Blood-ocular barrier disruption in patients with acute stroke

Emi Hitomi, BS, Alexis N. Simpkins, MD, PhD, Marie Luby, PhD, Lawrence L. Latour, PhD, R. John Leigh, MD, and Richard Leigh, MD

Neurology® 2018;90:e915-e923. doi:10.1212/WNL.0000000000005123

Correspondence

Dr. Richard Leigh
richard.leigh@nih.gov

Abstract

Objective

Prompted by the unexpected finding of gadolinium leakage into ocular structures (GLOS) in acute stroke patients, we studied the frequency and nature of this finding in 167 patients.

Methods

Patients were selected who had an MRI with gadolinium at baseline and another MRI with fluid-attenuated inversion recovery (FLAIR) imaging at 2 and/or 24 hours later. GLOS was detected as lack of vitreous and/or aqueous fluid suppression on postcontrast FLAIR images.

Results

GLOS, evident on postcontrast FLAIR MRI, occurred in 127/167 (76%) patients: 86/109 (79%) patients treated with tissue plasminogen activator and 41/58 (71%) who were untreated. At 2 hours after administration of the contrast, GLOS was more common in the aqueous chamber alone, occurring in 67% of patients, compared to the vitreous chamber alone, seen in 6% of patients; it occurred in both chambers in 27% of patients. At 24 hours, GLOS was present in 121/162 (75%) patients, always involving the vitreous chamber, but also affecting the aqueous chamber in 6% of cases. Vitreous GLOS at 24 hours was associated with increasing age ($p = 0.002$) and a higher burden of cerebral white matter hyperintensities ($p = 0.017$). Patients with rapid diffuse GLOS, defined as GLOS involving both chambers at 2 hours, had larger infarcts ($p = 0.022$) and a higher degree of blood-brain barrier permeability ($p = 0.025$).

Conclusions

We found GLOS to be common in patients with acute stroke; delayed GLOS was a marker for chronic vascular disease. The mechanism for acute GLOS remains uncertain but may be a remote effect of acute cerebral injury on the blood-ocular barrier.

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From the National Institute of Neurological Disorders and Stroke (E.H., A.N.S., M.L., L.L.L., R.L.), NIH, Bethesda, MD; and Department of Neurology (R.J.L.), Case Western Reserve University, Cleveland, OH.

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Glossary

BBB = blood-brain barrier; BBPI = blood-brain permeability imaging; BOB = blood-ocular barrier; dWMH = deep white matter hyperintensities; FLAIR = fluid-attenuated inversion recovery; GLOS = gadolinium leakage into ocular structures; HARM = hyperintense acute reperfusion marker; MMP = matrix metalloproteinase; mRS = modified Rankin Scale; NIHSS = NIH Stroke Scale; pvWMH = periventricular white matter hyperintensities; TE = echo time; tPA = tissue plasminogen activator; TR = repetition time; WMH = white matter hyperintensities.

Patients with cerebrovascular disease run an increased risk of concomitant vascular disease of the eye,^{1–3} presumably due to similar vascular risk factors. The eye is protected from the peripheral circulation by the blood-ocular barriers (BOBs).^{4–6} Like the blood-brain barrier (BBB), the integrity of the BOB can be affected by vascular disease.⁶

Disruption of the BBB can occur in acute⁷ and chronic⁸ cerebral ischemia. In the absence of BBB disruption, gadolinium contrast given during MRI remains in the intravascular compartment and does not enter brain parenchyma or CSF. When gadolinium leaks into brain parenchyma, it can be detected with dynamic susceptibility contrast imaging.⁹ When gadolinium leaks into the CSF, it can be detected with post-contrast fluid-attenuated inversion recovery (FLAIR) imaging, referred to as hyperintense acute reperfusion marker (HARM) in the setting of acute stroke.¹⁰ The T1 MRI relaxation time-constant of fluid in the aqueous and vitreous humor of the eye are similar to that of CSF, and like CSF, their signals are suppressed and appear dark on FLAIR images. When gadolinium leaks into ocular structures (GLOS), T1 is shortened resulting in a relative hyperintensity, analogous to HARM. GLOS has been reported in the setting of central retinal artery occlusion¹¹ and kidney disease,¹² and may therefore be a marker for disruption of the BOB. We serendipitously noted GLOS as a common finding in patients with acute stroke, prompting us to conduct a retrospective study to determine its prevalence and assess its relationship to clinical and radiographic findings.

Methods

Standard protocol approvals, registrations, and patient consents

All patients in this study were enrolled in the NIH Combined NeuroSciences Institutional Review Board–approved study, Natural History of Stroke: Cause and Development. The study identification number for this protocol is NCT00009243.

Patients

Patients enrolled in the NIH Natural History of Stroke study during 2013 and 2014 were screened for inclusion in this analysis. Included patients needed to have had an MRI with gadolinium administration at baseline and then another MRI scan with FLAIR imaging at approximately 2 and/or 24 hours later (table).

MRI protocol

Images were acquired on a 3T Siemens Skyra scanner (Siemens AG, Munich, Germany), a 1.5T GE Signa scanner (General Electric Medical Systems, Milwaukee, WI), or a 3T Philips Achieva scanner (Philips Healthcare, Best, the Netherlands). Image sequences and typical parameter ranges were as follows: FLAIR imaging (repetition time [TR] 9,000 milliseconds [ms], echo time [TE] 120–145 ms, 3.5-mm slice thickness, 40 slices); diffusion tensor imaging (TR 4,461–10,500 ms, TE 61.6–91.3 ms, 3.5-mm slice thickness, 40 slices) used to generate trace diffusion weighted images using 3 orthogonal directions ($b = 0$ and 1,000 s/mm²) and apparent diffusion coefficient maps; time-of-flight magnetic resonance angiography images (TR 18–23 ms, TE 3.43–6.8 ms, 0.75- to 1.4-mm slice thickness, 73–95 slices); gradient recall echo images (TR 700–800 ms, TE 12–20.4 ms, 3.5- to 7-mm slice thickness, 20–40 slices); dynamic susceptibility contrast perfusion-weighted images (TR 1–1.5 seconds, TE 25–45 ms, 7-mm slice thickness, 20 slices, 40–80 dynamics), which was collected during the injection of a weight-based dose of gadolinium (0.1 mmol/kg of gadolinium-DTPA [Magnevist; Bayer Schering Pharma, Whippany, NJ] or gadolinium-BOPTA [MultiHance; Bracco Diagnostics, Monroe Township, NJ]).

Image analysis

GLOS was identified by comparing the baseline pre-gadolinium FLAIR scan with the FLAIR scans performed at the 2-hour and/or 24-hour time points. Gadolinium seen on the second MRI scan (which in some cases was the 2-hour scan and in other cases was the 24-hour scan) was attributable to the gadolinium administered during the baseline MRI scan. However, in cases in which the patient had 3 MRI scans (baseline, 2 hours, and 24 hours), the third scan reflected the effect of 2 prior administrations of gadolinium. The presence of GLOS was rated by one reviewer (E.H.) who was blinded to the results of the BBB analysis. GLOS was graded as present or absent, unilateral or bilateral, and as involving the aqueous chamber and/or the vitreous chamber at each time point after the baseline scan (figure 1, A and B). When GLOS was present in both the aqueous and the vitreous chambers at the 2-hour time point, it was considered to be *rapid diffuse GLOS* (figure 1C).

Gadolinium leakage into brain parenchyma was quantified using blood-brain permeability imaging (BBPI). BBPI is a method for measuring the permeability of the BBB from a dynamic susceptibility contrast image acquisition.⁹ The

Table Demographic, clinical, radiographic, and outcome characteristics for the entire population as well as for various subgroups

	All patients (n = 167)	Patients with GLOS at 2 and/or 24 h (n = 127)	Patients with no GLOS (n = 40)	Patients with rapid diffuse GLOS (n = 14)	Patients without rapid diffuse GLOS (n = 153)	Patients with GLOS at 24 h (n = 121)	Patients without GLOS at 24 h (n = 41)
Demographic characteristics							
Age, y, median (IQR)	71 (59–82)	74 (61–84)	63 (51–72)	81 (70–88)	71 (59–82)	74 (61–84)	63 (48–72)
Sex, F, n (%)	80 (50)	58 (45)	22 (56)	6 (43)	74 (48)	53 (44)	23 (56)
Medical history, n (%)							
Hypertension	123 (74)	99 (77)	24 (62) n = 38	11 (79)	112 (73) n = 152	92 (76)	26 (65) n = 40
Diabetes mellitus	40 (24)	28 (22)	12 (31) n = 38	2 (14)	38 (25) n = 152	27 (22)	11 (28) n = 40
Hyperlipidemia	67 (40)	55 (43)	12 (31) n = 38	6 (43)	61 (40) n = 152	51 (42)	14 (35) n = 40
Tobacco use	19 (11)	12 (9)	7 (18) n = 38	1 (7)	18 (12) n = 152	10 (8)	8 (20) n = 40
Clinical characteristics							
Baseline NIHSS score, median (IQR)	7 (3–14) n = 166	8 (4–15) n = 127	5 (2–12)	18 (7–20)	7 (3–13) n = 152	7 (4–13) n = 120	5 (2–14) n = 41
2-h NIHSS score, median (IQR)	5.5 (3–12) n = 96	6 (3–14) n = 81	3 (1–11) n = 15	11 (7–20)	5 (2–11) n = 82	5 (3–13) n = 75	3.5 (1–11.25) n = 16
24-h NIHSS score, median (IQR)	4.5 (1–11) n = 130	5 (1–11) n = 101	4 (1–7) n = 29	6 (2–22)	4 (1–10) n = 116	4 (1–10) n = 96	4 (1–9.5) n = 30
Systolic BP on arrival, mm Hg, median (IQR)	153 (138–173) n = 159	153 (139–173) n = 121	150 (134–169) n = 38	164 (132–176)	152 (138–171) n = 145	152 (137–169) n = 114	152 (137–173) n = 40
Glucose level, mg/dL, median (IQR)	119 (105–147) n = 156	120 (104–150) n = 120	117 (113–139) n = 36	109 (97–179)	119 (106–143) n = 142	122 (104–153) n = 113	116 (111.5–134) n = 38
Hb _{A1c} level % glycohemoglobin, median (IQR)	5.8 (5.3–6.4) n = 154	5.8 (5.4–6.3) n = 116	5.9 (5.3–7.2) n = 38	5.7 (5.5–6) n = 13	5.8 (5.3–6.4) n = 141	5.8 (5.4–6.4) n = 110	5.8 (5.28–6.75) n = 40
LDL cholesterol level, mg/dL, median (IQR)	87 (65–112) n = 160	83 (63–106) n = 122	102 (70–134) n = 38	66 (59–105) n = 13	88 (66–113) n = 147	83 (64–104) n = 115	101 (69–135) n = 40
Preadmission statin use, n (%)	51 (31)	43 (34) n = 127	8 (21)	4 (29)	47 (31) n = 152	41 (34) n = 120	10 (24) n = 41
Creatinine level, mg/dL, median (IQR)	1 (0.8–1.2) n = 156	1 (0.9–1.2) n = 120	1 (0.8–1.1) n = 37	1.15 (0.9–1.3)	1 (0.8–1.2) n = 143	1 (0.9–1.2) n = 113	1 (0.8–1.1) n = 39
Imaging characteristics, mean (SD)							
Fazekas score	3.30 (1.71)	3.48 (1.70)	2.72 (1.62)	3 (1.41)	3 (1.73)	1.6 (0.87)	2.71 (1.57)
Perfusion lesion volume, mL	49.27 (66.46) n = 99	55.18 (70.81) n = 79	25.91 (38.45) n = 20	110.44 (105.36) n = 13	45.39 (54.08) n = 60	53.53 (67.18) n = 72	35.71 (62.94) n = 22

Continued

Table Demographic, clinical, radiographic, and outcome characteristics for the entire population as well as for various subgroups (continued)

	All patients (n = 167)	Patients with GLOS at 2 and/or 24 h (n = 127)	Patients with no GLOS (n = 40)	Patients with rapid diffuse GLOS (n = 14)	Patients with rapid diffuse GLOS (n = 153)	Patients with GLOS at 24 h (n = 121)	Patients without GLOS at 24 h (n = 41)
Average permeability, %				3.62 (0.75) n = 12	3.13 (0.85) n = 53		
Diffusion lesion volume, mL				28.34 (38.20) n = 12	8.16 (13.67) n = 49		
Outcome measures							
mRS score, median (IQR)	1 (0–3) n = 134	2 (0–4) n = 102	1 (0–2) n = 32	3 (0–5) n = 13	1 (0–3) n = 121	1 (0–4) n = 98	1 (0–2) n = 33
Parenchymal hematoma type 2, n (%)				2 (14) n = 10	3 (2) n = 62		

Abbreviations: BP = blood pressure; GLOS = gadolinium leakage into ocular structures; Hb_{A1c} = hemoglobin A1c; IQR = interquartile range; LDL = low-density lipoprotein; mRS = modified Rankin Scale; NIHSS = NIH Stroke Scale. The table shows demographic, clinical, radiographic, and outcome characteristics for the entire population as well as for various subgroups. The size of the sample, n, is listed at the top of the column. For entries in which the sample is less than that listed at the top, the n is listed in the individual cell.

BBPI method was preferred over HARM because BBPI provides a continuous measure of BBB permeability, whereas HARM provides a binary measure. BBPIs were generated for the subset of patients who had a successful dynamic susceptibility contrast image acquisition on their baseline MRI. BBB permeability was measured relative to the unaffected hemisphere. Only patients with unilateral supratentorial strokes isolated to one hemisphere were included in the BBB analysis. Gadolinium leakage into the brain parenchyma was measured at the time of the baseline gadolinium administration. The average permeability within the acute ischemic regions was calculated, as previously described.⁷

For this subpopulation, the volume of the stroke and the volume of the perfusion deficit were also measured. The perfusion volumes were calculated from the time-to-peak maps using a threshold of 4 seconds. Stroke volumes were calculated within the perfusion deficit using an apparent diffusion coefficient threshold of 600 $\mu\text{m}^2/\text{s}$.

White matter hyperintensities (WMH), which have been associated with ocular disease,³ were also graded for this analysis. The Fazekas scoring system was applied using baseline FLAIR scan for all patients.¹³ The Fazekas score ranges from 0 (absent) to 3 (confluent) WMH. The Fazekas score was graded by one reviewer (E.H.) for both the periventricular white matter (pvWMH) and the deep white matter (dWMH).

Clinical outcome measures

The NIH Stroke Scale (NIHSS) scores were assessed by the stroke team at the time of each MRI scan. The modified Rankin Scale (mRS) score was obtained, whenever possible, at 30 and 90 days. The 90-day score was used when available; however, for patients with only a 30-day mRS score, it was used in the place of the 90-day score.

Statistics

Statistical analysis was performed using logistic regression. The presence or absence of GLOS was treated as a binary dependent variable. A *p* value <0.05 was considered significant. Statistical analysis was performed using the STATA software package (StataCorp, College Station, TX).

Results

Of the 288 enrolled patients in the NIH Natural History of Stroke Study during 2013 and 2014, 182 had an evaluable baseline FLAIR scan followed by administration of gadolinium. Of these, 167 patients had a subsequent evaluable FLAIR scan at 2 hours and/or 24 hours and were eligible for this analysis. Of these, 109 patients were treated with IV tissue plasminogen activator (tPA) and 58 were not. Of the tPA-treated patients, 80 had a 2-hour FLAIR and 104 had a 24-hour FLAIR. Five of the treated patients had a 2-hour, but not a 24-hour, FLAIR. Of the untreated patients, 58 had a 24-hour scan. Figure 2 outlines how the final dataset was

Figure 1 Examples of GLOS

Pre- and postgadolinium fluid-attenuated inversion recovery images are shown for patients demonstrating GLOS of the aqueous chamber (A, indicated by arrows), the vitreous chamber (B, indicated by arrows), and both (C, indicated by arrows). (C) Example of rapid diffuse GLOS. (D) Ocular structures pertinent to the development of GLOS on a T1 postgadolinium MRI (image courtesy of Dr. Joseph L. Demer). Potential continuity between the subretinal space and CSF is indicated by the dotted arrow line; this and microanatomical details of the blood-ocular barrier are discussed in the text. GLOS = gadolinium leakage into ocular structures.

defined. To summarize, a total of 167 patients were included in the analysis; when looking at 2-hour GLOS, 80 treated patients were included; when looking at 24-hour GLOS, 162 patients (104 treated + 58 untreated) were included.

Prevalence of GLOS

GLOS at any time point in any chamber was detected in 127/167 (76%) patients. It was present in 86/109 (79%) treated patients and 41/58 (71%) untreated patients. Limiting the comparison to patients who only had a baseline and 24-hour scan (removing the effect of multiple gadolinium doses), GLOS was present in 19/29 (66%) treated patients and 41/51 (80%) untreated patients. In this subpopulation, there was no association between the administration of tPA and the occurrence of GLOS ($p = 0.695$). Thus, for the remainder of the analysis of the 24-hour time point, treated and untreated patients are combined.

GLOS at the 2-hour time point was present in 51/80 (64%) patients and was more common in the aqueous chamber (34/51 = 67%) than in the vitreous chamber (3/51 = 6%). *Rapid diffuse GLOS*, defined as GLOS in both the aqueous and vitreous chambers at 2 hours, occurred in 14/80 (18%) patients. At 24 hours, GLOS was slightly more common than at 2 hours, occurring in 121/162 (75%) patients. However, at this time point, all 121 occurrences of GLOS involved the vitreous chamber, while in only 10 of these patients GLOS also involved the aqueous chamber. We identified a typical temporal pattern where aqueous GLOS occurred at 2 hours, resolved by 24 hours, and was replaced with vitreous GLOS (figure 3A). This pattern was seen in 36/51 (71%) patients who had GLOS.

GLOS was typically bilateral; however, the intensity of the finding was in some cases asymmetric (figure 3, B and C). In 2 patients, there was complete asymmetry. In both cases of complete asymmetry, the involved globe was contralateral to the side of the stroke; however, with partial asymmetry, the brighter globe was not typically on the contralateral side (13/127 = 10%).

Demographics of GLOS

The presence of GLOS was compared with age, sex, history of hypertension, history of diabetes, history of hyperlipidemia, tobacco use, glucose level on arrival, creatinine level on arrival, low-density lipoprotein cholesterol level, and hemoglobin A_{1c} level. No significant associations were found with the presence of GLOS at 2 hours. However, at 24 hours, the presence of GLOS was associated with increasing age ($p = 0.002$). There was also a tendency for increased GLOS in patients with a history of hypertension ($p = 0.054$) with an odds ratio of 2.07 (confidence interval 0.98–4.36). There was also a tendency for decreased GLOS with higher low-density lipoprotein ($p = 0.074$), but there was no association detected between the prior use of statin

Figure 2 Patient selection flowchart

A flowchart details how the population included in the study was determined. See text for details of criteria used. FLAIR = fluid-attenuated inversion recovery; tPA = tissue plasminogen activator.

medications and the occurrence of GLOS ($p = 0.542$). Of note, there was no association with diabetes or any of the other variables tested; however, this may be attributable to the limited sample size.

GLOS and WMH

To assess for an association between WMH and GLOS, the Fazekas score was compared with the presence of GLOS. No associations were found for GLOS at 2 hours. However, for GLOS at 24 hours there was a tendency for increased pvWMH score ($p = 0.071$). For dWMH, GLOS was significantly associated with a higher score ($p = 0.011$) with an odds ratio of 1.75 for each point increase in Fazekas score. Combining pvWMH + dWMH into a single

score also demonstrated a significant relationship ($p = 0.017$).

GLOS and BBB

To examine whether there is an association between the BBB disruption of the acute stroke and disruption of BOB in the eye, the average permeability measured in the region of cerebral ischemia was compared with the presence or absence of GLOS at 2 hours. Of the 80 patients studied at 2 hours, 65 patients had a unilateral, supratentorial ischemic lesion and thus were included in this analysis. Elevated average BBB permeability of the stroke was associated with GLOS of the vitreous chamber ($p = 0.042$) but not the aqueous chamber ($p = 0.408$). However, the strongest correlation was in patients

Figure 3 Examples of different patterns of GLOS

(A) Typical temporal pattern of GLOS, with no enhancement on the first pretreatment scan, followed by aqueous enhancement at 2 hours on the second scan, followed by vitreous enhancement at 24 hours on the third scan. (B) Example of unilateral GLOS, and (C) example of asymmetric GLOS. Arrows indicate regions of enhancement. GLOS = gadolinium leakage into ocular structures.

who had both vitreous and aqueous GLOS ($p = 0.025$). Given the typical temporal time course of GLOS described above (first aqueous, then vitreous), this subgroup of patients who demonstrate rapid diffuse GLOS (aqueous + vitreous) at the 2-hour time point presumably represent a more severe disruption of the BOBs. Rapid diffuse GLOS at 2 hours was also associated with the size of the stroke on arrival ($p = 0.022$) and the size of the perfusion deficit ($p = 0.006$).

Outcome with GLOS

There was no association detected between GLOS and NIHSS score on arrival, at 2 hours, or at 24 hours. There also was no association detected between GLOS and mRS score at 30–90 days. However, in patients treated with tPA who had rapid diffuse GLOS at 2 hours, there was a tendency toward increased incidence of posttreatment formation of a cerebral parenchymal hematoma type 2 (classified by one author, A.N.S., using the ECASS2 definition¹⁴) on follow-up imaging ($p = 0.071$, $n = 67$).

Of the 167 patients in the study, 60 scored one or more points on the visual fields section of the NIHSS prior to their first MRI. Thirteen patients had an increase in the visual section of the NIHSS at a time point after receiving gadolinium. An independent reviewer (A.N.S.), blinded to the results of the study, evaluated these patients' records for potential causes of visual field loss. Only one patient did not have an imaging abnormality of the optic tracts, radiations, or visual cortex to explain the increase in score. Thus, we did not find any evidence suggesting that progressive visual field involvement was

either due to ocular disease or was caused by gadolinium leaking into ocular structures.

Discussion

In this study, we followed up on a serendipitous finding: patients with acute stroke being evaluated in a natural history study showed evidence of BOB disruption detected as gadolinium leakage into the aqueous and vitreous fluids of the eye (GLOS). Several key findings emerged. First, BOB disruption is common in stroke patients, occurring in 79% of tPA-treated patients and 71% of untreated patients. Second, BOB disruption, when detected with GLOS, often follows a temporal pattern with GLOS in the aqueous fluid within minutes to hours, followed by GLOS in the vitreous fluid on the order of hours to days. Third, a subset of patients has an accelerated time course with rapid diffuse GLOS affecting both the aqueous and vitreous compartments at 2 hours; these patients also had more severe BBB disruption, larger ischemic lesions, and may have had an increased risk of complications when treated with tPA. Lastly, patients with chronic small vessel disease of the brain are more likely to have vitreous GLOS at 24 hours.

GLOS is not well recognized and there are few papers that have previously reported hyperintense signals in the ocular structures on FLAIR.^{11,12} In contrast, GLOS was a common finding in our patient population regardless of whether they were treated with IV tPA. We attribute this discrepancy to our schedule of serial imaging, which is not typically performed in

the clinical setting, where GLOS would go unrecognized, despite its common occurrence. Nonetheless, further studies are needed to determine, for example, whether GLOS is present in otherwise healthy individuals.

What could be the mechanism of GLOS? Three components of the BOB can be recognized⁴⁻⁶: (1) an inner blood-retinal barrier, consisting of endothelial cells with tight junctions surrounding the vessels of the inner layers of the neural retina; (2) an outer blood-retinal barrier, consisting of the retinal pigment epithelium, which lies outside the outer neural retina (photoreceptors); (3) the blood-aqueous barrier, located in the ciliary body, which secretes aqueous humor into the anterior chamber of the eye and consists of nonpigmented epithelial cells with tight junctions forming a continuous layer with the retinal pigment epithelium. Given the significant correlation between a rapid diffuse GLOS (involving both chambers), the severity of the lesion, and BBB permeability index, we propose that either the acute cerebral event is having a remote effect on the eye, or that there is a systemic process affecting both the eye and the brain. Our study suggests a temporal sequence of BOB leak, with initial leakage of the blood-aqueous barrier of the ciliary body (anterior chamber) followed by GLOS in the vitreous humor, indicating leakage of the internal or pigmented retinal layers.

What molecular mechanisms could underlie GLOS? One possibility concerns changes of the tight junctions of the inner neural retina, which is most susceptible to ischemia.⁶ Müller cells of this inner retinal layer secrete matrix metalloproteinases (MMPs), which cause proteolytic degradation of occludin proteins at tight junctions. In the BBB, MMP2 has been demonstrated to cause a reversible phase of leak, whereas MMP9 causes permanent BBB disruption.¹⁵ Alternatively, leakage of gadolinium into the vitreous chamber might originate via tight junctions in the retinal pigment epithelium, which are regulated by claudin proteins.⁴ The subretinal space that lies between retinal pigment epithelium and neural retina is a potential space that remains continuous with the ventricular system of the brain. The ciliary body also abuts the subretinal space.⁴

If release of MMPs is the mechanism underlying GLOS, how could the acute stroke trigger this process? One possibility is leakage of MMPs from brain to eye, either via shared vasculature, or via the ventricular system and subretinal space. Although some patients showed more predominant GLOS contralateral to the cerebral infarction, many patients showed binocular gadolinium leak that was not consistently lateralized with respect to the side of the stroke. Nonetheless, the occurrence of GLOS correlated with the severity of BBB leak in the focal cerebral lesion. Alternatively, GLOS might be due to a reflexive release of MMPs, triggered by acute cerebral ischemia. It also remains possible that the eyes and brain are both affected by a common ischemic process triggering BBB and BOB leak; a link between retinal microvascular abnormalities has been proposed.¹⁶

Whatever the mechanisms for GLOS, prospective studies of acute stroke patients that include bedside evaluation of visual acuity, visual fields, and ophthalmoscopy, are needed. Such studies may also determine whether hypertension, obesity, and tobacco use, in addition to age, predispose to the development of GLOS in patients with acute stroke.

Finally, does the phenomenon underlying GLOS represent a way to detect the extent of BBB disruption in acute stroke? Measurement of BBB permeability directly in acute stroke patients¹⁷ requires dynamic susceptibility contrast MRI (perfusion-weighted imaging), which may not be available in all centers. However, it might be possible to detect BOB disruption using ophthalmologic approaches, such as modern fluorescein angiography, which detects leakage of the inner ocular barrier,¹⁸ or with ocular coherence tomography, since retinal thickness and edema are markers for BOB disturbances.¹⁹

This study has several limitations. It was exploratory in design, thus all findings should be considered hypothesis-generating not hypothesis-testing; further studies are required that include nonstroke controls. However, by allowing the eye to be the window to the brain, substantial advances could emerge in the management of patients with acute stroke.

Author contributions

Emi Hitomi: analysis and interpretation of data, first draft. Alexis N. Simpkins: analysis and interpretation of data. Marie Luby: critical revision of manuscript for intellectual content. Lawrence L. Latour: critical revision of manuscript for intellectual content. R. John Leigh: critical revision of manuscript for intellectual content. Richard Leigh: study concept and design, data processing, critical revision of manuscript for intellectual content, study oversight and guarantor.

Acknowledgment

This research was possible because of contributions from the NIH Natural History of Stroke Investigators, including: Richard T. Benson, Amie W. Hsia, Lawrence L. Latour, Richard Leigh, Marie Luby, John K. Lynch, José G. Merino, and Zurab Nadareishvili.

Study funding

Funded by the NINDS intramural research program of the NIH.

Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Received August 4, 2017. Accepted in final form November 13, 2017.

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Blood-ocular barrier disruption in patients with acute stroke

Emi Hitomi, BS, Alexis N. Simpkins, MD, PhD, Marie Luby, PhD, Lawrence L. Latour, PhD, R. John Leigh, MD, and Richard Leigh, MD

Cite as: *Neurology*® 2018;90:e915-e923. doi:10.1212/WNL.0000000000005123

Correspondence

Dr. Richard Leigh
richard.leigh@nih.gov

Study question

What is the frequency and nature of post-MRI gadolinium leakage into ocular structures (GLOS) in patients with acute stroke?

Summary answer

GLOS occurs in most patients with acute stroke, and different patterns of GLOS reflect the burden of acute and chronic cerebrovascular disease.

What is known and what this paper adds

Cerebrovascular diseases are associated with an increased prevalence of vascular disease of the eye. This study reports that the pattern of GLOS in patients with acute stroke is associated with the severity of their cerebrovascular disease.

Participants and setting

This study examined 167 patients with acute stroke who were enrolled in the NIH Natural History of Stroke study during 2013 and 2014.

Design, size, and duration

Each participant underwent a baseline and at least one follow-up fluid-attenuated inversion recovery (FLAIR) MRI scan without and with gadolinium. Follow-up MRI scans occurred at approximately 2 and 24 hours after the baseline. The MRI results were used to generate blood-brain barrier (BBB) permeability images.

Primary outcomes

The presence of GLOS as determined by comparing the baseline FLAIR scan with the follow-up FLAIR scan performed later.

Main results and the role of chance

GLOS was detected in 127 (76%) patients. GLOS did not have any associated visual disturbance. Fifty-one (64%) of the 80 patients who underwent a FLAIR scan 2 hours after their baseline scan had GLOS, which was more commonly isolated to the aqueous chamber, occurring in 34 (67%), compared to 3 (6%) involving the vitreous chamber alone; 14 (27%) had GLOS in both chambers. Of the 162 patients who underwent FLAIR scans 24 hours after baseline scans, GLOS was detected in 121 (75%),

all of whom had vitreous chamber GLOS, and 10 (6%) of whom also had aqueous chamber GLOS. GLOS occurred more commonly in elderly patients ($p = 0.002$) and occurred no more frequently in patients treated with thrombolysis. No other characteristics differed between those with and without GLOS, but future work should consider the potential role for a history of hypertension (odds ratio, 2.07; 95% CI, 0.98–4.36; $p = 0.054$). These results identified a typical temporal pattern in which GLOS appeared in the aqueous chamber at 2 hours and in the vitreous chamber at 24 hours in most cases. A subset of patients who showed rapid accumulation of GLOS in both chambers suffered more severe strokes. In the patients assessed at 2 hours post-baseline who had unilateral, supratentorial ischemic lesions, more severe BBB disruption was significantly associated with rapid accumulation of GLOS in both chambers ($p = 0.025$).

Bias, confounding, and other reasons for caution

This study included no healthy controls without stroke, so it should be considered hypothesis-generating rather than hypothesis-testing.

Generalizability to other populations

The GLOS prevalence in otherwise healthy individuals was not studied, thus it is not known if these results are specific to stroke patients making generalization unclear.

Study funding/potential competing interests

This study was funded by the NIH. The authors report no competing interests. Go to Neurology.org/N for full disclosures.

A draft of the short-form article was written by M. Dalefield, a writer with Editage, a division of Cactus Communications. The authors of the full-length article and the journal editors edited and approved the final version.