High-Resolution Diffusion-Weighted Imaging Identifies Ischemic Lesions in a Majority of Transient Ischemic Attack Patients

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Transcerebral ischemic attack (TIA) is defined as focal neurological deficit caused by ischemia resolving within 24 hours. In a secondary analysis of a large monocentric cohort of 446 TIA patients, we explored the frequency and determinants of diffusion-weighted imaging (DWI) lesions on high-resolution magnetic resonance imaging. Overall, 240 (54%) of all TIA patients presented with DWI lesions. These patients had higher National Institute of Health Stroke Scale (NIHSS) scores at admission, (4) a higher risk for recurrent events as measured by the ABCD2 score, and/or (5) worse functional outcome (higher modified Rankin Scale [mRS] score) at 3 months.

Patients and Methods

Patient Selection and Imaging
We performed an a priori defined secondary analysis of the 1000Plus observational cohort (clinicaltrials.gov NCT00715533), which was reviewed by our institutional ethics committee. A detailed protocol was published previously. Briefly, consecutive adult patients presenting within 24 hours of a suspected cerebrovascular event between September 2008 and June 2013 were included if they or their legal representative had provided informed consent. Magnetic resonance imaging (MRI) was performed as primary imaging during daytime, or in addition to acute computed tomographic scans the next morning if patients presented after regular hours (ie, “admission MRI”). If admitted to the stroke unit, patients received an early (next day) and late (after 4–6 days) follow-up MRI. Demographics and clinical data were prospectively recorded, and all discharge letters were reviewed for final diagnosis. We included all patients fulfilling the WHO criteria for TIA (with a complete clinical remission within 24 hours) in this analysis. Patients who received recanalization treatment were considered to

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have had ischemic strokes, irrespective of symptom duration, and therefore excluded. All MRI examinations were performed on a Magnetom Trio (Siemens, Erlangen, Germany). Imaging and postprocessing parameters on hrdWI, time-of-flight MRA, fluid-attenuated inversion recovery (FLAIR), T2*, and perfusion imaging were reported previously.8

**Statistical Analysis**
Standard descriptive statistics were used for variance of variables. An independent-samples Student t test or Mann–Whitney U test was used to analyze differences in scalar and nonparametric parameters, respectively, between groups separated based on DWI lesions. Fisher’s exact test was used for Boolean variables. Alpha level was set at 0.05.

**Results**
We identified 446 patients presenting with a TIA according to the time-based WHO definition within the 1000Plus dataset of 1,472 patients (Fig 1). Mean age was 68 years (standard deviation [SD] = 13), and 190 patients were female (42.6%). Median NIHSS score at presentation was 0 (interquartile range [IQR] = 0–1). Further baseline characteristics, risk factors, and outcome parameters are presented in the Table.

A total of 240 patients (53.8%) had a DWI lesion on baseline and/or follow-up MRI, of which 231 (51.8%) were visible at admission. Perfusion deficits were present in 135 (35.2%) at any timepoint, and a corresponding vessel occlusion was present in 72 (16.1%) patients. Moreover, the lesion pattern (lacunar, territorial, etc), vessel territory, or hemispheric distribution did not differ between TIA and ischemic stroke patients (n = 773) in the 1000Plus dataset (Supplementary Table 1).

In comparison, no DWI lesion was identified in 206 TIA patients (46.2%), who had a mean age of 67.8 years (SD = 13.1) and median NIHSS score of 0 at presentation (IQR = 0–1). Perfusion deficits were present in 18.1%; a corresponding vessel occlusion was found in 6.8% (see also the Table). There was no significant difference between the 2 differently defined TIA cohorts in terms of other vascular MRI markers such as number of microbleeds on T2* or extent of vascular leukoencephalopathy on FLAIR.

In addition, we analyzed several predefined clinical and radiological characteristics for association with DWI lesions. Occlusion of the corresponding vessel and perfusion deficit were strongly associated (odds ratio [OR] = 4.37, 95% confidence interval [CI] = 2.36–8.11 and OR = 4.06, 95% CI = 2.51–6.56, respectively) with presence of DWI lesions, as was the volume of perfusion deficit (p = 0.005). In addition, admission NIHSS score was associated with DWI lesions (p = 0.024); however, functional outcome measured by mRS at 3 months was not. Patients with DWI lesions had significantly higher ABCD2 scores (p = 0.002). For an overview of clinical score distribution, refer to Figure 2.

**Discussion**
The main finding of this study is that the majority (ie, 54%) of TIA patients have DWI lesions as measured by high-resolution MRI, which is significantly higher than in previous reports.5 Perfusion deficits and occlusion of the corresponding artery showed a robust association with DWI lesions. NIHSS score at presentation predicted presence of DWI lesions on imaging, as previously described.9 Although previous reports described an association of DWI lesion in TIA to symptom duration, we could not reproduce this finding.10 However, patients with DWI lesions did present significantly sooner after the event. By design, we cannot comment on the rate of reversible DWI lesions in the patients without DWI pathology on the admission MRI.

Functional outcome was not different between TIA patients with and without DWI lesions, suggesting an overall similar midterm prognosis of the acute event.
## TABLE. Overview of the cohort’s baseline characteristics, risk factors and outcome parameters

| Time-based TIA | DWI- | DWI+ | P     | OR/Method |
|---------------|------|------|-------|-----------|
| n             | 446 (100) | 206 (46.2) | 240 (53.8) | 0.001 | 0.53 (0.36-0.77) |
| Sex, n (%) female | 190 (42.6) | 105 (51.0) | 85 (35.4) | 0.001 | 0.53 (0.36-0.77) |
| Age, years | 68.0 ± 12.8 | 67.8 ± 13.1 | 68.2 ± 12.6 | 0.793 | t-test |
| pre-stroke mRS | 0 (0-0) | 0 (0-0) | 0 (0-0) | MWU |
| Risk Factors, n (%) | | | | | |
| Hyperlipoproteinemia | 261 (58.7) | 133 (64.6) | 128 (53.3) | 0.016 | 0.62 (0.42-0.91) |
| Diabetes mellitus | 80 (18.0) | 38 (18.5) | 42 (17.5) | 0.805 | 0.93 (0.57-1.51) |
| Arterial Hypertension | 329 (73.9) | 145 (70.7) | 184 (76.7) | 0.161 | 1.36 (0.89-2.08) |
| previous Stroke | 121 (27.2) | 44 (21.5) | 77 (32.1) | 0.014 | 1.73 (1.13-2.66) |
| previous TIA | 55 (12.4) | 37 (18.0) | 18 (7.5) | 0.001 | 0.37 (0.20-0.67) |
| Atrial Fibrillation | 65 (14.6) | 24 (11.7) | 41 (17.1) | 0.138 | 1.55 (0.90-2.67) |
| Admission NIHSS | 0 (0-1) | 0 (0-1) | 0 (0-1) | 0.024 | MWU |
| Clinical Syndrome ABCD2, n (%) | | | | <0.001 | MWU |
| Unilateral Weakness | 192 (43.0) | 65 (38.3) | 127 (52.9) | 0.213 | MWU |
| Speech disturbance | 115 (25.8) | 62 (30.1) | 53 (22.1) | 0.213 | MWU |
| Other | 139 (31.2) | 79 (38.3) | 60 (25.0) | 0.213 | MWU |
| Duration of symptoms, n (%) | | | | 0.213 | MWU |
| <10 minutes | 77 (17.3) | 38 (18.4) | 39 (16.3) | 0.213 | MWU |
| 10-60 minutes | 103 (23.1) | 52 (25.2) | 51 (21.3) | 0.213 | MWU |
| >60 minutes | 266 (59.6) | 116 (56.3) | 150 (62.5) | 0.213 | MWU |
| ABCD2 Score | 4 (3-5) | 4 (3-5) | 5 (3.25-6) | 0.002 | MWU |
| mRS at discharge | 0 (0-1) | 0 (0-1) | 0 (0-1) | 0.533 | MWU |
| mRS at 3 months | 0 (0-1) | 0 (0-1) | 0 (0-1) | 0.533 | MWU |
| 0 | 227 (63.1) | 106 (65.0) | 121 (61.4) | 0.001 | MWU |
| 1 | 70 (19.4) | 28 (17.2) | 42 (21.3) | 0.001 | MWU |
| 2 | 26 (7.2) | 14 (8.6) | 12 (6.1) | 0.001 | MWU |
| 3 | 13 (3.6) | 6 (3.7) | 7 (3.6) | 0.001 | MWU |
| 4 | 18 (5.0) | 7 (4.3) | 11 (5.6) | 0.001 | MWU |
| 5 | 2 (0.6) | 1 (0.6) | 1 (0.5) | 0.001 | MWU |
| 6 | 4 (1.1) | 1 (0.6) | 3 (1.5) | 0.001 | MWU |
| Delay ACS to imaging, minutes | 775 ± 421 | 855 ± 411 | 706 ± 418 | 0.001 | t-test |
| DWI lesion in hospital stay, n (%) | 240 (53.8) | 0 (0) | 240 (100) | — |
| DWI lesion admission MRI | 231 (51.8) | 0 (0) | 231 (96.3) | — |
| DWI lesion early follow up MRI* | 198 (80.2) | 0 (0) | 198 (96.1) | — |
| DWI lesion late follow up MRI* | 104 (94.5) | 0 (0) | 104 (98.1) | — |
| DWI lesion vol at admission, ml | 1.5 ± 4.1 | — | 1.5 ± 4.1 | — |
| DWI lesion vol next day, ml | 2.2 ± 8.9 | — | 2.2 ± 8.9 | — |
| DWI lesion vol at follow-up, ml | 2.0 ± 4.7 | — | 2.0 ± 4.7 | — |
| Perfusion deficit at admission, n (%) | 135 (35.2) | 29 (18.1) | 106 (47.3) | <0.001 | 4.06 (2.51-6.56) |
| Perfusion deficit volume, ml | 40.8 ±74.3 | 44.9 ± 43.3 | 40.4 ± 77.2 | 0.005 | MWU |
| relevant MRA pathology, n (%) | 72 (36.1) | 14 (6.8) | 58 (24.2) | <0.001 | 4.37 (2.36-8.11) |
| Wallhard-Score | 6 (3-9) | 6 (3-9) | 6 (4-9) | 0.696 | MWU |
| Microbleeds on T2*, n (%) | | | | 0.248 | MWU |

Data presented as mean ± SD or median (IQR), as appropriate, unless specified otherwise.

*percentage given relates to patients having received the specified MRI scan and not to the total cohort. p-values obtained by use of Fischer’s exact test if not otherwise specified.

MWU = Mann-Whitney-U-Test; t-test = Student’s t-test; DWI = Diffusion weighted imaging; ACS = acute cerebrovascular syndrome; def. = definition; vol = volume.
FIGURE 2: Distribution of National Institute of Health Stroke Scale (NIHSS) score at admission (A), ABCD2 risk score (B), and functional outcome (modified Rankin Scale [mRS]) at discharge (C) and after 3 months (D), dependent on tissue status. Black bars indicate time-based/World Health Organization (WHO)-defined transient ischemic attack (TIA). White bars indicate tissue-based/American Heart Association/American Stroke Association–defined TIA. Hatched bars indicate time-based/WHO-defined TIA with diffusion-weighted imaging (DWI) lesion.
Importantly, however, it has been well documented that patients suffering from transient ischemic events with proof of infarction have a significantly higher rate of recurring events.\textsuperscript{11,12} Although they were reflected by higher ABCD2 scores in the patients with DWI lesions, our study protocol was not designed to either clinically or radiologically assess recurring events, due to short-term follow-up.

This cohort is the largest comprehensive study on hrDWI and perfusion imaging in TIA. Apart from a few smaller case series,\textsuperscript{13,14} it is the first robust analysis of multiparametric stroke MRI at 3T in TIA patients. Few reports so far have studied perfusion imaging in TIA.\textsuperscript{13,15,16} Previous reports frequently included patients with MRI significantly later than 24 hours after the event,\textsuperscript{17,18} or included minor strokes in their analyses.\textsuperscript{17,19} We included patients with persisting deficits at presentation, if their syndrome resolved within 24 hours of onset to reflect the time-based definition of TIA.

Our study is limited by relatively high rates of loss in follow-up. Although this weakens conclusions about outcome, the cohort remains thoroughly characterized in terms of the event and imaging characteristics. We cannot completely rule out that early recurrent ischemia and not the initial TIA caused DWI lesions on imaging, as especially patients with DWI lesions show a higher risk of early recurring events.\textsuperscript{11,20} Given that of the 240 total subjects presenting with DWI lesions, 231 already presented with it at initial MRI examination, however, we consider this possible bias negligible. Patients with DWI lesions presented significantly later after the event, rendering reversible lesions in the DWI-negative group possible. We found no reversible DWI lesions in the follow-up scans of TIA patients with DWI lesions, and therefore consider this possible bias negligible. Although the report of lesions on DWI may have affected the diagnostic workup and secondary prevention regime of the patients, withholding that information from the treating physicians would have been ethically unacceptable.

In conclusion, we found a higher incidence of ischemic lesions in TIA patients than previously reported when using hrDWI. Differences in clinical severity corroborate the tissue-based definition of TIA. hrDWI is a sensitive surrogate marker, and may serve in clinical research for improved secondary prevention. It furthermore guides patient workup after first ischemic event.

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Author Contributions

B.H., G.J.J., A.V., M.E., and J.B.F. contributed to conception and design of the study. B.H., I.G., C.K., P.B., K.V., and J.B.F. contributed to acquisition, post-processing, and analysis of the data. B.H. and J.B.F. drafted the text and prepared the figures. All authors revised the manuscript. B.H. conducted all statistical analyses.

Potential Conflicts of Interest

Nothing to report.

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