Neuroinflammation in Late-Onset Schizophrenia: Viewing from the Standpoint of the Microglia Hypothesis

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Keywords

Late-onset schizophrenia · Microglia · Neuroinflammation · Cytokine · Oxidative stress

Abstract

Schizophrenia develops mainly in adolescence, but late-onset schizophrenia (LOS) is not uncommon. According to the international consensus, schizophrenia which develops over 40 years old is called LOS and psychosis which develops over 60 years old is called very late-onset schizophrenia-like psychosis (VLOS). Compared to early-onset schizophrenia (EOS) that develops before the age of 40 years, LOS and VLOS are reported to be more common in women, and there are clinically clear differences such as less involvement of genetic factors than EOS. This review outlines the abnormalities of the neuroimmune system in the pathophysiology of LOS, especially focusing on the role of microglia.

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Introduction

Schizophrenia is a chronic and serious mental illness that affects about 1% of the total population and imposes significant costs on affected patients and their

families. The main symptoms are psychotic symptoms such as hallucinations and delusions, decreased motivation/spontaneity, and cognitive decline. Generally, it develops from puberty to adolescence, and the male-female ratio is approximately 1:1. Hypotheses such as hyperdopaminergic function in the limbic system, decreased dopaminergic function in the frontal cortex, or decreased excitatory amino acid function have been pointed out, but the etiology of schizophrenia remains unclear. There are many. Although it has been pointed out that genetic factors are involved in schizophrenia, no gene has a strong effect on increasing the risk of developing schizophrenia. It is presumed that schizophrenia develops due to environmental factors in the early life, including the embryonic period, and childhood and adolescents based on a predisposition to schizophrenia. Recent studies have often pointed out that neuroinflammation, or the role of the neuroimmune system, plays an important role in the pathophysiology of schizophrenia. We have conducted studies focusing on microglia, which play a central role in innate immunity in the central nervous system (CNS) and have reported on schizophrenia and neuroinflammation [1, 2]. This article outlines the relationship between neuroinflammation in the pathophysiology of late-onset schizophrenia (LOS).

Table 1. Clinical differences in schizophrenia at each age onset

Features	EOS	LOS	VLOS
Age of onset, years	<40	40–60	>60
Female preponderance	No	Yes	Definitely
Negative symptoms	Definitely	May be	Less likely
Learning	Ok	Ok	Impaired
Retention	Ok	Ok	Impaired
Progressive cognitive deterioration	Yes	Yes	Yes (very high)
Brain structural abnormalities	No	No	Yes
Family history	Present	Present	Weak association
Early childhood maladjustments	Present	Present	Absent
Antipsychotic dosing	Higher	Lower	Lower
Risk of tardive dyskinesia	Present	Present	Very high

Author's modification from Tampi et al. [4]. EOS, early-onset (<40 years of age) schizophrenia; LOS, late-onset (>40 years of age) schizophrenia; VLOS, very late-onset (>60 years of age) schizophrenia-like psychosis.

Characteristics of Senile-Onset Schizophrenia

Psychosis that develops in old age is increasing its clinical importance with the aging of the population. Approximately 60% of senile-onset psychosis is secondary psychosis caused by neurodegenerative diseases, including dementia, prescription drugs, and delirium. Therefore, clinicians must distinguish secondary psychosis from senile-onset schizophrenia. Adolescent onset is common in schizophrenia, but senile-onset schizophrenia is by no means rare. The pathophysiology of LOS varies, and it develops through complex interactions such as biological, psychological, social, and environmental factors. According to the international consensus, schizophrenia which develops over 40 years is called LOS and psychosis which develops over 60 years old is called very late-onset schizophrenia-like psychosis (VLOS). Compared to early-onset schizophrenia (EOS), which develops before the age of 40, LOS and VSOS LP are said to be more common in women and genetic factors are less involved than EOS. In addition, while delusions of reference that occur in relationships with family members and neighbors tend to occupy the center of the disease image, treatment responsiveness and outcomes are generally considered to be good. As shown in Table 1, there are clinically distinct differences among EOS and LOS and VLOS, especially between EOS and VLOS [3–7]. Treatment of LOS requires individual treatment due to its characteristics, especially drug selection in consideration of complications such as lifestyle-related diseases, and appropriate combination of non-drug therapy is also required [4, 8]. In addition, although the necessity of distinguishing senile-onset schizophrenia,

or VLOS from neurodegenerative diseases was mentioned above, it is necessary to keep in mind that schizophrenia itself is a risk factor for developing dementia for long-term treatment [9].

Outlines of the Microglial Hypothesis of Schizophrenia

Microglia, which account for about 10% of the total number of cells in the CNS, are derived from the mesoderm like blood and immune system cells and were thought to be monocyte-macrophage lineage cells. However, it has recently been reported that microglia originate from precursor cells generated in embryonic oval sac and they have a gene expression pattern different from those of bone marrow-derived monocytes and macrophages. As “brain macrophages,” microglia play a central role in the innate immunity of the CNS, and activated microglia are a major source of cytokines and free radicals. There is also the idea of conveniently dividing the direction of activation into tissue-damaging M1 and tissue-protecting M2. Inactivated microglia are called “resting microglia,” and their role has been unknown for a long time, but recent studies have revealed that they also play an important role in the development of the CNS and maintenance of homeostasis and are now called “surveying microglia” [10, 11]. The conceptual scheme of microglia in the pathophysiology of schizophrenia is as shown in Figure 1. At present, the pathophysiology of schizophrenia and the neuroinflammation or neuroimmune system centered on microglia. Regarding the abnormalities of neuroimmune

Fig. 1. Conceptual scheme of the role of microglia in the pathophysiology of schizophrenia. Author's modification from Monji et al. [2]. PAMPs, pathogen-associated molecular patterns; DAMPs, danger-associated molecular patterns; (+), promotion; (-), inhibition; EOS, early-onset schizophrenia; LOS, late-onset schizophrenia.

systems in schizophrenia, the following points are mainly mentioned [10–14]:

1. In schizophrenia, the expression of inflammatory cytokines and related molecules is increased in the initial stage and the acute stage, and decreased after the drug treatment.
2. In a PET study of schizophrenia using a ligand that detects TSPO (translocator protein) that is strongly expressed in activated microglia, microglial activation was significantly enhanced compared to the healthy subject group and these findings are also found in the high-risk group for psychosis.
3. The higher the peripheral blood concentration of CRP, a typical inflammatory marker, the more remarkable the cognitive impairment of schizophrenia.
4. In the postmortem brain of schizophrenia, the density of microglia is significantly higher in the frontal cortex and hippocampus than in the healthy subject group.
5. Infection during pregnancy, malnutrition, and trauma during childbirth increase the risk of developing schizophrenia.
6. Microglia play a major role in “synaptic pruning,” which is important for the pathology of schizophrenia
7. Anti-inflammatory therapy targeting neuroinflammation (with antipyretic analgesics and anti-cytokine an-

tibodies), antioxidant therapy, and minocycline, which has an inhibitory effect on microglial activation, are effective for schizophrenia.

8. Some antipsychotics have a neuroinflammation-regulating effect, especially an inhibitory effect of microglial activation.

According to a report focusing on the relationship between schizophrenia onset in old age and neuroinflammation, high peripheral blood CRP levels increase the risk of developing LOS and VLOS by 6–10 times [15]. In the next section, we will discuss some points that have received particular attention in recent years regarding schizophrenia and neuroinflammation in relation to LOS.

A PET Study of Schizophrenia on Microglial Activation

The aforementioned TSPO has a molecular weight of 18 kDa and was once called a peripheral benzodiazepine receptor. TSPO is abundant in peripheral organs such as the adrenal gland and kidney, and its presence in the CNS is relatively poor. By utilizing the phenomenon that TSPO expression is remarkable in the mitochondria of activated

microglia, PET imaging using a TSPO ligand is performed to detect activated microglia. In a study using [^{11}C] PK11195 as a ligand, van Berckel et al. [16] reported that microglial activation was significantly stronger in the entire gray matter of schizophrenic patients within 5 years after onset of schizophrenia than in healthy subjects. Doorduyn et al. [17] reported that the same ligand was used to significantly enhance microglial activation in the hippocampus of schizophrenic patients. In a study using another TSPO ligand, [^{11}C] DAA1106, Takano et al. [18] reported that the degree of microglial activation throughout the cortex in patients with chronic schizophrenia was not significantly different from that in healthy subjects, while the degree of increased microglial activation has a significant positive correlation with positive symptom scores and duration of illness. In a study using the second-generation TSPO ligand [^{18}F] FEPPA, Kenk et al. [19] reported that no significant increase in microglial activation was observed in comparison to healthy subjects, while these results were due to the effect of antipsychotic drugs on suppressing microglial activation. In a study by Bloomfield et al. [20] using another second-generation TSPO ligand, [^{11}C] PBR28, microglial activation was significantly higher than in healthy individuals, not only in schizophrenia patients, but even in the high-risk group of schizophrenia. In addition, a study using the same ligand by Selvaraj et al. [21] has shown a correlation between increased microglial activation and decreased cortical volume. The above reports support a significant increase in microglial activation in patients with schizophrenia, but recent reports have denied these results [22, 23]. The heterogeneity conundrum of TSPO PET Imaging in psychiatric disorders including schizophrenia and major depressive disorders has been discussed in recent relevant reviews [24, 25]. To our knowledge, there is no microglial PET study focusing only on LOS, but a recent study focusing on changes in microglial activation over time in schizophrenia has shown TSPO binding ability to change with age [26]. Therefore, it is expected that research will progress in cross-sectional and longitudinal comparison of microglial activation changes among EOS, LOS, and VLOS [27].

Microglial Synaptic Pruning and Schizophrenia

Conventionally, inactivated microglia are called “resting microglia,” and their role has been unknown, but recent studies have revealed that they also play an important role in the development of the CNS and the maintenance

of homeostasis. By using the imaging method, using a two-photon excitation microscope, it has been reported that the dynamics of the microglial processes are very dynamic, and that they are constantly retracted within a certain region and that they repeatedly contact with synapses in the live mouse cerebral cortex. In this phenomenon, microglia perform an appropriate management function of synapses called synaptic pruning, specifically, the action of removing synapses that are no longer needed during the developmental stage of the CNS [10, 28–30]. Therefore, the abnormal conditions of synaptic pruning carried by microglia and its correction are considered to be targets for the treatment of a wide range of neuropsychiatric disorders [10, 30]. Sekar et al. [31] found that microglial synaptic pruning is regulated by complement C4, and that the genetic polymorphism is involved in the risk of developing schizophrenia. The stronger the complement C4 activity is, the higher the risk of developing schizophrenia is. In addition, excessive synaptic pruning in schizophrenia has been demonstrated by a tissue model derived from the schizophrenic brain [32]. Excessive synaptic pruning during the onset of schizophrenia is considered to be an important target for suppressing the onset of the disease and delaying the progression of the disease. Interestingly, this excessive synaptic pruning phenomenon has also been found in Alzheimer’s disease [33]. Traditionally, there have been discussions on the pathophysiology of schizophrenia from the perspective of “accelerated aging” [34–36] and a recent report suggested the involvement of microglia in these processes [26]. Excessive synaptic pruning phenomenon will thus be important targets for the diagnosis and treatment of LOS in the future.

Possibility of Schizophrenia Treatment Targeting Neuroinflammation

If neuroinflammation contributes to the pathophysiology of schizophrenia, the effect of anti-inflammatory therapy is naturally expected. Non-steroidal anti-inflammatory drugs, antioxidants, anti-cytokine therapy targeting the inflammatory cytokines TNF- α , and IL-6, or minocycline, which has an inhibitory effect on microglial activation, are added as an adjunctive therapy and it has a certain effect. Regarding the subtypes or stages for which anti-inflammatory therapy is effective, treatment-resistant cases, severe cases, and cases showing suicide-related behavior are assumed. Accumulation of further knowledge including the biomarkers for detecting neuro-

inflammation is essential for clinical application of anti-inflammatory therapy [37]. Oxidative stress by redox dysregulation, a disturbance of balance between oxidants and antioxidant species, is known to play an important role in the pathophysiology of schizophrenia and it is closely related to neuroinflammation through microglial activation [38, 39]. Whether or not the effect of anti-inflammatory or anti-oxidant therapy is different among EOS, LOS, and VLOS should also be clarified.

It is a well-known fact that chronic inflammation is the basis of the pathophysiology of metabolic syndrome including diabetes [40]. On the other hand, schizophrenia has a predisposition to be complicated with metabolic syndrome such as diabetes. A recent report has also shown inflammation to be a common cause of insulin resistance and schizophrenia [41]. The formation of advanced glycation end products (AGEs) is a key pathophysiological event linked to the onset and progression of diabetic complications. Oxidative stress leverages the formation of AGEs, which is also called “carbonyl stress.” It has been reported that 20% of schizophrenia patients reportedly exhibit increased blood levels of pentosidine, one of AGEs and that lowered levels of vitamin B6 and that the administration of vitamin B6 pyridoxamine to patients with schizophrenia under enhanced carbonyl stress can effectively ameliorate their symptoms [42, 43]. Despite advances in psychiatry, the lifespan difference between psychiatric patients including schizophrenia and healthy individuals is widening, and the main cause of the lifespan difference is cardiovascular disorders caused by metabolic syndrome such as diabetes [44]. It is also well

known that most psychotropic drugs, including antipsychotics, have weight gain effects and that cognitive impairment is more pronounced in schizophrenia with diabetes [45]. The above points are more clinically problematic in LOS.

Conclusion

As mentioned above, LOS, especially VLOS, has a clear clinical difference from EOS. We will finish the article with the hope that the pathophysiology of LOS will be elucidated from the perspective of “neuroinflammation” and that it will become a breakthrough in the diagnosis and treatment of LOS.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Akira Monji created the concept and wrote the manuscript. Yoshito Mizoguchi reviewed and critiqued the manuscript. Both authors read and approved the final version of the manuscript.

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