Clinicoradiological Spectrum of Reversible Splenial Lesion Syndrome (RESLES) in Adults

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Abstract: The presence of reversible lesions that involve the splenium of the corpus callosum (SCC) has been reported in patients with a broad spectrum of diseases and conditions and is referred to as reversible splenial lesion syndrome (RESLES).

To describe the clinicoradiological features and establish a clinical position for this disease, we retrospectively examined the clinicoradiological features of adult RESLES patients, as well as discuss the potential pathophysiological mechanisms of this disease.

The clinical and MRI findings of patients who presented with RESLES accompanied by symptoms of neurological disorders were retrospectively reviewed. The patients were classified into 2 subgroups (favorable and poor outcome subgroups), which corresponded to the severity of the disability using the Modified Oxford Handicap Scale. In addition, we compared the clinical and neuroimaging features between the 2 outcome subgroups.

Eight patients with RESLES associated with various diseases and conditions were included. The clinical presentation was nonspecific; however, MRI exhibited consistent lesions in the SCC with a hypointensity on apparent diffusion coefficient maps and a hyperintensity via diffusion-weighted imaging, which disappeared after a variable lapse. The number of patients with a severe disturbance of consciousness, extracallosal lesions, or diffuse slow waves in the poor outcome subgroup was significantly increased compared with the favorable outcome subgroup (P < 0.05). Thus, the clinicoradiological spectrum of RESLES could be classified into 2 principal categories according to differential outcomes.

RESLES is a rare entity with a broad clinicoradiological spectrum because of the various diseases and conditions. Although the overall symptoms of RESLES patients tend to be alleviated, the prognosis of patients with a severe disturbance of consciousness, extracallosal lesions, or diffuse slow waves is likely unfavorable.

INTRODUCTION

Acquired lesions of the corpus callosum (CC) are present in a variety of disorders, such as multiple sclerosis, ischemia, bleeding, diffuse axonal injury, acute disseminated encephalomyelitis, chronic alcoholism, tumors, and trauma. During the previous decade, magnetic resonance imaging (MRI) studies have provided evidence of a reversible isolated lesion with transiently reduced diffusion in the splenium of the corpus callosum (SCC) in patients with a wide spectrum of diseases and conditions. These findings have led to a specific clinical and radiological entity, which is referred to as reversible splenial lesion syndrome (RESLES). RESLES has been reported secondary to several disorders, including acute or subacute encephalitis/encephalopathy, antiepileptic drug (AED) toxicity or withdrawal, high-altitude cerebral edema, hypoglycemia, or hyponatremia. Broadly speaking, the spectrum of RESLES also includes specific diseases, such as clinically mild encephalitis/encephalopathy with a reversible splenial lesion (MERS) and Marchiafava–Bignami disease (MBD).

Many cases of RESLES in children have been reported, and most cases were diagnosed as MERS as a result of the various etiologies. However, during the previous 3 years, we have encountered adult patients with RESLES, which may be associated with various diseases and conditions other than MERS. It has been speculated that the spectrum of RESLES in adults is different from children. To describe the clinicoradiological features and establish a clinical position for this disease, we retrospectively examined the clinicoradiological features of adult RESLES patients, including the clinical course, laboratory data, MRI and electroencephalography (EEG) findings, potential therapies, and disease prognoses. Additionally, we also discuss the potential pathophysiological mechanisms of RELES, with respect to the results of previous studies.
PATIENTS AND METHODS

Patients

We reviewed the clinical and neuroimaging data of RESLES patients (age ≥14 years) who presented symptoms of neurological disorders, such as seizure, the disturbance of consciousness, delirious behavior, and visual hallucinations. The Glasgow Coma Scale (GCS) was used to assess the severity of consciousness impairment. All patients were hospitalized in the Department of Neurology in Shenyang, China, between January 1, 2011, and January 1, 2014. Two board-certified neurologists examined each patient to provide a definite diagnosis of RESLES.

RESLES was diagnosed based on the inclusion criteria of Garcia et al (2011), which included the following: patients present with neurological deficits and have lesions in the SCC with or without extracallosal lesions, evidenced through MRI, which either disappeared or significantly improved during follow-up. To minimize selection bias, specific diagnoses, such as MOHS, which fulfilled the inclusion criteria, were also included. The presence of additional brain lesions or other involved regions in the CC were also considered as long as the primary lesion centered on the SCC. Patients in whom splenial lesions were persistent (or follow-up data were not available) were excluded.

Eight adult patients (age of onset range 18–70 years, with a mean age of 39.4 ± 19.4 years, median 30.5 years) with RESLES, including 5 men and 3 women, were identified. Three suspected cases were excluded because these individuals did not undergo follow-up MRI scans.

Analysis of MRI Images and Other Examinations

For all patients, the initial MRI examinations were performed 0 to 3 days after hospitalization. MRI was performed using 1.5 or 3.0 T units that comprised axis T1- and T2-weighted sequences, with or without contrast agents; fast fluid attenuated inversion recovery (FLAIR) sequences and diffusion-weighted imaging (DWI) were performed using an axial multi-section single-shot echo-planar SE sequence. The apparent diffusion coefficient (ADC) maps were calculated on a pixel-by-pixel basis. The standard mean ADC values of each region of interest from the splenial lesions and normal-appearing white matter were calculated automatically and expressed in 10⁻³ mm²/s.

MRI findings, such as the shape of the splenial lesion, other involved regions of the CC, extracallosal lesions, DWI and FLAIR findings, additional parenchymal lesions, and the clinical course of the splenial lesion from the first episode, were comprehensively analyzed.

Other laboratory tests and EEG findings, including biochemical and microbiological examinations of the cerebrospinal fluid (CSF), were available in all cases.

The neurological outcome was determined using the Modified Oxford Handicap Scale (MOHS), and the patients were subsequently classified into 2 subgroups that corresponded to the severity of the disability. A favorable outcome was defined as “no or minor disability” (MOHS ≤2), and a poor outcome was defined as a “major disability” (MOHS ≥3). Additionally, the clinical course and outcome were compared with the MRI findings for these patients. This study was approved by the Ethics Committee of Shengjing Hospital, China Medical University. All participants provided written informed consent prior to inclusion in the study.

Statistical Analysis

We compared the clinical and neuroimaging features between the “poor outcome” subgroup, which presented with major disability in the recovery stage, and the “favorable outcome” subgroup, which presented with no or minor disability. Fisher exact test and the Mann–Whitney U two-independent-samples test were used for statistical analysis. A value of P < 0.05 was considered statistically significant. All statistical analyses were executed using SPSS Statistics software, version 17.0.

RESULTS

Clinical Features and Patient Outcomes

The clinical records and radiological information regarding these 8 patients were reviewed as the basis of the present study. All patients were previously healthy and had no history of neurological disease, with the exception of epilepsy. The detailed clinical data for the 8 patients are shown in Table 1.

The etiologies of RESLES included MERS, which was associated with pathogen infections in 3 patients (37.5%), MBD in 2 patients (25%), AED withdrawal in 1 patient (12.5%), and hypoxic-ischemic encephalopathy in 2 patients (25%). Fever (>37.5 °C) preceded the appearance of neurological symptoms in all patients with MERS. A disturbance of consciousness of acute to subacute onset was the predominant clinical finding in 6 patients. In 7 of the 8 patients, seizure or a prodromal stage with cognitive impairment preceded the onset of the disturbance of consciousness by 2 days to 2 weeks, and coma was often accompanied by seizure and limb hypertonia. Other symptoms recorded prior to the onset of the disturbance of consciousness included cognitive impairment, visual hallucination, ataxia, signs of interhemispheric disconnection, and dysarthria. The mean GCS for all 8 patients was 10.63 ± 3.70 (range 6–15, median 10.5). Although 4 patients (cases 2, 3, 4, and 6) completely recovered from their primary neuropsychiatric symptoms, to some extent, through prompt and effective treatment, not all patients had favorable outcomes. Specifically, the symptoms of seizure and focal neurological deficits in 4 patients (cases 1, 5, 7, and 8) were significantly improved and the general neurological function was partially recovered, but they retained a moderate-to-severe handicap. The main residual symptoms were severe disturbances of consciousness and cognitive function impairment, which left patients unable to live independently; therefore, the patients who exhibited a moderate-to-severe handicap required constant attention for life.

Sufficient information to estimate clinical outcomes, according to the MOHS, was provided in all included cases. The mean MOHS value, which was determined at 35 days after admission, was 2.4 ± 2.3 (range 0–5, median 2.5).

MRI Findings

The details of the MRI features are summarized in Table 2. The mean days from symptom onset to hospital admission was 5.0 ± 4.17 days (range 2.0–14.0, median 3.5 days). The initial MRI findings, which were obtained, on average, at 6.0 ± 3.63 days (range 3.0–14.0, median 5.0 days) after the onset of early symptoms, were recorded for all 8 patients; these findings indicated a consistent pattern of neuroimaging abnormalities, which were characterized by circumscribed, oval or extended lesions, high signal intensity on FLAIR, T2-weighted sequences, and DWI, with minimal or no signal reduction on T1-weighted sequences and no contrast...
| Patient No. | Sex | Age (y) | Diseases and Conditions | Form of Onset | Time From Onset to Admission | Neurological Manifestation (GCS) | Therapy | Neurological Outcome at 35 d After Admission (MOHS) | EEG Findings |
|------------|-----|---------|------------------------|---------------|-----------------------------|--------------------------------|---------|-------------------------------------------------|-------------|
| 1          | M   | 18      | Delayed encephalopathy following acute carbon monoxide poisoning (hypoxic-ischemic encephalopathy) | Subacute (at 1 mo after carbon monoxide poisoning) | 7 d | Cognitive impairment, seizure, visual hallucination, extrapyramidal symptoms, delirium/coma (6) | Hyperbaric oxygen therapy, AED, compound levodopa | PR, epilepsy well controlled, but remained in a minimally conscious state (5) | DSW |
| 2          | F   | 27      | Encephalopathy associated with AED (valproate) withdrawal | Acute (at 8 d after sudden AED withdrawal) | 2 d | Recurrent visual disturbance (15) | Continuation of valproate | CR within 1 wk (0) | Normal |
| 3          | F   | 26      | MERS as a result of mycoplasma infection | Acute | 6 d | Headache, fever, seizure, somnolence (14) | Mannitol, diazepam, macrolides antibiotics and moxifloxacin | CR within 10 d (0) | OSW |
| 4          | F   | 34      | MERS as a result of mumps virus infection | Acute | 2 d | Dizziness, fever, somnolence (14) | Interferon, ribavirin | CR within 8 d (0) | OSW |
| 5          | M   | 54      | Marchiafava–Bignami disease | Subacute | 14 d | Cognitive impairment, seizure, somnolence/coma, limb hypertonia (8) | Vitamin B12, vitamin B12, baclofen, nutritional support | PR, hypermyotonia, convulsion well controlled, but remained somnolent (5) | DSW |
| 6          | M   | 25      | MERS as a result of herpes simplex virus infection | Acute | 5 d | Headache, fever, cognitive impairment, behavioral disorders, confusion (13) | Ganciclovir, mannitol, antibiotics | CR, but with mild cognitive impairment within 12 d (1) | OSW |
| 7          | M   | 70      | Hypoglycemia as a result of the misuse of insulin (hypoxic-ischemic encephalopathy) | Acute | 2 d | Ataxia, cognitive impairment, convulsion/seizure, stupor/coma, limb hypertonia (7) | Administered intravenous doses of glucose | PR, epilepsy well controlled, but cognitive function impairment remained (4) | DSW |
| 8          | M   | 61      | Marchiafava–Bignami disease | Acute | 2 d | Dysarthria, interhemispheric disconnection, cognitive impairment, delirium/coma (8) | Vitamin B12, vitamin B12, nutritional support | PR, cognitive function impairment (4) | DSW |

AED = antiepileptic drug, CR = complete recovery, DSW = diffuse slow wave, EEG = electroencephalography, GCS = Glasgow Coma Scale, MERS = mild encephalitis/encephalopathy with a reversible splenial lesion, MOHS = Modified Oxford Handicap Scale, OSW = occipital slow wave, PR = partial recovery.
### TABLE 2. MRI Findings for the 8 Patients With Reversible Splenial Lesion Syndrome

| Patient No. | Interval (d) After Onset | Shape of Splenial Lesion | Other Involved Parts in Corpus Callosum | Extracallosal Lesions (Extent of Lesions) | Initial MRI (Performed 0 to 3d After Hospitalization) | Reversal of Lesion in Follow-up MRI: Interval (d) After Onset |
|-------------|--------------------------|--------------------------|----------------------------------------|------------------------------------------|------------------------------------------------------|-------------------------------------------------------------|
| 1           | 7                        | Extended                 | Yes (genu)                             | Bilateral PWM and SWM of the frontal and parietal lobes | H sH NE 0.31 3 wk                                   |                                                         |
| 2           | 4                        | Circumscribed            | No                                     | No                                       | H H No 0.64 15 d                                   |                                                         |
| 3           | 7                        | Circumscribed            | No                                     | No                                       | H H No 0.39 22 d                                   |                                                         |
| 4           | 3                        | Ovoid                    | No                                     | No                                       | H sH No 0.34 16 d                                   |                                                         |
| 5           | 14                       | Extended                 | Yes (body)                             | Bilateral SWM of the occipitotemporal lobes and the frontoparietal and occipital lobes | H H No 0.28 16 d                                   |                                                         |
| 6           | 6                        | Lobulated                | No                                     | No                                       | H sH NE 0.45 17 d                                   |                                                         |
| 7           | 4                        | Extended                 | No                                     | Right caudate nucleus and bilateral fornical columns | H sH NE 0.35 19 d                                   |                                                         |
| 8           | 3                        | Extended                 | Yes (genu)                             | Bilateral centrum semiovale white matter of the frontoparietal lobes | H H NE 0.56 2 wk                                   |                                                         |

ADC = apparent diffusion coefficient, DWI = diffusion-weighted imaging, FLAIR = fluid attenuated inversion recovery, H = high signal, MRI = magnetic resonance imaging, NE = not examined, PWM = periventricular white matter, sH = slight high signal, SWM = subcortical white matter.
enhancement, primarily located in the central region of the SCC. No cystic or necrotic lesions in the SCC were identified in the MRI sequences.

The follow-up MRI examinations, which were performed at $17.5 \pm 2.88$ days (range 14–21, median 16.5 days) after onset, indicated the complete disappearance or a clear reduction in the lesion size and signal intensity (Figures 1 and 2). In 2 patients, DWI indicated restricted diffusion with low ADC map values (mean $0.42 \pm 0.13$, range $0.28–0.64$, median $0.37 \times 10^{-3} \text{mm}^2/\text{s}$), which suggests cytotoxic edema, consistent with the normality of magnetic resonance angiography and venography.

An isolated SCC lesion without an extracallosal lesion was apparent in 4 patients (cases 2, 3, 4, and 6), and an isolated SCC lesion with an extracallosal lesion was identified in a single patient (case 7); lesions with restricted diffusion in other regions of the CC were identified in 3 patients (cases 1, 5, and 8). Extracallosal lesions were recorded in 4 patients (cases 1, 5, 7, and 8), which predominantly involved the periventricular white matter, subcortical white matter, and basal ganglia. In 3 of these 4 patients (cases 5, 7, and 8), the high-signal-intensity DWI identified in the extracallosal lesions reassumed a normal signal intensity during follow-up (Figure 3). Overall, the splenial lesion was not isolated; however, it was consistently associated with other more specific abnormalities in RESLES, which were associated with metabolic encephalopathy. Moreover, under disease conditions, such as hypoglycemia or other metabolic disorders, reversible lesions were also identified in other regions of the brain.

**CSF and EEG Findings**

Lumbar punctures were performed in 3 patients with MERS because of pathogen infections (cases 3, 4, and 6). The existing CSF findings did not indicate the characteristic appearance of CSF for RESLES, including some disorders caused by MERS. Table 3 shows the results of the CSF analyses.

Well-controlled EEGs were obtained for all patients after seizures, but prior to the follow-up MRI. The marked slowing of basic activity with characteristics of encephalitis/encephalopathy was identified in 7 of the 8 examined patients; these findings included diffuse slow waves in 4 patients (cases 1, 5, 7, and 8) and occipital slow waves in 3 patients (cases 3, 4, and 6). An EEG abnormality was not detected in 1 patient (case 2), which indicated the transient and isolated SCC lesion did not have a

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**FIGURE 1.** In case 4, a 43-year-old woman presented with dizziness, fever, and somnolence. The patient was clinically diagnosed with mild encephalitis and a reversible splenial lesion MERS that resulted from a mumps virus infection. The initial 3.0 T MRI indicated an ovoid symmetrical midline lesion in the central region of the splenium, a hypointensity on the ADC map (A), and hyperintensities on the DWI image (B) and FLAIR (C). The follow-up 1.5 T MRI at 2 weeks later indicated the complete disappearance of the splenial lesion (D). ADC = apparent diffusion coefficient, DWI = diffusion-weighted imaging, FLAIR = fast fluid attenuated inversion recovery, MERS = clinically mild encephalitis/encephalopathy with a reversible splenial lesion, MRI = magnetic resonance imaging.
disadvantageous effect on advanced brain functions in this patient.

**Comparative Analysis of 2 Subgroups and Prognostic Factors**

A favorable outcome (defined as MOHS ≤2) was determined in 4 of the 8 patients (cases 2, 3, 4, and 6, which included 3 cases with MERS and 1 case with AED withdrawal); these patients were classified as the “favorable outcome subgroup” (no or minor disability, MOHS ≤1, no one was scored a 2). Three patients in the favorable outcome subgroup fully regained consciousness within 2 weeks, without any sequel. The mean MOHS value in the favorable outcome subgroup was 0.25 ± 0.5 (range 0–1, median 0.5). The outcomes were poor (MOHS ≥4, no one was scored a 3) in the other 4 patients (cases 1, 5, 7, and 8), who were classified as the “poor outcome subgroup” (major disability, MOHS ≥4, no one was scored a 3). No further deterioration with a lethal course has been reported for any patient. The mean MOHS value in the poor outcome subgroup was 4.5 ± 0.53 (range 4–5, median 4.5). Moreover, there was a significant difference in the MOHS values between the 2 subgroups (Z = −2.40, P = 0.017).

All 4 patients in the poor outcome subgroup exhibited symptoms of coma at early onset, whereas no patient with coma or extracallosal lesions was identified in the favorable outcome subgroup. Compared with the patients with mild consciousness impairment (such as somnolence), a severe disturbance of consciousness at the early stage was significantly associated with an unfavorable prognosis (P = 0.029). Similarly, there was also a significant difference in the GCS value between the 2 subgroups (P = 0.029).

Compared with the patients without extracallosal lesions, the patients with extracallosal lesions were significantly associated with poor outcomes (P = 0.029); however, the unfavorable prognosis did not exhibit a similar relationship with lesions in other regions of the CC (P = 0.143). Similarly, the patients with diffuse slow waves in EEG tended to have poor outcomes (P = 0.029), whereas the patients with occipital slow waves did not exhibit similar tendencies (P = 0.143).

The comparisons between the 2 subgroups with different outcomes in demographic, clinical, and radiological data are summarized in Table 4.

**DISCUSSION**

**Clinical Spectrum and Manifestations**

RESLES is a rare and complicated clinicoradiological entity that reflects various diseases and conditions. This retrospective study demonstrated that RESLES, which is characterized by reversible SCC abnormalities, is associated with a wide
spectrum of disorders, including infections, AED withdrawal, and metabolic disorders. Although these findings implied that the overall symptoms of patients with RESLES tend to subside, some clinicoradiological features, including a severe disturbance of consciousness, extracallosal lesions, and diffuse slow waves, may indicate an unfavorable prognosis in patients with RESLES.

It has been suggested that lesions in the SCC cause visual simultanagnosia. However, the diagnosis of this syndrome is complex, and specific tests must be performed.2,13 In previous studies regarding RESLES, such symptoms were rarely reported and almost never isolated, which likely reflects the prevalent symptoms of the underlying disease that determine splenial abnormalities. Overall, the common symptoms associated with RESLES identified in the present study included cognitive impairment, seizures, confusion, coma, ataxia, somnolence, visual disturbance, and delirium.

The lack of large-scale clinical prospective studies with long-term follow-up and nonunified international criteria suggests that the incidence of RESLES under different conditions is difficult to ascertain because MRI examination is not routinely performed in many patients of different etiologic groups.14 Drug-resistant epilepsy has been estimated to occur in 0.7% of patients who undergo presurgical evaluation and in whom AEDs are rapidly reduced to provoke seizures and ictal EEG discharges.15,16 During the previous 3 years, our hospital has treated more than 800 patients diagnosed with acute or subacute encephalitis/encephalopathy syndrome and 134 patients with splenial lesions as a result of various disorders; only 8 patients were diagnosed with RESLES and presented with reversible SCC lesions. These results suggest that the incidence of RESLES is less than 1% in patients with encephalitis/encephalopathy and less than 6% in patients with splenial lesions. However, these incidences are likely underestimated and substantially biased because of the limitation of this study type and the uncertainty of the patient sampling.

Patients with isolated focal reversible diffusion restriction in the SCC in epilepsy have been described, and these symptoms were different from the other forms of epilepsy-related brain edema. RESLES has been reported in patients without epilepsy during the rapid withdrawal of carbamazepine for trigeminal neuralgia, which strongly suggests carbamazepine or the withdrawal of carbamazepine could be a contributing factor.

FIGURE 3. Initial MRI from RESLES patients (cases 1, 2, 3, 5, 6, and 7) showed hyperintense signal in the splenial lesion of the CC on DWI. Follow-up MRI showed the resolution of splenial lesion during follow-up. (Case 1: 1A, 1B; case 2: 3A, 3B; case 3: 5A, 5B; case 5: 2A, 2B; case 6: 4A, 4B; and case 7: 6A, 6B.) CC = corpus callosum, DWI = diffusion-weighted imaging, MRI = magnetic resonance imaging, RESLES = reversible splenial lesion syndrome.
The clinical findings of patient 2 are consistent with these results. However, the definite mechanism of RESLES associated with AED withdrawal is currently not known. Some reversible lesions in the SCC have been identified in acute encephalitis/encephalopathy, which is referred to as a MERS. Three young patients with symptoms of acute encephalitis, who fulfilled the diagnosis of MERS, were described in the present study. Although children with reversible splenial lesions are typically observed in MERS, the present findings suggested the disease spectrum associated with reversible lesions in the SCC of adult patients might be different from children with brain development. Furthermore, the broad concept of RESLES should include MERS. Another common cause of RESLES is metabolic disorders; as a typically metabolic disease that involves the CC, MBD has primarily been reported in patients with chronic and severe alcoholism and multiple vitamin deficiencies. MBD preferentially affects the central and medial regions of the CC, with the splenium as the most frequently involved region of the CC. Lesions in most patients with MBD have been previously considered irreversible because of the profound necrosis and progressive demyelination of the CC. However, the disappearance or significant improvement of splenial lesions had been described in some patients, which is consistent with the inclusion criteria of RESLES. Thus, MBD with a reversible splenial lesion was included in this study. The complete resolution of callosal and extracallosal hyperintensities of MBD in DWI was unusual. It has been proposed that this phenomenon might reflect reversible myelin vacuolization or intramyelinic edema, which has been described in patients with epilepsy and MERS. Moreover, these findings also indicated that prompt treatment of MBD with parenteral thiamine is more favorable than reversible splenial lesion and clinical recovery.

### Radiological Features

The MRI findings of RESLES have exhibited a low ADC, which indicates the presence of cytotoxic edema in the SCC. DWI indicates the earliest signs of lesions and identifies more extensive CC lesions in RESLES compared with FLAIR. Cytotoxic edema has also been observed in other brain regions for RESLES associated with metabolic disorders, and this condition might precede the development of SCC alterations and predict a poor outcome. However, this observation is not always the case; indeed, complete or partial recovery after prompt therapy has previously been reported and was observed in the present study. DWI could be employed to investigate the clinical correlates of RESLES and the recovery process.

### Pathophysiological Mechanism of RESLES

The pathophysiological mechanism of RESLES is not well known, and several theories have been speculated in several

| Patient No. | Pressure (mm H2O) | Protein (g/L) | Cell Count (cells/mm³) | Sugar (mmol/L) | Chlorine (mmol/L) | Antibody to Pathogen |
|-------------|------------------|---------------|------------------------|---------------|-------------------|---------------------|
| 3           | 200              | 0.16          | 3                      | 4.3           | 127.9             | Mycoplasma-IgM       |
| 4           | 170              | 0.37          | 7                      | 4.04          | 126.3             | Mumps virus-IgM      |
| 6           | 230              | 1.1           | 112                    | 3.81          | 122.1             | Herpes simplex virus (I+II)-IgM |

* Includes 44% monocytes, 36% lymphocytes, and 20% neutrophils.

† Elevated.

For comparisons between the 2 subgroups, $P$ values $<0.05$ were considered statistically significant. ADC = apparent diffusion coefficient, CC = corpus callosum, EEG = electroencephalography, GCS = Glasgow Coma Scale, MOHS = Modified Oxford Handicap Scale.
studies without firm conclusions. The potential mechanisms for transitory restricted diffusion include intramyelanic edema, the breakdown of the blood–brain barrier, reversible demyelination, arginine vasopressin release, and inflammatory cell-related cytotoxic edema. Despite numerous pathology and neuroimaging studies, it remains uncertain why reversible splenial lesions selectively occur in the SCC. It has been proposed that the specific affinity of viral antigens or induced antibodies to the splenial axonal receptors is responsible for the splenial involvement in viral encephalitides. Moreover, it has been postulated that the SCC has a specific vulnerability to excitotoxic injury in metabolic diseases, which makes this area selectively involved in different pathological events. However, neither of these mechanisms explains the involvement of the SCC in other disorders. Despite these theories, a common pathophysiological mechanism that explains splenial predilection in different disorders has not been suggested because of the heterogeneous nature of these diseases.

Prognostic Factors and 2 Categories

The prognostic relevance of extracallosal lesions and defects in other involved regions in the CC is controversial, and these factors have been repeatedly suggested as markers for a poor prognosis. The results of a previous study indicated that the absence of a clear neurological decit is observed when the SCC lesion is solitary and small, in contrast to diffuse CC lesions or SCC lesions with multifocal extracallosal lesions that often result in severe neurological decits because of diffuse brain impairments. These results indicate that patients with extracallosal lesions, but not lesions in other involved regions of the CC, would have a less favorable outcome (MOHS ≥4). Similarly, an EEG abnormality has been identified in almost all cases, and all patients with severe disturbances of consciousness exhibited diffuse slow waves on EEG. The involvement of the bilateral white matter may disrupt higher cortical function, which also results in transient diffuse slow waves on EEG.

From a clinical standpoint, the clinicoradiological spectrum of RESLES can be classified into 2 principal categories, including categories A and B. Patients with category A RESLES are characterized by a severe disturbance of consciousness, extracallosal lesions, diffuse slow waves, and poor outcomes. In contrast, patients with category B RESLES exhibit slightly impaired levels of consciousness, isolated splenial lesions without extracallosal lesions, occipital slow or normal waves on EEG, and favorable outcomes. The differentiation of these 2 principal categories may provide a better prognosis via these clinicoradiological features.

Study Limitations and Strength

Although these results elaborated the clinicoradiological features of RESLES in adults in a systematic manner, the present study still has some limitations. First, a major limitation is the relatively small number of patients with various disorders included in the present study, which might preclude formal subgroup analyses according to the classification of diseases and conditions. Achalia et al. (2014) speculated that the prognosis of RESLES depends on the underlying disorder and not on other factors. We did not reach a unified conclusion regarding the relationship between these disorders and the prognosis. A prolongation of the range of studied time intervals and the enrollment of additional patients from other regional medical centers might resolve this major limitation. However, we consider the sample described herein as representative.

Second, in the present study, we did not perform a standardized protocol for follow-up. Whether different lengths of follow-up affect the reversibility of splenial lesions remains unknown. Additionally, the dynamic presentation of splenial lesions on MRI might indicate the pathological nature of RESLES. Third, the neuropsychological analysis of patients with cognitive impairments was not performed because of the incompleteness of the clinical data. Nevertheless, an increasing number of case studies regarding patients with reversible lesions in the SCC, which are associated with a variety of diseases and conditions, have been reported; however, to date, there is no a systematic analysis of these clinicoradiological features, and the clinical significance of RESLES remains unclear. The present retrospective study may remedy these defects. The major strength of the present study is that the data were continuously collected in all MRI-verified cases diagnosed with RESLES in a regional medical center. Moreover, this study provided reliable evidence that it might be more relevant to clinical practice to differentiate 2 categories of RESLES.

CONCLUSION

To sum up, the results of the present study indicated that the prognosis of RESLES patients characterized by an acute to subacute onset of a severe disturbance of consciousness, particularly with extracallosal lesions and diffuse slow waves on EEG, is poor with considerable disability. In contrast, in RESLES patients without a severe disturbance of consciousness, extracallosal lesions, or diffuse slow waves, the clinical course is likely benign with a favorable outcome. A predictive evaluation according to the 2 different categories of RESLES could provide better information regarding the prognosis in survival and functional impairment compared with traditional neuroimaging alone.

REFERENCES

1. Renard D, Castelnovo G, Campello C, et al. An MRI review of acquired corpus callosum lesions. J Neurol Neurosurg Psychiatry. 2014;85:1041–1048.
2. Gallucci M, Limbucci N, Paonessa A, et al. Reversible focal splenial lesions. Neuropathology. 2007;49:541–544.
3. Maeda M, Tsukahara H, Terada H, et al. Reversible splenial lesion with restricted diffusion in a wide spectrum of diseases and conditions. J Neuroradiol. 2006;33:229–236.
4. Tada H, Takanashi J, Barkovich AJ, et al. Clinically mild encephalitis/encephalopathy with a reversible splenial lesion. Neurology. 2004;63:1854–1858.
5. Garcia-Monero JC, Cortina IE, Ferreira E, et al. Reversible splenial lesion syndrome (RESLES): what’s in a name? J Neuroimag. 2011;21:e1–e14.
6. Takanashi J, Tada H, Maeda M, et al. Encephalopathy with a reversible splenial lesion is associated with hyponatremia. Brain Dev. 2009;31:217–220.
7. Kometani H, Kawatani M, Ohta G, et al. Marked elevation of interleukin-6 in mild encephalopathy with a reversible splenial lesion (MERS) associated with acute focal bacterial nephritis caused by Enterococcus faecalis. Brain Dev. 2014;36:551–553.
8. Morichi S, Kawashima H, Ioi H, et al. High production of interleukin-10 and interferon-gamma in influenza-associated MERS in the early phase. Pediatr Int. 2012;54:536–538.
9. Kashiwagi M, Tanabe T, Shimakawa S, et al. Clinico-radiological spectrum of reversible splenial lesions in children. Brain Dev. 2014;36:330–336.
10. Fluss J, Ferey S, Menache-Starobinski C, et al. Mild influenza-associated encephalopathy/encephalitis with a reversible splenial lesion in a Caucasian child with additional cerebellar features. *Eur J Paediatr Neurol.* 2010;14:97–100.

11. Fuchigami T, Goto K, Hasegawa M, et al. A 4-year-old girl with clinically mild encephalopathy with a reversible splenial lesion associated with rotavirus infection. *J Infect Chemother.* 2013;19:149–153.

12. Bamford J, Sandercock P, Dennis M, et al. A prospective study of acute cerebrovascular disease in the community: the Oxfordshire Community Stroke Project 1981-86. 1. Methodology, demography and incident cases of first-ever stroke. *J Neurol Neurosurg Psychiatry.* 1988;51:1373–1380.

13. Chechlacz M, Rotshtein P, Hansen PC, et al. The neural underpinnings of simultanagnosia: disconnecting the visuospatial attention network. *J Cogn Neurosci.* 2012;24:718–735.

14. Tseng YL, Huang CR, Lin CH, et al. Risk factors of hyperammonemia in patients with epilepsy under valproic acid therapy. *Medicine (Baltimore).* 2014;93:e66.

15. Krishnaiah B, Ramaratnam S, Ranganathan LN. Subpial transection surgery for epilepsy. *Cochrane Database Syst Rev.* 2013;8:CD008153.

16. Nelles M, Bien CG, Kuthen M, et al. Transient splenium lesions in presurgical epilepsy patients: incidence and pathogenesis. *Neuroradiology.* 2006;48:443–448.

17. Guven H, Delibas S, Comoglu SS. Transient lesion in the splenium of the corpus callosum due to carbamazepine. *Turk Neurosurg.* 2008;18:264–270.

18. Mori H, Maeda M, Takanashi J, et al. Reversible splenial lesion in the corpus callosum following rapid withdrawal of carbamazepine after neurosurgical decompression for trigeminal neuralgia. *J Clin Neurosci.* 2012;19:1182–1184.

19. Prilipko O, Delavelle J, Lazeyras F, et al. Reversible cytotoxic edema in the splenium of the corpus callosum related to antiepileptic treatment: report of two cases and literature review. *Epilepsia.* 2005;46:1633–1636.

20. Heinrich A, Runge U, Khaw AV. Clinicoradiologic subtypes of Marchiafava-Bignami disease. *J Neurol.* 2004;251:1050–1059.

21. Hillbom M, Saloheimo P, Fujioka S, et al. Diagnosis and management of Marchiafava-Bignami disease: a review of CT/MRI confirmed cases. *J Neurol Neurosurg Psychiatry.* 2014;85:168–173.

22. Tung CS, Wu SL, Tsou JC, et al. Marchiafava-Bignami disease with widespread lesions and complete recovery. *AJNR Am J Neuroradiol.* 2010;31:1506–1507.

23. Duray MC, De Maeseneire C, Rutgers MP, et al. Acute reversible Marchiafava-Bignami disease with hypernatremia: a “callosal myelinolysis”? *Rev Neurol (Paris).* 2014;170:232–234.

24. Takanashi J, Barkovich AJ, Yamaguchi K, et al. Influenza-associated encephalitis/encephalopathy with a reversible lesion in the splenium of the corpus callosum: a case report and literature review. *AJNR Am J Neuroradiol.* 2004;25:798–802.

25. Yamasita S, Kawakita K, Hosomi N, et al. Reversible magnetic resonance imaging changes associated with hypoglycemia. Case report. *Neuroradiology.* 2010;50:651–654.

26. Stiffredi V, Anderson V, Leventer RJ, et al. Neuropsychological profile of agenesis of the corpus callosum: a systematic review. *Dev Neuropsychol.* 2013;38:36–57.

27. Achaia R, Andrade C. Reversible abnormality of the splenium in a bipolar patient with neuroleptic malignant syndrome. *Bipolar Disord.* 2014;16:773–775.