Case Report

Human herpesvirus-6 encephalitis: Estimated by semi-quantitative analysis of ^{99m}Tc-ECD Brain Single Photon Emission CT.

Teisuke HASHIMOTO, Hiroko CHIKATSU, Hiroko ENDO, Tatsuo KONO, Hiromune NISHIYAMA, Hiroaki ARAKAWA, Fumitoshi IIMURA, Shigeko KUWASHIMA, Hirohisa SAWADA, Natoru SAIKI, Minoru YAMATO, Mutsuhisa FUJIOKA

Department of Radiology, Dokkyo University School of Medicine

Abstract

Repeated examinations with ^{99m}Tc-L,L-ethyl cysteinate dimer(ECD) single photon emission computed tomography(SPECT) and magnetic resonance imaging(MRI) were performed in a one-year-old boy with Human herpesvirus-6(HHV-6) encephalitis. CT and initial MRI showed no remarkable abnormality. Second MRI revealed localized faint high intensity areas in the right frontal and temporal subcortical area on T_2-weighted imaging. In contrast to the obscure MRI findings ^{99m}Tc-ECD Brain SPECT disclosed larger areas of decreased uptake in the wide area of the right frontal, parietal, temporal lobes and right thalamus. Follow-up ^{99m}Tc-ECD Brain SPECT depicted more decreased uptake in the same area with crossed cerebellar diaschisis(CCD). One year after the onset, follow-up MRI revealed the mild atrophy of the right parietal and temporal lobes. Left hemiparesis is still recognized. Therefore ^{99m}Tc-ECD Brain SPECT is thought to be useful to estimate the extent of damaged cerebral area in the early stage of illness and also helpful in predicting the clinical neurologic outcome.

key words: ^{99m}Tc-L,L-ethyl cysteinate dimer(^{99m}Tc-ECD), Human herpesvirus-6 (HHV-6),Crossed cerebellar diaschisis(CCD)

running title: ^{99m}Tc-ECD SPECT of HHV-6 encephalitis.

INTRODUCTION

Human herpesvirus-6 (HHV-6) is one of the seven human herpesviruses. It is a large (185-200 nm), enveloped, double-stranded DNA virus of approximately 170 kilobases. HHV-6 is the etiologic agent of roseola in at least 80-92% of cases. Neurologic involvement is rarely observed during HHV-6 infection, including meningoencephalitis or encephalopathy. The clinical manifestations, however, are usually transient and the persistent neurologic changes are observed in only rare cases. Recent progress in neuroimaging studies has thrown much light on the etiology of viral encephalitis. For the cerebral perfusion imaging agents, ^{123}I-N-isopropyl-p-[^{123}I]-iodoamphetamine (^{123}I-IMP), ^{99m}Tc-hexamethyl propylene-amine oxime (^{99m}Tc-HMPAO) and ^{99m}Tc-L, L-ethyl cysteinate dimer (^{99m}Tc-ECD) are clinically available in Japan[1]. Early in the course of viral encephalitis, CT images are usually normal[2]. Early diagnosis and therapy during the first 2 or 3 days of symptomatic illness are essential if high mortality and serious neurologic sequelae are to be avoided[3,4]. To our knowledge, reports of viral encephalitis estimated by ^{99m}Tc-ECD SPECT have rarely

Contact address of the principal author :

Department of Radiology, Dokkyo University School of Medicine880 Kitakobayashi Mibu-machi Simotsuga-gun Tochigi-ken, 321-0293, Japan.

TEL. 0282-87-2171 FAX. 0282-86-4940

been described[5,6]. This time we present a rare case of HHV-6 encephalitis firstly detected by ^{99m}Tc-ECD Brain SPECT.

CASE REPORT

A 1-year-old boy was born after a normal term pregnancy and uncomplicated delivery at 40 weeks of gestation with a birth weight of 3,410 g. Two days prior to admission he developed cough, nasal discharge and fever. He was admitted to our hospital with pyrexia, repeated generalized symmetrical tonic-clonic convulsions followed by unconsciousness and intermittent eye deviation to the right and left upper side. On admission he was somnolent and responded only to painful stimuli. Light reflex was prompt. Body temperature was 40.2° C. The throat was slightly injected but there were no abnormal findings in the chest or abdomen. Muscle tone and deep tendon reflexes were normal. Pathological reflexes, nuchal rigidity and Kernig's sign were absent. Optic fundi were normal. Blood cell counts (except for slight increase in polymorphonuclear leukocytes), serum electrolytes, BUN, creatinine and total protein were normal. Blood glucose was 156mg/dl, and ammonia 51 μ g/dl. The erythrocytes sedimentation rate was normal and C-reactive protein was negative. Serum amino acids and urine organic acids were normal. Urinalysis was normal. Six hours after the admission high fever persisted and a slight weakness of the left upper limb was noticed. Deep tendon reflexes were slightly exaggerated but not evident and there was no remarkable difference between the right and left sides. CT scan revealed no remarkable abnormality and no abnormal vascular enhancement **(Fig.1a)**. The cerebrospinal fluid(CSF) examination showed no pleocytosis and protein and sugar were normal. CSF neuron-specific enolase (NSE) was normal (2.8 ng/ml). He was treated with glyceol, antibiotics, acyclovir and phenytoin. Four days after the admission repeated seizures were again recognized, thereafter unconsiousness developed. Next day he regained consciousness but left hemiparesis was noticed. Patellar tendon reflex was reduced and Babinsky reflex was positive in the left side. Electroencepahlography (EEG) showed slow waves in the right side of the cerebral hemisphere. Initial MRI showed no remarkable abnormality **(Fig.1b)** and MRA showed no specific vascular abnormality. After the normalization of high fever skin exanthema (macular and maculopopular eruption) were recognized. Second MRI revealed a localized faint high intensity area in the right frontal and temporal subcortical area on T_2-weighted imaging **(Fig.1c)**. ^{99m}Tc-ECD Brain SPECT disclosed larger areas of decreased uptake in the wide area of the right frontal, parietal, temporal lobes and the right thalamus as compared with MRI **(Fig.2a)**. Follow-up ^{99m}Tc-ECD SPECT

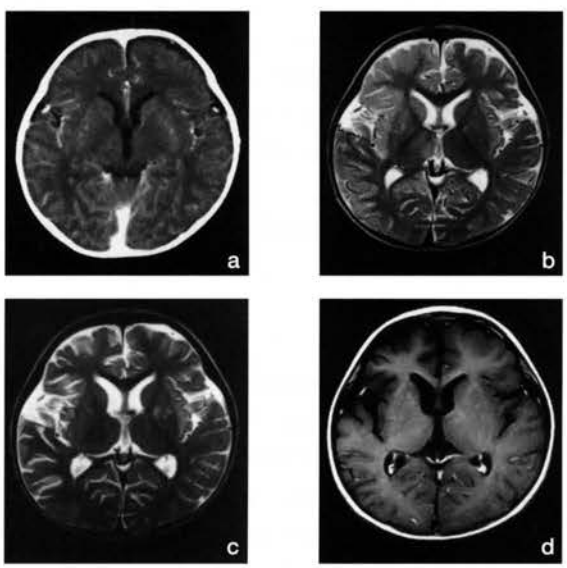


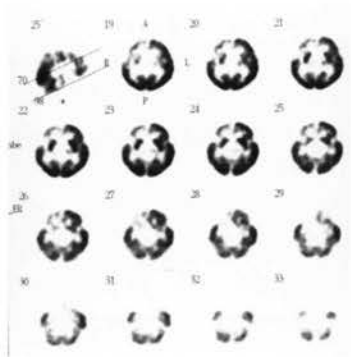
Fig. 1

a contrast-enhanced CT on the admission showed no remarkable abnormality and no abnormal vascular enhancement.

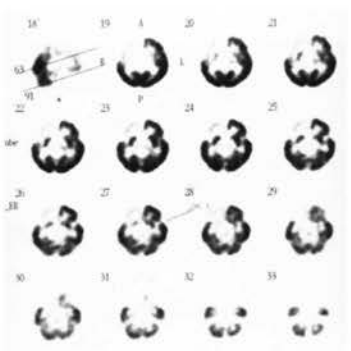
b T_2-weighted MRI(SE, TR/TE 3800/110) obtained 2 days after the onset revealed no remarkable abnormality in the cerebral cortex, deep white matter or basal ganglia.

c T_2-weighted MRI(SE, TR/TE 3800/110) on the13th day of hospitalization disclosed localized faint high intensity area in the frontal subcortical white matter.

d Follow-up MRI performed one year after the onset revealed the atrophic change of the right frontal and temporal lobes on Gd- DTPA enhanced T_1-weighted MRI(SE, TR/TE 710/15)



a



b

Fig. 2
a ^{99m}Tc-ECD Brain SPECT on the 20th day after the onset demonstrated larger areas of decreased cerebral uptake in the wide area of the right frontal, parietal, temporal lobes and the right thalamus.
b Follow-up ^{99m}Tc-ECD SPECT on the 49th day after the onset revealed more decreased uptake in the the right frontal, parietal, temporal lobes and the right thalamus with crossed cerebellar diaschisis.

demonstrated more decreased cerebral blood flow in the same area with crossed cerebellar diaschisis **(Fig. 2b)**. For the semi-quantitative analysis of the changes in regional cerebra blood flow on the SPECT studies, regions of interest (ROI) were placed on the suspected lesions, the corresponding regions of the contralateral hemispheres and on the cerebellum. The mean counts of each ROI were measured, and uptake ratios of the lesions to the cerebellum (L/C ratio) and right to left ratios of each ROI (R/L ratio) were calculated. L/C ratios of initial SPECT in the right frontal, temporal lobes and the right thalamus were 0.91, 0.50 and 0.74 respectively. L/C ratios of follow-up SPECT in each lesion were decreased to 0.66, 0.46 and 0.65. R/L ratios of initial SPECT in the right frontal, temporal lobes and the thalamus were 0.76, 0.50 and 0.83 respectively. R/L ratios of follow-up SPECT in each lesions were also decreased to 0.66, 0.42 and 0.79. In addition to the visual qualitative diagnosis of the cerebral blood flow in the affected lesions, the semi-quantitative analysis of the changes in the regional cerebral blood flow on the SPECT showed more decreased cerebral blood flow in the affected lesions in the follow-up SPECT, suggesting the likelihood of poor clinical neurologic outcome. Follow -up MRI revealed the atrophic change of the right frontal and temporal lobes on Gd-DTPA enhanced T_1-weighted imaging **(Fig.1d)**. Follow-up EEG showed focal sharp and spike waves in the right side of F-C area. Paired serum complement fixation titres for herpes simplex virus (HSV) specific IgG and IgM were not elevated at the admission. Fourteen days after the onset, the titres for HHV-6 specific IgM was elevated (1:20) but that of HHV-6 specific IgG was not elevated. Thereafter HHV-6 specific IgG titre was elevated to 1:640. Therefore the final clinical diagnosis was made as HHV-6 encephalitis. Four weeks after the admission, he was discharged with left hemiparesis and one year after remained almost unchanged.

DISCUSSION

Acute hemiplegia syndrome (AHS) in childhood is the generalized name of sudden onset of an acute hemiplegia in infants and children. The causes of AHS are acute encephalopathy, cerebral vascular diseases, brain tumor and central nervous infectious diseases and so on[7]. Acute encephalopathy type of AHS results in the serious neurologic sequelae and the explanation of its pathophysiological mechanism is highy desirable. AHS which is estimated by cerebral perfusion scintigraphy have rarely been described previously.

For the cerebral perfusion imaging agents, ^{123}I-IMP, ^{99m}Tc-HMPAO and ^{99m}Tc-ECD are

clinically available. ^{123}I-IMP is useful for the detection of cerebral ischemia, because of its sensitivity, non-invasiveness and accurate reflection of the cerebral blood flow distribution[8]. ^{99m}Tc-HMPAO has been shown to improve the sensitivity and accuracy of cerebral imaging in cases of epilepsy, dementia and stroke[9-11]. But the cases of viral encephalitis estimated by ^{99m}Tc-ECD have rarely been reported. Hirayama et al reported[6] one case of respiratory syncytial virus encephalitis. Nagamachi et al reported[5] 6 cases of viral encephalitis estimated by ^{99m}Tc-ECD. They also repoted 3 cases of HHV-6 encephalitis estimated by ^{99m}Tc-HMPAO (2 cases) and ^{123}I-IMP (1case). Nevertheless no report of HHV-6 encephalitis estimated by ^{99m}Tc-ECD has been described. To our knowledge this is the first report on HHV-6 encephalitis detected by ^{99m}Tc-ECD SPECT.

Crossed cerebellar diaschisis (CCD) was termed by Baron et al[2]. Using positron emission tomography (PET), they observed a parallel reduction in blood flow and oxygen use in the cerebellar hemisphere, contralateral to a supratentorial cerebral infarction. SPECT is also capable of demonstrating CCD in cerebral infarction and ischemia[13-15]. Most likely, CCD results from a crossing of the cortico-ponto-cerebellar pathways and a functional connection between the contralateral cerebellar hemisphere and the cerebral cortex[12]. Hamano et al reported[15] that in 5 cases out of 25 CCD was recognized on the ^{123}I-IMP SPECT (2 cases of cerebral infarction, 1 case of moyamoya disease, 1 case of cerebral hemorrhage and 1 case of AHS). The ages of the patients in 5 cases were over 7 years. Tada et al also reported[17] that 2 out of the 50 patients showed CCD on the ^{123}I-IMP SPECT. The ages of the patients in 2 cases were also over 7 years. They supposed that the cortico-ponto-cerebellar pathways are immature and still under development in smaller children under 7 years old. Therefore CCD might not be recognized under 7 years old children. But Higuchi et al reported[18] a case of 3-year-old girl with AHS which revealed CCD on the ^{123}I-IMP SPECT. This time we have experienced a case of 1-year-old boy with acute encephalopathy which revealed CCD on the 99mTc-ECD SPECT. This is the youngest case ever reported.

The use of SPECT in viral encephalitis has been controversial. Nara et al reported[19] a case of acute encephalitis which exhibited hyperperfusion. The neurologic outcome of that case was poor. According to Lee et al[20], in stroke or HSV encephalitis, hyperperfusion is believed to be induced by tissue acidosis from the endproduct of impaired cellular metabolism, therefore the demonstration of hyperperfusion indicates the necrosis of brain tissue.

Jarjour et al reported[21] it is important to emphasize that SPECT studies cannot quantify absolute values of brain perfusion. Only marked regional asymmetric findings will be seen. Global changes most likely will be missed. Therefore, it is difficult to define hyperperfusion in SPECT except in relative terms, whereby one region of the brain is hyperperfused relative to adjacent regions or to the contralateral homologous region.

In contrast to them Kao et al reported[22] ^{99m}Tc-HMPAO brain SPECT in the acute phase showed increased regional cerebral blood flow in the initial brain SPECT scans in 17 out of their 18 cases included herpes simplex virus, Epstein-Barr virus and Japanese B virus encephalitis. Follow-up brain SPECT showed that 12 cases out of 17 had normal second brain SPECT and 5 cases 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 clinical outcome (no neurologic defect) than the group of patients with decreased regional cerebral blood flow (learning disability or decreased intelligence). They concluded that ^{99m}Tc-HMPAO brain SPECT has a high diagnostic accuracy as well as good localization in children with viral encephalitis. Serial ^{99m}Tc-HMPAO brain SPECT should serve as a good guide for predicting the outcome in children

with viral encephalitis. The decreased regional cerebral blood flow on the SPECT may suggest more severe damage to the brain secondary to viral encephalitis. This could explain the observation that patients with decreased regional cerebral blood flow had poor clinical outcomes.

Fujii et al reported[23] a case of influenzal encephalitis which revealed larger areas of decreased uptake on ^{123}I-IMP SPECT. One year after the onset of encephalitis, these findings continued to be observed, although the patient had no apparent neurologic sequelae. They have discussed decreased uptake on SPECT brain scans indicates that neuronal function has been impaired and/or that the peripheral circulation is disturbed but not suggestive of widespread infarction or necrosis.

Nagamachi et al reported[4] MRI showed no remarkable abnormality in 51.4% of hypoperfused SPECT lesions of viral encephalitis. About 30 % of hypoperfused area returned to normal in follow-up SPECT.

In our case the initial brain SPECT could not detect increased regional cerebral blood flow but showed already decreased regional cerebral blood flow. ^{99m}Tc-ECD is metabolized to monoacids by enzyme activity from the biester compound[24]. Therefore, it is supposed that ^{99m}Tc-ECD may reflect the viability of neuronal tissues. The decreased ^{99m}Tc-ECD accumulation might suggest the severe damage of the affected area in the early stage of illness. Follow-up SPECT revealed more decreased regional cerebral blood flow in the visual qualitative images and the semi-quantitative analysis, suggesting poor clinical neurologic outcome. Although further cases should be investigated to confirm its significance, ^{99m}Tc-ECD SPECT is recommended in addition to ^{123}I-IMP and ^{99m}Tc-HMPAO as an early investigation for patients with acute encephalitis.

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