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## ORIGINAL ARTICLE

# Magnetic Resonance Imaging to Predict Neurological Outcome in Children with Acute Encephalitis

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## ABSTRACT

***Objective:*** *To identify magnetic resonance imaging (MRI) variables that are predictive of neurological outcome in children with acute encephalitis.*

***Methods:*** *We retrospectively reviewed all consecutive patients younger than 18 years who presented to the Tuen Mun Hospital, Hong Kong, between January 2006 and July 2014 with the diagnosis of acute encephalitis. The location and extent of hyperintense lesions on T2-weighted or fluid-attenuated inversion recovery images and the presence of restricted diffusion were assessed. The extent of lesions was quantified using a scoring system ranging 0 to 9. Clinical outcome was assessed at 1 year using the Pediatric Cerebral Performance Category Scale (PCPCS). Neurological outcome was dichotomised to good (PCPCS score of 1) or adverse (PCPCS score of 2 to 6). Multiple logistic regression analysis was used to determine the association between neurological outcome and lesion location or restricted diffusion. Spearman's rank correlation test was used to evaluate the association between lesion extent score and the PCPCS score.*

***Results:*** *Of 46 patients, 12 were excluded and the remaining 15 male and 19 female patients aged 2 months to 17 years were included. The mean time from admission to MRI was 7 days (median, 4 days; range, 1-40 days); only two patients underwent MRI after 3 weeks. At 1 year, 24 patients achieved good outcomes with no neurological sequelae (PCPCS score of 1), six patients had mild to moderate (n = 4) or severe (n = 2) residual neurological deficits (PCPCS score of 2 to 5), and four patients died (PCPCS score of 6). All patients with adverse outcomes had T2-weighted or fluid-attenuated inversion recovery images that showed hyperintense parenchymal lesions. Adverse neurological outcome was associated with involvement of basal ganglia and/or thalami (odds ratio [OR] = 12.7; p = 0.004) and involvement of the brainstem (OR = 8.8; p = 0.023). Lesion extent score was moderately correlated with PCPCS score ($r^2$ = 0.35; p = 0.01). Restricted diffusion was a predictor of adverse neurological outcome (OR = 5.7; p = 0.033).*

***Conclusion:*** *Restricted diffusion and involvement of the deep grey nuclei and brainstem are predictive of adverse neurological outcome. Patients with a greater extent of lesions tend to have worse neurological outcomes.*

***Key Words:*** *Encephalitis; Magnetic resonance imaging; Pediatrics; Treatment outcome*

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# 中文摘要

## 用磁共振成像預測兒童急性腦炎的神經結果

陳頌恩、楊子慧、王耀忠

**目的：**確定能預測兒童急性腦炎神經結果的磁共振成像（MRI）變數。

**方法：**回顧分析於2006年1月至2014年7月期間入院的18歲以下連續急性腦炎兒童患者。評估T2加權 / 流體衰減反恢復（FLAIR）高信號病變的位置和範圍以及有否限制性擴散。病變範圍被量化為0到9分。一年臨床結果用小兒腦性能量表（PCPCS）評估。神經結果分為良好（PCPCS分數為1）或不良（PCPCS分數為2至6）。用多重邏輯回歸分析來確定神經結果與病變位置或限制性擴散之間的關聯。用Spearman等級相關評估病變範圍與PCPCS之間的相關性。

**結果：**46例患者中，12例被排除，其餘15例男性和19例女性患者年齡介於2個月至17歲之間。入院至接受MRI檢查的平均時間為7天（中位數4天，範圍：1-40天）；只有兩名患者在3週後接受MRI檢查。一年後，24例患者無神經功能障礙（PCPCS分數為1）、6例患者有輕度至中度（n = 4）或嚴重（n = 2）殘留神經功能缺損（PCPCS分數為2至5）、4例患者死亡（PCPCS分數為6）。所有預後不良的患者均有T2加權或FLAIR高信號實質病變。不良神經結果與基底神經節和/或丘腦病變（比值比[OR] = 12.7；p = 0.004）和腦幹病變（OR = 8.8；p = 0.023）相關。病變範圍與PCPCS中度相關（$r^2$ = 0.35；p = 0.01）。限制性擴散是不良神經結果的預測因子（OR = 5.7；p = 0.033）。

**結論：**限制性擴散和深灰色核和腦幹病變能預示不良的神經結果。病變範圍較大的患者傾向有較差的神經結果。

## INTRODUCTION

Acute encephalitis in children is often associated with severe neurological morbidity and mortality. Its diagnosis is based on pathological analysis of brain tissue. Clinical and laboratory findings include cerebrospinal fluid leukocytosis and electroencephalographic and neuroimaging abnormalities. Magnetic resonance imaging (MRI) is used in the diagnosis, evaluation, and monitoring of encephalitic lesions in patients presenting with fever, sepsis, and / or neurological symptoms. The prognostic value of MRI findings for neurological outcome remains controversial.[1-8] An adverse outcome has been reported to be associated with restricted diffusion,[4,5] increasing lesion extent,[4] and parenchymal T2 hyperintensities.[3] However, one study has shown resolution of neurological symptoms despite different patterns of parenchymal involvement.[8] This study aimed to identify MRI variables that were predictive of neurological outcome in children with acute encephalitis.

## METHODS

The study was approved by the Hong Kong Hospital Authority's New Territories West Cluster Research Ethics Committee, which waived the requirement for patient consent, and conducted in compliance with the Declaration of Helsinki. The definition of encephalitis was based on an epidemiological study by Granerod et al.[9] The database of the Tuen Mun Hospital, Hong Kong, was searched using the International Classification of Diseases (ICD) terms 'encephalitis' and 'encephalomyelitis' (ICD9 323 and ICD10 G04 and G05). We retrospectively reviewed all consecutive patients younger than 18 years who presented to the hospital between January 2006 and July 2014 with the diagnosis of acute encephalitis. Patients with known neurological disease or abnormality, acute encephalopathy due to metabolic or toxic causes or other pre-existing diseases were excluded, as were those with no MRI records or incomplete follow-up.

A 3-T or 1.5-T MRI scanner was used. Pulse sequences included axial T1-weighted, T2-weighted, post-contrast T1-weighted, diffusion-weighted, apparent diffusion coefficient map, coronal T2-weighted fluid-attenuated inversion recovery (FLAIR), post-contrast T1-weighted, and sagittal T1-weighted sequences. Images were reviewed by two radiologists and a consensus was reached.

The location and extent of T2-weighted/FLAIR hyperintense lesions and the presence of restricted diffusion were assessed (Figure 1). The extent of lesions was quantified using a scoring system ranging from 0 to 9 (involvement of one or two lobes of one cerebral hemisphere = 1, involvement of three or four lobes of one cerebral hemisphere = 2, unilateral involvement of basal ganglia and/or thalamus = 1, bilateral involvement of basal ganglia and/or thalamus = 2, involvement of brainstem = 1, involvement of one cerebellar hemisphere = 1, involvement of bilateral cerebellar hemispheres = 2). Restricted diffusion was defined by hyperintensity on diffusion-weighted images and hypointensity on the apparent diffusion coefficient map (Figure 2).

Clinical outcome was assessed at 1 year using the Pediatric Cerebral Performance Category Scale (PCPCS),[10] in which a score of 1 indicates normal neurological function, 2 indicates mild neurological disability, 3 indicates moderate disability, 4 indicates severe disability with dependence on others for daily support, 5 indicates a coma or vegetative state, and 6 indicates brain death.

Neurological outcome was dichotomised to good (PCPCS score of 1) or adverse (PCPCS score of 2 to 6). Multiple logistic regression analysis was performed to determine the association between neurological outcome and lesion location or restricted diffusion. Spearman's rank correlation test was used to evaluate the association between the lesion extent score and the PCPCS score. A p value of $<0.05$ was considered statistically significant.

## RESULTS

Of 46 consecutive patients, 12 were excluded owing to incomplete follow-up (n = 4), lack of MRI records (n = 7), or a history of epilepsy (n = 1), and the remaining 15

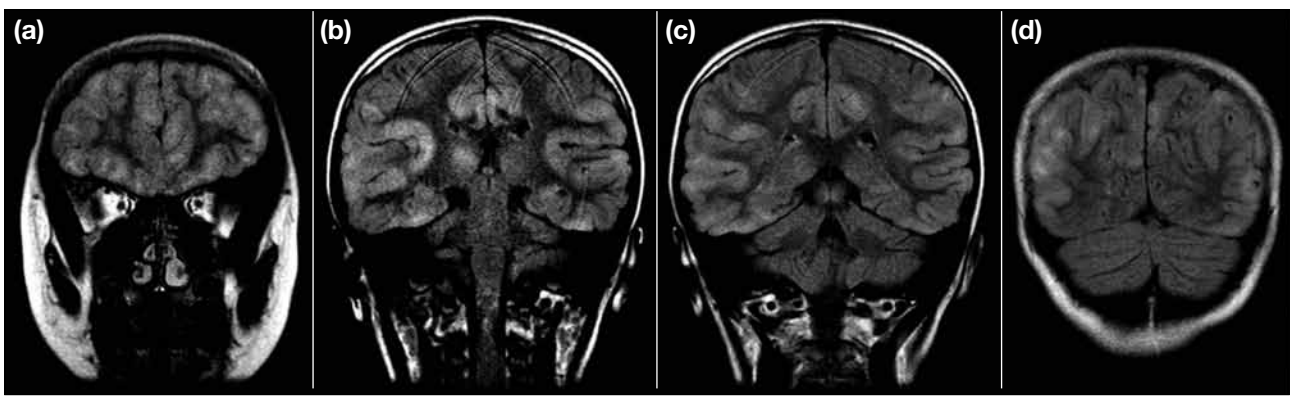


**Figure 1.** Fluid-attenuated inversion recovery magnetic resonance images showing extensive hyperintense parenchymal lesions at bilateral (a) frontal, (b) temporal, (c) parietal, and (d) occipital lobes, as well as the right thalamus. The lesion extent score was 5.

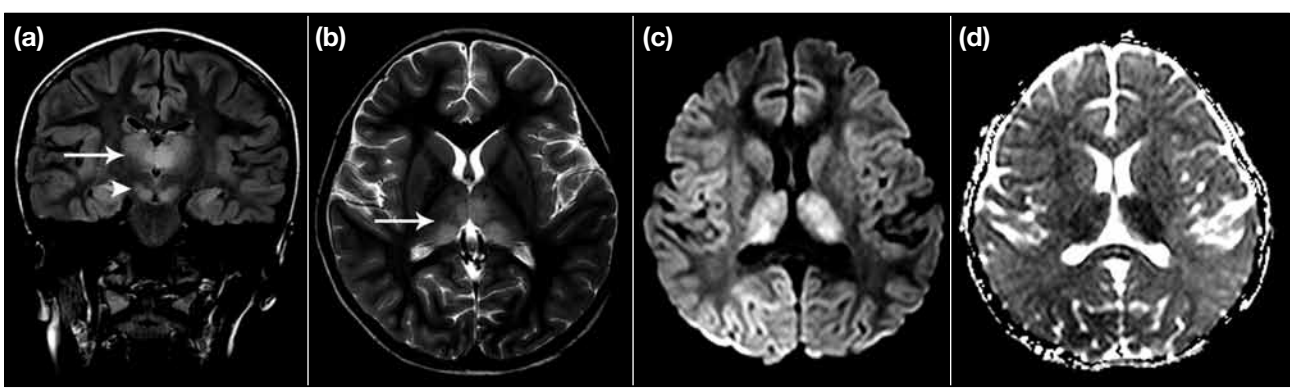


**Figure 2.** Bilateral thalami (arrow) and brainstem (arrowhead) lesions are hyperintense on (a) fluid-attenuated inversion recovery magnetic resonance image, (b) T2-weighted image, and (c) diffusion-weighted image, and are hypointense on (d) apparent diffusion coefficient map, indicative of restricted diffusion. The lesion extent score was 3.

male and 19 female patients aged 2 months to 17 years (mean, 8.8 years; median, 8 years) were included. The mean time from admission to MRI was 7 days (median, 4 days; range, 1-40 days); only two patients underwent MRI after 3 weeks.

The aetiology of encephalitis in 17 patients was unknown. In 12 patients, the aetiology was infection or infection-associated; the infectious agents identified were enterovirus (n = 3), influenza A virus (n = 2), influenza B virus (n = 3), Japanese encephalitis virus (n = 2), mycoplasma (n = 1), and norovirus (n = 1). In five patients, the aetiology was immune-mediated or autoantibody-associated; the diagnosis was acute disseminated encephalomyelitis (n = 3) or anti–N-methyl-D-aspartate receptor encephalitis (n = 2).

At 1 year, 24 patients achieved a good outcome with no neurological sequelae (PCPCS score of 1), six patients had mild to moderate (n = 4) or severe (n = 2) residual neurological deficits (PCPCS score of 2 to 5), and four patients died (PCPCS score of 6). All patients with an adverse outcome had T2-weighted/FLAIR hyperintense parenchymal lesions (Table 1). Half of the surviving patients had more than one type of neurological impairment.

Of 34 patients, 14 had no parenchymal abnormality and all had good neurological outcome, and 20 had T2-weighted/FLAIR hyperintense parenchymal lesions at the cortex (n = 17), basal ganglia and/or thalami (n = 12), brainstem (n = 7), and/or cerebellum (n = 6). In a logistic regression analysis, adverse neurological outcome was associated with involvement of the basal ganglia and/or thalami (odds ratio [OR] = 12.7, 95% confidence interval [CI] = 2.3-70.0; p = 0.004) and involvement of brainstem (OR = 8.8, 95% CI = 1.34-57.0; p = 0.023) [Table 2].

The lesion extent score was 0 in 14 patients, 1 to 3 in five patients, 4 to 6 in 13 patients, and 7 to 9 in two patients. The lesion extent score was moderately correlated with the PCPCS score ($r^2$ = 0.35; p = 0.01) [Figure 3].

Restricted diffusion was present in 10 patients and absent in 24 patients. In a logistic regression analysis, restricted diffusion was a predictor of adverse neurological outcome (OR = 5.7, 95% CI = 1.15-28.3; p = 0.033) [Table 2].

## DISCUSSION

Acute encephalitis is uncommon, with an incidence of 10.5 to 13.8 per 100,000 children.[11] It can cause severe morbidity and mortality. Clinical prognosticators such as rapid clinical deterioration, lower Glasgow

**Table 1.** Characteristics and clinical details of the 10 patients with adverse neurological outcomes.

| Sex / Age, y | Aetiology | No. of days from admission to scan | Lesion location | Restricted diffusion | Pediatric Cerebral Performance Category Scale score | Outcome |
|---|---|---|---|---|---|---|
| M / 1 | Norovirus | 3 | Cortex, basal ganglia and/or thalami, cerebellum | Present | 4 | Global developmental delay |
| F / 4 | Unknown | 2 | Cortex, basal ganglia and/or thalami | Present | 6 | Death |
| F / 5 | Influenza B | 1 | Cortex, basal ganglia and/or thalami, cerebellum, brainstem | Absent | 6 | Death |
| M / 6 | Unknown | 1 | Cerebellum | Absent | 3 | Motor impairment, ataxia |
| F / 6 | Unknown | 11 | Cortex, cerebellum | Absent | 6 | Death |
| M / 7 | Influenza A | 2 | Cortex, basal ganglia and/or thalami, brainstem | Absent | 6 | Death |
| F / 7 | Japanese encephalitis | 1 | Basal ganglia and/or thalami, brainstem | Present | 4 | Dystonic quadriplegia, oropharyngeal dysphagia, language impairment |
| M / 10 | Japanese encephalitis | 4 | Cortex, basal ganglia and/or thalami, brainstem | Present | 2 | Motor impairment, memory impairment |
| M / 13 | Unknown | 2 | Cortex, basal ganglia and/or thalami | Present | 2 | Memory impairment |
| F / 14 | Anti–N-methyl-D-aspartate receptor encephalitis | 7 | Cortex | Present | 2 | Memory impairment |

**Table 2.** Results of logistic regression analysis of association between imaging variables and adverse neurological outcome.

| Imaging variable | Odds ratio (95% confidence interval) | p Value |
|---|---|---|
| Restricted diffusion* | 5.70 (1.15-28.33) | 0.033 |
| Lesion location† | | |
| Cortex | 4.15 (0.86-19.92) | 0.076 |
| Basal ganglia and/or thalami | 12.67 (2.29-70.02) | 0.004 |
| Cerebellum | 1.79 (0.90-40.15) | 0.065 |
| Brainstem | 8.75 (1.34-57.01) | 0.023 |

* Reference group: No restricted diffusion
† Reference group: No lesion at each location

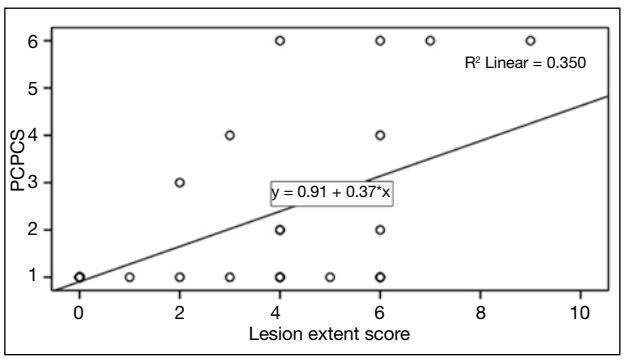


**Figure 3.** Scatterplot showing moderate correlation between lesion extent score and Paediatric Cerebral Performance Category Scale (PCPCS) score.

Coma Scale score, and intensive care unit admission have been reported to be associated with adverse neurological sequelae and death.[1,12,13] The association between neuroimaging findings and clinical outcome is less clear. The clinical endpoint at 1 year after the acute episode was chosen, as patients may experience improvement or deterioration after hospital discharge. Those who made a full recovery did so within 6 to 12 months.[13,14] The mortality (12%) and morbidity (18%) rates of our cohort are comparable to those of another study.[15] Restricted diffusion was a strong predictor of unfavourable neurological outcome, consistent with another study.[4]

The histopathological basis of restricted diffusion in encephalitis remains unclear owing to the difficulty of radio-pathological correlation.[4] Restricted diffusion indicates cytotoxic oedema, which is a premorbid cellular process that usually leads to cell death.[16,17] Viral invasion of the brain is postulated to cause acute pathological changes including congestion, perivascular cuffing, and thrombus formation, and lead to ischaemia and cytotoxic oedema.[18-20] In infants with herpes simplex type 2 encephalitis, many lesions with restricted diffusion progress to necrosis and cystic encephalomalacia.[21] Patients with incomplete neurological recovery have localised brain-tissue loss and residual T2-hyperintense lesions indicating tissue destruction.[22,23] Thus, patients with restricted diffusion are more likely to have poor neurological outcomes, as cytotoxic oedema causes irreversible brain-tissue destruction.

In our study, lesion extent was moderately correlated with neurological outcome. Worsening clinical outcome is associated with increasing lesion severity and extent in acute necrotising encephalopathy.[6] In children with infection-associated acute encephalopathy, diffuse lesions are associated with poor outcome.[7] More extensive brain lesions may reflect a widespread disease process and underlying systemic dysfunction that contribute to an increased morbidity and mortality.

We also found that adverse neurological outcome was associated with involvement of deep grey matter and the brainstem but not with involvement of the cortex or cerebellum; the extent of lesions was associated with severity of adverse outcome. These associations may be because involvement of the deep grey matter and brainstem had more impact on clinical outcome than other areas of the brain, and patients with involvement of such areas tended to have more extensive parenchymal lesions overall. In children with acute measles encephalitis, those with involvement of grey matter in addition to white matter have the worst outcome in terms of severity and duration of illness.[24] In children with acute necrotising encephalitis, extensive and marked T2-weighted hyperintense signal changes in the brainstem with restricted diffusion or haemorrhage are associated with mortality.[25] Extensive damage in the medulla and pons is a sign of profound progression of disease, as severe brainstem dysfunction may lead to neurogenic oedema, respiratory insufficiency, cardiopulmonary collapse, and mortality.[25] Nonetheless, the lack of association between cerebellar lesions and adverse neurological outcome may indicate that MRI has no prognostic value in acute cerebellitis.[26] Further studies are needed to elucidate the patterns of association.

One limitation in our study was the small sample size (owing to the low incidence of the disease) and lack of subgroup analysis. The study was also retrospective, and the time from admission to MRI varied. Restricted

diffusion is more pronounced during the early stages of encephalitis and decreases after 3 weeks; T2-weighted imaging becomes the more sensitive sequence for lesion detection.[19,20] Nonetheless, as only two patients underwent MRI after 3 weeks, heterogeneity in time to MRI would not have had a great impact on the overall results. In addition, a 3-T or 1.5-T scanner was used; regional variations in signal intensities within the cerebral cortices on diffusion-weighted imaging may be accentuated on a 3-T scanner.[27] Still, such differences are unlikely to have been large enough for an observer to miss a lesion.

## CONCLUSION

In children with acute encephalitis who have undergone MRI examination, restricted diffusion and involvement of the deep grey nuclei and brainstem are predictive of adverse neurological outcome. Patients with a greater extent of lesions tend to have worse neurological outcomes.

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