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Original Article

Sagittal diffusion-weighted imaging in preventing the false-negative diagnosis of acute brainstem infarction: Confirmation of the benefit by anatomical characterization of false-negative lesions

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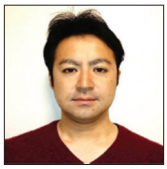

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ABSTRACT

Background: In some cases of acute brainstem infarction (BI), standard axial diffusion-weighted imaging (DWI) does not show a lesion, leading to false-negative (FN) diagnoses. It is important to recognize acute BI accurately and promptly to initiate therapy as soon as possible.

Methods: Of the 171 patients with acute cerebral infarctions in our institution who were examined, 16 were diagnosed with true-positive BI (TP-BI) and six with FN-BI. We evaluated the effectiveness of sagittal DWI in accurately diagnosing acute BI and sought to find the cause of its effectiveness by the anatomical characterization of FN-BIs.

Results: Considering the direction of the brainstem perforating arteries, we supposed that sagittal DWI might more effectively detect BIs than axial DWI. We found that sagittal DWI detected all FN-BIs more clearly than axial DWI. The mean time between the onset of symptoms and initial DWI was significantly longer in the TP group (17.6 ± 5.5 h) than in the FN group (5.0 ± 1.2 h; $P < 0.0001$). The lesion volumes were much smaller in FN-BIs (259 ± 82 mm^3) than in TP-BIs (2779 ± 767 mm^3; $P = 0.0007$). FN-BIs had a significant inverse correlation with the ventrodorsal length of infarcts (FN 3.5 ± 1.1 mm, TP 11.4 ± 3.6 mm; $P < 0.0004$) and no correlation with other size parameters such as rostrocaudal thickness and lateral width.

Conclusion: Anatomical characterization clearly confirmed that the addition of sagittal DWI to the initial axial DWI in suspected cases of BI ensures its accurate diagnosis and improves the patient's prognosis.

Keywords: Brain stem infarctions, Diffusion-weighted magnetic resonance imaging, False negative

INTRODUCTION

Acute brainstem infarctions (BIs) account for about 10% of all acute ischemic strokes.[17] The causes of BIs include large vessel diseases of the vertebral or basilar arteries, small vessel diseases of the small perforating arteries, and cardioembolism.[17] Axial diffusion-weighted MR imaging (DWI) is

highly sensitive in diagnosing acute cerebral infarctions.[21,24] However, its effectiveness in diagnosing acute BIs has not been established.[1,16,18,20] The previous reports show that the rate of false-negative (FN) DWI findings in BIs within the first 24 h of symptom onset ranges from 17% to 63%,[11,15,16,22] which is higher than that in cerebral hemispheric infarcts.[4] As recent advances in therapies such as intravenous thrombolysis with tissue plasminogen activator for acute cerebral infarction have remarkably improved patient outcomes,[5] prompt and accurate diagnosis is very important. Hence, reducing the rate of FN-BIs is of great interest. Recently, it has been shown that combing axial and thin-sliced sagittal DWI improves the detectability of acute BIs,[19] although the cause for the benefit has not been studied.

As the anatomical direction of BI formation is along the paramedian arteries, we supposed that sagittal DWI would more effectively detect acute BI than axial and coronal DWI. Hence, we used sagittal DWI to accurately detect acute BIs in our study and found that all the BI lesions that were FN on the initial axial DWI were detected clearly on sagittal DWI. We also examined the features of FN-BIs and found that the inverse correlation between the FN lesions and the sagittal ventrodorsal length of the infarction was significant and might explain why sagittal DWI was more effective in detecting FN lesions than axial and coronal DWI. Thus, we recommend the use of sagittal DWI combined with standard axial DWI for making a more prompt and accurate diagnosis of acute BI, which might improve the patient's prognosis, on the basis of anatomical characterization of FN-BIs.

MATERIALS AND METHODS

Subjects

This study was approved by the Institutional Review Board of Kurume University School of Medicine, Fukuoka, Japan. The procedures followed in this study were in accordance with the Helsinki Declaration of 1975, as revised in 2000. All authors had access to the data and statistical analysis and take responsibility for its integrity.

The clinical and radiological data of 171 consecutive patients with acute cerebral infarctions admitted in our hospital between January 2013 and December 2017, including data of 33 patients with BIs, were reviewed.

All patients with BIs who underwent DWI within 24 h of the onset of symptoms were included in this study, whereas patients whose final diagnoses were not infarction but included demyelinating diseases, central nervous system infections, and transient ischemic attacks were excluded from the study.

Before DWI examination, each patient was clinically evaluated by a neurologist and underwent computed tomography (CT) brain to rule out intracranial hemorrhage. In each case, the final diagnosis was made by the neurologist, who reviewed all the clinical and radiologic data available. DWI findings were assessed by two neurosurgeons and one neuroradiologist who were blinded to clinical data. The two neurosurgeons first examined each DWI and measured the size of the BI. Subsequently, as soon as possible, a neuroradiologist examined and confirmed their results and the BI size. In case of disparate opinions, the three doctors carefully reviewed the findings for the final results by observing and analyzing the DWI in detail. The diagnostic criteria of FN-BIs were as follows: (1) acute and clear brainstem symptoms and signs on arrival, even if subtle; (2) no high-intensity appearances on the initial axial DWI scan, with low apparent diffusion coefficient; and (3) definite diagnosis of BI on sagittal or coronal DWI performed just after the initial axial DWI scan.

Outcomes were presented as the scores with the modified Rankin scale (mRS) which is a simplified global assessment of function, in which a score of 0 indicates no impairment while a score of 5 indicates severe disability.[23]

Imaging

All patients underwent DWI examinations on a 3 Tesla Skyra scanner (Siemens, Germany). The standard axial DWI with single-shot echo-planar imaging covering the whole brain was initially performed with 5-mm thick slices and 1-mm gaps. Thin-sliced sagittal or coronal DWI only covered the width of the brainstem to decrease imaging time and was performed with 3-mm thick slices and 0.6-mm gaps each. The size of the ischemic lesion was measured on DWI by manually delineating the regions of interest. In each section, these areas were added and were multiplied with the slice thickness to determine the volume using the OsiriX (Pixmeo SARL, Bernex, Switzerland; Rosset, Spadola, and Ratib, 2004).

Statistical analysis

Statistical analyses were performed using the JMP® 13 (SAS Institute Inc., Cary, NC, USA). Results of all calculations are expressed as mean ± SD values. Descriptive data were analyzed using the Chi-square test or the Mann–Whitney U-test as appropriate. The lesion sizes on DWI were compared using the Mann–Whitney U-test. $P < 0.05$ was considered statistically significant.

RESULTS

Patients

Among the 171 patients with acute cerebral infarction who were included, 33 showed symptoms or signs suggestive of BI on admission. Five patients in whom DWI was not performed within 24 h of the onset of symptoms were excluded from the study. The remaining 28 patients were analyzed further. Six of

them had etiologies other than BI: one had ischemia in other territories and one had nonischemic etiologies. Twenty-two patients (22/171: 13%) had BI which was confirmed as the final diagnosis. Among these 22 patients, 16 patients were diagnosed with BI using the initial axial DWI scan (true positive [TP]) and six patients were not (FN). Their lesions (FN lesions) were detected on sagittal or coronal DWI performed immediately after the axial DWI scan.

Thin-section sagittal DWI facilitating the accurate diagnosis of acute BI

Table 1 shows the effectiveness of thin-section sagittal or coronal DWI in detecting the BI lesions in the six patients in whom it had not been determined using the initial axial DWI scan taken 4.5–7 h after the onset of symptoms. All six lesions (6/6: 100%) were detected using the thin-section sagittal DWI scan. Coronal DWI was performed additionally in three FN cases; however, the lesion was detected in only one (1/3: 33.3%). The representative DWI scan shown in Figure 1 demonstrates that the lesion of the acute BI could be detected as a high intensity on sagittal DWI, but not on standard axial or coronal DWI. The outcomes of all six cases at 6 months were relatively good (mRS; 0–2: 67% and 3: 33%) as the lesions were detected promptly using thin-section sagittal DWI and appropriate treatment was initiated. The lesions were mainly located in the pons, consistent with a previous report.[8,19] When the second magnetic resonance imaging (MRI) was

Table 1: The false-negative lesions of acute brainstem infarction on axial DWI were clearly detected on sagittal DWI.

Age and sex	Symptom	Location	Time to DWI (h)	Axial DWI	Sagittal DWI	Coronal DWI	Outcome (mRS)
85 M	MLF syndrome	Pons	5	−	+	−	2
58 M	Hemiplegia	Pons	6	−	+	−	1
72 F	MLF syndrome	Pons	5	−	+	+	2
65 M	Hemiplegia	Midbrain	6	−	+	Not measured	3
74 M	MLF syndrome	Pons	7	−	+	Not measured	2
77 F	Hemiplegia	Pons	4.5	−	+	Not measured	3

DWI: Diffusion-weighted magnetic resonance imaging, M: Male, F: Female, MLF: Medial longitudinal fasciculus, +: Visible, −: Invisible, mRS: Modified Rankin scale

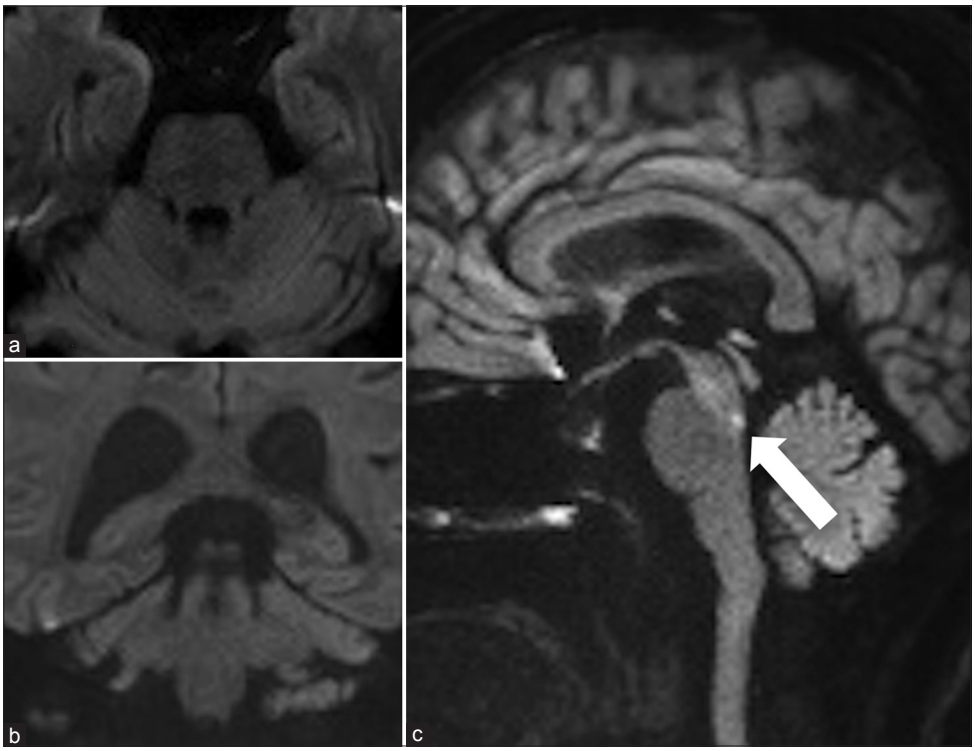

Figure 1: The representative DWI of case 1 (an 85-year-old man with medial longitudinal fasciculus syndrome) that were taken 5 hours after the onset of symptoms is shown. No abnormal intensity is seen on a) standard axial, and b) coronal DWI scans; c) sagittal DWI scan shows a clear hyper-intensity, which is indicated by an arrow.

performed 7 days after the initial MRI, all six patients were shown to have infarction lesions on axial DWI.

Six patients who were suspected to have BI on admission were consequently diagnosed as not having BI. Their sagittal DWI scan did not show positive signals in the brainstem, suggesting that sagittal DWI had a high negative predictive value for acute BI (6/6: 100%). This indicated that sagittal DWI had not only high sensitivity but also high specificity in diagnosing acute BI.

Characterization of false-negative DWI in acute BI

The FN rate of diagnosing BIs using axial DWI was 27.6% (6/22) while that of hemispheric infarctions was 1.2% (2/134) ($P < 0.0001$). The results were similar to those of the previous studies.[3,4,9-11,14-16] To find the reason why sagittal DWI more effectively detected BI lesions than axial and coronal DWI, we studied the characteristics of the FN lesions. The mean time from the onset of symptoms to performing the first DWI was 19.1 h (range 3.0–24.0 h). The difference between these mean times in patients in the TP group (17.6 ± 5.5 h [mean ± SD]) and those in the FN group (5.0 ± 1.2 h [mean ± SD]) was significant ($P < 0.0001$) [Figure 2]. Among the 16 patients in the TP group, the first DWI scan was taken within 6 h in one, 6–12 h in three, 12–18 h in eight, and 18–24 h in four. Among the patients in the FN group (six patients), the first DWI was performed within 6 h in five patients and 6–12 h in one patient [Figure 2].

The DWI lesions in the FN group were significantly smaller (final volume: 259 ± 82 mm^3 [mean ± SD]) than those in the TP group (final volume: 2779 ± 767 mm^3 [mean ± SD]) as determined by the Mann–Whitney U-test ($P = 0.0007$) [Figure 3].

Next, we compared the three-dimensional infarct size in the rostrocaudal, lateral, and ventrodorsal lengths [Figure 4]. FN lesions inversely correlated with the sagittal ventrodorsal length (FN 3.5 ± 1.1 mm, TP 11.4 ± 3.6 mm [mean ± SD]; $P = 0.0004$) [Figure 4c and f]. However, FN lesions did not correlate with other infarct size parameters such as sagittal rostrocaudal thickness (FN 5.6 ± 1.4 mm, TP 7.7 ± 2.2 mm [mean ± SD]) [Figure 4a and d] and lateral width (FN 4.4 ± 0.7 mm, TP 7.8 ± 1.9 mm [mean ± SD]) [Figure 4b and e]. These results indicate that thin-section sagittal DWI can detect very small acute BI lesions more effectively than axial or coronal DWI.

DISCUSSION

The value of DWI in detecting acute BI is still controversial. Some studies report a high detection rate,[6,8,13,21] whereas others report high rates of FN diffusion changes, especially within the first 24 h.[3,11,14-16] Recent advances in therapies for acute cerebral infarction have remarkably improved patient outcomes. Hence, early and accurate diagnosis is critical since misdiagnosis may have serious consequences to the patient such as delayed treatment and recurrent strokes.[12] Therefore, a reduction in the FN diagnosis of acute BI is desirable. Recently, it has been reported that combining standard axial and thin-sliced sagittal DWI improve the detectability of acute BI, although the cause of the improvement has not been studied.[19] In the present study, we also showed that the FN diagnosis of acute BI can be prevented by combining thin-section sagittal DWI with standard axial DWI. We found that the combination showed high sensitivity and specificity for the diagnosis of acute BI. Furthermore, we characterized the FN lesions of acute BI and found that the result may explain the reason why thin-section sagittal DWI could more effectively detect small BI lesions than axial or coronal DWI.

Although the exact reason why FNs for acute BI occur remains unclear, several mechanisms have been suggested, such as the dense nuclei and fibers within the brainstem,[2] the higher sensitivity to partial volume effects,[2] and the ischemic tolerance of the brainstem.[25]

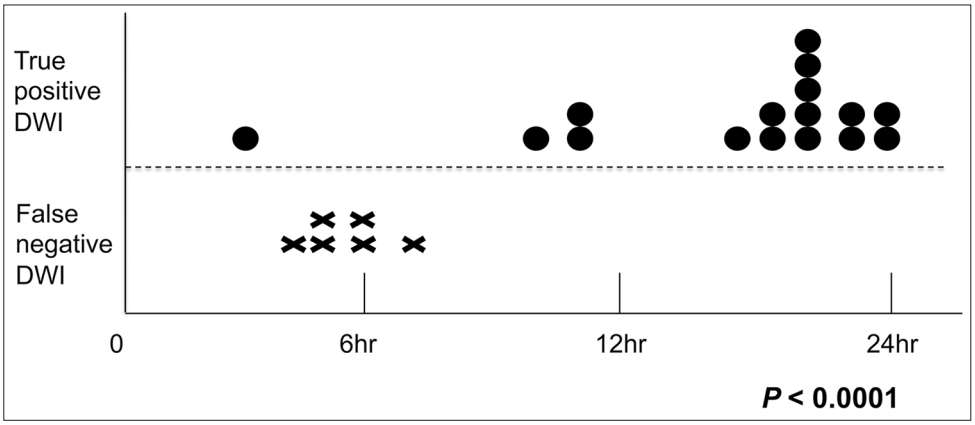

Figure 2: The time after the onset of symptoms when the patients were diagnosed to have true-positive or false-negative brainstem infarctions on DW is shown. hr: hours.

There are a few previous reports on the clinical features of FN-BIs within 24 h of the onset of symptoms.[4,11,22] However, there is no report focusing on FN-BIs within 6 h of onset, which is the "golden period" when a broad range of treatment options can be used. Thus, we examined the characteristics of FN-BIs diagnosed within 6 h of the onset of symptoms.

We found that FN-BIs were more frequently diagnosed using standard axial DWI performed within 6 h of the onset of symptoms [Figure 2] and that the volumes of the FN

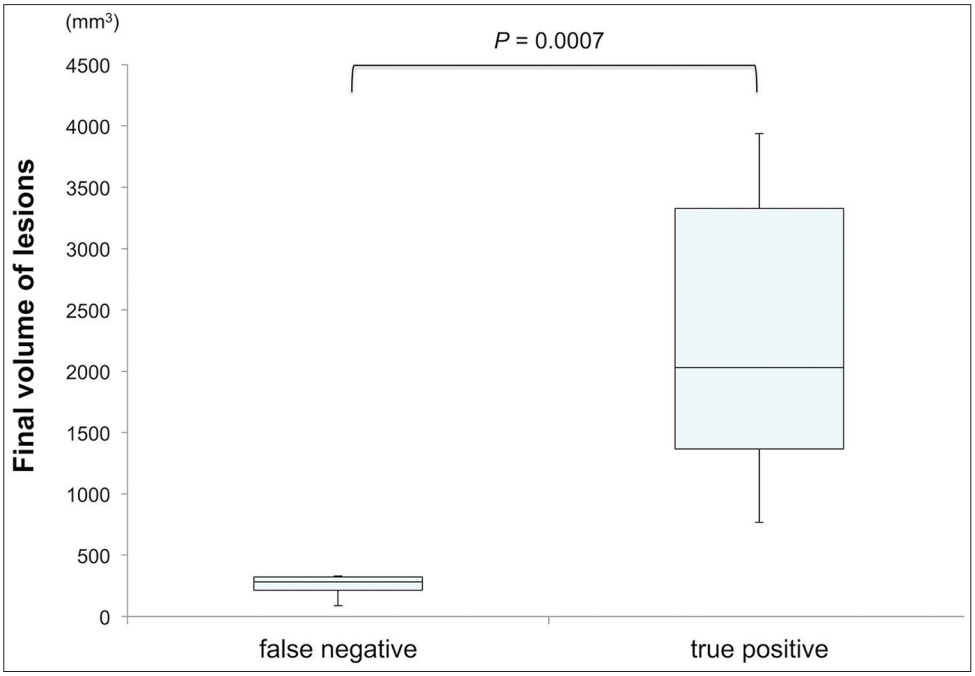

Figure 3: The final volume of the false negative or true positive brainstem infarction lesions is shown. The volumes of the false-negative lesions are significantly smaller than that of true-positive lesions.

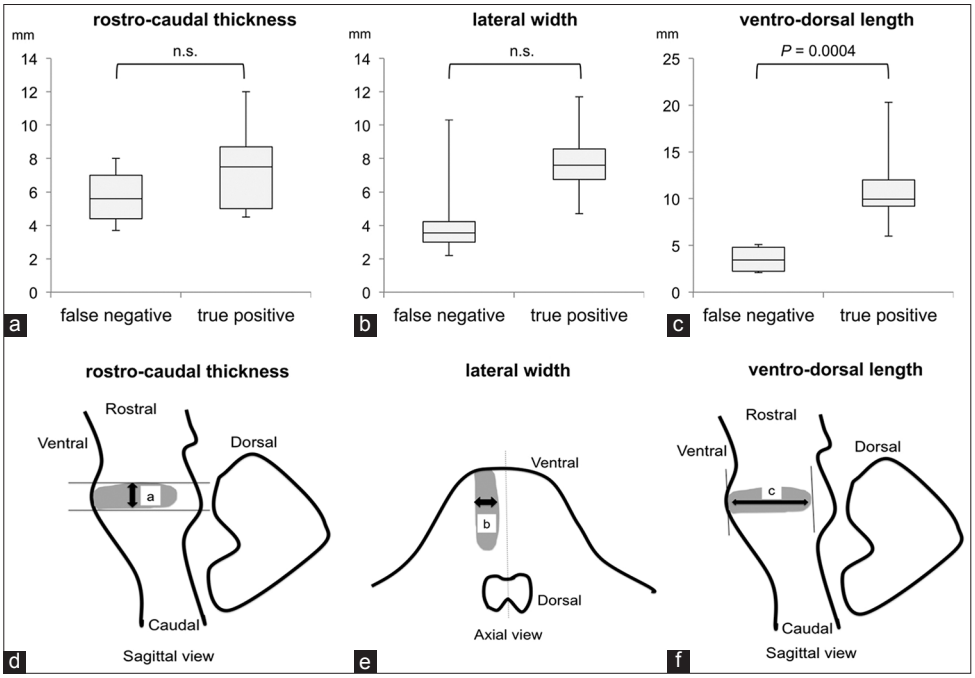

Figure 4: The illustrations show a and d) the sagittal view of rostro-caudal thickness, b and e) axial view of lateral width, and c and f) sagittal view of ventrodorsal length.

lesions were significantly smaller than those of the TP lesions [Figure 3]. We also found that FN lesions had a significant inversely correlation with the ventrodorsal thickness of the BI [Figure 4c and f]. These findings indicate that an infarction with a short ventrodorsal length and a small volume is hardly detectable using only axial DWI and that the axial plane slices are too thick and have poor resolutions to detect the infarct. Thin-section sagittal DWI is more effective in detecting BIs due to the following anatomical features of brainstem infarcts. BI at the level of the pons and medulla oblongata tends to extend in the ventrodorsal direction rather than the rostrocaudal direction, reflecting the blood flow of the paramedian artery.[17] The sagittal plane slices in sagittal DWI are positioned parallel to the course of the perforating brainstem arteries and capture a wider cross-sectional area of the brainstem per slice than do the slices in axial DWI. Thus, even very small BI lesions could be detected on thin-section sagittal DWI when compared with axial DWI [Table 1].

Furthermore, we also examined the effectiveness of coronal DWI in detecting BIs using three cases of FN-BIs [Table 1]. Only one case could be detected. Recently, Felfeli *et al*.[7] demonstrated that only a very low rate of acute BI cases was detected using thin-section coronal DWI (2%), which is comparable to our data (5.3%). The BI lesions sometimes appear as a dot-like shape without stretching continuously in the ventrodorsal direction. In such small lesions, the slices of coronal DWI seemed to be too thick to detect the BIs.

The retrospective design and small number of participants limit our study. The reasons why the number of participants was small in this study were as follows. First, all patients with suspected BI on admission first underwent examination with CT scan to rule out hemorrhage and some patients subsequently underwent MRI examinations. We excluded the cases who underwent MRI examinations after 24 h of the onset of symptoms. Second, for the second MRI examination after the axial MRI, thin-sliced sagittal DWI was not performed for all cases.

CONCLUSION

Thin-section sagittal DWI combined with standard axial DWI was effective for the prompt and accurate diagnosis of BI in patients with suspected acute BI, thereby facilitating improved prognoses. The effectiveness was confirmed by the analyses comparing the three-dimensional infarct size in the ventrodorsal, lateral, and rostrocaudal lengths.

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Conflicts of interest

There are no conflicts of interest.

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