Quanterix®
Discovery Fueled by Ultra-Sensitivity

APP NOTE

Unraveling Inflammation in Neurological Disorders with Ultra-sensitive, Fully Automated Simoa® Cytokine Advantage PLUS

Key Takeaways

- **Neuroinflammation** plays a critical role in the pathological processes of neurological disorders, such as traumatic brain injury, neurodegenerative diseases, and psychiatric conditions.
- The **complex, dynamic communication** between the CNS and the periphery immune system links neuroinflammation with systemic inflammatory processes.
- **Cytokines are key mediators and biomarkers** of the pathophysiology of neurological disorders, providing valuable insights into disease mechanisms, aiding in diagnosis and prognosis, and informing treatment strategies.
- The **Simoa® Cytokine Advantage PLUS Assays** offer an ultrasensitive, fully automated solution for cytokine measurement, providing the scalability and reliability needed to accelerate both research and clinical applications in neurological disorders.

Neuroinflammation and its interplay with peripheral immune system in neurological disorders

Neuroinflammation is an immune response triggered under physiological conditions by infections, injuries, and cellular dysfunction or damage in the central nervous system (CNS) system. Upon infection or CNS cell damage, glial cells, the brain's resident innate immune cells, become activated and release immune mediators, including both pro-inflammatory and anti-inflammatory cytokines. These mediators help to mount a rapid immune response, defending against pathogens, limiting tissue damage, and promoting healing. This process may also involve the infiltration of peripheral immune cells from circulation, further amplifying the immune response to inflammatory events in the CNS.

However, when neuroinflammation is dysregulated or chronic, it can become harmful, contributing to the progression of various pathologies. Chronic neuroinflammation is associated with the development of neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS).[1] In fact, all neurological diseases, whether traumatic, ischemic, infectious, autoimmune, degenerative, or neoplastic, can involve direct or indirect pathological neuroinflammation.[2]

There is a complex and dynamic communication between the CNS and the periphery immune system, especially in conditions when the BBB permeability increases. For example, neuroinflammation triggered by traumatic brain injury (TBI) is linked to a substantial increase of cytokine levels in blood during the acute phase.[3,4] Additionally, systemic factors such as aging, hypertension, diabetes, drugs and toxins, can exacerbate neuroinflammation, contributing to the pathological processes of neurological disorders.[1]

Measuring Cytokine Biomarkers in Neurological Disorders

Cytokine levels measured in blood, especially in the chronic conditions, can be significantly influenced by inflammatory activities outside of the CNS. Conversely, peripheral inflammatory events can also impact neuroinflammation. Thus, inflammatory mediators, including cytokines, measured locally in the CNS or in circulation, can serve as important indicators neurological disorder pathology, including neurodegenerative diseases, TBIs, and psychiatric conditions.

Cytokines biomarkers can be combined with biomarkers of neuronal or glial cell damage, or biomarkers of

activated glial cells, such as neurofilament light chain (NfL), glial fibrillary acetic protein (GFAP), Tau, and soluble triggering receptor expressed on myeloid cells 2 (sTREM2), offering a more comprehensive understanding of disease mechanisms.[1] An emerging application is the analysis of biomarkers in brain-derived extracellular vesicles (BDEV), which offers promising insights into the study of neuroinflammation.[6]

Key Cytokine Biomarkers in Neurological Disorders

Traumatic Brain Injury (TBI)

TBI, regardless of severity, elicits a robust, acute immune response with significant increase in cytokine levels, which is critical for initiating the recovery process. However, TBI can also result in chronic inflammation, contributing to persistent neurological symptoms and an increased risk for neurodegenerative diseases. Chronic neuroinflammation is believed to be a major cause of secondary neural injury following TBI.

Acute increase in pro-inflammatory cytokines, including tumor necrosis factor alpha (TNF-α), interleukin-1 beta (IL-1β), interleukin-6 (IL-6), and IL-8 have been reported across the severity spectrum of TBIs, with varying longitudinal trajectories. The anti-inflammatory cytokine interleukin-10 (IL-10) also increases acutely post head injuries.[5]

Given the role of inflammation in TBI pathology, cytokines have been extensively explored for their diagnostic and prognostic potential. IL-8 and TNF-α have been suggested as promising serum biomarkers of impending intracranial hypertension (ICH) and cerebral hypoperfusion (CH) following severe TBI (sTBI).[6] In cases of mild TBI (mTBI), a peripheral biomarker approach incorporating cytokines such as IL-6 and TNF-α may improve sensitivity in detecting mild injuries and aid in differential diagnosis for timely care decision.[7]

Overall, there are mixed findings regarding the elevated cytokines levels, with some studies indicating a protective function in acute phase TBI, while other suggest that they may be a risk factor for unfavorable TBI outcomes. Research on cytokine biomarkers has primarily focused on severe TBI, with their roles in mTBI and the chronic phase of TBI of across all severity levels remain to be fully understood.[5,6]

Neurodegenerative Diseases

Classical neurodegenerative diseases, such as Alzheimer's disease (AD), Parkinson's disease (PD), Amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD) and Huntington's disease (HD) each has its defining pathological and clinical characteristics. Nonetheless they share the hallmark of chronic neuroinflammation.[8] Chronic neuroinflammation can be caused by persistent stimulus such as genetic susceptibility, abnormal CNS protein aggregates, unbated CNS cell damage from primary insult (e.g. TBI), or peripheral inflammatory conditions.

Peripheral inflammatory conditions, such as systemic inflammation due to infection or gut microbial perturbation, chronic diseases like diabetes and obesity, and aging-related low grade systemic inflammation, are known risk factors for neurodegeneration.[9]

Regardless of the underlying cause, neuroinflammation is now widely recognized as playing a central role in the development of neurodegenerative diseases. Therapeutic strategies aimed at modulating neuroinflammation are becoming an attractive approach for controlling CNS pathologies. Cytokines are important mediators and indicators of inflammation process and have been linked to the pathologies of neurodegeneration. These include cytokines such as IL-1β, IL-6, IL-4, IL-10, TNF-α, and IFN-γ.[9,10]

Analyzing cytokine levels provides critical insights into the complex role of inflammation in both the pathology and treatment of neurodegenerative diseases.

Multiple Sclerosis (MS)

MS is a CNS autoimmune disease characterized by myeline degeneration and axonal damage. A cytokine-mediated inflammatory response plays a key role in the autoimmune attack in MS. While traditionally studied in CSF samples, certain cytokines in serum, such as IL-1β, IL-2, IL-4, IL-8, IL-10, IFN-γ, and TNF-α, may serve as valuable biomarkers for assessing disease activity and status of MS.[11,12]

Serum cytokine biomarkers provide a more accessible and repeatable method for characterizing inflammation and monitor therapeutic response in patients with MS, providing an alternative to the more invasive CSF sampling.

Psychiatric Illness

Emerging evidence highlights the pathological role of neuroinflammation and immunological abnormalities in psychiatric illnesses, including notable links between neuropsychiatric disorders and autoimmunity. Recent research has increasingly focused on the impact of peripheral immune factors on CNS inflammation associated with psychiatric disorders.[13]

Assessing measures of peripheral inflammation is important for understanding the role of inflammation in psychiatric disorders. Alterations of circulating levels of cytokines including IFN-γ, IL-1β, IL-6, IL2, IL-4, IL-8 and TNF-α have been reported in wide range of psychiatric disorders, including major depressive disorders (MDD), post-traumatic stress disorders (PTSD), bipolar disorder (BPD), attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder.

Specifically, serum IL-6 and TNF-α have been suggested as biomarkers associated with the pathophysiology of MDD. Additionally, TNF-α and IFN-γ may serve as markers that help identify schizophrenia, while IL-1β and IL-6 are markers that help assess disease activity.[13, 14,15, 16]

Advancing Research into Neurological Disorders with Simoa® Cytokine Advantage PLUS Assays

Mapping the dynamics of cytokine biomarkers offers critical insights into the pathogenesis, diagnosis, and long-term management of neurological disorders through the lens of inflammation. However, cytokines are among the least abundant proteins in the normal blood proteome, with some key cytokines such as IL-1β, IL-2, IL-6, IL-10 are often undetectable at baseline levels in plasma and serum samples using conventional immunoassays.[17] This makes highly sensitive and reproducible technologies essential for reliable cytokine measurement.

Building on our industry-leading neurology biomarker assay menu, including NfL, GFAP, Tau, p-Tau, Quanterix has developed ultrasensitive, fully automated cytokine assays with the Advantage PLUS assay platform The new Simoa® Cytokine 4-Plex Advantage PLUS assays cover 11 essential cytokines for neurological research. Fully automation on the HD-X Analyzer, these assays offer a seamless, scalable, and consistent solution for both research and clinical studies, accelerating the translation of key cytokine biomarkers into real-world applications.

Ready to elevate your neurological disorder research?

Explore the power of Simoa® Cytokine Advantage PLUS assays to drive meaningful discoveries. Contact us today to learn more. Let's accelerate your research together.

Learn More About Quanterix

Click here for more information on how Quanterix is a leader in neurology research

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Simoa® Cytokine 4-Plex Advantage PLUS Assays

Product Name	Target Cytokines	Product Number
Simoa® Cytokine 4-plex A (C4PA) Advantage PLUS	IL-1β, IL-6, IL-10, TNF-α	104979
Simoa® Cytokine 4-plex B (C4PB) Advantage PLUS	IL-17A, IL-4, IL-13, IL-5	104997
Simoa® Cytokine 4-plex C (C4PC) Advantage PLUS	IL-2, IL-6, IL-8, IFN-γ	105066
Simoa® IL-17A Advantage PLUS	IL-17A	104428
Simoa® IFN-α Multi-Subtype Advantage PLUS	Total IFN-α	103836

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