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INFLAMMATION, NEURODEGENERATION AND THE PSYCHOPATHOLOGY OF SCHIZOPHRENIA

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In recent years, the possible cause of schizophrenia has switched from an emphasis on neurotransmitter dysfunction to possible genetic and neurodevelopmental abnormalities. The link between the loci for insulin-dependent diabetes mellitus type 2,the human lymphocyte antigen system and schizophrenia suggests that a dysfunctional immune system plays a role in this disorder. This hypothesis is supported by a link between viral infections in utero and schizophrenia in the offspring; the negative correlation between rheumatoid arthritis and schizophrenia lends further support to this view.

Recent studies have indicated that changes in the adaptive immune system in schizophrenia result in an imbalance between the pro-inflammatory and anti-inflammatory cytokines. Of the changes in the pro-inflammatory cytokines that have been detected in the blood and CSF of schizophrenic patients, interleukin-6 (IL-6) has received particular attention. In the plasma, high concentrations of IL-6 are associated with both the duration of the disorder and its resistance to drug treatment while the increase of IL-6 in the CSF is associated with the paranoid symptoms of the disorder.. It is now known that IL-6 increases the activities of dopaminergic and serotonergic neurons in the hippocampus and the frontal cortex. Thereby linking the immune changes with those neurotransmitters reputed to be causally connected to the psychopathology of the disorder. IL-6 is suppressed by effective treatment of the psychotic state by atypical antipsychotics.

The link between the immune system and neurodegenerative changes that frequently occur in those with chronic schizophrenia is provided by the increased synthesis of quinolinic acid, the final product of the tryptophan-kynurenine pathway. This pathway involves the activation of indoleamine 2,3 –dioxygenase (IDO) by IL-6 and other pro-inflammatory cytokines in many peripheral tissues and in microglia in the brain. In schizophrenia, there appears to be an imbalance between the neurodegenerative component (quinolinic acid, a NMDA glutamate agonist) and the neuroprotective component (kynurenic acid,a NMDA glutamate antagonist) in which the neurodegenerative pathway predominates. Thus recent clinical and experimental evidence suggests that a dysfunctional immune system contributes to both the acute symptoms and to long-term pathological changes in the brains of those suffering from schizophrenia.