Infection After Acute Ischemic Stroke
A Manifestation of Brain-Induced Immunodepression
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Background and Purpose—Infection after experimental focal ischemia may result from brain-induced immunodepression, but it is unsettled whether a similar syndrome occurs in human stroke.

Summary of Review—Many patients develop infections shortly after acute stroke regardless of optimal management. Mortality is higher in these patients and the severity of stroke is the strongest determinant of the infectious risk. However, it is controversial whether infections promote neurological worsening or alternatively represent a marker of severe disease. The brain and the immune system are functionally linked through neural and humoral pathways, and decreased immune competence with higher incidence of infections has been demonstrated in several acute neurological conditions. In experimental brain ischemia, infections are associated with the activation of the autonomous nervous system and neuroendocrine pathways, which increase the strength of anti-inflammatory signals. A strong cytokine-mediated anti-inflammatory response was recently observed in stroke patients at higher risk of infection, although infection could not demonstrate an independent association with the progression of the symptoms.

Conclusions—The appearance of infection in patients with acute stroke obeys in part to immunological mechanisms triggered by acute brain injury. An excessive anti-inflammatory response is a key facilitating factor for the development of infection, and it is likely that this immunological response represents an adaptive mechanism to brain ischemia. Contrarily, it is unclear whether infection contributes independently to poor outcome in human stroke. Overall, a better understanding of the cross-talk between the brain and the immune system might lead to more effective therapies in patients with acute stroke. (Stroke. 2007;38:1097-1103.)

Key Words: acute stroke ■ complications ■ immunology ■ infectious disease ■ pathogenesis

Evidence is accumulating in support of a role for inflammatory, innate immune and adaptive immune mechanisms in many facets of vascular disease.1,2 Numerous studies and recent reviews have addressed the role of infection as a risk factor of stroke,3,4,5,6,7 and the main clinical traits,8,9 and immunohematologic characteristics of strokes preceded by recent infection have also been described.10,11,12 However, the mechanisms and neurological consequences of infections complicating the clinical course of acute stroke have received less attention. A growing body of evidence currently indicates that the central nervous system and the immune system are 2 supersystems closely linked13 and that this functional interaction could pave the way to the appearance of immunological manifestations as the result of central nervous system injury, and vice versa. In the same line, the emergence of systemic infection after acute brain damage could be a symptom of central nervous system–mediated decrease of immune competence, as described in patients with brain tumors, epilepsy, or traumatic brain injury.14,15 This review brings up to date the cross-talk between the central nervous system and the immune system in patients with acute stroke and how this interaction affects their clinical course. The mechanisms and clinical consequences of poststroke infection are emphasized because a better understanding of these processes is essential to consider in the future the application of immunomodulatory therapies in patients with acute brain ischemia.

Infection After Acute Stroke: Magnitude of the Problem
Autopsy series indicate that death within the first week after stroke is attributable primarily to the direct effects of brain damage, such as brain edema with transtentorial herniation.16 Subsequent mortality is attributable in autopsy,16 and population-based studies,17 to medical complications such as infection. The frequency and nature of the medical complications that follow acute stroke have been addressed in several clinical studies18–27 using a wide range of different designs, methods of patient selection, diagnostic criteria, timing of assessment, or duration of follow-up, as shown in the Table. Hence, it is not surprising that the reported incidence of specific medical complications varies from 40%...
Is Infection a Cause of Worsening Stroke? Uncertain

The proportion of patients experiencing infections is higher in patients with severe stroke, unlike other stroke complications such as falls, depression or pain. Infections can facilitate electrolytic unbalance, hypoxia, and fever, which could theoretically impair neuronal survival within the ischemic penumbra. Fever may increase the cerebral metabolic demands, change the blood-brain barrier permeability, and promote acidosis and release of excitatory amino acids. Entry of bacteria and lypopolisaccharide into the bloodstream also favors thrombosis through tumor necrosis factor (TNF)-α release, activation of the tissue factor–mediated extrinsic pathway of blood coagulation, reduction of thrombomodulin (anticogulant), and inhibition of the fibrinolytic system. With few exceptions, subfebrile temperatures (37.5°C to 39°C) and fever (>39°C) during the first days of stroke are associated with larger infarct volumes, higher mortality, and poorer functional outcome. However, the support to infection as an independent cause of stroke worsening is controversial. Only few studies accounted for the critical effect of the initial severity of stroke, and in some studies, the recognition of stroke worsening relied on the neurological scale used for assessment. Recent prospective studies did not find an independent association between infection and stroke worsening in multivariate analysis. It has been argued that the inclusion of soft end points, such as acute bronchitis, could have minimized the clinical relevance of poststroke infection although acute bronchitis in the elderly—an age group representative of the stroke population—conveys a similar risk of death than pneumonia: 10% and 8%, respectively. Further, acute respiratory infection with “normal” chest x-rays may indicate pneumonia in about 30% of the cases, if a high resolution lung tomography is performed.

Could Infection Be a Manifestation of Stroke-Induced Immunodepression in Human Stroke? Most Likely

The appearance of infections after acute stroke could be related to mechanisms other than the application of invasive maneuvers, decreased consciousness, or abnormal brain stem reflexes. Thus, predominance of infections during the phase of maximal neurological impairment (first 3 days), and comparable incidence of infection in conventional wards, neurological wards, intensive care units, or stroke units suggest that infection might also be explained by stroke-induced immunological mechanisms. In addition to the support of this proposition is the rich bidirectional communication existing between the central nervous system and the immune system. As it is schematically represented in Figure 1, the central nervous system modulates the activity of the immune system through complex humoral and neural pathways that include the hypothalamic pituitary adrenal (HPA) axis, the vagus nerve, and the sympathetic nervous system.

Humoral Pathways for Brain to Immune System Communication

The HPA axis is a major part of the neuroendocrine system with important functions in health and disease, and with key elements located in the paraventricular nucleus (PVN) of the hypothalamus, the anterior lobe of the pituitary gland, and the
mediators, including IL-1β, TNF-α, and IL-6, secreted by cells in different tissues and organs including the brain can stimulate specialized neurons in the PVN to synthesize corticotropin-releasing factor. Blood-borne cytokines derived from white blood cells may also reach the PVN through activation of specific carriers, binding to endothelial receptors that mediate the production of diffusible mediators, such as prostaglandins or NO, or through anatomical structures lacking blood-brain barrier, like the organum vasculare of the lamina terminals, or the area postrema. Once released into the pituitary portal blood system, corticotropin-releasing factor interacts within the anterior pituitary with a specific G protein-coupled receptor that gives rise to preganglionic cholinergic efferent fibers. Postganglionic sympathetic fibers run from paravertebral or prevertebral ganglia to release norepinephrine in different tissues, and parallel increases in brain norepinephrine concentrations and plasma corticosterone support the existence of a reverberatory feedback loop between the HPA and the sympathetic nervous system. Activation of the locus coeruleus leads to release of norepinephrine from an extraordinarily dense network of neurons throughout the brain, and from peripheral organs, resulting in enhanced arousal and vigilance, increased heart rate, respiratory rate, vascular tone, and gastrointestinal motility, but also in the induction of pronounced immunological changes. The latter effects mainly result from the inhibition of T helper (h) type 1 pro-inflammatory activities, giving way to the predominance of Th type 2 anti-inflammatory activities.

The Cholinergic Neural Pathway

The PVN is functionally linked with autonomic centers such as the nucleus of the solitary tract (NST) or the locus coeruleus. The PNV-NST pathway allows the synchronization of neuroendocrine responses with the cholinergic anti-inflammatory pathway to suppress the peripheral release of cytokines through macrophage nicotinic receptors. Indeed, direct electrical stimulation of the efferent vagus nerve inhibits the synthesis of TNF-α in different organs during experimental endotoxemia and in animals subjected to ischemia-reperfusion.

The Adrenergic Pathway to Immunodepression

The sympathetic nervous system also plays a crucial role in the communication between neural and immune structures. The sympathetic division originates in brain stem nuclei such as the locus coeruleus and the rostral ventrolateral medulla that give rise to preganglionic cholinergic efferent fibers. Postganglionic sympathetic fibers run from paravertebral or prevertebral ganglia to release norepinephrine in different tissues, and parallel increases in brain norepinephrine concentrations and plasma corticosterone support the existence of a reverberatory feedback loop between the HPA and the sympathetic nervous system. Activation of the locus coeruleus leads to release of norepinephrine from an extraordinarily dense network of neurons throughout the brain, and from peripheral organs, resulting in enhanced arousal and vigilance, increased heart rate, respiratory rate, vascular tone, and gastrointestinal motility, but also in the induction of pronounced immunological changes. The latter effects mainly result from the inhibition of T helper (h) type 1 pro-inflammatory activities, giving way to the predominance of Th type 2 anti-inflammatory activities.

The Adrenal Medullary Gland

The chromaffin cells of the adrenal medulla are homologs of the sympathetic ganglia derived from the neural crest, and activation of cholinergic preganglionic sympathetic neurons innervating these cells may lead to increased release of catecholamines in the bloodstream, where they act as hormones. Unlike the adrenergic nerves which preferentially release norepinephrine, the adrenomedullary gland secretes epinephrine at a ratio of 4:1 over norepinephrine. Catecholamines from the adrenal medulla are metabolized by catechol-O-methyl-transferase (COMT) and monoamine oxidase, respectively, and metanephrine and normetanephrine are the main products mediated by COMT. Because sympathetic nerves do not contain COMT, metanephrine and normetanephrine mirror the catecholaminergic activity from non-neuronal sources. Indeed, 91% of plasma metanephrine and up to 40% of normetanephrine are produced under stress conditions within the adrenal medullary gland. In clinical situations such as hypoglycemia, hemorrhagic hypotension, asphyxiation, circulatory collapse, and distress, higher plasma concentrations of epinephrine (adrenal gland) than norepinephrine (terminal nerves) have been reported, suggesting greater adrenomedullary hormonal than sympathetic neuronal activation. However, as further discussed below, the adrenal
The Lymphoid Organs Are Also Wired

The neural control of the immune system is further facilitated by the rich supply of sympathetic nerve fibers to primary (thymus and bone marrow) and secondary (spleen, lymph nodes, and tissues) lymphoid organs. Likewise, with the exception of Th type 2 cells, virtually all immune cells express adrenoreceptors, including lymphocytes, granulocytes, monocytes, macrophages, and natural killer cells. Catecholamines released within the microenvironment of immune cells located in lymphoid organs increase their intracellular levels of cAMP and activate protein kinase A. The net result is the inhibition of TNF-α, IL-1, IL-12, interferon-γ, and nitric oxide production, and the increased production of IL-6 and IL-10 by the immune cells. Elevation of central sympathetic outflow also induces a local release of norepinephrine within the bone marrow and affects in vivo myelopoiesis and erythropoiesis, because the production of granulocytes and macrophages is under a sympathetic inhibitory tone, whereas lymphocyte and erythrocyte formation require adrenergic stimulation.

Immunological Changes After Acute Brain Ischemia: Experimental and Clinical Studies

In patients with acute stroke, increased or abnormally low secretion of ACTH and cortisol are associated with larger infarctions, poorer functional outcome, and increased mortality, indicating that both extremes of the HPA axis response may be deleterious. Patients with increased cortisol may have a strong inflammatory response, with increased temperature, fibrinogen, white blood cell counts, β-thromboglobulin, and IL-6 levels. High cortisol has also been associated in some studies, but not in others, with higher catecholamine excretion, and frontal lobe, or insular infarctions. Unfortunately, the rate of infection and immune competence were not described in the patients included in these studies.

In brain ischemic mice, stroke induces a long-lasting depression of the cell-mediated immunity, including monocyte deactivation, lymphopenia, and a Th1/Th2 shift associated with spontaneous bacteremia and pneumonia. In mice, focal cerebral ischemia also reduces spleen cellularity and response to mitogens, and results in a rapid and widespread production of pro-inflammatory factors by splenocytes in relation to adrenergic signaling. Propranolol prevents these infections, emphasizing the relevance of a catecholamine-mediated immune defect for impaired antibacterial defenses. Lypopolisaccharide preconditioning has also shown to induce significant neuroprotection against middle cerebral artery occlusion, suppressing both neutrophil infiltration into the brain and microglia/macrophage activation in the ischemic hemisphere, and monocyte activation in the peripheral blood.

In patients, reported defects in immune function after stroke include reduced peripheral blood lymphocyte counts and impaired T- and natural killer cell activity, and reduced mitogen-induced cytokine production and proliferation in vitro. One small study found a higher incidence of severe infections after left hemisphere infarctions although in the larger ESPIAS trial the incidence of infection was not lateralized, in agreement with observations in ischemic rats. In this clinical trial, levofloxacin was not able to
prevent the incidence of infection in patients with nonseptic acute stroke. However, antibiotic therapy with moxifloxacin prevented infection in ischemic mice, and ongoing studies of antibiotic prophylaxis in stroke patients might indicate that the efficacy of this approach relies on patient selection, differences in antibiotics, or the administration regime.

The longitudinal changes of plasma cytokines and circulating white blood cells were also assessed in the patients included in the ESPIAS trial. As described in Figure 2, patients with stroke have a rapid increase of circulating cytokines in plasma, with a low ratio of pro-inflammatory TNF-α to anti-inflammatory IL-10 preceding the appearance of infection, in agreement with experimental data and clinical studies of patients with fatal community-acquired infection. These observations caution about the potential risks of pro-inflammatory cytokine inhibition in patients with sepsis. Monocytes, neutrophils, and total counts of white blood cells are also increased before infections, as shown in Figure 3. Recently, poststroke infection has also been associated with higher admission levels of metanephrine, emphasizing the relevance of sympathoadrenal function for immune competence. Indeed, in human adrenals, the medullary tissue (catecholamines) and the cortex (glucocorticoids) are extensively intermingled, and this anatomical disposition allows important intraadrenal paracrine interactions.

Conclusions

As previously described in experimental conditions, accumulating clinical evidence also suggests that acute stroke may induce significant immunological changes that could facilitate the appearance of infection in human stroke. Whereas infections predominate in patients with severe stroke who frequently may undergo invasive maneuvers facilitating the entry of pathogens, recent clinical studies underscore the relevance of immunological changes such as an excessive counter-inflammatory cytokine response. These cytokines may come from injured brain cells or from peripheral organs, including circulating white blood cells—mostly monocytes and neutrophils—which are significantly increased before clinical signs of infection. The autonomous nervous system, the HPA axis, lymphoid organs and adrenal medulla provide reverberating pathways for rich neuroimmunological interactions. Indeed, the strength of adrenomedullary activity has recently been proved to be associated to the risk of infection in patients with acute stroke. The support for an independent causal relationship between infections and additional ischemic brain damage is challenged by recent data. Yet, the existence of a stroke-induced immunodepression syndrome might be an adaptive mechanism to brain ischemia although further research will be required to unravel the clinical consequences of these immunological changes. Hopefully, a better understanding of the complex cross-talk between the central nervous system and the immune system might lead in the future to more effective stroke therapies.

Disclosures

None.

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