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A new infectious encephalopathy syndrome, clinically mild encephalopathy associated with excitotoxicity (MEEX)

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ABSTRACT

Acute infectious encephalopathy is often observed in children in East Asia including Japan. More than 40% of the patients remain unclassified into specific syndromes. To investigate the underlying pathomechanisms in those with unclassified encephalopathy, we evaluated brain metabolism by MR spectroscopy. Among seven patients with acute encephalopathy admitted to our hospital from June 2016 to May 2017, three were classified into acute encephalopathy with biphasic seizures and late reduced diffusion (AESD). The other four showed consciousness disturbance lasting more than three days with no parenchymal lesion visible on MRI, which led to a diagnosis of unclassified encephalopathy. MR spectroscopy in these four patients, however, revealed an increase of glutamine with a normal *N*-acetyl aspartate level on days 5 to 8, which had normalized by follow-up studies on days 11 to 16. The four patients clinically recovered completely. Among 27 patients with encephalopathy, including the present seven patients, admitted to our hospital from January 2015 to March 2017, seven (26%) were classified into this type, which we propose is a new encephalopathy syndrome, clinically mild encephalopathy associated with excitotoxicity (MEEX). MEEX is the second most common subtype, following AESD (30%). This study suggests that excitotoxicity may be a common underlying pathomechanism of acute infectious encephalopathy, and prompt astrocytic neuroprotection from excitotoxicity may prevent progression of MEEX into AESD.

1. Introduction

Acute infectious encephalopathy is frequently observed in children in East Asia including Japan (around 600 patients per year) [1], and is usually preceded by infection, most often by influenza virus or human herpesvirus (HHV) 6 and 7. Based on the suspected pathomechanisms, acute encephalopathy has been classified into three categories, metabolic errors (e.g., Reye syndrome), cytokine storms (acute necrotizing encephalopathy [ANE], hemorrhagic shock and encephalopathy syndrome), and excitotoxicity (acute encephalopathy with biphasic seizures and late reduced diffusion [AESD]) [1–3]. In Japan, AESD is the most common (29%, around 200 patients per year), followed by clinically mild encephalitis/encephalopathy with a reversible splenial lesion (MERS, 16%) and ANE (4%) [1]. A large number of patients, however, remain unclassified into specific syndromes (43%). We previously reported three patients with unclassified encephalopathy showing complete clinical recovery without a biphasic clinical course or parenchymal lesion on MR imaging, but a transient increase of glutamine (Gln) observable on MR spectroscopy [4]. We herein report additional four patients with this type of encephalopathy, and propose to name it clinically mild encephalopathy associated with excitotoxicity (MEEX).

2. Patients and methods

We retrospectively evaluated the clinical records, MRI, and MR spectroscopy of patients with encephalopathy admitted to our hospital during the period June 2016 to March 2017. A diagnosis of encephalopathy was defined as acute onset of impaired consciousness lasting more than 12 h, often associated with seizures or delirious behavior without inflammatory changes, such as pleocytosis of the CSF, according to the guidelines for acute encephalopathy [5]. We defined the day of encephalopathy onset as day 1. According to the clinical and radiological features, the patients were classified into subtypes, i.e., AESD, MERS, ANE, and unclassified encephalopathy [1–3]. These patients had undergone MRI, including diffusion-weighted image, T1- and T2-weighted images, and MR spectroscopy. The details of the MR spectroscopy and its analysis were previously reported [4,6,7].

Abbreviations: AESD, acute encephalopathy with biphasic seizures and late reduced diffusion; ANE, acute necrotizing encephalopathy; Gln, glutamine; Glu, glutamate; MEEX, clinically mild encephalopathy associated with excitotoxicity; MERS, clinically mild encephalitis/encephalopathy with a reversible splenial lesion.

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3. Results

Seven patients were given a diagnosis of encephalopathy during the study period and were enrolled in this study. Three were classified into AESD based on the clinical and radiological features, and the other four into unclassified encephalopathy. These four patients were clinically mild ones, recovered completely with at least 3 month follow-up, and showed no abnormal lesion on MRI performed two times (Fig. 1-A, Table 1). They showed no biphasic seizures or biphasic consciousness disturbance, which are typical of AESD. MR spectroscopy revealed increases of Gln on days 5 to 8 with a normal glutamate (Glu) level, which had normalized by the time of follow-up studies on days 11 to 16 (Table 2 and Fig. 1-B, C). Other metabolites, including *N*-acetyl aspartate (NAA) and choline, were all normal. The clinical and MR spectroscopy data for the four patients are presented in Tables 1 and 2.

4. Discussion

We continuously studied 20 patients with infectious encephalopathy in our hospital during the period of January 2015 to May 2016 [4], prior to the present study. Among 27 patients including the 20, seven patients (26%, Fig. 2), including the present four patients, showed identical clinical, MR imaging and MR spectroscopic findings, that is, mild neurological manifestations and complete clinical recovery without a biphasic course, and no parenchymal lesion on MRI, but exhibited a transient increase of Gln on days 3 to 8. Because MRI shows typical findings in the subacute stage of each encephalopathy syndrome, i.e., subcortical reduced diffusion in AESD, a splenial lesion in MERS, and bilateral thalamic lesions in ANE, the seven patients were classified into unclassified encephalopathy according to the conventional criteria [1,3,5]; however, we propose a diagnosis of a new encephalopathy syndrome for them, namely, clinically mild encephalopathy associated with excitotoxicity (MEEX).

MR spectroscopy in the seven patients with MEEX showed a similar MR spectroscopic pattern to that observed in AESD patients. AESD clinically shows biphasic seizures, a prolonged febrile seizure on day 1, followed by partial seizures on days 4 to 6, and radiologically reveals delayed subcortical reduced diffusion, the so-called 'bright tree appearance', on days 3 to 9 [2,8–11]. MR spectroscopy in AESD patients revealed acute Glu elevation on days 1 to 4, which changed to subacute Gln elevation on days 4 to 12 [6–7]. Because no Glx (Glu + Gln) elevation was observed in patients with a prolonged febrile seizure alone (no encephalopathy or sequelae) on days 2 to 5 [8–9], it is reasonably considered that Glu and/or Gln elevation does not result from fever or prolonged seizures per se.

Glutamatergic neurons release Glu into the synaptic cleft, where it is taken up by surrounding astrocytes through glutamate transporters to maintain a proper intrasynaptic Glu concentration [12,13]. Glu taken up by astrocytes is amidated to a harmless compound, Gln, by glutamine synthetase, which is only present in astrocytes [14,15]. Gln is then returned to the neurons for re-use as Glu, completing the Glu (in neurons)-Gln (in astrocytes) cycle [13–14]. Under excitotoxic conditions, astrocytes are thought to be neuroprotective due to their ability to clear Glu. If Glu is released in quantities that cannot be processed by astrocytes, the excessive Glu results in excessive activation of *N*-methyl-D-aspartate receptors, which allows entry of Ca^{2+} into the postsynaptic neurons, which in turn triggers various processes resulting in necrotic cell death or apoptosis [12,13,16]. The elevation of Glu followed by Gln observed on MR spectroscopy in AESD patients suggests excitotoxicity as a possible pathomechanism.

MR spectroscopy in the seven patients with MEEX showed acute Glu elevation on day 3 in 1 patient so examined [4], followed by subacute Gln elevation on days 3 to 8 in all seven patients, which is similar to that observed in AESD patients. MR spectroscopic findings in MEEX patients may indicate a neurochemical process whereby the excessive Glu released from presynaptic neurons under mild excitotoxic conditions is successfully processed into Gln by astrocytes through a prompt Glu-Gln cycle, which may protect neurons from delayed death. This may explain why the MEEX patients did not present biphasic clinical courses or neurological sequelae, and why MR spectroscopy showed normal

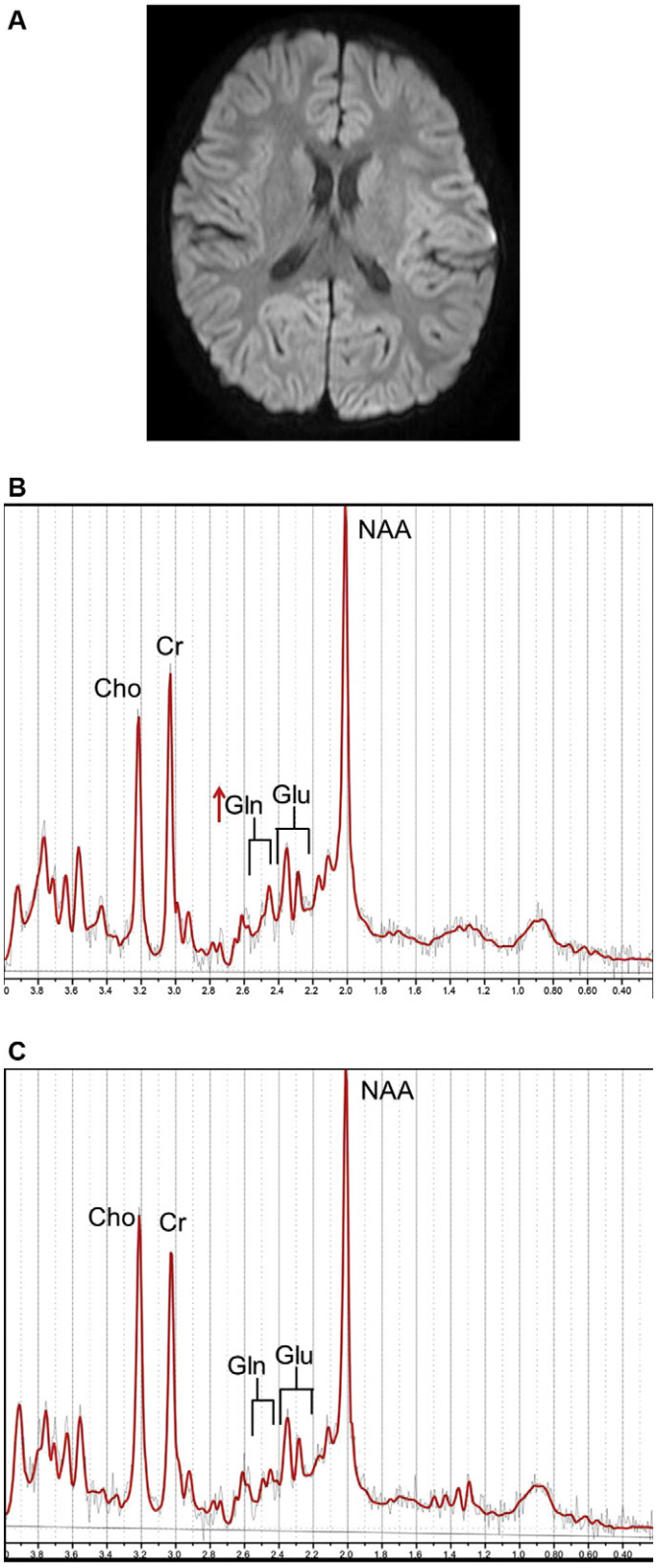

Fig. 1. Diffusion-weighted image of patient 1 on day 7 showed no parenchymal lesion (A). MR spectroscopy of patient 1 showed normal Glu and increased Gln on day 7 (B), followed by normal concentrations of Glu and Gln on day 14 (C). MR spectroscopy also showed normal *N*-acetylaspartate (NAA) and choline (Cho) levels on days 7 and 16.