Diagnosis of Acute Ischemic Stroke Based on Time-To-Peak and Diffusion-Weighted Magnetic Resonance Imaging

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Abstract

Rapid and accurate diagnosis of the hemodynamics of the brain is essential for the treatment of acute ischemic stroke. This study investigated whether time-to-peak and diffusion-weighted magnetic resonance (MR) imaging are useful for predicting the course of stroke. Fourteen patients with non-lacunar acute ischemic stroke underwent emergent MR imaging within 24 hours from the onset followed by cerebral angiography and xenon-enhanced computed tomography (CT). Serial CT was obtained to monitor changes in the size and nature of the infarct. Volumes of the abnormal lesions demonstrated on time-to-peak (VT) or diffusion-weighted (VD) images were measured, and the ratio of VT to VD was calculated. Based on this ratio, patients were classified into three groups: Group 1 (VT/VD 0.5–1.5, n = 9), Group 2 (VT/VD > 1.5, n = 3), and Group 3 (VT/VD < 0.5, n = 2). The size of the infarct detected as a low-density area on serial CT scans did not change significantly throughout the course in Group 1 patients, but showed enlargement in all three patients in Group 2. Two patients in Group 3 had major trunk occlusion followed by spontaneous reperfusion, and both developed hemorrhagic transformation. Our study showed that classification of ischemic stroke based on the VT/VD ratio was predictive of the time course of the infarct, and may be useful in selecting the initial therapeutic procedure immediately after the onset of stroke.

Key words: ischemic stroke, magnetic resonance imaging, reperfusion, time-to-peak

Introduction

Acute ischemic stroke continues to be a major cause of death and disability in the developed world, and efforts to improve treatment methods still continue. The most straightforward treatment is to recanalize the occluded vessel using thrombolytic agents, such as tissue plasminogen activator and urokinase, and restore the blood circulation. This approach is effective in some patients, but causes serious hemorrhagic complications in about 20% of patients and induces poor outcome. Therefore, appropriate patient selection is the key for the success of this potentially harmful treatment. The most important factor to be considered is the time from onset, and the current consensus is that thrombolytic agents must be administered within 3 hours. Another important factor is the status of cerebral perfusion, which can be monitored by various imaging techniques.

Diffusion-weighted magnetic resonance (MR) imaging can detect ischemic lesion earlier than any other MR imaging sequence, and most, but not all, of the detected lesion will evolve into complete infarction. Perfusion-weighted MR imaging provides several parameters with different implications, including time-to-peak, mean transit time, relative cerebral blood volume, and cerebral blood flow (CBF). The time-to-peak imaging is one of the most sensitive and useful functional images in acute stroke, and requires only about 15 minutes to obtain. Recent studies have showed that the combination of diffusion-weighted and time-to-peak MR imaging might predict the patterns of infarction enlargement in patients with ischemic stroke. This study investigated whether diffusion-weighted and time-to-peak MR imaging can predict the clinical course in patients with acute ischemic stroke.
Materials and Methods

Thirty-eight consecutive patients with acute ischemic stroke were treated at our institution from October 1999 to November 2000. Computed tomography (CT) was used to exclude hemorrhagic lesions. All patients were immediately treated with 3000 units of heparin intravenously administered. A series of emergent studies were performed including diffusion-weighted and time-to-peak MR imaging, angiography, and CBF measurements by cold xenon-enhanced CT or by technetium-99m hexamethylpropyleneamine oxime (99mTc-HM-PAO) single photon emission computed tomography (SPECT). The clinical course of the cerebral infarct was monitored by serial CT and neurological evaluations. The thrombolytic therapy was successful in one patient who was excluded. Patients with suboptimal imaging study due to motion artifact (n = 4), technical failure of imaging studies (n = 1), longer than 24 hours interval from onset (n = 4), or lacunar infarction (n = 14) were also excluded. The characteristics of the remaining 14 patients were analyzed in this study.

MR imaging was performed with a 1.5-T MR scanner (Magnetom Vision; Siemens, Erlangen, Germany). Spin-echo diffusion-weighted imaging obtained 20 axial slices (slice thickness 5 mm, interslice gap 1 mm, echo time [TE] 103 msec, field of view [FOV] 230 mm, and matrix 96 × 128) with b values of 0 and 1000 sec/mm². The high b value measurements were performed with diffusion gradients in three orthogonal (x, y, z) directions in space. Perfusion-weighted imaging (gradient echo, 5 slices, slice thickness 5 mm, interslice gap 1 mm, TE 60.7 msec, FOV 230 mm, and matrix 128 × 128) consisted of 60 T₁*-weighted measurements obtained every 2 seconds, with 0.2 ml/kg body weight of gadopentetate dimeglumine (Magnevist; Schering AG, Berlin, Germany) injected manually at the time of fifth scan. The perfusion-weighted sequence automatically generated a time-to-peak map for each section. Time-to-peak was calculated as the interval between the time of the contrast agent injection and the time of maximum concentration in the brain tissue. Approximately 15 minutes on average was required to obtain all the images.

The volumes of the ischemic lesion demonstrated as the high-intensity lesion on diffusion-weighted (V_D) and time-to-peak (V_T) imaging were measured using CIS Image/Viewer for Windows (IBM Japan Ltd., Tokyo), an imaging software installed for the original electronic medical record system in our hospital (Kameda Health Informatics Institute, Inc.). Five of the 20 diffusion-weighted imaging slices that corresponded to the time-to-peak image were selected. The edges of the hyperintense area were traced manually and the areas were calculated on each image. The average areas of the three diffusion-weighted images in the x, y, and z directions were calculated. The volume of the lesion was approximated by multiplying the areas of sections by the slice thickness plus the interslice gap.

The final infarction size was defined as the volume of the low-density area detected by CT more than 7 days after the onset. Infarction enlargement was defined as a larger final infarction size on CT compared to the lesion volume on initial diffusion-weighted imaging.

Results

The clinical characteristics of the 14 patients are summarized in Table 1. There were 10 men and four women aged from 49 to 93 years (mean 74 years). The occluded vessel causing the stroke was the middle cerebral artery (MCA) in eight patients, the internal carotid artery (ICA) in three, the basilar artery in one, the anterior cerebral artery in one, and multiple vessels in one. The interval between the onset and MR imaging examination ranged from 2.5 to 23 hours (mean 8.1 hours). The ratio of V_T to V_D (VT/VD) ranged from 0.15 to 14.24 (mean 2.2).

The 14 patients were classified into three groups: Group 1 (VT/VD 0.5–1.5), Group 2 (VT/VD > 1.5), and Group 3 (VT/VD < 0.5) (Fig. 1). Group 1 contained nine patients, of whom eight had intracranial major artery occlusion and four underwent decompressive hemicraniectomy for massive hemorrhagic infarction (n = 3) or severe brain swelling (n = 1). However, none of the nine patients demonstrated enlargement of infarction size. Group 2 contained three patients, all of whom demonstrated enlargement of infarction size. The stabilized areas of infarction were identical to the hyperintensity areas on the initial time-to-peak imaging. Group 3 contained two patients, who had intracranial major artery occlusion and spontaneous reperfusion in the acute stage as confirmed by conventional angiography or MR angiography. SPECT showed luxury perfusion of the recanalized territory, and CT revealed hemorrhagic transformation in both patients. Decompressive hemicraniectomy for massive hemorrhagic transformation and brain swelling was performed in one patient.

Illustrative Cases

Case 8: An 87-year-old man with sudden onset of left hemiparesis was transferred to our hospital.
Fig. 1 Lesion volumes on time-to-peak (V_T) and diffusion-weighted (V_D) images demonstrating that cases in Group 2 (V_T/V_D > 1.5) and Group 3 (V_T/V_D < 0.5) had infarction enlargement and spontaneous reperfusion, respectively. ○: cases showing infarction enlargement, △: cases showing spontaneous reperfusion, ×: cases showing neither infarction enlargement nor reperfusion.

Diffusion-weighted imaging performed 2.5 hours after the onset showed an abnormal intensity lesion in the right MCA territory (Fig. 2). Diffusion-weighted and time-to-peak imaging demonstrated a similar size lesion, with a V_T/V_D ratio of 1.02 (Group 1). MR angiography and conventional angiography demonstrated occlusion of the right ICA. There was no enlargement of the infarction size on the 7th day after the onset.

Case 13: A 72-year-old man developed acute right hemiparesis and motor aphasia and was transferred to our hospital. Diffusion-weighted imaging performed 6 hours after the onset showed an abnormal lesion limited to the left basal ganglia, whereas time-to-peak imaging showed a hyperintense lesion involving the whole left MCA territory (Fig. 3). The V_T/V_D ratio was 5.18 (Group 2). Left carotid angiography showed left MCA occlusion at a portion immediately distal to the ICA bifurcation. CT showed a low-density area limited to the basal ganglia on the 2nd day, but involved the whole MCA territory on the 5th day.

Case 1: A 72-year-old man with sudden onset of right hemiparesis and global aphasia was brought into our hospital. CT showed high density of the right ICA lumen suggesting ICA embolus, which was confirmed by emergent angiography 5 hours after the onset (Fig. 4). Diffusion-weighted imaging performed 19.5 hours after the onset demonstrated a hyperintensity lesion including the whole left MCA territory, whereas time-to-peak imaging showed an abnormal high intensity lesion limited to the left temporo-occipital area. The V_T/V_D ratio was 0.15 (Group 3). MR angiography visualized the bilateral ICAs and the basilar artery. ⁹⁹mTc-HM-PAO SPECT showed similar findings to time-to-peak imaging, and luxury perfusion in the anterior half of the left MCA territory. The patient rapidly deteriorated neurologically with decerebrate posture on the 3rd day.
and CT revealed massive hemorrhagic infarction. Emergent decompressive hemicraniectomy was performed. Two months after the onset, he had right hemiparesis and motor aphasia, but could follow commands and feed himself.

**Discussion**

Our study demonstrated that the relationship between the lesions detected by time-to-peak imaging and that detected by diffusion-weighted imaging in a patient with stroke reflects the perfusion status of the brain, and is closely associated with the time course of the cerebral infarction. Both imaging methods are non-invasive and can be obtained within a relatively short time, so are potentially useful for predicting the time course of the disease, which will help to choose the treatment options for patients with acute ischemic stroke.

Time-to-peak imaging was compared with the T2-weighted imaging in the late phase of ischemic stroke, which suggested classification into four groups: hemodynamic, embolic, arteriosclerotic, and unclassified. Although our study is based on a similar concept, the diffusion-weighted imaging used in our study is more sensitive for detecting infarcted lesion in the acute stage, and should be more valuable in the management of patients with acute stroke.

In our series, cerebral infarction detected by CT did not show significant enlargement throughout the course in patients with a V_T/V_B ratio around 1.0 (0.5–1.5, Group 1). A V_T/V_B ratio larger than 1.5 (Group 2) indicated a hypoperfused area surround-
Fig. 3  Case 13 (Group 2). Diffusion-weighted image taken 6 hours after the onset (A) showing hyperintensity limited to the left basal ganglia, and time-to-peak image (B) showing hypoperfusion areas involving the whole left middle cerebral artery territory. Left carotid arteriogram (C) showing left M1 occlusion. Computed tomography scans initially showing no infarction (D) and the enlarged infarction on the 2nd (E) and 4th days (F).

Classifying the completed infarction core. This hypoperfused area, or penumbra, is highly likely to progress into infarction with time, and is detected as enlargement of the low-density area on serial CT. A \( V_T/V_D \) ratio smaller than 0.5 (Group 3) suggested recanalization of the occluded vessels and presence of an area with reperfusion, which carries a high risk of progressing into hemorrhagic transformation. Patients belonging to Groups 2 and 3 are extremely important to identify because the management plans for these two groups have opposite intentions. Patients in Group 2 have a large portion of hypoperfused but still alive brain tissues, which could be saved by rapid restoration of the blood supply by thrombolytic treatment or other measures. In contrast, patients in Group 3 are considered to have undergone spontaneous reperfusion, so thrombolytic therapy is contraindicated because of the increased risk of hemorrhagic infarction. Similar MR imaging findings suggesting spontaneous reperfusion were previously reported,\(^{12}\) and our study further confirmed the recanalization by angiography or MR angiography. Spontaneous recanalization after ischemic stroke occurs in up to 42% of cases within the 1st week,\(^{2}\) so detection of patients in Group 3 may have a significant impact.

Whether decision-making based on the \( V_T/V_D \) ratio would actually improve the overall outcome of ischemic stroke remains to be proven. However, the relative ease of obtaining diffusion-weighted and time-to-peak imaging suggests that this imaging technique could become an important tool in the clinical management of patients with acute ischemic stroke.
Fig. 4 Case 1 (Group 3). Initial diffusion-weighted image (A) showing hyperintensity in the whole left middle cerebral artery (MCA) territory. Time-to-peak image showing a hypoperfused lesion limited to the left temporo-occipital area (B). Initial carotid angiogram (C) showing the left internal carotid artery (ICA) occlusion. Magnetic resonance angiogram performed after angiography (D) indicating recanalization of the left ICA. Technetium-99m hexamethylpropyleneamine oxime single photon emission computed tomography (E) demonstrating hypoperfusion of the left temporo-occipital region and luxury perfusion in the anterior half of the left MCA territory. Computed tomography (CT) scans initially showing no infarction (F), but hemorrhagic infarction and brain swelling with severe midline shift on the 3rd day (G). CT scan on the 4th day (H) showing that midline shift decreased after decompressive hemicraniectomy.

References

Classification of Time-To-Peak MR Imaging in Acute Ischemic Stroke


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Commentary on this paper appears on the next page.
Commentary

In the past, diagnostic imaging of ischemic stroke has been hampered by the delay between the clinical event and the imaging characteristics of infarction. Maruyama and colleagues have demonstrated the utility of time-to-peak and diffusion-weighted magnetic resonance imaging (MRI) in predicting the time course of infarction. The authors studied 14 patients with MRI, angiography and xenon CT within 24 hours of their stroke. By calculating the volume of infarction on the time-to-peak ($V_T$) and diffusion ($V_D$) MRI, the authors calculated a $V_T/V_D$ ratio which allowed them to divide patients into three groups. Group I ($V_T/V_D$ 0.1–1.5) included 9 patients whose infarction as detected by CT did not show any significant enlargement throughout their clinical course. Group II ($V_T/V_D$ >1.5) predicted a hypoperfused area surrounding the completed infarction. This penumbra was likely to progress to infarction with time. Group III ($V_T/V_D$ <0.5) suggested recanalization of occluded vessels and presence of reperfusion. These patients predictably have a high risk of hemorrhagic transformation. If these findings can be confirmed in a larger series of patients, the observation is of more than academic interest. It is important to identify these different groups of patients early in the course of their infarction as the goals of treatment may be quite different in these three groups of patients.

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The authors analyzed time-to-peak ($V_T$) and diffusion-weighted ($V_D$) magnetic resonance (MR) imaging in 14 patients with non-lacunar acute ischemic stroke, and proposed a classification based on $V_T/V_D$ ratio for predicting the course of stroke. This $V_T/V_D$ ratio classification is reasonable, and the required examination time of MR was reported as less than 15 minutes. As the authors mentioned, these considerations provide a simple and useful method to predict the following clinical course and treatment strategy on an emergency basis, especially in patients with enlargement of infarction, spontaneous reperfusion, and hemorrhagic transformation (Groups 2 and 3). In this study, however, MR imaging and related data were obtained between 2.5 to 23.0 hours after onset and analyzed. There were only four cases in which examinations were done within 3 hours after onset, and one patient with successful thrombolytic therapy was excluded in this series. In the recent emergency treatment of thrombolysis for the MCA or ICA occlusion, the golden time has been recognized to be within 3 hours. The presented results did not provide a suitable answer for the treatment selection and clinical results of “hyperacute” recanalization for ischemic stroke, especially in cases under serious clinical conditions. I hope that this method will become more common and investigation to assess the treatment selection can be done in a larger series.

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Early prediction of the outcome of ischemic stroke by perfusion and diffusion modalities of magnetic resonance imaging (MRI) has been an interesting topic attracting many investigators in recent years. In the present study, the authors used the ratio of volume of abnormal signals demonstrated on time-to-peak imaging and diffusion-weighted imaging to correlate the outcome of patients with ischemia from large vessel occlusive disease. Indeed, abnormal signal in time-to-peak imaging represents the status of cerebral blood flow depletion and abnormal signal in diffusion-weighted imaging represents the area of neuronal death where interstitial edema is prominent. The ratio of volume of these two kinds of signals indicates the size of penumbra after an ischemic insult. It is reasonable to conclude that a patient with a larger area of penumbra, i.e. higher volume ratio, would have a better outcome and a smaller infarction size after treatment to improve cerebral blood flow. The results of this article demonstrate this tendency, however, there are some drawbacks. The method to delineate the abnormal signals in time-to-peak imaging is not clearly described and the choice of different delineation methods may affect the results. The number of patients is too few to obtain a significant conclusion.

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