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Clinical Short Communication

Gadolinium leakage in ocular structures: A novel MRI finding in transient global amnesia

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ABSTRACT

Background and purpose: We investigated the frequency and pattern of blood-brain barrier as well as blood-retina barrier impairment in transient global amnesia (TGA) as demonstrated by hyperintense acute reperfusion marker (HARM) and gadolinium leakage in ocular structures (GLOS) respectively on fluid attenuated inversion recovery images (FLAIR).

Methods: Patients with TGA who underwent repeated MRI after intravenous contrast agent administration were identified and the presence of GLOS in the anterior chamber and vitreous body and HARM noted on FLAIR.

Results: Overall 10 patients (IQR 64.25–71.75 years; 4 (40%) patients were male) were included. On contrast-enhanced FLAIR, GLOS was observed in 3 (30%) patients; in all of these in the anterior chamber and vitreous body as well as bilateral and symmetrical. HARM was observed in none of the patients. Frequency of hippocampal DWI lesions, as well as extent of age related white matter lesions did not differ significantly between patients with and without GLOS.

Conclusions: In contrast to HARM, GLOS is a relatively common finding in TGA patients. As GLOS is thought to share its pathophysiology at least to some extent with HARM and is associated with HARM in ischemic stroke, it might be used as surrogate marker for blood-brain barrier impairment in TGA.

1. Introduction

In acute ischemic stroke two imaging findings caused by blood-brain barrier (BBB) and blood-retina barrier (BRB) impairment respectively were described on contrast-enhanced fluid attenuated inversion recovery (FLAIR): the hyperintense acute reperfusion marker (HARM) [1] and gadolinium leakage in ocular structures (GLOS) on a relatively early follow-up MRI with FLAIR, few hours after the initial MRI performed with gadolinium-based contrast agent application [2–4]. While contrast enhancement in the eye due to BRB impairment has been described previously in ophthalmological disorders [5], the observation in neurological diseases not affecting the eye is a novel observation. Both phenomena are caused by minute concentrations of gadolinium-based contrast agents resulting in T1 shortening and relative hyperintensity in the cerebrospinal fluid as well as the fluid of ocular structures on FLAIR as these share similar T1 MRI relaxation time-constants [2]. In transient global amnesia (TGA), a neurological disorder with sudden and transitory antero- and retrograde amnesia [6], an association with BBB impairment has been hypothesized previously as well [7], however, so far no study focused on BBB or BRB alterations in TGA.

In the present study we sought to investigate the frequency and pattern of (1) HARM, as well as (2) GLOS, and the (3) possible association of both phenomena in patients with TGA.

2. Methods

2.1. Patients

From an MRI report database (2005–2018), we identified 32 TGA patients who underwent an emergency MRI at the treating physician's discretion in the acute phase. Of these, only those patients were included who had a first MRI including contrast agent administration as well as follow-up MRI within 96 h. Demographic details, and clinical presentation were abstracted from the case records. This study has been approved by the local institutional review board and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Patient consent was waived for this analysis due to its retrospective nature.

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2.2. Magnetic resonance imaging

All patients underwent MRI on a 1.5 or 3 Tesla scanner (Magnetom Sonata/Avanto/Trio/Skyra; Siemens Medical Systems, Erlangen, Germany) using a protocol including transverse, coronal and sagittal localizing sequences followed by (1) T1-weighted; (2) T2-weighted; and (3) T2*-weighted images; (4) diffusion-weighted images (DWI); (5) FLAIR; (6) 3D time-of-flight (TOF) MR angiography (7) perfusion-weighted images; or (8) contrast-enhanced T1-weighted images using the contrast agent gadoteric acid (Dotarem, Guerbet, Aulnay-sous-Bois, France) with a dose of 0.1 mmol/kg of body weight.

2.3. MRI analysis

All MRI scans were reviewed in consensus by two readers (A.F., H.W.) blinded to the clinical information. OsiriX v.5.0.2 (Pixmeo SARL, Bernex, Switzerland) was used for all analyses. On DWI, hyperintense lesions in the hippocampus typical for TGA were noted. On FLAIR, the degree of age related white matter lesion (ARWML) severity was rated as described previously [2]. GLOS was defined and categorized as established recently [2]. HARM was defined as described previously [3].

2.4. Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

2.5. Statistical analysis

All statistical analyses were performed using Statistical Product and Service Solutions (SPSS) statistics for Windows (Release 17.0; SPSS, Chicago, IL, USA). Descriptive data was analyzed by use of Chi^2-based tests, or Mann-Whitney *U* test as appropriate. All statistics were performed with a 0.05 level of significance.

3. Results

3.1. Baseline characteristics and clinical presentation

In the final analysis, 10 (31%) TGA patients were included who met the pre-specified inclusion criteria. Most patients were excluded because of an MRI examination without contrast agent ($n = 17$) or lack of MRI follow-up ($n = 5$). The median age of patients was 68 (IQR 64.25–71.75) years; 4 (40%) patients were male, 6 (60%) female. Comorbidities and cerebrovascular risk factors included arterial hypertension (50%), hyperlipidemia (50%), coronary heart disease (20%), cancer (20%), diabetes mellitus (10%), and atrial fibrillation (10%). None of the patients had an ophthalmological disorder. A TGA typical clinical presentation was reported in all patients. Further clinical symptoms comprised nausea (20%), and vomiting (20%).

3.2. MRI findings

On DWI, hyperintense lesions in the hippocampus were detected in 8 (80%) patients on the initial or follow-up MRI. On FLAIR images, the median Fazekas scale score was 1 (IQR 0–1). Follow-up MRI was performed within a median time of 43 (IQR 30.25–76) hours after the initial MRI. On FLAIR images, HARM was observed in none of the patients. GLOS was observed in 3 (30%) patients: in all of these in the anterior chamber and vitreous body (for an example see Fig. 1). In all patients, GLOS was bilateral and symmetrical. With regard to risk factors, comorbidities, and clinical presentation, no significant differences were found between patients with and without GLOS (data not shown). Time between initial and follow-up MRI, frequency of DWI lesions in the hippocampus, as well as extent of ARMWL on FLAIR as assessed with the Fazekas scale did not differ significantly between both groups. For a comparison of demographics, and further MRI findings see Table 1.

4. Discussion

Although various possible pathomechanisms of TGA have been suggested (e.g. cortical spreading depression, ischemic stroke, and venous congestion), none of these satisfactorily explain its underlying pathophysiology. Different associated risk factors such as age, emotional stress, physical exertion, psychiatric disorders, and migraine have been established. Until today, small punctuate lesions in the hippocampus on DWI in the acute phase and more frequently after 24 to 72 h are the only characteristic – even if not pathognomonic - imaging finding in TGA [8] with highly variable detection rates [9].

In the present study, we focused on HARM and GLOS in patients with TGA and describe a novel and essential finding: GLOS is a relatively common finding and may be a novel imaging marker in TGA. Only recently, GLOS on contrast-enhanced FLAIR images has been described in acute ischemic stroke patients [2,3]. While the underlying pathophysiology is still not known, similarities in the anatomy and function of the BRB and BBB [10] as well as the association of GLOS and HARM in acute ischemic stroke suggest a shared pathophysiology of both phenomena [2].

An association of TGA with BBB dysfunction has also been hypothesized previously, in particular in TGA after conventional angiography presumably caused by iodinated contrast media [7]. Remarkably, most of the reported risk factors of TGA have also been shown to be associated with BBB dysfunction: e.g. normal aging [11], stress [12], psychiatric disorders [13], and migraine [14]. In the present study GLOS was observed in approximately one third of TGA patients which underscores that the phenomenon may be present not exclusively in ischemic infarction. Whether GLOS is directly related to TGA or rather associated with a pre-existent generally increased BBB permeability in TGA patients remains an open question. On the contrary, HARM was not observed in TGA patients in the present study. On first glance counterintuitive, this discrepancy may be at least partly explained by differences in dynamics of gadolinium-based agents in the cerebrospinal fluid, and the aqueous as well as vitreous humour in the eye. Furthermore, it has been shown in general that HARM is less frequently detectable in small vessel occlusion infarctions in comparison to larger infarctions [3,15].

The present study has some limitations. First, this is a preliminary clinical study of small size. However, to our knowledge this is the first series investigating GLOS in TGA. Second, the study was performed with different MRI scanners. However, the MRI sequences, in particular the FLAIR sequences, have been customized for optimal comparability in daily clinical routine and consequently are generally comparable. Third, so far GLOS has only been reported in the setting of an acute neurological disease, and as a consequence, we do not know whether healthy volunteers would also demonstrate GLOS dependent on age or comorbidities. Thus, further studies including healthy volunteers are required in order to elucidate the occurrence/frequency of GLOS in this population. Finally, the hospital-based retrospective study design might cause several types of bias and statistical errors such as selection bias, sample bias, or image-based selection bias.

In conclusion, in contrast to HARM GLOS is a relatively common finding in TGA patients. As GLOS is thought to share its pathophysiology at least to some extent with HARM and is associated with HARM in ischemic stroke, it might be used as surrogate for BBB impairment in TGA.

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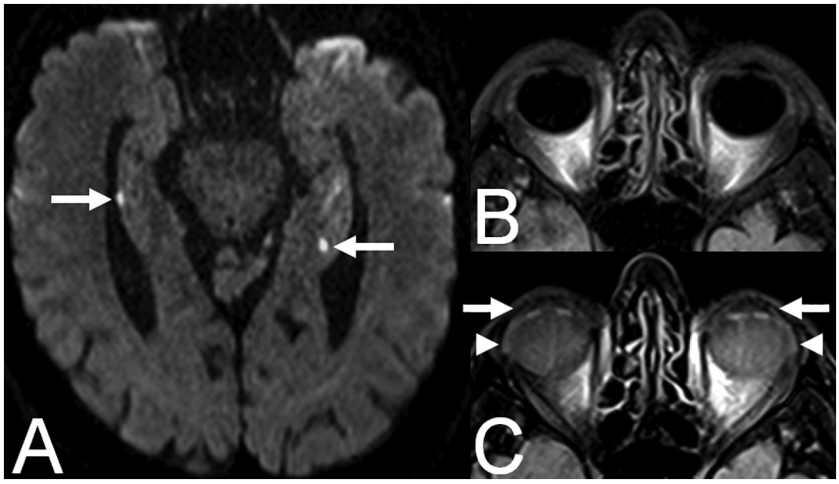

Fig. 1. Transient global amnesia patient with bilateral symmetrical GLOS on contrast enhanced FLAIR. (A) DWI shows small circumscribed lesions in bilateral in the hippocampus (arrows). (B) Native FLAIR is unremarkable. (C) Contrast-enhanced FLAIR after 40 h shows bilateral symmetrical GLOS in the anterior chamber (arrows) and vitreous body (arrowheads).

Table 1
Characteristics of TGA patients with gadolinium leakage in ocular structures (GLOS) on contrast-enhanced FLAIR images.

		GLOS		
	All, $n = 10$	Yes, $n = 3$	No, $n = 7$	p Value
Age, years, median (IQR)	68 (64.25–71.75)	74 (71–77)	67 (59–68)	0.09
Male sex, n (%)	4 (40)	2 (66.7)	2 (28.6)	0.26
Time between MRI 1/2, hours, median (IQR)	43 (30.25–76)	40 (20–76)	46 (31–76)	0.67
MRI findings				
Small punctuate DWI lesions in the hippocampus, n (%)	8 (80)	3 (100)	5 (71.4)	0.30
ARWML on FLAIR, Fazekas score, median (IQR)	1 (0–1)	1 (0–1)	1 (0–1)	1.00

Legend: GLOS = gadolinium leakage in ocular structures; IQR = interquartile range; DWI = diffusion-weighted imaging; ARWML = age related white matter lesions; FLAIR = fluid attenuated inversion recovery.

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Declaration of Competing Interest

None.

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