Eotaxin-1 (CCL11) in neuroinflammatory disorders and possible role in COVID-19 neurologic complications

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Abstract
The related neurologic complications of SARS-CoV-2 infection in COVID-19 patients and survivors comprise symptoms including depression, anxiety, muscle pain, dizziness, headaches, fatigue, and anosmia/hyposmia that may continue for months. Recent studies have been demonstrated that chemokines have brain-specific attraction and effects such as chemotaxis, cell adhesion, modulation of neuroendocrine functions, and neuroinflammation. CCL11 is a member of the eotaxin family that is chemotactic agents for eosinophils and participate in innate immunity. Eotaxins may exert physiological and pathological functions in the central nerve system, and CCL11 may induce neuronal cytotoxicity effects by inducing the production of reactive oxygen species (ROS) in microglia cells. Plasma levels of CCL11 elevated in neuroinflammation and neurodegenerative disorders. COVID-19 patients display elevations in CCL11 levels. As CCL11 plays roles in physiosomatic and neuroinflammation, analyzing the level of this chemokine in COVID-19 patients during hospitalization and to predicting post-COVID-19-related neurologic complications may be worthwhile. Moreover, using chemokine modulators may be helpful in lessening the neurologic complications in such patients.

Keywords Eotaxin-1 · SARS-CoV-2 · COVID-19 · Neuroinflammation · CCL11

Introduction
Neurological complications in previous coronavirus epidemics, severe acute respiratory syndrome coronavirus (SARS) and Middle East respiratory syndrome coronavirus (MERS) infections, were demonstrated in a high prevalence [1, 2]. Different forms of myopathy and prolonged muscle weakness have been reported among survivors of SARS-CoV-1 infection [3]. SARS complications related to involvement of the nervous system and the related effects on mood like chronic fatigue, even years after the initiation of infection, was reported in patients of previous SARS epidemics [4]. Many records of prolonged neurological-related complications such as symptoms of varying degrees of depression, sleep impairment, anxiety, headaches, dizziness, muscle pain, fatigue, and anosmia/hyposmia, myopathies that sometimes continuing for were reported in COVID-19 patients [5–8]. Chemokines as biomarkers that involved in psychiatric disorders can be used as targets for treatment of depressive disorders. Elevated levels of serum chemokines in major bipolar disorder, depressive disorder, and schizophrenia have previously been reported [9]. Increased levels of CCL11 in serum and lung tissue have been demonstrated in COVID-19 patients, in spite of eosinopenia [9, 10]. Although some reports demonstrated the increase and activation of peripheral eosinophils in severe cases of COVID-19 but the role of eosinophils in COVID-19 inflammation still remains obscure [11–13]. CCL11 leads to the degranulation of human eosinophils and release of eosinophil-derived neurotoxin (EDN) which could potentially clarify about the eosinopenia and secondary elevation of eosinophil-related granule contents [9, 14–16]. As physiosomatic symptoms are related to...
eotaxins, and especially CCL11, eotaxin-1 may play a role in COVID-19 neurologic syndrome.

Chemokines

The chemokine family consists of low molecular weight cytokines (7–12 kDa) that involved in the direct chemotaxis, leukocytes trafficking migration, inflammatory responses and immune system functions [17–19]. Chemokines are involved in neuroendocrine, neurotransmission, and neurodegeneration [20]. Chemokines are classified in four families according to the relative position of their cysteine residues and their functions. Chemokines bind G protein-coupled receptors and activate cell signaling cascades, and by changes in cell shape and movement induce directed chemotaxis [20, 21]. Recent studies have demonstrated that chemokines have specific effects on the neuroinflammation, chemotaxis, and modulation of neuroendocrine functions. In addition to chemokines and chemokine receptors residing in the brain system, the molecules have critical roles in the maintenance of the CNS homeostasis through autocrine or paracrine activity [22]. Elevated serum levels of chemokines in major bipolar disorder, depressive disorder, and schizophrenia have previously been reported [9]. Chemokines are suggested as biomarkers in pathophysiology of psychiatric disorders [23].

Chemokines and neuroinflammation

Inflammation in the brain, known as neuroinflammation, is a process that lead to activation of microglia that secrete inflammatory cytokines, free oxidative radicals, and chemokines [24, 25]. Chemokines recruit peripheral immune cells into damaged areas of the CNS, subsequently amplifying inflammation in the CNS and triggering adaptive immune responses [26]. Blood source chemokines can increase the permeability of the blood–brain barrier (BBB), and may destroy its integrity to accelerate the entrance of peripheral leukocytes to the brain inflammation site [20, 27]. The activation of chemokine receptors impairs neuronal activity in the CNS by affecting neurotransmitter releasing mainly through inhibiting calcium channels in nerve terminals [28].

CCL11 (eotaxin-1)

The eotaxin family comprises chemokines including CCL11 (eotaxin-1), CCL24 (eotaxin-2), and CCL26 (eotaxin-3), which are chemotactic agents for eosinophils and take part in innate immunity. CCL11, or eosinophil chemotactic protein (eotaxin-1), can selectively lead to the recruitment of eosinophils into inflammatory sites. Elevations in CCL11 levels occur in allergic reactions, allergic rhinitis, asthma, and other eosinophil-related conditions [29]. T-helper 2 cytokines, such as IL-4, IL-10 (Interleukin-10), IL-13, complement factors, and immune complexes, induce CCL11 production by eosinophils, T and B cells, macrophages, endothelial cells, fibroblasts, epithelial cells, chondrocytes, microglia, keratinocytes, and smooth muscle cells [29–31]. CCL11 is synthesized by microglia, and in addition transported to the brain by BBB [32]. Previous studies have shown that CCL11 reduces neurogenesis and is related to aging [33]. Elevations in CCL11 have been demonstrated in neuroinflammatory disorders like multiple sclerosis (MS), in neurodegenerative situations such as Alzheimer’s disease, and in psychiatric disorders such as major bipolar disorder, depression, and schizophrenia [29, 30, 34–36]. CCL11 binds to its main receptor; CCR3 is expressed on mast cells, eosinophils, Th2 lymphocytes, and keratinocytes and is demonstrated as one of the most important cytokines involved in tissue inflammation. CCL11 may be important in the pathophysiology Alzheimer’s disease and depression in age-old persons [33, 37]. As the association between psychiatric disorders and CCL11 and its possible pathologic role in these situations, it may be used as a neuroinflammation biomarker and therapeutic target in these disorders.

CCL11 in neuroinflammation and neurodegeneration diseases

CCL11 concentration is raised in the CSF and sera of patients suffering from neuroinflammatory disorders but the exact function of CCL11 in the CNS is not completely clear [33]. Activated astrocytes and microglia predominantly release and express CCL11 and its main receptor (CCR3), respectively [38]. CCR2 and CCR5 are the other CCL11 receptors with a lower affinity than CCR3 [39]. Microglia as macrophage-like cells in the CNS are capable to initiating inflammatory response [40]. Glial activation contributes to neuronal death in neurodegenerative diseases [41, 42]. CCL11 released from activated astrocytes or BBB crossed source in systematic infections and inflammation can promote the upregulation of nicotinamide adenine dinucleotide phosphate-oxidase 1 (NOX1) and production of ROS by microglia that induce neuronal death [43, 44]. Blood originated CCL11 can be produced by leukocytes, fibroblasts, chondrocytes, and endothelial cells, in systemically inflammation [45]. Parajuli et al. showed a possible mechanism independent of eosinophil recruitment of CCL11-mediated neuronal dysfunction through activated glial cells. [46].

Previous studies have indicated that increased (sera or CSF) CCL11 levels may contribute to the pathogenesis of MS by promoting eosinophil infiltration and subsequent neural damage in the affected areas [47, 48]. The CCL11
is related to MS duration and is a potential biomarker for the disease progression. Elevated localization of eosinophils and various eotaxins concentration was found in disease-associated lesions [49–53].

In Parkinson’s disease (PD), neuroinflammation and loss of neuronal connections are the main cause of neural impairment, and loss of brain cells. The accumulation of misfolded α-synuclein protein in the damaged cells, proteasomal and lysosomal dysfunction and reduced mitochondrial activity [53–55]. Iron accumulation with the misfolded α-synuclein protein could be due to oxidative stress, protein aggregation, or neuronal death [56]. In the regulation of the release and transmission of neurotransmitters and in the growth and development of related neurons some chemokines demonstrated have major roles. In addition, PD is related to immune and inflammatory mechanisms and suggested the role of chemokines in the underlying mechanisms. Administration of anti-CCL11 neutralizing antibody reduced the production of pro-inflammatory factors and the CD4+ / CD8+ T cells infiltration in the substantia nigra of mice, and improves motor symptoms in PD mice [57].

In Alzheimer’s disease (AD), microglial activation and neuroinflammation contribute to hippocampal atrophy. The hippocampus region is critical in learning and memory processes and is one of the strongest predictors of disease progression [58]. Eotaxin-1 levels increase throughout life and contribute to the possibility that CCL11 is an effector molecule in aging, the main risk factor for developing AD. Previous studies have reported the elevation and importance of CCL11 with age at the onset of AD [33]. Among carriers of the CCL11, A23T mutation in the region of eotaxin-1 binding and activation of its receptor CCR3 modulate eotaxin-1 signaling and neuroinflammation [59].

CCL11 and COVID-19 infection

Elevation of CCL11 levels in the sera and CSF of patients with neuroinflammatory disorders such as neuromyelitis optica, multiple sclerosis, and HTLV-1-associated myelopathy have been previously demonstrated [49, 60]. Many reports have shown the elevation of chemokines in COVID-19 patients [50, 61]. Determination of CCL11 with CBC indexes may be helpful in the early prediction of the severity, diagnosis, and follow-up of critical COVID-19 patients in the course of the disease [62]. In COVID-19 infection, immune responses mediated by T-helper 2 are related mainly to CCL11 and IL-4 and the recruitment of NK cells, eosinophils, and macrophages, a similar immune response to that seen with other respiratory viruses [63]. Analysis of soluble biomarker levels in COVID-19 cases ranging from mild/moderate to critically severe revealed that elevations in CCL11 and CCL26 levels were correlated with disease severity [62]. As physiosomatic symptoms are related to eotaxins, they, especially CCL11, may play a role in COVID-19 neurologic syndrome. Previous evidence supports this hypothesis, with special emphasis on the role of eotaxin-1 in neural demyelination [50]. It is recommended that eotaxin-11 levels be monitored as a predictor for COVID-19 neurologic syndrome.

Conclusion

It has been documented that in systematic inflammation, cytokines may damage the BBB and potentially play a role in neurological complications. CCL11 is synthesized by microglia, and in inflammatory and cytokine storm conditions, its blood-originated source could transport across the BBB and enter the brain [32]. Previous studies have shown that CCL11 reduces neurogenesis and is related to aging [33]. Elevated CCL11 levels have been demonstrated in neuroinflammatory disorders like multiple sclerosis (MS), in neurodegenerative situations such as Alzheimer’s disease, and in psychiatric illnesses such as major depression, bipolar disorder, and schizophrenia [29, 30, 34–36]. Considering the recent COVID-19 pandemic, it seems to be too soon to describe the full clinical features of COVID-19 neurological syndrome; however, published evidence shows an increased number of patients with neuropsychological effects of COVID-19, such as various degrees of depression, sleep impairment, and anxiety, in the survivors, irrespective of severity [7]. With regard to the role of CCL11 in physiosomatic and neuroinflammation, it may be valuable to analyze the level of this chemokine in the sera or SCF of COVID-19 patients. Elevated levels of CCL11 may be used to predict neuroinflammation related post-COVID-19 complications, and using the chemokine modulators may help to lessen the neurologic complications in these patients.

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Declarations

Conflict of interest The authors declare that they have no competing interests.

Ethical approval As the current study was a review and hypothesis, there was no ethics committee to approve the study.

Consent for publication The authors have consent for publication.
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