Viral Encephalitis in Children: Detection with Technetium-99m HMPAO Brain Single-Photon Emission CT and Its Value in Prediction of Outcome

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PURPOSE: To assess the role of regional cerebral blood flow measured by technetium-99m hexamethyl propyleneamine oxime (HMPAO) brain single-photon emission CT (SPECT) in viral encephalitis of children. **METHODS:** Eighteen children diagnosed as having viral encephalitis (12 Epstein-Barr virus, 4 herpes simplex virus, and 2 Japanese B virus) underwent Tc-99m HMPAO brain SPECT and brain MR and/or CT. **RESULTS:** During the acute episode, 4 (22%) of the 18 patients had localized abnormality on brain MR and/or CT. Tc-99m HMPAO brain SPECT in the acute phase showed that 17 (94%) of the 18 patients had increased regional cerebral blood flow and 1 (6%) of the 18 children had a normal brain SPECT. Follow-up brain SPECT was performed at least 15 days after the acute episode. In 17 patients with abnormal first brain SPECT, 12 (71%) had normal second brain SPECT and 5 (29%) had decreased regional cerebral blood flow. The group of patients with normal regional cerebral blood flow on the follow-up brain SPECT had a better outcome than the group of patients with decreased regional cerebral blood flow. **CONCLUSIONS:** (*a*) The Tc-99m HMPAO brain SPECT was abnormal more often than CT or MR in children with acute viral encephalitis and provided better location. (*b*) In acute episodes of encephalitis, most patients showed locally increased regional cerebral blood flow. (*c*) After acute episodes, the regional cerebral blood flow returned to normal in most cases. (*d*) A normal Tc-99m HMPAO brain SPECT in the subacute phase usually indicates a good clinical outcome (no neurologic defect) 1 year after the acute illness in children with viral encephalitis.

Index terms: Encephalitis; Viruses; Single-photon emission computed tomography (SPECT); Cerebral blood flow; Pediatric neuroradiology

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Technetium-99m hexamethyl propyleneamine oxime (HMPAO) brain single-photon emission computed tomography (SPECT) has been shown to improve the sensitivity and accuracy of cerebral imaging in cases of epilepsy, dementia, and stroke (1–3). Early in the course of viral encephalitis, CT images are usually normal (4). During the first 2 or 3 days of symptomatic illness, early diagnosis and therapy are essential if high mortality and serious neurologic sequelae are to be avoided (5, 6). In this report, we present our experience with changes in regional cerebral blood flow as a predictor of outcome of viral encephalitis in children assessed with Tc-99m HMPAO brain SPECT.

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Materials and Methods

Eighteen children (10 girls, 8 boys, 8.8 ± 5.0 years of age) who were diagnosed as having viral encephalitis based on typical clinical symptoms and signs, serologic results, and electroencephalograms were included in our study. Twelve had Epstein-Barr virus, 4 had herpes simplex virus, and 2 had Japanese B virus encephalitis. All patients had Tc-99m HMPAO brain SPECT and magnetic

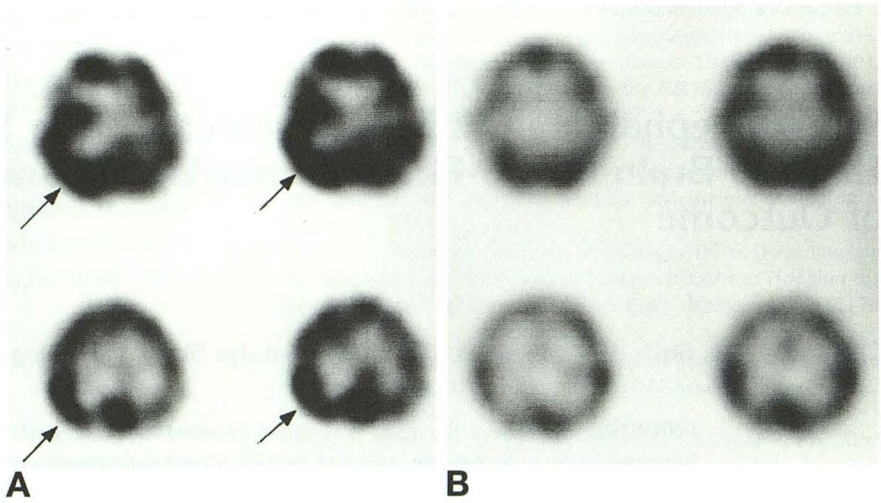

Fig 1. Case 15, 9-year-old girl with Epstein-Barr virus encephalitis.

A, The first HMPAO brain SPECT revealed increased regional cerebral blood flow in the right temporooccipital areas (*arrows*) during the acute episode.

B, Regional cerebral blood flow was normal on follow-up 15 days later. The patient had a good outcome.

resonance (MR) and/or CT. The diagnosis of encephalitis was based on; (*a*) typical clinical findings and the course of the disease, (*b*) at least a fourfold increase of cerebrospinal fluid virus titers in successive cerebrospinal fluid specimens or a persistently high cerebrospinal fluid antibody level, (*c*) an electroencephalogram showing focal sharp and slow-wave complexes in the affected cortex during the early phase of the encephalitis, and (*d*) exclusion of other central nervous system disease.

Tc-99m HMPAO brain SPECT scanning to evaluate regional cerebral blood flow was performed 10 minutes after an intravenous injection of 370 MBq of Tc-99m HMPAO. The Tc-99m HMPAO was prepared from a freeze-dried kit (Ceretec, Amersham International, Amersham, United Kingdom) by adding 1110 MBq of freshly eluted Tc-99m pertechnetate to 5 ml of a saline solution. The injection was made within 30 minutes after kit preparation. Quality-control procedures were performed with thin-layer chromatography using three different solvent systems.

Patients were positioned supine on the imaging table with their foreheads and chins strapped to prevent motion. Scanning equipment consisted of a rotating, large field-of-view gamma camera fitted with a low-energy and high-resolution collimator. Sixty images were acquired for 10 seconds each, during a 360° camera rotation. Each image was stored in a 64 × 64-pixel matrix. Reconstruction of the image was performed with attenuation correction, using Hanning filters to produce transaxial sections. These were reoriented parallel to the base of the brain, and sagittal and coronal reconstructions were then obtained.

Postcontrast brain CT was performed in 9 cases. Brain MR with gadopentetate dimeglumine was done in 12 cases with a 1-T scanner with a spin-echo T1-weighted sequence of 500–700/20/2 (repetition time/echo time/excitations) and a T2-weighted sequence of 2800-3000/80-100/1. The section thickness was 5 to 7 mm with an intersection gap of 1 mm.

For analysis of the changes in regional cerebral blood flow on the SPECT studies, regions of interest were drawn on the suspected lesions and on the corresponding regions of the contralateral hemispheres. If bilateral disease was suspected, another region of interest was drawn on the cerebellum of the same transaxial sections. Images were classified as abnormal if a region of cortical activity had a larger or less than 30% difference in counts from the contralateral hemisphere or cerebellum. The transaxial images were interpreted by two experienced nuclear medicine physicians unfamiliar with the clinical information.

Two experienced radiologists interpreted the brain CT and MR scans. The criteria for diagnosing encephalitis on CT scans included the presence of a high-density lesion consistent with a small infarction or hemorrhage, patchy peripheral gyral enhancement, or other lesions such as low density of brain edema. The diagnosis on MR scans was based on the presence of increased signal intensity caused by brain edema on T2-weighted images.

Results

During the acute episodes, 4 (22%) of the 18 cases had localized abnormalities on brain MR or CT. Seventeen (94%) of the 18 cases had increased regional cerebral blood flow on Tc-99m HMPAO brain SPECT examination. One (6%) of the 18 cases had a normal brain SPECT. Follow-up brain SPECT was done at least 15 days after the acute episodes. In the 17 patients with abnormal first SPECT, 12 (71%) returned to normal on the second examination (Fig 1), and 5 (29%) had decreased regional cerebral blood flow (Fig 2). The group of cases with normal regional cerebral blood flow on the follow-up SPECT scans had a better outcome (no neurologic defects) than the cases with decreased regional cerebral blood flow (learning disability or decreased intelligence) (10 [83%] of 12 cases versus 0 [0%] of 5 cases; $P < .05$ by a χ^2 test) (Table).

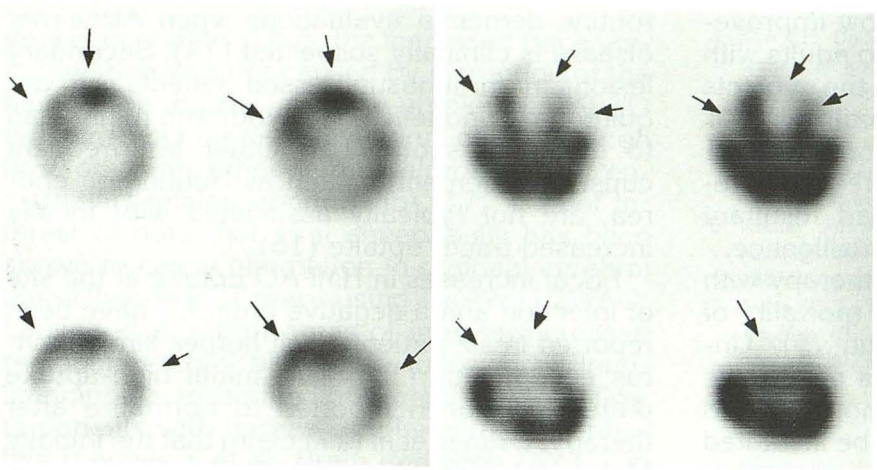

Fig 2. Case 16, 1-year-old girl with herpes simplex virus encephalitis.

A, HMPAO brain SPECT revealed increased regional cerebral blood flow in both frontoparietal areas (*arrows*) during the acute episode.

B, Twenty days after the acute episode, the SPECT showed decreased regional blood flow in those areas (*arrows*). The patient had a poor outcome.

Discussion

Viruses producing a nonpurulent meningitis syndrome also may produce severe encephalitis (7). The clinical picture of childhood encephalitis is nonspecific (7). The onset of symptoms may be abrupt or gradual, and initial complaints may include fever, headache, vomiting, and lethargy (7). However, nuchal rigidity and photophobia may be present, depending on the degree of associated meningeal inflammation (7). Alternatively, the onset may be subtle, manifested only by changes in behavior and sleep. As the disease progresses, children can develop irritability, disorientation, stupor, and, finally, coma. Focal neurologic signs include aphasia, hemiparesis, hemiplegia, ataxia, and cranial nerve palsies. Alteration in the state of consciousness, seizures, and focal neurologic signs indicate involvement of the brain parenchyma (7). Even desperately ill patients may recover completely. The mortality rate varies with the causes, and epidemics with the same virus vary in severity in different years. Permanent cerebral disorders are more likely to occur in infants,

Imaging and outcomes of 18 children with viral encephalitis

Case	Age, y	Sex	Virus	Regional Cerebral Blood Flow on the First SPECT Examination	Brain CT during the Acute Phase	Brain MR during the Acute Phase	Regional Cerebral Blood Flow on the Second SPECT Examination	Outcomes
1	6	M	EBV	I:B-F-P-T		N	N	Good
2	11	F	JBV	I:L-T-O	N		N	Good
3	12	M	EBV	I:R-T	N	N	N	Good
4	5	F	EBV	I:B-P		N	D:B-P	Poor
5	13	F	EBV	I:R-F-P;L-F		N	N	Good
6	11	M	EBV	I:B-F-P	N		N	Poor
7	14	M	EBV	I:B-P		A:B-P	N	Poor
8	17	F	JBV	I:R-F-P	N		N	Good
9	5	F	EBV	I:R-T-O	N		N	Good
10	3	F	EBV	I:L-T		N	N	Good
11	18	M	HSV	I:R-P-T	N		D:L-P-T	Poor
12	1	M	HSV	I:B-F;R-P-T	N	N	N	Good
13	4	F	EBV	I:L-F-P		A:L-F-P	D:L-F-P	Poor
14	6	F	EBV	N	N		N	Good
15	9	F	EBV	I:R-T-O		N	N	Good
16	1	F	HSV	I:B-F-P		A:B-F-P	D:B-F-P	Poor
17	13	M	EBV	I:B-F		A:B-F	N	Good
18	11	M	EBV	I:B-F	N	N	D:B-F	Poor

Note.—EBV indicates Epstein-Barr virus; JBV, Japanese B virus; HSV, herpes simplex virus; N, normal; A, abnormal; D, decreased; I, increased; L, left; R, right; B, bilateral; F, frontal area; P, parietal area; T, temporal area; and O, occipital area.

but young children continue to show improvement during a longer period than do adults with similar infections (8). In our study, the subjects with normal follow-up HMPAO brain SPECT scans had a better neurologic outcomes after 1 year than did the patients with decreased cerebral perfusion, many of whom had resultant learning disabilities or decreased intelligence.

Early diagnosis and initiation of therapy with acyclovir is essential, because the mortality of untreated viral encephalitis is high (5). Untreated survivors often have serious neurologic sequelae. Treatment can reduce mortality and the incidence of sequelae but must be instituted before the onset of coma (6).

The clinical picture alone may be misleading. Even brain biopsy, the most accurate method for demonstrating the presence of viral encephalitis, may give a false-negative result (9). For reasonable diagnostic accuracy in the early stage of viral encephalitis, it has been necessary to use a combination of clinical, laboratory, electroencephalographic, CT, MR, and brain scintigraphic data, as well as brain biopsy when available (10, 11).

In our study, the electroencephalograms in some patients showed localized slow cortical activity. This may have reflected focal motor seizure in these patients. More widespread slow cortical activity was found in others. Electroencephalographic abnormalities generally reflected the anatomic localization found on the brain MR or CT. In patients with localized abnormalities on Tc-99m HMPAO brain SPECT there was good agreement with the clinical, electroencephalographic, CT, or MR findings. However, early in the course of the disease, at a time when CT scanning may be negative, the HMPAO brain SPECT was often positive.

In our study, 17 (94%) of the 18 cases demonstrated increased regional cerebral blood flow. However, a "hot spot" on a SPECT brain regional cerebral blood flow scintigram does not lead to a specific diagnosis but suggests that a number of pathologic processes should be considered. SPECT might display areas of malignancy with abnormally high uptake of tracer (12). Seizure activity is another important cause for an unusually high focal uptake of tracer in the brain. Seizure foci have elevated metabolic rates and high blood flow during the ictal phase and accumulate high amounts of HMPAO at the time (13). A focal area of markedly elevated uptake of HMPAO is unusual in routine dementia evaluations when Alzheimer disease is clinically suspected (14). Secondary lesions in immunosuppressed patients with acquired immunodeficiency syndrome might lead to focal hot spots (15). Other less-frequent causes for dementia, such as Huntington chorea, are not typically associated with focally increased tracer uptake (16).

Focal increases in HMPAO uptake at the site of infection and a negative brain CT have been reported in six patients with herpes simplex virus encephalitis (17). This initial high-uptake pattern has been reported to normalize after therapy. Launes et al (17) claim that the initially high uptake pattern is specific for herpes simplex virus encephalitis, yet a case report by Duncan et al (18) demonstrated that increased uptake also can be seen in nonherpes encephalitis, and decreased uptake has been noted in a patient with acute herpes simplex virus encephalitis (19). A recent study by Lane et al (20) demonstrated both MR and SPECT to be superior to CT in the diagnosis of encephalitis. These findings resembled ours except in one patient of theirs who had herpes simplex virus encephalitis with focally elevated HMPAO uptake in the left temporal lobe 53 days after onset of the illness.

Among 540 SPECT brain studies done in Finland (17), focal unilateral increased regional cerebral blood flow of this magnitude has been noted in association with early herpes encephalitis but was absent in nonherpes encephalitis with focal neurologic symptoms or focal electroencephalographic abnormalities early in the illness. However, the results are not similar to our study. Seventeen (94%) of our 18 cases included herpes simplex virus, Epstein-Barr virus, and Japanese B virus encephalitis with increased regional cerebral blood flow in the initial brain SPECT scans. Increased regional cerebral blood flow has been described in the ictal phase of focal epilepsy (21) and in the luxury perfusion phase of stroke (22), but in the report of Launes et al, the magnitude and duration of increased regional cerebral blood flow in these two conditions has been considerably less than that seen in herpes simplex virus encephalitis.

A review of the literature reveals that conventional brain scintigraphy on some patients with herpes simplex virus encephalitis may be negative, while SPECT showed increased tracer accumulation (17), during the acute episode of

viral encephalitis. Thus, the increased tracer accumulation was not caused by disruption of the blood-brain barrier, and the uptake of HMPAO reflects either increased regional cerebral blood flow or some other herpes simplex virus encephalitis-related abnormality (17). It is of interest to note that viral encephalitis has been shown to cause alternation in regional cerebral blood flow SPECT maps using Tc-99m HMPAO. Launes et al report areas of intense increased regional cerebral blood flow followed by longstanding decreased regional cerebral blood flow in patients with herpes simplex virus encephalitis (Launes Y et al, Brain Perfusion SPECT in Patients with Herpes Simplex Virus [HSV] and non-HSV Encephalitis, abstract Presented at the International Isotope Symposium, Badgastein, 1988). The decreased accumulation at a later stage probably represents true decreased regional cerebral blood flow, because neuronal death results in decreased metabolism and thus a fall in regional cerebral blood flow. In our study, 5 (28%) of the 18 cases demonstrated decreased regional cerebral blood flow on the follow-up scans. This finding may suggest severe damage to the brain caused by viral encephalitis. This could explain the observation that patients with decreased regional cerebral blood flow had poor outcomes (5 [100%] of 5 cases).

Our conclusions suggest that: (*a*) the Tc-99m HMPAO brain SPECT tends to be abnormal in children with acute viral encephalitis and is better at detection of the disease than are CT or MR; (*b*) in acute episodes of encephalitis, most cases showed locally increased regional cerebral blood flow; (*c*) after acute episodes, the regional cerebral blood flow returned to normal in most cases by day 15; and (*d*) patients with decreased regional cerebral blood flow on Tc-99m HMPAO brain SPECT 15 days after an episode of acute viral encephalitis seem to have greater likelihoods of poor neurologic outcomes than do patients whose SPECT examinations are normal at that time.

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