Long-Term Outcome in Transient Global Amnesia Patients with and without Focal Hyperintensities in the CA1 Region of the Hippocampus

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Key Words

Hippocampus • DWI lesions • MRI • Amnesia • Transient global amnesia

Abstract

Focal hippocampal diffusion-weighted imaging (DWI) lesion patterns are detected in transient global amnesia (TGA) patients in different frequency. It has been speculated that acute diffusion restrictions are associated with a worse outcome. Therefore, we evaluated the influence of acute DWI lesions on the cognitive long-term outcome in TGA patients. Seventeen otherwise healthy patients with the clinical syndrome of TGA, who had MRI investigations on admission as well as 1 day later, were investigated with a comprehensive neuropsychological test battery 2 years later. Acute hippocampal DWI lesions in TGA patients were detected in almost two thirds of the patients. Psychometric evaluation revealed no differences in cognitive performance between patients with and without DWI lesions as well as compared to healthy subjects. In addition, no relapse of the attack has been recognized in either group of TGA patients.

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Introduction

Transient global amnesia (TGA) is a clinical condition characterized by sudden memory loss without further signs of cognitive impairment or concomitant focal neurological features. During the attack patients are conscious and alert, but show a severe anterograde amnesia which may extend also to variable retrograde parts of the episodic memory. Although clinical, psychometric and neuroimaging data suggest an explicit involvement of cerebral structures implicated in memory processing, the exact etiology of the disorder is still a matter of debate.

Proposed mechanisms include migraine, epilepsy and focal ischemia as well as venous congestion due to retrograde venous cerebral blood flow [1].

However, according to the overall low relapse rates of 10% for a second and of only 2–3% for a third or further episode, none of these pathophysiological theories seems to be convincing as these diseases show a substantially higher recurrence. Alternatively, stress-related causes have been discussed, as in more than 90% of the patients emotionally disturbing situations have been reported. It was also hypothesized that hippocampal sulcal cavities, residual cysts arising from a lack of vestigial hippocampal fissure obliteration during fetal development, contribute

Table 1. Demographic characteristics of the two TGA subgroups and the healthy controls

Group	Age (median; range)	Gender	Years of education	Verbal intelligence (WST) (median; range)	Months between TGA and follow-up examination (median; range)
Patients without DWI changes (n = 6)	70; 61–82	female: 2 male: 4	8–9: 3 10–13: 3	97; 79–129	24; 14–33
Patients with DWI changes (n = 11; 3 bilateral)	68; 55–77	female: 9 male: 2	8–9: 8 10–13: 3	95; 82–122	30.5; 15–38
Healthy controls (n = 15)	65; 47–77	female: 7 male: 8	8–9: 6 10–13: 9	104; 90–133	

to the pathophysiology of this enigmatic condition [2]. A central point of discussion concerns the question of whether the small focal hippocampal lesions which were seen in the diffusion-weighted imaging (DWI) in approximately 70% of the TGA patients 24–72 h after symptom onset [3–5] reflect a certain etiology. Although these lesions are generally unspecific they typically are detected in cases of ischemic stroke representing a zone of irreversible damage. Therefore, they should be associated with a higher probability of at least partially persistent cognitive impairment and of a detectable neuronal loss. Whereas numerous investigators have reported such long-lasting neuropsychological deficits [6–11], several studies devoted to imaging parameters [12], and especially the few dealing with the time course of the DWI changes, describe a complete remission of the hippocampal lesions without structural sequelae [3, 4]. The important question, i.e. whether the cognitive long-term outcome of patients with DWI lesions differs from those who reveal no signal alterations in the magnetic resonance imaging (MRI), has not been addressed so far.

In this study, therefore, we compared the neuropsychological performance of well-defined TGA patients with and without initial DWI changes at a mean of 2 years after the attack (median 25; range 14–38 months).

Subjects and Methods

Subjects

Eleven patients with acute diffusion restrictions (DWI lesion group: 8 unilateral, 3 bilateral) and 6 patients without diffusion lesions (non-DWI lesion group) in the 1.5T MRI during or directly after the amnesic episode were investigated. All patients had been admitted to the Department of Neurology of the University of Ulm between 2005 and 2006 because of the occurrence of a single TGA attack. At the time of investigation, the median follow-up since the TGA was 30.5 months in the DWI lesion

group and 24 months in the non-DWI lesion group (table 1). All patients fulfilled the criteria of TGA according to Caplan [13]: (a) acute onset anterograde amnesia, witnessed by an observer and resolved within 24 h; (b) no accompanying focal neurological symptoms during the attack; (c) no recent head injury; (d) no epileptic features either in the past or during the attack; (e) intact consciousness and personal orientation, and (f) no other cognitive impairment other than anterograde amnesia.

Further exclusion criteria were: the presence of psychiatric diseases since the TGA (such as dementia), treatment with corticosteroids in the last 12 months and a history of drug or alcohol abuse which could interfere with the cognitive performance.

The control group consisted of 15 healthy subjects (7 women, 8 men; median age 65 years; range 47–77 years). To achieve a balance concerning age, sex and nutritional factors as well as intellectual stimulation and social status, spouses if available or close relatives were chosen. The groups did not differ in terms of arteriosclerotic risk factors, such as arterial hypertension, hypercholesterolemia, smoking, obesity, and former cardiovascular events. All subjects gave written informed consent to their participation in the study. The study protocol was approved by the Ethics Committee of the University of Ulm.

Neuroimaging

Complete MRI investigations were performed on a 1.5 Tesla Siemens Symphony clinical routine scanner (Siemens, Erlangen, Germany) equipped with a 1-channel standard head coil. The MRI protocol encompassed the acquisition of T₁-, T₂-, T₂*- and fluid-attenuated inversion recovery (FLAIR)-weighted imaging as well as arterial time-of-flight magnetic resonance angiography and DWI. Three DWI sequences were acquired of which one was oriented axial in AC-PC (anterior commissure to posterior commissure) angulation and covered the whole brain with a slice thickness of 5 mm, while the two others covered the hippocampal region of both hemispheres in axial and coronal orientation with a 3-mm slice thickness. The sequence parameters of these hippocampus-angulated DWI sequences were as follows: repetition time 3,500 ms, echo time 104 ms, field of view 200 mm, image matrix 128 × 128, slice thickness 3 mm, 19 slices, 4 averages, bandwidth 1,184 Hz/px, EPI factor 128, 3-scan Trace and a b value of 1,000 s/mm². Total acquisition time of the conducted protocol was about 18 min. All patients were investigated by MRI at the time of admission as well as on the next day.

Table 2. Neuropsychological test battery as performed in TGA patients and healthy controls reflecting the different cognitive domains with special emphasis on verbal and nonverbal memory functions

Test, reference	Domain/assessed function	Task/recorded parameters
Digit span [24]	Verbal memory	Number of digits forward/backward
California verbal learning test, German adaption [25]		Encoding (sum; max: 75), 30/60 min delayed free recall of a 16-word list presented for 5 trials
Logical memory [24]		Free recall of a story 60 min after presentation (max: 25)
Block span, [24]		Number of correctly replicated figures forward/backward
Visual paired associates [24]	Nonverbal memory	Encoding, 60 min delayed recognition of 6 visually presented symbols and colors (max: 6)
Rey complex figure test [26]		Free recall of a figure 40 min after presentation (max: 36)
Famous faces test		A 15-portrait sample of well-known politicians (5 recent, 5 who were active in the years 1970–1985, 5 who were active between 1950 and 1970); subjects were asked for name, party membership and political function (max: 45)
Controlled oral word association test [27]	Phonemic/categorical word fluency	Number of words beginning with F, A, S in 3 min
Word production task [28]		Number of words associated with the category ‘supermarket’ in 1 min
Tonic alertness [29]	Processing speed	Motor reaction time (ms) on a single visual stimulus with (phasic condition)/without (tonic condition) preceding of an acoustic signal
Phasic alertness [29]		
Divided attention [29]	Attentional capacity	Motor reaction time (ms) on simultaneously presented visual and acoustic stimuli
Incompatibility [29]	Selective attention; interference	Motor reaction time (ms) on left- or right-side-directed visual stimuli, which interfere with the side of presentation

Neuropsychological Assessment

A comprehensive neuropsychological test battery consisting of paper-pencil and PC-supported tests (table 1) was given to both patients and controls in the same order and at the same time of day to minimize distortion by influences of circadian rhythm. Also, to detect subtle memory deficits, a broad range of functions including working, declarative and retrograde memory was assessed. In addition, attentional and executive functions as well as global intellectual capacity were examined.

Data Analysis

Due to the small sample size, nonparametric tests were used for group comparisons. Results were regarded as being significant if $p \leq 0.05$.

Results

Demographic Characteristics

Demographic data of the TGA samples and the healthy controls are given in table 2. General intelligence as estimated by a vocabulary test was comparable ($p = 0.13$,

Kruskal-Wallis test), as well as years of education ($p = 0.56$, χ^2 test), age ($p = 0.12$, Kruskal-Wallis test) and gender ($p = 0.23$, χ^2 -test). Patients with and without hippocampal DWI lesions did not differ in the time interval between TGA onset and follow-up investigation ($p = 0.078$, Mann-Whitney U test).

DWI Lesions

A first MRI was performed immediately after the patients’ admission to hospital. According to the history reported, the median time delay between the first clinical symptoms and the imaging was approximately 255 min (range 90–405 min). In all patients a second MRI was done on the following day. The median time delay to this imaging was 29.5 h (range 16.5–41 h) after the beginning of the episode. In the primary imaging 6 acute DWI lesions in 4 out of 17 patients (23.5%) were detected. There was a slight difference in the time delay to imaging between both groups of DWI-positive and DWI-negative patients (300 vs. 237.5 min, respectively).

Fig. 1. Diffusion-weighted MRI at two different time points: 4 h (**a**) and 26 h (**b**) after onset of TGA symptoms. Image **b** shows a slight dot-like DWI restriction in the left dorsolateral hippocampal region. L = Left.

The proportion of DWI-positive patients increased to nearly two thirds (64.7%) at the time of the second imaging, when 14 acute DWI lesions were detected in 11 out of 17 patients. Three patients demonstrated bilateral lesions, while in 8 patients unilateral diffusion restrictions were detected. All lesions were situated in the CA1 section of the hippocampus (fig. 1). There was a slight predominance of the left side, which was affected in 62.5% of cases.

Cognitive Performance

As shown in figure 2, patients and controls performed quite equally in the neuropsychological assessment. Significant group differences were observed only with respect to the Digit Span forward ($p = 0.026$, Kruskal-Wallis test) and backward ($p = 0.008$, Kruskal-Wallis test), and to the encoding section of the California verbal learning test ($p = 0.003$, Kruskal-Wallis test). Subsequent single contrasts by means of the Mann-Whitney U test showed a significantly lower learning rate in the TGA patients without DWI lesions compared to those with DWI lesions ($p = 0.015$) and the controls ($p = 0.001$), whose test performances did not differ ($p = 0.087$, Mann-Whitney U test). Concerning the Digit Span forward and backward, controls scored significantly better than the patients with DWI lesions ($p = 0.005$, $p = 0.004$, Mann-Whitney U test). Performance of the patients without DWI lesions did not differ from that of the controls ($p = 0.235$, $p = 0.055$, Mann-Whitney U test) or of the TGA patients with DWI lesions ($p = 0.525$, $p = 0.462$, Mann-Whitney U test).

Discussion

Despite numerous attempts to uncover its pathophysiology, TGA remains a clinical syndrome of unknown etiology. A broad range of diseases has been considered to be the underlying cause of the amnesic episodes including epileptic seizures, ischemic stroke and migraine. The detection of acute DWI lesions in the hippocampal area by high-resolution MRI was primarily interpreted in favor of ischemic stroke [14]. However, further investigations did not support this idea [3, 15, 16]. In concordance with the literature in our investigation acute DWI lesions developed in about two thirds of the TGA patients after a time delay of more than 24 h, while 6 out of 17 patients did not show any acute diffusion restrictions even at that late time point. Based on a multifactorial etiology these different imaging characteristics (DWI lesion and non-DWI lesion patients) might reflect different underlying pathologies leading to a clinically identical or at least very similar syndrome. However, our results do not suggest a crucial role for acute DWI lesions discriminating patients with pathophysiologically different diseases leading to neuropsychologically different long-term sequelae. According to our comprehensive test battery the patient groups differed in only one single test parameter – the California Verbal Learning Test learning rate, which was higher in the patients with DWI lesions. This is in contrast to the assumption that these patients are the ones who should have a greater risk of memory deficit. Although the interval between TGA onset and neuropsychological assessment did not significantly differ between both patient groups, patients without DWI lesions were investigated somewhat earlier (24 vs. 30.5 months). This time difference could possibly contribute to the better encoding performance in the group with DWI lesions [11, 17, 18].

Moreover, the highly concordant test performance of patients and controls underlines the benign character of TGA [19] and suggests that the disease does not lead to substantial cognitive restrictions independently of DWI lesions.

Interestingly, the pattern of patients with and without DWI lesions within one syndrome is very well known from transient ischemic attacks. It has been shown that transient ischemic attack patients with DWI lesions, classified as ‘transient symptoms associated with infarctions’ [20] seem to have a significantly higher risk of recurrent disease already in the short term. Recently, a similar phenomenon has been reported even for TGA patients, when patients suffering from a second TGA episode have been shown to have a higher frequency of acute DWI lesions

Fig. 2. Test performance (median and interquartile range) of the patients with (n = 11) and without (n = 6) DWI lesions in the hippocampus and of the controls (n = 15). DS-f/-b = Digit Span forward/backward; CVLT-enc/-r30/-r60 = California verbal learning test, encoding, 30/60 min delayed free recall; LM = logical memory, 60 min delayed recall; BS-f/-b = Block Span forward/backward; VPA-enc/-r60 = visual paired associates, encoding, 60 min delayed recognition; RCFT = Rey complex figure test, 40 min delayed recall; FFT = famous faces test, recall; tAI/pAI = tonic/phasic alertness; DA = divided attention; Incom = incompatibility; COWAT = controlled oral word association test; WPT = word production test.

[21]. However, in our cohort we did not see even one single relapse either in patients with or without acute DWI lesions over a time period of at least 2.5 years. Moreover, the frequency of DWI lesions in our cohort of first ever TGA patients was twice as high as in the report of Auyeung et al. [21], as we demonstrated, like several other groups [1, 14, 22, 23], acute DWI lesions in two thirds of patients. In addition, the clinical course without recurrence over a long time period does not argue for any impact of the DWI lesions on the long-term prognosis. Al-

though we cannot exclude different etiologies leading to the different imaging patterns, we finally did not find differences in terms of neuropsychological outcome, prognosis and/or the risk of recurrent events according to the detection of DWI lesions in TGA patients.

Disclosure Statement

The authors report no conflict of interest.

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