the Korea Autoimmune Synaptic and Paraneoplastic Encephalitis Registry (KASPER), which is a prospective, nation-wide multicenter registry for autoimmune and paraneoplastic encephalitis, to identify subjects between Jan. 2013 and Nov. 2015. From the registry, we selected patients with anti-NMDAR encephalitis that were treated in our institution (Seoul National University Hospital (SNUH)). The institutional review board of the SNUH approved this study, and all patients provided written informed consent to participate in the registry.

The presence of autoantibodies was initially screened by immunostaining rat brain sections with patients' serum (1:200) and cerebrospinal fluid (CSF) (1:20), as previously described (Lancaster et al., 2010). Then, the presence of autoimmune synaptic antibodies was tested using a cell-based immunocytochemistry method (Euroimmune Ag, Germany). Autoantibodies to classic paraneoplastic antigens were tested using the immunoblotting method (Euroimmune Ag, Germany).

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2.2. Analysis of clinical, laboratory and treatment profiles

Clinical information was obtained by a review of medical records. Symptoms were categorized into eight groups: psychiatric symptoms, seizures, movement disorders, memory dysfunctions, language dysfunctions, autonomic instability, hypoventilation, and decrement of consciousness (Dalmau et al., 2008; Titulaer et al., 2013). CSF examinations, brain magnetic resonance imaging (MRI), electroencephalography (EEG), and radiologic screening for a systemic tumor were reviewed. Clinical outcome was assessed by the modified Rankin scale (mRS).

Rhabdomyolysis was defined as an elevation of serum creatinine kinase (CK) above the normal range (20–270 IU/L). DRB-related rhabdomyolysis (DRB-rhabdomyolysis) was defined as a serum CK elevation that occurred within 72 h of exposure to DRB. DRB includes the administration of typical and atypical antipsychotic medication and metoclopramide, which are known to cause NMS. The pre-/post-immunotherapy period was defined as the period before and after starting any immunotherapy for anti-NMDAR encephalitis.

3. Results

Eighteen patients were diagnosed with anti-NMDAR encephalitis during the study period. Among them, two were excluded because of insufficient clinical information. Nine (56.2%) developed rhabdomyolysis. Table 1 summarizes the demographic and clinical characteristics of the patients. There was no difference in the baseline clinical characteristics between patients with rhabdomyolysis and those without it. However, all patients with rhabdomyolysis showed aggravation of dyskinesia, dystonia, or catatonia before CK elevation. None of the patient with rhabdomyolysis had exacerbation of seizure or development of status epilepticus. Fig. 1 shows the timeline of patients with rhabdomyolysis. The median interval from symptom onset to rhabdomyolysis was 34 days (ranging from six to 303 days).

Rhabdomyolysis was more frequent after immunotherapy. Seven patients had rhabdomyolysis during the post-immunotherapy period, while only two had rhabdomyolysis during the pre-immunotherapy period. Median time from immunotherapy to rhabdomyolysis was 25 days (ranging from five to 259 days).

Introduction of DRB during the post-immunotherapy period increased the risk of DBD-rhabdomyolysis. During the post-immunotherapy period, the administration of DRB to 17 of the selected patients resulted in three cases of DRB-rhabdomyolysis [frequency = 0.18 per one DRB; number needed to harm (NNH) = 5.7]. In the pre-immunotherapy periods, a DRB was introduced three times, however, none of them elicited rhabdomyolysis within 72 h of DRB exposure. The DRB included antipsychotics and antiemetics, including haloperidol ($n = 3$), risperidone ($n = 2$), olanzapine ($n = 5$), quetiapine ($n = 7$), aripiprazole (n = 2), and metoclopramide ($n = 1$). Among these treatments, haloperidol, olanzapine, and metoclopramide induced DRB-rhabdomyolysis. None of the patients without rhabdomyolysis received DRB treatment. The CK level was significantly elevated in the patients who were received the DRB (583 IU/L vs 2745 IU/L, $p = 008$). Initial disease severity assessed by mRS within the first week of symptom onset was not correlated with the CK level ($\rho = -0.103$, $p = 0.714$).

Table 2 presents the treatment and outcome of rhabdomyolysis. Two patients recovered spontaneously. Three patients received high-dose benzodiazepine, which resulted in a successful recovery. Four of the six patients who received DRBs discontinued their use, and dopamine agonists, such as dantrolene and bromocriptine, were administered to three of them. To avoid azotemia, seven patients received intravenous hydration, and two patients were treated with urinary alkalization. One patient developed acute kidney injury and required renal replacement therapy.

At the time of the last follow-up (median 11.2 months, range 1.2–22.9), 33.3% with rhabdomyolysis showed a poor outcome (mRS > 2), while 85% of the patients without rhabdomyolysis showed a good outcome (median follow up 14 months, range 4.0–26.0).

Table 1
Demographics and clinical characteristics of patients.

Subject characteristics	All (n = 16)	With rhabdomyolysis ($n = 9$)	Without rhabdomyolysis ($n = 7$)	p-Value
Age (range)	19.5 (1–44)	22 (12–44)	18 (1–37)	0.470
Female	13	8 (88.9%)	5 (71.4%)	0.550
Clinical symptoms				
Psychiatric symptoms	13	9 (100%)	4 (57.1%)	0.063
Seizure	15	9 (100%)	6 (85.7%)	0.438
Movement disorders	15	9 (100%)	6 (85.7%)	0.438
Memory disturbance	7	4 (44.4%)	3 (42.7%)	1.000
Language dysfunction	10	7 (77.8%)	3 (4.27%)	0.302
Autonomic instability	13	9 (100%)	4 (25%)	0.063
Hypoventilation	4	2 (22.2%)	2 (28.6%)	1.000
Decreased mentality	14	9 (100%)	5 (50%)	0.175
Tumor	4	3 (33.3%)	1 (14.3%)	0.585
Abnormal CSF	11	6 (66.7%)	5 (71.4%)	1.000
Pleocytosis	11	6 (75%)	5 (71.4%)	1.000
Increased protein	5	2 (25%)	3 (50%)	0.608
Abnormal EEG	16	9 (100%)	7 (100%)	
Interictal epileptiform discharge	8	6 (66.7%)	2 (25%)	0.315
Abnormal MRI	5	2 (22.2%)	3 (42.7%)	0.596
Peak CK level, IU/L (range)	–	2551 (692–6653)	154 (26–239)	0.000

CSF, cerebrospinal fluid; EEG, electroencephalography; MRI, magnetic resonance imaging; Pleocytosis, CSF white blood cell count > 5/mm^3; increased protein level, CSF protein concentration > 45 mg/dL. Statistical analyses were performed using the Mann-Whitney U test or Fisher's exact test, depending on the variables. CSF data are available for eight patients in the rhabdomyolysis group.

4. Discussion

This study indicates that rhabdomyolysis is a frequent complication in anti-NMDAR encephalitis. Seven (77.7%) patients developed rhabdomyolysis in post-immunotherapy and that the use of DRB after immunotherapy increases the risk. NNH for rhabdomyolysis of DRB was 5.7 after immunotherapy, which is high compared to the general incidence of rhabdomyolysis during the use of DRB (Packard et al., 2014).

Although the mechanism of rhabdomyolysis in anti-NMDAR encephalitis is uncertain, it might be related to the aggravation of dyskinesia and hypersensitivity to DRB after immunotherapy, as we observed. The severity of disease was not correlated with the development of rhabdomyolysis. However, CK level was higher with the patients who received DRB and abnormal movements were aggravated after the introduction of DRB. With the removal of antibodies and the recovery of the synaptic NMDARs after immunotherapy, clinical improvement occurred in reverse order of the symptom presentation (Dalmau et al., 2011). Therefore, abnormal movements can be aggravated after immunotherapy with the recovery of consciousness. In addition, it has been known that NMDAR antagonists increase dopamine release, and NMDAR agonists decrease dopamine release (Lorrain et al., 2003). Accordingly, as synaptic NMDARs recover after immunotherapy, they can suppress the dopaminergic system, thereby inducing a hypersensitivity to DRBs.

Rhabdomyolysis can be fatal. Acute kidney injury has been reported in 15%–46% of cases that include rhabdomyolysis. The rate of mortality varies from 3.4% to 59% (Bosch et al., 2009). In our population, one patient required renal replacement therapy, and one patient died. The fatal case showed spontaneous aggravation of rigidity and dyskinesia during immunotherapy, without the use of DRBs. Accordingly, after immunotherapy, close monitoring of rhabdomyolysis and prompt management are necessary.

Rhabdomyolysis is treatable when managed properly. A strategy that can be used to preserve renal function is important. Massive

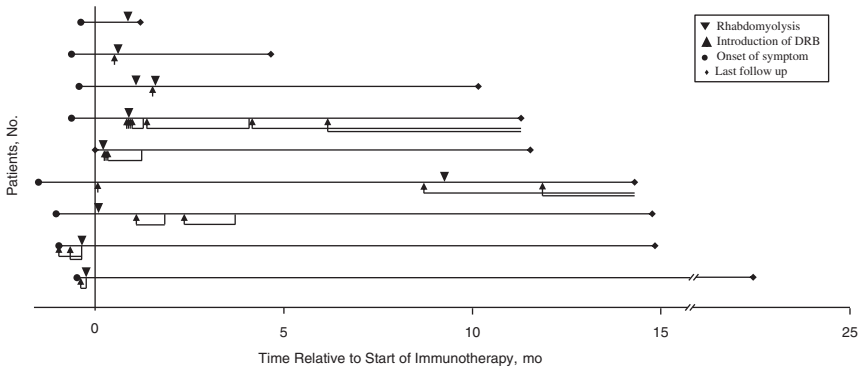

Fig. 1. Rhabdomyolysis before and after immunotherapy. The charts illustrate the occurrence of rhabdomyolysis in patients with anti *N*-methyl-D-aspartate receptor encephalitis before and after immunotherapy and its temporal relation with the introduction of dopaminergic receptor blockers. On the x-axis, a 0 denotes the start of immunotherapy. Each line of the y-axis describes a patient.

hydration primarily prevents azotemia. Urine alkalization could protect the kidney against the nephrotoxic effects of myoglobinuria and hyperuricosuria (Bosch et al., 2009). After fluid resuscitation, management varies according to etiologies. For toxins or medications that are related to rhabdomyolysis, the removal of the causative agent is the most important. In NMS, dopamine agonists are recommended for restoring dopaminergic tone. Benzodiazepines are reported to prevent mortality in NMS (Tural and Onder, 2010).

High-dose benzodiazepine might be helpful in anti-NMDAR encephalitis with rhabdomyolysis. Patient 2 developed rhabdomyolysis after the administration of metoclopramide. Her dystonia was aggravated, and her CK levels were elevated up to 6000 IU/L. The patient was hydrated massively, and her urine was alkalinized. Bromocriptine and the routine dose of diazepam did not improve her dystonia, while diazepam was increased up to 30 mg every 4 h. After high-dose diazepam, her dystonia and CK levels were improved. Two more patients received high-dose benzodiazepine due to the aggravation of abnormal movements. These patients responded effectively to this treatment.

Physicians should be aware of the possibility of rhabdomyolysis when treating the NMDA encephalitis. Psychiatric symptoms are prominent in most anti-NMDAR encephalitis patients (Dalmau et al., 2008; Kruse et al., 2014; Titulaer et al., 2013). While antipsychotics are frequently administered, there is a risk of rhabdomyolysis and aggravated dyskinesia in anti-NMDAR encephalitis, as described in our study. In these instances, benzodiazepines can be used to control agitation, which is associated with untreated psychosis and is also recommended for managing catatonia as well (Kruse et al., 2014). Seizures or severity of disease are not a precipitating factor of rhabdomyolysis, but the use of DRBs after immunotherapy could increase the risk of patients experiencing seizures. Accordingly, rhabdomyolysis, if developed, should be treated promptly with the withdrawal of DRB and the administration of a high dose of benzodiazepine.

Table 2
Treatment and outcome of patients with rhabdomyolysis.

Pt #	DRB use	Stop DRB	Hydration	Urinary alkalization	CRRT	Dopamine agonist	High-dose BDZ	Final mRS
1	−	−	+	+	−	−	−	6
2	+	+	+	+	−	+	+	2
3	+	+	+	−	+	+	−	5
4	+	−	−	−	−	−	−	1
5	−	−	+	−	−	−	+	1
6	+	−	−	−	−	−	−	3
7	−	−	+	−	−	−	+	2
8	+	+	+	−	−	+	−	1
9	+	+	+	−	−	+	−	0

DRB, dopaminergic receptor blocker; CRRT, continuous renal replacement therapy; BDZ, benzodiazepine; mRS, modified Rankin scale, which was calculated during the last follow up appointment.

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