Infection After Acute Ischemic Stroke

A Manifestation of Brain-Induced Immunodepression

Ángel Chamorro, MD, PhD; Xabier Urra, MD; Anna M. Planas, PhD

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 linked[13] 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 studies[18–27]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%

Received September 28, 2006; accepted October 12, 2006.

From the Stroke Unit (A.C., X.U.), Hospital Clínic and Institut d' Investigacions Biomédiques August Pi i Sunyer (IDIBAPS). University of Barcelona, Spain; and the Pharmacology and Toxicology Department (A.M.P.), Consejo Superior de Investigaciones Científicas (IIBB-CSIC) and IDIBAPS, Barcelona, Spain.

Correspondence to Prof Ángel Chamorro, Hospital Clínic, 08036, Barcelona, Spain. E-mail achamorro@ub.edu

Stroke **is available at http://www.strokeaha.org** **DOI: 10.1161/01.STR.0000258346.68966.9d**

Major Studies Analyzing the Infection Rate in Stroke Patients

Authors	Reference No.	Design	Stroke Subtypes	Sample Size	Infection Rate, %	Follow-Up, days
Davenport et al	21	Retrospective	Ischemic/Hemorrhagic	597	35	37
Johnston et al	22	Retrospective	Ischemic	279	8*	90
Langhorne et al	23	Prospective	Ischemic/Hemorrhagic	311	65	35
Grau et al	24	Prospective	Ischemic	119	10†	2
Heuschmann et al	25	Retrospective	Ischemic	13 440	6‡	10.6
Hamidon et al	26	Prospective	Ischemic	163	16	3
Hilker et al	27	Prospective	Ischemic/Hemorrhagic§	124	15‡	3
Weimar et al	28	Retrospective	Ischemic	3866	13.7	7
Vargas et al	29	Prospective	Ischemic/Hemorrhagic	229	27	7
Katzan et al	30	Retrospective	Ischemic/Hemorrhagic	14 293	7‡	30
Smithard et al	31	Prospective	Ischemic/Hemorrhagic	121	24‡	7

*Only serious complications were reported (those that were immediately life-threatening, prolonged or resulted in hospitalization, or resulted in death).

†This figure excludes additional 11% of patients in whom infection was considered to precede ischemia.

‡Pneumonia only.

§Patients included in a neurological intensive care unit.

to 96% of patients, with the highest frequency reported in prospective studies.[22] The most common medical conditions encountered in these studies include urinary tract infections, venous thrombi, pneumonias, joint and soft-tissue pain, sepsis, and falls.[28] Most poststroke infections involve the respiratory or urinary tracts, although chest infections prevail during the first few days after stroke.[20,29] Pneumonia is reported to complicate the course of 7% to 22% of the stroke patients,[21,22,23,30] and dysphagia and aspiration are the most commonly incriminated factors.[31,32]

Is Infection a Cause of Worsening Stroke? Uncertain

The proportion of patients experiencing infections is higher in patients with severe stroke[29,33,26] unlike other stroke complications such as falls, depression or pain.[23] Infections can facilitate electrolytic unbalance, hypoxia, and fever, which could theoretically impair neuronal survival within the ischemic penumbra.[34] Fever may increase the cerebral metabolic demands,[35] change the blood-brain barrier permeability, and promote acidosis and release of excitatory amino acids.[36] Entry of bacteria and lypopolisaccharide into the bloodstream also favors thrombosis through tumor necrosis factor (TNF)-α release,[37] activation of the tissue factor–mediated extrinsic pathway of blood coagulation,[38] reduction of thrombomodulin (anticoagulant), and inhibition of the fibrinolytic system.[39] With few exceptions,[40] 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.[41,42] However, the support to infection as an independent cause of stroke worsening is controversial.[29,43,44] Only few studies[29,43] accounted for the critical effect of the initial severity of stroke, and in some studies,[22] 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.[29,44] It has been argued that the inclusion of *soft* end points, such as acute bronchitis, could have minimized the clinical relevance of poststroke infection[45] 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.[46] 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.[47]

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),[48] 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.[13,49] 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.[13]

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

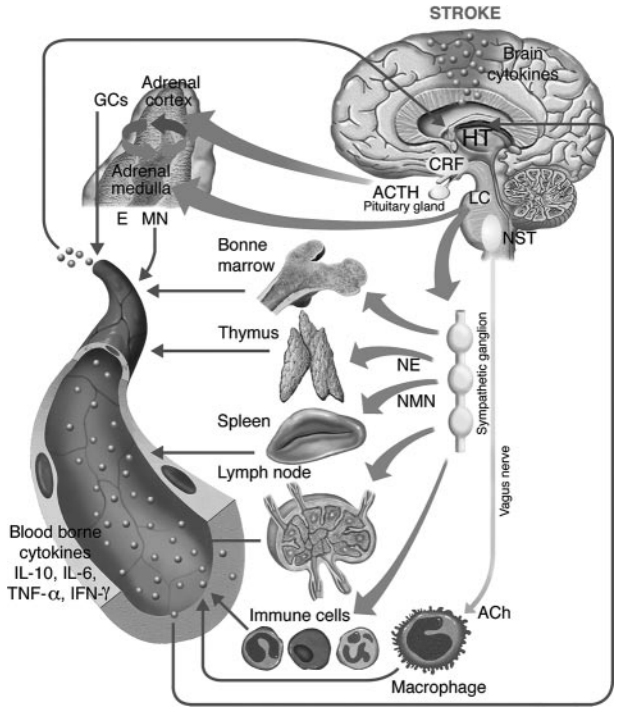

Figure 1. Schematic representation of the main communication pathways between the central nervous system and the immune system. ACTH indicates adrenocorticotropin hormone; CRF, corticotropin releasing factor; E, epinephrine; GCs, glucocorticoids; HT, hypothalamus; LC, locus coeruleus; MN, metanephrine; NE, norepinephrine; NMN, normetanephrine; NST, nucleus of the solitary tract.

cortices of the adrenal gland. Cytokines such as interleukin (IL)-1β, TNF-α, and IL-6, secreted by cells in different tissues and organs including the brain[50] can stimulate specialized neurons in the PVN to synthesize corticotropin-releasing factor.[51] 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 vascularis of the lamina terminals, or the area postrema.[50,52] Once released into the pituitary portal blood system, corticotropin-releasing factor interacts within the anterior pituitary with a specific G protein–coupled receptor (corticotrophin-releasing factor-F1) facilitating the secretion of adrenocorticotropin hormone precursor peptide proopiomelanocortin, and adrenocorticotropin hormone (ACTH).[53] Secondarily, ACTH induces the secretion of glucocorticoids from the zona fasciculata of the adrenal cortex which suppress the production of pro-inflammatory mediators, including IL-1β, IL-11, IL-12, interferon-γ, TNF-α, chemokines (IL-8), prostaglandins and NO.[54] Glucocorticoids also facilitate the release of anti-inflammatory mediators such as IL-4, IL-10 and transforming growth factor-β,[55] and have strong antiproliferative properties, and apoptotic effects in immune cells.[56] In the end, cytokines can activate the release of glucocorticoids, which in turn suppress further cytokine synthesis in a classic negative feedback loop.[57]

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.[58] 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.[59] 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.[60]

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[61] support the existence of a reverberatory feedback loop between the HPA and the sympathetic nervous system.[62] 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.[52,63] 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.[13]

The Adrenal Medullary Gland

The chromaffin cells of the adrenal medulla are homologs of the sympathetic ganglia derived from the neural crest,[64] 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 adrenomedullar 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.[65] 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.[66] 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.[67] However, as further discussed below, the adrenal

medullary gland has received little attention in clinical and experimental studies of acute stroke.

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.[68] Likewise, with the exception of Th type 2 cells,[69] virtually all immune cells express adrenoreceptors, including lymphocytes, granulocytes, monocytes, macrophages, and natural killer cells.[63,70] Catecholamines released within the microenvironment of immune cells located in lymphoid organs increase their intracellular levels of cAMP and activate protein kinase A.[71] 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,[72] and this affects in vivo myelopoiesis and erythropoiesis,[73] because the production of granulocytes and macrophages is under a sympathetic inhibitory tone, whereas lymphocyte[74] and erythrocyte[73] formation require adrenergic stimulation.

Immunological Changes After Acute Brain Ischemia: Experimental and Clinical Studies

In patients with acute stroke, increased[75,76,77,78] or abnormally low[78,79] 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.[79,80] High cortisol has also been associated in some studies,[81] but not in others,[81,82] with higher catecholamine excretion, and frontal lobe, or insular infarctions.[83,84] 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.[85] In mice, focal cerebral ischemia also reduces spleen cellularity and response to mitogens,[86] and results in a rapid and widespread production of pro-inflammatory factors by splenocytes in relation to adrenergic signaling.[87] Propranolol prevents these infections,[85] 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.[88]

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.[89,90] One small study[91] found a higher incidence of severe infections after left hemisphere infarctions although in the larger ESPIAS trial the incidence of infection was not lateralized,[48] in agreement with observations in ischemic rats.[92] In this clinical trial, levofloxacin was not able to

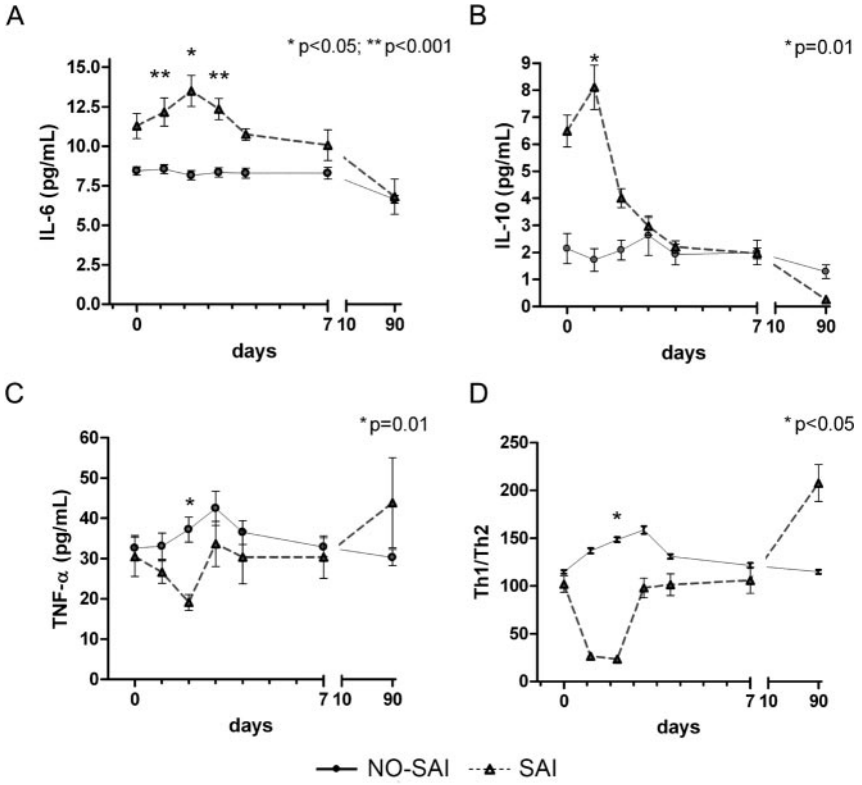

Figure 2. Temporal course of cytokine levels in plasma in patients with stroke-associated infection (SAI) within 7 days of clinical onset as compared with patients without stroke-associated infection (NO-SAI). A, IL-6; B, IL-10; C, TNF-α; D, IL-10 to TNF-α ratio.

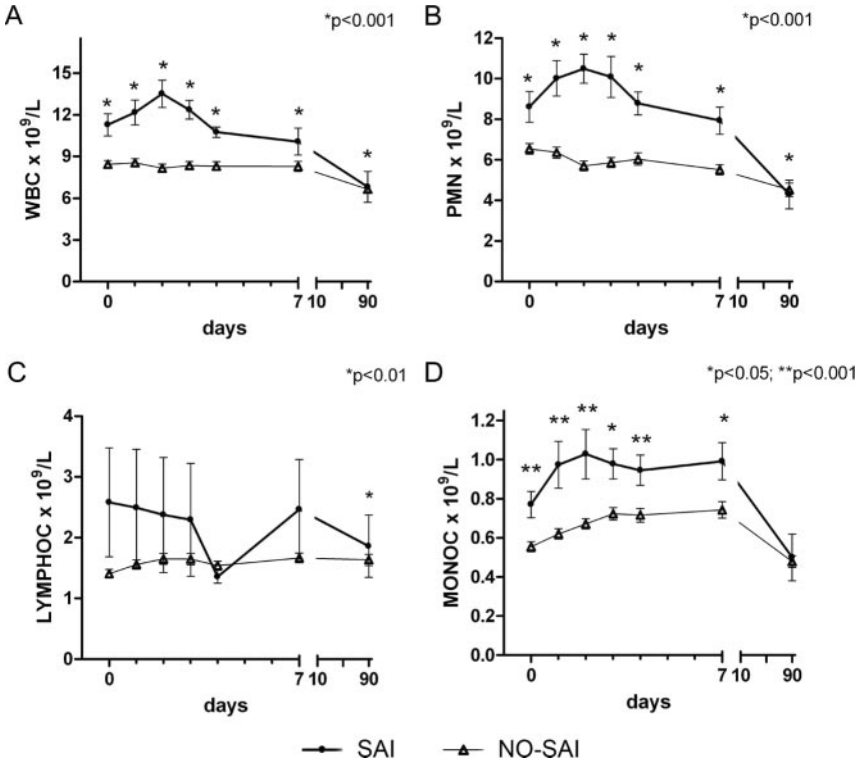

Figure 3. Temporal course of circulating white blood cells (WBCs) in stroke-associated infection (SAI) within 7 days of clinical onset as compared with patients without stroke-associated infection (NO-SAI). A, Total WBCs count; B, polymorphonuclears; C, lymphocytes; D, monocytes.

prevent the incidence of infection in patients with nonseptic acute stroke.[48] However, antibiotic therapy with moxifloxacin prevented infection in ischemic mice,[93] 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.[94]

The longitudinal changes of plasma cytokines and circulating white blood cells were also assessed in the patients included in the ESPIAS trial.[48,95] 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,[95] in agreement with experimental data,[96,97] and clinical studies of patients with fatal community-acquired infection.[98] 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 sympathoadrenomedullary function for immune competence.[99] Indeed, in human adrenals, the medullary tissue (catecholamines) and the cortex (glucocorticoids) are extensively intermingled, and this anatomical disposition allows important intraadrenal paracrine interactions.[100]

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.

References

1. Chamorro A, Hallenbeck J. The harms and benefits of inflammatory and immune responses in vascular disease. *Stroke*. 2006;37:291–293.
2. Vila N, Castillo J, Dávalos A, Esteve A, Planas AM, Chamorro A. Levels of anti-inflammatory cytokines and neurological worsening in acute ischemic stroke. *Stroke*. 2003;34:671–675.
3. Syrjanen J. Vascular diseases and oral infections. *J Clin Periodontol*. 1990;17:497–500.
4. Lindsberg PJ, Grau AJ. Inflammation and infections as risk factors for ischemic stroke. *Stroke*. 2003;34:2518–2532.

5. Hindfelt B, Nilsson O. Brain infarction in young adults with particular reference to pathogenesis. *Acta Neurol Scand*. 1977;55:145–157.
6. Mattila KJ, Valtonen VV, Nieminen MS, Asikainen S. Role of infection as a risk factor for atherosclerosis, myocardial infraction, and stroke. *Clin Infect Dis*. 1998;26:719–734.
7. Smeeth L, Thomas SL, Hall AJ, Hubbard R, Farrington P, Vallance P. Risk of myocardial infarction and stroke after acute infection or vaccination. *N Engl J Med*. 2004;351:2611–2618.
8. Grau AJ, Buggle F, Steichen-Wiehn C, Heindl S, Banerjee T, Seitz R, Winter R, Forsting M, Werle E, Bode C, Nawroth PP, Becher H, Hacke W. Clinical and biochemical analysis in infection-associated stroke. *Stroke*. 1995;26:1520–1526.
9. Valtonen V, Kuikka A, Syrjanen J. Thrombo-embolic complications in bacteraemic infections. *Eur Heart J*. 1993;14:20–23.
10. Ameriso SF, Wong VL, Quismorio FP Jr, Fisher M. Immunohematologic characteristics of infection-associated cerebral infarction. *Stroke*. 1991;22:11004–11009.
11. Macko RF, Ameriso SF, Gruber A, Griffin JH, Fernandez JA, Barndt R, Quismorio FP Jr, Weiner JM, Fisher M. Impairments of the protein C system and fibrinolysis in infection-associated stroke. *Stroke*. 1996;27:2005–2011.
12. Zeller JA, Lenz A, Eschenfelder CC, Zunker P, Deuschl G. Platelet-leukocyte interaction and platelet activation in acute stroke with and without preceding infection. *Arterioscler Thromb Vasc Biol*. 2005;25:1519–1523.
13. 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;52:595–638.
14. Woiciechowsky C, Asadullah K, Nestler D, Eberhardt B, Platzer C, Schoning B, Glockner F, Lanksch WR, Volk HD, Docke WD. Sympathetic activation triggers systemic interleukin-10 release in immunodepression induced by brain injury. *Nat. Med*. 1998;4:808–813.
15. Docke WD, Randow F, Syrbe U, Krausch D, Asadullah K, Reinke P, Volk HD, Kox W. Monocyte deactivation in septic patients: restoration by IFN-gamma treatment. *Nat. Med.* 1997;3:678–681.
16. Viitanen M, Winblad B, Asplund K. Autopsy-verified causes of death after stroke. *Acta Med Scand*. 1987;222:401–408.
17. Vernino S, Brown RD Jr, Sejvar JJ, Sicks JD, Petty GW, O'Fallon WM. Cause-specific mortality after first cerebral infarction: a population-based study. *Stroke*. 2003;34:1828–1832.
18. Dromerick A, Reding M. Medical and neurological complications during inpatient stroke rehabilitation. *Stroke*. 1994;25:358–361.
19. Bamford J, Dennis M, Sandercock P, Burn J, Warlow C. The frequency, causes and timing of death within 30 days of a first stroke: the Oxfordshire Community Stroke Project. *J Neurol Neurosurg Psychiatry*. 1990;53:824–829.
20. Kalra L, Yu G, Wilson K, Roots P. Medical complications during stroke rehabilitation. *Stroke*. 1995;26:990–994.
21. Davenport RJ, Dennis MS, Wellwood I, Warlow CP. Complications after acute stroke. *Stroke*. 1996;27:415–420.
22. Johnston KC, Li JY, Lyden PD, Hanson SK, Feasby TE, Adams RJ, Faught RE Jr, Haley EC Jr. Medical and neurological complications of ischemic stroke: experience from the RANTTAS trial. RANTTAS Investigators. *Stroke*. 1998;29:447–453.
23. Langhorne P, Stott DJ, Robertson L, MacDonald J, Jones L, McAlpine C, Dick F, Taylor GS, Murray G. Medical complications after stroke: a multicenter study. *Stroke*. 2000;31:1223–1229.
24. Grau AJ, Buggle F, Schnitzler P, Spiel M, Lichy C, Hacke W. Fever and infection early after ischemic stroke. *J. Neurol. Sci*. 1999;171:115–120.
25. Heuschmann PU, Kolominsky-Rabas PL, Misselwitz B, Hermanek P, Leffmann C, Janzen RW, Rother J, Buecker-Nott HJ, Berger K; German Stroke Registers Study Group. Predictors of in-hospital mortality and attributable risks of death after ischemic stroke: the German Stroke Registers Study Group. *Arch Intern Med*. 2004;164:1761–1768.
26. Hamidon BB, Raymond AA, Norlinah MI, Jefferelli SB. The predictors of early infection after an acute ischaemic stroke. *Singapore Med J*. 2003;44:344–346.
27. Hilker R, Poetter C, Findeisen N, Sobesky J, Jacobs A, Neveling M, Heiss WD. Nosocomial pneumonia after acute stroke: implications for neurological intensive care medicine. *Stroke*. 2003;34:975–981.
28. Weimar C, Roth MP, Zillessen G, Glahn J, Wimmer ML, Busse O, Haberl RL, Diener HC; German Stroke Date Bank Collaborators. Complications following acute ischemic stroke. *Eur Neurol*. 2002;48:133–140.
29. 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;37:461–465.
30. Katzan IL, Cebul RD, Husak SH, Dawson NV, Baker DW. The effect of pneumonia on mortality among patients hospitalized for acute stroke. *Neurology*. 2003;60:620–625.
31. Smithard DG, O'Neill PA, Parks C, Morris J. Complication and outcome after acute stroke: does dysphagia matter? *Stroke*. 1996;7:1200–1204.
32. Marlene AH, Kathleen LD, Michael JR. Aspiration and relative risk of medical complications following stroke. *Arch Neurol*. 1994;51:1051–1053.
33. Roth EJ, Lovell L, Harvey RL, Heinemann AW, Semik P, Diaz S. Incidence of and risk factors for medical complications during stroke rehabilitation *Stroke*. 2001;32:523–529.
34. Ginsberg MD, Busto R. Combating hyperthermia in acute stroke: a significant clinical concern. *Stroke*. 1998;29:529–534.
35. Nemoto EM, Frankel HM. Cerebral oxygenation and metabolism during progressive hyperthermia. *Am J Physiol*. 1970;219:1784–1788.
36. Busto R, Globus MY, Dietrich WD, Martinez E, Valdes I, Ginsberg MD. Effect of mild hypothermia on ischemia-induced release of neurotransmitters and free fatty acids in rat brain. *Stroke*. 1989;20:904–910.
37. Martinez MA, Pena JM, Fernandez A, Jimenez M, Juarez S, Madero R, Vazquez JJ. Time course and prognostic significance of hemostatic changes in sepsis: relation to tumor necrosis factor-α. *Crit Care Med*. 1999;27:1303–1308.
38. Conway EM, Bach R, Rosenberg RD, Konigsberg WH. Tumor necrosis factor enhances expression of tissue factor mRNA in endothelial cells. *Thromb Res*. 1989;53:231–241.
39. Moore KL, Esmon CT, Esmon NL. Tumor necrosis factor leads to the internalization and degradation of thrombomodulin from the surface of bovine aortic endothelial cells in culture. *Blood*. 1989;73:159–165.
40. Boysen G, Christensen H. Stroke severity determines body temperature in acute stroke. *Stroke*. 2001;32:413–417.
41. Castillo J, Martinez F, Leira R, Prieto JM, Lema M, Noya M. Mortality and morbidity of acute cerebral infarction related to temperature and basal analytic parameters. *Cerebrovasc Dis*. 1994;4:66–71.
42. Reith J, Jorgensen HS, Pedersen PM, Nakayama H, Raaschou HO, Jeppesen LL, Olsen TS. Body temperature in acute stroke: relation to stroke severity, infarct size, mortality, and outcome. *Lancet*. 1996;347:422–425.
43. Aslanyan CJ, Weir CJ, Dienerc HC, Kaste M, Lees KR; for the GAIN International Steering Committee and Investigator. Pneumonia and urinary tract infection after acute ischaemic stroke:a tertiary analysis of the GAIN International trial. *Eur J Neurol*. 2004;11:49–53.
44. Dziewas R, Ritter M, Schilling M, Konrad C, Oelenberg S, Nabavi DG, Stogbauer F, Ringelstein EB, Ludemann P. Pneumonia in acute stroke patients fed by nasogastric tube. *J Neurol Neurosurg Psychiatry*. 2004;75:852–856.
45. Kwan J, Roberts HC; Englyst N. Do we really understand the pathophysiology and clinical impact of poststroke infection? *Stroke*. 2006;37:1656.
46. Basi S, Marrie TJ, Huang JQ, Sumit R, Majumdar S. Patients admitted to hospital with suspected pneumonia and normal chest radiographs: epidemiology, microbiology, and outcome. *Am J Med*. 2004;117:305–311.
47. Chamorro A, Vargas M, Mensa J. Do we really understand the pathophysiology and clinical impact of poststroke infection? *Stroke*. 2006;37:1657.
48. 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;36:1495–1500.
49. Blalock JE. A molecular basis for bidirectional communication between the immune and neuroendocrine systems. *Physiol Rev*. 1989;69:1–32.
50. Turnbull AV, Rivier CL. Regulation of the hypothalamic-pituitary-adrenal axis by cytokines: actions and mechanisms of action. *PhysiolRev*. 1999;79:1–71.
51. Chrousos GP. The hypothalamic-pituitary-adrenal axis and immune-mediated inflammation. *N Engl J Med*. 1995;332:1351–1362.
52. Buller KM. Circumventricular organs: gateways to the brain: role of circumventricular organs in pro-inflammatory cytokine-induced activation of the hypothalamic-pituitary-adrenal axis. *Clin Exp Pharmacol Physiol*. 2001;28:581–589.
53. Rivier C, Plotsky PM. Mediation by corticotrophin-releasing factor (CRF) of adenohypophysisal hormone secretion. *Annu Rev Physiol*. 1986;48:475–494.

54. Wilckens T, De Rijk R. Glucocorticoids and immune function: unknown dimensions and new frontiers. *Immunol Today.* 1997;18:418–424.
55. Barrat FJ, Cua DJ, Boonstra A, Richards DF, Crain C, Savelkoul HF, de Waal-Malefyt R, Coffman RL, Hawrylowicz CM, O'Garra A. In vitro generation of interleukin 10-producing regulatory CD4+ T cells is induced by immunosuppressive drugs and inhibited by T helper type 1 (Th1)- and Th2-inducing cytokines. *J Exp Med*. 2002;195:603–616.
56. Tuosto L, Cundari E, Montani MS, Piccolella E. Analysis of susceptibility of mature human T lymphocytes to dexamethasone-induced apoptosis. *Eur J Immunol*. 1994;24:1061–1065.
57. Besedovsky H, del Rey A, Sorkin E, Dinarello CA. Immunoregulatory feedback between interleukin-1 and glucocorticoid hormones. *Science*. 1986;233:652–654.
58. Sawchenko PE, Brown ER, Chan RKW, Ericsson A, Li HY, Roland BL, Kovacs KJ. The paraventricular nucleus of the hypothalamus and functional neuroanatomy of viscereomotor responses to stress. *Prog Brain Res.* 1996;107:201–222.
59. Pavlov VA, Wang H, Czura CJ, Friedman SG, Tracey KJ. The cholinergic anti-inflammatory pathway: a missing link in neuroimmunomodulation. *Mol Med.* 2003;9:125–134.
60. Bernik TR, Friedman SG, Ochani M, DiRaimo R, Ulloa L, Yang H, Sudan S, Czura CJ, Ivanova SM, Tracey KJ. Pharmacological stimulation of the cholinergic antiinflammatory pathway. *J Exp Med.* 2002;195:781–788.
61. Berkenbosh F, de Goeij DE, Rey AD, Besedovsky HO. Neuroendocrine, sympathetic and metabolic responses induced by interleukin 1. *Neuroendocrinology*. 1989;50:570–576.
62. Chrousos GP, Gold PW. The concepts of stress and stress system disorders. Overview of physical and behavioral homeostasis. *JAMA*. 1992;267:1244–1252.
63. Kin NW, Sanders VM. It takes nerves to tell T and B cells what to do. *J Leukoc Biol*. 2006;79:1–12.
64. Eisenhofer G, Friberg P, Pacak K, Goldstein DS, Murphy DL, Tsigos C, Quyyumi AA, Brunner HG, Lenders JW. Plasma metadrenalines: do they provide useful information about sympatho-adrenal function and catecholamine metabolism? *Clin Sci*. 1995;88:533–542.
65. Eisenhofer G, Rundquist B, Aneman A, Friberg P, Dakak N, Kopin IJ, Jacobs MC, Lenders JW. Regional release and removal of catecholamines and extraneuronal metabolism to metanephrines. *J Clin Endocrinol Metab*. 1995;80:3009–3017.
66. Eisenhofer G, Keiser H, Friberg P, Mezey E, Huynh T-T, Hiremagalur B, Ellingson T, Duddempudi S, Eijsbouts A, Lenders J. Plasma metanephrines are markers of pheochromocytoma produced by catechol-O-methyltransferase within tumors. *J Clin Endocrinol Metab.* 1998;83:2175–2185.
67. Goldstein DS, Eisenhofer G, Kopin IJ. Sources and significance of plasma levels of catechols and their metabolites in humans. *J Pharmacol Exp Therap*. 2003;305:800–811.
68. Felten DL. Neural influence on immune responses: underlying suppositions and basic principles of neural-immune signaling. *Prog Brain Res*. 2000;122:381–389.
69. Sanders VM, Baker RA, Ramer-Quinn DS, Kasprowicz DJ, Fuchs BA, Street NE. Differential expression of the beta2-adrenergic receptor by Th1 and Th2 clones: implications for cytokine production and B cell help. *J Immunol*. 1997;158:4200–4210.
70. Kohm AP, Sanders VM. Norpeinephrine and β 2-adrenergic receptor stimulation regulates CD4+ T and B lymphocyte function in vitro and in vivo. *Pharmacol Rev*. 2001;53:487–525.
71. Woiciechowsky C, Schöning B, Lanksch WR, Volk HD, Docke HD. Mechanisms of brain-mediated systemic anti-inflammatory syndrome causing immunodepression. *J Mol Med*. 1999;77:769–780.
72. Tang Y, Shankar R, Gamelli R, Jones S. Dynamic norepinephrine alterations in bone marrow: Evidence of functional innervation. *J Neuroimmunol*. 1999;96:182–189.
73. Fink GD, Fisher JW. Stimulation of erythropoiesis by beta adrenergic agonists. I. Characterization of activity in polycythemic mice. *J Pharmacol Exp Ther*. 1977;202:192–198.
74. Maestroni GJ, Conti A. Modulation of hematopoiesis via alpha 1-adrenergic receptors on bone marrow cells. *Exp Hematol*. 1994;22:313–320.
75. Fassbender K, Schmidt R, Mossner R, Daffertshofer M, Hennerici M. Pattern of activation of the hypothalamic-pituitary-adrenal axis in acute stroke: relation to acute confusional state, extent of brain damage, and clinical outcome. *Stroke*. 1994;25:1105–1108.
76. Olsson T, Marklund N, Gustafson Y, Nasman B. Abnormalities at different levels of the hypothalamic-pituitary-adrenocortical axis early after stroke. *Stroke*. 1992;23:1573–1576.
77. Johansson A, Ahren B, Nasman B, Carlstrom K, Olsson T. Cortisol axis abnormalities early after stroke—relationships to cytokines and leptin. *J Intern Med*. 2000;247:179–187.
78. Marklund N, Peltonen M, Nilsson TK, Olsson T. Low and high circulating cortisol levels predict mortality and cognitive dysfunction early after stroke. *J Intern Med*. 2004;256:15–21.
79. Schwarz S, Schwab S, Klinga K, Maser-Gluth C, Bettendorf M. Neuroendocrine changes in patients with acute space occupying ischemic stroke. *J Neurol Neurosurg Psychiatry*. 2003;74:725–727.
80. Slowik A, Turaj W, Pankiewicz J, Dziedzic T, Szermer P, Szczudlik A. Hypercortisolemia in acute stroke is related to the inflammatory response. *J Neurol Sci*. 2002;196:27–32.
81. Olsson T. Urinary free cortisol excretion shortly after ischaemic stroke. *J Intern Med*. 1990;228:177–181.
82. Myers MG, Norris JW, Hachninski VC, Sole MJ. Plasma norepinephrine in stroke. *Stroke*. 1981;12:200–204.
83. Smith KE, Hachinski VC, Gibson CJ, Ciriello J. Changes in plasma catecholamine levels after insula damage in experimental stroke. *Brain Res*. 1986;375:182–185.
84. Robinson TG, James M, Youde J, Panerai R, Potter J. Cardiac baroreceptor sensitivity is impaired after acute stroke. *Stroke*. 1997;28:1671–1676.
85. Prass K, Meisel C, Hoflich C, Braun J, Halle E, Wolf T, Ruscher K, Victorov IV, Priller J, Dirnagl U, Volk HD, Meisel A. Stroke-induced immunodeficiency promotes spontaneous bacterial infections and is mediated by sympathetic activation reversal by poststroke T helper cell type 1-like immunostimulation. *J Exp Med*. 2003;198:725–736.
86. Offner H, Subramanian S, Parker SM, Wang C, Afentoulis ME, Lewis A, Vandenbark AA, Hurn PD. Splenic atrophy in experimental stroke is accompanied by increased regulatory T cells and circulating macrophages. *J Immunol*. 2006;176:6523–6531.
87. Offner H, Subramanian S, Parker SM, Afentoulis ME, Vandenbark AA, Hurn PD. Experimental stroke induces massive, rapid activation of the peripheral immune system. *J Cereb Blood Flow Metab.* 2006;26:654–665.
88. Rosenzweig HL, Lessov NS, Henshall DC, Minami M, Simon RP, Stenzel-Poore MP. Endotoxin preconditioning prevents cellular inflammatory response during ischemic neuroprotection in mice. *Stroke*. 2004; 35:2576–2581.
89. Czlonkowska A, Cyrta B, Korlak J. Immunological observations on patients with acute cerebral vascular disease. *J Neurol Sci*. 1979;43: 455–464.
90. Tarkowski E, Blomstrand C, Tarkowski A. Stroke induced lateralization of delayed-type hypersensitivity in the early and chronic phase of the disease: a prospective study. *J Clin Lab Immunol.* 1995;6:73–83.
91. Kawaharada M, Urasawa K. Immunological functions and clinical course of elderly patients with cerebrovascular diseases. *Nippon Ronen Igakkai Zasshi*. 1992;29:652–660.
92. Gendron A, Teitelbaum J, Cossette C, Nuara S, Dumont M, Geadah D, du Souich P, Kouassi E. Temporal effects of left versus right middle cerebral artery occlusion on spleen lymphocyte subsets and mitogenic response in Wistar rats. *Brain Res*. 2002;955:85–97.
93. 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;35:2–6.
94. Dirnagl U, Klehmet J, Braun JS, harás H, Meisel C, Ziemssen T, Prass K, Meisel A. Stroke-induced immunodepression: experimental evidence and clinical relevance. *Stroke*. 2006. In press.
95. Chamorro A, Amaro S, Vargas M, Obach V, Cervera A, Torres F, Planas AM. Interleukin-10, monocytes, and increased risk of infection in ischemic stroke. *J Neurol Neurosurg Psichiatry*. 2006;77:1279–1281.
96. Akdis CA, Blaser K. Mechanisms of interleukin-10-mediated immune suppression. *Immunology*. 2001;103:131–136.
97. O'Farrell AM, Liu Y, Moore KW, Mui AL. IL-10 inhibits macrophage activation and proliferation by distinct signalling mechanisms: evidence for Stat3-dependent and -independent pathways. *EMBO J*. 1998;16:1006–1018.
98. van Dissel JT, van Langevelde P, Westendorp RG, Kwappenberg K, Frolich M. Anti-inflammatory cytokine profile and mortality in febrile patients. *Lancet*. 1998;351:950–953.
99. Chamorro A, Amaro S, Vargas M, Obach V, Cervera A, Gomez-Choco M, Torres F, Planas AM. Catecholamines, infection, and death in acute ischemic stroke. *J Neurol Sci*. 2007; 252:29–35.
100. Bornstein SR, González-Hernández JA, Ehrhart-Bornstein M, Adler G, Scherbaum WA. Intimate contact of chromaffin and cortical cells within the human adrenal gland forms the cellular basis for important intraadrenal interactions. *J Clin Endocrinol Metab*. 1994;78:225–232.