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Clinical characterization of unknown/cryptogenic status epilepticus suspected as encephalitis: A multicenter cohort study

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ABSTRACT

Autoimmune and unknown/cryptogenic encephalitis have been increasingly noted in the inflammatory etiology of new-onset status epilepticus (SE). We aimed to investigate clinical characteristics and the potential role of immunotherapy in encephalitis-related adult SE through our multicenter prospective SE registry. Among the 274 patients with SE, 35 (12.8%) patients demonstrated an inflammatory etiology and 19 out of 35 (54.3%) patients demonstrated unknown/cryptogenic cause. Patients with autoimmune and unknown/cryptogenic encephalitis shared similar clinical features. In unknown/cryptogenic encephalitis, the proportion of favorable outcomes (mRS 0–3) showed a different propensity at 3–6 months after discharge between patients receiving active immunotherapy and not receiving any immunotherapy, although it was not statistically significant (at admission 28.6% vs 20%, $p = 0.603$; at discharge 57.1% vs 60%, $p = 0.570$; at 3–6 months after discharge 90% vs 60%, $p = 0.214$ in patients treated with active immunotherapy or without immunotherapy, respectively). Extensive autoantibody screening should be carried out and empirical immunotherapy may be potentially helpful even in patients without antibodies, although longer term and multi-national studies may be necessary to make a stronger recommendation.

1. Introduction

Status epilepticus (SE) is a common neurologic emergency and a frequent reason for admission to the intensive care unit (ICU) (Bermeo-Ovalle and Bleck, 2016). From the1900s to 2000s, most studies in this field focused on the incidence and etiology of SE, and investigated the factors that can predict the prognosis of refractory SE. In retrospective and prospective studies, encephalitis and an absence of history of

Abbreviations: CNS, central nervous system; SE, status epilepticus; ICU, intensive care unit; NORSE, new onset refractory status epilepticus; EEG, electroencephalogram; NCSE, non-convulsive statue epilepticus; STESS, status epilepticus severity score; mRS, modified Rankin Scale; AEDs, antiepileptic drugs; PCR, presence of a pathogen demonstrated by culture; CSF, cerebrospinal fluid

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previous seizure were presented as one of factors for the poor outcome of SE among several predictive factors (Hocker et al., 2013; Holtkamp et al., 2005; Mayer et al., 2002; Novy et al., 2010; Sutter et al., 2013), and the etiology was major factor that determined an increased risk of mortality and morbidity associated with SE (Delaj et al., 2017). However, until early 2000s few cases of encephalitis with new onset refractory status epilepticus (NORSE) have been described (Wilder-Smith et al., 2005) and there was no large study for clinical features and prognosis, even though cases of refractory SE due to 'presumed viral encephalitis' were not uncommon in neurological practice (Costello et al., 2009).

Since 2004, autoimmune encephalitis including neuronal surface autoantibodies such as the anti-N-methyl-D-aspartate antibody has been introduced and autoimmune encephalitis characterized by seizures have been recognized (Dalmau et al., 2007; Vincent et al., 2004). After increasing recognition in neuroinflammation with autoimmune encephalitis in seizure, some studies investigated the etiology of NORSE including autoimmune encephalitis (Gaspard et al., 2015; Jayalakshmi et al., 2016). They reported proportions of cryptogenic cause were more than half in all etiologies of NORSE, and patients with a cryptogenic etiology had clinical characteristics similar to those of patients with autoimmune encephalitis. A recent study highlighted the increasing number of ICU admissions due to autoimmune encephalitis over time and the most common reason for ICU admission in this study population was SE (Harutyunyan et al., 2017). Despite the increasing recognition of neuroinflammation as an important cause of SE, studies on neuroinflammation in SE are still limited, and research on unknown/cryptogenic cause in neuroinflammation is even rarer.

Our study aimed to investigate the prevalence of and the clinical features of patients with inflammatory CNS disease including unknown/cryptogenic cause in a large prospective cohort of patients with SE. We also investigated the potential role of immunotherapy in inflammatory CNS disease through clinical outcomes.

2. Methods

2.1. Study design and participants

A nationwide multicenter prospective cohort study across 10 academic medical centers in Korea was performed. The clinical, electroencephalography, and brain imaging data of all the patients who visited between September, 2012 and August, 2016 were derived from a web-based SE registry (http://KAISER-reg.org). All participants received a follow-up examination until 3–6 months after discharge. This study was approved by the institutional review boards of the lead study center (Korea University Anam Hospital, Seoul, Republic of Korea; IRB no. ED-13157) and all other participating hospitals (Online Resource 1) in accordance with the standards of the Declaration of Helsinki. Informed consent was waived.

The inclusion criteria were as follows: Patients (1) were 18 years of age or older at the time of diagnosis; (2) were diagnosed with SE, defined as the presence of clinical and electroencephalographic (EEG) evidence of seizures lasting for at least 5 min, or of repeated seizures without intervening recovery of consciousness (Trinka et al., 2015). We excluded (1) patient who were younger than 18 years of age (pediatric age with potentially different epidemiologic implications), and (2) patients with incomplete clinical data, after reviewing the database.

2.2. Definitions and clinical information

We collected demographic data including age, sex, history of seizures or SE, general medical history, current medication use, and time taken to reach the first SE treatment in institution.

The seizure semiology was classified into convulsive or non-convulsive SE according to the initial manifestation. Convulsive SE was divided into 4 categories: (1) simple partial, (2) complex partial, (3) generalized myoclonic, and (4) generalized convulsive SE. Non-convulsive SE (NCSE) was defined as a condition with prolonged electrographic seizure activity resulting in non-convulsive behavior and/or cognitive changes from the baseline (Hocker et al., 2013). NCSE was divided into 3 categories: (1) absence SE, (2) simple partial and complex partial SE without jerks, and (3) non-convulsive SE in coma. Refractory SE was defined as SE that was unresponsive to first- and second-line antiepileptic drugs administered to control seizures within a given timespan, indicating the requirement of an additional specific treatment (Brophy et al., 2012).

Upon admission, the patients were evaluated using an SE-specific clinical severity score (status epilepticus severity score, STESS) (Novy et al., 2010) and the modified Rankin Scale (mRS). The etiology was classified as acute symptomatic, remote symptomatic, progressive symptomatic, and idiopathic/cryptogenic according to the International League Against Epilepsy (ILAE) criteria (1993). We investigated and classified the individual etiology of SE as follows: inflammatory central nervous system (CNS) disease, cerebrovascular disease, secondary brain damage including hypoxic brain damage, trauma, neoplasia, cortical development malformation, metabolic cause, substance-associated low level of antiepileptic drugs (AEDs), alcohol-associated or drug associated condition, and other including unknown. Inflammatory etiology was defined as (1) acute or subacute onset of symptoms of encephalitis or meningitis, and/or (2) evidence of CNS inflammation by either brain image or CSF analysis, and (3) exclusion of other possible etiologies. The inflammatory SE group was divided into 4 subsets: (1) infection (presence of a pathogen demonstrated by culture, PCR, or serologic tests), (2) autoimmune encephalitis (presence of an autoantibody in cerebrospinal fluid (CSF) or serum), (3) unknown/cryptogenic cause, and (4) other causes of inflammation.

Brain imaging data, which included computed tomography scan and/or magnetic resonance imaging and electroencephalogram (EEG) results, were collected. We classified the EEG findings according to the American Clinical Neurophysiology Society's (ACNS) Standardized Critical Care EEG Terminology, 2012 version (Hirsch et al., 2013). The background and main patterns were recorded, and the periodic main patterns were classified into periodic discharge, rhythmic delta activities, and rhythmic sharp or spike and wave.

We investigated the treatment protocol that included information on the first- and second-line AEDs with concomitant AEDs used to control SE and third-line therapy such as anesthetic drugs or ketamine treatment. Additional information on treatments such as immunotherapy, hypothermia, and surgery was also obtained.

In addition, we retrospectively reviewed if patients underwent extensive testing including that for the presence of autoimmune antibodies (anti-NMDAR, -LGI1, -CASPR2, -AMPA1, -AMPA2, -GABAB-R, Hu, -Yo, -Ri, -Ma2, -CV2/CRMP5, and -amphiphysin) and laboratory examination for infectious etiology in CSF, treatment duration, and type of immunotherapy, the time period between the onset of SE and initiation of immunotherapy in patients with unknown causes for the inflammatory CNS disease.

2.3. Outcome measurements

The primary outcome measure was the mRS score (good or fair outcome defined as mRS 0–3) at discharge, 3–6 months after discharge. At 3–6 months after discharge, patients or care-givers visited outpatient clinic and clinician examined the patient's status or checked the status an interview with their care-giver. The secondary outcome measure was the frequency of complications including the need for admission to an intensive care unit, respiratory distress, cardiac distress, and duration of hospitalization.

2.4. Statistical analysis

Statistical analyses were performed using SPSS for Windows