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Psychotropic viruses
W Ian Lipkin* and Mady Hornig

Viruses are increasingly being recognized as important factors in the pathogenesis of acute and chronic mental illness. Here we review clinical and epidemiologic data concerning viral infection and mental illness, as well as animal models that provide insight into the myriad of mechanisms by which infection can cause brain dysfunction.

Addresses
Greene ID Lab/MSPH/Columbia, 722 West 168th Street, Rm. 1801, New York, New York 10032, USA
*e-mail: wil2001@columbia.edu

Abbreviations
BDV Borna disease virus

Introduction

The concept of psychotropic infection dates to antiquity, with the association of rabies virus and altered behavior. However, our appreciation of the complex mechanisms by which infectious agents can disrupt behavior is relatively recent. Both genetic and environmental factors contribute to the pathogenesis of autism, affective disorders, mental retardation and schizophrenia. Although some heritable mental disorders, such as autism, approach 100% penetrance, clinical severity, age at onset or treatment response can be influenced by the environment. Animal model studies and retrospective epidemiological analyses of human neuropsychiatric illness following exposures to toxins, infectious agents and famine indicate that exogenous factors and the timepoint(s) during nervous system development at which they are introduced modulate expression of disease. Elucidation of the mechanisms that guide the intricate interplay between host response genes and environmental agents, and the neurodevelopmental context within which these interactions occur, is necessary to understand the continuum of clinical outcomes.

Establishing a causal relationship between infection and a behavioral disturbance can be difficult. In some instances, an agent is readily implicated because it is present at high titer in brain at the time of an acute clinical presentation and anatomic and functional pathology are correlated; examples include limbic system disturbances with rabies virus or herpes simplex encephalitis. In others, particularly chronic disorders, there might be only indirect evidence (e.g. serology) to indicate a history of infection. Although Koch's postulate (i.e proof of a causative relationship by isolation, propagation outside the original host, and reintroduction into a new host resulting in disease) may never be demonstrated in the latter, they represent a focus of increasing interest because animal models indicate the plausibility of an infectious basis for a wide range of neuropsychiatric disorders and sensitive tools are becoming available for testing potential associations. The significance of this type of research is highlighted by the observation that the global burden of mental illness is estimated by the WHO to be 450 million [1].

Psychiatric manifestations of acute viral encephalitides

Virus replication can result in focal or global neural dysfunction, due to structural or metabolic damage. Herpes simplex type I (HSV-1) most commonly infects frontotemporal regions, with frequent involvement of cingulate and insular cortex [2], presumably due to viral spread via olfactory and/or trigeminal pathways during primary infection or upon reactivation in cranial ganglia. Tropism for limbic structures may result in psychosis, abnormalities in cognitive [3,4] or social processing [5], or a syndrome resembling autism [6,7] particularly early in the course of disease; however, these presentations are less common than hemiparesis or seizures, and rarely persist in isolation [8]. There are instances where victims recover from acute herpes encephalitis but have persistent behavioral deficits that relate to frontotemporal damage [9]. CNS infections with other herpesviruses, such as Epstein-Barr virus, can lead acutely to visual metamorphosia ('Alice in Wonderland' syndrome; an unusual syndrome where objects appear larger or smaller than their actual size, frequently associated with an abnormal sense of time or place), occasionally with persistent complications [10]. Sporadic case reports have implicated La Crosse (a bunyavirus) [11–13], Japanese encephalitis [14,15] and West Nile (flaviviruses) [16], and influenza A [17] or B [18] in acute encephalitis with resultant behavioral disturbances that are similar to those described in herpes encephalitis. Influenza A H1N1 infection in young children has resulted in encephalopathy and visual and somatosensory hallucinations [19]; such effects can also occur following influenza A H3N2

[20] or B infections [21]. Thalamic involvement is common in neuroimaging [20] but diffuse cortical manifestations may be observed; a wide range of neuropathologic features, including necrosis and disseminated intravascular coagulation may be observed [22]. Rabies virus can initially present as acute psychosis with hallucinations; it almost invariably progresses to other signs of disease, including convulsions, coma and death. Histology does not reveal classical hallmarks of viral encephalitis and the pathogenesis of encephalopathy is controversial [23].

Psychiatric manifestations of persistent viral infections
HIV and AIDS
Cognitive impairment occurs with great frequency in HIV infection, ranging from subclinical deficits of motor reaction time [24] and visual spatial attention [25,26] to minor cognitive motor disorder or HIV-associated dementia [27]. Severity of cognitive outcomes can increase with age and in correlation with higher viral loads and reduced CD4^{+} cell counts, or age-related decline in functioning of subcortical or frontostriatal circuitry [28]. Mild cognitive impairments can predict mortality, independent of clinical stage or CD4^{+} cell counts [27]; such impairments are correlated with increased kynurenine pathway (tryptophan degradation) activity and quinolinic acid levels in cerebrospinal fluid (CSF) [29,30]. Kynurenine:tryptophan ratios increase with disease stage in HIV-infected individuals [31] through interferon (IFN)-γ-mediated activation of indoleamine-2,3-dioxygenase in macrophages [32], and may be linked to neuropsychiatric symptoms [33]; conversely, these ratios and the neurotoxic end product of the kynurenine pathway, quinolinic acid [34], decrease in parallel with risk of AIDS dementia complex when treated with effective retroviral therapy [35]. Of the highly active antiretroviral therapies, regimens including nucleoside reverse transcriptase inhibitors might provide specific protection against progression to HIV-associated dementia beyond those effects that are attributable to improved CD4^{+} cell counts or reduced risk of opportunistic infections [36]. Additionally, infection with selected strains of HIV may enhance the risk of dementia. Some investigators suggest that envelope sequences determine neurotropism [37,38], whereas others fail to find evidence of brain-specific signature sequences [39].

New-onset psychosis is reported in up to 15% of HIV patients and can occur without encephalopathy [40,41]. Involvement of subcortical dopaminergic systems, particularly basal ganglia structures, is supported by high rates of antipsychotic-related extrapyramidal symptoms [42] and neuropathologic studies in HIV-infected patients [43]. Depression is reported in 15–40% of patients [44]. Mania without preexisting bipolar disorder or family history is found in 8% of patients in the late stages of disease, typically in the context of dementia and immunosuppression; early in HIV infection, episodes of mania are more commonly related to preexisting bipolar disorder or family history [45]. The pathogenesis of psychiatric disturbances in AIDS is unknown. The dopamine neurotransmitter system appears to be vulnerable. Dopamine blockade causes tardive dyskinesia (involuntary movements of the tongue, lips, face, trunk and extremities) more frequently in psychotic AIDS patients than other psychotic individuals [46]. Furthermore, dopaminergic drugs accelerate viral replication and disease in SIV (simian immunodeficiency virus)-macaques [47]. Mood disturbances in HIV infection appear to be related to altered serotonin metabolism via immune activation of the kynurenine pathway [33]; selective serotonin reuptake inhibitors (SSRIs) are better tolerated by HIV patients than are agents with anticholinergic effects, such as tricyclic antidepressants [48].

Other retroviruses
A role for endogenous retroviruses has been proposed in the pathogenesis of schizophrenia [49]. In individuals with schizophrenia, antibodies to retroviral antigens in peripheral blood [50] and retroviral RNA in cerebrospinal fluid and brains [51] are reported. Aberrant patterns of methylation of retroviral-related sequences are one potential mechanism [52]. It is equally plausible that endogenous retroviral gene expression is an epiphenomenon that is related to inflammation.

Herpesviruses
Conflicting results are reported for the association of various herpesviruses with the risk of neuropsychiatric disorder. In one study, the propensity to develop schizophrenia and related psychotic disorders in adulthood was found to be specifically linked to the presence of maternal humoral immunity to herpes simplex virus type 2 during gestation. No such relationship was found for herpes simplex virus type 1 in this cohort [53]. Presence of serum antibodies to herpes simplex virus type 1 might relate to severity of cognitive deficits in psychiatric disorders, including schizophrenia [3] and bipolar disorder [4]. Sequences that are consistent with human herpesvirus-6 have been identified in orbitofrontal cortex of patients with schizophrenia [54], but other studies examining CSF or other areas of brain for a range of herpesviruses have yielded negative results [55].

Borna disease virus (BDV)
BDV is an RNA virus that causes meningoencephalitis in a wide variety of warm-blooded animals. BDV targets limbic structures, replicates at low levels and causes noncytopathic, persistent infection for the lifespan of the host. Natural infection is reported only in horses and sheep; however, experimental infections are described in a wide variety of vertebrates and can present as immune-mediated disease or subtle behavioral alterations without inflammation [56]. In rodent models,

immunocompetent adults have meningoencephalitis, a progressive movement disorder and dementia; neonates have cerebellar and hippocampal dysgenesis, and disturbances in learning, mood and behavior that are reminiscent of those observed in schizophrenia, mood disorders and autism. Disease in neonatal infection appears to be mediated through specific effects on neuronal plasticity and cellular signaling pathways [57]. The epidemiology and consequences of human infection are currently unclear. Most reports that implicate BDV and human disease have focused on neuropsychiatric disorders, including major depression, bipolar disorder or schizophrenia; however, BDV has also been linked to chronic fatigue syndrome, multiple sclerosis, motor neuron disease and high-grade gliomas. Isolation of infectious virus from humans is only rarely reported. Infection is typically diagnosed by serology or PCR analyses of peripheral blood mononuclear cells or tissues. Serologic studies, including cell-based immunofluorescence, ELISA, western blot and immune complex assays, have revealed antibodies to BDV in 0 to 93% of subjects with selected neuropsychiatric disorders, versus 0 to 15% of normal controls. Several groups have reported identification of BDV nucleic acids from blood or brain tissue by nested RT–PCR (reverse transcriptase polymerase chain reaction) [58]. Although sensitive, this method is prone to artifact, due to inadvertent introduction of template from laboratory isolates or cross-contamination of samples. In most viral systems, specific signatures readily facilitate the determination of provenance; however, in BDV, similarities in sequence between putative new isolates and confirmed isolates cannot be used to exclude the former as artifacts. The epidemiology of BDV and its significance in neuropsychiatric disease awaits the results of multicenter studies that are now in progress [59].

Prenatal and perinatal viral infection

Exposure to a wide range of viruses pre- or peri-natally has been implicated in the pathogenesis of neuropsychiatric disorders. Direct viral effects on developing brain circuitry or mediation through indirect maternal or fetal immune responses are among the proposed mechanisms. The timing of the insult is an important determinant of outcome. A substantial body of data supports the coincidence of the second trimester of gestation with influenza epidemics and later diagnoses of schizophrenia [60•,61], schizotypal personality features [62] or affective disorder [63,64], but not all studies support these associations [65,66]. Bias related to retrospective reporting techniques might confound the relationship in some studies [67]; also, few studies provide confirmatory serologic evidence of microbial specificity. Associations between first trimester respiratory infections and cycloid psychosis [68], first trimester rubella exposure and nonaffective psychosis [69], and third trimester cytomegalovirus infection and autism [70] are also reported. Cytomegalovirus is the leading cause of mental retardation resulting from

congenital viral infection [71], although multiple viruses are linked to the condition. There is suggestive evidence from animal models that influenza infection during pregnancy can result in neurodevelopmental damage that is reminiscent of schizophrenia. Prenatal administration of influenza virus strain H1N1 or A/NWS/33CHINI results in behavioral [72•] and neuropathologic features [73–76] in mice, consistent with several types of neurodevelopmental disturbance that have been noted in schizophrenia. In one study from this research group, no evidence of viral RNA or proteins or encephalitis was found in the brains of offspring [72•], and administration of a viral mimic, polyinosinic-polycytidylic acid, causes similar disturbances of prepulse [72•] or latent [77,78] inhibition in offspring in the absence of virus; another study, however, found persistent viral RNA in the brains of offspring through to at least postnatal day 90 [79].

The precise mechanisms that are associated with virus-related, prenatal neurodevelopmental damage are not yet defined. Considering the multiplicity of viruses that are implicated in a multitude of neuropsychiatric conditions, common mediators of maternal immune or neuroendocrine responses are suspected. A spectrum of observed outcomes might be explained by the introduction of such factors that are relative to windows of vulnerability arising during CNS maturation. Direct effects on developing neural or glial populations that may be shared by some viruses, including the capacity to alter gene expression relating to apoptosis-related products, neurotrophic factors, excitotoxicity, or molecular pathways involved in migration or neurotransmitter function, are also likely to contribute to the subsequent neuropsychiatric disturbances. Intrauterine elevations of proinflammatory cytokines [80] are thought to play a role; increased maternal levels of TNF (tumor necrosis factor)-α, but not other proinflammatory cytokines, were found to correlate with increased risk of psychosis in adult offspring [81]. Additionally, physiologic and behavioral changes related to maternal sickness behaviors in the acute period following infection, such as altered body temperature regulation and reduced food intake, may interact with effects of cytokines or other immunomodulators to interfere with normal brain development [82].

Perspectives

A comprehensive approach to investigating the pathogenesis of neurodevelopmental disorders must consider the interaction of host and environmental factors in a temporal context. Evidence that is emerging from epidemiology and animal models suggests that prenatal infection with a variety of agents can trigger complex behavioral disorders by impacting the function of specific neural cells and circuits. Future work should focus on dissecting the mechanisms of developmental neuropathology in animal models and using clues derived from these more simple systems to target infectious disease investigation

in human populations. Given that the 'footprints' of infection might not be present at the time when a syndrome is manifest, it is imperative that microbial epidemiologists pursue such studies in prospective birth cohorts, where associations can be established by examining prenatal and cord blood samples from affected individuals.

Acknowledgements

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