

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.¹ 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.² 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.³ 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.⁴ Dysphagia, in addition to reduced bulbar reflexes and drowsiness, are other factors. Despite early swallowing assessment and intervention, pneumonia remains common.⁵ 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.⁶

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.⁷ 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.⁸ During infection, monocytes remain a lead contributor to the innate response and a principal source of proinflammatory mediators. One mediator, IL-1 β 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 β and that such cells are active in the subacute phase of clinical stroke.⁹

Other cytokines play a role here. In a number of experimental stroke models, cytokines such as TNF- α 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- γ 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 α from macrophages.¹⁰ 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



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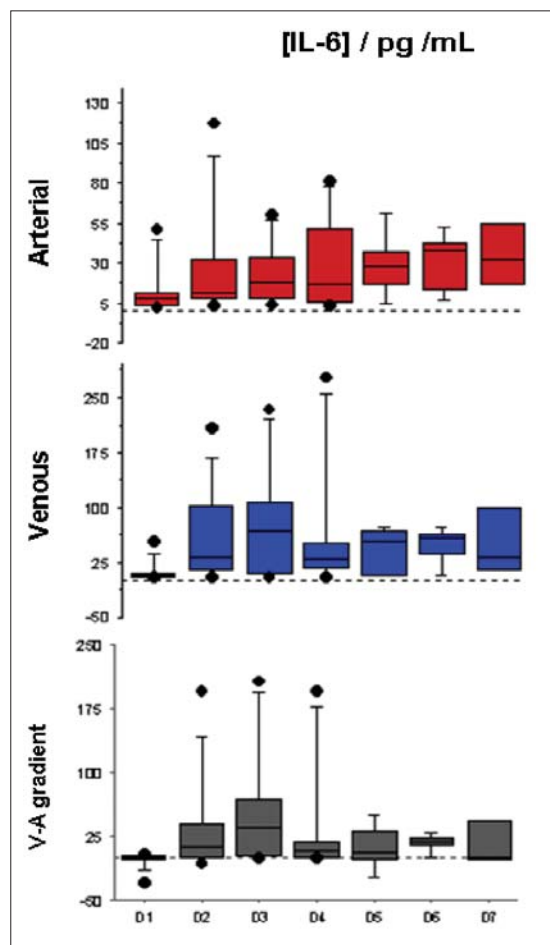


Figure 1: Box plot of arterial, venous (jugular) and arterio-jugular (V-A) gradients for IL-6 for days (D1-D7) in 12 patients with radiologically-confirmed ischaemic stroke. Significant gradients were detected on day 3 only ($p=0.02$, one sample sign test), consistent with a central mechanism.

