

The clinical significance of diffusion-weighted MR imaging in stroke and TIA patients

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Summary

Background and purpose: Diffusion-weighted magnetic resonance imaging (DWI) is an advanced imaging technique that allows non-invasive evaluation of water diffusibility in brain tissue. The following report focuses on the clinical significance of DWI in stroke and TIA patients

Summary of review: (1) TIA patients demonstrate DWI lesions at a rate of 1 in 6 to 2 in 3. Symptom duration, speech or motor symptoms and aetiology seem to correlate with the rate of DWI positivity. (2) In stroke patients, the DWI detection rate of ischaemic lesions is >95%. Small lesion size and location in the brainstem increase the risk of false-negative DW-images. A negative DW-image in a patient with stroke-like symptoms should stimulate the search for an alternative diagnosis. However, one half of such patients can be expected to have ischaemic stroke as the best final diagnosis. (3) Infarct age determination based on DWI characteristics is not possible in the first few hours. However, the combined interpretation of DWI-images and apparent diffusion coefficient (ADC) maps enables the distinction of infarcts ≤5 day old from infarcts >10 days old. On average in DW-images alone, the hyperintense signal disappears after two months. Normalisation can occur as early as one month and as late as four and a half months. (4) DWI lesion size is a prognostic marker of stroke outcome. However, in a mixed stroke population, outcome prediction by DWI cannot replace clinical outcome scores. (5) The mismatch concept hypothesises that DWI lesions reflect irreversibly infarcted tissue that is surrounded by an area of reduced perfusion. The larger the perfusion-diffusion mismatch the more tissue is potentially salvageable, e.g., by early reperfusion. Although this concept is appealing, more recent data have shown that DWI lesions are not necessarily irreversibly damaged tissue and that perfusion abnormalities tend to overestimate the ischaemic penumbra. More recently, the mismatch between clinical stroke severity as measured with the NIH-stroke Scale Score (NIHSS) and the volume of DWI lesions has been introduced. (6) In posterior circulation stroke, DWI lesion detection rate is significantly lower than in anterior circulation stroke. (7) DWI

features provide important information about stroke aetiology. Multiple DWI lesions in more than one circulation suggest cardioembolism. However, this assignment should be restricted to DWI lesions showing the same appearance on ADC-maps. In patients with lacunar syndromes, every fourth to sixth patient can be expected to have >1 DWI lesion, indicating an embolic mechanism. Thus, DWI findings may be clinically useful to tailor the aetiological work-up, which may result in early implementation of specific treatment for secondary stroke prevention. (8) DWI may detect clinically silent ischaemic lesions after carotid interventions. A systematic review reported the rate of new DWI lesions as being significantly higher in carotid stenting patients (37%) compared to carotid endarterectomy patients (10%). As caveats, all studies included were non randomized trials. In addition, the clinical significance of these lesions is unclear. Studies, comparing the risk of silent ischaemia in carotid stenting versus endarterectomy patients and evaluating the value of DWI as surrogate marker in a randomised, prospective setting are currently under way.

Conclusion: DWI provides clinically useful information and has the means to improve the quality of diagnosis, treatment, and outcome prediction in stroke and TIA patients.

Key words: diffusion-weighted imaging; MRI; stroke; ischaemia; IA; outcome; prognosis; treatment

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Abbreviations

ADC	apparent diffusion coefficient
CAS	carotid artery stenting
CEA	carotid endarterectomy
DWI	diffusion-weighted imaging
DW-images	diffusion-weighted images
NIHSS	National Institute of Health Stroke Scale
MR	magnetic resonance
TIA	transient ischaemic attack
TGA	transient global amnesia

Introduction

Diffusion-weighted Magnetic Resonance (MR) imaging (DWI) is an advanced MR imaging technique, which allows non-invasive evaluation of water diffusibility in brain tissue [1, 2] as first described by Stejskal and Tanner [3]. DWI is sensitive to the random translational motion of water molecules due to Brownian motion. Diffusion-weighted images (DW-images) are generated by adding an opposing pair of diffusion gradients to spin-echo or echo planar imaging sequences [1, 2]. For stationary molecules, the effects of the first (tagging) and the second (untagging) gradient pulses cancel each other out. For mobile, diffusible molecules there is incomplete rephasing resulting in a net phase shift, which leads to a signal loss. The degree of signal loss is proportional to the exponent of the diffusion coefficient and to the duration, distance and strength of the applied diffusion gradients (so-called "B-value") [1, 2]. The diffusion coefficient measured by DWI is referred to as the "apparent" diffusion coefficient (ADC) rather than the true diffusion coefficient. Regions with low diffusion coefficients have lower signal drop than tissue with a high diffusion coefficient. In practice, tissue with restricted diffusion will appear hyperintense to normal tissue on DW-images.

The following biophysical mechanisms contribute to changes of the ADC values. Alterations

in the ratio between intra- and extracellular volumes, water permeability of cell membranes, direction of axonal pathways, tissue microstructure (e.g., intracellular organelles, macromolecules) have been reported to influence ADC values [2, 4].

Studies in animal stroke models have shown that brain ischaemia is mirrored by an immediate decrease in the ADC value, which is thought to reflect cytotoxic oedema, energy depletion and ionic imbalance immediately after stroke [5, 6]. Acute cerebral ischaemia appears as a hyperintensity on DW-images and a hypointensity on ADC maps. After the acute stage, ADC values return to pseudonormal values and subsequently increase above baseline, which is assumed to reflect vasogenic oedema and cell lysis [7, 8]. Observations that DWI enables visualisation of acute ischaemia earlier than conventional MR or computed tomography, i.e., within minutes as compared to several hours [9, 10], triggered further research about clinical applications of DWI.

The following report focuses on the clinical significance of DWI in stroke and TIA patients. It starts with the assessment of DWI findings in normal aging in order to distinguish physiological processes from pathological conditions in humans.

Diffusion-weighted imaging and normal aging

Autopsy studies have shown that increasing age is associated with a decrease of myelinated fibres in white matter. Myelinated tracks are known to constrain water diffusibility. Hence, water diffusibility, measured as ADC value is expected to increase with advancing age. Indeed, a small but statistically significant increase in the ADC value of white matter with advancing age has been observed [11–13]. In addition, the age related increase in ADC values occurred mainly in subjects

older than 60 years. This observation is in line with autopsy data reporting on a mild loss of myelin between the 6th and the 8th life decades but not before [14].

In the diagnosis of acute brain ischaemia, age-related ADC changes are not a confounding factor because the increase in ADC value from patients in their 20th to those in their 70th year was less than 10%, which is marginal compared to the 40–50% ADC decrease seen after acute stroke.

Diffusion-weighted imaging and transient ischaemic attack (TIA)

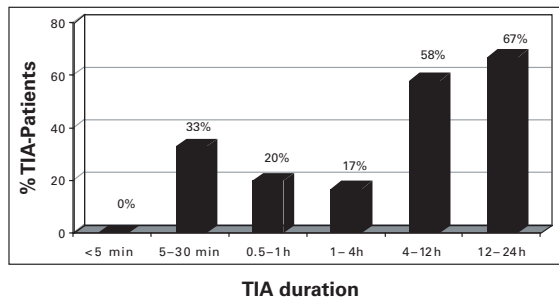
TIA is classically defined as a sudden, focal neurological deficit due to focal brain or retinal ischaemia that completely resolves within 24 hours. In 1999 the first reports on DWI studies in TIA patients [15, 16] showed that although the symptoms had disappeared, several patients had lesions visible on DWI. Patients with very brief TIAs lasting <5 minutes had no abnormalities. In patients with symptoms lasting between 12 and 24 hours, about two thirds had DWI lesions. Symptom duration correlates with the likelihood of visualised

lesion (fig. 1). A recent meta-analysis across nineteen DWI-TIA studies demonstrated that symptom duration ≥ 60 minutes, symptoms such as dysphasia, dysarthria, or motor weakness as well as the presence of atrial fibrillation or carotid stenosis were associated with a higher likelihood of DWI lesions [17].

Currently (June 1st 2008), we are aware of twenty six DWI studies [15, 16, 18–41] that report on a total of 1980 TIA patients. An overview of the main results is given in the table 1. The fre-

Figure 1

Symptom duration correlates with the likelihood of visualised DWI lesion in TIA patients (adapted from [16]).



quency of positive DWI findings ranged from 13% to 67% across the twenty six DWI studies. This variation might reflect differences in latency to DWI, symptom duration, aetiology or in patient selection criteria. The lowest rates of DWI positive patients (13% and 16%) were reported in studies focusing on TIA patients presenting in the subacute stage (>3 days). In 11 of 17 studies, the likelihood of positive DWI lesions (i.e., identifiable ischaemic injury) increased with advancing duration of clinical symptoms. The chance of detecting a DWI lesion might be lower within the first hours after TIA [40]. However, the odds for detectable lesions on DWI seem to decline in the subacute stage with advancing latency between symptom onset and MR imaging [42]. Moreover, optimised DWI-sequences with reduction of the slice thickness may even increase the detection rate in TIA patients [41].

Four research groups including our own [15, 16, 24, 34] observed that the ADC decrease of the ischaemic lesion (if present) was less pronounced in patients with complete recovery in less than

24 hours compared to patients with completed strokes. These data may indicate that the degree of ischaemic compromise is less severe in (classically defined) TIA patients than in stroke patients.

TIA patients with DWI lesions may have a higher stroke risk than DWI-negative TIA patients [30, 34]. However, it remains to be shown whether DWI-positivity is an independent marker for a higher stroke risk. In detail, whether adding DWI findings to existing clinical risk scores in TIA patients [43] improves the predictability of recurrent ischaemic events is currently under investigation.

Among others, these DWI observations triggered the proposal for a new definition of TIA. Replacing the arbitrary 24-hour time limit of the current definition, the authors proposed a so called “tissue-based” TIA definition [44]. Applying this definition, patients with clinical symptoms of focal brain or retinal ischaemia lasting ≥ 1 hour or, alternatively, with “characteristic imaging abnormalities” [44] such as acute DWI-lesions, regardless of the duration of neurological signs, had a stroke rather than a TIA, even if complete clinical recovery occurred within 24 hours [44].

In TIA patients, DWI can be clinically helpful in demonstrating the acuity of the ischaemic lesion. A hyperintense signal on DWI identified acute ischaemic lesions among multiple hyperintensities on T2-weighted images, which alone did not differentiate between new and pre-existing lesions [16, 42].

Diffusion-weighted imaging in acute ischaemic stroke: diagnostic accuracy

DWI can depict early ischaemic lesions earlier and more precisely than CT scans or classical MR-images [45–48]. Nevertheless, there are reports on diffusion-negative strokes [49, 50] illustrating that the diagnosis of acute ischaemic stroke can not be excluded solely on the base of DWI without visible lesions. In most series, >95%

of acute ischaemic lesions were visualised by DWI [51–57]. Small lesion size, brainstem lesions, small cortical lesions and DWI performed within a few hours after stroke onset were features associated with a particular risk of false-negative DWI-images [49, 51, 58].

In turn, patients with stroke or TIA mimicking diseases such as hypoglycaemia (fig. 2) or hyperglycaemia [59], epileptic seizures [60–63], multiple sclerosis or even brain tumours [64] can show signal increase on DW-images. Compared to acute ischaemic stroke, the signal increase on DWI is often mild. The degree of alterations of the ADC values varied [59, 60]. In epileptic seizures, even increased ADC values have been reported [61]. In partial status epilepticus, the hippocampus [62] or the pulvinar region of the thalamus seem to be frequently involved [65]. These structures are rarely involved in acute stroke.

In transient global amnesia (TGA), focal DWI lesions in the mesiotemporal region, including the hippocampus, have been described [66, 67]. The temporal evolution of the ADC-values resembles that of ischaemic lesions in stroke pa-

Figure 2

DWI lesion in a TIA mimic. DWI shows a mild signal increase in the right internal capsule of a patient with transient left hemiparesis attributable to hypoglycaemia.

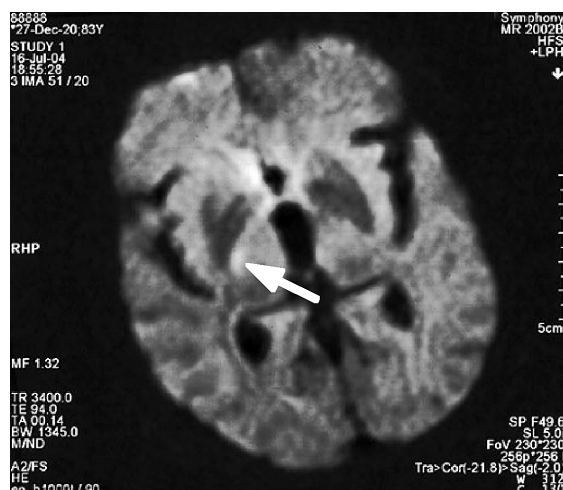


Table 1

Summary of studies about diffusion-weighted MR imaging in TIA patients [15, 16, 18–41].

Study 1st author, year	TIA patients [n]	mean age [yrs]	Latency to DWI [hours]	DWI positive patients		TIA duration correlated with DWI- positivity	Shortest TIA in DWI ⊕ patients	Special features
				All TIA patients	TIA ≤5 min			
Kidwell 1999	42	68	17 hrs	20 (48%)	n.m.	yes	10 min	Lesion volume smaller and ADC-value ↓ less pronounced than in strokes
Engelter 1999	40	61	36.5 hrs	14 (35%)	0 of 5	yes	10 min	ADC-value ↓ less pronounced than in strokes, focussed on brief TIA
Takayama 2000	19	71	n.m.	7 (37%)	n.m.	yes	n.m.	All DWI ⊕ lesions were irreversible
Rovira 2002	58	60	5 days	39 (67%)	n.m.	yes	n.m.	no association between DWI lesion size and TIA duration
Kamal 2002	28	n.m.	n.m.	13 (46%)	n.m.	n.m.	n.m.	In DWI negative patients: Quantitative DWI abnormalities
Kastrup 2002	42	69	5 d DWI ⊕ 6 d DWI -	19 (45%)	n.m.	yes	1 min.	Hemispheric TIA in symptomatic carotid stenosis
Ay 2002	57	68	39 hrs	27 (47%)	6 of 11	no	<5 min	
Marx 2002	14	71	10.7 hrs	4 (29%)	n.m.	n.m.	n.m.	brainstem TIA
Nagura 2003	45	69	17.3 hrs	14 (31%)	n.m.	no	n.m.	DWI ⊕ related to intracranial occlusions
Crisostomo 2003	75	67	23 hrs	16 (21%)	1 of 10	yes	40 sec	
Nakamura 2003	18	n.m.	n.m.	9 (50%)	n.m.	no	n.m.	DWI ⊕ related to atrial fibrillation
Inatomi 2004	129	67	4.7 days	57 (44%)	n.m.	yes	n.m.	
Winbeck 2004	60	62	2.1 hrs	18 (30%)	n.m.	no	n.m.	ADC-value ↓ less pronounced than in strokes
Restrepo 2004	22	62	n.m.	12 (55%)	0 of 1	no	20 min.	DWI/PWI-mismatch in 4/22
Purroy 2004	83	66	n.m.	27 (33%)	n.m.	n.m.	n.m.	DWI ⊕ plus TIA duration >1h → ischemic event risk ↑
Ay 2005	87	73	22 hrs	36 (41%)	n.m.	no	n.m.	Lesion volume smaller than in strokes, 'transient symptoms with infarction': stroke risk ↑
Coutts 2006**	106	n.m.	n.m.	41(38%)	n.m.	n.m.	n.m.	Large artery atherosclerosis associated with DWI ⊕ lesions
Schulz 2006	136		17 days*	17 (13%)	n.m.	n.m.	n.m.	focussed on late presenters
Oppenheim 2006	103	60	30 hrs	36 (35%)	n.m.	yes	n.m.	ADC-value ↓ less pronounced than in strokes, 76% of DWI⊕ lesions → infarcts
Lamy 2006	98	61	42 hrs	34 (35%)	n.m.	yes	5 min	DWI ⊕ independently related to TIA ≥1hrs, aphasia, motor deficits
Cucchiara 2006	61	59	n.m.	15 (25%)	n.m.	n.m.	n.m.	DWI ⊕: risk; ↑; low correlation with ABCD score
Redgrave 2007	200	71	15 days*	31 (16%)	n.m.	yes	n.m.	imaging ≥3 days after TIA
Prabhakaran 2007	146	70	n.m.	37 (25%)	n.m.	n.m.	n.m.	'transient symptoms with infarction': risk ↑
Calvet 2007	203	61	20 hrs*	64 (32%)	n.m.	n.m.	n.m.	Independent predictors of stroke: DWI ⊕, ABCD-score
Uno 2008	72	69	4.5d DWI⊕ 2.0d DWI-	24 (33%)	1 of 12	yes	n.m.	DWI ⊕ related to cardio- embolism only carotid TIA
Bertrand 2008	36	66	34 hrs	19 (53%)	n.m.	n.m.	n.m.	Optimized DWI: lesion detection rate ↑ (8%)

n.m.: not mentioned DWI: diffusion-weighted imaging ⊕: positivity ADC: apparent diffusion coefficient *median

tients, which might indicate an ischaemic pathogenesis. In turn, TGA patients have no increase in stroke risk. Furthermore, DWI negative and DWI-positive TGA patients do not differ in vascular risk factors and outcome [67]. These findings do not support a cerebrovascular aetiology of TGA, even in DWI-positive-TGA patients [67].

As a practical consequence, a negative DWI result should stimulate the search for a non is-

chaemic cause of the symptoms (“stroke mimic”). However, a negative DWI must not be considered as proof of the absence of an ischaemic stroke, as one half of such patients have an ischaemic cause as the best final diagnosis [53]. A signal increase on DW-images in combination with a low signal on ADC map must not be considered a definite proof of brain ischaemia. However, this feature has a specificity of 95–100% [54, 55].

Diffusion-weighted imaging and assessment of infarct age

Experimental stroke models have shown that DWI can visualise brain ischaemia within a few minutes. In human stroke, DWI findings have been reported to indicate cerebral ischaemia as early as eleven minutes after stroke onset [68]. Early visualisation of ischaemic compromise is based on the rapid decrease of the ADC within ischaemically compromised tissue. Later, ADC values within infarcts return to pseudo-normal values and subsequently increase above baseline. This change in ADC-values over time reflects different pathophysiological stages of brain ischaemic, i.e., cytotoxic oedema initially, followed by vasogenic oedema and eventually the occurrence of cell lysis [7, 69].

From a clinical perspective, the age of infarction might be estimated on DW images based on the time course of ADC values. However, the signal intensity on DW-images reflects not only the diffusion characteristics but also the T2 properties of tissue [70]. The contribution of increasing T2-signal on the signal intensity on DW-images has been termed “T2-shine through” effect [71, 72]. ADC maps, which display the spatial distribution of ADC values, have no T2-shine through effects. Thus, ages of infarctions can be estimated by the signal appearance on ADC maps. However, ADC maps are characterised by poor signal contrast and acute infarcts appear hypointense against an isoin-

tense background causing low lesions conspicuity. Therefore, in clinical practice, DW-images plus ADC maps are required for both detecting ischaemic tissue and adequate estimation of infarct age. An illustrative example of the “T2-shine through” effect is shown on figure 3.

Studies with a cross-sectional design have shown that infarcts up to five days old usually appear hyperintense on DW-images plus hypointense on ADC maps, whereas this pattern is usually absent beyond ten days. Notably, within the first 120 hours, no significant differences were found. Thus, DWI plus ADC reliably differentiate infarcts ≤ 5 days old from infarcts > 10 days old. However, within the first 120 hours, more precise determination of infarct age is not possible by DWI [69, 73].

The combined assessment of DW-images and ADC maps is important, because the isolated infarct age estimates based solely on DW-images can be misleading. On average, ischaemic brain infarcts remain hyperintense for 57 days. However, normalisation of the DW-image (i.e., isointensity) can occur as early as 34 days and as late as 138 days (i.e., 4.5 months) after stroke onset [74].

Thus, among patients with unknown stroke onset, signal intensity on DWI can not be used as a surrogate marker to distinguish patients with brain ischaemia less than three hours old as po-

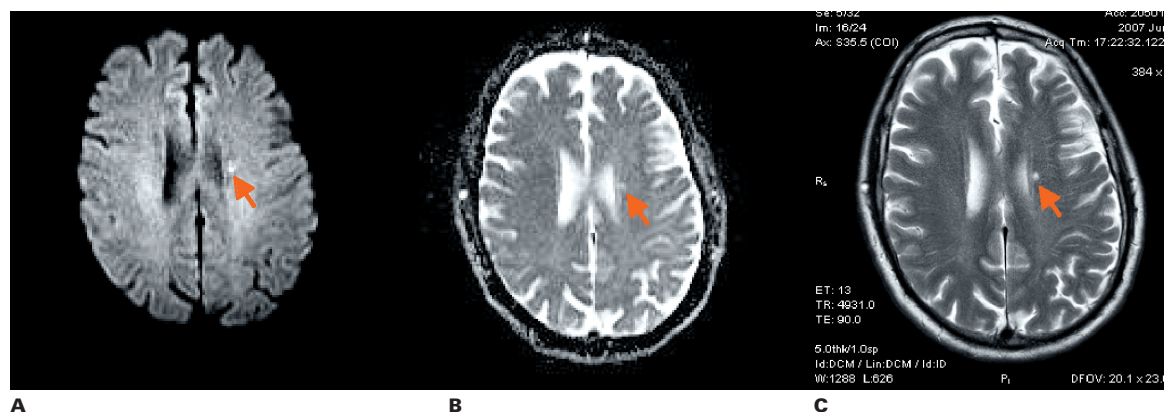


Figure 3

“T2-shine-through effect” On the DW-image (A) a tiny ‘bright’ lesion (red arrow) suggested acute ischaemia. However, the bright appearance on the ADC map (B, red arrow) clarified that this lesion is weeks old. The lesion appearance being still “bright” on the DW-image (A) is explained by the fact, that signal intensity on DW-images reflects not only diffusion characteristics but also T2 properties of tissue. On the T2-weighted image (C, red arrow) the lesion also appears “bright”. The contribution of increasing T2-signal on the signal intensity on DW-images has been termed “T2-shine through” effect [71, 72].

tential candidates for thrombolysis from those patients with brain ischaemia lasting longer than the established time-window for thrombolysis.

Nevertheless, infarct age estimation based on the combined interpretation of DW-images plus ADC maps in the magnitude of days to weeks may be clinically useful. In patients with progres-

sive strokes, DWI enables the distinction of multiple infarctions from a single progressive infarction [75]. In addition, among patients with multiple infarctions, infarct age determination is helpful in the evaluation of the effectiveness of stroke preventive means.

Diffusion-weighted imaging and the mismatch-concept

In acute ischaemic stroke, DWI lesions expand over a period of about 24 hours [76] unless there is early reperfusion. DWI lesion expansion occurred in patients with a perfusion deficit larger than the DWI lesion [77]. These observations triggered the hypothesis that an area of decreased perfusion surrounding the smaller DWI lesion, labelled “perfusion-diffusion mismatch,” reflects potentially salvageable tissue. The perfusion-diffusion mismatch concept is attractive as it assumes that DWI lesion size reflects the infarct core whilst the mismatch area reflects the penumbra. However, this concept may be an oversimplification. DWI lesions are reversible to some degree, as, for example, in the case of early reperfusion. This observation challenges the idea that DWI lesions solely reflect the infarct core. In addition, perfusion abnormalities tend to overestimate the penumbra by including areas of benign oligoemia [78]. Nevertheless, relationships between radio-

logically defined “tissue at risk” and clinical outcomes support the use of this concept [79, 80]. In addition, the perfusion-diffusion mismatch concept has been used to select patients in thrombolysis trials beyond three hours and up to nine hours, the Desmoteplase in Acute Ischaemic Stroke Trial (DIAS) and the Desmoteplase for Acute Ischaemic Stroke (DEDAS) trial [81, 82].

Because the complexity of perfusion studies restricts their use, the mismatch between clinical stroke severity as measured with the NIH-stroke Scale Score (NIHSS) and the volume of DWI lesions has been introduced [83]. A clinical-diffusion mismatch, defined as a NIHSS <8 plus a DWI lesion volume >25 ml, predicted early neurological deterioration [83] as well as perfusion-diffusion mismatch with a high specificity [84]. Despite the seeming appeal of such concepts, their usefulness in clinical practice remains to be proven.

Diffusion-weighted imaging and functional outcome after stroke

In acute ischaemic stroke, several studies showed that in middle cerebral artery stroke, infarct size on DW-images is an important outcome predictor [57, 85, 86]. As a limitation, these observations can not necessarily be transferred to a mixed stroke population [87]. Thus, clinical outcome predictors such as stroke severity or age can not simply be replaced by DWI lesion characteristics [88]. Nevertheless, it has been shown that among models used to predict outcome, those which include the variable “DWI lesion volume” had a higher power compared to models lacking this variable. However, the increase of predictive power was not large enough to be clinically important [89]. In mixed stroke populations with a broad range of stroke severities, lesion size on DWI was not independently associated with functional outcome [87, 90]. In particular, among patients with small artery occlusion, infratentorial strokes [51] or low stroke severities [90], the correlation between lesion size on DWI and outcome was weak.

Among ischaemic stroke patients, DWI lesion size seems to be associated with the risk of in-

tracranial bleeding complications with [91] or without thrombolysis [92].

In addition, the pattern of DWI lesions has also recently been shown to be predictive. Patients with internal border zone infarcts had a significantly higher risk for a clinically progressive course (“progressive stroke”) than those with other lesion patterns [93]. Patients with multiple DWI lesions of varying ages had a higher risk of having new lesions on day 30 compared with those having lesions of the same age [94].

These observations point to variables such as lacunar type lesions, stroke aetiology and infarct location which seem to limit outcome prediction based on lesion size in diffusion imaging in mixed stroke populations [87].

The best additional value of DWI lesion size with respect to functional outcome prediction is to be expected in moderate to severe non lacunar ischaemic stroke in the carotid circulation. DWI lesion characteristics other than lesion size might be able to identify patients with a high risk for clinical worsening or recurrent strokes.

ADC values and prognosis

Furthermore, the prognostic impact of ADC values has been studied [95, 96]. These studies are based on two ideas. Firstly, DWI lesion size is potentially reversible. Secondly, the extent of tissue injury corresponds to the degree of ADC alteration, which is quantified in (relative) ADC values. ADC maps display the spatial distribution of ADC values. The most important findings were as follows. 1) ADC infarct volume was significantly correlated with length of stay as marker of short term outcome and with functional outcome after six months [96]. 2) ADC values were inversely correlated with neurological impairment after six

weeks [97]. 3) ADC values combined with DWI lesions size better predicted malignant middle cerebral artery infarctions than DWI lesion size alone [98]. 4) Intermediate ADC values were present in the ischaemic penumbra [99]. 5) TIA patients had a less pronounced ADC decrease than patients with completed stroke [15, 16]. Nevertheless, the idea of a potential ADC-threshold that determines irreversible tissue damage [95, 96] is not widely accepted. 6) Measurements of ADC values were more reproducible than determination of lesion size on DW-images in acute stroke [100].

Diffusion-weighted imaging in infratentorial stroke

Results from DWI studies performed in anterior circulation strokes can not necessarily be applied to posterior circulation strokes. DWI studies in posterior circulation strokes [27, 58, 101–103] showed that there are indeed important differences. Firstly, the rate of false negative DWI findings was significantly higher in posterior (up to 19%) compared to anterior circulation strokes (2%) if DWI was performed within 24 hours of stroke onset [49]. In particular, lesions in the medulla oblongata harbour the highest risk of being missed [51, 58].

Secondly, as in anterior circulation stroke, the number and the distribution of DWI lesions significantly correlated with stroke aetiology. In particular, multiple DWI lesions and the presence of subsidiary, clinical silent DWI lesion in the anterior circulation suggested cardioembolism as underlying stroke aetiology. However, in the posterior circulation, patients with cardioembolic stroke had more DWI lesions than patients with stroke attributable to large artery atherosclerosis of the vertebrobasilar arteries [51], while in the anterior circulation, strokes attributable to large artery atherosclerosis were associated with more DWI lesions than cardioembolic strokes [104].

Thirdly, among vertebrobasilar stroke patients and, in particular those with infratentorial strokes DWI, lesion volume did not correlate with stroke severity as assessed with the National Institute of Health Stroke Scale (NIHSS) [51, 101]. This discrepancy may be due to the NIHSS favouring anterior circulation over posterior circulation stroke symptoms [101].

Fourthly, there seems to be no correlation between DWI lesion volume and length of stay and functional outcome after three months [51]. These negative findings are in contrast to numerous studies in supratentorial strokes in which DWI lesion volume correlated well with disability [85]. This discrepancy may be explained by the smaller lesion volume of infratentorial compared to supratentorial strokes. Small lesion volumes have been shown to weaken the correlation between infarct volume and outcome [86, 96]. Furthermore, due to the different anatomic architecture of the posterior fossa, it seems that it is more important which functional pathways are ischaemically damaged rather than how large the ischaemic injury is.

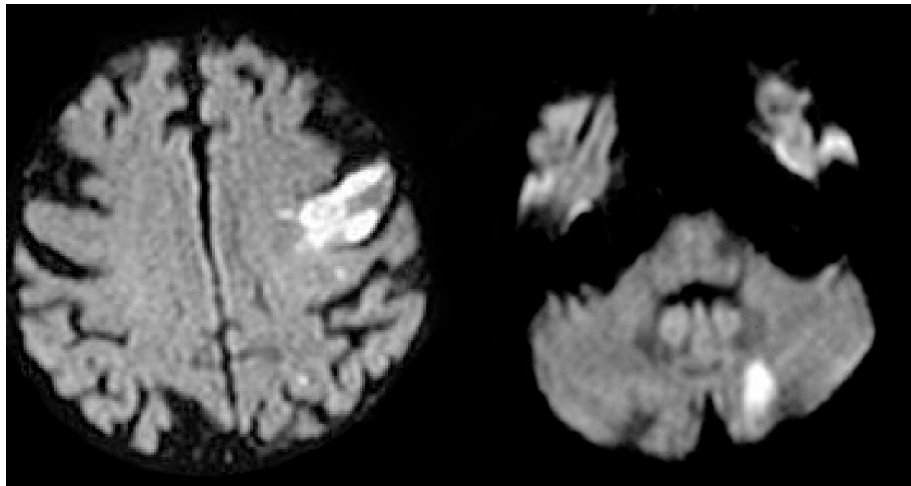
Diffusion-weighted imaging and stroke aetiology

Diffusion weighted imaging (DWI) has the potential to distinguish patterns of cerebral ischaemia associated with different stroke aetiologies. The number, size and topographic distribution of DWI lesions can provide insights in the mechanisms leading to cerebral ischaemia [105]. Multiple acute DWI lesions could be caused by multiple emboli or the breakup of an embolus [106]. In patients with multiple DWI lesions, arterial or cardiac embolic sources are more frequent than in patients with single lesions [107].

In addition, DWI lesion characteristics significantly correlate with stroke aetiology [104, 108] as assessed using the established TOAST-classification [109]. Thus, DWI findings may be clinically useful to tailor and accelerate the aetiological work-up, which may result in early implementation of specific treatment for re-stroke prevention. The latter is clinically important because the risk for recurrent stroke within seven days differed significantly between the aetiological stroke subtypes and was the highest for patients with stroke due to large artery arteriosclerosis [110].

Figure 4

Topographic distribution of acute DWI lesions and stroke aetiology. DWI visualised acute lesions in the left middle cerebral artery territory (low ADC values; not shown), corresponding to the clinical symptom of aphasia and mild hemiparesis on the right. Additional – clinically silent – acute DWI lesions were shown in the left cerebellum. Stroke aetiology was atrial fibrillation.



Clinically silent DWI lesions in the contralateral hemisphere or in the posterior circulation suggest cardioembolism [108] as the underlying stroke aetiology (fig. 4). However, there are important caveats. Firstly, anatomic variants such as the bilateral supply of both anterior cerebral arteries by one internal carotid artery can lead to bi-hemispheric DWI lesions. Secondly, acute DWI lesions in more than one circulation should only be designated cardioembolic if they all show a hypointense appearance on ADC-maps [104]. Concomitant DWI lesions of older age (i.e., ADC appearance isointense or hyperintense) located in the contralateral hemisphere can occur in patients with unilateral high-grade stenosis of the internal carotid artery. These additional lesions were mostly attributed to accompanying, clinically silent, small vessel disease [104].

In patients with lacunar stroke syndromes, DWI can provide clinically important information with respect to the underlying stroke mechanism. In every fourth [111] to sixth [112] patient, multiple rather than the clinically expected single DWI lesion (e.g., in the internal capsule) have been visualised. The clinically unexpected additional lesions include lesions in the same circulation suggesting large artery disease, and distant lesions in another circulation suggesting cardioembolic stroke aetiology. Even if the clinical presentation suggests a subcortical infarct, DWI can also depict small cortical lesions suggestive of embolism [113].

In daily clinical practice, DWI findings can be used to tailor and accelerate the aetiological work-up, which may result in early implementation of specific treatment for re-stroke prevention. The latter is clinically important, because the risk for recurrent stroke differs significantly between the aetiologic stroke subtypes and has been shown to be highest for patients with stroke attributable to large artery arteriosclerosis [110].

In addition, DWI findings may be useful in identifying clinically important subgroups. In patients with stroke attributable to internal carotid artery stenosis, the pattern of DWI lesions differed across different stages of carotid stenosis. More than half of the patients with high-grade or subtotal stenoses had DWI lesions in haemodynamic risk areas [114].

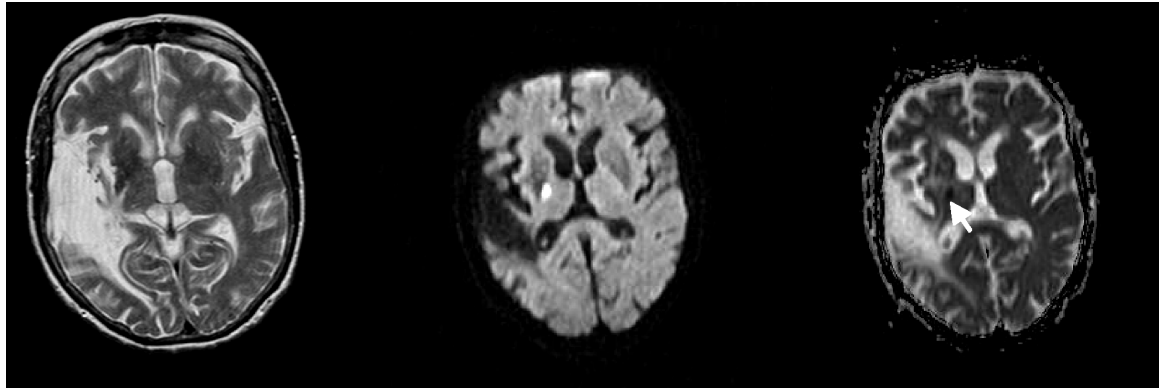
Among patients with stroke attributable to internal carotid artery dissection, patients with carotid occlusion had larger infarcts, usually associated with a worse prognosis, than patients with dissection leading to carotid artery stenosis (rather than occlusion) [115].

In patients with stroke attributable to patent foramen ovale (PFO), those who had a concomitant atrial septum aneurysm (ASA) more often had multiple DWI lesions than those without ASA. This observation suggests that the presence of PFO plus ASA results in a higher embolic risk than PFO alone [116].

Diffusion-weighted imaging in recurrent stroke

In patients who have had a stroke and present with a worsening of residual findings (e.g., hemiparesis) it can be challenging to identify the reason for the increased weakness. The differential diagnoses encompass (focal) epileptic seizure with Todd's paresis and breakdown of compensation mechanism due to infection and recurrent strokes. In this situation, DWI is clinically useful because

it can distinguish old from pre-existing lesions, which is usually beyond the capability of a CT-scan or classical (e.g, T2-weighted) MR-sequences. A bright DWI lesion with low ADC values next to an old infarction (i.e., dark appearance on DWI and bright on ADC maps) verifies the diagnosis of recurrent stroke (fig. 5).



A

B

C

Figure 5

New infarction adjacent to a chronic ischaemic lesion. In a patient with worsening of the pre-existing left hemiparesis, T2-weighted images (A) showed a right temporo-parietal lesion. DW-images (B) visualised a hypointense ("dark") cortical temporo-parietal lesion plus a single hyperintense ("bright") punctate lesion in the right internal capsule. This lesion (arrow) appeared hypointense ("dark") on ADC maps (C) in line with a new infarction. These findings clarified that a recurrent stroke was the cause of the worsened hemiparesis.

Diffusion-weighted imaging for surveillance of carotid interventions

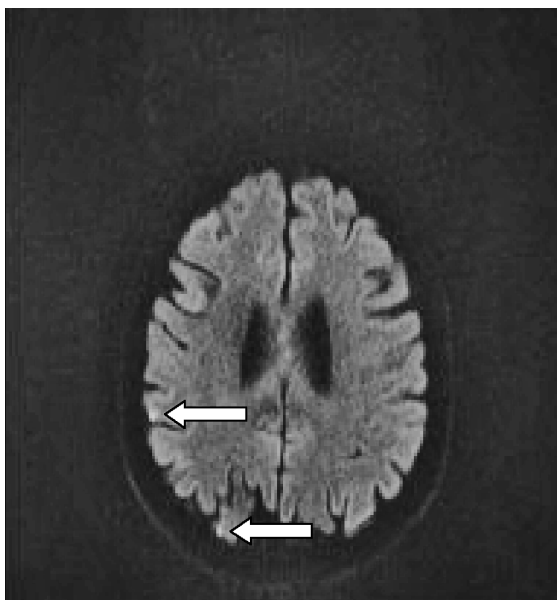
DWI may detect ischaemic lesions after carotid interventions in patients who experience no clinical symptoms. Pilot data show that impaired cerebrovascular autoregulation increases the risk of such peri-procedural DWI lesions among patients with carotid interventions for symptomatic high grade internal carotid stenosis [117]. Several studies have shown that asymptomatic DWI lesions occur in 4% to 34% patients undergoing carotid endarterectomy (CEA) [118–121]. In patients who had carotid artery stenting

(CAS), 9% to 67% had new DWI lesions [33, 122–124]. The first, though non randomized trial, comparing both interventions showed DWI lesions in 2/23 (9%) of CEA patients and 9/21 (43%) of CAS patients ($p = 0.02$) [125]. In the meantime, similar studies were done by other groups. Recently, a systematic review summarised the DWI findings across 32 studies with 1363 CAS and 754 CEA patients. The rate of new DWI lesions was significantly higher in CAS (37%) than in CEA (10%) patients [126]. Likewise, according to the six studies directly comparing the frequency of DWI lesions among CAS (264) versus CEA (356) procedure, the odds for new, procedure associated DWI lesions were approximately six times higher for CAS compared to CEA patients [126].

As caveats, all of the studies included were non randomized trials. As such studies are prone to the risk of a selection bias, these findings should be interpreted with caution. In addition, the clinical significance of these lesions is unclear; the more so as most DWI lesions did not turn into infarcts during follow-up [121]. Thus, it has yet to be studied how silent DWI lesions relate to (i) clinically apparent ischaemic events or (ii) cognitive decline during follow-up. Studies, comparing the risk of peri-procedural silent ischaemia in CEA and CAS in a randomised, prospective setting are therefore mandatory and are currently under way [127].

Figure 6

Clinically silent lesions after carotid interventions. One day after angioplasty and stenting for a high-grade, symptomatic internal carotid stenosis, DWI revealed two punctate lesions (arrows), not visible on the pre-stenting DW-image. The patients had neither transient nor persistent clinical symptoms nor complaints.



Conclusion

DWI characteristics provide clinically useful information with respect to diagnosis, aetiological work-up, treatment decisions, surveillance of stroke preventive means and outcome prediction. The integration of DWI-derived information into daily clinical work has increased the quality of management in stroke and TIA patients.

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