Cytokine Imbalance in Treatment-Resistant Schizophrenia

Subjects: Neurosciences

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Treatment-resistant schizophrenia (TRS) is an important and unresolved problem in biological and clinical psychiatry. Approximately 30% of cases of schizophrenia (Sch) are TRS, which may be due to the fact that some patients with TRS may suffer from pathogenetically “non-dopamine” Sch, in the development of which neuroinflammation is supposed to play an important role. There are many factors leading to a chronic neuroinflammatory process in TRS.

Keywords: cytokines ; cytokine status ; treatment-resistant schizophrenia

1. Changes in the Functional Activity of Microglia in Treatment Resistance Schizophrenia

Microglia account for 10–20% of all cells found in the brain and are an important component of immune system of central neural system (CNS) [1]. Microglia play an important role in neuroinflammation, providing protection in the event of damage or disease to the CNS. When neuroinfection occurs, activation of microglia, synthesis and release of central pro-inflammatory cytokines, which leads to various mental and behavioral disorders [2]. There is now evidence that aging [3], neurodegeneration [4] and stress [5] lead to “sensitization” or “priming” of microglia, which subsequently causes an exaggerated immune response. Exposure of primed microglia to, for example, minor systemic inflammation leads to proliferation and increased production of pro-inflammatory cytokines [6], which, in turn, can exacerbate the immune response in the CNS and be expressed in a change in behavior [7]. One drug thought to reduce microglial activation is minocycline, a broad-spectrum tetracycline antibiotic with broad anti-inflammatory activity [8]. First and second generations of APs regulate the secretory profile of microglia in vitro. They inhibit the release of proinflammatory cytokines from activated microglia and alleviate oxidative stress [9]. However, some recent reports have shown conflicting results on the effect of some APs on the release of pro-inflammatory cytokines [10]. At the same time, not all antipsychotics (APs) have an anti-inflammatory effect, which may be due to the role of microglia in the development of TRS.

2. Sensitization or Kindling in Treatment Resistance Schizophrenia

“Firing”/“sensitization” refers to the process by which the initial immune response to some stimulus (stress or infection) raises or lowers the threshold to respond to the next exposure to the same stimulus. At the same time, a weaker stimulus is required to activate the immune response or release cytokines than with the initial exposure to an unfavorable (damaging) factor. It is believed that the memory function of the acquired immune system is responsible for this process [5]. The action of factors such as systemic inflammation or stress on healthy people leads to the stimulation of the immune response. As a result, cell proliferation is activated, an increase in the production and release of pro-inflammatory cytokines is observed [11]. “Firing up”/“sensitization” supports the hypothesis that neuroinfection in early childhood may lead to increased release of cytokines when the immune system is activated later in life. These processes lead to neurotransmitter disorders. Stress induces a pro-inflammatory immune response in CNS. However, this is usually reduced after a stressful event. Psychopathological symptoms and neuroinflammation are associated with the immune response of CNS cells to stress, and neuroinflammation is involved in stress-related behavioral changes induced by cytokines and mediated by neurotransmitters. Studies have found that after exposure to chronic stress or repeated stressful events, the threshold for physiological responses of the CNS to stress decreases. As a result, less stimulus is enough to activate an immune or neurotransmitter response. In an animal study, it was shown that with age, the brain is in a sensitized state and produces more cytokines for inflammatory stimuli than the brain of young animals [6]. Repeated exposure to pro-inflammatory cytokines leads to increased neurotransmitter responses [12] as, for example, with tumor necrosis factor alpha (TNF-α) [13]. Stress causes activation and proliferation of microglia in the CNS, which may possibly mediate these cytokine effects [6]. Chronic stress is known to affect the glutamatergic system, ionotropic and metabotropic glutamate

receptors and excitatory amino acid transporters [14], which may also play a role in the development of TRS, as it is associated with higher levels of glutamate in the anterior cingulate cortex [15].

3. Vulnerability-Stress-Inflammation in Treatment Resistance Schizophrenia

The risk of developing TRS increases with stressful life events or psychological stress, especially those that act at key periods in the development of the CNS. The Sch vulnerability-stress model was first proposed by Zubin and Vesna [16], who suggested that stress above the vulnerability threshold in humans contributes to the development of a psychotic episode. It is important to add inflammation to this model, forming the vulnerability-stress-inflammation model, since neuroinflammation plays an important role in the pathogenesis of TRS and can in turn be caused by stress [17]. For example, if an inflammatory response in the CNS is stimulated in a second trimester of pregnancy or offspring while the CNS is still developing, the offspring may be a risk of developing Sch. Animal studies have shown that exposure to stress at an early age leads to an increase in the level of pro-inflammatory cytokines [18], which play an important role in the development of Sch and TRS. Vulnerability-stress-inflammation-induced immune dysregulation is associated with dysregulation of many neurotransmitter systems that APs cannot therapeutically address. Thus, the development of TRS is likely associated with stress-induced inflammation [19].

4. Prenatal, Perinatal and Postnatal Infection in Treatment Resistance Schizophrenia

Existing epidemiological studies give us the idea that prenatal exposure to maternal infection is associated with an increased risk of Sch in the offspring [20]. The risk of developing Sch may be related to the direct effects of neuroinfection (e.g., disruption of structure due to cyst formation, exposure to inflammatory factors) as well as neurochemical changes such as increased dopamine levels associated with poor performance. Catechol-O-methyl transferase (COMT) and increased dopamine synthesis caused by *Toxoplasma gondii* infection [21]. Exposure to viruses and other infectious agents—influenza, herpes simplex virus type 2, Coronavirus Disease 2019 (COVID-19) during pregnancy and at the time of conception—is associated with a greater risk of psychotic disorders [22]. Given the changes in pro-inflammatory cytokine production in pregnant women with COVID-19, schizophrenic and psychotic disorders may potentially be a long-term risk in the offspring of pregnant women who have experienced COVID-19 [23]. Animal studies have also provided evidence for the role of pre- and perinatal infections in the later development of Sch [24]. For example, after prenatal exposure to viruses, offspring show typical symptoms of Sch, such as cognitive impairment or startle reflex abnormalities [25]. Maternal bacterial infection during pregnancy is closely associated with the development of psychosis in the offspring and varied depending on the severity of the infection and the sex of the offspring. At the same time, the effect of a multisystem bacterial infection was almost two times higher than that of a less severe localized bacterial infection [26]. Of interest are studies that have demonstrated the association of Sch development with prenatal or early childhood exposure to various viruses [27], respiratory infections [28] and infections of the genital organs or reproductive tract [29]. Because Sch develops more frequently during adolescence or adulthood, it is important to establish a possible mechanism for the association between early infection and Sch in adults. Studies in animal models show that early infection or immune activation affects several processes of neurogenesis, including dopaminergic and glutamatergic neurotransmission [30]. The study of bacterial [26] and some other infections in humans [31] are examples that highlight this connection. The risk of developing TRS is also indicated by an increased level of C-reactive protein (CRP) or cytokines in childhood [32]. In addition, neuroinfection at a later age has been shown to be associated with an increased risk of developing TRS. A large epidemiological study conducted in Denmark showed that autoimmune disorders, as well as severe infections, increase the risk of developing Sch and Sch spectrum disorders. This is especially true for patients with both risk factors for TRS [33].

5. Cytokine Imbalance in Treatment Resistance Schizophrenia

Based on the meta-analyses by Momtazmanesh et al. [34], it is possible to conditionally classify cytokines according to their serum levels in patients with TRS into four groups: group 1—elevated cytokines, including interleukin 6 (IL-6), tumor necrosis factor alpha (TNF-α), interleukin 1 beta (IL-1β), interleukin 12 (IL-12) and transforming growth factor beta (TGF-β); group 2—unchanged cytokines, including interleukin 2 (IL-2), interleukin 4 (IL-4) and interleukin 17 (IL-17); group 3—elevated or unchanged cytokines, including interleukin 8 (IL-8) and interferon gamma (IFN-γ); group 4—interleukin 10 (IL-10) with increased, decreased and unchanged serum levels. However, this grouping is not unambiguous and includes mainly pro-inflammatory cytokines. In addition, the authors did not provide an analysis of the relationship between the levels of pro-inflammatory and anti-inflammatory cytokines in patients with TRS.

Higher serum levels of pro-inflammatory cytokines are characteristic of both patients with the first episode of Sch and patients with relapse and TRS, compared with the control group [35]. IL-1β, IL-6 and TGF-β were elevated at the first psychotic episode, and Sch flare normalized after AP treatment. Conversely, the levels of IL-12, IFN-γ, TNF-α and soluble interleukin 2 receptor (sIL-2R) remained elevated during exacerbations and during AP therapy [36]. A study of interleukins in the cerebrospinal fluid (CSF) showed that the levels of interleukin 6 (IL-6) and IL-8 were increased in Sch, but not significantly increased in affective disorders [37]. A meta-analysis of CSF cytokines showed higher levels of pro-inflammatory cytokines and lower levels of anti-inflammatory cytokines in patients with Sch and TRS [38].

It is known that dopaminergic dysfunction is a significant feature in the pathophysiology of TRS [39]. Interactions between cytokines and neurotransmitters in certain areas of the brain, and also during brain development, are important in the pathophysiology of TRS. Apparently, the pro-inflammatory cytokine IL-1β, which induces the transformation of rat mesencephalic progenitor cells into a dopaminergic phenotype [40], and IL-6, which reduces the survival of serotonergic neurons in the fetal brain, seem to play an important role in influencing neurotransmitter systems in TRS. [41]. Studies have found abnormalities in the cytokine system in patients with TRS [42][43]. There is evidence that the levels of IL-2 and IL-6 were elevated in patients with TRS, which is probably associated with the activation of the inflammatory response system (IRS). Moreover, serum IL-2 or IL-6 and cortisol are positively correlated with Sch, supporting the hypothesis that hypercortisolemia may also be caused by pro-inflammatory cytokines [44][45].

The delicate balance between pro-inflammatory and anti-inflammatory cytokines determines the net effect of a neuroinflammatory response in patients with TRS. Perturbations in this equilibrium can drive the patient defense immune response towards chronic neuroinflammation (pro-inflammatory) or towards healing (anti-inflammatory). Thus, a cytokine imbalance may be beneficial to the patient with TRS by initiating the neuroinflammatory response. However, overproduction or underproduction of pro-inflammatory or anti-inflammatory endogenous mediators (cytokines) may actually be deleterious to the patient with “non-dopamine” TRS. In addition, chronic neuroinflammation, supported by an imbalance between pro-inflammatory and anti-inflammatory cytokines, and persistent dopaminergic neurotransmission disorder can be considered as an overlap syndrome in patients with “dopamine” TRS.

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