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Review article

Reviewing the evidence for viruses as environmental risk factors for ALS: A new perspective

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ABSTRACT

Amyotrophic lateral sclerosis is a devastating neurodegenerative disease whose etiology remains poorly understood. Since the genetic basis of disease is known in only a small subset of cases, there has been substantial interest in determining whether environmental factors act as triggers of ALS. Viruses have received longstanding attention as potential ALS triggers. Yet, existing studies have not provided a compelling case for causation. This review summarizes the evidence supporting a link between viral infection and motor neuron disease, with a focus on ALS. Limitations of prior studies are discussed and contextualized, and recent work that has provided stronger mechanistic evidence for viruses in disease pathogenesis is highlighted. Finally, we offer a new perspective on the association of viruses with ALS, and underscore the need for multidisciplinary approaches bridging neurology and infectious diseases research to move the field forward in the future.

1. Introduction

Amyotrophic lateral sclerosis (ALS) is the most common motor neuron disease (MND), with a lifetime risk of approximately 1 in 400 [1]. Yet, it remains a fatal and largely untreatable condition. Onset of ALS generally occurs between the ages of 50 and 75, and patients typically succumb to disease within 3-4 years of diagnosis [1]. While several abnormal cellular and molecular pathways have been implicated in ALS pathophysiology, the features that are responsible for disease onset/progression remain controversial and incompletely understood [2]. To-date, mutations in over 100 genes have been identified as potential ALS risk factors. However, only a small subset of these have been studied in enough depth for them to be considered bona fide ALS genes [3]. Despite the fact that in some populations a genetic basis for ALS can be identified in as little as 10% of cases, twin-based heritability studies provide support for a genetic link in 38-78% of patients [3,4]. Nevertheless, only 11-25% of ALS cases are attributable to common genetic variants [4,5], and thus rare de novo variants and gene-environment interactions are thought to play on important role in disease etiology.

One of the most longstanding and controversial environmental risk factors investigated for its potential association with ALS is viral infection [6]. Historically, the most extensively-studied viruses in this context have been those that exhibit neurotropism, including enteroviruses (e.g. Poliovirus), retroviruses and herpesviruses. However, these studies have largely been limited to observational data reporting elevated rates of seropositivity and/or enriched detection of viral antigens in pathological specimens of an ALS cohort relative to a control population. Studies of this nature, while useful for hypothesis generation, are unable to resolve the critical question of whether elevated rates of a given infection are a cause or consequence of ALS. As a result, little compelling mechanistic data exists to explain how viral infections might elevate disease risk.

The core assumption tested by the aforementioned studies is that a particular virus, by virtue of elevated rates of detection in an ALS population, might be responsible for triggering disease. However, a more straightforward possibility that previous studies have largely failed to address is that common viral infections cause disease by perturbing pathways that are already dysregulated in individuals who go on to develop ALS. Indeed, almost all viruses stimulate and/or modulate many of the pathways that are known to be pathophysiological features of disease (Fig. 1). Induction of oxidative stress, as well as manipulation of protein folding/misfolding pathways, mitochondrial dynamics, stress granules, and induction of inflammation are all common consequences of viral infections. Virus-mediated perturbation of these pathways in individuals who have an underlying genetic predisposition could then serve as a trigger for disease onset and would not require that rates of a given infection be higher in individuals with ALS relative to controls.

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Fig. 1. Cellular pathways involved in ALS pathogenesis are manipulated during viral infection. Viral infections rely on and/or manipulate many pathways associated with ALS pathophysiology, including oxidative stress, inflammation, toxic protein aggregation and intercellular spread, ER stress pathways, stress granule dynamics and RNA metabolism, and mitochondrial functions. Viral perturbations of pathways already under stress due to underlying genetic factors may be responsible for triggering ALS onset, or speeding disease progression.

In contrast to multiple sclerosis (MS) patients, who often report relapse/flare-ups after infection, individuals who are diagnosed with ALS do not frequently report associations between acute infections and onset of disease [7]. Incidents of relapse in the context of MS typically occur in close proximity to infection, and in a patient population who has already received a diagnosis. In contrast, the onset of ALS begins very slowly, and there is no definitive diagnostic test to confirm ALS. After reporting initial symptoms, there is often a 1- to 2-year period of clinical evaluation before a diagnosis of ALS is reached. Thus, it would be very difficult for patients to associate an "everyday" infection with the onset of disease after such a long diagnostic lag. Importantly, there may also be a delay between acute infection and symptom onset. These factors make associations between infection and ALS onset difficult to detect.

In the sections that follow, we will summarize and discuss the current state of the literature pertaining to viral infections as a risk factor for ALS (Table 1). We will then provide a new framework for understanding how viral infections might act as triggers of disease, and

highlight some of the major outstanding questions that future studies should address.

2. Reported associations between viral infections and ALS

2.1. Historical associations of Poliovirus and ALS

The neurotropic nature of Poliovirus and its propensity to cause paralytic poliomyelitis (which shares clinicopathogenic properties with MND) has fueled dozens of studies investigating possible relationships between enteroviruses and MND. One of the first epidemiological studies of the relationship between ALS and prior Poliovirus infection reported an unusually high proportion of ALS patients (11 of 127) having antecedent Poliovirus infection [8]. However, others have suggested that these data are likely to have suffered from statistical flaws and selection bias for ALS patients [9]. The earliest epidemiological report suggesting a possible etiological role for viral infection in MND demonstrated a modest correlation between cases of poliomyelitis in

Table 1

Summary of reports investigating involvement of human viruses in ALS.

Virus	Existing Data
Enteroviruses	Several attempts to detect enterovirus sequences in the CNS (brain, spinal cord, CSF) of ALS patients using RT-PCR have provided mixed results regarding the association of these viruses with ALS [16,18–21] Enteroviral proteases have been shown to cleave TDP-43 into fragments, which aggregate akin to what occurs in ALS patients exhibiting
Poliovirus	TDP-43 pathology [23] Initially correlated notifications of Poliomyelitis in England and Wales with deaths by motor neuron disease ~40 years later[10], although many motor neuron disease diagnoses may have been post-polio syndrome [11]
Echovirus 7	A polymorphism in the human convorus receiptor gene is increasingly prevalent anong progressive muscular autophy (but not ALS) patients, possibly contributing to alternate consequences of infection or alteration of the receptor's normal function [13] Enteroviral RNA detected in spinal cord neurons of ALS patients exhibited significant homology to Echovirus 7, but detection of such sequences in brains and spinal cords of patients in another study was not reproducible [18] Increased seroprevalence among ALS patients compared to controls regardless of disease progression [17]
Retroviruses	A higher proportion of patients with non-inherited ALS (59%) had serum reverse transcriptase activity compared to HIV-/HTLV-
Human immunodeficiency virus (HIV)	seronegative controls (5%) [33] About 70% of HIV-infected patients experience nuerological complications, though these are usually cognitive in nature [26] An HIV-associated neurological syndrome can present identically to ALS, perhaps due to secretion of neurotoxic viral proteins and cytokines by infected microglia or evolution of a neurotropic quasispecies [28]
Human T-lymphotropic virus (HTLV)	Expression of the HIV genome in neurons of transgenic mice leads to neurological disease [32] Infection can lead to a pseudo-ALS syndrome manifesting as HTLV-associated myelopathy (tropical spastic paraparesis), muscular
Human endogenous retrovirus (HERV)	atrophy, and fasciculations [11] ALS patients exhibit tremendous HERV activation, expressing HERV-K <i>pol</i> in neurons and <i>gag</i> , <i>pol</i> , and <i>env</i> in the brain [34]. <i>Env</i> expression in mice leads to degradation of upper and lower motor neurons [35] TDP-43 directly regulates HERV-K expression [35] Expression of HERV-K is upregulated during HIV infection, and potentially reduced upon treatment with antiretroviral therapy [36]
Herpesviruses HHV-6/-8	Increased seroprevalence among ALS patients compared to controls regardless of disease progression [17], but no difference in PBMC and CSF DNA levels for HHV-8 [39]

young individuals and death by MND approximately 40 years later [10]. Reports were collected in the form of notifications at the population level for England and Wales, and thus are correlative and cannot be used to imply causation. Nevertheless, the authors emphasized the need for further studies focused on defining the relationship between Poliovirus and MND. Several case-control studies assessing the relationship between MND and past poliomyelitis were subsequently performed and have not found a significant association [11]. It is worth noting that many historical notifications of MND from individuals with prior polio may have been confused with what we now know to be postpolio syndrome [11], which shares several common features with ALS.

A potential genetic predisposition to MND in individuals with antecedent polio has also been reported. Heterozygous Ala68Thr polymorphisms in domain 1 of the Poliovirus receptor protein (PVR), which are associated with increased susceptibility to infection in cell culture [12], appeared to be more prevalent among those with progressive muscular atrophy [13]. However, these mutations were not enriched among ALS patients when compared to the control population. Whether the association between polymorphisms in PVR and progressive muscular atrophy are due to an increased susceptibility to infection, or to abnormal protein activity (as PVR is reported to play a role in neuronal differentiation during embryonic development) remains unclear [14]. It is worth noting that acute neurological sequalae which typically occur as a result of enterovirus infection involve lower motor neurons due to targeting of the anterior horn cells. By definition, ALS involves both upper and lower motor neurons. Thus, if enterovirus infection were to serve as an ALS trigger, its features would have to be distinct from those that occur during acute infection [15]. Taken together, the evidence supporting a relationship between Poliovirus and MND remains controversial due to a lack of mechanistic data supporting causation. Thus, there is a dire need to develop laboratory models capable of recapitulating the clinical features of ALS, and of differentiating between ALS and post-polio syndrome. These studies would provide more detailed mechanistic insight into the association between infection and disease.

A specific association between ALS and Echovirus 7 infection was also documented after enteroviral RNA sequences detected in ALS

patient spinal cords displayed 86-94% homology with Echovirus 7 [16]. However, while one follow-up study also reported an association between ALS and Echovirus 7 seropositivity [17], another failed to isolate Echovirus 7 sequences from the brains and spinal cords of ALS patients [18], bringing into question the strength and breadth of this association.

Numerous studies investigating enteroviruses more broadly as etiological agents involved in ALS have provided mixed results after performing RT-PCR analyses of samples from the central nervous system (CNS) of ALS patients [16,18–21]. Most recently, analysis of cerebrospinal fluid (CSF) from 242 ALS patients and 354 controls revealed a significantly elevated frequency of enteroviral RNA in ALS patient samples [21]. However, even in cases where ALS patients were more likely to harbor enterovirus sequences in their CSF, it is unclear whether this association is a cause or consequence of disease [22].

2.2. Biochemical evidence of enterovirus involvement in ALS

More recently, biochemical evidence has emerged suggesting a role for enteroviral proteases in ALS pathogenesis through cleavage of TDP-43 (an important ALS-associated protein) to produce potentially pathogenic fragments [23]. Fung and colleagues demonstrated that Coxsackievirus B3 protease 2A translocates TDP-43 from the nucleus to the cytoplasm, where the viral protease 3C cleaves it into N- and C-terminal fragments of ~ 35 and ~ 8 kDa, respectively [23]. The stable N-terminal fragment exhibited reduced solubility and localized to stress granules to form ubiquitinated protein aggregates [23] – a phenotype similar to that observed with pathological TDP-43 in the context of ALS [24,25]. While this data provides an attractive mechanistic model through which enteroviruses may specifically cause disease, more studies are needed to determine whether, and in which contexts, protease 2Acleaved TDP-43 is associated with ALS.

2.3. Retroviruses in ALS and other neuropathies

About 70% of human immunodeficiency virus (HIV)-infected patients experience nuerological complications, though these are usually cognitive in nature [26]. A small number of infections with HIV or human T-lymphotropic virus (HTLV) progress to an ALS-like syndrome, which lead to the hypothesis that exogenous retroviruses may play a role in ALS pathogenesis. Specifically, 0.25-3.8% of individuals infected with HTLV-1 develop associated myelopathy/tropical spastic paraparesis (HAM/TSP) [27], and at least 35 HAM/TSP cases have met the diagnostic criteria for an ALS-like syndrome [28]. However, since risk of developing ALS and rates of HTLV-1 seropositivity are both highest in one's sixties, it is difficult to assess the reliability of these associations [28]. Additionally, at least 29 cases of an HIV-associated ALS-like syndrome have been reported [28]. These cases typically exhibit a younger age of onset, rapid progression, high protein concentrations in CSF, and stabilization or improvement after beginning antiretroviral therapy [28]. Since HIV infects microglia and macrophages in the CNS, rather than neurons [29], these infected immune cells may produce neurotoxic viral proteins or cytokines that damage motor neurons [30]. Alternatively, it has been suggested that in rare cases, neurotropic HIV quasispecies may arise within an individual and cause an ALS-like syndrome, though no there is currently no evidence of this occurring [28].

Interestingly, murine retroviruses are known to cause MND in mice. Specifically, murine leukemia virus (MuLV) has been shown to invade the mouse CNS and lead to spongiform myeloencephalopathy, possibly through an *env*-mediated mechanism [31]. It was later found that expression of the entire HIV genome in the neurons of transgenic mice also led to neurological disease [32].

2.4. Neurotoxic products of HERV-K

While the evidence supporting a role for exogenous retroviruses as triggers of ALS remains limited, there is now considerable evidence to suggest that human endogenous retroviruses (HERVs) play an important role in ALS pathogenesis. Detailed investigations of the relationship between HERVs and ALS stemmed from a report citing unexpectedly high reverse transcriptase (RT) activity in the serum of HIVand HTLV-negative ALS patients when compared to healthy controls [33]. Analysis of post-mortem brain tissue from ALS patients revealed increased expression of HERV-K env, gag and pol, along with expression and colocalization of HERV-K RT with TDP-43 [34,35]. Interestingly, TDP-43 also binds to HERV-K long terminal repeats, directly regulating their expression [35]. In what is perhaps the most compelling evidence to-date supporting a role for HERVs in ALS pathogenesis, experiments performed by the Nath laboratory demonstrated neurotoxic properties of env in vitro [35]. This data was supported by the finding that transgenic mice expressing env went on to develop upper and lower motor neuron degeneration [35].

As with enteroviruses, more research will be necessary to definitively determine whether observations of enrichment of HERV specimens in ALS patients come as a consequence of disease, or whether disease comes as a consequence of HERV expression. HERV-K-mediated toxicity is thought to play a major role in driving neurological consequences of HIV infection. Expression of HERV-K is upregulated during HIV infection, and potentially reduced upon treatment with antiretroviral therapy [36]. TDP-43 expression is also upregulated during HIV infection, however, this is accompanied by hyperphosphorylation and subsequent loss of the protein's native functions [36] - one of which is negative regulation of HERV-K expression [37]. Therefore, it appears that aberrant expression and post-translational modification of TDP-43 during HIV infection leads to increased HERV-K expression and subsequent neuroinflammation. While challenging, more detailed studies aimed at defining the temporal relationship between expression of HERV-K elements and other classical markers of ALS onset/progression may shed more light on this issue.

2.5. Elevated rates of herpesvirus seropositivity in ALS patients

Human herpesviruses (HHVs) have also been investigated for their possible role in neurodegenerative diseases. Relatively strong evidence has accumulated to support a role for Herpes Simplex Virus Type 1 (HSV-1) in Alzheimer's Disease [38]. In ALS pathogenesis, however, the data supporting a causative role for these viruses in the disease is very weak. The only experimental evidence available to suggest that HHVs might act as a risk factor for ALS are isolated reports of elevated rates of seropositivity for HHV-6 and -8 among ALS patients [17,39]. However, reactivation of HHV-6 occurs non-specifically in response to a wide variety of illnesses, suggesting that any association with ALS may be non-specific [40]. Nevertheless, these findings should be tested in future studies, as independent replication of these results using different ALS cohorts would increase the quality of evidence and provide justification for more detailed studies.

3. A new outlook on viral associations with ALS

Despite considerable efforts, the number of viruses associated with ALS to-date has been relatively small, and in most cases little evidence exists to suggest a causal role in disease. Nevertheless, there remain compelling reasons to study viruses as environmental risk factors – albeit perhaps in a different light. The paucity of strong data showing enrichment of particular viral infections in ALS cohorts may simply reflect the fact that ALS patients do not exhibit major differences in *susceptibility* to particular viruses prior to disease onset relative to healthy individuals. However, an unexplored possibility is that common viral infections may trigger disease by stressing pathways that are already disfunctional due to genetic predisposition. Existing studies that have reported associations between viruses and ALS overlook this possibility. In such a scenario, incidence of infection would not be expected to differ between individuals who go on to develop ALS and those who do not.

We, and others, have previously noted the extensive associations of inflammation with neurodegenerative diseases, and have postulated that virus-induced inflammation may therefore trigger/perpetuate illness [41–43]. In support of this hypothesis, chronic stimulation of the innate immune system with lipopolysaccharide has been shown to accelerate the course of disease in the SOD1^{G37R} mouse model of ALS [44]. However, a more careful examination of the pathophysiological features of ALS that have already been described highlights far more extensive interconnectedness of viral infections with pathways thought to be involved in disease. Indeed, manipulation of one or more of the pathways known to be associated with ALS (as shown in Fig. 1) is a ubiquitous property of viral infections. Particular examples of how viral modulation of these pathways may contribute to ALS are summarized in the sections that follow.

3.1. Viral infections induce ER stress

Induction of endoplasmic reticulum (ER) stress is commonly observed in ALS and other neurodegenerative diseases [45]. ALS patients with disease characterized by *SOD1* mutations, and related mouse models, exhibit abnormal ER morphology, including dilation of the rough ER and Golgi fragments, that coincides with altered calcium homeostasis [46]. Misfolded SOD1 is known to accumulate in the ER, inhibit components of the ER-associated protein degradation pathway, and sequester important chaperone proteins [47]. Repeat expansions within C9ORF72, along with mutantions of fused in sarcoma (FUS) and vesicle-associated protein B (VAPB)—all of which are implicated in ALS—have also been reported to induce ER stress through interactions with components of the unfolded protein response (UPR), ultimately altering proteostasis [45]. Certain cell types, including neurons, appear to be particularly sensitive to ER stress and are more likely to undergo apoptosis [48]. However, death of non-neuronal cells undergoing ER stress—especially those that directly contribute to neuronal health (e.g. microglia, astrocytes)—could also perpetuate disease.

Viral infections exert tremendous stress on the ER. Many viruses (e.g. enteroviruses) hijack ER membranes to generate replication compartments in the cytoplasm [49]. Additionally, viral glycoproteins, which are often highly-expressed at late stages of infection, can overwhelm the host cell's glycosylation machinery, leading to the accumulation of misfolded proteins that stimulate the UPR. If not resolved, this stress can lead to cell death [50]. The ER is also frequently targeted by virally-encoded membrane channels ("viroporins") to alter intracellular calcium homeostasis, often for the purpose of triggering efficient viral release from infected cells [51]. In the context of ALS, these viral alterations of the ER could prove to be particularly problematic. since protein misfolding (e.g. SOD1) may play an important role in disease etiology. Accumulation of misfolded protein in virally-infected cells, followed by lysis of those cells, could potentiate the spread of these toxic molecules in a non-cell autonomous fashion, even from tissues outside of the CNS [52].

3.2. Viral manipulation of mitochondrial functions

Mitochondrial dysfunction is a well-described characteristic of ALS; alterations in metabolism, calcium homeostasis, reactive oxygen species and apoptotic pathways have all been reported [53]. Given the multifaceted roles of mitochondria in the regulation of these processes, the extensive interactions of viruses with mitochondria is not surprising. Mitochondrial antiviral signaling protein (MAVS) plays a central role in the signaling cascade activated upon sensing of viral infection, leading to transcription of antiviral genes that restrict replication and stimulate apoptosis. Many viruses, therefore, encode proteins capable of localizing to the mitochondria that can restrict antiviral signaling and/or modulate apoptosis [54]. They also alter mitochondrial dynamics (i.e. fission, fusion, mitophagy) as required to sustain productive infection [55]. Therefore, the substantial additional stresses placed on mitochondria during viral infections may promote disease onset/progression.

3.3. Regulation of stress granules during viral infections

Many of the genes associated with ALS have roles in RNA metabolism and stress granule (SG) regulation. While formation of SGs usually promotes cell survival, they may serve as sites of abnormal protein aggregation in the context of ALS [56]. To facilitate their own replication, all viruses have adopted strategies to hijack the translational machinery of the cell. Over the past decade, an ever-growing number of viruses have been found to interact with the SG pathway [57]. While some viruses (like HSV-1) seem to inhibit SGs, other viruses (like Respiratory Syncytial Virus) induce SGs to promote viral replication [58,59]. The promotion of SG formation during infection would be predicted to potentiate the aggregation of misfolded proteins in the context of ALS. However, even viruses that inhibit SGs should be investigated, as a reduced capacity to form SGs hampers the ability of cells to survive many other types of stresses that are known to occur in the context of ALS. The complexity of viral intersections with the SG pathway underscores the need to understand more deeply the consequences of particular viral infections with specific ALS-associated genes.

4. A framework for future studies of viruses as triggers of ALS

Given the extensive overlap in pathways known to be associated with ALS and those manipulated during viral infections, more thorough investigations are sorely needed to define if/how viruses influence the course of disease. The ubiquity of viral infections makes them a particularly important and difficult trigger to study, since exposure is so widespread. As discussed above, the existing literature does not provide compelling support for a causative role for specific viruses in ALS on the basis of elevated rates of detection. However, these studies have not addressed the more straightforward possibility that viral infections, which occur at equal rates among those who develop ALS and those who do not, trigger disease by perturbing pathways that are already vulnerable in ALS-susceptible individuals due to underlying genetic mutations. It is important to note that the aforementioned studies do not exclude the likelihood that certain viruses might act as more potent triggers than others – only that rates of infection are typically not elevated in those with ALS. Therefore, a more mechanistic approach is necessary to define the consequences of infection in relevant ALS models.

Reductionist studies in model systems will be particularly important due to the intrinsic challenges associated with studying possible environmental triggers in humans. Since most cases of ALS occur sporadically, and the genetic basis of disease is often unknown, it is extremely difficult to characterize the influence of environmental triggers in prospective cohorts. Determining differences in exposure histories of ALS populations and control populations is relatively straightforward with *post hoc* analyses. However, understanding how exposures that occur at *equal rates* may influence disease prior to diagnosis is a considerable challenge. In the context of ALS, this challenge is compounded by the relatively protracted period that elapses between initial recognition of symptoms and eventual ALS diagnosis. Furthermore, the consequences of viral infections that occur prior to symptom onset are unlikely to be immediately realized – especially those that may be caused by "routine" infections like the common cold.

A more feasible starting point for exploring the consequences of viral infections on ALS in humans might then be to focus on characterizing how infections impact those who have already been diagnosed with disease. This approach would allow for the evaluation of differential biological responses to infection in ALS patients relative to controls. It would also permit stratification of patients in cases where the genetic basis of disease is known, since the ability for viruses to exacerbate disease may occur in only a subset of genetic backgrounds. Such a situation would not be surprising considering the known heterogeneity among ALS cases under normal circumstances.

Given the cloak of mystery that continues to surround the etiology of ALS, and the current lack of effective treatment options, multidisciplinary approaches to studying this complex disease are imperative. The recent emergence of pathogens like Zika Virus and West Nile Virus in the Americas has helped to fuel significant advancements in the understanding of neuro-virological and neuro-immunological axes. The current lack of data supporting a causative role for viruses in ALS highlights the need to develop a new framework for investigating these complex associations. Closer collaboration of experts in infectious diseases with those who study neurodegeneration may yield tremendous biological insights that provide therapeutic promise in the future.

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