Journal of the Neurological Sciences 292 (2010) 24–27

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Differences in the time course of splenial and white matter lesions in clinically mild encephalitis/encephalopathy with a reversible splenial lesion (MERS)

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ARTICLE INFO

Article history:
Received 24 December 2009
Received in revised form 5 February 2010
Accepted 11 February 2010
Available online 16 March 2010

Keywords:
Clinically mild encephalitis/encephalopathy with a reversible splenial lesion (MERS)
MRI
Diffusion
Splenium
White matter

ABSTRACT

Two patients with clinically mild encephalitis/encephalopathy with a reversible splenial lesion (MERS) exhibiting lesions in the white matter and entire corpus callosum (type 2) are reported. The time course differed between the splenial lesion and other lesions in the white matter and corpus callosum other than the splenium; the latter disappeared earlier than the former. These findings strongly suggest that MERS type 2 resolves completely through MERS type 1 exhibiting an isolated splenial lesion, and MERS types 1 and 2 have the same pathophysiology. The possible prior white matter lesions in patients with MERS type 1 may explain the neurological symptoms or EEG abnormalities.

1. Introduction

The MR imaging finding of a reversible isolated lesion with transiently reduced diffusion in the splenium of the corpus callosum (SCC) has been reported in patients with clinically mild encephalitis/encephalopathy, leading to a new clinical–radiological syndrome, clinically mild encephalitis/encephalopathy with a reversible splenial lesion (MERS) [1–3]. Reversible lesions with transiently reduced diffusion have also been found with lateral extension from the splenium into the subcortical white matter [4], and with anterior extension involving the entire corpus callosum [5]. Because of the clinical and radiological similarities, we have suggested that these comprise a clinico-radiological spectrum (MERS spectrum), type 1 with an isolated SCC lesion and type 2 with extensive white matter and/or entire callosal lesions. We herein report two patients with MERS in whom MRI on admission revealed type 2 lesions, but on the next day revealed an isolated SCC lesion (type 1), the other lesions having greatly decreased in size and signal intensity, which suggests that MERS type 2 resolves completely through MERS type 1.

2. Case report

2.1. Patient 1

A previously healthy 10-year-old boy was admitted because of recurrent seizures after a 3-day prodromal high fever, which were stopped by intravenous administration of mitazolam. There was no family history or past history of neurological disorders, including epilepsy and developmental retardation. Afterwards, he was drowsy for around 24 h, leading to a clinical diagnosis of acute encephalopathy. The results of neurological examination were unremarkable except for his consciousness level and a positive extensor plantar response. Routine laboratory examination showed a slightly increased C-reactive protein level (0.53 mg/dl) and hyponatremia (Na 131 mEq/l). Cerebrospinal fluid (CFS) examinations revealed normal cell counts, and protein and glucose levels. He was treated with a steroid, acyclovir, and became alert on day 5. Diffusion-weighted images (DWI) on admission (day 4) showed markedly hyperintense lesions in the bilateral white matter and entire corpus callosum with a reduced apparent diffusion coefficient (ADC) (Fig. 1A, B). Second DWI on day 5 showed a markedly hyperintense lesion in the SCC (Fig. 1C), but the lesions in the white matter and corpus callosum other than the SCC had decreased in size and signal intensity (Fig. 1D). Third DWI on day 17 showed the complete resolution of these lesions (Fig. 1E, F). Electroencephalography (EEG) on day 11 showed bilateral occipital slow waves, but no follow-up study was performed. A diagnosis of

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doi:10.1016/j.jns.2010.02.013

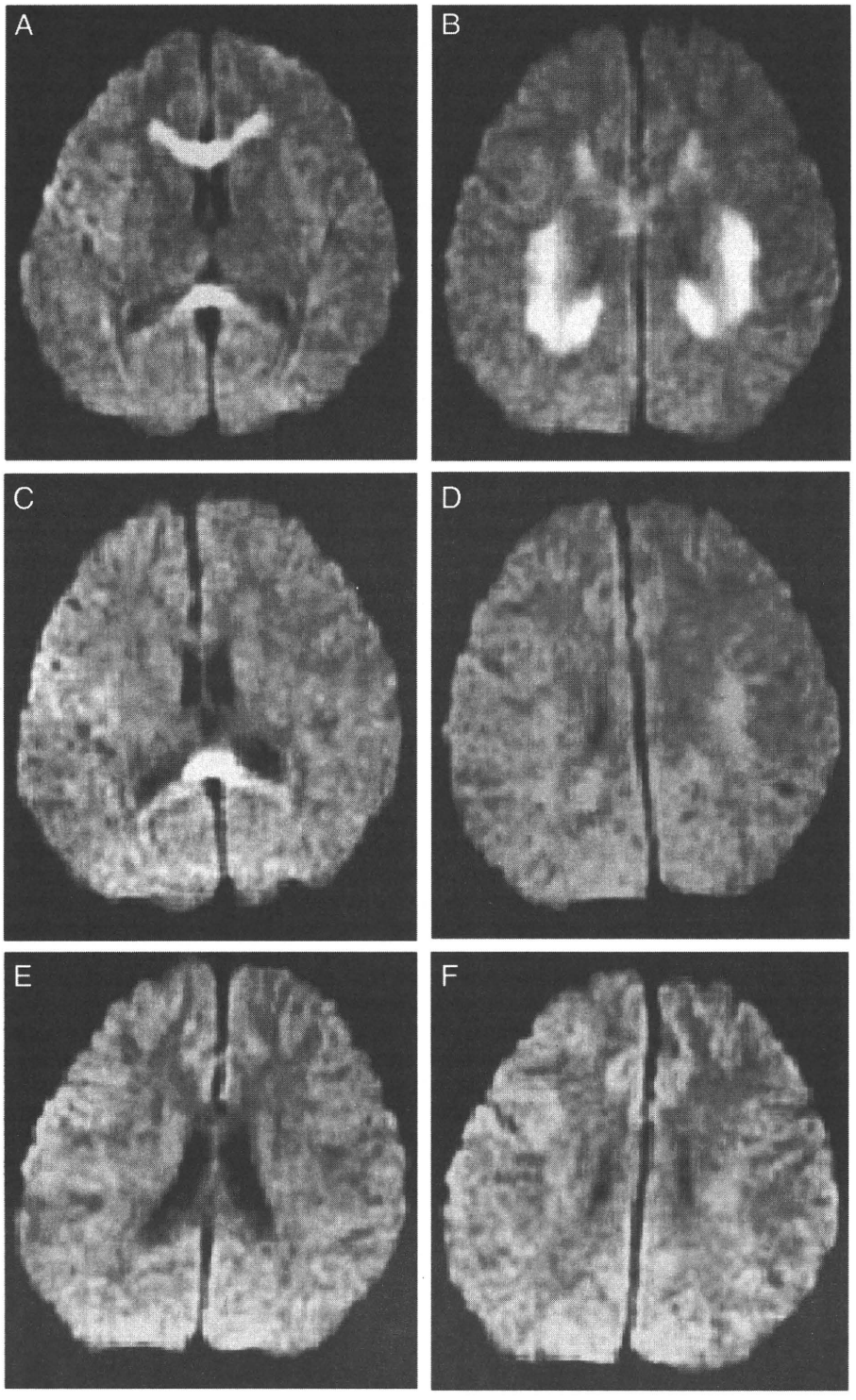

Fig. 1. DWI on admission (day 4) showed markedly hyperintense lesions in the bilateral white matter and entire corpus callosum (A, B). Second DWI on day 5 showed a markedly hyperintense lesion in the SCC (C), but lesions in the white matter and corpus callosum other than the SCC had decreased in size and signal intensity (D). Third DWI on day 17 showed complete resolution of these lesions (E, F).

MERS (type 2) was retrospectively made based on the clinical and radiological features.

2.2. Patient 2

A previously healthy 6-year-old Japanese girl was admitted with recurrent delirious behavior and consciousness disturbance, following a 1-day prodromal fever, cough, and rhinorrhea. Before admission, she had received zanamivir hydrate and acetaminophen based on the diagnosis of influenza A with a positive rapid antigen-detection assay result. There was no family history or past history of neurological disorders, including epilepsy and developmental retardation. On admission (day 2), she was drowsy and presented with recurrent delirious behavior, such as laughter and dancing, but the results of neurological examination were unremarkable. Blood examination revealed an increased white blood cell count (13.300/μl), an increased C-reactive

protein level (5.8 mg/dl), and hyponatremia (Na, 127 mEq/1), but normal levels of ammonia and glucose. CSF examination showed normal cell counts, and protein and glucose levels. EEG on day 1 showed bilateral occipital high voltage slow waves, which had normalized on day 5. She was treated with zanamivir hydrate, and her clinical manifestations improved and completely recovered within 24 h (day 3). MR imaging on admission (day 2) revealed lesions in the diffuse white matter and entire corpus callosum with marked hyperintensity on DWI with a homogenously reduced ADC (Fig. 2A). Second DWI on day 3 showed a markedly hyperintense lesion only in the SCC (Fig. 2B), and mildly hyperintense lesions in the white matter and corpus callosum other than the SCC, which had completely resolved on day 6 (Fig. 2C). A diagnosis of MERS (type 2) was made based on the clinical and radiological features.

3. Discussion

The most important finding in our two patients is that the time course differed between a lesion in the SCC and lesions in the white matter and corpus callosum other than the SCC; the latter disappeared earlier than the former. Only one patient with clinically mild encephalopathy exhibiting the same longitudinal MRI changes has been reported [6]. MRI of the patient on admission showed extensive lesions in the white matter and entire corpus callosum with homogenously reduced diffusion (type 2); a follow-up study after 60 h revealed an isolated SCC lesion (type 1) with no lesions in the white matter or corpus callosum other than the SCC [6]. Our two patients and the previously reported one suggest that type 2 lesions resolve through a period with a type 1 lesion (isolated SCC lesion) within a few days, finally complete resolution; and strongly support the hypothesis that types 1 and 2 have the same pathophysiology.

Among the 54 patients with MERS previously reported, 40 were classified as MERS type 1 with an isolated SCC lesion, and the other 14 as MERS type 2, i.e., 3 patients with lesions in the splenium plus genu, 2 with ones in the entire corpus callosum, and 9 with ones in both the corpus callosum and symmetrical white matter [1]. Among the 14 patients with MERS type 2, there were none in whom MRI showed a longitudinal change from type 2 to type 1, and finally complete resolution. The interval between the initial and follow-up MRI in the 14 patients with MERS type 2 was more than 4 days, during which all the lesions might have disappeared. Follow-up MRI within a few days may have revealed a longitudinal change from type 2 to type 1. Among the 40 patients with MERS type 1, it is reasonable to consider that some had had lesions in the white matter and/or entire corpus callosum prior to the initial MR study.

The most common neurological symptom of MERS is delirious behavior in 54% (29/54), as observed in patient 2, followed by consciousness disturbance in 35%, and seizures in 33%, all of which completely disappear within a month [1,7]. No clinical difference between types 1 and 2 has been reported. Though the pathophysiology of delirium is poorly understood, delirium is more likely to involve both cerebral hemispheres than the hemisphere on one side or the brainstem alone [8]. Neuroimaging and neuropsychological studies have revealed generalized disruption of higher cortical functions in adults with delirious behavior [9]. Therefore, lesions in the bilateral white matter and corpus callosum seen in patients with MERS type 2 may result in disconnection of the bilateral cerebral hemispheres, leading to disruption of higher cortical function, and finally delirium. If patients with type 1 MERS have prior white matter lesions, or have white matter involvement too faint to be detected on routine DWI, that would also explain the neurological symptoms, including delirium. An EEG abnormality has been found in around half of the patients with MERS (21/39 patients), including diffuse slow waves in 17 patients, occipital slow waves in four (as observed in the present two patients), and paroxysmal discharges in two [1]. Almost all the EEG abnormalities normalized on the follow-up study. Transient involvement of the bilateral white matter in MERS may result in disruption of higher cortical function, also leading to transient slow waves on EEG.

The reason for the transiently reduced diffusion within the lesions, and that for the longitudinal difference in the lesions are unknown; we have suggested transient development of intramyelinic edema due to separation of the myelin layers as a possible mechanism [1,2]. A reversible SCC lesion with transiently reduced diffusion, however, has been reported in a 12-day-old neonate [10]. At that age, the SCC is still completely unmyelinated; therefore, another mechanism must be responsible for the reversible SCC lesion in at least some cases. Laboratory evaluation revealed that hyponatremia is common in patients with MERS [11], as observed in the present two patients. Hypotonic hyponatremia results in entry of water into the brain, resulting in cerebral edema. As the axons in the SCC are very tightly packed, it is possible that interstitial edema (water situated between the unmyelinated axons) could have reduced diffusion. The lesions in the white matter, however, cannot be explained by this hypothesis, because interstitial edema in the white matter usually causes increased diffusion. Another possible explanation is the development of a transient inflammatory infiltrate, which might cause reduced

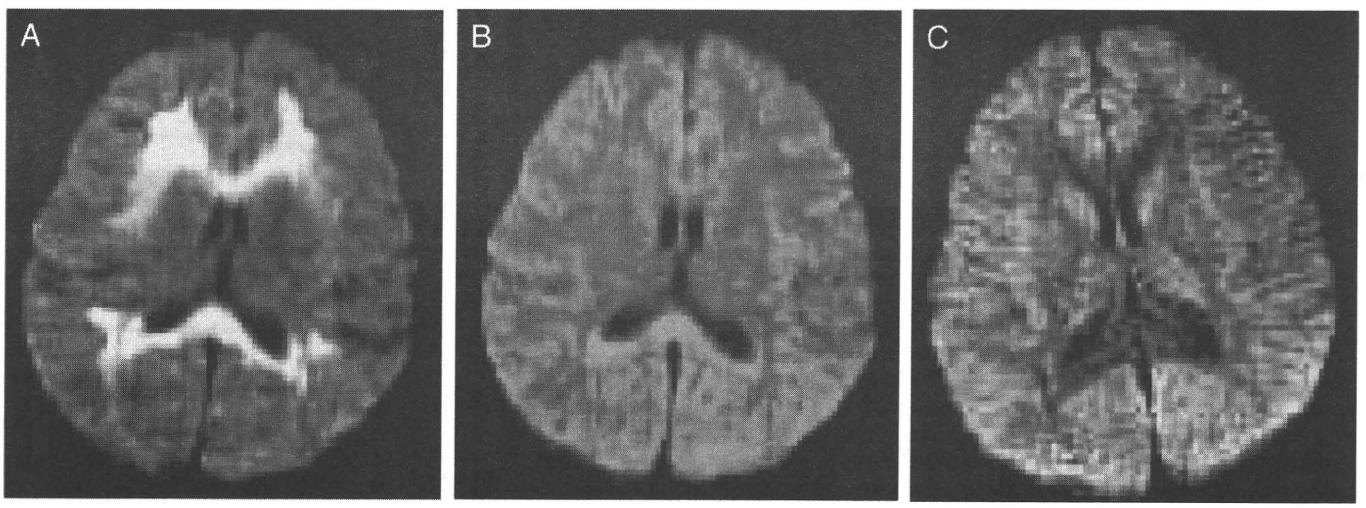

Fig. 2. MR imaging of patient 2. MR imaging on admission (day 2) revealed lesions in the diffuse white matter and entire corpus callosum with marked hyperintensity on DWI (A). Second DWI on day 3 showed a markedly hyperintense lesion only in the SCC (B), which had completely resolved on day 6 (C).

diffusion, as observed in multiple sclerosis. These speculation, however, do not explain why the SCC is specifically involved, why the SCC is involved longer than the white matter or corpus callosum other than the SCC, or why the cerebellar white matter is not affected. Recently, some familial patients with MERS were reported, suggesting a genetic factor might be involved in at least some patients [12]. Further clinical, radiological and genetic studies are, of course, necessary for a definite conclusion.

Acknowledgement

This study was supported in part by the Research Grant (20A-14) for Nervous and Mental Disorders from the Ministry of Health, Labor and Welfare of Japan.

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難治性疾患克服研究事業
「重症・難治性急性脳症の病因解明と診療確立に向けた研究」
平成 22 年度　研究報告書

発行：平成 23 年 3 月
発行者：水口　雅（研究代表者）
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