

Sequential brain perfusion abnormalities in various stages of Japanese encephalitis

Abstract

There is a paucity of regional cerebral blood flow studies on Japanese encephalitis (JE) with none of these studies describing brain perfusion abnormalities in all three stages of the disease. In this communication we report the changes noted in brain perfusion as detected by single photon emission tomography (SPET), in the acute, subacute and chronic stages of JE. Between December 2000 and March 2006, 31 patients, 19 men and 12 women, mean age 49 y, range 6-64 y of various stages of JE underwent brain perfusion SPET. These patients were at the following stages of the disease: acute stage, five patients, subacute stage 17 and chronic stage nine. The acute stage was considered as up to seven days from the onset of symptoms, the subacute, from seven to 56 days and any duration beyond 56 days was considered as the chronic stage. In the acute stage all five patients demonstrated focal areas of hyperperfusion involving mainly the thalamus. Additionally, bilateral thalamic involvement was noted in three, frontal lobe involvement in four and parietotemporal hyperperfusion in three of these patients. In the subacute stage group, hypoperfusion of the thalamus was noted in all patients while frontoparietal hyperperfusion in seven patients. In the chronic stage group, hypoperfusion of thalamus was noted in four, one patient demonstrated additional occipital lobe hypoperfusion whereas normal perfusion was noted in the remaining five patients. *In conclusion*, the brain perfusion abnormalities observed depended on the stage of the disease. In the acute stage there was focal hyperperfusion to sites of the brain where JE virus is considered to replicate. In the subacute stage focal hypoperfusion was found to be possibly due to virus induced damage of cellular protein synthesis and in the chronic stage perfusion returns to normal due to regeneration of cellular organelles. Our results also confirm the high frequency of thalamic involvement in JE.

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Introduction

Japanese encephalitis (JE) is a zoonotic disease caused by a group-B arbovirus (flavi-virus) and is transmitted by culicine mosquitoes. JE primarily affects children between the ages of one and 15 y, causing annually an estimated number of 35,000-50,000 cases of JE. The disease has a mortality rate of 20%-40% and produces a diverse neurological and psychiatric effect in 25%-40% of the survivors [1]. The characteristic neurological findings in the acute stage are extra pyramidal signs such as tremor, dystonia and rigidity. When a patient of probable viral encephalitis has these neurological signs, JE is suspected and the diagnosis is confirmed by serological tests.

In the acute stage of JE, computed tomography and magnetic resonance imaging (MRI) are usually normal, and it takes two to three weeks to establish the diagnosis of JE serologically. It is important to distinguish JE from other types of encephalitis particularly herpes simplex encephalitis, as herpes simplex encephalitis responds well to specific antiviral treatment [2]. Literature on cerebral blood flow changes in JE is very limited. None of the studies available, addresses brain perfusion abnormalities in all three stages of the disease, nor any attempt has been made to relate single photon emission tomography (SPET) brain perfusion, in JE to the pathology of the disease. The aim of this communication was to report the changes noted in brain perfusion in the acute, subacute and chronic stages of JE as detected by the SPET study and discuss or relate the observed lesions in the light of known pathology changes that occur during the course of JE.

Subjects and methods

Between December 2000 and March 2006, 31 patients, 19 men and 12 women of mean age 49 y and range: 6-64 y with JE, underwent brain perfusion SPET study and MRI during

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various stages of the disease. Patients (n=31) were divided into three categories namely those in the acute stage (n=5), in the subacute stage (n=17) and in the chronic stage (n=9). The acute stage was considered as up to seven days from the onset of symptoms, the subacute was considered from seven to 56 days and any duration of JE beyond 56 days was considered as the chronic stage of the disease. The diagnosis of JE was confirmed in all cases by the serological haemagglutination test. All patients were referred to our Department by their attending neurologist as for a routine brain scan.

Cerebral perfusion SPET study

Brain SPET was performed 30 min post the intravenous injection of 740-925 MBq of technetium-99m-ethyl cystine dimer (^{99m}Tc -ECD), using a dual head gamma camera (SMV DxTL from Ranalsoft, Buc, France) fitted with a high-resolution collimator. The dose of the radiopharmaceutical was calculated as follows: the body surface area was divided by 1.73 and then multiplied by the adult dose of 1,000 MBq. Energy settings were 140 keV with a 20% energy window. The SPET data were acquired in 128 x 128 matrix using step and shoot method with a view at every 4° for 25 sec per view, with a total of 90 views. Reconstruction was done by filtered back projection, Projection data were filtered before back projection and reconstruction was performed using a two-dimensional Metz filter (cut off:0.43 cm, P:30, value of max:124, position of max: 23, FWHM:100). Attenuation correction was done by Chang's method [3]. No scatter correction was done in this study. Reconstructed images had a slice thickness of 7 mm and were displayed and analyzed using transverse, sagittal and coronal views.

Results

In the acute stage all five patients demonstrated focal areas of hyperperfusion involving mainly the thalamus (Fig. 1). Additionally, bilateral thalami involvement was noted in three, frontal lobe involvement in four and parieto-temporal hyperperfusion in three of these patients.

In the subacute stage, hypoperfusion of the thalamus was noted in all patients and frontoparietal hypoperfusion in seven patients (Fig. 2). In the chronic stage hypoperfusion of the thalamus was noted in four patients, one patient demonstrated additional occipital lobe hypoperfusion whereas no perfusion defects were noted in the remaining five patients (Fig. 3).

Discussion

JE represents a serious health problem in Asia. This disease had been first described in Japan as early as 1871; however, Japanese encephalitis flavivirus (JEV) was first isolated only in 1935 [4]. Patients may rapidly progress to coma and there is high mortality rate in the elderly. There is no specific treatment. The aim of the diagnostic workup is to separate JE from other treatable encephalitis like herpes simplex encephalitis. After the onset of symptoms it takes two to three weeks for the serological tests, like the haemagglutination test,

to become conclusively positive [5]. MRI is currently widely used in the diagnostic workup and may be normal in the early stages of the disease [6]. As it is well known that neuronal function should be deranged before a structurally detectable lesion appears in the MRI examination and also that symptoms of JE appear early, it is likely that brain perfusion study may be helpful even in the early stages of the disease.

Our results confirm the frequent involvement of thalamus in JE, which has been reported in earlier studies [7,8]. JE has been regarded as a diencephal-mesencephalitis. In the acute stage, the histopathological changes include degeneration, congestion, microhaemorrhages, thrombi formation and neuronophagia. In the subacute stage, the inflammatory response is reduced. Only a small proportion of those infected by the JE develop clinical features, and these may range from a non-specific flu-like illness to a severe fatal meningoencephalitis, often with Parkinsonian features, or a poliomyelitis-like flaccid paralysis. The factors governing the clinical presentation and outcome of JEV infection are poorly understood. Studies have

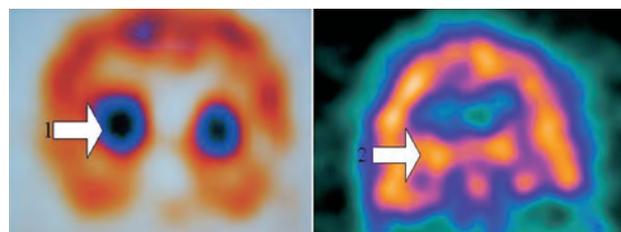


Figure 1. A. Coronal section of ^{99m}Tc -ECD brain SPET in the acute stage of Japanese encephalitis showing bilateral hyperperfused thalami (arrow). B. Image from a normal control

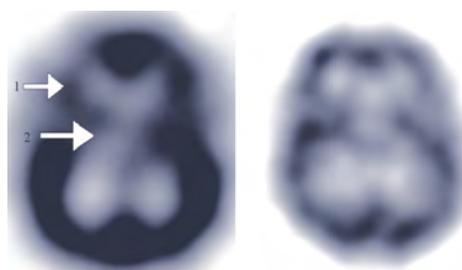


Figure 2. A. Transverse section of ^{99m}Tc -ECD brain SPET in the subacute stage of Japanese encephalitis showing right frontoparietal hypoperfusion (arrow). B. Image from a normal control

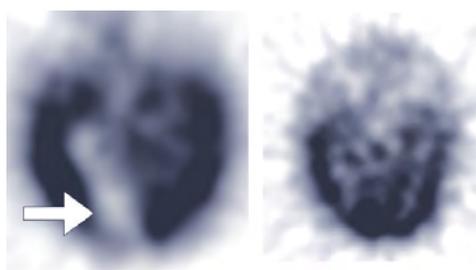


Figure 3. A. Transverse section of ^{99m}Tc -ECD brain SPET in the chronic stage of Japanese encephalitis showing right occipital lobe hypoperfusion suggestive of permanent cortical damage (arrow). B. Image from a normal control

shown that innate immunity, as manifested by interferon alpha (IFa) levels, is important in JE, but treatment with IFa did not improve the outcome. A failure of the humoral immune response in JE is associated with death caused by JEV and West Nile virus. Cellular immunity has been poorly investigated, but CD8+ and CD4+ T cells are thought to be important [9].

In the acute stage of the disease JEV selectively affects the neurons, causing ultrastructural changes in association with viral replication in the cellular secretory system, principally involving rough endoplasmic reticulum (RER) and the Golgi apparatus. Also, in the acute stage, the RER is infected and neurons show hypertrophic changes. Also, cisternae are dilated and contain assembling virions [7]. This viral replication triggers intense immune response from host defense mechanisms. Infection by JEV increases in the expression of class I and II major histocompatibility complex and in various adhesion molecules, resulting increased susceptibility to both virus- and major histocompatibility complex-specific cytotoxic T lymphocyte lysis. These changes are comodulated by T1 and T2 cytokines, as well as by cell cycle position and by the adherence status of the infection [10]. Moreover there is increased expression of macrophage migration inhibitory factor (MIF), which is a proinflammatory cytokine and contributes to broad-spectrum immune and inflammatory responses [11]. Quantitation of perivascular inflammatory responses showed a preponderance of T cells, but only 7%-30% of these cells were T suppressor/cytotoxic cells. Inflammatory cells invading the parenchyma were predominantly macrophages and few were T cells. B cells remained localized to perivascular cuffs [12]. Activation of these various mediators of inflammation in JE induces increased cerebral blood flow. As the viral antigen is localized to neurons, especially in the thalamus and brainstem, the above pathology changes in the acute stage of JE, show great increment in cerebral blood flow along with active viral replication [12].

Once the phase of active viral replication is over, the viral antigen is progressively cleared from most parts of the brain. In this phase (subacute stage), the RER becomes cystic, degenerative and is dissolved into the cytoplasm. Also, the Golgi apparatus contains multiple virions, presumably transported from the RER, which are released into the cytoplasm within coated vesicles for secretory-type exocytosis. In this process, the Golgi apparatus is also fragmented and degenerated through vesiculation, vacuolation, and dispersion [13]. Thus, the JEV infection of neurons results in obliteration of RER and of the Golgi apparatus, leaving behind the rarefied cytoplasm devoid of these organelles. With the destruction or stunning of the protein synthetic machinery of the cell, neuronal metabolism reduces, and is followed by reduction in cerebral blood flow. These changes induce the hypoperfused areas in the brain perfusion studies [13].

However, destruction of the neurons themselves is not prominent and in the later stage of JE infected neurons show some regenerative changes of these membranous organelles [14]. This regenerative activity restores cellular metabolism, which in turn results in normalization of the perfusion defects in the chronic stage of the disease. Where these regenerative

activities are incomplete, perfusion defects persist, as we have noticed in 4/9 of our patients being in the chronic stage. This difference in the regeneration of cellular membranous organelles results in a spectrum of clinical outcome ranging from complete clinical recovery to debilitating paralysis and even death. The cause of death in JE, therefore, appears to be extensive neuronal dysfunction rather than extensive neuronal destruction of the brain [15].

Results of the brain SPET perfusion studies depend on the timing of the study. In the acute stage of JE, hyperperfusion in the thalamus and the putamen has been reported [8]. When patients survive beyond six days, the viral antigen progressively clears from most parts of the brain and SPET cerebral perfusion studies of focal hyperperfusion, return to normal. However, due to reasons poorly understood, the thalamus starts showing hypoperfusion from this stage of the disease and may remain so even 13 months after the onset of JE. This thalamic hypoperfusion could be due to neuronal death or dysfunction, which results in decreased metabolism and in reduction of regional cerebral blood flow. The focal thalamic hypoperfusion observed in the subacute stage reverts to normal in the chronic stage in the majority of patients.

Changes in the blood supply of thalamus are likely to have some prognostic significance. All our patients who demonstrated thalamic hypoperfusion in the chronic stage had slow recovery of the neurological deficits and incomplete recovery compared to patients in whom thalamic hypoperfusion had returned to normal.

In conclusion, the brain perfusion abnormalities observed in our study depend on the stage of the disease. In the acute stage there is focal hyperperfusion at sites of active viral replication. In the subacute stage focal hypoperfusion is noted that may be due to virus induced damage in cellular protein synthesis. Finally, perfusion tends to return to normal in the chronic stage possibly as cellular organelles regenerate. Our results also confirm high frequency of thalamic involvement in JE. According to our findings all stages of JE can be detected by the brain perfusion SPET study making it an immensely useful diagnostic tool in the staging and follow-up of JE.

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