



## Clinical short communication

Marked elevation of urinary  $\beta$ 2-microglobulin in patients with reversible splenial lesions: A small case series

Junji Azuma <sup>a,\*</sup>, Shin Nabatame <sup>b</sup>, Toshiya Katsura <sup>a</sup>, Kyoko Yamamoto <sup>a</sup>, Hiroshi Kaneno <sup>a</sup>, Eri Kijima <sup>a</sup>, Yoshimi Mizoguchi <sup>a</sup>, Tunesuke Shimotsuji <sup>a</sup>, Takehisa Yamamoto <sup>a</sup>, Keiichi Ozono <sup>b</sup>

<sup>a</sup> Department of Pediatrics, Minoh City Hospital, Minoh, Japan

<sup>b</sup> Department of Pediatrics, Osaka University Graduate School of Medicine, Suita, Japan

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## ABSTRACT

The magnetic resonance imaging findings of reversible isolated lesions with transiently reduced diffusion in the splenium of corpus callosum of patients with a wide spectrum of pathological conditions are referred to as reversible splenial lesion syndrome (RESLES). Clinically mild encephalitis/encephalopathy with a reversible splenial lesion (MERS) is probably included within the spectrum of RESLES; however, its exact pathophysiology is not known. Here, we describe three patients with MERS and one patient with RESLES, all of whom showed elevated urinary  $\beta$ 2-microglobulin regardless of diagnosis and presence of pathogens. Elevated urinary  $\beta$ 2-microglobulin suggested that an excessive immune response might play a role in the pathophysiology of reversible splenial lesions.

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## 1. Introduction

The magnetic resonance imaging (MRI) findings of reversible isolated lesions with transiently reduced diffusion in the splenium of corpus callosum (SCC) have been reported in patients with a wide spectrum of pathological conditions such as infections, rapid withdrawal of anti-epileptic drugs, and various metabolic disorders. These specific radiological findings are collectively referred to as reversible splenial lesion syndrome (RESLES) [1,2]. Conversely, as described by Tada, clinically mild encephalitis/encephalopathy with a reversible splenial lesion (MERS) is defined as a mild clinical course with neurological symptoms including seizures, delirium, and altered consciousness followed by subsequent recovery without sequelae [3] and is observed in various etiologies [4,5]. MERS is considered as a clinical entity within the spectrum of RESLES [2]. While the majority of patients with RESLES and MERS have a

good outcome [3], few patients may have moderate or severe sequelae [2,5,6]. The pathophysiological mechanisms of RESLES and MERS have been speculated in several studies [1,2], including hyponatremic cerebral edema [7] and increased cytokine levels [8–11]. However, the exact pathophysiology and the cause for selective involvement of SCC are not known [2].

We describe four patients with reversible SCC lesions: all cases showed markedly increased urinary  $\beta$ 2-microglobulin ( $\beta$ 2MG) levels regardless of the diagnosis and pathogens.

## 2. Materials and methods

Data from four patients (three females, one male) with reversible isolated SCC lesions that were admitted to Minoh City Hospital between 2012 and 2015 were retrospectively collected. Clinical data included type of infectious disease, neurological status, specific treatment for acute encephalopathy, and neurological outcome. Blood and urine samples were obtained both on the day of admission and a few days later (Table 1). Interleukin (IL)-6, IL-10, and interferon (IFN)- $\gamma$  were determined by chemiluminescence enzyme immunoassay (CLEIA), by enzyme-linked immunosorbent assay (ELISA), and enzyme immunoassay, respectively (Fujirebio; Tokyo, Japan).  $\beta$ 2MG was determined by latex immunoassay from Wako (Osaka, Japan). Normal levels of IL-6, IL-10, INF- $\gamma$ , and urinary  $\beta$ 2MG were <4 pg/mL, <5 pg/mL, <0.1 IU/mL (Fujirebio; Tokyo, Japan), and <200  $\mu$ g/gCr [12], respectively. MRI was performed on a 1.5-T SignaHD device (GE Healthcare,

**Abbreviations:** ALT, alanine aminotransferase; AST, aspartate aminotransferase;  $\beta$ 2MG,  $\beta$ 2-microglobulin; CK, creatine kinase; CLEIA, chemiluminescence enzyme immunoassay; DWI, diffusion-weighted Image; EEG, electroencephalography; ELISA, immunosorbent assay; GTC, generalized tonic-clonic seizures; IFN, interferon; IL, Interleukin; IVIG, intravenous immunoglobulin; MERS, clinically mild encephalitis/encephalopathy with a reversible splenial lesion; MHC, major histocompatibility complex; mPSL, methylprednisolone; MRI, magnetic resonance imaging; RESLES, reversible splenial lesion syndrome; SCC, splenium of corpus callosum.

\* Corresponding author at: Department of Pediatrics, Minoh City Hospital, 5-7-1 Kayano, Minoh, Osaka 562-0014, Japan.

E-mail address: [jjazuma2009@gmail.com](mailto:jjazuma2009@gmail.com) (J. Azuma).

**Table 1**  
Clinical features of the patients.

	Case 1	Case 2	Case 3	Case 4
Age (years)/sex	8/M	3/F	4/F	2/F
Pathogen	Influenza virus	<i>Enterococcus faecalis</i>	Rotavirus	Rotavirus
Altered consciousness interval (days)	1–2	1–2	None	1–3
Seizure	None	GTC	None	GTC cluster
EEG	Diffuse slow	Slow alpha activity	n/a	Occipital slow
Treatment	mPSL pulse, IVIG	ABPC	IVIG	mPSL pulse
Outcome	CR	CR	CR	CR
Serum analysis				
WBC (/ $\mu$ L)	12,600	25,600	17,700	8500
CRP (mg/dL)	2.14	16.3	0.1	0.62
Na (mEq/L)	135	130	141	132
BUN (mg/dL)	15	17	21	28
Cr (mg/dL)	0.6	0.42	0.31	0.23
Uric acid (mg/dL)	n/a	3.9	3.9	3.5
IL-6 (pg/mL)	108	91.4	7	n/a
IL-10 (pg/mL)	n/a	8	4	n/a
IFN- $\gamma$ (IU/mL)	n/a	n/a	0.9	n/a
CSF data				
IL-6 (pg/mL)	n/a	n/a	n/a	3.3
IFN- $\gamma$ (pg/mL)	n/a	n/a	n/a	1.1
Urinalysis				
	936 (Day 2)	51,285 (Day 1)	3917 (Day 1)	20,751 (Day 1)
$\beta$ 2MG ( $\mu$ g/gCr)	19,219 (Day 3)	37,096 (Day 3)	41,945 (Day 3)	4012 (Day 3)
	158 (Day 7)	188 (Day 7)	327 (Day 9)	870 (Day 8)

Abbreviations – y; years old, M; male, F; female, EEG; electroencephalography, GTC; generalized tonic-clonic convulsions, ABPC; ampicillin, mPSL; methylprednisolone, IVIG; intravenous immunoglobulin, CSF; cerebrospinal fluid, IL; interleukin, IFN; interferon,  $\beta$ 2MG;  $\beta$ 2-microglobulin, CR; complete recovery, n/a; not assessed.

Milwaukee, WI) using a standard head coil, and electroencephalography (EEG) and brain imaging findings in acute and chronic phases were examined in all patients.

### 3. Results

#### 3.1. Case 1

An 8-year-old boy receiving prednisolone and the immunosuppressant mizoribine for nephrotic syndrome was admitted to our hospital with fever and pneumonia due to influenza A virus. On the day of admission, he presented with drowsiness and reduced consciousness. EEG showed diffuse high-voltage slow waves. There was no evidence of hyponatremia, proteinuria, or glycosuria; however, urinary  $\beta$ 2MG level was 936  $\mu$ g/gCr. He was tentatively diagnosed with influenza encephalopathy and was treated with methylprednisolone (mPSL) pulse (30 mg/kg for 3 days) and intravenous immunoglobulin (IVIG) (1 g/kg/day). On the third day of admission, brain diffusion-weighted MRI (DWI) showed a high-intensity lesion in the SCC (Fig. 1); urinary  $\beta$ 2MG and serum IL-6 levels were markedly elevated as well (Table 1). He was thus diagnosed with MERS. Drowsiness and impaired consciousness rapidly resolved with mPSL pulse and IVIG therapies.

#### 3.2. Case 2

A 3-year-old girl with fever and impaired consciousness was admitted to our hospital after two episodes of generalized tonic-clonic seizures (GTC). Laboratory data on the second day revealed elevated white blood cells, C-reactive protein, urinary  $\beta$ 2MG, serum IL-6, and

hyponatremia (Table 1). Proteinuria and glycosuria were not present. EEG showed slow alpha activity. Brain DWI showed a high-intensity lesion in the SCC. On the third day, *Enterococcus faecalis* was detected on urine culture, and abdominal DWI and T2-weighted MRI showed bilateral, high-intensity, wedge-shaped lesions in the kidneys as previously reported [13]. She was diagnosed with MERS and concomitant acute focal bacterial nephritis with vesicoureteral reflux and was treated with ampicillin, which led to a rapid and complete recovery.

#### 3.3. Case 3

A 4-year-old girl with fever and dehydration due to repeated vomiting was admitted to our hospital. A rapid diagnostic stool test was positive for rotavirus antigen, which was subsequently confirmed as G1 type. On the day of admission, laboratory data showed elevated levels of aspartate aminotransferase (AST, 36 U/L), alanine aminotransferase (ALT, 18 U/L), creatine kinase (CK, 159 U/L), and urinary  $\beta$ 2MG (3917  $\mu$ g/gCr). She was alert and conscious with no neurological symptoms but appeared lethargic. Laboratory data on the third day revealed markedly elevated levels of AST (258 U/L), ALT (62 U/L), CK (9020 U/L), and urinary  $\beta$ 2MG (Table 1). There was no evidence of hyponatremia, proteinuria, or glycosuria. Lethargic condition and elevated levels of these enzymes led to a differential diagnosis of encephalitis/encephalopathy. Therefore, MRI was performed, and treatment with IVIG (1 g/kg/day) was started. Brain DWI revealed a high-intensity lesion in the SCC (Fig. 1), which led to a diagnosis of RESLES but not MERS due to the absence of overt neurological signs. Her condition and fever rapidly improved after IVIG therapy.

#### 3.4. Case 4

A 2-year-old girl with fever and vomiting was admitted to our hospital after five episodes of GTC with altered consciousness. Convulsions ceased with administration of midazolam followed by fosphenytoin. On the day of admission, laboratory data revealed hyponatremia, hypoglycemia (51 mg/dL), and elevated urinary  $\beta$ 2MG levels (Table 1). Proteinuria and glycosuria were not observed. A rapid diagnostic stool test for rotavirus antigen was positive, which was subsequently confirmed as G2 type. EEG showed occipital slow waves. Brain DWI showed a high-intensity lesion in the SCC (Fig. 1); thus, she was diagnosed with MERS. Her condition and altered consciousness recovered rapidly after mPSL pulse therapy (30 mg/kg for 3 days).

### 4. Discussion

In Japan, the most frequent precedent infection in MERS was influenza virus (34.4%), followed by rotavirus (11.7%) [5]. Although the rate of bacterial infection was only 3.3% [5], a relatively large number of patients with MERS accompanying acute focal bacterial nephritis with or without vesicoureteral reflux were reported [9,11]. Although reversible SCC lesions have been reported in patients with a wide spectrum of pathological conditions, it is unclear whether a specific underlying disease is related to RESLES and MERS. To the best of our knowledge, this is a first case report of MERS accompanying nephrotic syndrome (Case 1). Some patients with MERS who received no specific treatment for encephalitis/encephalopathy recovered completely within a month [4]. Conversely, immunomodulatory therapies such as corticosteroids and IVIG may be effective in patients with MERS, as was observed in Cases 1, 3, and 4. Indeed, increased serum or cerebrospinal fluid cytokines, such as IL-6, IL-10, and IFN- $\gamma$ , were reported in some patients with MERS resulting from viral or bacterial infections, including acute focal bacterial nephritis [8–11], suggesting that inflammatory stimuli might be associated with MERS development regardless of the causative pathogen.

Approximately half of  $\beta$ 2MG is produced by lymphocytes and is freely filtered through the glomerular basement membrane; thus,

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