

# Mild encephalitis/encephalopathy with a reversible splenial lesion: five cases and a literature review

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**Abstract** The aim of this study was to explore the clinical characteristics and etiology of mild encephalitis/encephalopathy with a reversible splenial lesion (MERS) in China by retrospectively analyzing five MERS cases from the Jiangsu Provincial Hospital within a total of 27 reported MERS cases from available Chinese literature. Most of the 27 cases originated near the eastern and southern parts of China. Ages for 23 MERS cases were under 30 years and the female-to-male ratio was 1:1.25. The major causes of MERS included infection, antiepileptic drug withdrawal, high-altitude cerebral edema, and cesarean section (C-section). Hyponatremia was also observed in 10 MERS cases. All patients had a complete recovery within a month. Steroids and IVIG were the most commonly used therapy for MERS, but their efficiency remained questionable.

**Keywords** Mild encephalitis/encephalopathy with a reversible splenial lesion (MERS) · Hyponatremia · MRI · Splenium of the corpus callosum

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## Introduction

Mild encephalitis/encephalopathy with a reversible splenial lesion (MERS) is a clinico-radiological syndrome first identified by Tada et al. [1], characterized by transient splenial lesions with high-signal-intensity on T2-weighted images (T2WI), fluid-attenuated inversion recovery images (FLAIR), and diffusion-weighted images (DWI); and hyper-isointense signals on T1-weighted imaging (T1WI) sequences without contrast enhancement [1–3]. In general, MERS patients with mild central nervous system (CNS) symptoms such as disturbance of consciousness (DC) or seizures recover within a month [4].

The pathogenesis of MERS is still not fully understood. There are several reports that MERS may be associated with infective agents, such as influenza virus and Epstein–Barr (EB) virus [1, 2, 5]. In addition, Kawasaki disease and epilepsy are also reported to be associated with MERS [6, 7]. From a geographical point of view, most cases are reported in Asia, especially in Japan. People in all age groups are likely to be infected.

In this study, five cases from the Jiangsu Provincial Hospital, together with other available MERS cases from Chinese literature were analyzed to elucidate the possible characteristics and mechanisms of MERS in China.

## Materials and methods

With approval from the Institutional Review Board of Jiangsu Provincial Hospital, Nanjing Medical University, Patient or Parental Consent Forms were obtained before data collection. The diagnosis of MERS cases was established according to the diagnostic criteria [4]. The five MERS cases from Jiangsu Provincial Hospital along with

22 other MERS cases reported from previous studies in China were all involved in this study. We searched the previous studies by browsing three Chinese medical journal search engines since the establishment of databases [Cqvip (<http://www.cqvip.com/>), Wanfang Data (<http://www.wanfangdata.com/>), and Science China (<http://www.scichina.com/>)] using keywords ‘mild encephalitis/encephalopathy with a reversible splenic lesion’ or ‘reversible splenic lesion.’ At last 31 reports were found, after carefully reviewing and extracting data from the publications, nine studies were further excluded because of inconsistent research content pertaining to our topic or an absence of relevant clinical data. Clinical manifestations, laboratory data, and imaging information were collected for the retrospective analysis.

## Results

### The five MERS cases from Jiangsu Provincial Hospital

#### Medical history

Between January 2012 and December 2014, five cases of MERS, including two men and three women, were admitted to the Jiangsu Provincial Hospital. The ages on admission were 2, 18, 21, 23, and 26 years (Table 1). None of the patients had a history of epilepsy, hypertension, kidney disease, or received any type of vaccinations or drugs.

#### Clinical manifestation

All five patients had a sudden onset of fever ( $>38.5\text{ }^{\circ}\text{C}$ ), with four adults having a headache. Patient no. 4, a 2-year-old girl, experienced recurrent vomiting and watery diarrhea, with generalized tonic–clonic seizures lasting 2–3 min for two times, although her body temperature was normal before admission. One of the female patients (no. 3)

had a history of C-section 8 days prior to admission, when she exhibited auditory hallucinations and unexpected emotional changes. During the progress of MERS, two male patients (no. 2 and 5) showed acute urinary retention, while Patient no. 5 also had abdominal distention, which developed into paralytic ileus eventually (Table 1).

#### Auxiliary examination

A series of auxiliary examinations were performed following admission. Routine chest X-rays, immunity function, and autoantibody tests all showed normal levels except on Patient no. 4 who just suffered from rotavirus infection. White blood cell (WBC), C-reactive protein (CRP), and serum sodium levels were recorded both on admission and at discharge (Table 2). WBC counts on admission ranged from  $6.08 \times 10^9$  to  $11.20 \times 10^9/\text{L}$ , but within normal range at discharge. Serum sodium level in Patients no. 2, 4, and 5 decreased ( $<135\text{ mmol/L}$ ) and Patient no. 5 also had an incorrigible hyponatremia before discharge. All patients accepted lumbar puncture (LP) on admission. The cell count in cerebral spinal fluid specimen increased in three patients (no. 1, 4, and 5), but protein and glucose levels were normal. Various bacterial cultures and viral isolations yielded negative results in all patients. In Patients no. 1, 2, and 5, the follow-up LP prior to discharge showed decreased cell counts in different degrees. MRI and EEG were performed within 96 h of admission. The MRI scans showed abnormal signals in the splenium of the corpus callosum (SCC) in all patients, which were hypo- or iso-intensity on T1W1 images, hyper-intensity on T2W2, FLAIR and DWI images, and low apparent diffusion coefficient (ADC) values. Patient no. 2 also had abnormal signals located in the temporal, insular, and caudate nucleus (Fig. 1). However, a follow-up MRI revealed normal findings in both the splenic and extra splenic lesions for all patients. EEG showed no abnormalities in Patients no. 4 and 5, while the other patients demonstrated global diffuse, slow waves during recording.

**Table 1** Clinical manifestation and prognosis of five MERS cases from Jiangsu Provincial Hospital

Patient no.	Gender	Age (years)	Etiology	Onset					Neurological examination	Time of improvement (days)	Prognosis
				Fever	Headache	Seizure	DC	Other symptoms			
1	F	18	NQ	Y	Y	N	N	N	(–)	16	CR
2	M	26	NQ	Y	N	N	N	AUR	Nuchal rigidity (+)	21	CR
3	F	23	C-section	Y	Y	N	Y	N	Kerning (+)	17	CR
4	F	2	Rotavirus	Y	N	Y, twice	N	N	Babinski (+)	5	CR
5	M	21	NQ	Y	Y	N	N	AUR, IB	Kerning (+)	17	CR

M male, F female, DC disturbance of consciousness, IB intestinal obstruction, AUR acute urinary retention, NQ not required, EEG electroencephalography, CR complete recovery

**Table 2** Auxiliary examination and treatment of five MERS cases from Jiangsu Provincial Hospital

Patient no.	Initial examination					Treatment				Examination at discharge			
	WBC (10 <sup>9</sup> /L)	CRP (mg/dL)	Serum sodium (mmol/L)	CSF WBC (10 <sup>6</sup> /L)	MRI	EEG	Corticosteroids	Antiepileptic drugs	IVIg	WBC (10 <sup>9</sup> /L)	Serum sodium (mmol/L)	CSF WBC (10 <sup>6</sup> /L)	MRI
1	6.08	N	137.0	90	SCC	A	Methylprednisolone pulse + oral prednisone	-	20 g/day × 5 days	9.70	141.2	66	Lesions disappeared
2	7.10	N	130.2	100	SCC, insula, caudate nucleus	A	Oral methylprednisolone + prednisone	-	-	9.32	142.5	30	Lesions disappeared
3	11.20	N	138.6	12	SCC	A	Oral methylprednisolone + prednisone	Clonazepam	-	10.01	140.7	-	Lesions disappeared
4	8.34	11	134.0	0	SCC	N	Methylprednisolone pulse + oral prednisone	-	-	8.97	149.8	-	Lesions disappeared
5	8.20	N	126.5	80	SCC	N	Oral prednisone	-	10 g/day × 3 days	9.13	140.5	40	Lesions disappeared

CRP C-reactive protein, CSF cerebrospinal fluid, MRI magnetic resonance imaging, IVIG intravenous immune globulin, SCC splenium of the corpus callosum, A abnormal, N normal

*Therapeutic procedure*

Basic treatment of intravenous osmotic diuretic (D-mannitol) and isotonic fluid infusions was ordered. All patients received corticosteroid treatments including methylprednisolone pulse therapy and oral prednisone. In addition, Patient no. 3 was treated with clonazepam for mood control, and Patients no. 1 and 5 were treated with intravenous immune globulin (IVIG).

*Outcome and prognosis*

MERS symptoms disappeared in all patients within a month with a mean recovery time of 15.20 ± 6.02 days. All patients were fully recovered before discharge.

**Literature review**

*Distribution of MERS in China*

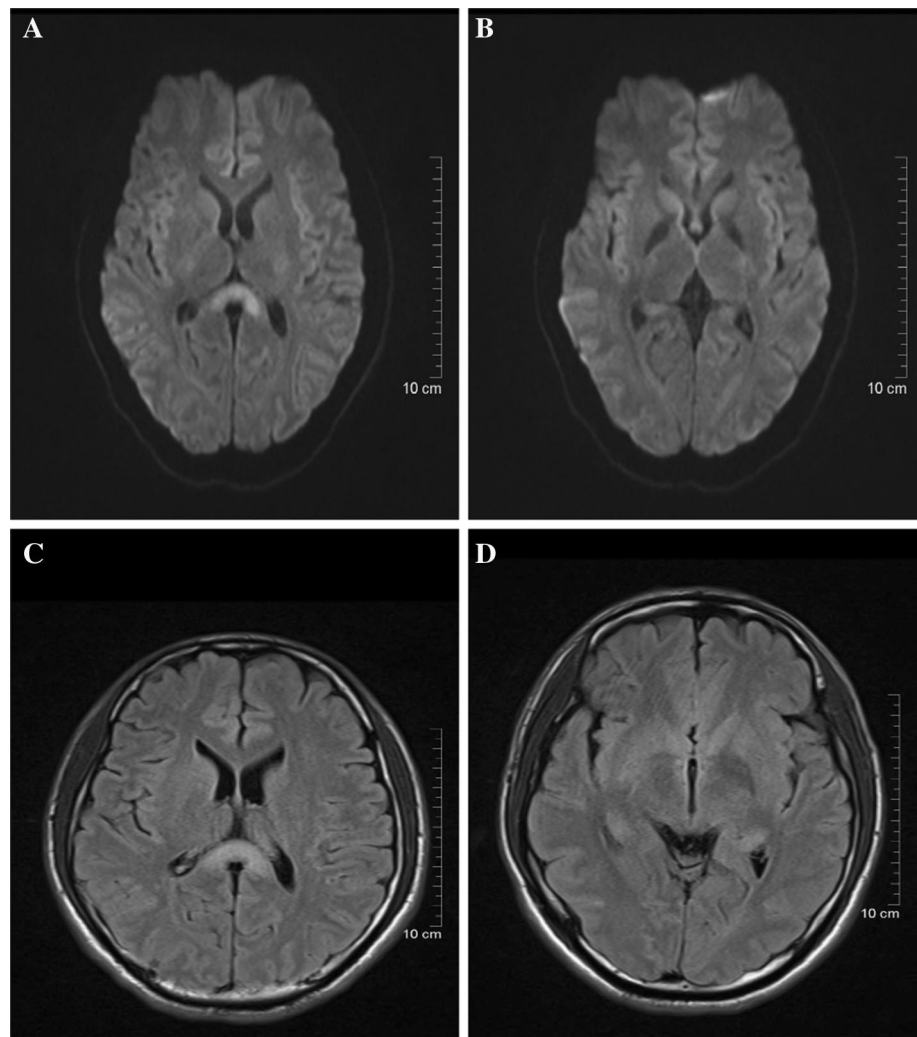
Of the 27 MERS cases reported previously, six were from Jiangsu province, five from Liaoning province, four from Jilin province, three from Jiangxi province, three from Anhui province, three from Beijing, two from Guizhou province, one from Zhejiang province, respectively. The majority of the provinces and cities were located near the eastern and southern coasts of China (Fig. 2).

*Clinical manifestations of MERS in China*

The clinical findings of the 27 cases are summarized in Tables 3 and 4. The age at onset was from 2 to 54 years (juvenile 2–11; adult 18–54 years), but less than 30 years for most of the cases (23/27). Twelve patients were females (44.4 %). The female-to-male ratio was 1:1.25. Only six patients had clinically proven pathogen infection, including two mycoplasma pneumonia (MP), two herpes simplex virus (HSV), one EB virus, and one rotavirus infections. Two patients had a sudden onset of MERS due to drug withdrawal. One patient had acute mountain sickness. Besides, two patients had emotional and behavior changes within 4 weeks after C-section, which showed vision abnormality, non-visual sensory misperceptions, unexpected emotional changes, and impulsive behavior.

Fever (≥38.0 °C) had preceded or simultaneously presented with the appearance of MERS in 22 patients (81.5 %). Fourteen patients (51.9 %) exhibited headache while having MERS, and seizure was observed in five cases. The cerebral spinal fluid examination results were abnormal in eight cases. Ten cases involved decreased serum sodium levels. EEG abnormality was encountered in 10 patients showing diffuse high-voltage slow waves. MRI

**Fig. 1** Brain MRI of Patient no. 2. DWI and FLAIR image reveals hyperintense lesions in the splenium of the corpus callosum (**a, c**) and slightly hyperintense in the symmetric white matter (**b, d**)



demonstrated abnormal signals in SCC in all cases and disappeared within 1 month.

All patients had received a basic therapy of intravenous osmotic diuretic (D-mannitol) and isotonic fluid. Three patients received a methylprednisolone pulse therapy. Three patients received IVIG treatment.

## Discussion

MERS is a clinical syndrome with mild CNS symptoms and the MRI finding of a transient lesion in SCC (type 1 MERS) or associated in the frontal white matter (type 2 MERS). It has been reported that MERS is the second most common infectious encephalitis/encephalopathy syndrome in Japanese children [21]. However, the specific pathophysiological mechanisms of MERS remain unclear. Accordingly, the all available data on Chinese MERS patients were collected, and the characteristics were analyzed in the present study.

Most MERS cases were located near the eastern and southern coasts of China, including Beijing, Jilin, Liaoning, Jiangsu, and Anhui provinces. Interestingly, all pediatric cases were reported after 2013. The reason for this distribution may be related to economic and social factors, as well as differential levels of awareness and diagnosis of MERS in different areas of China.

MERS was originally reported as reversible isolated SCC lesion on MRI images. More recently, transit lesions in the frontal white matter include SCC in some patients with encephalitis/encephalopathy were also regarded as MERS. As the radiologic spectrum of MERS has been expanded, it is reasonable to diagnose our Patient no. 2 as type 2 MERS. Moreover, we reported rotavirus, HSV and EB viruses were related to some MERS cases, which concurred with earlier findings [1, 14, 19]. MP was also found to be related to MERS in two cases. In addition, we also observed sudden fever in two female patients, also suffered disturbance of consciousness after C-section within a month. Postpartum psychosis was excluded in



**Fig. 2** Distribution of MERS in China

these patients. MRI found abnormal signals located in SCC, which further supported the diagnosis of MERS. To the best of our knowledge, this is the first patient who showed clinical features of MERS associated with C-section. The exact mechanism is still unknown, but the fluctuations of hormone levels after giving birth may be one possible reason.

The typical features of MERS on MRI are T2 signal prolongation, restricted diffusion evident upon DWI, restrict water diffusion with decreased ADC values in the SCC, and complete reversibility upon follow-up MRI. Satoru et al. [22] evaluated diffusion tensor imaging in three MERS cases and proposed that the reversible lesions occurred as a result of transient interstitial edema and that white matter architecture was preserved. This result implied us that diffusion tensor imaging may be a potential useful tool for diagnosis MERS in the early phase.

There are several hypotheses on pathogenesis of MERS, including intra-myelinic edema, hyponatremia, axonal damage, and oxidative stress [1, 23, 24]. Hyponatremia, defined as a lower serum sodium level of less than 136 mmol/L, is a common electrolyte disturbance that

occurs in patients with a wide range of disorders and clinical manifestations, from asymptomatic to critically ill. Takanashi et al. [25] reported that most patients with MERS had mild hyponatremia, with a mean serum sodium level of  $131.0 \pm 4.1$  mmol/L, which is lower than the control groups. Fuchigami et al. [26] summarized 10 cases of rotavirus-associated MERS, three had a sodium level  $<136$  mmol/L. In the present review, we reported that 10 out of 27 MERS cases had hyponatremia on admission. All these may indicate that hyponatremia may be a possible cause of MERS. But it is still clinically difficult to separate MERS from hyponatremic encephalopathy or to rule out hyponatremia as a contributing factor to MERS.

The differential diagnosis of MERS includes infections, ischemia, multiple sclerosis, lymphoma, acute disseminate encephalomyelitis, and posterior reversible encephalopathy. It is difficult to diagnose only based on the imaging features at the early phase. For example, in our five cases, two males had acute urinary retention, which was similar to meningitis retention syndrome (MRS). MRS was characterized with aseptic meningitis and acute urinary retention, with no other neurologic abnormalities except for a slightly

**Table 3** Information of 27 MERS cases in China

Reported by	Case no.	Gender	Age (years)	Etiology	Onset			Neurological examination		
					Fever	Headache	Seizure	DC	Other symptom	
Jiangsu Provincial Hospital	1	F	18	NQ	Y	Y	N	N	N	(-)
	2	M	26	NQ	Y	N	N	N	AUR	Nuchal rigidity (+)
	3	F	23	C-section	Y	Y	N	Y	N	Kerning (+)
	4	F	2	Rotavirus	Y	N	Y	N	N	Babinski (+)
	5	M	21	NQ	Y	Y	N	N	AUR, IB	Kerning (+)
Zhen et al. [8] (Jilin)	6 (2011)	F	37	Acute mountain sickness	-	Y	Y	Somnolence	-	Babinski (+)
Dong et al. [9] (Liaonin)	7 (2012)	M	30	NR	Y	Y	-	-	-	Cervical, Kerning (+)
	8 (2012)	F	17	MP	Y	-	-	-	-	Cervical, Kerning (+)
	9 (2012)	F	22	NR	-	-	-	Blurred vision	-	-
	10 (2012)	F	24	NR	-	-	-	Blurred vision	-	-
Liu et al. [10] (Liaonin)	11 (2012)	F	31	HSV	Y	-	-	Perioral numbness	-	-
Wu et al. [11] (Beijing)	12 (2012)	M	24	Drug withdraw <sup>a</sup>	-	-	Y	Y	-	-
Wang et al. [12] (Beijing)	13 (2012)	M	46	NR	Y	Y	-	-	-	Cervical
Han et al. [13] (Jilin)	14 (2013)	M	30	NR	Y	-	-	-	-	Cervical
	15 (2013)	F	54	NR	Y	-	-	Deliration	-	-
He et al. [14] (Jiangsu)	16 (2013)	M	7	EB virus	Y	Y	-	-	-	Cervical, Kerning (+), Babinski (+)
Fang et al. [15] (Guizhou)	17 (2014)	F	24	NR	Y	-	-	Dizzy, visual rotation	-	-
	18 (2014)	M	18	NR	Y	Y	-	Y	-	-
Ge et al. [16] (Anhui)	19 (2014)	F	25	Drug withdraw <sup>b</sup>	Y	-	-	Y	-	Cervical, Kerning (+), Babinski(+)
	20 (2014)	F	18	NR	Y	-	-	Behavior disorder	-	-
	21 (2014)	F	22	NR	-	-	Y	Y	-	Cervical, Kerning (+), Babinski (+)
Hu et al. [17] (Zhejiang)	22 (2014)	F	24	After C-section	Y	Y	-	Y	-	-
Huang et al. [18] (Jiangxi)	23 (2014)	M	15	NR	Y	Y	-	-	-	-
	24 (2014)	M	23	NR	Y	Y	Y	Coma	-	-
	25 (2014)	F	27	NR	Y	Y	-	Instability of gait	-	-
Yan et al. [19] (Jilin)	26 (2014)	M	11	HSV	Y	Y	-	-	-	Cervical, Brudzinski (+)
Zhao et al. [20] (Beijing)	27 (2014)	M	9	MP	Y	Y	-	Drowsiness, dysphagia, dyslalia	-	Babinski (+)

Table 3 continued

Reported by	Initial examination				Treatment			Time of improvement (days)	Prognosis	
	WBC (10 <sup>9</sup> /L)	Serum sodium (mmol/l)	CSF WBC (10 <sup>6</sup> /L)	MRI (lesion location)	EEG	Corticosteroids	Antiepileptic drugs			IVIg
Jiangsu Provincial Hospital	6.08	137.0	90	SCC	A	Methylprednisolone pulse + oral prednisone	-	20 g/day × 5 days	16	CR
	7.10	130.2	100	SCC, insula, caudate nucleus	A	Oral methylprednisolone + prednisone	-	-	21	CR
	11.20	138.6	12	SCC	A	Oral methylprednisolone + prednisone	Clonazepam	-	17	CR
	8.34	134.0	0	SCC	N	Methylprednisolone pulse + oral prednisone	-	-	5	CR
Zhen et al. [8] (Jilin)	8.20	126.5	80	SCC	N	Oral prednisone	-	10 g/day × 3 days	17	CR
Dong et al. [9] (Liaonin)	N	N	N	SCC	NR	DXM	-	-	6	CR
	N	N	14	SCC	NR	-	-	-	12	CR
	N	N	N	SCC	NR	-	-	-	15	CR
	N	N	Denial	SCC	NR	-	-	-	25	CR
	N	N	N	SCC	NR	-	-	-	20	CR
Liu et al. [10] (Liaonin)	N	134	Denial	SCC	NR	DXM	-	-	15	CR
Wu et al. [11] (Beijing)	N	N	NR	SCC	A	-	Y	-	27	CR
Wang et al. [12] (Beijing)	N	112.6	250	SCC	A	Hydrocortisone	-	-	15	CR
Han et al. [13] (Jilin)	10.9	134	64	SCC	NR	-	-	-	18	CR
	11.4	123.7	Denial	SCC	NR	-	-	-	18	CR
He et al. [14] (Jiangsu)	N	127	480	SCC	NR	DXM	-	-	10	CR
Fang et al. [15] (Guizhou)	N	N	N	SCC	A	Methylprednisolone	-	-	14	CR
	15.46	N	N	SCC	A	Prednisone	-	-	21	CR
Ge et al. [16] (Anhui)	16.96	157	N	SCC	A	-	-	-	14	CR
	N	131	N	SCC	N	-	-	-	30	CR
	N	107.9	N	SCC	A	-	-	-	14	CR
Hu et al. [17] (Zhejiang)	N	N	N	SCC + frontal lobe + occipital lobe + parietal lobe	N	Methylprednisolone	-	-	11	CR

Table 3 continued

Reported by	Initial examination				Treatment			Time of improvement (days)	Prognosis	
	WBC ( $10^9/L$ )	Serum sodium (mmol/l)	CSF WBC ( $10^6/L$ )	MRI (lesion location)	EEG	Corticosteroids	Antiepileptic drugs			IVIg
Huang et al. [18] (Jiangxi)	N	N	Denial	SCC	NR	-	-	-	22	CR
	10	N	20	SCC + mesocephalon	NR	Methylprednisolone pulse therapy	Y	Y	20	CR
Yan et al. [19] (Jilin)	N	N	N	SCC	NR	DXM	-	-	13	CR
	15.21	N	380	SCC	NR	Y	-	-	8	CR
Zhao et al. [20] (Beijing)	19.41	N	N	SCC + CSO	A	Y	-	Y	5	CR

F female, M male, DC disturbance of consciousness, NR not reported, N normal, HSV herpes simplex virus, MP mycoplasma pneumoniae, DXM dexamethasone, SCC splenium of the corpus callosum, CSO centrum semiovale, CR complete recovery

<sup>a</sup> Antiepilepsy drugs

<sup>b</sup> Antipsychotic drugs

Table 4 Summary of clinical manifestations of the 27 MERS cases

Category	n (%)
Gender	
Female	12 (44.4)
Male	15 (55.6)
Age	
Juvenile	4 (14.8)
Adult	23 (85.3)
Etiology	
Infection	6 (22.2)
Drug withdrawal	2 (7.4)
Acute mountain disease	1 (3.7)
After surgery (C-section)	2 (7.4)
Initial neurological symptom	
DC	16 (59.3)
Seizure	5 (18.5)
Initial examination	
WBC abnormal	9 (33.3)
Na (mmol/L) <136	10 (37.0)
CSF abnormal	8 (29.6)
EEG abnormal findings	10 (37.0)
MRI abnormal findings	
SCC	23 (85.2)
SCC + other	4 (14.8)
Therapy	
IVIg	3 (11.1)
Antiepileptic drugs	3 (11.1)
Methylprednisolone pulse	3 (11.1)

brisk reflex in the lower extremities. MRI studies of the brain, spinal and lumbar plexus, and nerve conduction generally showed no abnormalities [27]. So the complete diagnosis should combine transient features of the lesion with other clinical findings.

Methylprednisolone pulse therapy and IVIG are recommended for patients with infectious encephalopathy regardless of pathogen or clinico-radiological syndromes [28]. But there is still no evidence of efficacy of the treatments on MERS. In this study, only three MERS patients were treated with methylprednisolone pulse therapy and IVIG, respectively. However, all 27 MERS patients clinically recovered completely irrespective of the treatments, which suggest that methylprednisolone pulse therapy or IVIG may not be always necessary.

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**Conflict of interest** The authors declare that they have no financial or other conflicts of interest in relation to this research and its publication.



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