Updating the mild encephalitis hypothesis of schizophrenia.


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Abstract

Schizophrenia seems to be a heterogeneous disorder. Emerging evidence indicates that low level neuroinflammation (LLNI) may not occur infrequently. Many infectious agents with low overall pathogenicity are risk factors for psychoses including schizophrenia and for autoimmune disorders. According to the mild encephalitis (ME) hypothesis, LLNI represents the core pathogenetic mechanism in a schizophrenia subgroup that has syndromal overlap with other psychiatric disorders. ME may be triggered by infections, autoimmunity, toxicity, or trauma. A 'late hit' and gene-environment interaction are required to explain major findings about schizophrenia, and both aspects would be consistent with the ME hypothesis. Schizophrenia risk genes stay rather constant within populations despite a resulting low number of progeny; this may result from advantages associated with risk genes, e.g., an improved immune response, which may act protectively within changing environments, although they are associated with the disadvantage of increased susceptibility to psychotic disorders. Specific schizophrenic symptoms may arise with instances of LLNI when certain brain functional systems are involved, in addition to being shaped by pre-existing liability factors. Prodrome phase and the transition to a diseased status may be related to LLNI processes emerging and varying over time. The variability in the course of schizophrenia resembles the varying courses of autoimmune disorders, which result from three required factors: genes, the environment, and the immune system. Preliminary criteria for subgrouping neurodevelopmental, genetic, ME, and other types of schizophrenias are provided. A rare example of ME schizophrenia may be observed in Borna disease virus infection. Neurodevelopmental schizophrenia due to early infections has been estimated by others to explain approximately 30% of cases, but the underlying pathomechanisms of transition to disease remain in question. LLNI (e.g. from reactivation related to persistent infection) may be involved and other pathomechanisms including dysfunction of the blood-brain barrier or the blood-CSF barrier, CNS-endogenous immunity and the volume transmission mode balancing wiring transmission (the latter represented mainly by synaptic transmission, which is often described as being disturbed in schizophrenia). Volume transmission is linked to CSF signaling, and together could represent a common pathogenetic link for the distributed brain dysfunction, dysconnectivity, and brain structural abnormalities observed in schizophrenia. In addition, CSF signaling may extend into peripheral tissues via the CSF outflow pathway along brain nerves and peripheral nerves, and it may explain the peripheral topology of neuronal dysfunctions found, like in olfactory dysfunction, dysautonomia, and even in peripheral tissues, i.e., the muscle lesions that were found in 50% of cases. Modulating factors in schizophrenia, such as stress, hormones, and diet, are also modulating factors in the immune response. Considering recent investigations of CSF, the ME schizophrenia subgroup may constitute approximately 40% of cases.

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Supplement

The mild encephalitis (ME) hypothesis of psychiatric disorders was based on long standing research on the possible role of virus infections for psychiatric disorders, with a focus on affective and schizophrenic spectrum (Bechter 2001). ME subgroup may be defined by low level neuroinflammation (LLNI) as a core aspect within a complex pathogenesis including interaction between environmental factors and host factors. It was proposed that the age related variance of pathogenicity of infections may be involved in age of disease onset. One example was the pathogenicity curve in mumps-virus-infection, characterized by preferred pathogenicity in young ages, despite steadily increasing mumps antibody prevalence within the population. Assuming a variety of infections to be relevant, such scenario fitted with the curve for age of onset of schizophrenia and bipolar disorders (compare Bechter 2001). The age related variance of pathogenicity of the infection represents foremost a host factor which may represent immune genes. In an updated version of ME hypothesis (Bechter 2013) many more pathogenetic aspects and factors together with important recent epidemiological findings are discussed, which match with the ME hypothesis. Pathogenesis of ME may involve the brain and the CNS extracellular spaces and the CSF spaces. Such scenario would match well with the distribution of brain pathologies found, with some preference for CSF neighbouring structures. An interaction between environmental factors (especially infections) and genes is also well established in systemic autoimmune disorders.

Own investigations focused during the last 20 years on CSF, because CSF provides the most sensitive approach to neuroinflammation in the clinic. Based on established routine CSF laboratory markers we performed studies under strict external quality control, and found definite CSF abnormalities in 40 % of therapy resistant cases from the affective and the schizophrenic spectrum, and in later study in addition CSF-neopterin increase in about 30 %. Cumulated, more than 70 % of cases presented CSF pathologies (each case above cut-off values compared to > 4000 controls). Three types of CSF abnormalities were found in both spectrum disorder groups, a finding which remains to be fully understood (see figure 2). In depression, 20 % of cases demonstrated in addition systemic inflammation (defined by oligoclonal bands).

CSF has a role not only as diagnostic marker but surely is a pathogenic factor. The volume transmission mode, introduced and worked out by Fuxe and Agnati et al, describes signalling by extracellular CNS fluids within the CNS and a link to CSF signalling even over the long range. Beyond CSF signalling may extend via peripheral CSF outflow pathways into peripheral tissues (PCOP hypothesis, Bechter 2011). The PCOP hypothesis was developed from clinical observations during experimental treatments with cerebrospinal fluid filtration and extensive literature review. Research on CSF outflow pathways remains rather limited, yet, was focused on the outflow site at the cribriform plate from subfrontal subarachnoid spaces into nasal submucosa and cervical lymphatic system. We recently showed that not only fluid but also CSF cells can follow the outflow pathway along spinal nerves (Schmitt et al 2011). The PCOP hypothesis may contribute to better understand the full range of symptoms and findings in major psychoses, including such at surprising anatomical sites in the periphery. For example the old and replicated finding of muscle lesions in 50 % of patients (depression and schizophrenia), which resembled muscle lesions found in meningoencephalitis (Meltzer and Crayton 1974), awaited a pathogenetic explanation.

Diagram of the ME scenario
Cumulated results of CSF pathologies from several own studies (see references)

CSF pathologies in therapy-resistant schizophrenia (n=39)
CSF pathologies in therapy-resistant depression (n=24)

Schedule of the CSF outflow pathways
Figure 3 (from Bechter 2011, NPBR)

References:


