neuroReport

NeuroReport 6, 1203–1206 (1995)

Hyperfixation of ^{99m}Tc-HMPAO and hypofixation of ^{123}I-iomazenil in acute herpes encephalitis

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We studied two patients with herpes encephalitis (HSE) by [^{99m}Tc]HMPAO and [^{123}I]iomazenil single photon emission computed tomography. Increased uptake of HMPAO was seen for up to 63 days in the HSE affected brain area. Iomazenil binds to benzodiazepine receptors and can measure neurone loss. Decreased iomazenil uptake was observed a few days after onset, at a time when hyperfixation of HMPAO occurred. Because in HSE neurone loss occurs simultaneously with hyperfixation of HMPAO, it is unlikely that this hyperfixation is caused by increased neuronal activity, as in epilepsy. This suggests that the hyperfixation of HMPAO in HSE occurs in glia and is sustained by inflammation-related hypermetabolism and acidity. The early neurone loss in HSE stresses the importance of immediate antiviral treatment.

Key words: Herpes encephalitis; HMPAO; Iomazenil; Single photon emission computed tomography; Fractional fixation

Introduction

Focal hyperfixation of [^{123}I]iodoamphetamine (IMP) and [^{99m}Tc]hexamethylpropyleneamine oxime (HMPAO) in single photon emission computed tomography (SPECT) brain images of patients with herpes simplex encephalitis (HSE) is a valuable diagnostic clue for this disease.[1] Our finding has now been verified by others.[2–5] To date, follow-up SPECT studies with HMPAO have been performed by us in 15 patients with serologically proven HSE. In all cases, except for one patient imaged 2 days after the first symptoms, there was hyperfixation of HMPAO in the diseased brain area; in the single case with initial hypofixation typical hyperfixation of HMPAO was seen 2 days later. However, the pathophysiological mechanism of this phenomenon in HSE is unknown. Initially, we thought that either there is true hyperperfusion or the inflammation exposes binding sites for IMP and HMPAO. The latter idea has been challenged by Cleator and colleagues[6] who found no apparent increase in the uptake of HMPAO in either a rat model of HSE or herpes virus infected vero cells. Recently, serial investigations using [^{18}F]fluorodeoxyglucose (^{18}FDG) and positron emission tomography on a patient suffering from HSE was reported.[7] This study revealed hypermetabolism of glucose during the early course of HSE and hypometabolism at a later stage, findings which are consistent with initial hyperperfusion and subsequent hypoperfusion.

[^{123}I]iomazenil (IMZ) is a recently developed imaging agent for measuring the density of central type benzodiazepine receptors in the human brain.[8,9] These receptors are most abundant in the cerebral cortex and are expressed almost exclusively by cortical neurones.[8] Decreased binding of IMZ apparently reflects neuronal loss. Here we report on IMZ and HMPAO SPECT findings in two HSE cases followed up.

Methods

SPECT scanning was performed with a Picker DDC 4096 square detector gamma camera interfaced with a PDP11/73 computer. Reconstruction of images was performed by filtered back projection using NUD-SPETS software. Doses of 700–970 MBq HMPAO and 215–225 MBq IMZ were used. Imaging was started a few minutes after injection of HMPAO and 4–5 h after injection of IMZ. Early IMZ scans, which reflect the non-specific binding of IMZ were performed in patient 1 30 min following the injection. Transversal and coronal tomographic slices were printed with a thermal transfer colour printer. The lower threshold value was set at 30%. For calculation of the side-to-side differences regions of interest (ROIs) were drawn on the affected brain areas and standardized using the cerebellar lobes as reference areas. Lassen's linearity correction algorithm was used for the HMPAO images.

CT was performed using a Siemens Somatom DR scanner with additional contrast enhancement. Slice thickness was 4 mm in the posterior fossa and 8 mm in the more cranial slices.

MRI was performed using at a 1.0 T Siemens Magnetom unit with a standard head coil. Axial T2-weighted spin-echo (SE) (repetition time (ms)/echo time (ms), TR/TE = 2500/22–90) and T1-weighted (600/15) images were obtained. T2-weighted images

were 5 mm thick with a 1 mm interslice gap and with one excitation. T1-weighted slices were 4 mm thick with a 0.4 mm interslice gap and with two excitations. The field of view was set to 230 mm with an image matrix of 256*256.

Patients

Patient 1 (E.S.) was a previously healthy 56-year-old female. She had had headache, fever and general malaise for five days and was in a delirious state when taken to the hospital. Dysphasia, disorientation, memory disturbance and extensor plantar reflex on the right were observed on neurological examination. There was no meningism. CSF protein content was 1075 mg l^{-1}, glucose concentration 3.7 mmol l^{-1} and leukocyte count 311 × 10^6 l^{-1} (99% mononuclear). Blood and urine chemistry were unremarkable. I.v. acyclovir 750 mg three times daily was started and continued for 10 days. On the same day CT revealed a hypodensity in the left temporal lobe (Fig. 1a) and hyperfixation of HMPAO was seen in SPECT in the corresponding area the next day (Fig. 1b). On that day the patient had a few generalized seizures, which were treated with peroral carbamazepine. Benzodiazepines were not given at any time. EEG revealed lateralized periodical complexes typical of HSE. HMPAO SPECT was repeated 16 days after admission (Fig. 1c) and IMZ SPECT was performed on day 8 after hospitalization (Fig. 1d). The diagnosis of HSE was verified by exclusion of other diseases, a typical course of disease, typical MRI findings on day 6 on the left mesial aspect of the temporal lobe (Fig. 1e), and diagnostic increased antibody titres both in serum and in the CSF. Neuropsychological testing at 21 days disclosed diffuse impairment of reasoning and severe memory defects. In a thorough neuropsychological evaluation 6 months later the patient was still found to have an amnestic memory defect, additional defects in visual and verbal memory, occasional disorientation, anomia, and disturbances in executive functions. The patient was unable to return to work but was independent at home.

Patient 2 (M.L.) was a 57-year-old female with a history of elevated blood pressure and adult type diabetes. Four days prior to hospitalization she had fever, headache, dizziness and vomiting. On hospitalization she was dysphasic, disoriented to time and place but did not have any localizing symptoms or signs on neurological examination. The CSF protein content was normal, but the leukocyte count was elevated: 130 × 10^6 l^{-1} (84% mononuclear). Blood and urine chemistry was unremarkable. I.v. acyclovir 750 mg three times a day was given for 12 days. On the day of admission there was a minimal hypodense area in the left temporal lobe on CT and HMPAO SPECT on day 3 revealed hyperfixation in the left temporal lobe (Fig. 2a). On EEG typical lateralized periodic complexes were seen to the left in addition to a disturbance of the background activity. MRI on day 21 revealed an area with hyperintensive signal extending to the left anterior temporal lobe and insula (Fig. 2b) compatible with HSE. HMPAO SPECT was repeated on days 19 and 40 (Fig. 2c, d). IMZ SPECT was performed on days 6 and 20 (Fig. 2e, f). Benzodiazepines were not given at any time. The diagnosis of HSE was verified by exclusion of other diseases, a typical course of disease,

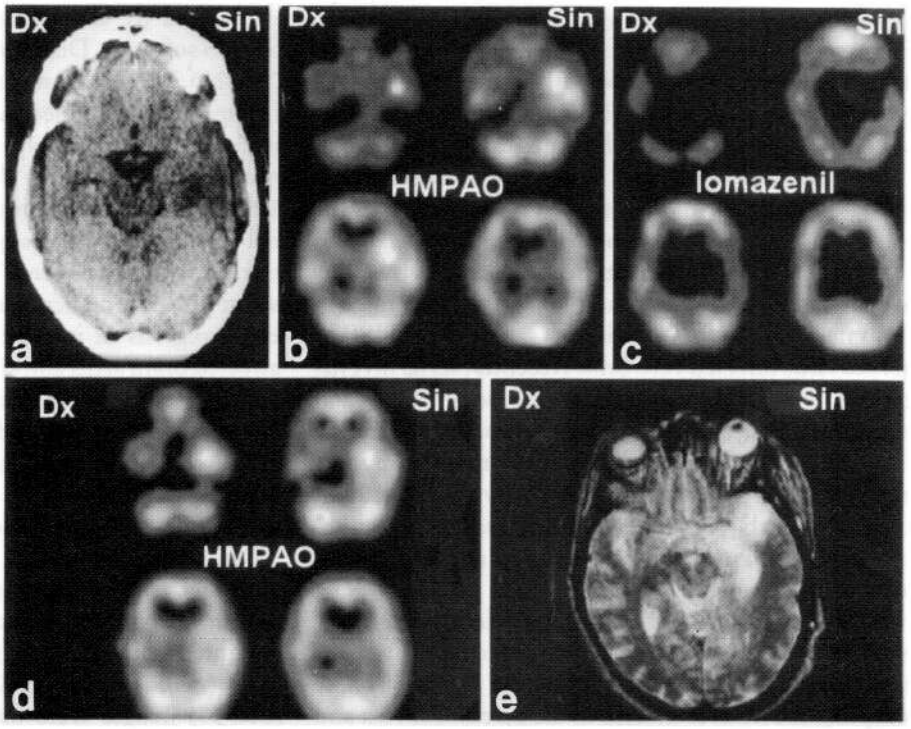

FIG. 1. Patient 1. (**A**) Left temporal hypodensity on CT on day of admission. (**B**) Hyperfixation of HMPAO in the corresponding region the day after admission. There is a 21% side-to-side difference in the temporal areas. The patient had periodical lateralized complexes on EEG and a few seizures. (**C**) [^{123}I]iomazenil SPECT on day 8 after admission. Hypofixation of the tracer can be seen on the left as an indicator of neuronal loss. (**D**) Follow-up ^{99m}Tc-HMPAO SPECT on day 16 after hospitalization. Note the continuing hyperfixation of ^{99m}Tc-HMPAO in the left temporal lobe. Periodic complexes were not seen at this time and the patient no longer had seizures. (**E**) 1.0 T T2 weighted MRI on day 6 showing hyperintense signal on the left temporal lobe, mainly on the mesial aspect. Note, that the most intense hyperfixation of ^{99m}Tc-HMPAO is also located in the mesial temporal lobe.

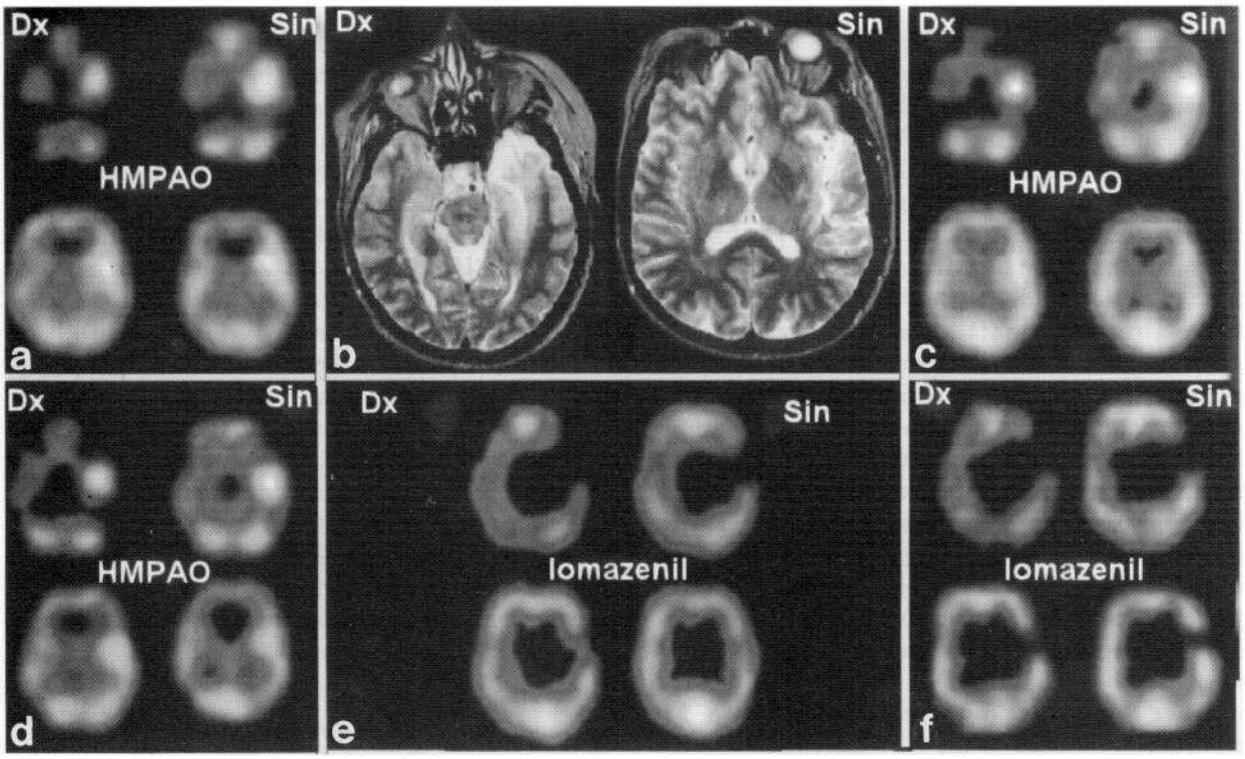

FIG. 2. Patient 2. (**A**) Hyperfixation of ^{99m}Tc-HMPAO on the left temporal lobe on day 3 after admission. There is a 26% side-to-side difference in the temporal areas. At this time the patient had periodical lateralized complexes on EEG, but no seizures. (**B**) 1.0 T T2-weighted MRI demonstrating typical increased signal intensity for HSE on the left anterior temporal lobe extending to insula. (**C, D**) Follow-up [^{99m}Tc]HMPAO SPECT on days 19 and 40 demonstrating the continuing hyperfixation of [^{99m}Tc]HMPAO in the left temporal lobe. There is a side-to-side difference of 26% and 25%, respectively. Although the hyperfixation remained almost unchangeable, the patient improved markedly and the periodical complexes had vanished. (**E, F**) [^{123}I]iomazenil SPECT scans performed on days 7 and 20 after admission demonstrating worsening neuronal loss on the left temporal lobe. In the first scan there is a 32% and in the second a 44% side-to-side difference in the temporal areas.

typical MRI findings (Fig. 2b), and diagnostic HSV antibody titre increases both in serum and in the CSF, and a pathological CSF/serum HSV antibody ratio (16/64). Neuropsychological examination at day 31 revealed dysphasia, diffuse disturbance of memory functions, orientation, and reasoning. A detailed neuropsychological evaluation 4 months later disclosed only mild disturbances in verbal reasoning and memory, and very mild dysphasic features. The patient could not continue to work, but was independent.

Results

In both patients studied, hyperfixation of HMPAO in the affected region was encountered in the acute phase of HSE. The hyperfixation was apparent still on days 63 and 40 in cases 1 and 2, respectively, although clinical improvement was remarkable during the first 2 weeks in both cases. The side-to-side differences in HMPAO SPECT in favour of the diseased side were 21% (day 1), and 28% (day 16) in patient 1 and 26% (day 3), 26% (day 19), and 25% (day 40) in patient 2.

In both patients IMZ SPECT scans performed 4–5 h after injection revealed an area of hypofixation with a side-to-side difference of 25% (patient 1) and 32% (patient 2) in the early phase (days 8 and 6, respectively) on the same side where hyperfixation of HMPAO was seen. Hypofixation of iomazenil progressed in patient 2 during follow-up (side-to-side difference 44% on day 20). The scan performed 30 min after injection in patient 2 demonstrated a modest non-specific hypofixation of IMZ in the affected temporal lobe.

Discussion

As demonstrated by these two HSE cases HMPAO SPECT is an excellent method for the early detection of HSE, a disease which may have a relatively good outcome provided that acyclovir treatment is started immediately on suspicion of the infection.

The mechanism of hyperfixation of HMPAO and IMP in brain tissue affected by HSE is unknown. We have previously performed pertechnetate scans[1] and contrast enhanced CT at the time of hyperfixation excluding the possibility that this phenomenon would arise from mere blood–brain barrier disruption. In HSE the magnitude and length of the hyperfixation exceeds that seen in ictal scans of epilepsy patients[10,11] indicating that mechanisms other than just hyperperfusion might be important in HSE.

In the subacute phase of stroke the hyperfixation has been thought to reflect the hyperaemia following reperfusion and is called the luxury perfusion.[12,13] However, the ability of HMPAO to measure accurately the degree of post-stroke luxury perfusion has recently been challenged.[14] In the subacute phase of

stroke, HMPAO may grossly exaggerate the magnitude of luxury perfusion due to increased fractional fixation of HMPAO in the affected brain area compared with normal brain. [^{123}I]IMP, however, also shows hyperfixation in HSE[1] suggesting that an increase in fractional fixation may not be of great importance in HSE.

The hypofixation of IMZ seen in the early stage of HSE is obviously due to neuronal loss caused by the herpes virus infection. The area of hypoactivity in IMZ scans is approximately the size of the largest HMPAO hyperfixation area. Hyperintense areas in the T2-weighted MR-images also coincide with the largest abnormalities in HMPAO and IMZ scans. However, hyperfixation of HMPAO sometimes lasts beyond obvious clinical improvement as assessed clinically and by neuropsychological testing. Neuronal loss as demonstrated by decreased IMZ binding may be stable or progress somewhat (patient 2) while hyperfixation of HMPAO continues. This finding suggests that the hyperfixation of HMPAO is not directly related to neurone damage but is triggered and maintained by some factor initiated by the HSV infection.

Tissue pH is probably decreased in the infected brain area and therefore autoregulatory mechanisms could cause hyperperfusion and hyperfixation of HMPAO. This mechanism alone, however, is an unlikely explanation as increased prolonged acidity causes functional deterioration; clinical improvement was observed during acyclovir treatment in these patients. There is true hyperperfusion in HSE, as angiographic findings show.[15]

The herpes simplex virus is capable of infecting all the cells in the central nervous system.[16,17] Thus, the infection is not limited only to neurones and glia but also extends to the meninges and blood vessels. In such surroundings the regional fractional fixation of HMPAO may be elevated, in a similar way as in stroke.[14] The fact that Cleator and co-workers[6] did not observe an increased fixation of HMPAO in the HSE rat model probably merely reflects species-related differences. The decreased specific fixation of IMZ in both patients suggests early neuronal death in HSE. In HSE there is marked hypermetabolism of glucose,[7] which is closely linked to hyperperfusion. Thus we hypothesize that the increased fixation of HMPAO reflects mainly increased perfusion and only in part of the fixation is non-perfusion associated. As neuronal death seems to start early in HSE, the hyperfixation of HMPAO is maintained by hypermetabolism and inflammation of glial and other cells rather than by the hyperactivity of neurones as in epileptic seizures. The early loss of neurones in HSE, even with progression during proper medication, stresses the importance of starting antiviral therapy immediately.

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Received 13 March 1995; accepted 23 March 1995

General Summary

Herpes simplex virus resides in the peripheral nerves of most adults. In some individuals it recurrently manifests as harmless, but painful cold sores. Sometimes (5 cases/1000 000/year) the virus infects the brain causing the serious herpes encephalitis (HSE). Untreated, the mortality in HSE is 50–80%, but treatment with the antiviral drug acyclovir dramatically improves the prognosis. HSE often starts insidiously and has been difficult to diagnose, which has delayed treatment. Earlier, we discovered that imaging of the brain using a blood flow tracer ('HMPAO') and perfusion tomography ('SPECT') is very useful in the early diagnosis of HSE. We have now studied acute HSE with a new nerve cell specific imaging agent, radiolabelled iomazenil. Our results show, that destruction of nerve cells in the brain starts very early in HSE. This implies that acyclovir treatment should be started without delay, immediately on mere suspicion of this deadly disease.