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Personalized Psychiatry and Neurology

Letter

Neuroinflammatory Disorders: Perspectives for Personalization of Therapy

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Dear colleagues!

Inflammation is one of the most common pathological processes. As a typical process, it can originate anywhere in the body and often affects the central nervous system (CNS). Depending on the presence of microorganisms at the site of inflammation, it is traditionally classified into two types: septic (infectious) and aseptic. Infectious inflammation of the CNS includes meningoencephalitis and various neuroinfections, which are caused by neurotropic viruses, prions, bacteria and protozoa. A more complex picture emerges when considering the causes and mechanisms of aseptic inflammation in the CNS. This group includes: 1) autoimmune diseases; 2) other pathological processes accompanied by nervous tissue damage and inflammation; and 3) situations in which only CNS glial cells are activated and produce pro-inflammatory cytokines locally, due to current established terminology. Paradoxically, it is precisely this last scenario—in which microglia and astrocytes are activated in specific regions of the brain — that has come to be known as 'neuroinflammation'. In recent years, active research has been performed into the central and peripheral molecular signals that activate glial cells in systemic diseases such as obesity, hypertension and type 2 diabetes mellitus. It has been demonstrated that specific brain structures (e.g., hypothalamic nuclei, hippocampus and cerebral cortex) are involved in neuroinflammation in these diseases, allowing outcomes to be predicted. Furthermore, the spatial map of neuroinflammation may exhibit individual characteristics, providing a basis for personalized therapy. In the near future, it is likely that individual patient data will enable the selection of surgical (e.g., bariatric surgery), pharmacological (e.g., incretin mimetics, minocycline) and non-pharmacological (e.g., dietary modifications, physical activity) methods for treating neuroinflammation. While the results of this research are significant, leading experts are critical of the term 'neuroinflammation' in this context since it lacks a key feature of inflammation - the migration of leukocytes from the vascular lumen into damaged tissue. In light of this, the more accurate terms 'gliopathy' or 'gliosis' are proposed to describe these disorders.

Classic aseptic inflammation, characterized by the migration of leukocytes from the vascular bed into central nervous system (CNS) tissue, is associated with autoimmune diseases and nervous tissue damage in pathological processes such as neurotrauma, vascular pathology, tumor growth and neurodegeneration. In these cases, it is possible to analyze patterns of leukocyte infiltration, leukocyte accumulation dynamics, and microglial activation that are specific to each process (and, in the future, to each patient!). For example, it is known that demyelination lesions in multiple sclerosis primarily contain antigen-specific T and B cells, as well as monocytes. In 2024, arachnoid cuff exit points were discovered. These are specialized microscopic gaps in the arachnoid mater barrier through which bridging veins pass from the subarachnoid space to the dural venous sinuses. In multiple sclerosis, these gaps act as crucial conduits for immune cell trafficking from the immune-rich dura mater directly to the brain. This leads to the early activation of microglia, the severity of which increases as the disease progresses. Unlike multiple sclerosis, ischemic stroke is characterized by sequential infiltration of the necrotic area by neutrophils, monocytes and T cells, accompanied by local activation of microglia. Over time, however, this pattern becomes more generalized, affecting brain regions distant from the ischemic

focus. From this perspective, neuroinflammation in neurodegenerative diseases also exhibits characteristic features. For instance, in Alzheimer's disease, amyloid aggregates trigger the early activation of microglia, which gradually becomes more severe. Leukocyte infiltration occurs later and is much less pronounced than in ischemic stroke or multiple sclerosis, with T and B cells, as well as monocytes and neutrophils, migrating into the brain tissue. Thus, a detailed description of the dynamics of the two main components of neuroinflammation—leukocyte migration and microglial activation—provides the basis for the personalized treatment of inflammatory diseases of the central nervous system.

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