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NEWS & VIEWS

The search for infectious agents in neuropsychiatric disorders: lessons from multiple sclerosis

Central nervous system diseases, such as multiple sclerosis, may have an infectious basis; however, it has been particularly challenging to identify specific agents.

Multiple sclerosis (MS) is a demyelinating central nervous system (CNS) disorder of young adults. Although cognitive and behavioral disturbances may occur, motor and sensory dysfunction are more common manifestations of the disorder. Thus, why would a reader of *Molecular Psychiatry* take keen interest in a recent report suggesting identification of a novel retrovirus in patients with MS? The stretch is not so far as it first appears. There are lessons in studies of MS pathogenesis with implications for investigation of neuropsychiatric disorders. In spite of progress in therapeutics, the basis of MS and of most neuropsychiatric disorders clearly within the bailiwick of this audience such as autism, schizophrenia, and bipolar disorder, remain poorly understood. If we consider schizophrenia as a prototype for neuropsychiatric diseases, the history of MS research becomes a particularly compelling paradigm. An infectious basis was first proposed for MS in 1884 by Marie[1] and for schizophrenia in 1845 by Esquirol.[2] A long list of agents has been implicated in MS and schizophrenia (reviewed in References 3–5) (Table 1); however, the search for a specific infectious agent has not been successful in either disorder. While this failure is discouraging it is probably premature to abandon the infection hypothesis. The prevalence rates of MS[6] and schizophrenia[3] are higher in temperate zones than in tropical zones. This pattern is compatible with a genetic as well as an infectious basis (for example, individuals of Scandinavian descent are represented with higher frequency above the 37th parallel).[5] However, migration studies indicate that where one lives as a child is an important determinant in risk for MS. Indeed, movement from a low risk, tropical area to a higher risk, temperate area may be associated with the appearance of MS in a population where the disease was previously unknown.[6] Lending additional support for the notion of an infectious component is the observation that MS may cluster. The most familiar example of this phenomenon was a striking increase in the incidence of MS in the Faroe Islands during the second world war, coincident with the introduction of British troops and dogs.[7] Lastly, there is the finding that monozygotic twins are only 25–30% concordant for clinically apparent MS (30–35% when MRI is included in the evaluation).[8] Interestingly, similar concordance rates (approximately 28%) are reported for schizophrenia in monozygotic twins.[3] These data should not be taken as excluding a role for genetic inheritance in the pathogenesis of MS or schizophrenia—indeed, genetically determined aspects of the immune response are clearly important in MS—but rather to indicate that there is more to the story.

If we accept the hypothesis that MS (or other CNS

Table 1 Viruses suspected in the pathogenesis of MS and/or schizophrenia

Virus	*MS*	*Schizophrenia*
Measles	X	X
EBV	X	X
Rubella	X	X
Mumps	X	X
CMV		X
HSV, VZV, HHV-6	X	X
BDV		X
Influenza A		X
Parainfluenza		X
Adenovirus		X
Vaccinia		X
Canine distemper virus	X	
Marek's virus	X	
SV5	X	
JC	X	
Animal retroviruses	X	
Human retroviruses, HTLV-1	X	X
New retroviruses	X	

Modified from References 3 and 5.
EBV = Epstein–Barr virus; CMV = cytomegalovirus; HSV = herpes simplex virus; VSV = varicella-zoster virus; HHV-6 = human herpes virus 6; BDV = Borna disease virus; HTLV-1 = human T-cell lymphotropic virus 1.

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diseases) have an infectious basis, the obvious question is why has it been so difficult to identify the agent(s)? The several plausible explanations can be distilled into two. First, disease may reflect a complex interaction between the host and the pathogen in which the time of infection, genetic background of the host, or other factors are key determinants in pathogenesis. Alternatively, we may have failed as observers because we do not have the appropriate tools to demonstrate the presence of the infectious agent, have looked in the wrong compartments, or at the wrong time in the course of the disease. To make matters more complex, these possibilities may not be mutually exclusive. Furthermore, it is conceivable that more than one infectious agent may be implicated in pathogenesis of a single clinical syndrome either through common mechanisms for effecting direct or indirect (immune-mediated) damage, or through interaction as cofactors.

The recent report of Perron and coworkers[9] illustrates the type of baroque molecular gymnastics that are becoming standard operating procedure for investigating whether disorders like MS may have an infectious basis. In 1989, Perron and coworkers reported isolation of a retrovirus, LM7, from leptomeningeal cells cultured from the cerebrospinal fluid of a patient with MS.[10] Difficulties in establishing continuously productive cultures led to adoption of a molecular approach to characterization of LM7. Using reverse transcriptase activity as a guide, LM7 virions were purified over sucrose gradients. RNA was extracted and amplified by reverse transcription polymerase chain reaction using degenerate primers representing a region of the *pol* gene conserved amongst retroviruses. The resulting amplification product of approximately 140 nucleotides (designated MSRV-*cpol*) appears to be novel with 70–75% sequence similarity to ERV9, an endogenous retroviral sequence. Thereafter, MSRV-*cpol* specific primers were used in RT-PCR assays of CSF from patients with MS or various CNS disorders. MSRV sequences were detected in five of 10 MS patients and none of 10 controls. Intriguingly, MSRV sequences were not detected in MS patients who were currently or had previously been receiving either steroids or cyclophosphamide, a finding which suggests that a host factor associated with the immune response is critical to replication of MSRV. MSRV sequences were subsequently isolated from plasma as well as CSF of MS patients. In the latter portion of their paper, Perron *et al* incorporate reports linking other viruses to MS into a system focused on MSRV as the central protagonist. The most convincing arguments relate to herpesviruses (Epstein–Barr virus, HSV-1, and HHV-6) and invoke the capacity of some herpesviruses to transactivate MSRV *in vitro*. Finally, a mechanism for demyelination is proposed: cells infected with MSRV express a gliotoxin.

These are exciting findings. If confirmed in larger cohorts, MS research and clinical practice will chart a new course and the search for cryptic agents in CNS diseases will gain momentum. Whatever the outcome, this much is clear: the brave new world of pathogen discovery will require pluck, savvy, and rigorous epidemiology.

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