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Review Article

Complex interplay of multiple biological systems that contribute to post-stroke infections

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ABSTRACT

Stroke is a leading contributor of death and disability around the world. Despite its recognised debilitating neurological deficits, a devastating clinical complication of surviving stroke patients that needs more attention is infection. Up to half of the patients develop infections after stroke, and a high proportion of them will die as a direct consequence. Major clinical trials that examined preventive antibiotic therapy in stroke patients have demonstrated this method of prevention is not effective as it does not reduce incidence of post-stroke pneumonia or improve patient outcome. Additionally, retrospective studies evaluating the use of β-blockers for the modulation of the sympathetic nervous system to prevent post-stroke infections have given mixed results. Therefore, there is an urgent need for more effective therapeutic options that target the underlying mechanisms of post-stroke infections. The understanding that infections are largely attributable to the "stroke-induced systemic immunosuppression" phenomenon has begun to emerge, and thus, exploring the pathways that trigger post-stroke immunosuppression is expected to reveal potential new therapeutics. As such, we will outline the impacts that stroke has on several biological systems in this review, and discuss how these contribute to host susceptibility to infection after stroke. Furthermore, the emerging role of the gut and its microbiota has recently come to surface and intensifies the complex pathways to post-stroke infection. Finally, we identify potential avenues to combat infection that target the pathways of stroke-induced systemic immunosuppression to ultimately improve stroke patient outcome.

Contents

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1. Clinical relevance of post-stroke infection

Stroke is a highly prevalent and debilitating neurovascular disease that continues to be a leading cause of death and disability around the world. In 2015, strokes accounted for almost 12% of all deaths globally and contributed to the second highest loss of disability-adjusted life years (DALYs) (Feigin, 2016; Feigin et al., 2017). With better healthcare over the past decades, mortality rate from strokes has decreased, however the disease incidence continues to increase, and it is predicted to rise by 36% by 2030 (Strong et al., 2007). As a consequence, stroke creates a hefty financial burden on the health care system of society (Mozaffarian et al., 2015).

Stroke occurs when there is a blockage (ischemic) or rupture (haemorrhagic) of a cerebral blood vessel and impairs blood flow into the brain. Deprivation of blood and nutrients to areas of the brain during stroke can result in severe neurological deficits and patients suffer a range of functional impairments (Kimura et al., 2004). However, a less well known, but a highly prevalent clinical complication that stroke patients suffer is infection, with pneumonia and urinary tract infections (UTIs) being most common (Langhorne et al., 2000; Vernino et al., 2003). Infections have been reported to occur in up to two-thirds of stroke survivors, with patients that have more severe strokes at greater risk (Hug et al., 2009; Langhorne et al., 2000). Some studies have suggested that infection may be a marker/symptom of the extent of cerebral damage (Vargas et al., 2006). However, there has been more evidence to suggest that post-stroke infection (namely pneumonia) is independently associated with poor patient outcome and may even contribute to mortality in up to 30% of stroke patients (Aslanyan et al., 2004; Heuschmann et al., 2004; Hilker et al., 2003; Kwan and Hand, 2007; Vermeij et al., 2009). Furthermore, stroke patients with pneumonia may be at higher risk of recurring stroke (Erdur et al., 2015), potentially due to mechanisms such as alterations in immunohematological mechanisms, pro-inflammatory cytokine activation, platelet activation, and endothelial dysfunction (Emsley and Hopkins, 2008). The current standard treatment for stroke patients diagnosed with infection is prompt administration of antibiotics, however caution needs to be taken regarding this therapeutic approach due to potentially harmful adverse effects, and an alarming rise in antibiotic-resistant strains of bacteria (Yan et al., 2015). As such, there is an urgent unmet clinical need for more effective and targeted treatments to reduce infections after stroke. Therefore, this review will describe the current and emerging treatments to post-stroke infection, outline the biological mechanisms underlying the increased susceptibility to infections in stroke patients (focussing on the post-acute phase), and highlight some potential targeted therapeutics.

2. Clinical trials to prevent infections after stroke

2.1. Antibiotics

Antibiotics are antibacterial agents that target various essential bacterial components, processes, and functions to either inhibit the growth or directly kill the microbe. While antibiotics are heavily relied upon to treat infectious diseases, antibiotics have not improved over the last 20 years and there is a growing clinical concern of antibiotic-resistant strains of bacteria (Gould, 2016). Despite this, research has been conducted to assess the efficacy of preventive antibiotic therapy (PAT) to prevent infection, its associated complications and improve stroke patient outcome. Experimental models provide proof-of-concept by showing that PAT could improve survival rates in post-stroke animals by preventing infections and reducing neurological deficits (Hetze et al., 2013; Meisel et al., 2004). Indeed, these studies gave justification for the evaluation of PAT in randomized clinical trials, although the beneficial outcomes of PAT were not observed in stroke patients in preliminary trials (Chamorro et al., 2005; Harms et al., 2008). Consistent with these studies, trials within the last 5 years, including the Preventive Antibiotics in Stroke Study (PASS) (Westendorp et al., 2015) and STROKE-INF (Kalra et al., 2015) trials, did not show an improvement in patient outcome and suggest that PAT is not better than standard treatment. Recent meta-analyses also provide further overwhelming evidence that reaffirms the ineffectiveness of PAT in improving stroke patient outcome (van de Beek et al., 2009; Vermeij et al., 2018; Zheng et al., 2017). Importantly, while PAT could reduce the incidence of overall infection, most studies did not show a reduced incidence of pneumonia in patients that underwent PAT (Kalra et al., 2015; van de Beek et al., 2009; Vermeij et al., 2018; Westendorp et al., 2015), which may suggest that pneumonia is a greater contributor to worsened stroke patient outcome. Thus, while antibiotics are effective for therapeutic treatment of infection, their prophylactic benefits are not observed and cannot be recommended to clinically prevent infections in stroke patients.

The most recent published trial for PAT was the STRAWINSKI trial which used circulating procalcitonin (PCT) levels in patient blood to predict the onset of stroke-associated pneumonia and treat prophylactically with antibiotics (Ulm et al., 2017). Patients with a PCT level of greater than 0.05 ng/ml were considered likely to get infection and were treated with antibiotics, while the control group was given standard care. The types of antibiotics used in the trial were inconsistent between treating physicians and there was only a 65% compliance of protocol. As such, there was no difference in infection rates between PCT-guided group and the control group between 0 and 7 days after stroke and no improvement of stroke outcome was observed as assessed by modified Rankin Scale. Based on this study and others, PAT is not recommended as it was not better than standard treatment (Kalra et al., 2015; Ulm et al., 2017; Westendorp et al., 2015).

The use of PAT is furthermore discouraged as it comes with the growing concern of antibiotic resistance. A range of antibiotics were tested against bacteria in the sputum samples of stroke patients with pneumonia. Culturable bacteria commonly associated with pneumonia were tested for, including *Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa*, and *Klebsiella pneumoniae*. Surprisingly, there was a 100% resistance rate in *S. aureus* against penicillin, erythromycin, oxacillin and ciprofloxacin, 100% resistance rate in *E. coli* against ceftriaxone and ticarcillin, and 100% resistance rate in *P. aeruginosa* against ceftriaxone (Yan et al., 2015). Indeed, while this study was conducted in a single hospital and is not representative of hospitals around the world, this study may explain the failure of antibiotic treatment in patients with post-stroke pneumonia.

Antibiotics may also come with the cost of adverse effects. One example is in the Early Systemic Prophylaxis of Infection After

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