Pathophysiological Role of HERV-W in Schizophrenia

Awais Aftab, M.D., Asim A. Shah, M.D., Ali Madeeh Hashmi, M.D.

Schizophrenia is a neuropsychiatric disorder of complex etiology. Human endogenous retroviruses (HERVs) have been presented as possible candidates explaining the connections between the genetic, infectious, neurodevelopmental, and neuroinflammatory aspects of schizophrenia, with the human endogenous retrovirus type W family (HERV-W) showing the greatest evidence of association. Studies have identified retroviral nucleotide sequences, envelope and capsid proteins, and elevated transcription of HERV-W elements in CSF, blood, and brain samples from individuals with schizophrenia. The HERV-W elements can trigger the immune system in a variety of ways. HERV genetic elements may be activated by various prenatal maternal infections, leading to neuroinflammation and genetic abnormalities, altering the development of the brain, and eventually culminating in the development of schizophrenia. This review presents a concise synthesis of available evidence and theoretical speculation regarding the role of HERV-W in schizophrenia. The need for further investigation is highlighted before any conclusions can be stated with confidence.

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Schizophrenia is a severe and debilitating neuropsychiatric disorder, with a lifetime risk of approximately 0.7%.[1] It is one of the leading causes of disability worldwide, accounting for 1.1% of total disability-adjusted life years and 2.8% of years lived with disability, according to the Global Burden of Disease Study.[2] The condition is highly familial, with a robust contribution from genetic factors (approximately 80%).[3] Evidence indicates genetic heterogeneity, such that multiple genes of small effect are associated with the disorder and no single gene has been identified as necessary or sufficient by itself.[4] A number of environmental risk factors, each of individual small effect, have also been consistently identified for schizophrenia.[4] These include, among others, birth in an urban environment,[5] birth in winter and spring seasons,[6] maternal infections during pregnancy,[7] obstetric and perinatal complications such as preeclampsia,[8] and immunological disturbances.[9] Prenatal maternal infections associated with schizophrenia include influenza,[10] rubella,[11] herpes simplex virus,[12] cytomegalovirus,[13] and *Toxoplasma gondii*.[14] There is also some evidence that certain infections later in life (during childhood and adulthood), such as cytomegalovirus and *T. gondii*, can serve as secondary risk factors associated with the development of schizophrenia.[15,16] Many of these etiological factors are consistent with a neurodevelopmental model of schizophrenia, which is widely accepted.[17] Attention has also been devoted in past years toward the role of inflammation in schizophrenia, and there is evidence to support the presence of low-level neuroinflammatory processes in patients with the disorder.[18] Data from genome-wide association studies reveal that the genetic pathways likely associated with schizophrenia include loci involved in inflammation and the immune system.[19]

The genetic, infectious, neurodevelopmental, and neuroinflammatory aspects of schizophrenia are all interrelated. For instance, many of the genes discovered to have an association with schizophrenia play important roles in immunity.[20] An immune imbalance between type I and type II immune response has been reported in schizophrenia, and through a chain of events, it results in an accumulation of kynurenic acid in the CNS.[21] Kynurenic acid is an endogenous N-methyl-D-aspartic acid receptor antagonist, and its levels are shown to be elevated in schizophrenia. The immune system can be activated by various sorts of infections; prenatal infections, in particular, can disrupt the normal developmental trajectory of the brain through activation of the maternal immune system.[22]

How these various threads interweave and contribute to the pathophysiology of schizophrenia remains an area of active speculation and research. Human endogenous retroviruses (HERVs) have been presented as possible candidates explaining the connections among these various threads, at least in a subset of patients. HERVs belonging to the human endogenous retrovirus type W family (HERV-W) have garnered the most attention and have the most support from evidence. We will restrict ourselves only to the HERV-W family, although other HERV families are also being studied in schizophrenia.[23]

METHODS

We conducted a literature search in PubMed using the search words "schizophrenia" and "HERV" or "human endogenous retroviruses" or "endogenous retroviruses" appearing in the titles and abstracts of journal articles with no restriction on date of publication. The search algorithm used was as follows: schizophrenia[Title/Abstract] AND (HERV [Title/Abstract] OR human endogenous retroviruses[Title/Abstract] OR endogenous retroviruses[Title/Abstract]). There were 32 results, with publication dates ranging from 1999 to 2014. Abstracts of search results were reviewed, and eight studies investigating the role of HERV-W in schizophrenia were identified. Full texts of these eight studies were reviewed. These studies are summarized in Table 1, and they are discussed below in the section on the association of HERV-W with schizophrenia. Full texts of other review articles identified through the above search process were also studied. An outline of the most relevant aspects of the topic was created. We also individually searched prominent articles for additional important citations.

HERVs AND HERV-W

Retroviruses are enveloped viruses with the ability to convert their RNA into DNA using the reverse transcriptase enzyme. This retroviral DNA can be integrated into chromosomal DNA of the host cell in the form of a provirus. When expressed, the retroviral DNA produces more copies of the virus. In the vast majority of cases, retroviruses cannot be passed on to the next generation because they infect somatic cells only. Rarely, however, retroviruses can infect germ cells, in which case the provirus becomes integrated with the DNA passed on to the progeny. These retroviruses are transmitted and inherited through successive generations, along with the rest of the genetic material. The stable integration of a retrovirus into the host genome is called endogenization, and the result is an endogenous virus. Endogenous viruses that are part of the human genome are called HERVs.[23,24] HERVs are evolutionary archeological remains of retroviral infections that took place several million years ago during the course of mammalian evolution. They are classified in the family of transposable elements, which are essentially mobile genetic elements (DNA sequences capable of changing their position within the genome, and therefore called "jumping genes").[25] Given this mobility, HERVs can disseminate within the genomes. This ability of HERVs to replicate and insert copies into a new position in the genetic material explains their high genetic load in the human genome: it is estimated that as much as 8% of the human genome is of retroviral origin.[26] HERVs are grouped into three classes: I, II, and III. HERV-W belongs to class I, which is among the oldest group of HERVs.[24] This classification is based on the molecular sequence resemblance to different genera of infectious retroviruses. Class I resembles mammalian type C viruses; class II resembles mammalian type A, B, and D viruses; and class III resembles the foamy virus. Each class has a number of subgroups called "families," which are named using an older nomenclature still followed primarily for historical reasons.[27,28] The families are classified by letters denoting the binding site nucleotide sequence for the primer tRNA (these letters correspond to a one-letter code of amino acids). For instance, HERV-H is primed by tRNA-histidine, HERV-F is primed by tRNA-phenylalanine, and HERV-W is primed by tRNA-tryptophan.

Some of the common HERV families include HERV-T (typical of a small to medium-sized HERV family), HERV-L (the oldest family that infected a common ancestor of mammals), HERV-H (the most abundant family in humans), HERV-W (which has been co-opted by host to serve in placenta formation); and HERV-K (the only family for which a functional infectious virus has been reconstructed *in vitro*, and which is capable of producing retroviral particles).[27] It has been determined that the W family of endogenous retroviruses entered the mammalian evolutionary line after the speciation of Old World monkeys approximately 25 million years ago.[29]

Intact HERVs consist of an internal sequence of at least three genes (*pol*, *gag*, and *env*), along with long terminal repeats at both ends. The *pol* gene codes for the viral enzymes (primarily reverse transcriptase), *gag* encodes the structural capsid, and *env* encodes the viral envelope protein. Most HERV elements are no longer active and have traditionally been ascribed to be a part of "junk DNA." During the course of evolution, inactivating mutations such as point and frame-shift mutations, deletions, stop codons, and various epigenetic mechanisms (e.g., methylation) have rendered them defective and silenced. The human genome contains >600 HERV-W elements, but most of them are long terminal repeats without internal sequence genes.[25] Some HERV elements, however, retain (partial) functionality. Of particular note is an HERV-W element on chromosome 7q21 that possesses an intact *env* gene, encoding for the protein syncytin.[30] Syncytin plays a physiological role in the development of the placenta, with the gene active only during early embryonic life. It mediates the fusion of trophoblasts, which is not surprising given that membrane fusion is the function of the viral envelope protein. Syncytin provides an example of an HERV gene that has been "domesticated" during the course of evolution to serve a useful purpose for the host. Abnormal expression of this *env* gene has been associated with preeclampsia,[31] multiple sclerosis,[32] and motor neuron disease.[33]

HERV-W was first discovered during investigation into the role of retroviruses in multiple sclerosis. Perron et al.[34,35] discovered an unidentified retroviral element that was named the multiple sclerosis–associated retroviral element (MSRV). This opened the door to the discovery of the HERV-W family, of which MSRV is a member.[36]

ASSOCIATION OF HERV-W WITH SCHIZOPHRENIA

Hypotheses regarding the potential role of retroviruses in the pathophysiology of schizophrenia go back many decades.[37]

The review by Leboyer et al.[38] identifies a study by Deb-Rinker et al.[39] as the first experimental study linking an HERV with schizophrenia by demonstrating that MSRV-like sequences were differentially represented in the genome of individuals with schizophrenia compared with their monozygotic twins without the disorder.

Several studies since then have investigated the association between HERVs and schizophrenia, with the HERV-W family showing the greatest evidence of association (Table 1). Yolken et al.[40] investigated RNA expression in the frontal cortex of postmortem brains from four individuals with schizophrenia, four individuals with bipolar disorder, and six control participants. HERV-W expression was significantly elevated in individuals with schizophrenia compared with control participants.

Karlsson et al.[41] identified nucleotide sequences homologous to retroviral *pol* genes in the CSF of 10 of 35 patients (29%) diagnosed with recent-onset schizophrenia and schizoaffective disorder as well as in the CSF of one of 20 patients with chronic schizophrenia. These retroviral sequences, predominantly related to the HERV-W family, were not detected in any of the control participants. The same study reported differentially upregulated transcription of RNA homologous to HERV-W retroviruses in frontal cortices studied postmortem in patients with schizophrenia compared with control participants.

In a follow-up study, Karlsson et al.[42] examined the plasma of 54 patients (versus healthy control participants) for the presence of HERV-W–related DNA. The patients were individuals with first hospitalizations and they had been diagnosed with schizophrenia, schizoaffective psychosis, or schizophreniform disorder. Thirty-three of these patients were from the previous study.[41] HERV-W–related *gag* sequences were found in 9 of 54 patients (16.7%) versus 2 of 46 healthy control participants (4.3%).

Frank et al.[43] studied expression profiles of HERV in brain samples of patients with schizophrenia and bipolar disorder. They conducted a microarray-based analysis of HERV transcriptional activity in human brains, investigating 50 representative members of 20 HERV families in 215 brain samples with matched controls. Although the study reported an HERV expression profile specific for the human brain consisting of constitutively and differentially active HERVs, the study could not discover an abnormal expression of HERV-W elements in patients with schizophrenia and bipolar disorder.

Weis et al.[44] studied the expression of the *gag* protein of HERV-W in the anterior cingulate cortex and hippocampus of postmortem brain samples of patients with schizophrenia, bipolar disorder, and depression, compared with normal control samples. They discovered a physiological expression of *gag* proteins in neurons and glial cells in normal brains, which was significantly reduced in brains of patients with psychiatric conditions.

Yao et al.[45] reported elevated levels of HERV-W *gag* transcripts in the mononuclear blood cells obtained from 30 patients with first-episode schizophrenia-related psychoses (including schizophrenia, schizophreniform disorder, and schizoaffective disorder) compared with 26 healthy control participants. Elevated total levels of HERV-W *gag* (2.1-fold) were noted, but no difference between the levels of HERW-W *env* transcripts was detected in the study. Some of the transcripts detected appeared to be transcribed at a higher rate in patients during the transition from susceptibility to manifestation of symptoms. Mapping of the detected transcripts also identified elements that were previously believed to be transcriptionally silent.

Perron et al.[46] quantified HERV-W *gag* and *env* proteins in the serum of 49 individuals with schizophrenia and 49 healthy control participants. Positive antigenemia for envelope protein was found in 46% of patients, whereas 49% of patients had positive antigenemia for *gag* compared with 3% for *env* and 4% for *gag* in control participants. A significant correlation was also found between *gag* or *env* antigenemia and C-reactive protein levels, suggesting an inflammation-mediated pathophysiology.

Huang et al.[47] sought to detect genes with mRNA sequences homologous to the HERV-W *env* gene in the plasma of 118 patients with recent-onset schizophrenia and 106 normal control participants. The authors found the genes in 42 of 118 patients (35.6%) but in none of the control participants. Quantitative real-time polymerase chain reaction analysis indicated significantly increased reverse transcriptase activity in patients compared with control participants. Using human U251 glioma cells, the authors found that overexpression of HERV-W *env* upregulates brain-derived neurotrophic factor (BDNF), neurotrophic tyrosine kinase receptor type 2 (also called TrkB), and dopamine receptor D3 (DRD3). The phosphorylation of cAMP response element-binding protein was also increased; with the use of gene knockdown, it was found that cAMP response element-binding protein is required for the expression of BDNF regulated by *env*, providing some explanation of the signaling pathway that is responsible for HERV-W *env*-triggered BDNF upregulation.

PATHOLOGICAL LIAISONS OF HERV-W

The envelope protein produced by HERV-W is a potent activator of innate immunity, inducing the release of proinflammatory cytokines. Rolland et al.[48] report that MSRV envelope protein stimulates human monocytes to produce proinflammatory cytokines, such as interleukin-1β, interleukin-6, and tumor necrosis factor-alpha through interactions with the CD14 receptors and Toll-like receptor 4. These are pattern recognition receptors playing a vital role in innate immunity, which is the first line of defense against viruses. It has been shown that the activation of innate immunity in the CNS through a Toll-like receptor 4–dependent pathway leads to neurodegeneration by involvement of microgliocytes.[49] HERV-W–encoded syncytin is upregulated in glial cells within acute demyelinating lesions of

TABLE 1. Studies Investigating the Association of HERV-W With Schizophrenia[a]

Study	Sample	Measured Entity	Diagnosis of Patients	Results	Comments
Yolken et al. (2000)[40]	Frontal cortices (postmortem)	RNA *pol* sequences, which were compared with known retroviruses	Schizophrenia, bipolar disorder	45% of cloned sequences from individuals with schizophrenia were homologous to the MSRV retrovirus of the HERV-W family versus 10% of sequences from control participants. A large fraction of clones from individuals with bipolar disorder were homologous to HERV-K10	
Karlsson et al. (2001)[41]	CSF	HERV-W RNA *pol* sequences	Recent-onset schizophrenia and schizoaffective disorder	RNA detected in 29% of patients with recent-onset schizophrenia and schizoaffective disorder. Detected in 0.05% of patients with chronic schizophrenia. Detected in none of the patients with noninflammatory neurological diseases and no neurological or psychiatric diseases	Results of the study suggest that HERV-W transcriptional activity may be related to the acuteness of schizophrenia
	Frontal cortices (postmortem)	RNA transcription	Chronic schizophrenia	RNA transcription was upregulated differentially in the frontal cortex of individuals with schizophrenia compared with individuals with no psychiatric disorder	
Karlsson et al. (2004)[42]	Plasma	HERV-W RNA *gag* sequences	First hospitalized patients with schizophrenia, schizoaffective disorder, or schizophreniform disorder	RNA detected in 17% of patients and 4% of control participants	HERV-W–positive patients were noted to have more pronounced severity of psychotic symptoms
Frank et al. (2005)[43]	Postmortem brain samples from all four cortices, cerebellum, and basal ganglia	HERV RNA (50 representative members of 20 HERV families)	Schizophrenia, bipolar disorder	HERV-K10 was significantly overrepresented in both bipolar disorder– and schizophrenia-associated samples compared with healthy brains	No abnormal expression of HERV-W elements reported
Weis et al. (2007)[44]	Anterior cingulate cortex and hippocampus of postmortem brain samples	HERV-W *gag* protein expression	Schizophrenia, bipolar disorder, depression	Reduced physiological expression of *gag* protein in neurons and astroglial cells	The study showed that HERV-W *gag* protein is expressed in the CNS under normal conditions

continued

TABLE 1, *continued*

Study	Sample	Measured Entity	Diagnosis of Patients	Results	Comments
Yao et al. (2008)[45]	Mononuclear blood cells	HERV-W *gag* and *env* RNA transcripts	Schizophrenia, schizoaffective disorder, schizophreniform disorder	Elevated total levels of HERV-W *gag* (2.1-fold) but not *env* transcripts in the cells of patients	Mapping of the detected transcripts identified elements that were previously believed to be transcriptionally silent
Perron et al. (2008)[46]	Serum	HERV-W *gag* and *env* proteins	Schizophrenia	*env* found in 47% of patients and 3% of control participants, and *gag* found in 49% of patients and 4% of control participants. Significant correlation between *gag* and *env* antigenemia and C-reactive protein levels	HERV-W antigens detected in living patients. HERV-W antigenemia correlated with inflammatory markers
Huang et al. (2011)[47]	Plasma human U251 glioma cells were used to study the potential role of the HERV-W *env* gene	HERV *env* mRNA	Recent-onset schizophrenia	mRNA detected in 35.6% of patients and 0% of control participants	This is the first study to identify the signaling pathway responsible for the HERV-W *env*-induced upregulation of BDNF
		Viral reverse transcriptase activity		Increased viral reverse transcriptase activity in serum by 35.59% in patients versus 2.83% in control participants. Overexpression of HERV-W *env* in human U251 glioma cells upregulated BDNF and CREB is required for the *env*-induced increased expression of BDNF	

[a] BDNF, brain-derived neurotrophic factor; CREB, cAMP response element-binding protein; HERV, human endogenous retrovirus; HERV-W, human endogenous retrovirus type W family; MSRV, multiple sclerosis–associated retroviral element.

multiple sclerosis, and this upregulated syncytin expression in astrocytes mediates neuroinflammation and oligodendrocyte cytotoxicity through release of redox reactants.[50] Furthermore, the envelope protein can also induce a maturation process in human dendritic cells and stimulate the development of Th1-like responses. Perron et al.[51] showed that the MSRV envelope protein can trigger an abnormal immune response consisting of polyclonal T-lymphocyte activation with characteristics similar to those of superantigens.

As discussed above, *gag* or *env* antigenemia in schizophrenia was concomitant with elevated C-reactive protein levels, which is a biomarker of systemic inflammation.[46] Given the evidence that the HERV-W envelope protein is proinflammatory, the elevated C-reactive protein levels can be the result of a subacute or chronic inflammatory process driven by the HERV-W envelope protein. Elevated serum levels of C-reactive protein were associated with the severity of cognitive impairment in individuals with schizophrenia.[52] Tumor necrosis factor-alpha could be one of the central cytokines involved in this inflammatory process, because plasma levels of soluble tumor necrosis factor receptor 1 were significantly increased in patients with schizophrenia.[53]

Animal models of schizophrenia implicate the altered expression of BDNF as a risk factor for schizophrenia,[54] and an association of schizophrenia with the DRD3 gene was reported.[55] BDNF regulates the expression of DRD3 receptors, and interaction between BDNF and DRD3 receptor gene variants is significantly associated with an earlier emergence of psychosis in schizophrenia by up to 3 years.[56]

As mentioned above, HERV-W *env* overexpression upregulates BDNF and DRD3.[47] This finding suggests a role of HERV-W in schizophrenia-associated BDNF and DRD3 abnormalities.

Some HERVs use neuroactive molecules as receptors. The receptor for HERV-W is the family of neutral amino acid transporters (ASCT-1 and ASCT-2), which transport excitatory amino acids in the nervous system.[57] Weis et al.[58] reported a significant decrease in ASCT-1 immunoreactivity in neurons in the cingulate cortex as well as astrocytes of the white matter in schizophrenia. This reduced expression of ASCT-1 may be because of receptor modulation or because the receptors are being blocked by the HERV-W envelope protein. Blocking of these receptors could theoretically lead to decreased uptake of the amino acids that are required by the neurons to maintain their production of neurotransmitters. One can speculate here that certain neurons (e.g., dopaminergic neurons) may be more sensitive to this receptor-blocking effect of the HERV-W envelope protein, which may explain the dopaminergic dysfunction that underlies schizophrenia.[59]

The dysfunction of neurotransmitter GABA has been implicated in schizophrenia as well.[60] The GABA type B receptor 1 gene has been localized to 6p21.3, a region linked to schizophrenia.[61] An HERV-W long terminal repeat is present in the regulatory region of GABA type B receptor 1, which could potentially be involved in the altered expression of this gene.[62]

HERV-W ACTIVATION BY INFECTIONS

A number of viral infections have consistently been associated with schizophrenia, but decades of research have ruled out a simple infectious etiology for the disorder. Prenatal maternal infections have shown the greatest evidence of risk for schizophrenia, but evidence also implicates infections during adult life. Prenatal maternal infections associated with schizophrenia include influenza,[10] rubella,[11] herpes simplex virus type 2,[12] cytomegalovirus,[13] and *T. gondii*.[14] Certain infections later in life, such as cytomegalovirus and *T. gondii*, can serve as secondary risk factors associated with the development of schizophrenia.[15,16] Whereas herpes simplex virus type 2 infection has been associated with schizophrenia in the maternal prenatal stage, herpes simplex virus type 1 infection has been associated with schizophrenia in adulthood, with herpes simplex virus type 1 seropositivity related to gray matter volume.[63] It is difficult to explain the risk for schizophrenia in terms of direct effects of viral infections, although several hypotheses have been proposed on the direct inflammatory effects and consequences of infections,[64] and HERV-W is an excellent candidate to explain the link between the two.

HERV genetic elements are generally not expressed, given that most copies are defective and the remaining are silenced by epigenetic mechanisms such as DNA methylation of gene promoter regions. However, it is now established that certain infections can activate HERV-W elements.[38] They may do so directly by transactivating promoters, or they may cause demethylation of target genes and thus render them capable of responding to transactivating stimuli.[59] In an experiment by Nellåker et al.,[65] the influenza virus was shown to activate HERV-W expression with a cell-specific pattern. Elements with intact long terminal repeats as well as those elements flanked by truncated long terminal repeats were expressed and regulated secondary to the virus infection. Findings recently reported by Li et al.[66] suggest that an exogenous influenza A virus infection can transactivate HERV-W element ERVWE1 by increasing the transcription of GCM1 and reducing the repressive histone mark H3K9me3 in this region and in other regions harboring HERV-W elements. Perron et al.[67] demonstrated that in vitro infection of leptomeningeal cells in patients with multiple sclerosis with herpes simplex virus type 1 results in potent stimulation of the specific reverse transcriptase activity and coexpression of both herpes simplex virus type 1 virions and retrovirus-like particles. However, herpes simplex virus type 1 did not lead to this retroviral expression in non–multiple sclerosis cells, which were presumably devoid of such genetic potential.[67] Frank et al.[68] reported increased transcriptional activity of HERV elements from all three classes in cells infected with *T. gondii*, suggesting that *T. gondii* can activate the transcription of HERVs in neuronal cells. Nelson et al.[69] observed that mRNA expression of HERV-K10 was enhanced in fibroblasts infected with human cytomegalovirus. Similar activation of the HERV-W may also occur secondary to infection by cytomegalovirus. Assinger et al.[70] showed that experimental cytomegalovirus infection of human cells increases expression of several HERV families, including HERV-W. Depending on the tropism of the infective viruses, one can expect local activation and expression of HERV-W elements in different regions. Herpesviridae have dominant white matter tropism, whereas cytomegalovirus is said to be gray matter tropic. The white matter pathology of multiple sclerosis and the gray matter abnormalities of schizophrenia may be partly explainable by differing viral tropisms.[59]

Once activated, HERV elements can produce the envelope protein (possibly associated with retroviral particles), leading to neuroinflammation and neurotoxicity.[38] This viral activation can be of greater significance in early embryonic development because there is a significant reduction of DNA methylation in early embryonic cells,[71] which makes the HERV-W genetic elements more vulnerable to viral activation compared with adult life.[59] This activation can lead to production of more copies of the HERV-W genes through reverse transcription, and these DNA copies can be retroinserted into the embryonic DNA through retrotransposition, causing various recombinations, deletions, and copy number variations. This retrotransposition could be a plausible explanation for the DNA modifications that have been reported in schizophrenia.[72] These abnormal genetic modifications in combination with neuroinflammation can set the brain on the path of abnormal neurodevelopment.

Leboyer et al.[38] provide a conceptual framework for linking HERV-W and the natural history of schizophrenia. They hypothesize that prenatal viral (or protozoal) infections can trigger activation of HERV-W genetic elements, leading to retrotranspositions (accounting for various genetic modifications) and induction of chronic subacute neuroinflammation. This mechanism results in developmental, cognitive, and neurostructural deficits that have been reported in schizophrenia even in prodromal and first-episode psychosis.[73,74] Secondary infections such as cytomegalovirus, herpes simplex virus type 1, *T. gondii*, or other environmental triggers can reactivate the perinatally modified HERV-W copies, expressing the production of HERV-W envelope protein in the CNS, leading to inflammation and neurotoxicity culminating in the first episode of psychosis. Subsequent episodes and a deteriorating course could be linked to repeated instances of reactivation of HERV-W elements. This framework is also consistent with the two-hit hypothesis of schizophrenia.[22]

APPRAISAL AND LIMITATIONS

There are currently only a handful of studies providing evidence of an association between HERV-W and schizophrenia. These studies have investigated different tissues and fluids. In the studies we discussed above, one study investigated CSF, three studies used plasma, three studies utilized brain samples, and one study examined mononuclear blood cells.[40–47] The sample size was limited in all of them, the smallest being four cases of schizophrenia and the largest being 118 cases. These associations need to be replicated with larger sample sizes. For healthy skepticism, one should remember the numerous and mostly defective nature of most HERV proviruses, along with the existence of unfixed HERV proviruses lacking stable insertion sites. Most RNA produced from transcriptional activity of HERV genetic elements is defective or unstable in nature, lacking a biological impact because it is not capable of being translated to bioactive proteins leading to pathogenicity. The majority of the studies discussed in the section on the association of HERV-W with schizophrenia report the increased presence of genetic elements and/or transcripts, which by itself is no guarantee of a pathophysiological role because we can expect most of these genetic elements or transcripts to be defective. Only one study demonstrated an increased presence of HERV-W proteins with correlation between antigenemia and C-reactive protein levels.[46] It is also known that HERV RNA expression of a range of class I and II HERVs, rather than that of a specific provirus, is upregulated in several autoimmune diseases and cancers. It is unclear whether HERVs are the triggering agents of the inflammation or whether their upregulation is a consequence of existing inflammation, or perhaps a combination of both.[75] Clarification of this would require determining a temporal relationship between HERV expression, inflammatory processes, and disease manifestation. When it comes to HERVs, detection of virus expression alone is not proof of disease causation.

Many of the above-described studies included subjects diagnosed with schizophreniform disorder, schizoaffective disorder, bipolar disorder, and major depression in addition to schizophrenia. This trend indicates that the biological role of HERV-W is not quite limited to schizophrenia and may extend beyond this diagnostic category. It is also likely that biological and genetic etiologies of psychiatric disorders do not respect the symptom-based classifications of *DSM* and *ICD*. Future studies should investigate varying levels of expression of HERV-W elements during the course of schizophrenia and correlate them with its clinical progress and prognosis. Most of the discussion regarding pathophysiological liaisons is speculative and theoretical, given the various features of HERVs that have been investigated elsewhere. These pathophysiological mechanisms should be investigated directly in cases of schizophrenia as well. It also remains to be proven whether there is any overlap between patients with HERV expression, subsets of patients with infectious associations, and those with raised inflammatory markers. This would make sense given the existing evidence, but further experimental evidence is now required.

AUTHOR AND ARTICLE INFORMATION

From the Dept. of Psychiatry, University Hospitals Case Medical Center, Case Western Reserve University, Cleveland, OH (AA); the Menninger Dept. of Psychiatry and Family and Community Medicine, Baylor College of Medicine, Houston, TX (AAS); and the Dept. of Psychiatry, King Edward Medical University, Mayo Hospital, Lahore, Pakistan (AMH).

Send correspondence to Dr. Aftab; e-mail: awaisaftab@gmail.com

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REFERENCES

1. Saha S, Chant D, Welham J, et al: A systematic review of the prevalence of schizophrenia. PLoS Med 2005; 2:e141
2. Rössler W, Salize HJ, van Os J, et al: Size of burden of schizophrenia and psychotic disorders. Eur Neuropsychopharmacol 2005; 15: 399–409
3. Tandon R, Keshavan MS, Nasrallah HA: Schizophrenia, "just the facts": what we know in 2008 part 1: overview. Schizophr Res 2008; 100:4–19
4. Tandon R, Keshavan MS, Nasrallah HA: Schizophrenia, "just the facts" what we know in 2008. 2. Epidemiology and etiology. Schizophr Res 2008; 102:1–18
5. Pedersen CB, Mortensen PB: Evidence of a dose-response relationship between urbanicity during upbringing and schizophrenia risk. Arch Gen Psychiatry 2001; 58:1039–1046
6. Davies G, Welham J, Chant D, et al: A systematic review and meta-analysis of Northern Hemisphere season of birth studies in schizophrenia. Schizophr Bull 2003; 29:587–593
7. Penner JD, Brown AS: Prenatal infectious and nutritional factors and risk of adult schizophrenia. Expert Rev Neurother 2007; 7: 797–805
8. Byrne M, Agerbo E, Bennedsen B, et al: Obstetric conditions and risk of first admission with schizophrenia: a Danish national register based study. Schizophr Res 2007; 97:51–59

9. Ashdown H, Dumont Y, Ng M, et al: The role of cytokines in mediating effects of prenatal infection on the fetus: implications for schizophrenia. Mol Psychiatry 2006; 11:47–55
10. Brown AS, Begg MD, Gravenstein S, et al: Serologic evidence of prenatal influenza in the etiology of schizophrenia. Arch Gen Psychiatry 2004; 61:774–780
11. Brown AS, Cohen P, Harkavy-Friedman J, et al: A.E. Bennett Research Award. Prenatal rubella, premorbid abnormalities, and adult schizophrenia. Biol Psychiatry 2001; 49:473–486
12. Buka SL, Cannon TD, Torrey EF, et al: Collaborative Study Group on the Perinatal Origins of Severe Psychiatric Disorders: Maternal exposure to herpes simplex virus and risk of psychosis among adult offspring. Biol Psychiatry 2008; 63:809–815
13. Blomström A, Karlsson H, Wicks S, et al: Maternal antibodies to infectious agents and risk for non-affective psychoses in the offspring—a matched case-control study. Schizophr Res 2012; 140: 25–30
14. Mortensen PB, Nørgaard-Pedersen B, Waltoft BL, et al: Toxoplasma gondii as a risk factor for early-onset schizophrenia: analysis of filter paper blood samples obtained at birth. Biol Psychiatry 2007; 61:688–693
15. Dickerson F, Kirkpatrick B, Boronow J, et al: Deficit schizophrenia: association with serum antibodies to cytomegalovirus. Schizophr Bull 2006; 32:396–400
16. Leweke FM, Gerth CW, Koethe D, et al: Antibodies to infectious agents in individuals with recent onset schizophrenia. Eur Arch Psychiatry Clin Neurosci 2004; 254:4–8
17. Rapoport JL, Giedd JN, Gogtay N: Neurodevelopmental model of schizophrenia: update 2012. Mol Psychiatry 2012; 17:1228–1238
18. Müller N: Immunology of schizophrenia. Neuroimmunomodulation 2014; 21:109–116
19. Jia P, Wang L, Meltzer HY, et al: Common variants conferring risk of schizophrenia: a pathway analysis of GWAS data. Schizophr Res 2010; 122:38–42
20. Schizophrenia Working Group of the Psychiatric Genomics Consortium: Biological insights from 108 schizophrenia-associated genetic loci. Nature 2014; 511:421–427
21. Muller N, Schwarz M: Schizophrenia as an inflammation-mediated dysbalance of glutamatergic neurotransmission. Neurotox Res 2006; 10:131–148
22. Feigenson KA, Kusnecov AW, Silverstein SM: Inflammation and the two-hit hypothesis of schizophrenia. Neurosci Biobehav Rev 2014; 38:72–93
23. Alelú-Paz R, Iturrieta-Zuazo I: Human endogenous retroviruses: their possible role in the molecular etiology of the schizophrenia. Open J Genetics 2012; 2:70–76
24. Griffiths DJ: Endogenous retroviruses in the human genome sequence. Genome Biol 2001; 2:reviews1017.1–reviews1017.5
25. Pavlícek A, Paces J, Elleder D, et al: Processed pseudogenes of human endogenous retroviruses generated by LINEs: their integration, stability, and distribution. Genome Res 2002; 12: 391–399
26. Venter JC, Adams MD, Myers EW, et al: The sequence of the human genome. Science 2001; 291:1304–1351
27. Magiorkinis G, Belshaw R, Katzourakis A: 'There and back again': revisiting the pathophysiological roles of human endogenous retroviruses in the post-genomic era. Philos Trans R Soc Lond B Biol Sci 2013; 368:20120504
28. Nelson PN, Carnegie PR, Martin J, et al: Demystified. Human endogenous retroviruses. Mol Pathol 2003; 56:11–18
29. Voisset C, Blancher A, Perron H, et al: Phylogeny of a novel family of human endogenous retrovirus sequences, HERV-W, in humans and other primates. AIDS Res Hum Retroviruses 1999; 15:1529–1533
30. Mi S, Lee X, Li X, et al: Syncytin is a captive retroviral envelope protein involved in human placental morphogenesis. Nature 2000; 403:785–789
31. Chen CP, Wang KG, Chen CY, et al: Altered placental syncytin and its receptor ASCT2 expression in placental development and preeclampsia. BJOG 2006; 113:152–158
32. Perron H, Lazarini F, Ruprecht K, et al: Human endogenous retrovirus (HERV)-W ENV and GAG proteins: physiological expression in human brain and pathophysiological modulation in multiple sclerosis lesions. J Neurovirol 2005; 11:23–33
33. Oluwole SO, Yao Y, Conradi S, et al: Elevated levels of transcripts encoding a human retroviral envelope protein (syncytin) in muscles from patients with motor neuron disease. Amyotroph Lateral Scler 2007; 8:67–72
34. Perron H, Lalande B, Gratacap B, et al: Isolation of retrovirus from patients with multiple sclerosis. Lancet 1991; 337:862–863
35. Perron H, Garson JA, Bedin F, et al: The Collaborative Research Group on Multiple Sclerosis: Molecular identification of a novel retrovirus repeatedly isolated from patients with multiple sclerosis. Proc Natl Acad Sci USA 1997; 94:7583–7588
36. Blond JL, Besème F, Duret L, et al: Molecular characterization and placental expression of HERV-W, a new human endogenous retrovirus family. J Virol 1999; 73:1175–1185
37. Crow TJ: A re-evaluation of the viral hypothesis: is psychosis the result of retroviral integration at a site close to the cerebral dominance gene? Br J Psychiatry 1984; 145:243–253
38. Leboyer M, Tamouza R, Charron D, et al: Human endogenous retrovirus type W (HERV-W) in schizophrenia: a new avenue of research at the gene-environment interface. World J Biol Psychiatry 2013; 14:80–90
39. Deb-Rinker P, Klempan TA, O'Reilly RL, et al: Molecular characterization of a MSRV-like sequence identified by RDA from monozygotic twin pairs discordant for schizophrenia. Genomics 1999; 61:133–144
40. Yolken RH, Karlsson H, Yee F, et al: Endogenous retroviruses and schizophrenia. Brain Res Brain Res Rev 2000; 31:193–199
41. Karlsson H, Bachmann S, Schröder J, et al: Retroviral RNA identified in the cerebrospinal fluids and brains of individuals with schizophrenia. Proc Natl Acad Sci USA 2001; 98:4634–4639
42. Karlsson H, Schröder J, Bachmann S, et al: HERV-W-related RNA detected in plasma from individuals with recent-onset schizophrenia or schizoaffective disorder. Mol Psychiatry 2004; 9:12–13
43. Frank O, Giehl M, Zheng C, et al: Human endogenous retrovirus expression profiles in samples from brains of patients with schizophrenia and bipolar disorders. J Virol 2005; 79:10890–10901
44. Weis S, Llenos IC, Sabunciyan S, et al: Reduced expression of human endogenous retrovirus (HERV)-W GAG protein in the cingulate gyrus and hippocampus in schizophrenia, bipolar disorder, and depression. J Neural Transm 2007; 114:645–655
45. Yao Y, Schröder J, Nellåker C, et al: Elevated levels of human endogenous retrovirus-W transcripts in blood cells from patients with first episode schizophrenia. Genes Brain Behav 2008; 7: 103–112
46. Perron H, Mekaoui L, Bernard C, et al: Endogenous retrovirus type W GAG and envelope protein antigenemia in serum of schizophrenic patients. Biol Psychiatry 2008; 64:1019–1023
47. Huang W, Li S, Hu Y, et al: Implication of the env gene of the human endogenous retrovirus W family in the expression of BDNF and DRD3 and development of recent-onset schizophrenia. Schizophr Bull 2011; 37:988–1000
48. Rolland A, Jouvin-Marche E, Viret C, et al: The envelope protein of a human endogenous retrovirus-W family activates innate immunity through CD14/TLR4 and promotes Th1-like responses. J Immunol 2006; 176:7636–7644
49. Lehnardt S, Massillon L, Follett P, et al: Activation of innate immunity in the CNS triggers neurodegeneration through a Toll-like receptor 4-dependent pathway. Proc Natl Acad Sci USA 2003; 100: 8514–8519
50. Antony JM, van Marle G, Opii W, et al: Human endogenous retrovirus glycoprotein-mediated induction of redox reactants causes

oligodendrocyte death and demyelination. Nat Neurosci 2004; 7: 1088–1095
51. Perron H, Jouvin-Marche E, Michel M, et al: Multiple sclerosis retrovirus particles and recombinant envelope trigger an abnormal immune response in vitro, by inducing polyclonal Vbeta16 T-lymphocyte activation. Virology 2001; 287:321–332
52. Dickerson F, Stallings C, Origoni A, et al: C-reactive protein is associated with the severity of cognitive impairment but not of psychiatric symptoms in individuals with schizophrenia. Schizophr Res 2007; 93:261–265
53. Hope S, Melle I, Aukrust P, et al: Similar immune profile in bipolar disorder and schizophrenia: selective increase in soluble tumor necrosis factor receptor I and von Willebrand factor. Bipolar Disord 2009; 11:726–734
54. Angelucci F, Brenè S, Mathé AA: BDNF in schizophrenia, depression and corresponding animal models. Mol Psychiatry 2005; 10:345–352
55. Talkowski ME, Mansour H, Chowdari KV, et al: Novel, replicated associations between dopamine D3 receptor gene polymorphisms and schizophrenia in two independent samples. Biol Psychiatry 2006; 60:570–577
56. Gourion D, Goldberger C, Leroy S, et al: Age at onset of schizophrenia: interaction between brain-derived neurotrophic factor and dopamine D3 receptor gene variants. Neuroreport 2005; 16: 1407–1410
57. Marin M, Lavillette D, Kelly SM, et al: N-linked glycosylation and sequence changes in a critical negative control region of the ASCT1 and ASCT2 neutral amino acid transporters determine their retroviral receptor functions. J Virol 2003; 77:2936–2945
58. Weis S, Llenos IC, Dulay JR, et al: Changes in region- and cell type-specific expression patterns of neutral amino acid transporter 1 (ASCT-1) in the anterior cingulate cortex and hippocampus in schizophrenia, bipolar disorder and major depression. J Neural Transm 2007; 114:261–271
59. Perron H, Lang A: The human endogenous retrovirus link between genes and environment in multiple sclerosis and in multifactorial diseases associating neuroinflammation. Clin Rev Allergy Immunol 2010; 39:51–61
60. Taylor SF, Tso IF: GABA abnormalities in schizophrenia: a methodological review of in vivo studies. Schizophr Res (Epub ahead of print, Oct 25, 2014)
61. Zai G, King N, Wong GW, et al: Possible association between the gamma-aminobutyric acid type B receptor 1 (GABBR1) gene and schizophrenia. Eur Neuropsychopharmacol 2005; 15:347–352
62. Hegyi H: GABBR1 has a HERV-W LTR in its regulatory region—a possible implication for schizophrenia. Biol Direct 2013; 8:5
63. Prasad KM, Bamne MN, Shirts BH, et al: Grey matter changes associated with host genetic variation and exposure to Herpes Simplex Virus 1 (HSV1) in first episode schizophrenia. Schizophr Res 2010; 118:232–239
64. Kneeland RE, Fatemi SH: Viral infection, inflammation and schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 2013; 42:35–48
65. Nellåker C, Yao Y, Jones-Brando L, et al: Transactivation of elements in the human endogenous retrovirus W family by viral infection. Retrovirology 2006; 3:44
66. Li F, Nellåker C, Sabunciyan S, et al: Transcriptional derepression of the ERVWE1 locus following influenza A virus infection. J Virol 2014; 88:4328–4337
67. Perron H, Suh M, Lalande B, et al: Herpes simplex virus ICP0 and ICP4 immediate early proteins strongly enhance expression of a retrovirus harboured by a leptomeningeal cell line from a patient with multiple sclerosis. J Gen Virol 1993; 74:65–72
68. Frank O, Jones-Brando L, Leib-Mosch C, et al: Altered transcriptional activity of human endogenous retroviruses in neuroepithelial cells after infection with Toxoplasma gondii. J Infect Dis 2006; 194:1447–1449
69. Nelson PN, Lever AM, Smith S, et al: Molecular investigations implicate human endogenous retroviruses as mediators of antiretroviral antibodies in autoimmune rheumatic disease. Immunol Invest 1999; 28:277–289
70. Assinger A, Yaiw KC, Göttesdorfer I, et al: Human cytomegalovirus (HCMV) induces human endogenous retrovirus (HERV) transcription. Retrovirology 2013; 10:132
71. Nafee TM, Farrell WE, Carroll WD, et al: Epigenetic control of fetal gene expression. BJOG 2008; 115:158–168
72. International Schizophrenia Consortium: Rare chromosomal deletions and duplications increase risk of schizophrenia. Nature 2008; 455:237–241
73. Borgwardt SJ, McGuire PK, Aston J, et al: Reductions in frontal, temporal and parietal volume associated with the onset of psychosis. Schizophr Res 2008; 106:108–114
74. Lappin JM, Dazzan P, Morgan K, et al: Duration of prodromal phase and severity of volumetric abnormalities in first-episode psychosis. Br J Psychiatry Suppl 2007; 51:s123–s127
75. Brodziak A, Ziółko E, Muc-Wierzgoń M, et al: The role of human endogenous retroviruses in the pathogenesis of autoimmune diseases. Med Sci Monit 2012; 18:RA80–RA88