Recent studies have established diffusion weighted magnetic resonance imaging (MRI) (DWI) in the early diagnosis of ischaemic stroke.\(^\text{1–6}\) It measures the diffusion of water molecules mainly in the intercellular space, and DWI hyperintensities allow the diagnosis of ischaemic tissue damage within minutes of stroke onset in animal models.\(^\text{7–9}\) In the human, DWI has shown relevant changes even in a substantial proportion of patients with clinical criteria for a hemispheric transitory ischaemic attack (TIA).\(^\text{10–12}\) TIA is generally defined as acute neurological impairment with a vascular cause resolving within 24 hours. Obviously some of these patients may experience ischaemic tissue damage.\(^\text{13}\)

Little is known about the ability of DWI to show lacunar ischaemia in the brainstem, where routine computed tomography (CT) and MRI often fail to detect ischaemic abnormalities.\(^\text{14–16}\) We are not aware of any report on the sensitivity of DWI in the clinical diagnosis of brainstem transitory ischaemic deficits. Reliable diagnosis of ischaemic lesions, however, is essential in identifying patients with subsequent increased risk of stroke. The aim of our study was to evaluate the sensitivity of DWI in the diagnosis of clinically suspected reversible ischaemic deficits of the brainstem and to correlate the duration of neurological deficits and DWI abnormalities.

PATIENTS AND METHODS

From November 1997 to July 2000, we prospectively recruited 158 consecutive patients presenting with acute signs and symptoms of brainstem dysfunction suspicious of vertebrobasilar ischaemia. Clinical criteria included acute cranial nerve dysfunction, oculomotor deficits, and gait or limb ataxia. Patients underwent MRI following a fixed protocol (see below).

Ethical approval of the study was granted by the local ethics committee, and patients gave informed consent to the procedures.

MRI

Biplane echo planar imaging T2 and diffusion weighted (DWI) MRI was performed in all patients within 24 hours of the onset of symptoms with a 1.5 T system (Magnetom Vision; Siemens, Erlangen, Germany). We used DWI echo planar imaging (TR 4000 ms; TE 103 ms) with separately applied diffusion gradients in the three spatial axes ($b=1164 \text{ s/mm}^2$; 128 matrix; 250 ms per slice; 20 slices; thickness 3 mm; eight measurements). Axial and sagittal high resolution T2 weighted imaging (TR 3810 ms; TE 90 ms; 256 matrix; slice thickness 3 mm; FOV 220/210 for transversal and 220/230 for sagittal slices) and T1 weighted imaging (TR 600 ms; TE 14 ms; 256 matrix; slice thickness 3 mm; FOV 220/210 for transversal and 220/230 for sagittal slices) before and after intravenous application of gadolinium were performed as soon as patients could tolerate the longer MRI scan (median 6.5 days after the onset of symptoms).

Statistical analyses

Fisher’s exact test was used for statistical correlation analyses. Statistical significance was set at $p<0.05$.

RESULTS

Thirty of 158 patients presenting with signs and symptoms of acute brainstem impairment met the clinical criteria of a transient reversible neurological deficit. In 14 of these 33 patients, symptoms and signs resolved in less than 24 hours. Nineteen patients had a prolonged reversible neurological deficit (RIND) persisting for more than 24 hours but less than one week. Eleven of the 33 patients were women. Age ranged from 29 to 82 years (mean 63.5). The most common neurological sign was gait ataxia (25 patients). In 12 patients cranial nerves were affected, mainly the oculomotor and trigeminal nerve. Five patients presented with pathological nystagmus, four had an internuclear ophthalmoplegia, and...
four a skew deviation. Other common neurological signs were motor hemiparesis (ten patients) and dysarthria (seven patients). Table 1 gives basic and clinical details.

Sonography and MR angiography showed stenosis of one vertebral artery in three patients. In one patient, acute brain-stem signs occurred immediately after a chiropractical manoeuvre, but MR angiography and sonography did not verify vertebral artery dissection. In two patients, echocardiography gave evidence of a cardioembolic cause. Eighteen patients had multiple vascular risk factors, and sonography showed macroangiopathy of the internal carotid artery but no vertebral stenosis or occlusion. In nine patients, the cause of brainstem ischaemia remained unclear.

DWI was applied 2–22.5 hours after the onset of symptoms (mean interval 10.7 hours). It showed acute ischaemic lesions in 13 (39%) of the 33 patients with transient neurological impairment. This included four of 14 (29%) of the TIA group and nine of 19 patients (47%) with RIND (table 2). The difference in the detection rate between patients with TIA and RIND was not statistically significant.

The lesions were located in the pons in seven patients, in the mesencephalon in four patients, and in the medulla in two. High resolution T1 and T2 weighted MRI was performed after a mean of 6.5 days. Of the 13 patients with abnormal DWI, two had no corresponding relevant infarction on follow up imaging (one with TIA and one with RIND). In six patients, follow up imaging disclosed additional pre-existing ischaemic lesions. Lesions detected by high resolution MRI were judged non-acute if no topographically corresponding diffusion abnormality was found by DWI and if lesions did not show signs of acute ischaemia such as T2 hyperintensity or gadolinium enhancement.
DISCUSSION

In our study, DWI showed acute brainstem lesions in 39% of patients with reversible neurological impairment attributed to brainstem ischaemia. The number of structural abnormalities according to DWI was higher in the group of patients with longer lasting symptoms classified as RIND than in the TIA group. The difference, however, was not statistically significant. The rate of 29% of DWI detected ischaemic changes in the TIA group is lower than the 48% reported in the only formal DWI study on hemispheric TIs.8 The incidence of hemispheric DWI abnormalities in patients with RIND has not been reported so far. The rapid reversibility of symptoms and signs does not necessarily mean the absence of structural changes as shown by DWI. Resolution of the clinical impairment within 24 hours may be due to a lesion of a “non-eloquent” area—that is an area where a lesion does not result in any clinical signs—or the transient involvement of a functional structure by the perilesional penumbra. The high density of tracts and nuclei within the brainstem increases the risk of structural lesions becoming symptomatic as compared with the supratentorial condition. To the best of our knowledge, there have been no previous formal studies to evaluate the sensitivity of DWI in patients with transitory ischaemia of the brainstem. In a retrospective study, Linfante et al. reported a much higher yield of diffusion abnormalities in patients with posterior circulation stroke. Patients with reversible deficits, however, were explicitly excluded from the study. Moreover, the specificity and sensitivity of DWI cannot be reliably evaluated from this investigation, because the diagnosis of vertebrobasilar ischaemia was based in part on the result of the DWI.

Studies looking mainly at supratentorial lesions based on routine CT and MRI reported even lower frequencies of acute lesions in patients with TIA, ranging from 12% to 48%.9 However, CT and routine MRI do not allow accurate differentiation of acute from unrelated non-acute infarctions, and these data usually refer to hemispheric infarction. Brainstem ischaemia was either excluded or represented only in small numbers.

A positive correlation between the duration of symptoms and the development of structural infarction on CT and routine MRI has been reported.10–12 However, not all investigations could confirm these findings.13 Our results using DWI show no significant correlation, which is probably because of the small number of patients. In the rat, the development of DWI hypersensitivities and the number of necrotic neurones in the histopathological investigation correlated strongly with the duration of transient middle cerebral artery occlusion.14

Not all the DWI abnormalities in our study evolved into corresponding relevant infarctions on routine follow up imaging. Our data therefore suggest that DWI abnormalities may be fully reversible. Reversibility of DWI changes has consistently been shown in animal studies,15 in which DWI hyperintensities resolved with early interruption of a transient artery occlusion in follow up imaging. Only one major study reported corresponding findings in patients with hemispheric TIA.16 The small number of patients with early ischaemia detected by DWI and without a lesion on follow up imaging does not allow an accurate assessment of this population. Further studies focusing on patients with brief symptomatic episodes are needed. Such studies will, however, be challenging from a practical and logistic standpoint. Histopathological changes corresponding to this reversible DWI pathology in humans are not available so far. The lack of an independent yardstick limits the assessment of DWI sensitivity to a certain extent. Diagnosis of tissue damage is usually not available in subjects with temporary deficits, and patients with normal imaging results may have permanent injury, but this may be below the threshold of MRI detection.17

Patients with transient ischaemic symptoms and signs are at significant risk of subsequent ischaemic events.18 The nature of suspected brainstem impairment often cannot be judged from clinical signs alone and may be due to extra-axial lesions, as in peripheral vestibulopathy, vertebrobasilar migraine, or diabetic cranial nerve palsies.19–21 According to our study, DWI also classifies the gross anatomy in the posterior fossa and allows attribution to a vascular region and cause and thus identifies patients with transitory ischaemia and subsequent increased risk of stroke. Kidwell et al.14 showed that the identification of the vascular regions involved and the clinically suspected TIA mechanism had to be corrected in over one third of patients with transient neurological symptoms as the result of DWI findings. In our study, clinical signs and symptoms were used to make instant decisions about whether patients should be prospectively recruited. It cannot be excluded that some
patients with atypical presentations of brainstem ischaemia escaped investigation and may have altered the statistics.

In conclusion, we suggest that the use of DWI, particularly for infratentorial TIA or RIND, would achieve better identification of the localisation and acuity of ischaemic lesions and improve management of patients at risk of subsequent ischaemic stroke.

ACKNOWLEDGEMENT
The project was supported by the Deutsche Forschungsgemeinschaft (Ho 293/10-1).

Authors' affiliations
J J Marx, A Mika-Gruettner, F Thoemke, P P Urban, H C Hopf, Department of Neurology, University of Mainz, Germany
G Vucurevic, P Staeter, Department of Neuroradiology, University of Mainz
S Fitzek, Department of Neurology, University of Jena, Germany
C Fitzek, Department of Radiology, University of Jena

REFERENCES
19 Caplan LR. Are terms such as completed stroke or RIND of continuous usefulness? Stroke 1989;14:431–3.

Call for peer reviewers

Clinical Evidence is a regularly updated evidence based journal available world wide both as a paper version and on the internet. Clinical Evidence urgently needs to recruit a number of new contributors. Contributors are health care professionals or epidemiologists with experience in evidence based medicine and the ability to write in a concise and structured way.

Clinical Evidence needs to recruit a number of new peer reviewers. Peer reviewers are health care professionals or epidemiologists with experience in evidence based medicine. As a peer reviewer you would be asked for your views on the clinical relevance, validity and accessibility of specific topics within the journal, and their usefulness to the intended audience (international generalists and health care professionals, possibly with limited statistical knowledge). Topics are usually 2000–3000 words in length and we would ask you to review between 2–5 topics per year. The peer review process takes place throughout the year, and our turnaround time for each review is ideally 10–14 days.

If you are interested in becoming a peer reviewer for Clinical Evidence, please complete the peer review questionnaire at www.clinicalevidence.com or contact Polly Brown (pbrown@bmjgroup.com).