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The initial use of arterial spin labeling perfusion and diffusion-weighted magnetic resonance images in the diagnosis of nonconvulsive partial status epileptics

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ABSTRACT

Background: In the diagnosis of nonconvulsive status epilepticus (NCSE), capture of ongoing ictal electroencephalographic (EEG) findings is the gold standard; however, this is practically difficult without continuous EEG monitoring facilities. Magnetic resonance imaging (MRI), including diffusion-weighted imaging (DWI) and perfusion MRI with arterial spin labeling (ASL), have been applied mainly in emergency situations. Recent reports have described that ictal MRI findings, including ictal hyperperfusion on ASL and cortical hyperintensity of cytotoxic edema on DWI, can be obtained from epileptically activated cortex. We demonstrate the characteristics and clinical value of ictal MRI findings.
Methods: Fifteen patients diagnosed as having NCSE (eight had complex partial status epilepticus (SE) and seven subtle SE) who underwent an initial MRI and subsequent EEG confrmation, participated in this study. Follow-up MRI and repeated routine EEG were performed.
Results: In 11 patients (73%), ictal MRI findings were obtained on both DWI and ASL, while in four (27%) patients, ictal hyperperfusion was found on ASL without any DWI findings being obtained. In all 10 patients with an epileptogenic lesion, there was a tight topographical relationship between the lesion and the localization of ictal MRI findings. In the other five patients, ictal MRI findings were useful to demonstrate the pathophysiological mechanism of NCSE of non-lesional elderly epilepsy, or 'de novo' NCSE of frontal origin as situation-related NCSE. Ictal MRI findings are generally transient; however, in three cases they still persisted, even though ictal EEG findings had completely improved.
Conclusion: The present study clearly demonstrates that the initial use of ASL and DWI could help to diagnose partial NCSE and also combined use of the MRI and EEG allows documentation of the pathophysiological mechanism in each patient.

1. Introduction

Although there is no universally accepted definition of nonconvulsive status epilepticus (NCSE; Maganti et al., 2008), NCSE is generally defined as a deviation in behavior and/or mental process from the baseline, and is associated with ongoing seizure activity or continuous epileptiform discharges on electroencephalography (EEG), in the absence of convulsive symptoms (Hamamura et al., 2010; Kanazawa et al., 2015; Morioka et al., 2011, 2013; Sutter and Kaplan, 2012; Woodford et al., 2015). While convulsive status epilepticus (SE) is easily recognized, in the diagnosis of NCSE the capture of these ictal EEG findings is considered the gold standard (Hamamura et al., 2010; Kanazawa et al., 2015; Morioka et al., 2011,

Abbreviations: NCSE, nonconvulsive status epilepticus; ASL, arterial spin labeling; REDs, repetitive epileptiform discharges; RIDs, repeated ictal discharges; PLEDs, periodic lateralized epileptiform discharges; AVM, arteriovenous malformation; MTLE, medial temporal lobe epilepsy.

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2013; Woodford et al., 2015). However, it is practically difficult to record ictal discharges without continuous EEG monitoring facilities, such as are available in epilepsy centers or neuro-intensive care units (Kanazawa et al., 2015; Woodford et al., 2015). In many hospitals in Japan, even a routine EEG examination is often unavailable outside of working hours or at weekends (Hamamura et al., 2010; Kanazawa et al., 2015; Morioka et al., 2011), and a delay in the timing of EEG recording may cause a diagnosis of NCSE to be overlooked (Bottaro et al., 2007; Hamamura et al., 2010; Kanazawa et al., 2015; Morioka et al., 2011; Woodford et al., 2015).

Magnetic resonance imaging (MRI) with high magnetic-field scanners has become routinely available in the clinical field, especially with the advancement of intravenous tissue plasminogen activator therapy for acute ischemic stroke. In the diagnosis of acute stroke, the MRI techniques of diffusion-weighted imaging (DWI) and perfusion imaging (PI) are typically used. Recent studies have demonstrated that these techniques can provide information on the ictal (Hamamura et al., 2010; Wakisaka et al., 2016) or peri-ictal phase (Kanazawa et al., 2015; Matsuura et al., 2015; Szabo et al., 2005) in epilepsy patients.

In SE, the epileptogenic cortex is in an extreme electrophysiological state, with the activated cortex exhibiting increased glucose and oxygen usage, thereby causing compensatory regional hyperperfusion. Arterial spin labeling (ASL) is a non-invasive and repeatable PI technique that uses magnetically-labeled water in the blood as an endogenous tracer (Akiyama et al., 2016; Haga et al., 2016; Kanazawa et al., 2015; Shimogawa et al., in press; Wakisaka et al., 2016). Recent reports have described the appearance of ictal hyperperfusion with ASL (Kanazawa et al., 2015; Wakisaka et al., 2016). When this hyperperfusion is no longer sufficient to supply the hyperactive cortical area, pathophysiological changes leading to cytotoxic edema in epileptic cortical neurons can occur. These appear as an abnormally high signal in the cortical lamina (cortical hyperintensity) on DWI (Di Bonaventura et al., 2009; Hamamura et al., 2010; Kanazawa et al., 2015; Szabo et al., 2005; Wakisaka et al., 2016; Wieshmann et al., 1997). These SE findings of low apparent diffusion coefficient (ADC) and high signal on DWI resemble those of acute ischemic stroke, and indicate changes attributable to cytotoxic edema (Di Bonaventura et al., 2009; Kanazawa et al., 2015; Szabo et al., 2005; Wakisaka et al., 2016; Wieshmann et al., 1997). Such ictal MRI findings on ASL and DWI are reversible in most cases (Kanazawa et al., 2015; Szabo et al., 2005; Wakisaka et al., 2016).

This study examines patients with ictal MRI findings obtained from their first emergent MRI, with confirmation of an NCSE diagnosis by the capture of ictal EEG findings on subsequent routine EEG examination. We demonstrate the characteristics and clinical value of ictal MRI findings in the diagnosis of NCSE.

2. Methods

2.1. Subjects

We retrospectively analyzed 15 consecutive patients (six men, nine women, mean age 69 years, range 32–93 years) who were diagnosed as having NCSE based on the initial MRI and subsequent EEG in Kyushu Rosai Hospital from December 2011 to March 2015. The patients demonstrated deviations in behavior and/or mental processes from the baseline, in the absence of convulsive symptoms. In all 15 patients, the ictal MRI findings were obtained on the first emergent MRI on Day 0, with a subsequent routine EEG being scheduled within several hours, to confirm the diagnosis of NCSE by the capture of ongoing ictal EEG findings. Patients who were clinically suspected to have NCSE on the first MRI, but whose subsequent EEG did not demonstrate ictal findings, were excluded from this study. Each family provided written informed consent.

When the diagnosis of NCSE was made, a subsequent intravenous injection of diazepam, fosphenytoin (or phenytoin), and/or phenobarbital was performed, followed by oral administration of levetiracetam and/or carbamazepine, depending on the patients' conditions and the discretion of the doctors in charge. If required, follow-up MRI and routine EEG examinations were scheduled for clinical purposes, also depending on the patients' conditions and the discretion of the attendant physicians.

2.2. MRI

Brain MRI with routine protocols and PI was performed using a 3T-MR unit (Signa HDxt 3.0T version 23; GE Healthcare, Milwaukee, WI, USA). Routine protocols included axial diffusion-weighted echo planar (b value = 1500 s/mm^2; repetition time (TR)/echo time (TE), 6000/min), T1-fluid-attenuated inversion recovery (T1-FLAIR; TR/TE/T1, 2050/16.1/741), T2-weighted fast-spin-echo (FSE; TR/TE, 4400/100), and T2-FLAIR sequences (TR/TE/TI, 9000/140/2120).

ASL was performed using a three-dimensional spiral fast-spin echo sequence with background suppression for PI covering the entire brain. A continuous pulsed scheme was employed as previously described (Akiyama et al., 2016; Kanazawa et al., 2015; Haga et al., 2016; Shimogawa et al., in press; Wakisaka et al., 2016). Other acquisition parameters included: four arms with 1004 points in each spiral arm, phase encoding in the z direction = 32, section thickness = 4 mm, Time to repeat (TR) = 4728 (AUTO) s, post labeling delay = 1.525 s and number of excitations (NEX) = 3. The acquisition time was 2 min 22 s.

Evaluation of the ictal MRI findings was based on visual inspection by two experienced radiologists, who were blind to the clinical data. No differences in the radiologists' interpretations were noted on independent assessments (*kappa* = 1) (McHugh, 2012).

2.3. EEG

Subsequent routine EEG recordings were obtained from an 18-channel digital EEG machine (Neurofax; Nihon-Kohden, Tokyo, Japan) with electrode placement according to the International EEG 10–20 system, as described previously (Hamamura et al., 2010; Kanazawa et al., 2015; Morioka et al., 2011, 2013; Shimogawa et al., in press; Wakisaka et al., 2016). The EEG recordings were performed for at least 30 min for each patient, in the resting condition.

Evaluation of the ictal EEG findings was based on visual inspection by two experienced electroencephalographers (T.M. and A.S.) who were blind to the clinical data. Three kinds of EEG findings, namely; repeated ictal discharges (RIDs), repetitive epileptiform discharges (REDs) and periodic lateralized epileptiform discharges (PLEDs) (Morioka et al., 2011), were included in the ongoing ictal EEG findings. The definition of RIDs is repeated electrographic seizure activities, with ictal patterns that wax and wane with changes in amplitude, frequency, and/or spatial distribution (Hamamura et al., 2010; Morioka et al., 2013). That of REDs is repetitive (or highly frequent) or almost continuous epileptiform discharges, which show significant changes in intensity or frequency, when compared to the baseline EEG (Wakisaka et al., 2016). No differences in the electroencephalographers' interpretations were noted on independent assessments (*kappa* = 1) (McHugh, 2012).

2.4. Outcome

Functional outcomes were assessed at 1–3 months after the discharge using the modified Rankin Scale (mRS) (Shinohara et al., 2006) and compared with mRS value before the onset of NCSE.