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SHORT COMMUNICATION

Post-stroke Recrudescence from Infection: an Immunologic Mechanism?

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Abstract

Post-stroke recrudescence (PSR) usually occurs in the setting of infection, hypotension, hyponatremia, insomnia or stress, and benzodiazepine use. Animal studies have suggested an infection-related immunologic mechanism for PSR. This retrospective study was designed to assess whether infection-triggered PSR is related to a prior infection during the index stroke. We identified 95 patients admitted to Massachusetts General Hospital from 2000 to 2015 with post-stroke recrudescence who had adequate medical record information concerning the index stroke. The frequency of infections, as well as other triggers such as hypotension, hyponatremia, insomnia/stress, and benzodiazepine use, was compared between the index stroke and the PSR episode. Independent predictors of infection-related PSR were identified using a logistic regression model. The mean age was 66 ± 17 years (53% female); 29 (31%) had infections during the index stroke as compared to 40 (42%) during the PSR episode. The frequency of PSR triggered by infection was higher in patients with infections during the index stroke (65% vs 32%, $p = 0.003$). The same relationship occurred with benzodiazepine-triggered PSR (41% vs 12%, $p = 0.008$). The frequencies of other triggers such as hypotension, hyponatremia and insomnia/stress were not significantly different between the index stroke and the PSR episode. In a logistic regression model, infection during the index stroke was an independent predictor of infection-triggered PSR (odds ratio 4.85, 95% C.I. 1.7, 13.7). The association between infection during index stroke and infection-triggered PSR supports the immunologic mechanism postulated in animal models.

Keywords Stroke · Recrudescence · Infection · Immune response

Introduction

In a recent study, we showed that triggers of post-stroke recrudescence (PSR, transient worsening of residual deficits or transient recurrence of prior stroke-related focal deficits) include infection, hypotension, hyponatremia, insomnia or stress, and benzodiazepine use [1]. The postulated mechanisms for PSR include altered neuronal excitability in patients with hyponatremia, GABA-ergic abnormalities in patients with insomnia or benzodiazepine use, and a cytokine/immune response in patients with infections [2–4]. The infection-related immunologic hypothesis has emerged from the results of an animal study showing that lipopolysaccharide injection during acute stroke was associated with a greater delayed-type immune response to brain antigens, and transient neurological deterioration after antigen re-exposure [4]. To determine whether a similar mechanism occurs in humans, we investigated the association between infections and other known PSR triggers during the index stroke and the subsequent episode of PSR.

Materials and Methods

In this retrospective study approved by our institutional Human Research Committee, we identified 153 patients with post-stroke recrudescence admitted to Massachusetts General Hospital between January 1, 2000 and November 30, 2015. PSR was characterized by transient worsening or recurrence of stroke-related deficits, with no acute lesion on MRI and no evidence of transient ischemic attack or seizure. Detailed methods have been published [1]. Of the 153 patients, 95 had

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adequate medical record information concerning the index stroke. The following variables were extracted: fever (temperature ≥ 37.8 °C), white blood cell (WBC) count, and infection (pneumonia, urinary tract infection (UTI), gastroenteritis or other) occurring 10 days prior to 30 days after the index stroke. In addition, we collected data on other PSR triggers with a value of $p < 0.2$ on our prior study [1], including metabolic factors (levels of glucose, sodium, potassium, and creatinine), blood pressure, insomnia/stress, and medications such as benzodiazepines. We evaluated the admission NIHSS and discharge modified Rankin Scale (mRS) during the first stroke. Descriptive data are expressed in percentages, mean ± SD, or median (interquartile range). We compared the frequency of triggers between the index stroke and the PSR episode. Fisher Exact and Student's *t* tests were used as appropriate. Independent predictors of infection-related PSR were identified using a logistic regression model. A value of $p < 0.05$ was considered statistically significant.

Results

The mean age was 66 ± 17 years (53% female). Table 1 shows the frequency of potential triggers during the index stroke and the PSR episode. The overall frequency of fever and infection was not significantly different between both episodes. Specific infections, such as urinary tract infections and pneumonia, tended to be more frequent during PSR. None of the other variables were significantly different between episodes, except for hypertension, hypotension, anti-hypertensive, and statin medications, which were likely related to preventive therapies implemented after the index stroke.

A total of 29 patients had infections during the index stroke. The infection preceded the stroke in four of these cases, including one patient diagnosed with endocarditis, two with UTI and 1 with otitis. The other 25 patients had infections after the stroke, mostly UTI and pneumonia. We then investigated the relationship between triggers during the index stroke and the PSR episode. Of the 29 patients with infections during index stroke, 19

Table 1 Comparison of triggers during index stroke and post-stroke recrudescence

	Index stroke	PSR	*P* value
Fever, no. (%)	13 (14%)	10 (11%)	0.65
Infection, no. (%)	29 (31%)	40 (42%)	0.13
WBC count, mean (SD)	9522 (3933)	8573 (2834)	0.06
Urinary tract infection, no. (%)	14 (15%)	25 (26%)	0.07
Pneumonia, no. (%)	8 (8%)	18 (19%)	0.06
Other infection, no. (%)	7 (7%)	5 (5%)	1.0
Metabolic factors, no. (%)			
Glucose level, mean (SD), mg/dL	145 (67)	137 (72)	0.46
Hyperglycemia, no. (%)	18 (19%)	11 (12%)	0.22
Hypoglycemia, no. (%)	1 (1%)	5 (5%)	0.21
Serum sodium level, mean (SD), mEq/L	139 (4)	138 (4)	0.27
Hypernatremia, no. (%)	1 (1%)	1 (1%)	1.0
Hyponatremia, no. (%)	13 (14%)	18 (19%)	0.43
Potassium level, mean (SD), mEq/L	4 (0.7)	4 (0.5)	0.49
Hyperkalemia, no. (%)	5 (5%)	3 (3%)	0.72
Hypokalemia, no. (%)	9 (10%)	8 (8%)	1.0
Serum urea nitrogen level, mean (SD), mg/dL	18 (8)	20 (13)	0.17
Creatinine level, mean (SD), mg/dL	1.0 (0.3)	1.2 (1.5)	0.17
Acute renal failure, no. (%)	6 (6%)	4 (4%)	0.74
Blood pressure ≥ 200/100 mmHg, no. (%)	12 (13%)	3 (3%)	0.02
Hypotension, no. (%)	1 (1%)	13 (14%)	0.003
Insomnia or stress, no. (%)	9 (9%)	4 (4%)	0.25
Alcohol intoxication, no. (%)	3 (3%)	5 (5%)	0.72
Admission medications, no. (%)			
Statins	29 (31%)	75 (79%)	< 0.001
Anti-hypertensive agents	58 (61%)	73 (78%)	0.02
Benzodiazepines	17 (18%)	16 (17%)	0.95

PSR post-stroke recrudescence, *WBC* white blood cell

(65%) had PSR triggered by infection, while of the 66 patients without infection during index stroke, 21 (32%) had infection-triggered PSR ($p = 0.003$). There was no significant correlation between the type of infection (pneumonia, UTI, or other infection) during the index stroke and the PSR episode. The severity of stroke was higher in patients with infections during the index stroke, with higher median NIHSS (12 [7–20] vs. 8 [5–12], $p = 0.006$) and post-stroke modified mRS scores (2 [1–3] vs. 1 [0–1], $p = 0.04$).

The relationship of other triggers was similarly investigated. Seven of 17 patients with benzodiazepine exposure during the index stroke developed benzodiazepine-triggered PSR, versus only 9 of 78 without benzodiazepines in the index stroke ($p = 0.008$). The frequencies of other triggers were not significantly different between the index stroke and PSR episode (hypotension, $p = 1.0$; hyponatremia, $p = 1.0$; insomnia/stress, $p = 0.33$).

In a logistic regression model controlling for triggers during the index stroke (infection, hyponatremia, benzodiazepines, insomnia/stress), infection during the index stroke proved to be an independent predictor of infection-triggered PSR (Table 2a), and benzodiazepine exposure during the index stroke proved to be an independent predictor of benzodiazepine-triggered PSR (Table 2b).

Discussion

Infections occur in approximately 30% of acute stroke patients and are associated with higher mortality and increased disability [5, 6]. Consistent with prior studies, patients with infections during the index stroke were more severely impaired, with higher NIHSS and modified Rankin Scale scores [5]. The high frequency of infections in these patients is explained by an increase in anti-inflammatory signals and a strong cytokine-mediated anti-inflammatory response [5]. In rodent studies, a delayed-type hypersensitivity response to myelin basic protein precipitated a recrudescence of stroke-related deficits after antigen re-exposure [4], suggesting the potential for a delayed cytokine/immune-mediated mechanism for PSR in patients with infection during acute stroke, when the blood-brain barrier is open.

In this clinical study, we found an association between infection during index stroke and infection-triggered PSR. The frequency of infections during a control admission (i.e., during the interval between the index stroke and PSR, see Table 1 in our prior publication [1]) was much lower than either the acute stroke or PSR, suggesting that infection in the presence of an open blood-brain barrier is critical for the proposed immune-mediated mechanism. The lower mean WBC count during PSR, combined with the lack of correlation between infection sub-type during the index stroke and PSR admission, suggest that acute infections lower the threshold for subsequent PSR due to delayed cytokine/immune mediated mechanisms [4] that may not be specific to the microbe or type of infection.

The association with infections as well as benzodiazepine use suggests that multiple mechanisms for PSR exist, depending on the type of trigger. For example, GABA-ergic modulatory mechanisms presumably underlie benzodiazepine related PSR. There was no association with other triggers such as hypotension, hyponatremia, and stress/insomnia during index stroke.

Limitations of our study include the relatively small numbers, the retrospective study design, the lack of microbiological and immunological data, and the lack of information concerning repeated exposures to triggers. Our results should be considered hypothesis-generating and require validation, but should prompt more aggressive strategies to prevent and treat infections that are so common during acute stroke and are related to severe short and long-term complications [7]. Prospective studies may be warranted to investigate the specificity and mechanisms underlying the association between infection and PSR, focusing on factors such as the type and strain of the infectious organism during the acute stroke and the PSR episode, the levels of serum antibodies, and the importance of blood-brain barrier breakdown.

Table 2 Logistic regression: independent predictors of post-stroke recrudescence

Variable	Odds ratio	95% C.I.	*P* value
A. Infection-triggered PSR			
Infection	4.85	1.7, 13.7	0.003
Hyponatremia	1.53	0.39, 5.9	0.54
Benzodiazepines	1.28	0.40, 4.1	0.67
Insomnia/stress	0.35	0.07, 1.8	0.21
B. Benzodiazepine-triggered PSR			
Infection	1.1	0.3, 4.0	0.89
Hyponatremia	1.92	0.39, 9.3	0.41
Benzodiazepines	5.33	1.57, 18.1	0.007
Insomnia/stress	1.13	0.13, 7.4	0.90

PSR post-stroke recrudescence

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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