Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.4516-20
Intern Med 59: 2471-2480, 2020
http://internmed.jp

【 ORIGINAL ARTICLE 】

Reversible Splenial Lesion Syndrome with Some Novel Causes and Clinical Manifestations

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Abstract:

Objective Reversible splenial lesion syndrome (RESLES) is a clinical radiological syndrome characterized by a reversible lesion of the splenium of the corpus callosum with a decreased apparent diffusion coefficient (ADC) value. The clinical manifestations of RESLES are diverse.

Methods Fifteen cases of adult RESLES patients (10 males and 5 females) were retrospectively selected from the radiology system using the key word "corpus callosum" at a university-affiliated tertiary care hospital between May 1, 2015 and December 31, 2019. The possible precipitating factors, clinicoradiological findings and modified Rankin Scale (mRS) on follow-up were then analyzed.

Results The patient ages ranged from 22 to 53 years old. The mean age was 34 years old. The most common neurological symptoms included headache (3/15), dizziness (3/15), first onset of seizure (3/15), paroxysmal blurred vision (2/15), vertigo (2/15), amnesia (2/15), and confused consciousness without seizure (2/15), followed by drowsiness (1/15), paresthesia (1/15), dysmetria (1/15) and dysarthria (1/15). The precipitating factors included infection, seizure, anti-epileptic treatment with levetiracetam, carbamazepine, valproate, hyperglycemia, hypoglycemia, cerebral venous sinus thrombosis, and rabies vaccine injection prior to the onset of RESLES. All cases were carefully followed up and had excellent prognoses.

Conclusion RESLES manifests as variety of symptoms with less specificity and precipitating factors. Paroxysmal blurred vision may be a relatively specific symptom of RESLES. Levetiracetam, carbamazepine or valproate could be the cause of RESLES, exposure to the rabies vaccine could be another predisposing factors for RESLES as well. RESLES type 1 was therefore found to be highly "reversible" with an excellent prognosis.

Key words: reversible splenial lesion syndrome (RESLES), corpus callosum, magnetic resonance imaging, levetiracetam, carbamazepine, valproate

(Intern Med 59: 2471-2480, 2020)
(DOI: 10.2169/internalmedicine.4516-20)

Introduction

Reversible splenial lesion syndrome (RESLES) is a clinical radiological syndrome characterized by the presence of a reversible lesion involving the splenium of the corpus callosum (SCC) with a decreased apparent diffusion coefficient (ADC) value of the lesion on ADC maps. RESLES often resolves spontaneously with a favorable clinical outcome. In 1999, RESLES was first reported by Kim and colleagues (1). They reported a group of epileptic patients with concurrent lesions of the corpus callosum (CC), and speculated that these lesions were caused by the use of antiepileptic drugs. Garcia-Monco et al. (2) proposed RESLES with a diversity of etiologies in 2011, Since that time, an increasing number of RESLES cases have been reported, with most such studies being in the case report format. Besides seizures and withdraw from antiepileptic drugs (3-5), reports have revealed a variety of etiologies, including the use of other pharmacological agents such as metronidazole (6), olanzapine (7), infections like influenza A (8, 9), rotavirus infection (10), streptococcus pneumoniae (11), meningococcal meningitis (12), metabolic conditions such as hypoglycemia or hypernatremia (2, 13, 14), glufosinate ammonium

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Received: January 20, 2020; Accepted: May 11, 2020; Advance Publication by J-STAGE: June 30, 2020
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poisoning (15) and miscellaneous conditions including malnutrition, vitamin B12 deficiency (16), malnutrition (17), high-altitude cerebral edema (18), systemic lupus erythematosus (SLE) (19), Kawasaki disease (20), anti-voltage-gated potassium channel (VGKC) autoantibody syndrome (21), malignancy (13), cerebral venous sinus thrombosis (22), and preeclampsia (23). The heterogeneity in the clinical manifestations makes RESLES hard to predict before magnatic resonance imaging (MRI) and the precise pathophysiological mechanism of RESLES thus remains unclear. The subsequent cases are offered to provide the medical community with more evidence to stimulate research into the nature of these lesions. RESLES is reported to be a rare clinico-radiological disorder; nevertheless, in this cases series fifteen cases from different clinical settings are described, with our findings suggesting that it could be less rare than previously reported.

Materials and Methods

Criteria for RESLES

RESLES was diagnosed mainly based on the revised inclusion criteria of Garcia-Monco et al. (2011) (2); we included lesions involving the SCC as shown by MRI. Patients in whom lesions were persistent (or follow-up was not available) were not included. Other exclusion criteria included: the presence of extracallosal lesions, asymmetrical lesions, lesions without restricted diffusion on the MRI, or patients with acute disseminated encephalopathy and other common demyelinating disorders involving the CC.

Patient selection

The following is a retrospective observational study. Patients were treated at a tertiary hospital affiliated with Zhejiang University between May 1, 2015 and December 31, 2019. Two board-certified, fellowship-trained neurologists with more than 10 years of experience made an independent review and read the radiological images to confirm a diagnosis of RESLES. We selected patients by searching through our Picture Archiving and Communication Systems (PACS) using the keywords "corpus callosum." Reports of brain MR +diffusion-weighted images (DWI) with the words "corpus callosum" were found for 613 records and 485 cases of patients in our MRI record system. Each report was read, and those with "splenium of corpus callosum" were selected, thus resulting in a total of 197 cases. Each MRI was read, patients were selected according to inclusion criteria and exclusion criteria listed above. Finally, a total of fifteen patients were selected.

Imaging Evaluation

MRI was the main technique used for evaluation. Brain MR+DWI was conducted in each patient using a Siemens Skyra 3.0 Tesla MRI or GE Signa HDx 3.0 Tesla MRI scanner with 5-mm thick sections, including T1, T2, fluid attenuation inversion recovery (FLAIR), DWI and ADC.

Data collection

The medical history of each patient was reviewed. Information was collected including possible precipitating factors, demographics, clinical characteristics, biochemical results, pathogenic assessments, drugs, imaging findings, the treatments offered at baseline and during hospital stay, and the follow-up results. The prognosis of each patient was evaluated using a modified Rankin Scale (mRS): 0, No symptoms; 1, No significant disability. Able to carry out all usual activities despite some symptoms; 2, Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities; 3, Moderate disability. Requires some help, but able to walk unassisted; 4, Moderately severe disability. Unable to attend to own body needs without assistance and unable to walk unassisted; 5, Severe disability. Requires constant nursing care and attention, bedridden, incontinent.

Results

Two board-certified, fellowship-trained neurologists with more than 10 years of experience made an independent review and read the radiological images to confirm the diagnosis of RESLES. The consistency of the diagnosis was deemed to be 100%.

Our series of fifteen cases included ten males and five females. The patient ages ranged from 22 to 53 years old. The mean age was 34 years old. The clinical characteristics of the patients are shown in Tables 1 and 2. The most common neurological symptoms before MRI were headache (3/15), dizziness (3/15), first onset of seizure (3/15), paroxysmal blurred vision (2/15), vertigo (2/15), amnesia (2/15), and confused consciousness without seizure (2/15), followed by drowsiness (1/15), paresthesia (1/15), dysmetria (1/15) and dysarthria (1/15). One patient had recurrent seizures before and around the time of the discovery of the CC lesion. Most of the patients recovered completely with an mRS score of 0 except for case 3, in which the patient complained of slight amnesia after 3 months, which finally recovered without any sequelae a year later.

During the prodromal period, fever was the most common symptom (6/15; cases 1, 4, 8, 9, 12, 14); three out of six cases had a respiratory infection (cases 1, 6, 14), one patient had an intestinal infection, while causes of fever in the other two remain unknown. There was one case of pulmonary embolism (PE, case 6) and rabies vaccine injection (case 9) as shown in Fig. 1. Medications during the prodromal period included: antibiotics, such as piperacillin and tazobactam, amoxicillin, ceftriaxone, and levofloxacin; compound paracetamol; antiepileptic medications like levetiracetam, carbamazepine, valproate; antidiabetic drugs like gliclazide and dimethyldiguanide. There were six cases of hyponatremia (cases 2, 4, 5, 10, 12, 14, in cases 5 and 10, the sodium concentrations were under 130 mmol/L), one case of hyper-

Table 1. Clinical Characters of the Fifteen Patients with RESLES.

Patient no.	Sex/ age	CNS manifestations	Presumed etiology	Associated drugs	Therapy	Inpatient / outpatient	Hospital stays	mRS (up to 3m)
1	m/48	Sluggish in consciousness	Pneumonia	Piperacillin and tazobactam	Ceftriaxon, arithromycin (moxifloxacin)	Inpatient	11	0
2	m/43	Disarthria	Suspected hyponatremia	None	Clopidogrel,	Outpatient	0	
3	m/44	Seizure, drowsiness and amnesia	Hypoglycemia	Gliclazide, dimethyldiguanide 250 mg.bid	50% dextrose, potassium chloride, aspirin, atorvastatin	Inpatient	8	1
4	m/35	Headache	Infection	acyclovir, acetaminophen	saline	Inpatient	9	0
5	f/25	Seizure, confused consciousness	Hyporexia hyponatremia	None	Saline, acyclovir, levetiracetam	Outpatient		0
6	f/40	Headache	postpartum, Pulmonary embolism	None	Warfarin	Inpatient	11	0
7	f/24	Recurrent seizure	levetiracetam	Levetiracetam	Levetiracetam	Outpatient	0	
8	m/23	Paroxysmal blurred vision	bacterial respiratory infection	Levofloxacin, acetaminophen	Levofloxacin, Aspirin, atorvastatin	Inpatient	10	0
9	m/23	Dizziness with nausea and vomiting	Rabies vaccine injection	rabies vaccine, Amoxicillin and paracetamol	Ofloxacin, betahistine	Outpatient		0
10	m/25	Dizziness, paresthesia, dysmetria, memory problem, proxysmal vertigo, motor fine skills deficit	Hyperglycemia	None	Aspirin, atorvastatin, insulin, metformin	Inpatient	5	0
11	f/43	None	Carbamazepine		Cabamazepine	Outpatient	0	0
12	f/22	Hedache, loss of consciousness	Valproate/seizure	Valproate	Valproate	Inpatient	4	0
13	m/25	Dizzy, Paroxysmal blurred vision, unstable walk	Unknown	None	Aspirin	Outpatient	0	0
14	m/30	None	Presumed virus infection	None	Amoxicillin, ceftriaxone, levofloxacin, piperacillin and tazobactam, linezolid, compound paracetamol, indomethacin	Inpatient	8	0
15	m/53	Convulsion	Seizure	None	None	Outpatient	0	0

RESLES: reversible splenial lesion syndrome, Patient no.: patient number, m: male, f:female, CNS: central nervous system, mRS: modified Rankin Scale

glycemia (case 10) and one case of hypoglycemia (case 3). There were three cases of a decreased osmotic pressure (cases 4, 5, 14). Eight out of fifteen (8/15) were admitted to hospital for 4-12 days, while the other seven cases were followed up in an outpatient clinic. One underwent second generation sequencing (case 8), no virus or bacteria was found. 4/15 of the patients (4/15, case 1, 4, 8, 12, 14) underwent multiple virus antibody workups, which were all negative for IgM antibodies including cytomegalovirus (CMV), herpes simplex virus (HSV), Epstein-Barr virus (EBV) and measle virus, adenovirus, rubella virus and an influenza virus in a single patient.

All lesions were symmetrical and oval-shaped, and they were located in the midline of the splenium of the corpus callosum with DWI hyperintensity, T1 hypointensity, and T2 hyperintensity. Susceptibility weighted imaging (SWI) and diffusion tensor imaging (DTI) were conducted in case 8 as shown in Fig. 2; DTI showed no obvious abnormalities on the fractional anisotropy (FA) map. SWI showed no microbleeding. The mean duration between the presumed onset of RESLES and MRI 10 days (3-34 days).

Discussion

Most of the previous descriptions of RESLES have been in the case report format; thus, the incidence of RESLES remains unknown. Fifteen cases of RESLES were found among 197 cases of "splenium of corpus callosum" and 485 cases of "corpus callosum" in reports of brain MR+DWI, suggesting that it is not so rare.

This study is one of the biggest case series with a diversity of clinical manifestations and inducing factors, some of which are first time reported.

The patient ages ranged from 22 to 53 years old with a mean age of 34 years old, and this was similar to a previous report, the age of onset varied from 13 to 32 years (average

Table 2. Biochemical and Virus Results of Fifteen Patients with RESLES.

Patient no.	WBC (/μL) Normal range: 4,000-10,000	CRP (mg/L) Normal range: 0-5	Glu (mmol/L) Normal range: 4.16-5.8	Na^+ (mmol/L) Normal range: 137-147	Cl^- (mmol/L) Normal range: 99-110	ALT (U/L) Normal range: 9-50	Osmotic pressure (mmol/L) Normal range: 280-320	CSF: pressure (mmH_2O), WBC (/μL), protein (mg/L)	Virus workups
1	5,600	218.5↑↑	10.27	137	106	144↑	291	120, 6, 353	CMV-IgG(+), IgM(-), HSV1-IgG(+), IgM(-), HSV2-IgG(-), IgM(-), EBVCA-IgG(+), EBVCA-IgM(-), EHF Ab-IgM(-)
2	6,900	8.1↑	8.39	135↓	100	76↑	283.59	NE	HBsAb(+), HBcAb(+)
3	1,1000↑	1.41	<2↓	141	106	12	289.73	NE	HBsAb(+), HBcAb(+)
4	3,100	22↑	5.19	134↓	102	34	276.63↓	210, 4, 265.5	of Measle, EBVCA, rubella, CMV, HSV-1 virus IgG Abs(+), HSV-2 IgG(-), IgM(-), ADVAb(-)
5	8,300	4.8	6.54	124↓	91↓	24	257.44↓	NE	HBV(-)
6	4,200	0.6	7.76	145	107	23	305.06	NE	HBV(-)
7	7,600	14.2↑	5.63	142	105	53↑	293.83	NE	NE
8	9,700	61.9↑	5.03	141	100	27	291.93	120, 4, 176	HSV-Ab(-), HBs Ab(+), second generation sequencing(-)
9	10,300↑	4.4	NE	NE	NE	NE	NE	NE	NE
10	10,800	3	35.2↑	127↓	94↓	96↑	291.02	NE	NE
11	NE	NE	NE	NE	NE	NE	NE	NE	NE
12	11,100	75.1	7.27	136↓	101	10	282	80, 4, 205	HSV-I IgG-, HSV-I IgM-, HSV-II IgG-, HSV-II IgM-, Abs of influenza A,B-
13	7,300	1.5	5.79	139	106	NE	287	NE	NE
14	19,300	199.2	7.14	133↓	96	72	279↓	NE	Abs of influenza A, B-, CMV-DNA-, CMV-IgG+, IgM-, EBV Ab-, EBV-DNA-, HSV Ab-,
15	NE	NE	NE	NE	NE	NE	NE	NE	NE

RESLES: reversible splenial lesion syndrome, CSF: cerebrospinal fluid, BA: basic activity, NE: not examined, HBV: hepatitis B virus, CMV: cytomegalovirus, HSV: herpes simplex virus, EBV: Epstein-Barr virus, EHF epidemic hemorrhagic fever, IgG: immunoglobulin G, IgM: immunoglobulinM, Ab: antibody, NE: not examined

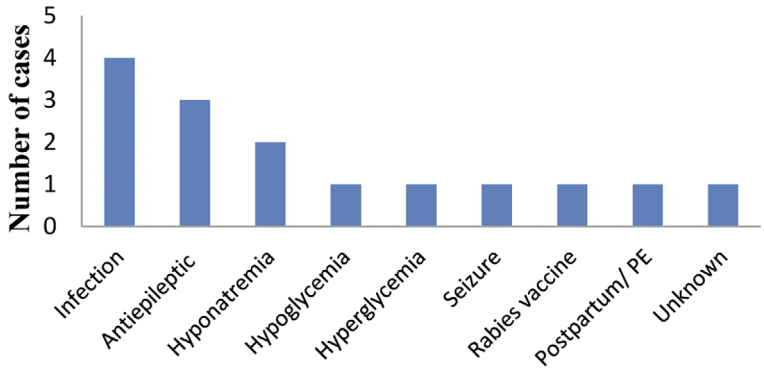

Figure 1. Number of cases with different etiologies of RESLES. RESLES: reversible splenial lesion syndrome

25.6±7.98) (24). Our series of fifteen cases included ten males and five females. However, a large number of cases is needed in order to claim that this condition has a male predominance.

Over the years, there have been various terms used to describe splenial lesions, including "mild encephalitis with a reversible lesion in the splenium (MERS)," "reversible splenial lesion syndrome (RESLES)," "cytotoxic lesions of the corpus callosum (CLOCCs)." MERS is an acute clinico-neuroradiological syndrome characterized by mild encephalitis or encephalopathy presenting as a reversible solitary mass in the central portion of the splenium of the corpus callosum (28). However, encephalitis/encephalopathy is not always mild. The spectrum of RESLES includes MERS. MERS cases were not excluded from our cases series of RESLES. In our case series, there were 2/15 cases of MERS (case 1, 12), besides, RESLES contains more heterogenic causes and symptoms such as Marchiafava-Bignami disease (MBD) (26). CLOCCs are various entities associated with a variety of causes with restricted diffusion, and some of these

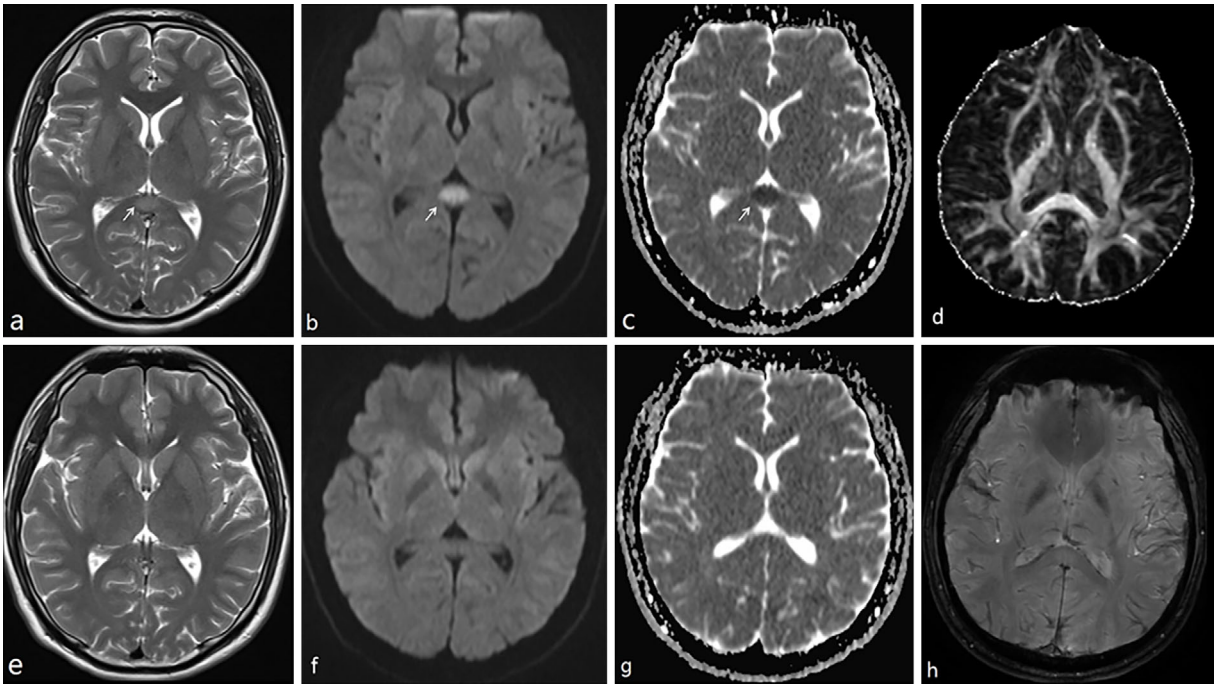

Figure 2. **The cerebral MRI features of case 8. a, b, and c were conducted seven days after the onset of his symptoms. d and h were taken 15 days after the onset of symptoms. e, f, and g were taken 33 days after the onset of his symptoms. MR demonstrated an isolated oval lesion in the splenium of the corpus callosum (arrows) with hypointensity on ADC (c), hyperintensity on T2 (a), and DWI (b). All abnormal signals disappeared upon a repeat of MR imaging (e: T2, f: DWI, g: ADC). No FA change was observed on DTI; no microbleeding was seen on SWI. ADC: apparent diffusion coefficient, DWI: diffusion-weighted images, FA: fractionary anisotropy, DTI: diffusion tensor imaging, SWI: susceptibility weighted imaging**

lesions are not reversible.

The splenial lesion of MERS and RESLES contains two different patterns according to the lesion location (27, 28): type 1, an isolated lesion located in the center of the splenium of CC, mostly are round or oval, some of the lesion extended along splenium; type 2, a lesion centered in splenium and extended into other brain areas (29). Our cases of RESLES were all isolated symmetrical lesions in SCC without any extracallosal lesions (type 1).

A broad spectrum of symptoms was reported in previously published papers of MERS and RESLES (Table 3). A disturbed consciousness and headache were common symptoms in RESLES. In our report, patients presented with significant clinical heterogeneity, ranging from headache, seizure, confusion and alterations in consciousness, paresthesia, dysmetria, memory deficits, paroxysmal vertigo, slurred speech, to paroxysmal blurred vision. Studying these cases helps to understand the functions of the SCC and the symptoms associated with its damage, thus making it easier to identify and diagnose RESLES in clinical practice.

Typical MRI features of RESLES are reversible, nonenhanced rounded or oval lesions located in the splenium of the corpus callosum; isointensity to slight hypointensity on T1WI without contrast enhancement, hyperintensity on T2-weighted images (T2WI), FLAIR, restricted diffusion on DWI, and a decreased ADC value of the lesion on ADC maps. The SCC abnormalities had disappeared upon the completion of follow-up MRI studies performed 10 to 32 days after the first MRI study by Zhu et al. (24), the DTI imaging value of the SCC lesion was reported to be mildly decreased in the FA map, but with a normal projecting direction of white matter fibers (24). In case 8 of our series (Fig. 2), no FA change was found, most likely due to the reversible character of the clinico-radiological change. The possible mechanisms for the restricted diffusion of the SCC include intramyelinic edema, reversible demyelination, damage to the blood-brain barrier, arginine vasopressin release, and inflammatory cell-induced cytotoxic edema. Follow-up assessment with DTI may help to distinguish the "real" reversibility of splenial lesions in future research.

RESLES and MERS were previously reported to have a diverse number of etiologies (Table 4). Though an increasing number of publications have focused on RESLES, its exact pathophysiology remains unknown. Because of the characteristic reversible restricted diffusion on DWI and low ADC values, transient intramyelinic cytotoxic edema has often been thought to be a cause rather than persistent ischemia. Antiepileptic drug toxicity and associated changes in salt homeostasis and transhemispheric seizure propagation are other suspected mechanisms (30, 31). Cell-cytokine interactions lead to massively elevated extracellular glutamate levels, and this phenomenon is thought to be important in

Table 3. Symptoms of MERS and RESLES Type 1 and 2.

RESLES type 1	MERS type 1	MERS type 2	RESLES type 2
Disturbed consciousness (24, 40), somnolence (40-42), confusion (15, 21, 40, 43), memory problems (15, 21, 42), disorientated (41, 43, 44), apathy (40, 45), mental abnormalities (46), delirious behavior (24), delirium (47), agraphia (48), ideomotor apraxia (49), alien hand syndrome (49), autotopagnosia (49)	Disturbed consciousness (7, 9, 12, 18, 56-58), lethargy (25), somnolence (25, 26, 59), confusion (26), cognitive impairment (26), behative impairment (26), behavioral disorders (26), hallucination (25), delirium (25, 57), disorientated (44), apathy (45)	Drowsiness (64-66), confusion (67), stupor (39), delirium (64)	Disturbed consciousness (70), stupor (26, 39), somnolence (26, 41), cognitive impairment (26), coma (26), interhemispheric disconnection (26), cognitive impairment (26)
Headache (22, 24, 41, 43, 47, 50-53), status migrainosus (54), vertigo (24, 51), dizziness (43)	Headache (18, 25, 26, 38, 45, 57, 60), vertigo (25), dizziness (26, 60), phonophobia (60), photophobia (60),	Headache (64, 65, 68), dizziness (67)	Headache (41)
Seizure (24, 26, 40)	Seizure (25, 61)	Seizure (67)	Seizure (26, 67)
Slurred language (24), dysarthria (40, 43), gait difficulty(49), tremor (24), tremulousness (40), dysmetria (21), ataxia (21, 26, 47), fatigue (21),	Alalia (62), monoparesis (63), gait difficulty (37, 57), tremor (57)	Dysarthria (26, 66), monoparesis (59), ataxia (67)	Dysarthria (70), ataxia (26), limb hypertonia (26)
Visual disturbance(26, 41, 50, 52), kaleidoscopic visual illusion (55)	Olfactory disturbance (9)		Visual hallucination (26)
Limb numbness (24) paresthesias (43)	Paresthesias (57)	Paresthesia (69), facial numbness (59),	
Urinary retention (43), diaphoresis (40)	Urinary retention (27, 57, 60)	Urinary retention (18, 68)	

All contents in MERS type 1 column also be contents of RESLES type 1. All contents in MERS type 2 column also be contents of RESLES type 2.
MERS: mild encephalitis with a reversible splenial lesion syndrome, RESLES: reversible splenial lesion syndrome

development of SCC lesions. Because of the heterogeneous nature of the etiologies, no definite common mechanism has yet been identified.

Two injections of the rabies vaccine preceded the onset of symptoms by 11 and 4 days in case 9. Hara et al. described an eight-year-old boy who appeared to have clinically-mild encephalitis with a reversible splenial lesion following a mumps vaccination (32). No other cases of this nature have been reported. Rabies vaccine may be one of the precipitating factors of RESLES. RESLES in case 9 manifested as fever and tinnitus five days after the second injection of rabies vaccine. The pathological mechanism is unknown, however, a vaccine may induce an inflammatory reaction and thus cause a transient influx of inflammatory cells. The effects of the rabies virus on RESLES has yet to be determined and thus requires further research.

Certain medications also induce RESLES. Besides the use and withdrawal of antiepileptic medications, such as oxcarbazepine (5, 33), levetiracetam (34), and phenytoin (35), psychiatric medication use, including olanzapine (7), and glufosinate ammonium poisoning (15) can also purportedly induce RESLES. It remains unclear, however, whether suspected seizures or valproate, which was used after a transient loss of conscious, may have induced RESLES in case 12. Valproate was not reported to induce RESLES previously.

Levetiracetam was suspected to play a role in the onset of RESLES in case 7, to the best of our knowledge, this is the first report of levetiracetam to be associated with the etiology of RESLES, while the withdrawal of levetiracetam has been previously reported to cause RESLES (34). After carbamazepine treatment was given because of vestibular paroxysmia in case 12, an SCC lesion was discovered 34 days later after carbamazepine treatment. The antiepileptic treatment without epilepsy attack followed by a subsequent SCC lesion strongly supports to the role of antiepileptic medications in the onset of RESLES.

Treatment with antiepileptic drugs like carbamazepine and the drugs' effects on rapid concentration changes of antiepileptic drugs (AEDs) can influence fluid balance systems through arginine vasopressin release. These drugs can also increase the number of proinflammatory and proconvulsive cytokines. Öztoprak et al. proposed a possible mechanism of onset in RESLES for patients experiencing seizures (36). The authors suggest that the discharge of the corpus callosum disseminated in seizures caused a decrease in free water dispersion in the corpus callosum. Further studies are needed to investigate this mechanism.

A marked elevation of urinary β2-microglobulin was reported in patients with RESLES. We found normal levels of blood and urinary β2-microglobulin in case 8. More research is needed to elucidate the relationship between β2-

Table 4. Etiologies of MERS and RESLES Type 1 and 2.

	RESLES type 1			RESLES type 2
		MERS type 1	MERS type 2	
Infection	Infuenza B (24), rotavirus, herpes virus-6 (24), Epstein-Barr virus (24), puumala hantavirus (50), mumps virus (26)	Infuenza A (9, 59), VZV (25), adenovirus (63), nonfulminant hepatitis A (62), klebsiella pneumoniae (46), meningococcal meningitis (12), Mycoplasma pneumoniae (26, 27, 41, 46, 56), legionella pneumophila (37), tick-bites (38)	Epstein-Barr virus (64, 67)	
Seizures	Seizure (71)			
Drug	Ipilimumba (57), sympathomimetic (55), minocycline (51)			
Use of AEDs	Phenytoin (1, 52), carbamazepine (3), vigabatrin (52)	Olanzapine (7)		
withdrawal of AEDs	Valproate (26), oxcarbazepine (5, 33), topiramate (30), levetiracetam (34), phenytoin (3, 42), carbamazepine (72)			Oxcarbazepine (33)
Autoimmune disease			Anti-Yo rhombencehhalitis (39)	
Metabolic disturbances	Hypoglycemia (40, 48), methyl bromide poisoning (43), glufosinate ammonium poisoning (15), anorexia nervosa (73)	Amanita phalloides intoxication (61), hemolytic uremic syndrome (44)		Carbon monoxide poisoning (26), hypoglycemia (26, 70), MBD (26), osmotic myelinolysis (13)
Miscellaneous conditions	cerebral venous thrombus (22), Anti-VGKC autoantibody syndrome (21), Charcot-Marie-Tooth disease (74), blood transfusion (49), migraine with aura (75)			

Notes: All etiologies in MERS column also be etiologies of RESLES but are not listed in RESLES column now. MERS: mild encephalitis with a reversible splenial lesion syndrome, AEDs: antiepileptic drugs, VZV: varicella zoster virus, VGKC: voltage-gated potassium channel, MBD: Marchiafava-Bignami disease

microglobulin and RESLES.

Hyponatremia has also been observed in RESLES. In our cohort, six of fifteen cases (cases 2, 4, 5, 10, 12, 14) had hyponatremia; in cases 5 and 10, sodium concentrations were under 130 mmol/L. There were no antiepileptic treatments before the onset of hyponatremia. Therefore, hyponatremia, in these cases, was not induced by antiepileptic medicine. Case 5 had been trying to lose weight and thus had a seriously restricted intake, and thus developed serious diarrhea, nausea and vomiting, which may explain her markedly decreased plasma sodium levels.

Hyponatremia has also been noticed in different reports (14, 18, 27, 37-39). Six out of sixteen MERS adult patients showed hyponatremia upon admission in a review by Yuan et al. (27), The etiologies of these cases with hyponatremia includes tick bites, anti-Yo rhombencehhalitis and Legionnaires' disease.

Hyponatremia may be secondary to these etiologies or predisposing factor in these cases. Takanashi et al. reported that there were significant differences between the sodium levels of patients with MERS and those with upper respiratory infection, other types of encephalopathy and febrile seizures, respectively (14). Hyponatremia itself may act as an important precipitating factor of RESLES in these cases.

Syndrome of inappropriate secretion of antidiuretic hormone (SIADH), AED administration or withdrawal, high altitude cerebral edema (HACE) seem to cause hyponatremia, water/electrolyte imbalance, cerebral edema as the underlying pathophysiological mechanism in RESLES (14).

Infections and metabolic abnormalities were the most common etiologies in our series (three cases had respiratory infection, one patient had intestinal infection, one with hypoglycemia, one with hyperglycemia and hyponatremia, and another with hyponatremia). In addition, One case of RESLES were induced by the use of levetiracetam, carbamazepine, valproate respectively in our series, thus supporting the fact that seizures and antiepileptic drugs were some of the most common etiologies in previous report (2).

In our series of fifteen cases, there was no obvious relationship between the clinical manifestations and the etiology, except in case 3 and case 10, both of which were presumably caused by an abnormality in their glucose metabolism -

hypoglycemia in case 3 and hyperglycemia in case 10. These two patients both had memory loss, possibly related to dysregulations in the energy utilization accompanying hyperglycemia and hypoglycemia.

The diverse pathologies reported in various manuscripts and neuroimaging studies cause significant uncertainty about the precise mechanisms of reversible splenial lesions in RESLES. It has been proposed that viral or induced antibodies show selected affinity for the splenial axonal receptors. SCC is specifically vulnerable to excitotoxic injury in metabolic causes - one possible mechanism of splenial involvement in various pathological events induced by viruses or certain medicines. However, no common pathophysiological mechanism has so far been able to explain the splenial predilection or diversity of heterogeneous etiologies in this disease. A large number of patients demonstrated such etiological problems as taking antiepileptic drugs, but only a small number of such patients developed RESLES. Further investigation is needed to determine whether a genetic susceptibility exists in RESLES patients.

Generally, RESLES has a highly benign prognosis and it is usually associated with a complete recovery without any obvious neurological sequelae shortly after the acute course, as illustrated by our cases. However, some cases have been previously reported with poor prognoses, such as those who entered a comatose or vegetative state, even after the abnormal lesions had disappeared (24). The results of previous studies indicate that severe disturbances in consciousness at the onset of the disease, diffuse slow waves on electroencephalogram (EEG) findings, and extracallosal lesions are indicative of a relatively poor prognosis in RESLES. Our case series excluded cases with extracallosal lesions, and thus it seemed that RESLES type 1 without any extracallosal lesions had a better prognosis.

There are several limitations associated with our study. First, this was a retrospective study. Functional MRI, such as the use of DTI, was only provided in one case of RESLES. Furthermore, β2-microglobulin was only tested in a single case. These initial findings, however, provide many clues about the factors contributing to the onset of RESLES and provide guidance for the future research into this clinico-radiological disease.

Conclusion

In this series of fifteen cases of RESLES, we reported a variety of clinical manifestations with identical radiological lesions located in SCC. These cases are groundbreaking in their contribution to medical knowledge about the functions of SCC. This report is also the first to show the involvement of levetiracetam, valproate and rabies vaccination in the etiology of RESLES. RESLES type 1 without extracallosal lesions are therefore deemed to be highly "reversible" with an excellent prognosis.

The authors state that they have no Conflict of Interest (COI).

Financial Support

This work was supported by by grant No. 81201722 from the National Natural Science Foundation of China, by grant No. LY 20H090001 from the Natural Science Foundation of Zhejiang Province, by grant No. 2018ZD025 from the Health Commission of Zhejiang Province, and by grant No. 2017ZYC-A18 from the clinical research foundation of Zhejiang Medical Association.

Acknowledgement

Thanks to Yating Lv from The Affiliated Hospital of Hangzhou Normal University for helping to process the DTI.

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