SHORT REPORT

Interleukin 10, monocytes and increased risk of early infection in ischaemic stroke

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Background and purpose: The pathophysiology of stroke-associated infection (SAI) is uncertain. The cytokine profile and peripheral white cell response were assessed in patients with or without SAI.

Methods: The incidence of SAI was assessed in 110 patients with ischaemic stroke allocated antibiotic prophylaxis or placebo within 24 h of clinical onset. Peripheral white cell counts, interleukin (IL)6, tumour necrosis factor (TNF) α and IL10 were measured in plasma.

Results: 17 (15%) patients developed infection and showed time-dependent increases of total white cell count, neutrophils, monocytes, lymphocytes, IL6 and IL10, whereas TNF α and the TNF α /IL10 ratio decreased. In logistic regression, IL10 (odds ratio (OR) 1.08, 95% confidence interval (CI) 1.01 to 1.16), monocyte count (OR 1.42, 95% CI 1.08 to 1.87) and National Institute for Health Stroke Survey score on admission (OR 1.17, 95% CI 1.05 to 1.31) were independent predictors of systemic infection.

Conclusions: SAI is associated with stroke severity, excessive IL10-mediated response and an increased number of circulating monocytes. These results support the finding that acute ischaemic brain injury triggers a blood-borne anti-inflammatory response that decreases the antimicrobial drive of the immune system.

Stroke-associated infection (SAI) has been reported in 21–65% of patients with stroke.^{1–4} A high rate of infection, despite avoidance of invasive manoeuvres³ or prophylactic antibiotics,⁵ suggests that a brain-mediated immunodepressive state can be an independent contributor to SAI, as recently suggested in a mouse model of transient focal brain ischaemia,⁶ and in patients with brain trauma or neurosurgery.⁷ Several cytokines may increase soon after stroke onset in patients and affect clinical outcome.^{8,9} Cytokines are essential mediators in the cross-talk between the brain and the immune system to maintain homeostasis,¹⁰ and acute brain injury may facilitate a cytokine-mediated systemic inflammatory response syndrome, activate neuroimmune pathways, such as the hypothalamic–pituitary–adrenal axis, or the autonomic nervous system,¹¹ and decrease the competence of the immune system.¹² Proinflammatory cytokines released by the injured brain tissue may also transfer to the plasma and set off a compensatory anti-inflammatory response syndrome that will re-establish homeostasis only if the degree of proinflammatory and anti-inflammatory responses is proportionate.¹² Here, our findings support the notion that in patients with acute ischaemic stroke, brain injury may set off a blood-borne response that decreases the antimicrobial drive of the immune system.

METHODS

Patients were part of the ESPIAS trial that assessed the value of antibiotic prophylaxis in acute stroke.⁵ To avoid stroke subtype heterogeneity, 26 patients with haemorrhagic stroke were excluded.

At admission, and at days 1, 2, 3, 4, 7 and 90, venous blood was drawn to assess total white cell count, neutrophils, monocytes, lymphocytes, IL6, TNF α and IL10, as reported.^{6,8,9} A ratio between TNF α and IL10 was calculated as a measure of T helper (h) 1/Th2 balance (proinflammatory and cellular v anti-inflammatory and humoral).¹¹

Fisher's exact test, Student's t test or the Mann–Whitney U test was used as appropriate. Analysis of covariance was used to assess changes in continuous parameters and logistic regression to evaluate independent predictors of SAI.

RESULTS

Main traits of patients who develop SAI

In this study, 110 patients with ischaemic stroke were assessed at a mean (standard deviation (SD)) time delay of 12.8 (7.2) h after clinical onset and, of these, 17 (15%) developed SAI within 7 days of stroke onset (table 1). Patients allocated levofloxacin (n = 50) or placebo (n = 60) had a similar incidence of SAI, clinical traits and course of peripheral blood cells and cytokines (data not shown), which showed that antibiotic treatment did not influence the results. The effect of SAI on outcome was not significant after adjustment for baseline National Institute for Health Stroke Survey score (p = 0.84).

Peripheral inflammatory response and SAI

SAI was associated with significant time-dependent increases of white cell counts, neutrophils and monocytes, but not of lymphocytes (table 1). IL6 (fig 1A) and IL10 (fig 1B) were considerably higher, and TNF α (fig 1C) and the TNF α /IL10 ratio (fig 1D) were lower in patients with SAI.

Predictors of SAI

Baseline IL10 (OR 1.08, 95% CI 1.01 to 1.16), monocytes (OR 1.42, 95% CI 1.08 to 1.87) and National Institute for Health Stroke Survey score (OR 1.17, 95% CI 1.05 to 1.31) were the only independent predictors of SAI in multivariate analysis.

DISCUSSION

The study confirmed a higher rate of infection in patients with severe stroke or tube feeding,^{3,13} and confirmed the existence of a stroke-mediated change in the immune system.^{6,12} We found that SAI was associated with higher levels of IL10 and circulating monocytes on admission and at follow-up, although subclinical infections cannot be totally excluded. IL10 is an anti-inflammatory cytokine associated with the mechanisms of brain-induced immunodepression¹⁴

Abbreviations: IFN, interferon; SAI, stroke-associated infection; TNF, tumour necrosis factor

Table 1 Main traits of the population in relation to incidence of stroke-associated infection

Traits	SAI		p Value
	No (n = 93)	Yes (n = 17)	
Demographics, risk factors			
Age (years), mean (SD)	73.2 (12.0)	76.5 (10.5)	0.29
Male, n (%)	42 (45)	10 (59)	0.42
Hypertension, n (%)	61 (66)	13 (77)	0.57
Diabetes, n (%)	22 (24)	2 (12)	0.35
Smoking, n (%)	14 (15)	2 (12)	0.85
Coronary heart disease, n (%)	15 (16)	1 (6)	0.45
Treatment allocation, n (%)			1.00
Levofloxacin	8 (47)	42 (45)	
Placebo	9 (53)	51 (55)	
Outcome assessment			
NIHSS score at entry, median (IQR)	11 (7–18)	20 (17–24)	<0.001
NIHSS score at day 7, median (IQR)	8 (3–18)	20 (12–21)	<0.01
NIHSS score at day 90, median (IQR)	4 (1–11)	20 (12–21)	<0.001
Death at day 90, n (%)	10 (11)	9 (53)	<0.001
White cells, median (IQR)			
Admission, $\times 10^9/l$			
Total white cell count	7.9 (6.5–9.6)	11.1 (8.3–14.3)	0.001
Monocytes	0.5 (0.3–0.7)	0.7 (0.5–0.9)	0.002
Lymphocytes	1.3 (0.9–1.8)	1.3 (1.0–2.5)	0.10
Day 1, $\times 10^9/l$			
Total white cell count	8.0 (6.7–9.6)	11.1 (9.5–16.0)	<0.001
Monocytes	0.6 (0.4–0.7)	0.8 (0.5–1.2)	0.001
Lymphocytes	1.3 (1.1–1.7)	1.5 (1.0–1.9)	0.50
Day 7, $\times 10^9/l$			
Total white cell count	8.0 (6.4–9.5)	10.9 (8.4–12.4)	0.01
Monocytes	0.6 (0.5–0.8)	0.9 (0.7–1.1)	0.01
Lymphocytes	1.5 (1.2–1.9)	1.6 (1.2–2.1)	0.64
Day 90, $\times 10^9/l$			
Total white cell count	6.2 (5.4–7.5)	6.6 (4.7–9.0)	0.89
Monocytes	0.4 (0.3–0.5)	0.4 (0.3–0.7)	0.96
Lymphocytes	1.5 (1.2–1.8)	1.4 (1.3–2.5)	0.85

NIHSS, National Institute for Health Stroke Survey; SAI, stroke-associated infection.

and worsening of stroke.⁸ Indeed, IL10 activity inhibits interferon (IFN) γ production by Th1 cells, suppresses T lymphocyte proliferation and cytokine responses,¹⁵ and downregulates TNF α by monocytes.¹⁶ Monocytes are antigen-presenting cells that initiate the innate immune response. The increased number of monocytes, with the lower plasma levels of TNF α observed in patients with SAI, might translate to a lower competence of these immune cells to produce TNF α ,¹⁷ as shown in patients with sepsis.¹²

Taken together, these findings suggest that SAI translates to an immunodepression state facilitated by the close interaction between the central nervous system and the immune system.¹¹ However, further studies will be required to define the central or peripheral source of blood-borne cytokines and to examine whether monocytes are deactivated in SAI. Meanwhile, this study emphasises that unravelling the crosstalk between the CNS and the immune system might help to improve the treatment of acute ischaemic stroke, including the prevention and management of infections.

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Figure 1 Course of cytokines in relation to the incidence of stroke-associated infection (SAI). (A) interleukin (IL) 6; (B) IL10; (C) tumour necrosis factor (TNF) α ; (D) TNF α /IL10 ratio. Values are expressed as mean (SEM).

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