

ETIOPATHOGENESIS OF PSYCHOSES

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1. Introduction

For a rather long period the known important genetic contribution to mental illness was understood in a framework of a common disease common variant hypothesis. In this view the genes play a major role. But according to more stringent results this now seems different (Uher 2009): gene environment interactions may be more important than previously thought, involving especially environments that have periodically changed throughout evolution. Furthermore, a cumulative effect of multiple pleiotropic variants of recent origin under mutation selection balance could account for the persistence of harmful and heritable mental illness despite the well known and strong reproductive disadvantage. Any valid hypothesis has especially to explain this latter aspect. The 'evolution-informed-framework-hypothesis' does.

2. Types of gene-environment-interaction

But what are environmental factors involved? New results support psychoimmunological mechanisms and infectious agents may be relevant. When applying modern CSF analytic methods, we found abnormal CSF in a considerable subgroup of therapy-resistant cases of both, affective and schizophrenic spectrum disorders, supporting or matching with the mild encephalitis (ME) hypothesis in a subgroup of more than 40% of patients (Bechter et al. 2010). The ME hypothesis explains various psychiatric syndromes by low level neuroinflammation, which may arise dependent from infections. Together with developmental and genetic factors, via common immunoinflammatory pathogenetic pathways, many different infectious agents may contribute to or initiate an autoimmune CNS-related or CNS-specific process (Bechter 2001).

The fact, that most infectious agents are characterized by only low pathogenicity (low number of diseased per number of infected) is also understandable in an evolutionary framework: the less aggressive an agent is to its host the more likely it adapts and survives. Low pathogenicity seems especially frequent in neurotropic viruses, and CNS represents a bradytrophic tissue and therefore a preferred survival niche for viruses (Johnson 1982). Now there is an increasing number of findings suggesting bacterial, protozoal or viral agents, likely involved in mental disorders, mumps virus infection representing even the highest risk factor for psychoses found up to now (Dalman et al. 2008). Other candidates are Borna disease virus (Bechter 2001), endogenous retrovirus Herv-W (Perron and Leboyer 2009), parvovirus B19 and persistent Adeno-associated virus 2 (Grant et al. 2009), and a series of others. An immunoinflammatory signature was found by highly sophisticated laboratory methods in blood monocytes in psychoses (Padmos et al. 2004). The diagnosis of neuropsychiatric disorders based on neuroimmunological studies, e.g. on blood cells by microRNA, is at the beginning but seems very promising (Keller et al. 2009). Shotgun proteome analysis of post-mortem tissue identified 84 differential expressed proteins, those involving the immune system, calcium homeostasis, cytoskeleton assembly and energy metabolism (Martins-de-Souza 2009). Such findings match with the ME hypothesis very well. Compare also the abstracts of the 10th Psychoimmunology Expert Meeting 2009 (free download available on www.psychoimmunology-experts.de).

Another key environmental factor to induce psychotic illness seems cannabis (Lutz 2009), apparently a specific subgroup.

3. Summary

Psychoimmunology is on the rise in neuropsychiatry, though not well accepted yet in the field of clinical psychiatry, but may be causally involved in a considerable subgroup of psychoses. Completely differing etiological subgroups, e.g. neurodevelopmental, may nevertheless exist. Well established is neuroimmunology in clinical neurology with well working laboratory methods, especially CSF investigation, yet the gold standard to diagnose inflammatory CNS diseases. Low level CNS inflammation detected in subgroups of patients with endogenous psychoses by modern CSF diagnostic methods (Bechter et al. 2010; Maxeiner et al. 2009) suggests, that CSF investigation plays an underestimated role in psychiatry, but can help to better understand severe or therapy-resistant psychiatric disorders.

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