

Probable etiology of mild encephalopathy with reversible isolated lesions in the corpus callosum in children: A review of 20 cases from northern China

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Abstract

Objective: To explore the etiological spectrum of solitary corpus callosum lesions in children. **Methods:** Retrospective analysis of clinical features, laboratory findings and brain MRI of 20 children with isolated corpus callosum lesions and treated in Taiyuan, northern China. **Results:** The average age of onset was 3.64 ± 3.25 years old. The main clinical symptoms were seizures (13 cases, 65%), fever (10 cases, 50%), gastrointestinal symptoms with vomiting or diarrhea (10 cases, 50%), neck stiffness (5 cases, 25%), altered states of consciousness (4 cases, 20%). Brain MRI showed the splenium lesion to be oval in shape. Repeat MRI showed reversal of the lesion after a mean of 29.5 days. Though the patients were suspected to have probable viral encephalitis, no etiology was found in 15 cases. There was associated gastroenteritis in 5 patients, and rotavirus confirmed in stool in 4 patients. Close to half the patients had hyponatremia. None of the patient had had persistent neurobehavioural symptoms on follow-up at 12-14 months.

Conclusions: This study from northern China confirmed that isolated solitary corpus callosum lesion is benign.

Keywords: Children, splenium of corpus callosum, reversible lesion

INTRODUCTION

Lesions in the splenium of the corpus callosum (SCC) in children are not rare, and various etiologies and associations have been reported. We retrospectively analyzed 20 cases seen over 40 months from the neurology department of a Children Hospital, Taiyuan, northern China. We examined the clinical manifestations, imaging studies, follow up, and possible etiologies of these children.

METHODS

This was a retrospective study, which enrolled 20 cases with isolated lesions in splenium of the corpus callosum, admitted as inpatients to the neurology department of Shanxi Provincial Children Hospital from January 2011 to April 2014, Taiyuan, capital of the Shanxi province, China.

The inclusion criteria of the study patients were: (1). Age less than 16 years; (2). MRI showed a solitary lesion in the splenium of the corpus callosum; (3) The MRI lesion of the splenium showed increased signal intensity on T2-weighted images and diffusion weighted

images, decreased signal intensity on T1 weighted images and apparent diffusion coefficient. Patients were excluded if: (1). The MRI also showed lesions in other brain regions, such as thalamus, basal ganglia, hippocampus, cerebral cortex, or subcortical white matter; (2). The corpus callosum lesion was attributed to multiple sclerosis, acute disseminated encephalomyelitis, trauma, tumor, or infarct.

The following clinical information was obtained: age, gender, clinical manifestations, laboratory investigations, cerebrospinal fluid findings and outcomes. Analysis was performed using SPSS10.0 software. Descriptive statistic data was presented as means and standard deviation.

The MRI was performed using the GE SIGMA HDE 1.5T MRI. All patients were given SE series axial T1WI (TR=1985ms, TE=25.2ms), T2WI (TR=5500ms, TE=135.1ms), T1WI sagittal, coronal T2WI-FLAIR (TR=9852ms, TE=116.5ms, TI=2400ms) and SE/EPI weighted axial DWI (TR=6000, TE=95ms, b=0 and b=1000s/mm²) scanning, layer thickness of 4 - 6mm.

RESULTS

There were 20 patients (11 males and 9 females) who met the inclusion criteria during the study period. The pregnancy, delivery and the neonatal period were uneventful in all patients, and they had normal developmental milestones. The mean age was 3.64 ± 3.25 years old, ranged from 1 year old to 14 years old. The most common clinical manifestation was seizures (13 patients, 65%), fever (10 patients, 50%), gastrointestinal symptoms with vomiting or diarrhea (10 patients, 50%), fatigue (6 patients, 30%), neck stiffness (5 patients, 25%), altered level of consciousness (4 patients, 20%), headache (2 patients, 10%), and Babinski's sign (1 patient, 5%). None of the patient had dehydration clinically. The clinical, laboratory features of the patients are shown in Table 1.

Stool rotavirus was detected in 4 out of 5 patients examined. RT-PCR did not reveal RV RNA in the blood or CSF.

Of the 13 patients with seizures, 10 patients had generalized tonic-clonic convulsions at onset of illness. The seizures lasted no more than 3 minutes and subsided spontaneously. The seizures did not recur after admission. The EEG was normal in 10 patients. There were interictal discharges (focal spike and wave) in 3 patients.

Fifteen patients had various tests done to identify a viral pathogen for the suspected encephalitis, with PCR, serological testing or virus isolation in the cerebrospinal fluid. In none of the patient was the test found to be positive.

The patients' serum sodium is listed in Table 1. The range of the sodium levels was from 127.3 to 140.0 mmol/L, the median was 134.35 mmol/L. Two patients have a serum sodium of < 130 mmol/l, and 11 patients have levels of < 135 mmol/l.

Treatment

Symptomatic treatments were given according to the patient's clinical symptoms, including intravenous fluid infusion, sedation, and antipyretic drugs. None of the patients was given intravenous gamma globulin or methylprednisolone. None of the patients required ICU care.

Brain MRI

Lesions in the splenium of corpus callosum on magnetic resonance imaging (MRI) showed high signal intensity on T2-weighted (TSE) and diffusion-weighted images (DWI), while hypointense or normal-intense on T1-weighted

(SE) sequences images and low ADC (apparent diffusion coefficient map) values (as showed in Figure 1). The lesions disappeared rapidly, the shortest being was 12 days, and the longest 51 days, with an average interval of 29.5 ± 10.28 days.

Follow-up

At a follow up study using telephone contact and face-to-face assessments 10-14 month after the illness, of the 10 patients contacted who had seizures during the acute illness, none had seizure recurrence of seizure. Of the 2 patients with headache, one was headache free, and the other had transient mild headache only. None of the 3 patients with dizziness had recurrence of the symptom. None of the patients had significant neurobehavioral symptoms, such as developmental delay, behavioral disorders or learning difficulties.

DISCUSSION

All 20 patients in this study are consistent with the diagnosis of mild encephalitis/encephalopathy with reversible splenial lesion (MERS). There have been many previous reports of children with MERS.¹⁻⁵ MERS is a reversible lesion of the splenium of the corpus callosum. Most cases that have been reported are accompanied by mild encephalitis/encephalopathy. Clinical symptoms often consists of mild neurological abnormalities: delirious, confusion, and seizures with complete clinical recovery. Cerebral MRI has reversible isolated corpus callosum lesions (MERS type I), sometimes accompanied by white matter lesions that are symmetrical in other brain regions (MERS type II).³ Our report confirmed the benign prognosis of MERS^{6,7}, as none of our patients had persistent neurological deficits, and the MRI lesion were reversible in all the patients, at a mean of 29.5 days.

Although patients with MERS are often suspected to have viral encephalitis, no definite etiological cause has been found, although various associated infection has been reported. No specific cause was found in 15 of our patients in this study, 5 patients had associated gastroenteritis, 4 were confirmed to have rotavirus infection. Pan *et al.* analyzed the findings of 27 patients with MERS reported in the literature, only 6 patients had associated infection, two from mycoplasma pneumoniae, two from herpes simplex virus, and one each from EB virus rotavirus.⁸ Bulakbasi *et al.* reported 5 patients with MERS associated with

Table 1: The clinical characteristics of children with SCC

Number	Gender	Age of onset	Symptoms	Physical examination	Blood sodium (mmol/L)	Stool rotavirus test	Past history	CSF findings
1	M	12Y	fever, headache	stiff neck (+)	140	no inspection	otitis media two weeks ago	normal
2	M	1Y3M	fever, convulsion	normal	135	no inspection	normal	normal
3	F	1Y2M	fever, vomiting, convulsion	somnolence stiff neck (+)	128.4	no inspection	normal	normal
4	M	2Y	fever, convulsion	somnolence, stiff neck (+)	133.7	no inspection	normal	normal
5	M	13Y	dizziness, fever	normal	138.6	no inspection	recurrent dizziness 3 times	normal
6	F	1Y11M	vomiting, convulsion	normal	137		normal	normal
7	M	1Y9M	vomiting, diarrhea, convulsion	normal	132.6	positive	normal	no lumbar puncture
8	F	2Y	vomiting, convulsion	somnolence	137	negative	normal	normal
9	M	2Y6M	vomiting, diarrhea, convulsion	normal	132.3	positive	normal	no lumbar puncture
10	M	1Y	diarrhea, drowsiness, convulsion	normal	134.7	positive	normal	no lumbar puncture
11	F	3Y	convulsion	normal	132.4	no inspection	normal	no lumbar puncture
12	F	1Y	drowsiness	stiff neck (+)	138	no inspection	normal	normal
13	F	3Y5M	fever, convulsion	normal	137.4	no inspection	normal	normal
14	F	3Y	fever, vomiting, drowsiness	stiff neck (+)	132.7	no inspection	normal	normal
15	F	4Y	fever, vomiting, drowsiness	bilateral Babinski sign (+)	135.4	no inspection	intracranial hemorrhage when 7 months old.	normal
16	M	1Y	drowsiness	normal	134	no inspection	normal	no lumbar puncture
17	M	3Y	fever, vomiting, convulsion	somnolence	131.3	no inspection	normal	normal
18	F	8Y	headache, convulsion	normal	138.1	no inspection	normal	normal
19	M	1Y4M	vomiting, diarrhea, convulsion	normal	127.3	positive	normal	no lumbar puncture
20	M	6Y	fever, dizziness, depression	normal	131.8	no inspection	normal	normal

Gender: male (M), female (F). Age of onset: year(Y), month (M),

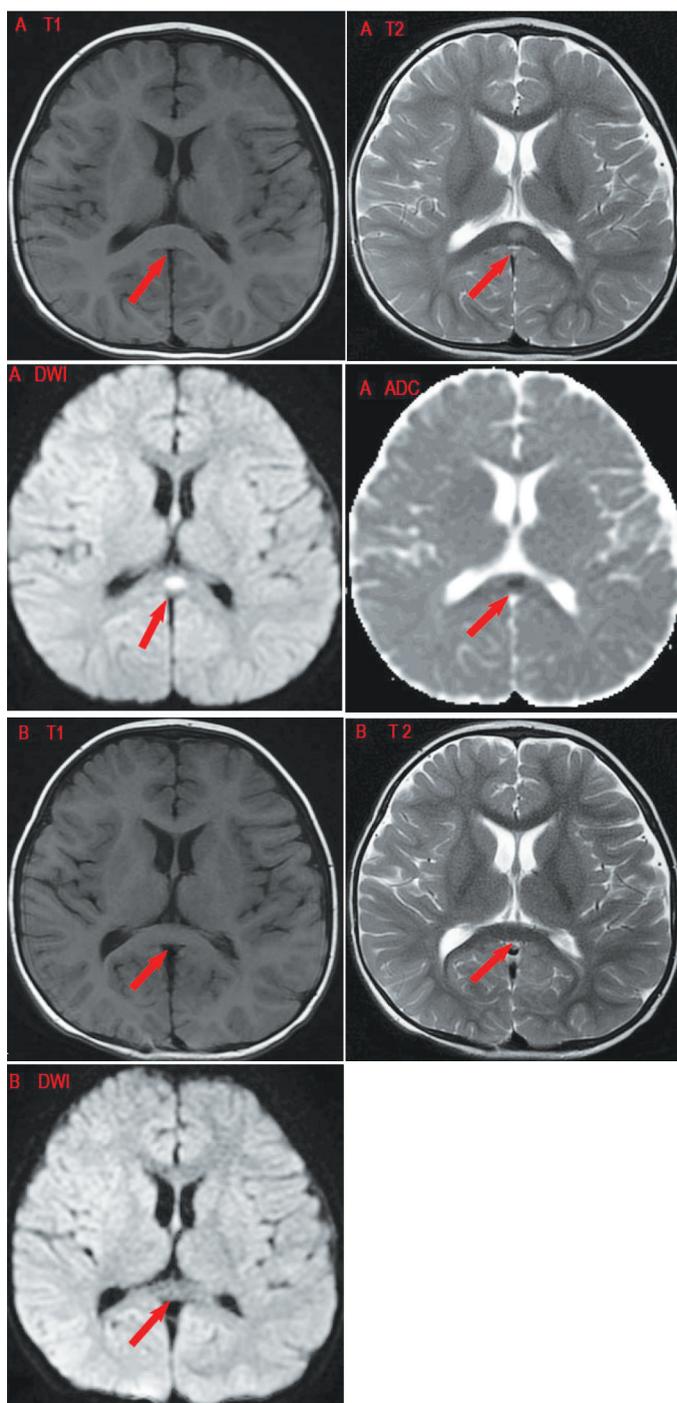


Figure 1. The 19th patient, male, 1 year 4 month old, complained of diarrhea and vomiting for 2 days, seizure 1 time on admission, was diagnosed as suspected intracranial infection and rotavirus infection.

Figure A-T1, A-T2, A-DWI, and A-ADC stand for brain magnetic resonance imaging scan with early onset, Figure A-T1 stands for T1W, Figure A-T2 stands for T2W, Figure A-DWI stands for DWI, and Figure A-ADC stands for ADC. Low signal were showed in T1W and ADC, high signal were showed in DWI and T2W. Figures B-T1, B-T2 and B-DWI stand for cranial magnetic results on the 11 days after the first MRI inspection, splenium of corpus callosum lesions disappeared after remission. Figure B-T1 stands for T1W, Figure B-T2 stands for T2W, and Figure B-DWI stands for DWI. The abnormal signal of all returned to normal on T1W, T2W and DWI.

influenza virus A infection. In all the patients, influenza A was isolated from the throat swabs and confirmed by polymerase chain reaction, but none had evidence of influenza virus in CSF. There was thus no evidence of direct viral infection of the brain.⁹ Kometani *et al.* reported two cases of MERS associated with acute focal nephritis caused by *enterococcus faecalis*. The patients showed fever and delirium, and after treatment, their consciousness improved without neurological sequelae.⁷

As for the association with the gastroenteritis and rotavirus infection in a quarter of our patients, this has been noted previously in the literature. Karampa *et al.* reported a case of a 4-year-old boy with MERS, who had mild encephalopathy, neuroimaging showed an isolated corpus callosum lesion, and rotavirus RNA was found in feces.¹⁰ Arakawa *et al.* reported two children with MERS, both of whom had symptoms of gastroenteritis. The rotavirus (GARV) antigen was detected in their fecal samples and in serum samples, but no GARV antigen was detected in the cerebrospinal fluid samples. Both patients have a good prognosis.¹¹ Fukuda *et al.* reported a 2-year-old boy with MERS who experienced diarrhea, vomiting, fever and sudden disturbance of consciousness, and detected rotavirus antigen in the feces. Electroencephalograms showed global diffuse slow-wave and intracranial magnetic resonance imaging showing enhanced signals in the corpus callosum. The prognosis was good.¹²

In our study, 11 of 20 patients were found to have hyponatremia (6 patients presented with vomiting or diarrhea, the other 5 cases did not have gastroenteritis symptom). The relationship between the hyponatremia and MERS is uncertain, whether hyponatremia is causative of SCC, or both are associations. Hyponatremia may be a result of syndrome of inappropriate antidiuretic hormone secretion (SIADH), or infection. Takanashi *et al.* thought the possible cause of hyponatremia is SIADH, which may be reflective of underlying cerebral dysfunction.¹³

When the brain tissue is in the state of low sodium, free water can enter the cell, leading to cytotoxic edema. The inflammatory infiltration was also associated with cytotoxic edema, possibly due to the high affinity of the pathogen to the corpus callosum.

Miyata *et al.* reported six patients with MERS and speculated that the disequilibrium of systemic metabolism including electrolytes could induce facilitation of oxidative stress and reversible white matter lesion.¹⁴ Further studies is required to confirm this.

DISCLOSURE

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Conflict of interest: None

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