Cytokine Response, Tract-Specific Fractional Anisotropy, and Brain Morphometry in Post-Stroke Cognitive Impairment

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Background: Post-stroke cognitive impairment is a clinically heterogeneous condition and its types have a different course and prognosis. The aim of the present study is to address the roles of inflammation, white matter pathology, and brain atrophy in different neuropsychological types of cognitive impairment in the acute period of ischemic stroke. *Methods:* In 92 patients, we performed an assessment of the cognitive status and measured concentrations of cytokines (interleukin [IL]-1β, IL-6, tumor necrosis factor-alpha, IL-10) in liquor and serum, as well as a number of magnetic resonance imaging (MRI) morphometric parameters and fractional anisotropy. The control group consisted of 14 individuals without cerebrovascular disease. *Results:* All patients had a higher level of IL-10 in serum than the control group. Patients with dysexecutive cognitive impairment had a higher concentration of IL-1β and IL-10 in liquor, IL-6 level in serum, and a lower fractional anisotropy of the ipsilateral thalamus than patients with normal cognition. Patients with mixed cognitive impairment were characterized by a lower fractional anisotropy of contralateral fronto-occipital fasciculus, compared with patients with dysexecutive cognitive impairment. Patients with both dysexecutive and mixed cognitive deficit had a wide area of leukoaraiosis and a reduced fractional anisotropy of the contralateral cingulum, compared with patients without cognitive impairment. Also, we found numerous correlations between cognitive status and levels of cytokines, MRI morphometric parameters, and fractional anisotropy of certain regions of the brain. *Conclusions:* The concentrations of cytokines in serum and cerebrospinal fluid studied in combination with MRI morphometric parameters and fractional anisotropy appear to be informative biomarkers of clinical types of post-stroke cognitive impairment. **Key Words:** Stroke—neuroinflammation—cytokines—fractional anisotropy—cognitive impairment.

Introduction

Every year, about 16 million people worldwide have a first-time stroke. Out of them, about 5.7 million people die and another 5 million remain disabled.[1] Stroke has been reported to increase the risk of cognitive impairment (CI) by at least 5-8 times.[2] Post-stroke cognitive impairment (PSCI) could be induced by mechanisms including the vascular CI because of the neuroanatomical lesions of strategic areas as a result of small-vessel diseases and mixed Alzheimer's disease (AD) with stroke.[3] Clinical data clearly indicate that the simultaneous occurrence of both stroke and AD leads to exacerbated PSCI.[4]

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Neuroinflammation is also an actively studied factor in the development of stroke, CI, and AD. Ischemic stroke causes a brain damage as a result of primary and secondary insults mediated by ischemia and inflammation.[5] Acute inflammation arises from the responses of resident immune cells and the microglia, as well as from infiltrating immune cells of the peripheral circulation.[6] This response results in an increase in levels of toxic inflammatory mediators including interleukins IL-1β, IL-6, IL-8, and tumor necrosis factor-alpha (TNF-α).[7] Furthermore, the resolution of inflammation in the brain, similar to systemic inflammation, involves the production of antiinflammatory, signaling molecules like IL-10 and transforming growth factor beta that both suppress inflammation and exert neuroprotective effects on the surviving cells.

IL-1, TNF-α, IL-6, and IL-10 have been the most extensively studied cytokines in brain ischemia. Among these cytokines, IL-1 has been shown to mediate ischemic, excitotoxic, and traumatic brain injury, probably through various actions on glia, neurons, and vasculature, whereas TNF-α may contribute to both neuronal injury and protection. IL-10 may be neuroprotective, whereas reports on the role of IL-6 appear to be conflicting.[8] Chronic inflammatory responses in the infarct core in general, and B-lymphocyte responses in particular, have been shown to cause delayed-onset cognitive impairment after stroke.[9] Recently, it has been demonstrated that memory deficits after acute brain ischemia are associated with increased levels of brain proinflammatory cytokines and neurodegeneration. These findings suggest a role for inflammatory mediators and brain damage in PSCI.[10]

Recent progress in brain imaging methods, especially the combination of microglia imaging using positron emission tomography and diffusion tensor imaging using magnetic resonance imaging (MRI),[11] has demonstrated that persisting white matter inflammation after subcortical stroke can lead to the degeneration of even intact fiber tracts over a 6-month observation period.[12] The aim of the present study is to address the roles of inflammation, white matter pathology, and brain atrophy in different neuropsychological types of PSCI during the acute period of ischemic stroke.

Materials and Methods

Study Participants and Clinical Assessment

Ninety-two patients with acute ischemic stroke and 14 healthy subjects of the same age were included. This study was reviewed and approved by the Medical Research Ethics Committee of the Perm State Medical University. All strokes were confirmed with MRI and classified according to the SSS-Trial of Org 10172 in Acute Stroke Treatment classification. The severity of the stroke was assessed using the National Institutes of Health Stroke Scale score. Patients with dementia before stroke were excluded. For the control group, we used samples from patients with no vascular or neurodegenerative diseases.

Cognitive Evaluation

All patients received a comprehensive neuropsychological assessment between the 7th and the 14th days, covering 4 domains including memory, executive function, language, and visuospatial skills, which included the Mini-Mental State Examination Test (MMSE), Montreal Cognitive Assessment (MoCA-test), Frontal Assessment Battery (FAB), Semantic Verbal Fluency Test, Five Word Test, Clock Drawing Test, and Schulte Test. According to the results of the testing, the cognitive statuses of patients with stroke were classified into normal cognition (NC), dysexecutive CI (DCI), and mixed CI (MxCI). Neuropsychological testing and physical examination were conducted by a study physician.

Blood and Liquor Collection, Cytokines Assay

For subjects with acute ischemic stroke, blood and liquor were collected in the period between day 4 and day 21 (both were obtained from the same patient on the same day). The levels of IL-1β, IL-6, IL-10, and TNFα were measured in the patient serum and liquor using a solid-phase sandwich enzyme-linked immunosorbent assay kits (Vector-Best, Russia)—A-8766 (IL-1β), A-8768 (IL-6), A-8774 (IL-10), and A-8756 (TNFα)—according to the manufacturer's instructions. The colorimetric reaction was measured at 450 nm on a Synergy H1 hybrid multi-mode microplate reader (BioTek, Bad Friedrichshall, Germany). For analysis, we calculated the median.

MRI Acquisition

All patients underwent MRI scanning on a 1.5 Tesla MRI system (BrivoMR355 General Electric Healthcare, Milwaukee, WI) with a high-resolution 8-channel head coil. The MRI protocol included a T1-weighted volumetric sequence (3D FSPGR «BRAVO», axial acquisition, 1 mm isotropic resolution and matrix size of 240 × 240; repetition time: 7.900 ms; echo time: 3.100 ms; flip angle: 12). We used DTI images acquired along 12 noncollinear directions (repetition time: 9.300 ms; echo time: minimum; flip angle: 151; field of view: 240 mm; voxel size: 2 × 2 × 2 mm, no gap; and b = 1000 s/mm^2) with an additional acquisition for each set without diffusion weighting (b = 0 s/mm^2) to visualize the fiber track and calculate the values of fractional anisotropy (FA). Also, we used axial fluid attenuation inversion recovery images (repetition time: 9.040 ms; echo time: 85 ms; inversion time: 2.500 ms; voxel size: 1.1 × 0.9 × 5 mm, gap: 1.5 mm) and axial T2-weighted images (repetition time: 5.520 ms; echo time: 92 ms; voxel size: 0.5 × 0.4 × 5 mm, gap: 1.5 mm).