Abnormal versus normal neuroimaging in acute infectious encephalitis and mortality

ORIGINAL ARTICLE

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ABSTRACT

OBJECTIVE

To identify the association between neuroimaging findings and the risk of acute infectious encephalitis and death

METHODS

We conducted the retrospective cohort study by using International Classification of Diseases (ICD) 10 A80-A89 and G04 from Khon Kaen Hospital database, including medical record of patients that was preliminarily diagnosed as acute infectious encephalitis and hospitalized at Khon Kaen Hospital from January 2011 to May 2017 to compare abnormal neuroimaging and normal neuroimaging from CT scan or MRI. The primary outcome was death. The secondary outcomes were seizures, status epilepticus, mechanical ventilation usage, nosocomial infection, intensive care unit (ICU) admission, length of ICU admission and cardiac arrest.

RESULTS

In a total of 376 patients with acute infectious encephalitis were included and divided into 2 groups; 158 patients with abnormal neuroimaging and 218 patients with normal neuroimaging. Characteristics of the two groups were similar. Risk of mortality of those with or without abnormal neuroimaging from CT scan or MRI was not significantly different (hazard ratio (HR), 0.97; 95% confidence interval (CI), 0.67 to 1.40).

CONCLUSION

In current retrospective cohort showed no significantly different risk of mortality between abnormal and normal neuroimaging from CT scan or MRI in patients with acute infectious encephalitis.

INTRODUCTION

Encephalitis is one of the central nervous system infections, and it can be caused by various etiologies and pathogens; viral encephalitis, autoimmune encephalitis, bacterial encephalitis, fungal encephalitis and encephalitis of the unknown cause.[1,2,3] The most common identified cause is from the viral infection.[3,4] Its annual worldwide incidence is 3.5 to 7.4 in 100,000 population.[5-9] Its case-fatality can be as high as 13 to 33%.[2,3,10-12]

Areas of brain involvement depend on types of the pathogen, for instance, herpes simplex encephalitis mostly involves temporal and frontal lobes of the brain while Japanese encephalitis mostly involves thalamus and basal ganglion.[13-18] Moreover, the areas of involvement also determine complications in those with encephalitis. In 2007; there was a case-control study in Taiwan in 330 children with postencephalitic epilepsy (PEE) stated that cortical involvement with or without subcortical lesion increased the risk for PEE.[19] However, a later retrospective cohort study in 2013 from the US in 103 patients with acute encephalitis stated that cerebral edema was associated with the higher mortality regardless of the areas of brain involvement.[2]

Until now, there is no evidence regarding the relationship between other types of abnormal neuroimaging of the brain and mortality. Thus, we aim to determine the relationship between abnormal neuroimaging of the brain in various forms in patients with acute infectious encephalitis, and the mortality in a larger study sample.

METHODS

STUDY DESIGN AND PATIENTS

We conducted a retrospective cohort study of the patients with acute infectious encephalitis hospitalized at Khon Kaen Hospital between January 2011 and May 2017 and preliminary diagnosed as acute encephalitis by using International Classification of Diseases (ICD) 10 A80-A89 and G04 from Khon Kaen Hospital database. Their medical records were reviewed and verified. Those without neuroimaging record approved by a radiologist were excluded.

EXPOSURE

Abnormal neuroimaging from computed tomography (CT) scan or magnetic resonance imaging (MRI) in various forms was exposure in the present study. This included brain edema, frontal lobe involvement, temporal lobe involvement, parietal lobe involvement, occipital lobe involvement, frontoparietal involvement, frontotemporal involvement, temporoparietal involvement, parieto-occipital involvement, basal ganglia involvement, thalamic involvement, cerebellar involvement, midbrain involvement.

STUDY OUTCOMES

Our primary outcome was death within 30 days. Death was ascertained from the medical records. The secondary outcomes included seizure, status epilepticus i.e., evidence of seizure more than five minutes or recurrence of seizure within five minutes with no fully recovered, mechanical ventilation usage, nosocomial infection i.e., present with hospital-acquired pneumonia, ventilator-

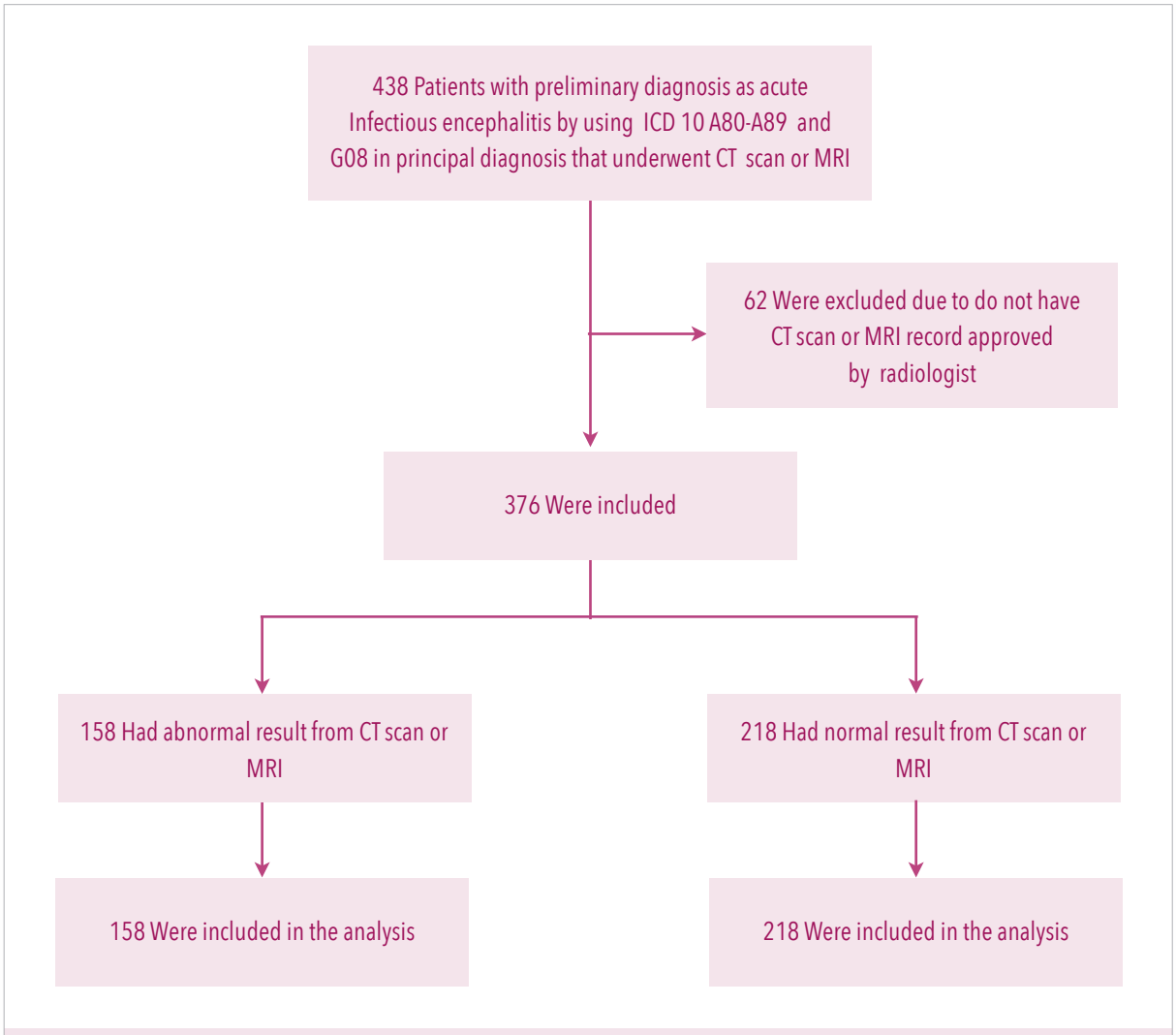

Figure 1. Study flow in the analysis

associated pneumonia, urinary tract infection and thrombophlebitis, intensive care unit (ICU) admission, length of ICU admission and cardiac arrest defined by evidence of cardiopulmonary resuscitation.

DATA COLLECTION

Aside from the exposure and the study outcomes. We also collected sex, age, presence of comorbidities (hypertension, diabetes mellitus, stroke, hematologic disease, cirrhosis, Human Immunodeficiency Virus (HIV) infection, tuberculosis (TB) infection, vital signs i.e., body temperature, systolic blood pressure, diastolic blood pressure and pulse rate, Glasgow coma scale (GCS), cranial nerve defect, focal neurological deficit i.e., hemiparesis, paraparesis and quadriparesis, vomiting, new onset of seizures, status epilepticus, alteration of consciousness, stiff neck, laboratory investigation i.e., blood leukocyte

count, thrombocytopenia and serum sodium level, mechanical ventilation on admission, acyclovir therapy, antibiotic use, type of antibiotic including penicillin group, cephalosporin group, polymyxin group, glycopeptide group, macrolide group, fluoroquinolone group, aminoglycoside group, metronidazole, carbapenems group and anti-tuberculosis drug, length of antibiotic use, steroid use, mannitol and cerebrospinal fluid (CSF) profile including leukocyte count, lymphocyte proportion, polymorphonuclear leukocytes (PMN) proportion, protein level, glucose CSF:blood ratio and open pressure.

STATISTICAL ANALYSIS

We used descriptive statistics to summarize the patient characteristics; we used frequencies and percentage for categorical variables, mean and standard deviation (SD) for normally distributed data and median and interquartile range (IQR) for non-normally distributed data.

For inferential statistics, either Pearson's chi-squared or Fisher exact test was used for categorical variables where appropriate. Mann–Whitney U test was used in continuous variables comparison. We used relative risk (RR) to describe the ratio of the probability of an event rate of the outcomes. Binary logistic regression analysis was used to examine how exposure related to the outcome as crude odds ratio (COR) and adjusted odds ratio (AOR). Moreover, we used the Cox proportional hazard model analysis to describe the risk of mortality as a hazard ratio (HR). For all inferential statistics, 95% confidence interval (CI) was used to describe statistical significance. Kaplan-Meier survival was also used to show the cumulative survival.

RESUILTS

PATIENTS

From January 2011 through May 2017, we included 438 patients with preliminary diagnosis as acute infectious encephalitis by using ICD 0 A80-A89 and G04 in principle diagnosis that underwent CT scan or MRI. Then we excluded 62 patients without CT scan or MRI record approved by radiologist. A total of 376 patients were included and divided into 2 groups; 158 patients with abnormal neuroimaging and 218 patients with normal neuroimaging from CT scan or MRI (Figure 1). Characteristics at the admission of the two groups were relatively similar (Table 1). Most of them were male with an average age of 50 years old. Very few of them had underlying diseases. Moreover, signs and symptoms on admission in the two groups were similar.

Treatment after the admission of the two groups including acyclovir therapy, Antibiotic use and therapy of cerebral edema was similar but in the former group received polymyxin group, metronidazole and mannitol more than the latter group. Besides, the former group had a longer length of antibiotic use (Table 2). CSF parameter in two groups was not significantly different and an average open pressure from the first lumbar puncture was 20 cmH_2O (Table 3).

OUTCOME

Mortality rates as our primary outcome of those with or without abnormal neuroimaging from CT scan or MRI were relatively similar (42.4% vs. 40.4%; RR, 1.05; 95% CI, 0.82 to 1.34). Furthermore, secondary outcomes were not significantly different (Table 4).

Table 1. Baseline characteristics of patients on admission (continued)

Characteristic	Abnormal neuroimaging (n=158)	Normal neuroimaging (n=218)	P Value
Male sex-no. (%)	93 (58.9)	131 (60.1)	0.81
Age-yr			0.15
Median	51	53	
Interquartile range	34.2-63.9	35.1-68	
Comorbidity-no. (%)			
Hypertension	32 (20.3)	53 (24.8)	0.31
Diabetes mellitus	25 (15.8)	51 (23.8)	0.06
Stroke	7 (4.4)	8 (3.7)	0.74
Hematologic disease	6 (3.8)	4 (1.9)	0.34
Cirrhosis	6 (3.8)	8 (3.7)	0.98
HIV infection	7 (4.4)	7 (3.3)	0.56
TB infection	7 (4.4)	6 (2.8)	0.40
Cranial nerve defect-no. (%)	10 (6.6)	22 (10.3)	0.22
New onset of seizures-no. (%)	50 (31.6)	60 (27.5)	0.39
Body temperature (degree celsius)			0.22
Median	37.7	37.5	
Interquartile range	37-38.4	36.7-38.5	
Systolic blood pressure (mmHg)			0.72
Median	130	129	
Interquartile range	113-152.3	111-150.3	
Diastolic blood pressure (mmHg)			0.47
Median	74.5	76	
Interquartile range	66-87	66.8-88	

Table 1. Baseline characteristics of patients on admission (continued)

Characteristic	Abnormal neuroimaging (n=158)	Normal neuroimaging (n=218)	P Value
Median	100	100	
Interquartile range	84.8-118	85.5-114	
Glasgow coma score			0.13
Median	11	10	
Interquartile range	7.8-14	7-13	
Focal neurological deficit-no. (%)			
Hemiparesis	10 (6.6)	9 (4.4)	0.36
Paraparesis	3 (2.0)	3 (1.5)	0.70
Quadriparesis	19 (12.6)	20 (9.8)	0.41
Vomiting-no. (%)	40 (25.3)	41 (18.8)	0.13
Status epilepticus-no. (%)	13 (8.2)	12 (5.5)	0.30
Alteration of conscious-no. (%)	135 (85.4)	191 (87.6)	0.54
Stiff neck-no. (%)	60 (39.2)	99 (46.7)	0.16
Blood leukocyte count, x 1000 cell/mL			0.84
Median	11.7	10.9	
Interquartile range	7.8-16	7.7-16.8	
Thrombocytopenia-no. (%)	15 (10.3)	27 (13.3)	0.40
Serum sodium, mmol/dL			0.23
Median	137	136	
Interquartile range	133-141	132-140	
Mechanical ventilation on admission-no. (%)[2,3,17]	55 (34.8)	78 (35.8)	0.85

* Thrombocytopenia defined as platelet count <100,000/mm3

Table 2. Treatment on admission

Treatment	Abnormal neuroimaging (n=158)	Normal neuroimaging (n=218)	P Value
Acyclovir therapy-no. (%)	48 (30.4)	76 (34.9)	0.36
Antibiotic use-no. (%)	149 (94.3)	211 (96.8)	0.24
Penicillin group	72 (45.6)	109 (50.0)	0.40
Cephalosporin group	136 (86.1)	197 (90.4)	0.20
Polymyxin group	17 (10.8)	11 (5.0)	0.04
Glycopeptide group	29 (18.4)	29 (13.3)	0.18
Macrolide group	11 (7.0)	14 (6.4)	0.84
Fluoroquinolone group	6 (3.8)	7 (3.2)	0.76
Aminoglycoside group	2 (1.3)	1 (0.5)	0.58
Metronidazole	17 (10.8)	10 (4.6)	0.02
Carbapenems group	37 (23.4)	60 (27.5)	0.37
Anti-tuberculosis drug	7 (4.4)	5 (2.3)	0.25
Length of antibiotic use (day)			0.01
Median	10	7	
Interquartile range	3-16.3	3-14	
Therapy of cerebral edema-no. (%)			
None	97 (61.4)	151 (69.3)	0.11
Steroid	52 (32.9)	61 (28.0)	0.30
Mannitol	22 (13.9)	15 (6.9)	0.02

FACTORS DETERMINING OUTCOME

From the crude analysis of the odds ratio, the mortality was relatively similar between abnormal and normal neuroimaging. The mortality was increased in higher age, female and lower GCS (Table 5). From logistic regression analysis of adjusted odds ratio, the mortality was slightly increased in higher age but was decreased in male with higher GCS who had a stiff neck on admission. In other factors, mortality was similar (Table 5). From Cox proportional hazard regression analysis, Risk of mortality was similar in abnormal and

Table 3. CSF profile

CSF Profile	Abnormal neuroimaging (n=158)	Normal neuroimaging (n=218)	P Value
CSF parameter			
Leukocyte count, cells/μL			0.74
Median	30	40	
Interquartile range	2-496.5	0-546	
Lymphocyte proportion %			0.87
Median	5	5	
Interquartile range	0-20	0-32	
PMN proportion %			0.58
Median	75.5	48	
Interquartile range	0-93.3	0-93	
Protein level, mg/dL			0.71
Median	94.2	116.2	
Interquartile range	43.8-352	51.9-289.2	
Glucose CSF:blood ratio			0.97
Median	0.47	0.47	
Interquartile range	0.34-0.62	0.28-0.61	
Open pressure (cmH2O)			0.53
Median	20	20	
Interquartile range	15-29.3	14-27	

normal neuroimaging (HR, 0.97; 95% CI, 0.67 to 1.40). Even though, it was increased 1.01 times in higher age (HR, 1.01; 95% 1.01 to 1.02) and was decreased 0.67 times in male (HR, 0.67; 95% CI, 0.47 to 0.96) and 0.9 times in higher GCS (HR, 0.9; 95% CI 0.86 to 0.95) (Table 5).

SUBGROUP ANALYSIS

In our subgroup analysis, we found that risk of mortality was relatively similar in the patients with or without brain edema in various areas involvement in brain parenchyma from the neuroimagings (Table 6).

Table 4. Outcomes

Outcome	Abnormal neuroimaging (n=158)	Normal neuroimaging (n=218)	Relative risk (95 % CI)	Mean difference (95 % CI)
Primary outcome				
Death-no. (%)	67 (42.4)	88 (40.4)	1.05 (0.82-1.34)	
Secondary outcome				
Seizure-no. (%)	27 (17.1)	38 (17.4)	0.98 (0.63-1.54)	
Status epilepticus-no. (%)	16 (10.1)	12 (5.5)	1.84 (0.90-3.78)	
Mechanical ventilation usage-no. (%)	97 (61.4)	131 (60.1)	1.02 (0.87-1.20)	
Nosocomial infection-no. (%)	46 (29.1)	74 (33.9)	0.86 (0.63-1.16)	
ICU admission-no. (%)	21 (13.3)	25 (11.5)	1.16 (0.67-1.99)	
Length of ICU admission (day)				-8.51 (-22.38 to 5.37)
Median	4.2	4.9		
Interquartile range	1.5-19	1.8-5.8		
Cardiac arrest-no. (%)	24 (15.2)	35 (16.1)	0.95 (0.59-1.53)	

DISCUSSION

In the current study, from 376 patients with acute infectious encephalitis, we found mortality rates were not significantly different between abnormal and normal neuroimaging from CT scan or MRI. The other outcomes also include seizure, status epilepticus, mechanical ventilation usage, nosocomial infection, ICU admission, length of ICU admission and cardiac arrest. Moreover, a result of binary logistic regression and Cox proportional hazard model analysis are still shown not significantly associated with risk for mortality.

COMPARISONS WITH OTHER STUDIES

We divided patients into two groups, comparing mortality outcomes in patients with or without abnormal neuroimaging. The result showed no significance between the two groups. The current study is the first study about abnormal neuroimaging of the brain in various forms and the mortality. However, there was a previous study in 103 patients with acute encephalitis receiving care in ICU stated that patients with cerebral edema had mortality 18.06 times higher than those without it (OR, 18.06; 95% CI, 3.14 to 103.92).[2] In contrast, our subgroup analysis of cerebral edema shown no

Table 5. Factors determine outcome

Factor	Odds ratio (95% CI)		Hazard ratio (95% CI)
	Crude analysis	Adjusted analysis	
Abnormal neuroimaging	1.09 (0.72-1.65)	1.19 (0.73-1.97)	0.97 (0.67-1.40)
Male sex	0.60 (0.39-0.91)	0.58 (0.36-0.95)	0.67 (0.47-0.96)
Age-yr	1.02 (1.01-1.03)	1.02 (1.01-1.04)	1.014 (1.005-1.023)
Systolic blood pressure (mmHg)	1.01 (1.001-1.017)	0.996 (0.98-1.01)	0.999 (0.99-1.01)
Diastolic blood pressure (mmHg)	1.01 (0.999-1.024)	1.01 (0.99-1.03)	1.01 (0.99-1.02)
Glasgow coma score	0.85 (0.80-0.91)	0.85 (0.79-0.91)	0.88 (0.84-0.92)
Body temperature (degree celsius)	1.12 (0.93-1.33)	1.19 (0.96-1.48)	1.07 (0.91-1.25)
Alteration of consciousness	1.43 (0.76-2.66)	0.94 (0.41-2.13)	1.02 (0.54-1.91)
Stiff neck	0.73 (0.48-1.11)	0.56 (0.33-0.94)	0.75 (0.51-1.09)
Serum sodium, mequiv/L	0.995 (0.97-1.02)	0.99 (0.96-1.02)	0.99 (0.96-1.01)
Blood leukocyte count, cell/mL	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)

significant difference in mortality between patients with or without cerebral edema. In our aspect, because they have a small sample size and included just only patients receiving ICU care that can affect the result of mortality. Moreover, our result was defined by the hazard ratio that has higher reliability and larger sample size. Thus, the result of the previous study may not precisely enough to present the relationship between cerebral edema and mortality in patients with encephalitis generally.

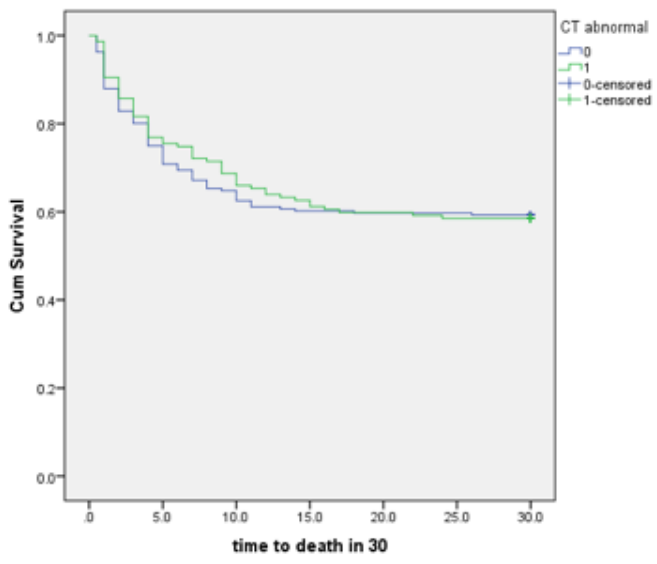

Figure 2. Probability of survival patients with or without abnormal neuroimaging in 30 day

STRENGTHS AND LIMITATIONS OF STUDY

Besides the fact that our findings were from the largest database of patients with acute encephalitis in the world, we still have some limitations in our study. First, missing data were

Table 6. Subgroup analysis

Abnormal neuroimaging	Number of patients death	Cumulative mortality (%)	Hazard ratio (95% CI)
Brain edema (n=45)	21	47	0.92 (0.50-1.67)
Frontal lobe involvement (n=72)	29	40	0.84 (0.52-1.36)
Temporal lobe involvement (n=33)	13	39	0.86 (0.45-1.66)
Parietal lobe involvement (n=39)	18	46	1.07 (0.60-1.93)
Occipital lobe involvement (n=21)	9	43	0.92 (0.40-2.11)
Frontoparietal region involvement (n=14)	6	43	1.07 (0.43-2.71)
Frontotemporal region involvement (n=14)	5	36	0.67 (0.25-1.84)
Temporoparietal region involvement (n=7)	3	43	1.03 (0.25-4.31)
Parieto occipital region involvement (n=11)	5	46	0.78 (0.24-2.50)
Basal ganglia involvement (n=13)	6	46	1.06 (0.45-2.50)
Thalamic involvement (n=10)	4	40	0.83 (0.25-2.69)
Cerebellar involvement (n=6)	3	50	1.96 (0.61-6.30)
Midbrain involvement (n=4)	2	50	0.80 (0.19-3.42)

inevitable due to the retrospective nature of the study. Second, a different time interval for undergoing the CT scan or MRI might affect the stages of the disease and our findings might not be correctly concluded. Third, the results of the CT scan or MRI was approved by only one radiologist.

CONCLUSIONS AND IMPLICATIONS

In our study, we found that risk for mortality of patients with acute infectious encephalitis with or without abnormal neuroimaging was not significantly different. Findings from CT scan or MRI in patients with acute infectious encephalitis might not be useful for predicting the mortality. For further research, three dimensional CT scan is our suggestion. It can show not only areas of brain involvement but also the volume of the lesion. The relationship between the neuroimaging findings and outcome in these patients might be clearer and more precise.

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