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Detection of Acute Brainstem Infarction by Using DWI/MRI

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Key Words
Brainstem infarction · Diffusion-weighted imaging · Different rater expertise

Abstract
Even using diffusion-weighted images (DWI) detection of acute brainstem infarction (BI) is still a challenge. To evaluate the clinical efficacy of a DWI protocol with improved spatial resolution all images of 44 patients with clinically possible BI on admission (24 patients with definite BI and 20 patients with other etiologies) and first DWI within 24 h after symptom onset were blindly reanalyzed for visibility and detection of BI on the first DWI by reviewers with different expertise levels. Neuroradiologists identified definite BI in 21 out of 24 patients (sensitivity 90%, specificity 100%); neurologists and junior house officers achieved similar results (sensitivity 86 and 83%, specificity 98 and 97%). The use of DWI allows a definite diagnosis of BI, even if raters have limited experience.

Introduction

Diffusion-weighted imaging (DWI) has become an important tool in the diagnosis of acute ischemic brain infarction. By detecting restricted diffusion of water molecules caused by cytotoxic edema it mostly allows the localization of ischemic or injured brain within the first hours of symptom onset [1–4]. Unless cranial nerve palsies, crossed hemiparesis or specific brainstem syndromes are present, clinical symptoms do not have sufficient power to indicate a brainstem location [5]. For example, pure motor hemiparesis or ataxic hemiparesis are frequently seen in pontine lesions but do not necessarily indicate a pontine location. Therefore, the diagnosis of brainstem infarction (BI) is limited if based solely on clinical grounds [6]. The value of DWI in acute BI is still controversial as some studies reported a high detection rate [7–10], but other studies found false-negative diffusion changes especially within the first 24 h [11–15]. We evaluated the clinical efficacy of DWI in detecting early diffusion changes in BI. To test daily clinical practice, images were separately and blindly reanalyzed by neuroradiologists, neurologists and junior house officers challenging the hypothesis that neuroradiologists do better than house officers in detecting BI on DWI.

Subjects and Methods

Subjects

We reviewed clinical and radiological data of 984 consecutive patients admitted to our Stroke Unit during January 2001 and January 2003 with a suspected acute ischemic stroke according to the World Health Organization criteria [16]. All patients with BI and

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time latency between onset of symptoms and the first DWI of less than 24 h were included in further analysis. Diagnosis of BI was based on clinical grounds and neuroradiological identification. As a control group, we used all patients in which a BI was suspected on admission but another location or etiology was found and in which the first DWI was also performed within 24 h. Based on the presenting symptoms and neurological findings on admission, a possible BI was considered if one of the following complete syndromes or at least fragments of it were present: medial or lateral medullary, pontomedullary, basilar artery, medial and lateral inferior pontine, medial and lateral midpontine, medial and lateral superior pontine syndrome [17, 18].

Imaging

All patients with suspected BI obtained the same imaging protocol, which was performed on an MRI scanner with 1.5 T (Magnetom Symphony Quantum gradient, Siemens Medical Systems, Germany) and included transversal T_1, transversal T_2 and two DWI sequences, usually transversal and sagittal plane. In selected cases, an additional coronal DWI plane was obtained. The DWI parameters were: TR 4,006 ms, TE 83 ms, slice thickness 4–6 mm, gap 1.5 mm, 128 × 128 pixel matrix, 220 × 220 mm field of view, three b values (0, 500, 1,000 s/mm^2) and apparent diffusion coefficient (ADC) maps. If MRI could not be obtained immediately, a brain CT was done first and MRI was performed as soon as possible. A second series of imaging including DWI was performed within the next 5 days, if initial imaging could not detect a BI and if no other etiology was found.

Image Analysis

All images were analyzed for visibility and detection of BI separately by two experienced neuroradiologists, three senior neurologists and three junior house officers. All raters regularly took part in the daily clinical conferences on neuroradiology and they were blinded to specific clinical details except for the question of acute ischemic lesion including brainstem. Three categories were defined: definite BI (= increased DWI signal intensity in two planes and corresponding ADC slice with decreased signal intensity), no BI (= no signal intensity changes) and possible BI (= signal intensity changes but not fulfilling all criteria of definite BI, e.g. increased DWI signal intensity in only one plane or without decreased signal intensity in the corresponding ADC slice). The findings were independently classified by each rater with subsequent calculation of the interrater reliability.

Diagnostic

All patients underwent intensive diagnostic follow-up, which included standard 12-lead ECG, monitor ECG, 24-hour ECG, echocardiography (usually transthoracic, if indicated transesophageal), neurosonography (extracranial continuous-wave and duplex sonography and transcranial Doppler sonography), routine laboratory, coagulation and vasculitis screening. If indicated, MR angiography or conventional angiography were additionally performed.

Statistical Analysis

Quantitative values are given as means with ranges, which were calculated using the GraphPad Prism version 3.02 (GraphPad Software, San Diego, Calif., USA). Sensitivity, specificity and predictive values [including 95% confidence intervals (CIs)], interrater reliability and unpaired t test were assessed by GraphPad InStat version 3.00 (GraphPad Software).

Results

Patients

Among 984 patients with symptoms of stroke, 116 (11.8%) showed symptoms or signs of possible BI on admission. Seventy-two patients were excluded from further analysis as DWI was not performed within 24 h. The remaining 44 patients with clinically possible BI on admission and DWI within 24 h were included in the analysis. In 24 patients, the diagnostic follow-up confirmed a BI; the characteristics and radiologic results are given in table 1. The remaining 20 patients had no BI and other etiologies (15 ischemias in other territories, 5 non-ischemic etiologies) were diagnosed (table 2).

Imaging

The mean time to first DWI for all patients was 13.2 h (range 2.5–24.0). There was no significant difference ($p = 0.15$) between the mean time to first DWI in patients with definite BI (14.6 h, range 2.5–24.0) and those without BI (11.0 h, range 3.0–24.0). Among patients with definite BI, first DWI could be obtained in less than 6 h in 7 patients, between 6 and 12 h in 1 patient, between 12 and 18 h in 4 patients and between 18 and 24 h in 12 patients.

The two neuroradiologists identified the ischemic brainstem lesion in 21 vs. 22 out of 24 patients with definite BI on the initial DWI (exemplary images in figure 1a and b). Sensitivity was 90% (95% CI 70.3–98.2), specificity 100% (95% CI 83.2–100), positive predictive value 100% (95% CI 84.2–100) and negative predictive value 89% (95% CI 68.6–98.1). In 3 vs. 2 patients, initial DWI detected possible BI, and follow-up DWI verified the presumed small infarctions (example in figure 2). All 20 patients without BI were correctly classified as no BI by both neuroradiologists resulting in a very good interrater reliability ($\kappa = 0.86$). The three neurologists and the three junior house officers reached similar results (table 3). Common characteristics of those 3 patients in which the initial DWI could not be rated as definite BI even by the neuroradiologists were technical imaging problems (no second plane in patient 10, motion artifacts directly adjacent to ischemic hyperintensity in second plane in patient 21), small lesion size (mean volume 0.12 cm^3 on control imaging) and localization (dorsal part of the medulla oblongata and pons, adjacent to the fourth ventricle).

Those lesions which were missed by the nonneuroradiologists but were detected by the neuroradiologists showed a small lesion volume and weak signal intensity.

Table 1. Clinical data and imaging results in patients with definite BI

Patient	Sex/age	Leading symptoms and clinical findings	DWI time, h	Lesion location
1	f/61	DYSA, VERT, L HP	2.5	R paramedian pons
2	f/68	DYSA, L III palsy, R HP L HS	3.5	L paramedian pons
3	m/68	R HP, L HS	3.5	L ventral medulla
4	m/65	R HP, ATX	4.75	L paramedian pons
5	m/55	DYSA, R HP + HS, ATX	5.0	L paramedian pons
6	f/72	nausea, R gaze palsy, R DYSM, R facial HS	5.25	L paramedian pons
7	m/68	DYSA, L HP, ATX	5.5	R paramedian pons
8	m/81	XII palsy, R HP, R + L Babinski	9.0	L midbrain
9	m/83	VIG, DYSA, DYSP, R HP, R + L Babinski	13.5	L paramedian pons
10	f/58	VERT, L IX palsy, DYSA, ATX	14.75	L dorsal medulla
11	m/61	DYSA, R VII/IX/XII palsy, R HP	17.75	L paramedian pons
12	m/72	VERT, L IV palsy, R HP	18.0	L dorsal pons
13	m/68	VERT, L VII palsy, ATX	18.5	R paramedian pons
14	f/61	VERT, DIPL, R HP	18.75	L paramedian pons
15	m/75	DYSA, ATX, L Babinski	19.0	R lateral medulla
16	m/71	VERT, L XII palsy, L HP, R + L Babinski	19.5	R paramedian pons
17	m/63	VERT, R INO, ATX	19.5	R dorsal pons
18	m/58	nausea, L HP + HS	20.0	R ventral medulla
19	m/61	R INO, L HS, ATX	20.0	R paramedian pons
20	m/75	VERT, DYSA, ATX, fixation nystagmus, R Horner, L Babinski, L HS	21.0	R lateral medulla
21	m/74	VERT, DYSA, DIPL, fixation nystagmus	22.0	L paramedian pons
22	m/59	DYSA, L HS	23.0	R lateral medulla
23	f/26	VIG, DIPL, DYSA, L HP	23.0	R paramedian pons
24	f/92	DYSA, R HP, R HS	24.0	L paramedian pons

f = Female; m = male; L = left; R = right; HP = hemiparesis; HS = hemihypesthesia; DYSA = dysarthria; VERT = vertigo; ATX = gait ataxia; III/IV/VI/VII/XII = cranial nerve palsy; DIPL = diplopia; DYSM = dysmetria; DYSP = dysphagia; VIG = impaired vigilance; INO = internuclear ophthalmoplegia.

Discussion

Neuroradiological detection of BI poses several difficulties: lesions are often small in size, and the brainstem is adjoined to bones of the skull base inducing susceptibility. Especially visibility of small infarctions [12] or infarctions within the first hours [11] has been reported as difficult. Our study revealed high sensitivity and specificity in the diagnosis of acute ischemic brainstem lesions by using DWI within the first 24 h, even if raters have limited experience. Infarctions within the first 6 h demonstrated good visibility.

Results of Other Studies

The results of this study contrast with those of previous studies indicating a high rate of false-negative DWI in the diagnosis of acute BI [11–15]. Lovblad et al. [15] retrospectively analyzed 194 cases of acute supra- and infratentorial ischemic stroke diagnosed clinically in which DWI could be performed within 24 h of onset. In 18 false-negative patients, who had negative DWI but were classified as stroke based on clinical grounds, small infarcts in the brainstem were presumed but not verified. Kuker et al. [11] concluded in an analysis of 45 acute brainstem and thalamic infarctions that the identification of all infarctions within 5 h was not possible and detectability of medulla oblongata infarctions remained difficult within the first 24 h. Ay et al. [12] observed 27 patients with

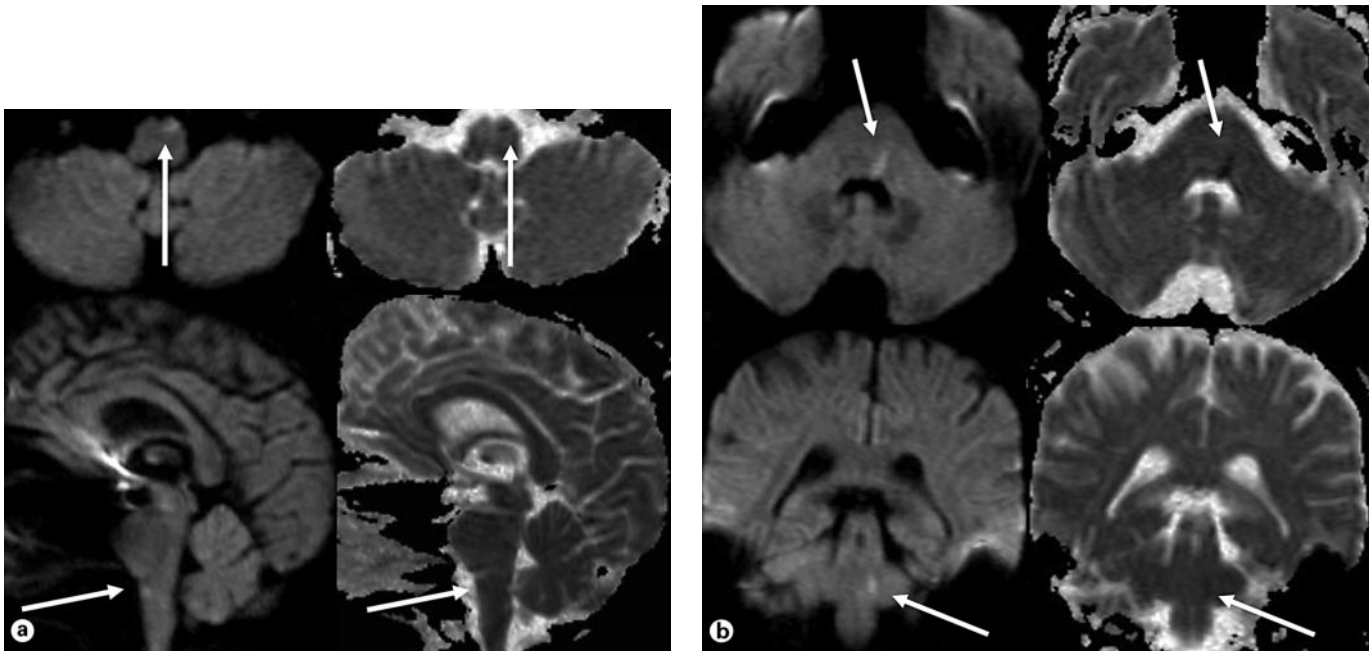

Fig. 1. Exemplary DWI (b = 1,000 s/mm^2 and ADC) of 2 patients performed within 6 h after symptom onset presented with patient's number, time latency and planes (clockwise from top left, arrows indicating ischemia). **a** Patient 3, 3.5 h (axial b = 1,000, axial ADC, sagittal ADC, sagittal b = 1,000). **b** Patient 5, 5.0 h (axial b = 1,000, axial ADC, coronal ADC, coronal b = 1,000).

Table 2. Clinical data and imaging results in patients without brainstem infarction

Patient	Sex/age	Leading symptoms and clinical findings	DWI time, h	Lesion location
26	f/72	VERT, L Babinski, L DYSM	3.0	L cerebellar ischemia
33	f/66	VERT, R HS	7.0	L cerebellar ischemia
27	f/94	VERT, DIPL	5.0	R cerebellar ischemia
42	m/48	DIPL, DYSA, ATX	20.5	R cerebellar ischemia
28	f/49	VERT, L HS, L DYSM	5.0	R thalamus ischemia
31	f/35	DYSA, VERT, L HP	6.0	R thalamus ischemia
32	f/77	R HP, DYSA	6.5	L MCA ischemia
37	m/67	VERT, ATX, DYSA, R HP	11.75	L MCA ischemia
25	f/82	VERT, DYSA, R HP	1.0	R MCA ischemia
29	m/70	VIG, L HP, DYSA, ATX	5.5	R MCA ischemia
34	m/70	ATX, L HP	7.0	R MCA ischemia
39	m/62	L HP, DYSA, ATX	12.25	R MCA ischemia
36	f/43	DYSA, R HP	7.5	R MCA ischemia
40	f/52	DYSP, ATX, L HP	16.0	R MCA ischemia
41	f/68	VERT, DYSA, L HP	19.5	R MCA ischemia
30	f/65	DIPL, ATX	6.0	R diabetic III palsy
44	m/89	DIPL, R facial HS	24.0	R diabetic VI palsy
35	m/32	L HP, DIPL, VERT, DYSA	7.0	migraine with aura
38	f/33	L HS, DYSA	12.0	multiple sclerosis
43	m/67	VERT, ATX	22.0	vestibular neuropathy

L = Left; R = right; HP = hemiparesis; HS = hemihypesthesia; DYSA = dysarthria; VERT = vertigo; ATX = gait ataxia; III/IV/VI/VII/XII = cranial nerve palsy; DIPL = diplopia; DYSM = dysmetria; DYSP = dysphagia; VIG = impaired vigilance; MCA = middle cerebral artery.

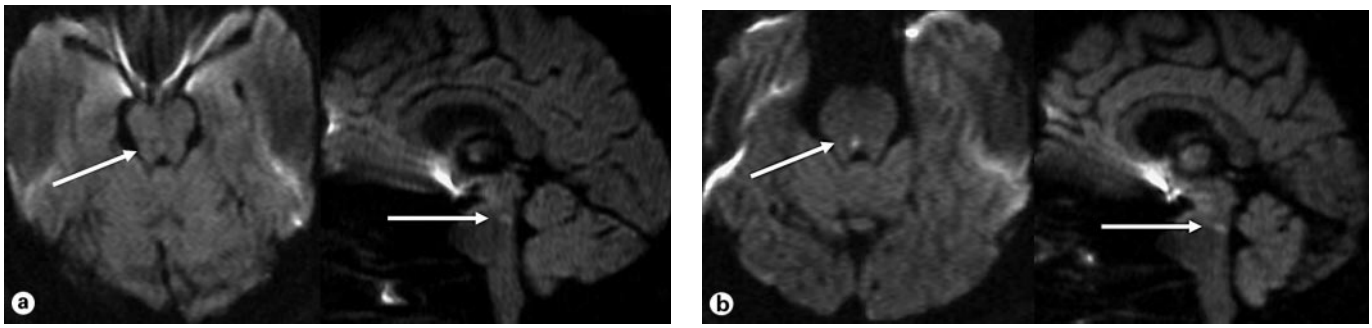

Fig. 2. DWI of patient 17 with initial DWI (b = 1,000 s/mm^2) displaying the ischemic lesion only clearly on the sagittal plane and follow-up DWI confirming the infarction in both planes (arrows indicating ischemia). **a** Axial and sagittal plane performed 19.5 h after symptom onset. **b** Axial and sagittal plane performed 36 h after symptom onset.

Table 3. Mean statistical results (%) of different rater groups, with 95% CIs in parentheses

	Neuroradiologists	Senior neurologists	Junior house officers
Sensitivity	90 (70.3–98.2)	86 (66.0–96.6)	83 (62.7–95.2)
Specificity	100 (83.2–100)	98 (80.5–100)	97 (77.8–99.9)
Positive predictive value	100 (84.2–100)	99 (81.4–100)	97 (78.5–99.9)
Negative predictive value	89 (68.6–98.1)	86 (64.7–96.5)	83 (61.8–95.1)
Interrater variability κ	0.86	0.80	0.75

normal DWI of 728 patients with clinical stroke-like deficits, and on radiological follow-up, they found small BI in 3 patients. Oppenheim et al. [13] reanalyzed 139 mixed stroke patients with initially negative MR images obtained at a mean of 8.8 h after stroke onset. Five of 8 initially false-negative cases had a lesion in the brainstem and no false-negative DWI was observed in patients imaged after 24 h. Narisawa et al. [14] reported that only in 16 out of 28 patients with the final diagnosis of BI could the initial DWI demonstrate the ischemic lesion, whereas in the remaining 12 cases subsequent MRI studies were necessary to detect the final lesion. Three newer studies described similar detection rates of DWI as compared to our results. Fitzek et al. [7] investigated 7 patients with BI within the first 24 h and found pathological DWI signal intensities in the brainstem in all patients. Linfante et al. [8] reported a detection rate of 100% in 7 medullary and 12 pontine infarctions investigated at a mean of 9.7 h after symptom onset. One recent report detected BI in 8 patients with DWI performed between 3 and 24 h after symptom onset, but failed to detect BI in those with DWI obtained within 3 h of onset [9]. The latest study found a detection rate of 95% in 22 infratentorial strokes including 14 patients with BI at a mean of 18 h [10].

Our detection rate and interrater variability is comparable to those reported in the study by Fiebach et al. [19] who investigated the expertise of different raters comparing CT and DWI in patients with clinical signs of anterior territory ischemic stroke. For DWI, their sensitivity and specificity of the experts were 91 and 95%, and of the novices 81 and 100%.

Analysis of Possible BI

The analysis of possible BI revealed some common characteristics which might have contributed to the problem of identification as definite BI. In addition to the technical imaging problems and the small lesion size, the localization of possible BI adjacent to the fourth ventricle may cause susceptibility effects due to the direct neighborhood to CSF complicating the identification as definite BI. In the case of patient 10 with infarction in the left medulla oblongata, the performance of a second plane might have shown the lesion more clearly resulting in a classification as doubtless ischemia and improving sensitivity. We did not investigate if in those doubtful cases the performance of an additional third DWI plane had resulted in a better detection.

Clinical Relevance

The results of this study demonstrate that a clear identification of BI even in the first hours of ischemia is possible. This point is of high clinical relevance for two reasons. First, as the diagnosis of BI is limited if based solely on clinical grounds, this early and clear identification of BI allows the otherwise difficult differentiation of similar clinical syndromes. Thus, using DWI one is able to make a definite diagnosis of brainstem versus capsular infarct, for example. Second, rapid identification of BI could be an important hint to a basilar thrombosis at an early stage that would influence further therapeutic management. Comparison between the results of neuroradiologists, neurologists and junior house officers revealed similar sensitivity, specificity and predictive values, which is in accordance with another study [19]. As in daily routine, patients and imaging results are first assessed by junior house officers, and the establishment of a reliable imaging modality would assist in the rapid initiation of therapy.

However, due to the risk of false-positive and false-negative findings implied by the study design, the results have to be interpreted cautiously.

In conclusion, our data have shown that DWI can reliably identify hyperacute BI and it allows a definite diagnosis of BI. This is also valid for raters with limited experience, which could help in the rapid initiation of an adequate therapy. Only small infarcts in the dorsal part of the pons or medulla oblongata may initially not present with a clear DWI deficit. The future use of DWI could substantially reduce the number of follow-up imaging, which would be cost-effective and more comfortable for the patient.

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