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REVIEW

Impact of Childhood Adversity, as Early Life Distress, on Cytokine Alterations in Schizophrenia

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Abstract: Even though inflammation theory has been introduced in the pathophysiology of psychosis almost a century ago, many of its aspects have remained unelucidated. Numerous studies have shown cytokine dysregulation in schizophrenia and a predominance of pro-inflammatory cytokines, but on another side, various cytokines in a pro-inflammatory group have different trends in all subtypes of schizophrenia. Alterations are also present in anti-inflammatory and regulatory cytokines, but findings are still not consistent. On the other hand, it is well known that abuse and neglect in childhood may be predictors of psychotic disorders, and childhood adversity is also associated with alterations of the immune and inflammatory response (through various mechanisms including HPA dysregulation as well). This review aims to analyze conducted studies and elucidate the link between childhood abuse, schizophrenia, and cytokine alterations. Putting together this complex psycho-immunological puzzle for the subgroup of schizophrenia-diagnosed patients with distinct immunological abnormalities and a history of childhood abuse can help us to answer the question about the future treatment of these patients.

Keywords: childhood neglect, childhood abuse, cytokines, schizophrenia

Understanding the Role of Cytokines in Brain Functioning

The role of the immune system in the pathophysiology of schizophrenia was proposed over a century ago.[1] It has been shown that patients with schizophrenia have innate and adaptive immune system abnormalities. The majority of recent literature focuses on cytokine changes due to their role in immune cell signaling. Cytokines are proteins of small molecular mass that play a role as mediators in the stimulation or interaction between the cells of the immune system.

According to the role in the immune reaction, or the type of cell that creates them, cytokines are divided into several groups: interleukins (IL), chemokines, tumor necrosis factors (TNF), interferons (INF) and transformation growth factors (TGF).[2] Today, more than 60 types of interleukins are known, named from IL-1 to IL-38.[3] Cytokines are produced by effector CD4+ T helper (Th) lymphocytes, crucial components of the adaptive immunity, to stimulate or interact with other leukocytes, including Th cells. Of note, many cytokines are produced by innate immune cells, such as monocytes and neutrophils. Due to their role in the inflammatory reaction, cytokines are listed into two groups: pro-inflammatory and anti-inflammatory cytokines. Major pro-inflammatory cytokines are IL-1, IL-2, IL-6, INF-γ and TNF-α. Most researched anti-inflammatory cytokines include IL-4, IL-10, IL-11, IL-13, and TGF-β.[4] Pro-inflammatory cytokines activate cyclo-oxygenase-2 (COX-2), increase the level of prostaglandin E2 (PGE2), activate leukocytes involved in the inflammation process, and stimulate the inflammatory response. Pro- and anti-inflammatory cytokines interact with each other to maintain homeostatic balance, but with chronic inflammation or tissue damage, the peripheral production of pro-inflammatory cytokines increases, and anti-inflammatory cytokines decrease, which can result in the development of various disorders including psychiatric ones.[5]

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Peripheral cytokine production is largely regulated by cortisol secretion, as a result of activation of the hypothalamic–pituitary–adrenal (HPA) axis. When cortisol levels are low, the production of pro-inflammatory cytokines increases, while high cortisol concentrations inhibit the synthesis of peripheral pro-inflammatory cytokines.[6] Neurotransmitters regulate peripheral cytokine synthesis via cortisol levels. For example, acetylcholine (Ach), dopamine (DA), and noradrenaline (NA) promote the secretion of corticotropin-releasing hormone (CRH) in the hypothalamus, while serotonin (5-HT) inhibits the secretion of CRH in the hypothalamus and consequently of adrenocorticotropic releasing hormone (ACTH) in the pituitary gland.[7,8] In addition, the autonomic nervous system regulates the production of peripheral cytokines. Parasympathetic directly inhibits cytokine production via the vagus and acetylcholinergic transmission, while sympathetic indirectly via noradrenergic stimulation of peripheral sympathetic ganglia.[9]

Cytokines synthesized outside the central nervous system under physiological conditions cannot pass through the blood–brain and blood–cerebrospinal fluid (CSF) barriers due to their hydrophilicity. However, the permeability of the blood–brain barrier increases in pathological conditions, which allows cytokines from the blood to find their way into the extracellular fluid of the brain.[10,11] Moreover, IL-1 receptors are densely distributed in glial cells near arterioles or the choroid plexus,[12] suggesting a possible role in the communication of IL-1 receptors in the CNS with mediators from the peripheric circulation. In addition, cytokines synthesized in the periphery can pass into the CNS by passive diffusion across the circumventricular regions (absent blood–brain barrier regions) and neural transport by the vagus.[6] Finally, the direct connection of the CNS and the immune system via lymphatic vessels was confirmed by the discovery of functional lymphatic vessels in the CNS.[13]

In physiological conditions, the central synthesis of cytokines is limited to T cells, astrocytes, and microglia, but in special circumstances, they can also be secreted by neurons.[14] Cytokine production takes place in different regions of the neuro-network – in the hypothalamus, hippocampus, cerebellum, basal ganglia, and prefrontal regions.[15] In the same regions, there is a distribution of receptors for centrally synthesized cytokines such as IL-1, IL-2, IL-6, and TNF-α. The role of central cytokine production has not yet been fully explored. Pro-inflammatory cytokines IL-1, L-6, TNF-α, and INF-γ are involved in the development of nerve tissue, neuroplasticity, synaptogenesis, and reparative mechanisms.[16] In addition, pro-inflammatory cytokines promote nerve necrosis after traumatic nerve tissue injury.[17]

Cytokine Alterations in Patients with Schizophrenia

Central immunological changes in patients with schizophrenia are well known for the last two decades. For example, it has been shown that subclinical neuroinflammation in the CNS can lead to changes in white matter substrate, changes in connectivity, and subsequent onset of schizophrenia symptoms.[18]

Although knowledge in this field is rapidly increasing, cytokine changes are the most complex part of the puzzle to understand. We now have a growing number of studies that explore changes in cytokine levels in schizophrenia, but we still do not have consistent and univocal findings. Numerous meta-analyses and systematic reviews suggest cytokine dysregulation in schizophrenia and a predominance of pro-inflammatory cytokines in the serum of patients.[19–25] Despite these findings regarding principally the three most studied pro-inflammatory cytokines: IL-6, IL-1β, and TNF-α, some studies did not confirm significantly higher levels of IL-6,[26] IL1- β[27] and TNF- α[28] in patients with schizophrenia. Concentrations of IL-2 do not alter in patients with schizophrenia according to the majority of studies.[23] Regarding levels of interferon γ (IFN-γ) as also one of the principality pro-inflammatory cytokines, several studies reported either no alteration[29,30] or higher levels,[19] but there are also rare findings on decreased levels of IFN-γ.[31] Due to these data that various cytokines in a pro-inflammatory group have different trends in all subtypes of schizophrenia, we cannot state that pro-inflammatory cytokines have higher levels in patients with schizophrenia.

Similar inconsistent results are regarding anti-inflammatory cytokines: the majority of findings suggest no alteration in IL-4 levels,[20,32] while few of them report decreased levels of IL-4[33,34] or increase ones.[35] Goldsmith et al found reduced levels of IL-10 in their meta-analysis,[20] in contrast to other meta-analyses reporting no alteration in levels of IL-10 in patients with schizophrenia[36] and reports showing elevated levels of this cytokine.[37] Similarly, concentrations of IL-13 also differ, although it has been reported elevated levels in adults with multiple episodes of schizophrenia.[38,39] TGF-β is also one of the cytokines with anti-inflammatory activity but with regulatory function as well. Meta-analysis of Goldsmith found elevated levels of TGF-β in the first psychotic episode (FEP) patients.[20] Also, other studies in chronic patients experiencing

an acute relapse showed higher levels of TGF-β.[29] No changes in concentration of this cytokine were also presented in some publications[40] as well as decreased levels of TGF-β in chronic treatment-resistant patients.[32]

It is also very important to emphasize that alterations in cytokine levels are associated with the severity of clinical symptoms and that alterations differ between first-episode psychosis patients, acutely relapsed inpatients, and chronic patients.[25]

All these findings indicate that we have to search for some other, more specific, causes of this alteration that will help us to put together this complex psycho-immunological puzzle in patients with schizophrenia. In the next lines, we will focus on childhood abuse as a few authors already indicated how childhood adverse experiences may lead to a constellation of specific ecophenotype,[41] subtypes of patients within the same group of disorders, eg, schizophrenia.

Childhood Abuse or Neglect, Early Life Distress, and Schizophrenia Risk

Childhood abuse or neglect includes all types of physical and/or emotional ill-treatment, sexual abuse, neglect, negligence, and commercial or other exploitation, which results in actual or potential harm to the child's health, survival, development, or dignity in the context of a relationship of responsibility, trust or power.[42] Maltreatment in childhood may occur once as acute distress, or in the form of a chronic stressor, and can be present in one or multiple forms.

Childhood abuse or neglect is among the most powerful risk factors for triggering varieties of psychiatric disorders. The incidence of child abuse trauma is very high in users of psychiatric services. Some published data suggest that approximately 50% of persons using psychiatric services mention experiences of abuse in childhood.[43] Some novel data suggest that around 61% of patients with the first psychotic episode reported having experienced some kind of childhood trauma.[44]

Early life distress can influence the development of the hypothalamic–pituitary–adrenal (HPA) axis.[45] If adverse experience occurs only once, as a strong acute stressor, HPA axis function will probably be reflected through hypercortisolemia. On the other side, childhood maltreatment usually tends to last or repeat and is associated with blunted cortisol levels. Furthermore, exposure to childhood adversity was associated with alterations of an immune and inflammatory response (due to HPA dysregulation as well) and stress-related accelerated telomere erosion.[46] In line with these findings, neuroimaging studies revealed changes in the brain structure of hippocampus, amygdala, corpus callosum, vermix, and in different areas of cortex[47–50] and also inhibition of maturation in neuron work in abused children.[51]

The impact of adverse childhood experiences on the development of psychosis and schizophrenia was confirmed by several studies and meta-analyses.[52–55] Meta-analyses of Matheson et al suggest increased rates of childhood adversity in schizophrenia compared to controls with medium-to-large effect.[54] Also, some novel data are stating positive associations between exposures to overall or specific subtypes of childhood adversity and experiencing or persistence of psychotic experiences.[56,57] Chase et al demonstrated a positive correlation between positive and negative syndrome scale (PANSS) positive symptoms and adverse childhood experiences (ACEs) total scores, including ACEs abuse, ACEs-neglect, and ACEs-dysfunction in patients with schizophrenia.[58] Patients with psychotic disorders who experienced childhood abuse share some common clinical characteristics, such as a higher hospitalization rate, a more continual course of the disorder, earlier onset of symptoms, more severe episodes, greater risk of suicide and substance disorders, etc.[59]

Although every type of abuse or neglect comes with a higher risk for psychosis, some subtypes are more often shown as predictors in literature. For example, studie by Chase and co-writers showed that patients with schizophrenia experienced the occurrence of ACE compared to non-clinical controls, especially sexual and physical childhood abuse.[58] Read and Larkin suggested a dose-dependent relationship between childhood sexual or physical abuse and psychosis later in life.[52,53] Grindey and his team recently published that, in a systematic review of literature, they found a significant relationship between hallucinations and childhood sexual and physical abuse.[60] It is important to highlight that individuals with multiple adverse events in childhood carry an elevated risk of experiencing positive psychotic symptoms.[57]

Cytokine Alteration in Patients with Schizophrenia Who Were Exposed to Childhood Abuse Trauma

Although first evidence emerged from animal models more than half a century ago, later observational human studies confirmed that childhood trauma affects later immune functioning. For example, Dance et al found that cumulative exposure to childhood maltreatment was associated with a significant elevation in inflammation levels 20 years later.[61] Not too many researches tried to explain the link between childhood abuse/adverse experiences, altered cytokine profile, and schizophrenia. Summarizing this scientific field, a few novel studies gave us important results concerning this relatedness.

The association of childhood adversity/trauma, immunity, and psychosis was examined in the study of Chase et al.[58] They have shown that adversity in childhood correlates with IL-6, and separately that adverse childhood experience is in positive association with positive symptoms of schizophrenia. Authors assume that childhood trauma, through alteration of IL-6, may be a risk factor for schizophrenia and that those patients may represent a distinct psychiatric phenotype. The pro-inflammatory phenotype was also demonstrated in research of Dennison et al, where patients suffering from schizophrenia with childhood trauma had higher levels of IL-6 and TNF-α than patients without trauma and healthy controls.[62] They assumed that childhood trauma drives changes through epigenetics. Novel research on gene methylation changes due to different types of trauma in childhood does confirm that.[63] Furthermore, in addition to epigenetics, early experience can shape the relationship between the brain and immune system,[64] and environmental factors, such as childhood maltreatment, though affecting the immune system have been related to the development of schizophrenia.[61]

In a similar study associations between schizophrenia and IL-6, TNF-α, and CRP were explored compared to healthy controls (HC), with an assessment of the Childhood Trauma Questionnaire.[65] They showed higher levels of IL-6, TNF-α, and CRP in patients with schizophrenia compared to the HC group, as well as a positive association between CRP and sexual abuse in patients with schizophrenia. Among the first researchers that explored this link, Aas et al demonstrated that childhood trauma altered immune activation via elevated highly sensitive CRPa in a large sample of patients with schizophrenia.[66] They emphasize that as patients had more types of abuse in childhood experience – CRP was higher. In the publication of Li et al, plasma concentrations of IL-6 and TNF-α were significantly elevated in patients with early-onset schizophrenia compared with healthy subjects, and plasma IL-6 and TNF-α concentrations were closely related to childhood maltreatment.[67] These results partly explain the previous thesis that pro-inflammatory cytokine gene complexes may be linked to an increased likelihood of developing schizophrenia.[68] Different types of trauma trigger different immunological mechanisms and lead to pertinent alterations in sensitive periods of preadolescent brain maturation,[69] making the susceptible field to the development of different psychopathologies. It is also important to emphasize that IL-6 and TNF-α can trigger hypothalamic-pituitary-adrenocortical activity,[70] suggesting that chronic inflammation contributes to the aberrant stress response found in patients with schizophrenia.[71]

Two other studies explored this link but comprised multiple cytokine profiles.[72,73] Foiselle et al investigated levels of 18 different cytokines among the 310 adult patients who meet DSM-IV criteria for schizophrenia or schizoaffective disorders, with 47% of those having suffered from moderate-to-severe childhood abuse. Results showed elevated levels of IL-6, IL-7, IL-12/23 p40, and IL-16 moreover lower levels of TNF-α were associated with metabolic syndrome. Unfortunately, they did not investigate the correlation with childhood abuse.[72] Corsi-Zuelli and colleagues examined cytokine levels (IL-1β, IL-6, TNF-α, IFN-γ, IL-4, IL-10, and TGF-β) in 114 patients with FEP, 57 unaffected biological siblings of FEP patients, and 251 community-based controls, with assessment for childhood abuse. They have found that FEP patients had a higher pro- and anti-inflammatory cytokine profile (IL-1β, IL-6, TNF-α, IL-10, and TGF-β), which was not observed in unaffected siblings. Physical childhood abuse was associated with increased levels of TGF-β in FEP patients, but they did not find similar findings for other cytokines.[73] Higher TGF-β, with both regulatory and anti-inflammatory function, is a potentially very important part of the puzzle that can explain a much older thesis on how chronic stress may be associated with more permanent inflammatory changes.[74] Having in mind the IL-6 and TGF-β interplay, it is possible to hypothesize that higher TGF-β levels could be a consequence of long-term increased IL-6 concentrations.[75]

Our knowledge is significantly updated with a novel multidisciplinary study (GAP study) carried out in South London, which recruited 410 first episode of psychosis patients and 370 controls that have demonstrated how biological pathways involved in the stress response (both HPA axis and immune system) provide important mechanisms linking risk factors (such as childhood adversity) to the development of psychotic symptoms.[55] TNF- α levels were particularly high in FEP patients with a history of childhood trauma.[76] Also in FEP patients, Hepgul et al showed higher serum levels of C-reactive protein in patients with experience of childhood sexual abuse than both healthy controls and patients without childhood sexual abuse.[77] Previously, researchers of GAP study showed that increased levels of IL-6, as well as low levels of the neurotrophic factor BDNF and high levels of cortisol during the day, independently affected hippocampal volume in FEP patients.[78,79] Higher IL-6 levels were associated with smaller left hippocampal volume,[79] directly implicating influence on brain architectonic changes.

Several limitations of these studies should be considered. These studies are rare and include relatively small sample sizes. Mostly, patients received respectable doses of medication. Due to this, it is impossible to exclude the effects of illness duration and pharmacodynamic effects of medication on results. Previous meta-analyses suggest different parameters of inflammation have different sensitivity to medication.[80] Simply, the inclusion of drug naïve patients would have been an advantage in this regard. At the same time, it is noteworthy, the possible use of anti-inflammatory drugs was not recorded. Moreover, we should bear in mind that these studies measure trauma exposure retrospectively in samples of adults which lay questions on recollection bias (especially since the age of onset or duration of trauma was not assessed). Finally, occasionally several important factors have not been recorded such as body mass index, nicotine consumption, and comorbid medical diseases that may have contributed to the observed findings.

Treatment Implications

The ultimate question is whether observed immunological abnormalities in patients with schizophrenia have therapeutic potential. First, treatment with anti-inflammatory drugs as an adjunct to standard antipsychotic therapy in patients with schizophrenia is nothing new. Several drugs have been tried (ie, celecoxib, minocycline), but studies are usually small, and we need large, double-blind, multicenter trials. Moreover, even Bleuler wrote about "a group of schizophrenia", not about schizophrenia, clearly meaning that there is not only one, etiologically homogenous disease but rather a group of etiologically different diseases with a probable common final pathway resulting in clinically diagnosed schizophrenia. Having this in mind, it is obvious that we have to divide patients into more precious groups based on their immune phenotype with a history of childhood abuse or neglect. Finally, these considerations about the role of immunoactive drugs in the treatment of schizophrenia can be viewed as a part of the fundamental question of the future of the treatment of schizophrenia, ie, do we need a magic bullet or a magic shotgun?[81] Clearly, establishing the therapeutic efficacy of immunoreactive drugs in schizophrenia would be a highly specific "bullet" for which treatment would be justified and indicated only in a subgroup of patients with distinct immunological abnormalities and a history of childhood abuse.

Conclusion

Despite such a long time since inflammation theory has been introduced in the pathophysiology of psychosis,[1] many of its aspects have remained unelucidated. For several years now, childhood trauma/adverse experience has been explored as a third important variable to additionally substantiate the hypothesis of a link between immune alterations and schizophrenia. Despite the big GAP multidisciplinary study,[55] we have found only 7 new original researchers regarding this connection.[58,62,65–67,72,73] All studies are published in the last 10 years and the majority of them in the last 4 years. Still, so far pro-inflammatory cytokines have been much more studied in this link, while regulatory and anti-inflammatory were investigated much less.[73] On the other side, we still have a crucial question to answer: does trauma leads to immune changes and the occurrence of psychopathology that coincide, or trauma triggers immune alteration that later drives the occurrence of psychopathology? The third option is that people with trauma experience are more susceptible to developing psychopathology (both dynamically and biologically) and that immune instability is just coinciding and contributing as a cofactor in the development of psychotic disorders. Present knowledge indicates that it is more likely that trauma induces immune alterations that become permanent and that immune alterations drive the pathogenesis of psychotic disorders. Nevertheless, we have enough strong evidence to promote the hypothesis that

childhood maltreatment is associated with permanent immune alterations and the development of schizophrenia. We now have parts of this complex psycho-immunological puzzle for the subgroup of schizophrenia-diagnosed patients with distinct immunological abnormalities and a history of childhood abuse that can help us to answer the question about the future treatment of these patients and promote a strong need for further research in this area.

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