

# Stroke-Associated Infection and the Stroke-Induced Immunodepression Syndrome

Stroke remains a leading cause of death and disability in industrialised and developing countries. Whilst new therapies evolve, attention is directed towards the mechanisms that underpin deterioration and complications. The role of infection in the aetiology and later complications of stroke is increasingly recognised. This occurs within the context of complex interplay between the brain and immune systems. Considerable debate continues as to the extent to which the brain itself contributes to the systemic response, and vice versa. The array of inflammatory/anti-inflammatory mechanisms in stroke is highly regulated at the gene and posttranslational levels.<sup>1</sup> One component of these is the cytokine family. These molecules are pivotal to cross talk between brain and immune systems and activate autonomic and hypothalamic-pituitary-adrenal axes. In turn these give rise to catecholamine and glucocorticoid responses that modulate immune function. This article reviews the emerging phenomenon of stroke associated infection (SAI), its mechanism and the role of antibiotic prophylaxis in stroke.

## Stroke associated infection

SAI is a common complication occurring in between 21-65% of stroke patients.<sup>2</sup> The degree to which this occurs depends on a number of factors including stroke severity and pre-existing comorbidity. Even within specialised stroke units, SAI occurs in up to 65% of patients, where pneumonia accounts for the highest mortality.<sup>3</sup> The high incidence of SAI has prompted the idea of a stroke induced immunodepression syndrome (SIIS).

Infectious complications account for 20% of deaths in stroke, where pneumonia and urinary tract infection (UTI) predominate.<sup>4</sup> Dysphagia, in addition to reduced bulbar reflexes and drowsiness, are other factors. Despite early swallowing assessment and intervention, pneumonia remains common.<sup>5</sup> There also remains a complex relationship between factors such as fever (possibly central), infection per se and thrombosis. Studies that are not prospective and do not control for initial severity and a rigorous diagnosis of infection warrant critical appraisal. More recent studies have suggested that infection and stroke worsening may be independent variables.<sup>6</sup>

## Evidence for a suppressed immune response

### Animal studies

In patients, aspiration alone appears insufficient to explain the high incidence of stroke associated pneumonia. Much of the evidence in favour of an autoregulated but suppressed immune system following stroke is derived from animal studies. In support of a double hit hypothesis combining aspiration and an immunodeficiency syndrome, is one key animal study. Here, a combination of experimental stroke and inoculation was sufficient to cause severe pneumonia.<sup>7</sup> The role of leucocytes in the mediation of immunosuppression is also considered. Both neutrophils and monocytes invade the brain in the acute/subacute phases of ischaemic stroke, but with respect to the former it remains unclear as to whether such recruitment is pathogenic or a marker of disease.<sup>8</sup> During infection, monocytes remain a lead contributor to the innate response and a principal source of proinflammatory mediators. One mediator, IL-1 $\beta$  is thought to be critically involved in neuronal apoptosis following ischaemia. There is evidence that resident brain

macrophages or microglia contribute centrally to generating IL-1 $\beta$  and that such cells are active in the subacute phase of clinical stroke.<sup>9</sup>

Other cytokines play a role here. In a number of experimental stroke models, cytokines such as TNF- $\alpha$  and IL-6 from a variety of sites prompt the production and release of corticotrophin releasing hormone (CRH) from the hypothalamus. CRH in turn mediates a pituitary based release of ACTH and consequent glucocorticoid release from adrenal cortex. Glucocorticoids in turn suppress, primarily at nuclear level, production of the proinflammatory cascade involving, in addition to those above, IL-11, IL-12, interferon- $\gamma$  and chemokines (IL-8) whilst facilitating release of anti-inflammatory mediators such as IL-10. Hypothalamic activation additionally downgrades, via nicotinic receptors, peripheral release of proinflammatory cytokines such as TNF $\alpha$  from macrophages.<sup>10</sup> In one model, rapid and extensive apoptosis of lymphocytes is observed for up to six weeks post stroke, and such animals develop spontaneous infection after initial evidence of immunosuppression. Such effects are thought to involve the autonomic nervous system, and to an extent may be blocked by propranolol. Sympathetic nervous system activation also gives rise to an exaggerated release of noradrenalin, both from brain and adrenal glands, that in



**Dr Christopher Price** is currently completing his clinical neurology training as an SpR at the Royal Devon & Exeter Hospital. He has an established interest in cerebrovascular disease, in particular neuroinflammatory aspects of ischaemic stroke and neuroprotection.

### Correspondence to:

Dr Christopher JS Price,  
PhD, MRCP,  
Department of Neurology,  
Royal Devon & Exeter Hospital,  
Barrack Road,  
Exeter, EX2 5DW.

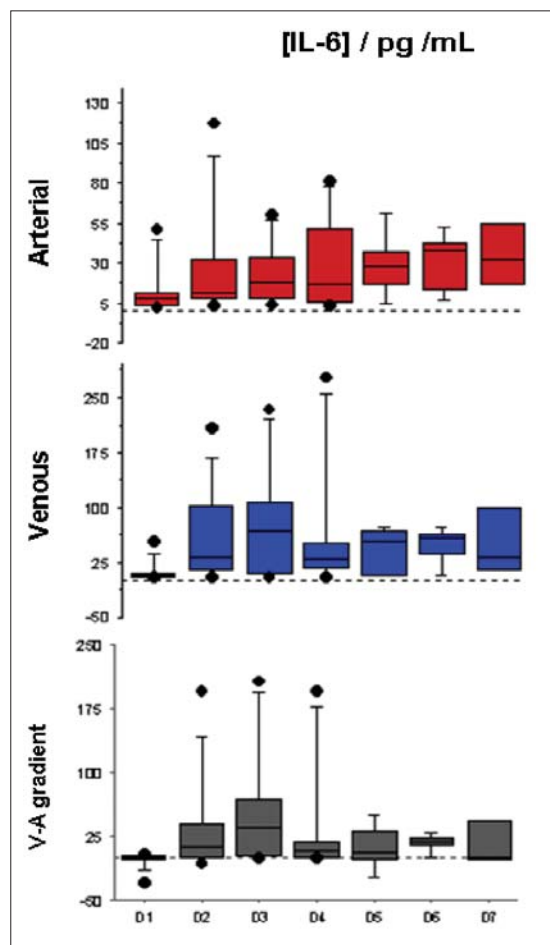


Figure 1: Box plot of arterial, venous (jugular) and arterio-jugular (V-A) gradients for IL-6 for days (D1-D7) in 12 patients with radiologically-confirmed ischaemic stroke. Significant gradients were detected on day 3 only ( $p=0.02$ , one sample sign test), consistent with a central mechanism.

turn has a net inhibitory effect on proinflammatory T helper type 1 lymphocyte activity whilst the Th2 response remains essentially unaffected.<sup>11</sup>

Finally, evidence is now emerging for a possible genetic component to SIIS. A number of polymorphisms relate to inflammatory processes linked to subtypes of stroke, whilst some evidence exists to suggest that the type of stroke is dictated by the host immune response.<sup>12</sup>

### Clinical studies

In stroke patients, a variety of systemic effects are reported within the aftermath of stroke. These include high or low levels of ACTH that have been reported in conjunction with poor outcome, larger volume infarcts, reduced peripheral lymphocyte counts and impaired natural and T cell activity.<sup>13</sup> Longitudinal data from acute stroke patients would suggest that the anti-inflammatory cytokine IL-10 and monocyte count were the two best immune based predictors of infection.<sup>14</sup> Within this cohort of patients, rapid rises in proinflammatory plasma cytokines such as TNF- $\alpha$  precede infection, as do increases in peripheral white blood cell counts and a high levels of catecholamines. Limited data from our own laboratory would suggest no clear brain derived cytokine gradients, although IL-6 may form a peak at three days post stroke (Figure 1, personal communication). In other forms of acute

brain injury, e.g. trauma, higher levels of IL-10 levels are associated with greater levels of infection, perhaps by switching off circulating monocytes. Overall the extent to which the brain influences such processes remains largely unknown.

### Interventional studies

In experimental models of stroke, antibiotics not only prevent pneumonia but also reduce mortality and improve outcome.<sup>15</sup> Based upon such data, clinical trials have sought to evaluate the effectiveness of prophylactic antibacterial therapy. The Early Systemic Prophylaxis of Infection After Stroke (ESPIAS) trial included 136 patients using levofloxacin 500mg daily for three days within 24 hours of non-septic stroke. The ESPIAS trial was stopped short as the drug did not prevent post stroke infection or improve outcome. Indeed a non-significant trend towards higher mortality was observed.<sup>2</sup> Many explanations have been put forward for this. They include choice of antibiotic, particularly with respect to the spectrum of levofloxacin against anaerobes, that the drug was given too early to prevent later complications, and that the study population comprised a highly heterogeneous group including haemorrhagic strokes. To an extent, such factors are addressed in a small study, the Preventative Antibacterial Therapy in Acute Stroke (PANTHERIS) trial (PLoS ONE. 2008; 3(5): e2158. Published online 2008 May 14. doi: .1371/jour-

nal.pone.0002158). This trial used moxifloxacin (thought to have a broader antibiotic profile) for longer periods with predefined protocols if pneumonia occurred subsequently. Despite lowered rates of pneumonia, this trial was insufficiently powered to detect improvements in survival and outcome.

### Conclusion

Post stroke infection is common. Active debate centres upon the contribution of neuroendocrine responses versus that of neurological worsening per se. Evidence is now emerging that mechanical factors alone are perhaps insufficient to account for the high rates of post stroke infection. SIIS may account for this where a series of interrelated events involve leucocytes, cytokines and the sympathetic nervous system occur. Only to a very limited degree has such data been taken forward in the form of a clinical trial. A number of methodological issues remain outstanding. To some extent these are being addressed in the design of future, larger scale clinical trials.

### Acknowledgments

The author wishes to acknowledge the support of the Medical Research Council, the Raymond & Beverley Sackler Fellowship, Dr Elizabeth Warburton, Mrs Diana Day and Dr Rainer Doffinger (Addenbrookes NHS Trust) and Professors David Menon and Jean-Claude Baron (University of Cambridge).

### References

- Samson Y, Lapergue B, Hosseini H. *Inflammation and ischaemic stroke: current status and future perspectives*. Rev Neurol (Paris) 2005;161(12 Pt 1):1177-82.
- Chamorro A, Horcajada JP, Obach V, Vargas M, Revilla M, Torres F, Cervera A, Planas AM, Mensa J. *The Early Systemic Prophylaxis of Infection After Stroke study: a randomized clinical trial*. Stroke 2005;36(7):1495-500.
- Katzan IL, Cebul RD, Husak SH, Dawson NV, Baker DW. *The effect of pneumonia on mortality among patients hospitalized for acute stroke*. Neurology 2003;60(4):620-5.
- Meisel C, Schwab JM, Prass K, Meisel A, Dirnagl U. *Central nervous system injury-induced immune deficiency syndrome*. Nat Rev Neurosci 2005;6(10):775-86.
- Dennis MS, Lewis SC, Warlow C. *Effect of timing and method of enteral tube feeding for dysphagic stroke patients (FOOD): a multicentre randomised controlled trial*. Lancet 2005;365(9461):764-72.
- Vargas M, Horcajada JP, Obach V, Revilla M, Cervera A, Torres F, Planas AM, Mensa J, Chamorro A. *Clinical consequences of infection in patients with acute stroke: is it prime time for further antibiotic trials?* Stroke 2006;37(2):461-5.
- Prass K, Braun JS, Dirnagl U, Meisel C, Meisel A. *Stroke propagates bacterial aspiration to pneumonia in a model of cerebral ischemia*. Stroke 2006;37(10):2607-12.
- Price CJ, Warburton EA, Menon DK. *Human cellular inflammation in the pathology of acute cerebral ischaemia*. J Neurol Neurosurg Psychiatry 2003;74(11):1476-84.
- Price CJ, Wang D, Menon DK, Guadagno JV, Cleij M, Fryer T, Aigbirhio F, Baron JC, Warburton EA. *Intrinsic activated microglia map to the peri-infarct zone in the subacute phase of ischemic stroke*. Stroke 2006;37(7):1749-53.
- Pavlov VA, Wang H, Czura CJ, Friedman SG, Tracey KJ. *The cholinergic anti-inflammatory pathway: a missing link in neuroimmunomodulation*. Mol Med 2003;9(5-8):125-34.
- Elenkov IJ, Wilder RL, Chrousos GP, Vizi ES. *The sympathetic nerve—an integrative interface between two supersystems: the brain and the immune system*. Pharmacol Rev 2000;52(4):595-638.
- Revilla M, Obach V, Cervera A, Davalos A, Castillo J, Chamorro A. *A -174G/C polymorphism of the interleukin-6 gene in patients with lacunar infarction*. Neurosci Lett 2002;324(1):29-32.
- Schwarz S, Schwab S, Klinga K, Maser-Gluth C, Bettendorf M. *Neuroendocrine changes in patients with acute space occupying ischaemic stroke*. J Neurol Neurosurg Psychiatry 2003;74(6):725-7.
- Chamorro A, Amaro S, Vargas M, Obach V, Cervera A, Torres F, Planas AM. *Interleukin 10, monocytes and increased risk of early infection in ischaemic stroke*. J Neurol Neurosurg Psychiatry 2006; 77(11):1279-81.
- Meisel C, Prass K, Braun J, Victorov I, Wolf T, Megow D, Halle E, Volk HD, Dirnagl U, Meisel A. *Preventive antibacterial treatment improves the general medical and neurological outcome in a mouse model of stroke*. Stroke 2004;35(1):2-6.



## Association of British Neurologists Annual Meeting

For more information contact  
Karen Reeves at the ABN,  
Email: Karen.Reeves@theabn.org

22-26 June, 2009  
Arena & Convention  
Centre, Liverpool  
Joint with the  
Spanish Society of Neurology

