Transient Global Amnesia
Diffusion-Weighted Imaging Lesions and Cerebrovascular Disease

Christian Enzinger, MD; Felix Thimary, MD; Peter Kapeller, MD; Stefan Ropele, PhD; Reinhold Schmidt, MD; Franz Ebner, MD; Franz Fazekas, MD

Background and Purpose—A hypoxic-ischemic origin of transient global amnesia (TGA) has been suggested on the basis of the observation of infarctlike diffusion-weighted imaging (DWI) abnormalities in some affected individuals. We tested this hypothesis by comparing vascular risk factors, magnetic resonance imaging (MRI) markers of cerebral small-vessel disease, and other evidence of a cerebrovascular disorder between TGA patients with (DWI+) and without (DWI–) DWI lesions and normal community-based controls.

Methods—We retrospectively identified 86 patients hospitalized for TGA (mean ± SD age, 65.9 ± 10.9 years; 62% female). Brain MRI at 1.5 T was assessed for DWI lesions exhibiting restricted diffusion (ie, DWI+), white-matter hyperintensities, lacunes, and chronic infarcts (median time lag to clinical onset, 66.6 ± 54.6 hours). Vascular risk factors and findings from duplex sonography, ECG, and echocardiography were recorded. A 1:2 age- and sex-matched sample of 172 elderly subjects (mean ± SD age, 65.6 ± 9.3 years; 62% female) free of neuropsychiatric disease served for comparison.

Results—DWI lesions were observed in 10 patients with TGA (11.5%; mean ± SD age, 68.3 ± 5.4 years; 8 women). They were all small and located in the mesiotemporal region (9 left hemisphere, 5 right hemisphere). The vascular risk profile of TGA patients and concomitant changes on brain MRI were comparable with those of healthy controls and did not show significant differences between DWI+ and DWI– subjects. A comprehensive diagnostic workup also provided no evidence for a higher rate of cerebrovascular disorder–related abnormalities in either the total group of TGA patients or TGA DWI+ patients.

Conclusions—These findings do not support a cerebrovascular etiology of TGA, even in those individuals showing acute DWI lesions. Other pathophysiologic mechanisms need to be explored. (Stroke. 2008;39:2219-2225.)

Key Words: transient global amnesia ■ amnestic syndrome ■ magnetic resonance imaging ■ diffusion-weighted imaging ■ risk factors

Transient global amnesia (TGA) is characterized by anterograde memory disturbance of sudden onset that lasts for 1 to 24 hours.1 Orientation in space and time is impaired while consciousness remains undisturbed. From a defined population, the minimum annual incidence of TGA has been estimated to be 3.4 per 100 000 in 1 study.1 TGA is commonly considered a benign syndrome because complete restitution occurs in most cases after a few hours, although a remaining amnesic gap may persist.2

A variety of mechanisms and eliciting events such as paradoxical embolism, vertebral angiography, physical exercise, sexual intercourse, emotional stress, arterial thromboembolism, hyperextension of the neck, psychologic disturbances, migraine, cerebral small-vessel disease, venous ischemia due to Valsalva-like maneuvers and, more recently, jugular vein incompetency, have been implicated in the pathophysiology of TGA. (For reviews, see Sander and Sander,3, Pantoni et al,4 and Quinette et al.5) However, almost 5 decades after Fisher and Adams coined this term,6 consensus on its etiology and pathogenesis is still lacking. Conceptually, cerebral ischemia, epileptic discharge, and migraine constitute the main pathogenic hypotheses.

Diffusion-weighted imaging (DWI) has become a powerful tool in the evaluation of patients with suspected stroke owing to its high sensitivity and specificity, even for small areas of acute ischemia, and thereby DWI often provides important etiologic hints.7,8 Consequently, this method has also been applied to TGA to gain further insights into the pathophysiology of this enigmatic condition.9 Indeed, some authors observed DWI lesions in the mesiotemporal region that were...
mostly punctuate and showed signal characteristics consistent with focal cerebral ischemia.10–19 This created new arguments for stroke in the overall group of individuals with TGA,1,20,21 except for a few larger studies with up to 41 patients.10,11,13

We therefore wished to further test the “vascular hypothesis” in a large, unselected cohort of patients hospitalized for TGA by first assessing the frequency of acute DWI+ ischemic lesions in patients with TGA and then comparing the vascular risk factor profile and other evidence for a cerebrovascular disorder between TGA patients with and without DWI lesions, also in relation to a cohort of sex- and age-matched population-based normal controls. Subjects and Methods

Patients

We retrospectively identified patients hospitalized for an acute episode of TGA at the Department of Neurology, Medical University Graz, within the time period January 2002 to December 2006, in whom an MRI of the brain including DWI was available. This yielded a cohort of 86 patients with a mean±SD age of 66±10 years (53 females, 44 males; Table 1). According to existing criteria,1 a diagnosis of TGA was reserved for witnessed attacks of definite amnesia without disturbance of consciousness, focal neurologic symptoms, or epileptic features in patients who did not have active epilepsy, who had not sustained a recent head injury, and that resolved within 24 hours.

Apart from a careful neurologic examination and medical history, patients underwent repeated blood pressure measurements (n=86), ECGs (n=86), transthoracic echocardiography (n=44), duplex sonography of the extracranial cerebral arteries (n=86), electroen-
cephalography (EEG; n=83), chest x-ray (n=86), and a routine laboratory workup including measurements of cholesterol, triglycerides, and fibrinogen (n=86). EEG findings were mostly normal (n=57, 66.3%) or nonspecific (n=11, 12.8%). Regional slowing of electrical activity was observed in 13 patients (15.1%). Only 2 subjects in the TGA group demonstrated EEG signs compatible with epileptogenic foci (2.3%), and these individuals were DWI+. This distribution of EEG findings (normal, nonspecific regional slowing of electrical activity, and epileptic foci) did not differ significantly between DWI+ and DWI− TGA patients (P=0.065). Vascular risk factors were defined as reported previously.25,26 Four patients had a history of migraine (4.6%), and 3 patients (3.4%) reported that they had experienced symptoms suggestive of a TGA previously (without confirmation by medical doctors).

Healthy Controls

A sample of 172 elderly subjects (mean±SD age, 66±9 years; 107 women and 65 men) was randomly drawn in consecutive order with the investigator unaware of clinical and (if present) MRI findings from the register of the Austrian Stroke Prevention Study (ASPS) to obtain a 1:2 age- and sex-matched control group for comparison of clinical, demographic, and paraclinical variables and risk factors (Table 1). MRI of the brain was performed in subcohorts of the ASPS and was available for 92 individuals with a mean age of 67±9 years. The ASPS is a single-center, prospective, follow-up study on the cerebral effects of vascular and genetic risk factors in the normal elderly population of Graz, Austria. Within the ASPS, individuals are excluded if they have a history of neuropsychiatric disease, including previous cerebrovascular attacks and dementia, or an abnormal neurologic examination determined on the basis of a structured clinical interview and a physical and neurologic examination. The design of the study, selection and sampling procedures for ASPS participants, and a detailed description of the assessment of risk factors within the setting of the ASPS have been given elsewhere.25,26

Magnetic Resonance Imaging

MRI of the brain was performed with 1.5-T scanners (Siemens Symphony, Siemens Erlangen, Germany; Philips Gyroscan NT and Gyroscan ACS, Philips, Eindhoven, the Netherlands). Patients underwent scanning according to a standard protocol used for the workup of patients with suspected stroke at our clinic. This included an axial T2-weighted spin-echo sequence (repetition time/echo time 4600 ms/80 ms, isotropic diffusion weighting, b value=0 and 1000 s/mm2, field of view=250 mm, matrix=128×128, 2 averages) with 20 axial slices (thickness=5.0 mm, slice gap=1 mm). Apparent diffusion coefficient (ADC) maps were calculated from the reference scan (b=0) and the diffusion-weighted scan. The time lag between clinical onset of TGA and imaging was 0 to 24 hours in 10 patients (11.6%), >24 but <48 hours in 20 patients (23.3%), >48 but <115 hours in 36 patients (41.9%), and ≥115 hours in 20 patients (23.3%). The MRI protocol for the control subjects included a dual-echo spin-echo sequence (TR/TE=2000 to 2500 ms/30 and 90 ms) in axial orientation and a sagittal T1-weighted spin-echo sequence (TR/TE=600 ms/30 ms). The ASPS MRI protocol did not include DWI.

Rating of Scans

All scans were rated by consensus by 2 blinded experts (T.F., K.P.) for the presence of lesions with focal restriction of diffusivity (DWI+) of ≥3-mm diameter (which had to be confirmed by a concomitant ADC reduction; Figure 1) and for clinically silent ischemic infarcts and lacunes (defined as focal lesions involving the basal ganglia, the internal capsule, the thalamus, or the brain stem and not exceeding a maximum diameter of 10 mm). According to our scheme, white-matter hyperintensities (WMHs) were rated by 2 blinded experts (E.C., S.R.) as described previously as absent (grade 0), punctate (grade 1), early confluent (grade 2), and confluent (grade 3).

Plotting of DWI Lesions

To visualize both the topographic distribution and overlap of DWI+ lesions in the TGA cohort, all DWI+ lesions were plotted into standard space (MNI 152 averaged standard brain). First, DWI lesions were outlined manually in a magnified view of the diffusion-weighted images, and corresponding lesion masks were produced. These masks then were transferred into standard space by using the transformation matrix that was defined by prior registration of the individual diffusion-weighted scans to standard space. Registration was done with an affine 12-parameter model with a correlation ratio–based cost function and trilinear interpolation (FLIRT, part of the FMRIB software library FSL; available at www.fsl.fmrib.ox.ac.uk). A probabilistic map for lesion occupancy was produced by calculating the relative frequency from all registered masks.

Statistical Analyses

The Statistical Package for the Social Sciences (PC+, version 14.01; SPSS Inc, Chicago, Ill) was used for data analysis. Categorical variables were tested by Pearson’s χ2 test or by 2×2 Fisher’s exact test in case of contingency tables containing <5 cases. Fulfillment or deviation from normal distribution of continuous variables was tested by Kolmogorov-Smirnov statistics with a significance level after Lilliefors and additional inspection of histograms. Normally distributed continuous variables were compared with Student t test or 1-way ANOVA. The Mann–Whitney U test and the Kruskal-Wallis test were used as analog nonparametric tests. Spearman’s rank correlation coefficients were calculated. The level of significance was set at 0.05 in all cases. Data are quoted as mean±SD unless otherwise stated.

Results

MRI Findings

In the TGA cohort, 14 punctate lesions with restricted diffusivity (DWI+) were observed in 10 subjects (11.5%; mean±SD age, 68.3±5.4 years; 8 women; Figure 2). As shown in the lesion plot in Figure 3, DWI+ lesions were seen exclusively in the mesiotemporal region, with a peak of lesion probability in the hippocampus (alveus, body, and head). Other anatomic areas affected were the collateral eminence, the gyrus dentatus and cornu ammonis, and the parahippocampal gyrus (T3; anatomic designations according to the Duvernoy atlas).28 Nine lesions were located in the left hemisphere, and 5 lesions lay in the right hemisphere. Four subjects demonstrated 2 lesions, which were bilateral in 2 of them. The size of lesions ranged between 3 and 6 mm. The interval between symptom onset and MRI was not significantly different between DWI+ and DWI− subjects (63.3±50.1 hours [median, 65.6 hours; range, 22.8 to 116.3 hours] vs 88.0±57.2 hours [median, 70.2 hours; range, 3.6 to 289.7 hours]; P=0.23). The proportion of subjects with a DWI+ lesion was not significantly different between TGA patients scanned ≥48 hours after symptom onset (n=4/30, 13.3%) and subjects scanned ≤48 hours (n=6/56, 10.7%; P=0.7). The duration of the TGA episode also did not differ significantly between the DWI+ and the DWI− patient groups (DWI+, 4.8±3.3 hours vs DWI−, 6.2±5.7 hours; P=0.54).

Markers of cerebral small-vessel disease such as early confluent or confluent WMHs were seen in one third of TGA subjects (Table 2). Thirteen TGA patients (15.1%) showed...
cerebral lacunes. Clinically silent territorial infarcts were observed in 2 DWI− patients, 1 in the area of the posterior cerebral artery and 1 in the cerebellum. Regarding the distribution and frequency of WMHs, lacunes, and clinically silent infarcts, no significant differences were found between DWI+ and DWI− TGA subjects or between the entire TGA group and matched controls (n=92).

Cerebrovascular Risk Factors and Other Evidence for a CVD
The cerebrovascular risk factor profiles between DWI+TGA subjects and DWI− subjects did not show significant differences. As shown in Table 1, TGA patients with DWI abnormalities had a similar frequency of arterial hypertension and demonstrated similar mean values for systolic and diastolic blood pressures and for total cholesterol, HDL, LDL, and triglyceride levels than those without DWI lesions, and there were also no differences in comparison to the control population. None of the 6 subjects with diabetes mellitus and none of the 2 subjects with atrial fibrillation was in the DWI+ group. In the entire TGA cohort, the degree of atherosclerosis of the extracranial cerebral vessels assessed by sonography in general was low (92% of subjects either showed a normal finding or had only a mild stenosis). All 7 patients with higher grades of carotid artery stenosis (>30%) were in the DWI− group. Cardiac abnormalities as evidenced by echocardiography were also infrequent in TGA patients and, if present, mild. Cases with more severe changes of the heart valves (an 83-year-old woman with mitral insufficiency III and 1 56-year-old man with a mitral stenosis of 1 cm² orifice area) or a patent foramen ovale (n=4) were found in the DWI− group.

As shown in Table 1, the distribution and frequency of cerebrovascular risk factors within the entire cohort of TGA patients were not significantly different from an age- and sex-matched population-based sample of normal elderly individuals. With regard to some factors like diastolic blood pressure, serum cholesterol, and HDL levels, the TGA cohort even demonstrated a more favorable risk profile. Furthermore, the proportion of subject with no or only minor cardiac abnormalities was similar between TGA patients (95.5%) and normal individuals (96.6%). Carotid artery abnormalities were more frequent in TGA patients compared with normal individuals, but this difference was driven by the 6 TGA subjects with moderate stenosis.

Discussion
Our analyses of a series of 86 patients with TGA at our institution confirmed the presence of small, focal, hyperin-
tense lesions on DWI in some of the affected individuals. To the best of our knowledge, this study represents the largest single-center MRI-based investigation on a consecutive series of TGA patients who underwent DWI. The signal abnormalities observed were associated with reduced diffusivity, as indicated by the ADC maps, a finding that otherwise is regarded as rather specific for acute ischemic infarction. When looking at evidence for a coexisting cerebrovascular disorder, however, we found no difference between TGA patients with and without DWI lesions. In confirmation of earlier reports, there was no difference in vascular risk factors compared with an age- and sex-matched group of normal elderly controls drawn from the ASPS.

The presence of infarctlike abnormalities on DWI in some patients with TGA has revived the discussion regarding a cerebrovascular etiology for such abnormalities in at least some individuals. Along these lines, a higher prevalence of atherosclerosis, as indicated by a higher intima-media thickness and substantial vascular risk factors in DWI+ patients, has been reported. This would imply the need for an

Figure 2. DWI+ TGA patients. Selected slices from the 10 TGA subjects, demonstrating lesions with focal restriction of diffusivity (arrows and insets). Nine lesions were located in the left hemisphere, and 5 lesions lay in the right hemisphere (only 3 are shown). Four subjects demonstrated 2 lesions, which were bilateral in 2 of them. Lesion size ranged between 3 and 6 mm. Images are shown in radiologic convention.

Figure 3. Probabilistic lesion distribution map of the cohort of DWI+ TGA patients. DWI lesions were located exclusively in mesiotemporal brain structures relevant for memory (brighter values on the hot metal scale indicate greater lesion probability; coordinates refer to MNI standard space). Note the preponderance of lesions in the dominant (left) hemisphere (right-hand image in the upper panel).
extensive vascular workup and long-term therapeutic strategies as indicated for the secondary prevention of stroke. Whereas avoidance of and correction for vascular risk factors are certainly appropriate in any individual, our data do not suggest a specific preponderance of cerebrovascular disorders, neither in the entire group of TGA patients nor in those with a DWI lesion, when compared with community-based controls. There was no evidence for an increased rate or intensity of cerebrovascular risk factors, and there was no indirect evidence for an increased rate of microangiopathy, as indicated by higher grades of WMHs and lacunes. Early confluent and confluent WMHs have been associated with microangiopathy, and their prevalence was similar in TGA subgroups as well as in comparison with ASPS participants. Other diagnostic workup procedures, including ECG, extracranial duplex sonography, and echocardiography, also did not provide more direct evidence for a cerebrovascular etiology.

This retrospective analysis showed acute DWI lesions in only 11% of individuals with TGA. This is relatively low compared with some previous reports. In a review of existing MRI studies on acute TGA, 52 of the published 99 patients had DWI abnormalities, corresponding to a rate of DWI positivity of 52%. In a careful serial study, a frequency of DWI lesions of even 84% was observed. This suggests that higher rates of lesion detection might be achieved with repeated scanning at later time intervals, dedicated protocols, or higher field strengths. As a consequence, it could be argued that in our study, some individuals might have been falsely labeled as DWI−, and this might have obscured the comparison between TGA subgroups. Although this cannot be ruled out, our main conclusions are supported by the fact that even those patients who were definitely DWI+ did not show any difference in regard to cerebrovascular risk factors or MRI findings suggestive of small-vessel disease when compared with population-based controls. It has also been speculated that the incongruence between imaging findings could be explained by the delayed detectability of DWI lesions in TGA compared with stroke. In this context, it is interesting that in our study, DWI− and DWI+ TGA patients did not show significant differences in the interval between the onset of TGA and MRI scanning, and there were also no significant differences in the rate of lesion detection between subjects scanned within or beyond 48 hours in this study. Differences in the timing of scanning therefore cannot be regarded as the sole explanation for the low rate of DWI+ lesions in the present study.

Although our results strongly argue against an association between CVD and TGA, the true etiology of DWI+ lesions in the context of TGA still remains speculative. Interestingly and in line with previous studies (for a review, see Sander and Sander), mapping of lesions consistently pointed to the involvement of the same brain regions relevant to memory function, with a predominance for the left hemisphere. Because the hippocampal artery supplies an internal anastomosis between an upper and a lower artery, some have suggested this to be a particularly hypoxia-susceptible watershed area (the so-called sector of Sommer). The similarity between DWI abnormalities in TGA and areas of acute ischemia is intriguing, but the consistency of lesion size and the absence of other DWI lesions argue against ischemic infarction per se. In this context, it is particularly interesting that the few existing longitudinal studies also did not document persistent abnormal signal changes in the hippocampus after TGA, which would have been compatible with postischemic structural damage. Indeed, in addition to cerebral ischemia, ADC reductions have also been observed after cortical spreading depression, ischemic depolarizations, status epilepticus, and hypoglycemia. A DWI lesion thus has to be considered a nonspecific finding with several possible underlying mechanisms, probably all leading to focal energy failure. Recently, a combined study with single-photon emission computed tomography and transcranial magnetic stimulation suggested a relation between hypoperfusion in several brain areas (in the thalami, and also in the temporal lobes in a subset of patients) and reduced activity in inhibitory circuits. Conceptually, studies in TGA patients would thus appear to benefit from a combination of DWI with perfusion-weighted MRI, but to date, this approach has been used only in a case study, which yielded negative results. Unfortunately, both the design of our study and the small numbers of migraneurs and subjects with pathologic EEG findings prohibit us from drawing further conclusions on some of these alternative hypotheses. Clearly, pathophysiologic mechanisms other than focal ischemia from CVD need to be explored further as causes of a temporal dysfunction in memory-relevant structures, as indicated by more recent reports on hemodynamic disturbances in venous flow patterns in TGA.

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<th>P Value</th>
<th>DWI+ TGA Patients (n=10)</th>
<th>DWI− TGA Patients (n=76)</th>
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Acknowledgment
We thank Erich Flooh, PhD, for help with database management.

Disclosures
None.

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Stroke. 2008;39:2219-2225; originally published online June 26, 2008;
doi: 10.1161/STROKEAHA.107.508655
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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