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SPECIAL ISSUE

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Immunological and infectious aspects of schizophrenia

The hypothesis that infection and immunity are involved in the pathogenesis of schizophrenia is a historical one. Infection and the immune system gained scientific attention from psychiatrists long before the scientific focus of schizophrenia research was set on the dopamine system and the effects of antipsychotics. The starting point for the development of fever therapy by the Nobel prize laureate Julius Wagner von Jauregg was based on the observation of international psychiatrists during typhus epidemics in the 19th century. They noted that psychiatric patients became sick less often but got better or were even mentally cured after surviving a typhus infection. This observation was published in 1887 [1]. J. Wagner von Jauregg performed studies over many years on the immune-stimulating therapies with mycobacterium tuberculosis, salmonella typhii, or plasmodium malariae in major psychoses before concentrating on the malaria-therapy of syphilis.

Due to the triumphal march and broad therapeutic application of the neuroleptics starting in the early 1950s to the atypical antipsychotics to date, topics such as infection, inflammation, and immunology eked out a peripheral existence over decades while always simmering over a low flame.

The increasing role of psychoneuroimmunology for psychiatry over the last fifteen years is on the one hand due to a lack of quick progress in research on the dopaminergic neurotransmitter system, but primarily due to the rapid development of sophisticated immunological techniques from flow cytometry or blotting techniques to advances in cell cultures and animal modelling. These techniques have helped us to identify the presence of immune-system transmitters and modulators like cytokines in the brain and have facilitated our understanding of the highly sophisticated, dynamic interplay that occurs within the immune system and between the nervous system and the immune system. These insights allow more differentiated scientific strategies about the functional interactions between the various components of the immune system such as monocytes, macrophages, T- and B-cells, cytokines etc. This has led to findings showing that the dopaminergic neurotransmission in the CNS and psychic states are modulated by cytokines. For schizophrenia, effects of immune components at the blood-brain barrier, microglial cells such as brain macrophages and their role in CNS infection, or astroglial cells, which also contribute to the immunological CNS–cytokine interplay, are of special interest.

Immunogenetics and the role of infection came into the focus of schizophrenia research, based on the fact that genetic and environmental factors contribute to the pathogenesis of schizophrenia. Environmental factors are not necessarily psycho-social factors but rather infectious pathogens.

In this context it has been discussed that candidate genes for functional abnormalities might be inherited in genes of the immune system. The highly complex HLA system has been studied in schizophrenia since the 1970s, but molecular genetic methods have since enabled more valid studies of the HLA system. These have not supplied convincing results in schizophrenia to date, although linkage studies point to the short arm of the chromosome 6 as a candidate region – the region where the HLA system is located. Moreover, mutations in the genes of cytokines, chemokines and other molecules of the immune system that play a role in inflammation, such as adhesion molecules, became a focal point. Despite initially encouraging results, a lot of further work will be required for the study of functional genes of the immune system in order to put together the pieces of the puzzle of oligo- or polygenically based dysfunction in this highly differentiated system that contributes to schizophrenia.

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Influence of infection to the developing brain and risk for later schizophrenia

A long lasting discussion in psychiatry concerns the role of infection in the aetiology of schizophrenia. Infection during pregnancy in mothers of off-springs later developing schizophrenia has been discussed in order to explain the increase of schizophrenic births between December and May ("seasonality of birth"). Interesting epidemiological studies have also focussed on the relationship between infection and increased risk of schizophrenia. Results of the Northern Finland 1966 birth cohort have shown that infection of the CNS in childhood increases the risk of becoming psychotic later on five-fold. Two papers concerning this issue address this topic: the data of Koponen and collegues contain the results of the follow-up study of the Northern Finland 1966 birth cohort, further supporting the hypothesis that (viral) CNS infections during childhood may play a role as a risk factor for schizophrenia. The relative risk to become schizophrenic later, however, declines from 4.8 to 2.5 during the three-year period between the two follow-up studies. This decline – based on a small number of cases – would suggest that the influence of viral infection on the risk for later schizophrenia decreases with increasing age. This implies that a viral infection during childhood might be associated with an earlier onset of schizophrenia.

The findings of Gattaz and collegues also support the role of infectious pathogens in the development of schizophrenia. In a follow-up study of children who had suffered from a (bacterial) meningitis at age 0 to 5 years during an epidemic in Brazil, they observed a five-fold increased risk for developing psychosis later on. Gattaz, Abrahao, and Foccacia also present an interesting model regarding the relationship between genetics, infection, brain maturation, and synapse modification. Since the development of the brain is not finalized at birth but is still ongoing during the first years of life, an infection during early childhood is still in line with the assumption that a disturbance in brain development – infection-triggered – plays a key role in schizophrenia.

Viral antibody titers in schizophrenic patients

Another line of evidence deals with the topic whether a persistent (chronic) infection, possibly sustained by the disability of the immune system in clearing such an infectious process, is a patho-aetiological factor in schizophrenia. The term 'mild localized chronic encephalitis' has been proposed by Bechter [2]. Being aware of the characteristics of infectious agents, that a virus possibly will infect cells by 'hitting and running away' on the one hand, and several viruses or other intracellular infectious agents may be silently hidden in cells of the lymphoid or the nervous system and exacerbate under certain conditions such as stress on the other hand, our methodological possibilities proving such a localized infection are limited. The estimation of serum-antibody titers against diverse infectious agents is a rough method with limited sensitivity for a localized mild infectious process. Nevertheless, antibody titers against viruses have been examined in the sera of schizophrenic patients for many years. The results, however, were inconsistent, possibly also due to the fact that interfering factors such as medication have not been controlled.

Leweke and collegues studied antibodies against infectious agents not only in the serum, but also in the cerebrospinal fluid of individuals with recent onset of schizophrenia. Antibodies against cytomegalovirus (CMV) and *toxoplasma gondii* were significantly increased in non-medicated patients, while this relationship could not be confirmed in medicated patients. The finding that the antibody levels are associated with the medication state might partly explain earlier controversial results, although studies with antibody titers have to be interpreted cautiously. The conclusion that certain infectious agents – not restricted to viruses – but not one single pathogen is related to the onset in some cases of schizophrenia infers the involvement of a possible immune mechanism. From an immunological point of view, a defect in the clearing of the pathogen by the cellular type-1 immune response might lead to a (chronic) type-2 activation. This effect might also take place in the developing brain, where an infection may prime an early type-1/type-2 imbalance of the CNS immune system mediated by cytokines.

Therapy with COX-2 inhibitors in schizophrenia

Several study groups are working on new treatment strategies, which are based on the inflammation hypothesis of schizophrenia. Liquor-pheresis has been described to be successful in very carefully chosen single cases of treatment resistant patients [2]. The hypothesis of our own study group refers to the shift of the immune response balance in schizophrenia to a type-2 response overweight, which seems to be rebalanced by the immunological effects of cyclooxygenase-2 (COX-2) inhibition, in particular by the selective COX-2 inhibitor celecoxib. This is of special interest since treatment with celecoxib in schizophrenia has shown a favourable outcome-effect compared to placebo in a prospective double-blind add-on study. This study, which uses an anti-inflammatory treatment approach in schizophrenia, might contribute not only to the development of new effective treatment methods but also to new insights into the pathomechanisms of schizophrenia.

Although methodological concerns such as laboratory artefacts, epiphenomena, or interfering variables in the highly complex and variable immune system and in regularly changing psychiatric classification have to be critically taken into account, immunological and infectious aspects of schizophrenia have always been a matter of interest for researchers. The new scope in this field

has yielded fascinating approaches for insights in pathomechanisms and treatment of schizophrenia, which will hopefully be shared by the reader.

References

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