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Original article

Cutaneous adverse drug reaction in patients with epilepsy after acute encephalitis

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Abstract

Patients with epilepsy after encephalitis/encephalopathy (EAE) often have refractory seizures, resulting in polytherapy with the risk of adverse reactions due to anti-epileptic drugs (AEDs). We focused on the characteristics of cutaneous adverse reaction (CAR).

In this retrospective study, the medical records of 67 patients who were diagnosed as having EAE in our hospital were reviewed and the clinical characteristics were analyzed. Immunological biomarkers including cytokines, chemokines, granzyme B, soluble tumor necrosis factor receptor 1 (s-TNFR 1), matrix metalloproteinase-9 (MMP-9) and tissue inhibitor of metalloproteinase-1 (TIMP-1) were measured in 22 patients. CARs attributed to AEDs were observed in 16 of 67 EAE patients (23.9%) (CAR group). High CAR rates were observed with phenytoin, lamotrigine, phenobarbital, and carbamazepine. Severe CARs were found in three of 67 patients (4.5%). The frequencies of CARs were significantly higher in patients with encephalitis onset older than five years of age. CAR occurred only in patients who had onset of EAE within 6 months after encephalitis. The durations from acute encephalitis to CARs were within one year for almost all AEDs, except lamotrigine. The proportion of patients with serumregulated on activation normal T cell expressed and secreted (RANTES) levels higher than the upper limit of normal range was significantly higher in CAR group than in non-CAR group. Patients in the early stage of EAE and patients with encephalitis onset older than five years of age may be at higher risk of CARs to AEDs, especially to phenytoin, lamotrigine, phenobarbital, and carbamazepine. RANTES may be a biomarker for susceptibility to CARs in EAE patients.

Keywords: Epilepsy; Encephalitis; Cutaneous adverse drug reaction; RANTES; Antiepileptic drug

1. Introduction

Epilepsy after encephalitis/encephalopathy (EAE) is reported to occur in 16.4% of patients with acute encephalitis [20,2]. Epileptic seizures in patients with EAE are often intractable. Among 383 pediatric patients admitted between 1993 and 1994 to our epilepsy center for the treatment of intractable epilepsy, 40 patients (10.4%) had EAE, 35 patients had epilepsy related to cerebral malformation, and 14 patients had epilepsy related to neuro-cutaneous syndrome [3]. Thus our data suggest that encephalitis/encephalopathy (encephalitis) is the most frequent etiology in pediatric patients with intractable epileptic seizures in Japan. Intractable epileptic seizures in patients with EAE tend to result in

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polytherapy with AEDs, with the risk of adverse reaction caused by AEDs.

Immunological mechanisms have been reported to be involved in the acute stage of some types of encephalitis [4–6]. Analysis of cytokine levels in influenza virus-associated encephalopathy revealed that cytokines are produced by peripheral blood mononuclear cells (PBMC), and that CSF IL-6 level is a useful indicator of the severity of disease [4]. The CSF concentrations of IL-6 in patients with nonherpetic acute limbic encephalitis (NHALE) were significantly higher than those in controls ($p < 0.001$) [5]. Antibodies to glutamate receptor (GluR) are known to contribute to the pathophysiological mechanisms in acute encephalitis including NHALE [6–8]. These immunological factors augmented by encephalitis may persist from the acute to chronic stage of acute encephalitis, and may affect EAE.

Cutaneous adverse reactions (CARs) are divided into maculopapular exanthema, exanthema pustulosis, Steven Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug-induced hypersensitivity syndrome (DIHS). Maculopapular exanthema is the most common CAR [9]. Although the pathophysiological mechanisms of CAR have not been fully elucidated, maculopapular exanthema may be ascribed to delayed hypersensitivity reactions (type IV) with activation of eosinophils and cytotoxic T cells (CTL) [10]. On the other hands, recent studies of severe CARs including SJS and TEN suggest that HLA-linked T-cell mediated pathophysiology may be associated with SJS caused by carbamazepine (CBZ) [11–13]. Cytokines are thought to play a role in acute and/or immune-mediated adverse drug reactions due to their ability to regulate the innate and adaptive immune systems. They control both the intensity and type of immune response mounted by stimulating or suppressing different cells [9]. We investigated the clinical characteristics of CARs, and attempted to identify the immunological markers for CARs in patients with EAE.

2. Methods

A total of 67 patients (39 males, 28 females) with a diagnosis of EAE were treated in our epilepsy center between February 1996 and May 2009. We conducted a retrospective study by reviewing the medical records of these patients and sending questionnaire to their primary physicians. The 67 patients were divided into a group with (CAR group, $n = 16$) and a group without CAR (non-CAR group, $n = 51$). We examined the serum cytokine and chemokine profile at the remote stage after CAR. Serum concentrations of IL-1β, IL-1ra, IL-2, IL-4, IL-5, IL-6, IL-7, IL-9, IL-10, IL-12, IL-13, IL-15, IL-17, IFN-γ, eotaxin, IL-8, IP-10, monocyte chemotactic protein (MCP-1), macrophage inflammatory protein (MIP)-1a, MIP-1b, tumor necrosis factor receptor (TNF)-α, and RANTES (regulated on activation normal T cell expressed and secreted, CCL5) were measured using the BioPlex suspension array system (BIO-RAD, San Francisco, CA). Soluble tumor necrosis factor receptor (sTNFR) 1 was determined by an enzyme-linked immunosorbent assay (ELISA) kit [Human sTNF-R (60 kDa) ELISA, Cosmo Bio BMS03], and granzyme B was also examined by an ELISA kit (Cat. No. KT-078, Kamiya Biomedical Company, Seattle, WA, USA). Serum concentrations of matrix metalloproteinase-9 (MMP-9) were determined using an activity assay kit and tissue inhibitor of metalloproteinase-1 (TIMP-1) with a sandwich-type ELISA kit (Amersham, Buckinghamshire, England) according to manufacturer's recommendation. The MMP-9 kit measures both the pro- and active forms of MMP-9. Statistical analyses were conducted by Mann–Whitney test and χ^2 test and singinicance was set at $p < 0.05$.

3. Results

3.1. Background of 67 patients with EAE

The etiologies of acute encephalitis were known in 37 patients (55%), including influenza virus in 14 patients (21%), herpes simplex virus in 7 patients (10%), and human herpes virus (HHV)-6 in 4 patients (6%). Norovirus, rotavirus, adenovirus, Kawasaki disease, Coxsackie virus A, Coxsackie virus B, herpangina, *Escherichia coli* O-157, and pertussis were also recorded as causative disease or agent in single patient. The others' etiologies were unknown and we have no date of their antibodies to VGKC, GAD, GABA-B, NMDAR complex, or GluRs in acute stage of encephalitis. The mean age of acute encephalitis onset was 8 years and 4 months (2 months to 64 years, median age 3 years and 11 months ; $n = 67$) (Fig. 1A). The mean latency from onset of acute encephalitis to onset of epilepsy was 6 months (0 month to 7 years and 3 months, median 0 month; $n = 67$) (Fig. 1B).

Adverse effects due to AEDs were recorded in 32 patients (47.8%), including sleepiness in 26 patients (38.8%) and CARs in 16 patients (23.9%) (Fig. 1C). Many patients were treated by polytherapy with AEDs, and the frequency of prescription was in the order of vaproic acid (VPA) > CBZ > zonisamide (ZNS) > clobazam (CLB) > phenobarbital (PB).

3.2. Clinical characteristics of CARs

The overall frequency of CARs in EAE patients was 23.9% (16 of 67 patients). The sex ratio was not significantly ($p = 0.054$) different between CAR (6 males and 10 females) and non-CAR group (33 males and 18 females). The causes of encephalitis and the past histories were not significantly different between two groups.