DIAGNOSIS OF ACUTE HERPES SIMPLEX ENCEPHALITIS BY BRAIN PERFUSION SINGLE PROTON EMISSION COMPUTED TOMOGRAPHY

JYRKI LAUNES[1] PÄIVI NIKKINEN[2]
LENA LINDROTH[2] ANNA-LIISA BROWNELL[2]
MATTI IIVANAINEN[1]

Department of Neurology,[1] and Central Laboratory Division of Nuclear Medicine,[2] Helsinki University Central Hospital, 00290 Helsinki, Finland

Summary Brain perfusion was studied in 14 patients with acute encephalitis by use of ^{123}I-iodoamphetamine or ^{99m}Tc-hexamethylpropyleneamine oxime and single photon emission computed tomography (SPECT), the first examination being made 4–11 days after onset of encephalitis symptoms. All 6 patients with herpes simplex virus encephalitis (HSVE) had strongly increased accumulation of radiotracer in the affected temporal lobe; in the remaining 8 results were normal. At the time of the first SPECT conventional CT images were normal in all patients. The SPECT abnormality in HSVE gradually converted over 4–10 weeks from increased tracer accumulation to greatly subnormal accumulation. Brain perfusion SPECT may be helpful in the early diagnosis of HSVE.

Introduction

CLINICAL symptoms and signs indicating temporal lobe dysfunction and viral infection are suggestive of herpes simplex virus encephalitis (HSVE).[1] However, the clinical picture alone may be misleading, and about 1 in 2 patients with suspected HSVE have some other disease.[1-4] Even brain biopsy, the most accurate method for demonstrating the presence of HSV,[1,2,5,6] may give a falsely negative result.[7] For reasonable diagnostic accuracy in the early stage of HSVE it has been necessary to use a combination of clinical, laboratory, electroencephalographic, computed tomographic, magnetic resonance, and brain scintigraphic data, as well as brain biopsy where available.[1,6,8,9] Because treatment of HSVE is most effective when started early, a sensitive and specific method for early diagnosis would be of great benefit. We have assessed the potential of brain perfusion scintigraphy using single photon emission computed tomography (SPECT).

Patients and Methods

We examined 14 patients with viral encephalitis, referred to the Department of Neurology, Helsinki University Central Hospital, using either ^{123}I-iodoamphetamine (IMP) or ^{99m}Tc-hexamethylpropyleneamine oxime (HM-PAO) and SPECT. The interval between first symptoms of encephalitis and the first SPECT varied from 4 to 11 days (mean 8·5 days in the HSVE group and 7·5 days in the non-HSVE group). Altogether 17 SPECTs were performed on 6 patients with HSVE and 10 SPECTs on 8 patients with non-HSVE. All patients received acyclovir (30 mg/kg per day).

Computed tomography (CT), electroencephalography (EEG), and tests on lumbar cerebrospinal fluid (CSF) were done on all patients during the first 2 days in hospital. Patients also had follow-up CT, CSF and serum were examined for HSV antibody; and microbial pathogens were sought by staining and culture of CSF. Blood tests were done for other infections and possible underlying systemic diseases.

Viral encephalitis was diagnosed if the patient had an abrupt or subacute onset of clinical signs and symptoms characteristic of encephalitis, EEG findings suggesting encephalitis, and CSF findings indicating central nervous system infection, bacterial and systemic diseases having been excluded. The conclusion that the diagnosis was specifically HSVE was based on (1) typical clinical findings and course of disease, (2) at least a fourfold increase of CSF HSV antibody titres in successive CSF specimens or a constantly very high CSF antibody level 10 (case 1 in table I), (3) an EEG showing focal sharp and slow wave complexes in the affected temporal lobe during the early phase of the encephalitis, and (4) exclusion of other CNS diseases. Tables I and II summarise the clinical and CT findings and the outcome of the disease.

SPECT imaging was done with a General Electric 400T large [illegible] camera equipped with a low-energy 64 frames with 1 frame per 30 s was used. Only one type of tracer was used in studies on a single patient. For analysis of side-to-side differences regions of interest (ROI) were drawn on 42 predefined sites on 6 tomographic slices of each study. Scaling was done by dividing mean counts/pixel per min (CPM) from each ROI with the mean CPM rate of all other ROIs.

CT scans were performed with General Electric 8080 or Siemens Somatom 2 scanners and contrast enhancement.

Results

All 6 patients with HSVE had a distinct area of increased tracer accumulation in the affected temporal lobe (figs 1A, 2A) in the first SPECT study. The hyperperfusion increased in 2 patients (case 2, fig 2A, B and case 3) between 4 and 13 days after first symptoms of encephalitis. The initial hyperperfusion was followed by progressive hypoperfusion (fig 1B, C, D and fig 2C) in the corresponding area. Hypoperfusion was seen at the earliest 37 days (case 4) and at the latest 165 days (case 1) after the first symptoms of HSVE.

None of the patients with non-HSV encephalitis had focal hyperperfusion during the first two weeks after initial symptoms of disease and no progression to hypoperfusion was seen in the two patients followed up (fig 3).

The initial CT scans were normal in all patients (table I). Conventional brain scintigraphy was done on 2 patients with HSVE and 1 with non-HSV encephalitis. The scintigrams were normal in both patients with HSVE (cases 1 and 3) during the period when SPECT showed hyperperfusion. In the patient with non-HSV encephalitis (case 8) both SPECT and scintigraphy results were normal.

Discussion

Among the 540 SPECT brain studies done in our laboratory to date, focal unilateral hyperperfusion of this magnitude has been noted only in association with early HSVE. The phenomenon was absent even in non-HSVE patients with focal neurological symptoms or focal EEG abnormalities early in the illness. Regional hyperperfusion has been described in the ictal phase of focal epilepsy[11] and the luxury perfusion phase of stroke,[12,13] but in our experience the magnitude and duration of hyperperfusion in these two conditions have been considerably less than in HSVE. Thus our experience indicates that the finding is specific.

Accumulation of HM-PAO and IMP reflects brain blood flow,[14,15] but we do not know whether this is the sole mechanism for increased tracer accumulation in HSVE. It could be due also to inflammation or other pathological mechanisms that may expose binding sites to lipophilic blood flow tracers. Nonetheless, coupled with previous angiographic data[16] our findings lead us to the view that the cause is mostly hyperperfusion. The decreased accumulation at a later stage probably represents true hypoperfusion, since neuronal death results in decreased metabolism and thus a fall in regional blood flow. Conventional brain scintigraphy on 2 patients with HSVE was negative, while at the same time SPECT showed increased tracer accumulation. Thus, the increased tracer accumulation was not due to disruption of the blood-brain barrier, and the uptake of IMP or HM-PAO reflects either hyperperfusion or some other HSVE-related abnormality.

Without treatment HSVE is fatal in more than 70% of cases and causes severe neurological impairment in about 90% of the survivors.[17] Treatment with acyclovir greatly improves the outcome[1] and this drug, lacking serious side-effects, should be started as soon as HSVE is suspected. However, about 46% of patients with suspected HSVE have other potentially curable diseases, the diagnosis of which may require brain biopsy.[6] HM-PAO and IMP SPECT both seem to be helpful in differentiating HSVE from other HSVE-like diseases. Therefore, when available, either IMP or HM-PAO SPECT is recommended as an early investigation for patients with suspected HSVE. However, we cannot at present recommend discontinuation of acyclovir when SPECT does not reveal any focal abnormalities.

Correspondence should be addressed to J.L., Department of Neurology, Helsinki University General Hospital, Haartmaninkatu 4, 00290, Helsinki, Finland.

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Fig 1—SPECT in HSVE case 1 examined with IMP.

A. An intensely hyperperfused area is seen in the right temporal lobe 8 days after onset of encephalitis. B. The intensity of the hyperperfusion has decreased, but is still very prominent 59 days after onset. C. Posterior frontal and temporal hypoperfusion is seen on the affected side, with some normal perfusion in the middle temporal area 165 days after onset. D. The area of hypoperfusion covers right frontal and temporal lobes 232 days after onset.

Fig 2—SPECT in HSVE case 3 examined with HM-PAO.

A. A clearly hyperperfused area in the right anterior and middle temporal lobe 4 days after onset of encephalitis. B. The rate of hyperperfusion has increased and the area covers also the posterior temporal aspects 12 days after onset. C. An area of hypoperfusion is seen 55 days after onset in the corresponding area where initial hyperperfusion was seen.

Fig 3—Percent side-to-side differences of temporal lobes in initial and follow-up SPECT in patients with HSVE and non-HSVE.

First SPECT imaging is represented by a shaded diamond (6/6 in HSVE and 8/8 in non-HSVE) and follow-up examinations (the last, if more than one) by a circle (6/6 in HSVE and 2/8 in non-HSVE group, respectively). Note the remarkable difference between the HSVE and non-HSVE group.

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CSF ab titre constantly 128–256

TABLE I—CLINICAL AND CT FINDINGS OF PATIENTS WITH HSV ENCEPHALITIS

Case	Tracer and day of imaging	Symptoms at onset and CSF serology	CT findings	Outcome
1. F 57 yr	IMP 8	Fever, grand mal, memory disturbances, moderate delirium leading to unconsciousness	CT initially normal leading to right frontotemporal atrophy	Moderate outcome. Moderate cognitive defects and depression with minor neurological symptoms
2. F 63 yr	HM-PAO 4	Fever, left focal seizures, mild left hemiparesis, and a lowered state of consciousness. CSF ab titre 2→8	Initially normal, leading to right temporal atrophy	Moderate cognitive defects and mild left hemiparesis
3. F 54 yr	HM-PAO 4	Fever, nausea, and headache. Left focal seizures, mild left hemiparesis, and progression to unconsciousness. CSF ab 2→16	Initially normal. Later right temporal hypodense lesion with some contrast enhancement	Poor outcome. Mild left hemiparesis, moderate cognitive defects and severe depression
4. F 32 yr	IMP 10	Headache, loss of initiative, and delirium. Generalising focal seizures and progression to unconsciousness. CSF ab titre 2→16.	Initially normal. Follow-up normal (run on)	Poor. Severe cognitive defects. Requires hospital care
5. M 40 yr	IMP 11	Fever, disorientation, lowered state of consciousness, and grand mal. CSF ab titre 4→16	Initially normal, leading to mild right temporal atrophy	Moderate cognitive defects; no focal neurological defects
# 6. F 22 yr	HM-PAO 11	Fever, left temporal homonymous hemianopia, generalising focal seizures, and progression to unconsciousness. CSF ab titre 4→16	Initially normal. Follow-up normal	Poor. Severe cognitive defects

CSF ab titre = CSF antibody titre measured by complement fixation technique.

TABLE II—CLINICAL AND CT FINDINGS OF PATIENTS WITH NON-HSV ENCEPHALITIS

Case	Tracer and day of imaging	Symptoms at onset and diagnosis	CT findings	Outcome
1. M 55 yr	HM-PAO 4	Fever, delirium and dysphasia, meningism, and slight left hemiparesis. Virological aetiology unknown	Initially normal. Follow-up normal	Moderate outcome. Moderate cognitive defects; unble to work
2. F 19 yr	HM-PAO 7	Fever, headache, dysphasia, and right hemiparesis mainly affecting the upper limb. Virological aetiology unknown	Initially normal. Follow-up not done	Good outcome; no cognitive or focal neurological defects
M 3. F 58 yr	HM-PAO 6	Fever, grand mal, disorientation, and left hemiparesis. Virological aetiology unknown	Initially normal. Right posterior temporal lesion with some contrast enhancement in follow-up	Moderate outcome. Mild cognitive defects, but no hemiparesis
4. F 69 yr	HM-PAO 10	Delirium, myoclonic jerks, and muscular hypotonia. Lowered state of consciousness. Virological aetiology unknown	Initially normal. Follow-up normal.	Moderate outcome. Mild cognitive defects
5. M 17 hr	IMP 9	Fever, disorientation and delirium, grand mal, right hemiparesis, and unconsciousness. Rubella virus encephalitis	Initially normal. Follow-up normal	Moderate outcome. Mild cognitive defects; able to continue school (range)
6. F 57 yr	HM-PAO 4	Fever, delirium, and lowered state of consciousness. Virological aetiology unknown.	Initially normal. Follow-up normal	Good outcome. Mild cognitive defects
7. M 18 yr	IMP 9	Fever, delirium, left focal generalising seizures, and left hemiparesis. Adenovirus encephalitis	Initially normal. Diffuse oedema in first follow-up. (run on) Third follow-up normal	Good outcome. Minimal cognitive defects
8. M 22 yr	HM-PAO 11	Fever, unconsciousness, and grand mal. Probable mumps encephalitis	Initially normal. Follow-up normal cognitive defects	Good outcome. Minimal (more right)