REVERSIBLE SPLENIAL LESION WITH RESTRICTED DIFFUSION IN A WIDE SPECTRUM OF DISEASES AND CONDITIONS

Report of eight additional cases and literature review


INTRODUCTION

Reversible lesions have been reported in the central area of the splenium of the corpus callosum (SCC), particularly among patients with encephalitis or encephalopathy and among patients with or without epilepsy receiving antiepileptic drugs (AED) [2, 3, 5, 10, 11, 13, 14, 16, 18, 19, 22-24, 26]. The MR imaging findings are unique because such lesions share characteristic findings, including the presence of a focal lesion in the central area of the SCC,
restricted diffusion on diffusion-weighted imaging (DWI), and complete reversibility on follow-up MR imaging. Clinical aspects and MR imaging findings of those transient lesions in the SCC raise several issues: Why is the central area of the SCC a site of predilection for these lesions? Why does this phenomenon tend to occur in particular diseases and conditions such as encephalitis or encephalopathy and epilepsy receiving AED? Why do the transient lesions show restricted diffusion on DWI? We have encountered eight additional cases with those characteristic MR imaging findings, which might be seen in various diseases and conditions other than encephalitis or encephalopathy and epilepsy receiving AED. This article reports MR imaging findings, clinical courses, and outcomes in these eight cases. Subsequently, we review a spectrum of diseases and conditions in light of the literature describing those unique MR imaging findings.

MATERIALS AND METHODS

Patients

Eight Japanese patients (3 male, 5 female, age 15-58 years, mean 33 years), each with a reversible SCC lesion, were reviewed retrospectively. A reversible SCC lesion was defined as a lesion, involving the central area of the SCC, which had disappeared before a follow-up study. Transiently restricted diffusion on DWI was a necessary condition for this study. The cases were collected from different hospitals in Japan. We reviewed data related to symptoms, clinical diagnoses, medications, and prognoses of neurological symptoms from these eight patients’ charts. Diseases and conditions that were related to a reversible lesion included epilepsy receiving AED (n=1), seizure from eclampsia receiving AED (n=1), mild infectious encephalitis (n=2), hypernatremia resulting in osmotic myelinolysis (n=1), and neoplasm (n=3) such as acute lymphocytic leukemia, spinal meningeal melanocytoma, and esophageal cancer.

MR imaging and image analysis

In all patients, MR imaging was performed using 1.5 T units consisting of axial T1-weighted spin-echo sequence with or without contrast agents, T2-weighted fast spin-echo sequence, fast fluid attenuated inversion recovery (FLAIR) sequence, and single shot echoplanar DWI sequence. Diffusion gradients were activated sequentially in each of three principal anatomic axes to yield DWI images at a $b$ value of 1 000 s/mm$^2$. The apparent diffusion coefficient (ADC) values for a splenial lesion and an apparently normal lateral area of the splenium were calculated.

We analyzed MR imaging findings such as the shape of the splenial lesion, DWI findings and ADC values, additional parenchymal lesions, and the time course of a splenial lesion. In addition, the clinical course and outcome were reviewed in comparison with MR imaging findings for those eight patients.

RESULTS

Clinical course and outcome of patients

Table I shows details of clinical data of the eight patients. Two patients receiving AED (cases 1 and 2) respectively had their last seizures 17 days and 22 days before MR examination. However, these two patients had no neurological symptoms at the

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age/sex</th>
<th>Initial symptom</th>
<th>Seizure (last seizure days prior to MR exam)</th>
<th>AED treatment (period of time before MR exam)</th>
<th>Diseases and conditions</th>
<th>Neurological course (time of CR after CNS manifestation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>29/F</td>
<td>headache, seizure</td>
<td>yes (17 d)</td>
<td>phenytoin (5 d iv), valproic acid (17 d po)</td>
<td>eclampsia, AED treatment</td>
<td>CR (3 d)</td>
</tr>
<tr>
<td>2</td>
<td>31/F</td>
<td>seizure</td>
<td>yes (22 d)</td>
<td>phenobarbital etc. (longer than 20 years po)</td>
<td>epilepsy, AED treatment</td>
<td>epilepsy well controlled</td>
</tr>
<tr>
<td>3</td>
<td>24/M</td>
<td>fever, drowsiness</td>
<td>none</td>
<td>none</td>
<td>encephalitis (unknown pathogen)</td>
<td>CR (10 d)</td>
</tr>
<tr>
<td>4</td>
<td>28/F</td>
<td>fever, headache, numbness of extremities</td>
<td>none</td>
<td>none</td>
<td>encephalitis (unknown pathogen)</td>
<td>CR (1 mo)</td>
</tr>
<tr>
<td>5</td>
<td>29/M</td>
<td>none</td>
<td>none</td>
<td>none</td>
<td>spinal meningeal melanocytoma</td>
<td>no CNS symptoms</td>
</tr>
<tr>
<td>6</td>
<td>15/F</td>
<td>none</td>
<td>none</td>
<td>none</td>
<td>acute lymphocytic leukemia</td>
<td>no CNS symptoms</td>
</tr>
<tr>
<td>7</td>
<td>58/M</td>
<td>somnolence</td>
<td>none</td>
<td>none</td>
<td>esophageal cancer, 5-FU treatment</td>
<td>CR (4 d)</td>
</tr>
<tr>
<td>8</td>
<td>49/F</td>
<td>coma</td>
<td>yes (21 d)</td>
<td>phenytoin (1 d iv)</td>
<td>hypernatremia (160 mEq/l) and osmotic myelinolysis</td>
<td>vegetative state</td>
</tr>
</tbody>
</table>

CNS, central nervous system; AED, antiepileptic drug; CR, complete recovery; 5-FU, 5-fluorouracil; iv, intravenous; po, per os.

time of MR examination. The clinical outcome was a complete recovery 3 days after the seizure in case 1, whereas the clinical course and outcome were good in case 2 because epileptic seizures were well controlled by AED treatment. Clinical outcomes were good in two patients with encephalitis (cases 3 and 4). These two patients recovered completely within 1 month. Two patients with neoplasm (cases 5 and 6) had no neurological symptoms. One patient with esophageal cancer (case 7) recovered neurologically after the withdrawal of 5-fluorouracil (5-FU). One patient with hypernatremia (case 8) eventually showed osmotic myelinolysis; her outcome was poor (vegetative state). Thus, clinical courses and outcomes were good in seven patients, but poor in one patient.

**MR imaging findings**

Details of MR imaging findings are summarized in table II.

**Splenial lesion shape**

The SCC lesion shapes were oval and less than 2 cm diameter in six patients (figures 1, 3 and 4). The shape was extended in two patients (figures 2 and 5). In the patient with encephalitis (case 3), extended small high signal intensity was seen discontinuously at the right side of the splenium (figure 2). The lesion extended from the center to the bilateral lateral portions of the SCC in the patient with hypernatremia (case 8) (figure 5).

**DWI findings and ADC values**

Splenial lesions showed markedly high signal intensity on DWI images in all cases (figures 1 to 5). The mean ADC value of the SCC lesion in the current cases was $0.40±0.16×10^{-3}\text{mm}^2/\text{s}$, ranging from $0.22$ to $0.64×10^{-3}\text{mm}^2/\text{s}$ (lateral area of normal splenium; $0.74±0.11×10^{-3}\text{mm}^2/\text{s}$). Table II shows respective ADC values of splenial lesions for all cases.

**Contrast enhancement**

In our case series, only one patient (case 5) was given contrast agent on MR imaging and showed no enhancement (figure 3).

Additional parenchymal lesions with restricted diffusion

Regarding this case series, an isolated SCC lesion was apparent in each of seven patients (cases 1-7), whereas additional parenchymal lesions with restricted diffusion were found in a single patient with osmotic myelinolysis (case 8). Additional lesions were located symmetrically in the temporo-occipital white matter (figure 5c). The ADC value of those white matter lesions was $0.52±0.11×10^{-3}\text{mm}^2/\text{s}$ on the initial MR images. These additional lesions were irreversible and more extensive on follow-up MR images (figure 5e).

**Time course of a reversible lesion in the SCC**

Times of reversal of a splenial lesion were varied (table II). The precise time course remained uncertain because all cases were evaluated retrospectively. Concerning the two patients with neoplasm (cases 5 and 6), follow-up MR imaging was performed several times until complete resolution of the SCC lesion. Splenial lesions in these two patients decreased gradually in signal intensity and size over time (figures 3c, 3e, and 3f). During that interval, the ADC values of SCC lesions were lower in all cases than those of normal lateral areas of the splenium in those two patients.

**DISCUSSION**

Relevant literature reveals reversible SCC lesions in 62 patients [1-5, 8-16, 18-20, 22-24, 26-32, 34]. Among those patients, DWI was obtained and restricted diffusion of a reversible SCC lesion was evident in 34 patients [1, 4, 8-10, 13, 14, 16, 18-20, 24, 27-32, 34]. Diseases and conditions of those 34 patients were varied. Patients (n=18) with infectious encephalitis or encephalopathy caused by various pathogens were most frequent [10, 13, 14, 19, 20, 28-30], followed by those (n=7) with or without epilepsy receiving AED [8, 16, 18, 24, 27]. Other putative causes include alcoholism and malnutrition (n=2) [4], hypoglycemia (n=2) [1, 32], hypernatremia engendering osmotic myelinolysis (n=1) [4], trauma

---

**Table II.** – MR imaging findings for patients with a reversible splenial lesion.

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Initial MR: interval (days) after CNS manifestations</th>
<th>Shape of splenial lesion</th>
<th>T2WI/FLAIR</th>
<th>Gd</th>
<th>DWI</th>
<th>ADC value ($\times10^{-3}\text{mm}^2/\text{s}$)</th>
<th>Reversal of splenial lesion: interval after the initial MR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17 d</td>
<td>oval</td>
<td>H</td>
<td>NE</td>
<td>H</td>
<td>0.22</td>
<td>7 wk</td>
</tr>
<tr>
<td>2</td>
<td>22 d</td>
<td>oval</td>
<td>sl H</td>
<td>NE</td>
<td>H</td>
<td>0.55</td>
<td>6 mo</td>
</tr>
<tr>
<td>3</td>
<td>1 d</td>
<td>extended</td>
<td>H</td>
<td>NE</td>
<td>H</td>
<td>0.25</td>
<td>10 d</td>
</tr>
<tr>
<td>4</td>
<td>7 d</td>
<td>oval</td>
<td>H</td>
<td>NE</td>
<td>H</td>
<td>0.62</td>
<td>17 d</td>
</tr>
<tr>
<td>5</td>
<td>no CNS symptoms</td>
<td>oval</td>
<td>H</td>
<td>–</td>
<td>H</td>
<td>0.38</td>
<td>37 d</td>
</tr>
<tr>
<td>6</td>
<td>no CNS symptoms</td>
<td>oval</td>
<td>H</td>
<td>NE</td>
<td>H</td>
<td>0.64</td>
<td>3 mo</td>
</tr>
<tr>
<td>7</td>
<td>2 d</td>
<td>oval</td>
<td>H</td>
<td>NE</td>
<td>H</td>
<td>0.28</td>
<td>9 d</td>
</tr>
<tr>
<td>8</td>
<td>10 d</td>
<td>extended</td>
<td>sl H</td>
<td>NE</td>
<td>H</td>
<td>0.50</td>
<td>21 d</td>
</tr>
</tbody>
</table>

CNS, central nervous system; Gd, gadolinium enhancement; FLAIR, fluid attenuated inversion recovery; DWI, diffusion-weighted imaging; ADC, apparent diffusion coefficient; H, high signal; sl H, slightly high signal; NE, not examined.
FIG. 1. – In case 1, a 29-year-old woman had been receiving antiepileptic drugs because she presented with seizure from eclampsia 17 days before MR examination. Neurological symptoms were not observed at the time of MR examination. Axial T2-weighted image (a) and trace DWI image (b) show increased signal intensity in the central area of the splenium of the corpus callosum (SCC). c, Axial ADC map shows decreased signal intensity of the lesion, indicating restricted diffusion of the lesion. d, Axial follow-up T2-weighted image shows that the SCC lesion disappears 7 weeks after initial MR examination.

Fig. 1. – (cas n° 1). Femme de 29 ans ayant reçu un traitement antépileptique en raison de la survenue d’une épilepsie après éclampsie, 17 jours avant l’IRM. Patient asymptomatique au moment de l’examen. Séquences T2 (a) et de diffusion (b) : hypersignal de la partie centrale du splenium du corps calleux. Cartographie du CAD (c) : diffusion réduite. Examen effectué 7 semaines après l’IRM initiale, séquence T2 (d) : disparition de la lésion.

FIG. 2. – In case 3, a 24-year-old man presented with fever and drowsiness. He was clinically diagnosed as viral encephalitis (unknown pathogen). Axial FLAIR image (a) and trace DWI image (b) show increased signal intensity in the SCC. Note that a high signal lesion extends discontinuously to the right lateral area of SCC (b, arrow). c, Axial follow-up FLAIR image shows the resolution of the SCC lesion 10 days after initial MR examination.

Fig. 2. – (cas n° 3). Homme de 24 ans atteint d’une encéphalite virale, fièvre et somnolence. Séquences FLAIR (a) et de diffusion (b) : hypersignal de la partie centrale du splenium du corps calleux. A noter, l’extension droite discontinue de l’hypersignal. Examen effectué 10 jours après l’IRM initiale, séquence FLAIR (c) : disparition de la lésion.
FIG. 3. – In case 5, a 29-year-old man with spinal meningeal melanocytoma, was examined for a brain-screening MR imaging. The patient had no neurological symptoms. a) Axial FLAIR image shows a small high signal lesion in the SCC. b) Axial contrast-enhanced T1-weighted image shows no lesion enhancement. c) Axial trace DWI image shows a high signal lesion in the SCC. d) Axial ADC map shows decreased signal intensity of the lesion, indicating restricted diffusion of the lesion. e) Axial follow-up trace DWI image still shows slightly high signal intensity of the lesion 7 days after the initial MR examination. f) Axial follow-up trace DWI image shows the resolution of the SCC lesion 37 days after the initial MR examination.

FIG. 4. – In case 7, a 58-year-old man with esophageal cancer, presented with somnolence during chemotherapy against the cancer. Neurologically, he recovered completely after withdrawal of 5-fluorouracil (5-FU). The diagnosis of 5-FU induced encephalopathy was made clinically. Axial T2-weighted image (a) and trace DWI image (b) show a high signal lesion in the SCC. c) Axial follow-up T2-weighted image shows the resolution of the SCC lesion 9 days after the initial MR examination.
(n=1) [4], asphyxia (n=1) [31], Marchiafava-Bignami disease (n=1) [9], and acute encephalopathy associated with intravenous immunoglobulin therapy (n=1) [34]. It is noteworthy that the literature describes such a wide spectrum of diseases and conditions for reversible splenial lesions with restricted diffusion.

Among the cases examined in the present study, five patients had the above-mentioned diseases and conditions, including encephalitis (cases 3 and 4), receiving AED (cases 1 and 2), and hypernatremia engendering osmotic myelinolysis (case 8). It should be noted that a reversible SCC lesion with restricted diffusion was found in three patients with neoplasm (cases 5-7). In the patient with esophageal cancer (case 7), 5-FU was likely to be causative because the patient’s symptoms were observed after induction of 5-FU and resolved after withdrawal of 5-FU in accordance with the MR imaging findings changes. Tha et al. [33] reported that restricted diffusion and patient’s symptoms induced by 5-FU recovered after drug withdrawal. We infer that 5-FU induced that phenomenon in the case we presented. A reversible SCC lesion in the patient with leukemia (case 6) might also be attributable to anticancer drugs that had been provided for treatment. However, we found no association between MR imaging findings and particular anticancer drugs. The patient with melanocytoma (case 5) received no treatment against neoplasm before or at the time of MR examination. For that reason, we inferred no causative conditions for reversible SCC lesions in the latter two patients with neoplasm. These two cases suggest that a reversible SCC lesion might be seen in a wider spectrum of diseases and conditions than ever reported.

It is interesting that most of the SCC lesions were oval. In contrast, the SCC lesion extended into the lateral areas of the splenium in two patients with encephalitis (case 3) and osmotic myelinolysis (case 8). The elongated shape of a SCC lesion might suggest that callosal lesions and the surrounding white matter are mutually connected, as implied in the DWI finding shown in case 8 (figure 5b and 5c). The DWI findings of an extended SCC lesion and surrounding white matter lesions were also reported in acute encephalopathy associated with intravenous immunoglobulin therapy and hypoglycemia [1, 34].

According to previous reports [1, 9, 13, 14, 16, 18, 30], the mean ADC value of a reversible SCC lesion was $0.31 \times 10^{-3} \text{mm}^2/\text{s}$, ranging from 0.13 to 0.48$\times 10^{-3} \text{mm}^2/\text{s}$: the mean ADC values in the current

---

**FIG. 5.** In case 8, a 49-year-old woman presented with coma. Hypernatremia (160 mEq/l) was indicated. The diagnosis of osmotic myelinolysis was made clinically. a) Axial FLAIR image shows high signal intensity in bilateral basal ganglia, as well as SCC. b, c) Axial trace DWI images show high signal intensity, particularly in the SCC and temporo-occipital white matter. d) Axial follow-up FLAIR image shows bilateral striatal lesions, but normal SCC 21 days after the initial MR examination. e) Axial follow-up FLAIR image shows brain atrophy and bilateral occipital white matter lesions 2 months after the initial MR examination.
cases (0.40×10⁻³ mm²/s) were close to that value. In the majority of clinical cases with stroke, follow-up MR examinations show that once ADC is decreased, the involved tissue nearly always becomes infarcted [6]. However, it has become evident recently in rare cases that regions with restricted diffusion can return to normal without persistent symptoms or T2 change in several diseases such as venous sinus thrombosis associated with seizure and hemiplegic migraine [7]. A reversible lesion of the SCC should be included in such cases with decreased ADC reversal.

The SCC is a site of predilection for this phenomenon, for reasons that remain uncertain. Some investigators have suggested that the SCC prevalence results from the robust spread through the splenium from bilateral independent seizure foci in patients with epilepsy [24]. This concept, however, is inapplicable to other cases that do not involve seizures. More recently, Gurtler et al. [8] reported that a SCC lesion in patients with epilepsy is not associated with toxic drug effects or high seizure frequency, but might be induced by a rapid and long-lasting reduction of AED. They speculated that effects of arginine-vasopression or rapid correction of hyponatremia caused by AED might be a mechanism. In patients with encephalitis or encephalopathy, two possible mechanisms for restricted diffusion are inferred: intramyelinic edema; and the influx of inflammatory cells, macromolecules, and related cytotoxic edema [30]. Such pathophysiologic changes might reduce ADC values of white matter lesions observed in patients with phenylketonuria [25] and in a few patients with multiple sclerosis [21]. Interestingly, it is reported that a neonate with mild asphyxia showed a reversible SCC lesion with transiently reduced ADC [31]. Pathologically, no myelinization of SCC occurs before age 2 months. Therefore, intramyelinic edema cannot occur in the neonatal period and is unlikely to be a possible mechanism underlying the reversible SCC lesion in this neonate case. Mechanisms of a reversible SCC with restricted diffusion might differ among diseases and conditions. Consequently, the exact etiology and mechanism of this phenomenon remain enigmatic [17].

Clinical courses and outcomes were good in seven of the eight cases reported here (cases 1-7). Previous reports describing encephalitis and encephalopathy cases showed good courses and outcomes in most cases: complete recovery within 1 month after the onset of neurologic symptoms [10, 13, 14, 19, 28, 29]. Therefore, it is suggested that an isolated reversible SCC lesion with restricted diffusion implies a good outcome, particularly in encephalitis or encephalopathy cases [28, 29]. According to previous reports [4, 9, 16, 18, 27, 31, 32], an isolated reversible SCC lesion with restricted diffusion also showed a less severe course or outcome for patients receiving AED and several other diseases, which is compatible with that of the cases we presented. Therefore, we speculate that an isolated reversible SCC lesion with restricted diffusion implies a less severe course or outcome irrespective of the associated disease or condition. On the other hand, in our case with osmotic myelination (case 8), tempo-occipital white matter lesions with restricted diffusion were not eventually reversible; the patient’s outcome was poor. Such a severe clinical outcome was also reported in patients with encephalitis or encephalopathy with a reversible SCC lesion, but additional parenchymal lesions [29]. Additional parenchymal lesions with restricted diffusion, however, do not necessarily suggest a severe outcome and irreversible MR imaging findings. Particularly, it has been reported that symmetrical fronto-parietal white matter lesions with restricted diffusion were reversible and that patients’ neurological recovery was excellent [1, 14, 29, 30]. In a patient with acute encephalopathy associated with intravenous immunoglobulin therapy [34], bilateral extensive parieto-occipital white matter lesions as well as an extended splenial lesion reportedly diminished in accordance with clinical improvement. Further investigations are required to assess the association between additional parenchymal lesions and clinical outcomes.

CONCLUSION

A reversible SCC lesion with transiently restricted diffusion is a unique phenomenon. We have described eight additional cases with a wide spectrum of diseases and conditions. The etiological mechanism remains uncertain and enigmatic. Neurological courses and outcomes are good, particularly in patients with isolated SCC lesions. Knowledge of MR imaging findings and the spectrum of diseases and conditions might prevent unnecessary invasive examinations and treatments.

REFERENCES


