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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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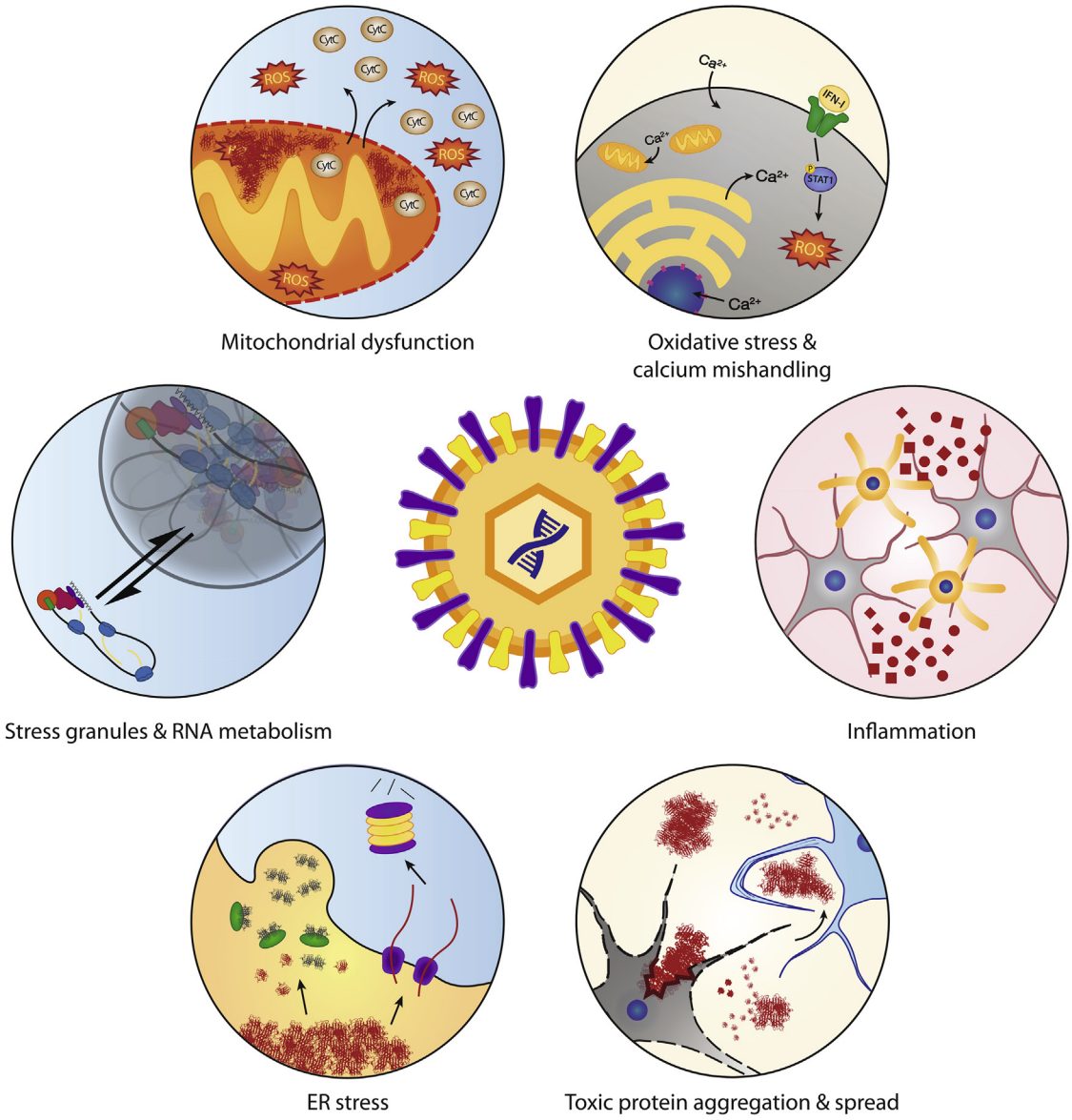

Fig. 1. Cellular pathways involved in ALS pathogenesis are manipulated during viral infection. Viral infections rely on and/or manipulate many pathways associated with ALS pathophysiology, including oxidative stress, inflammation, toxic protein aggregation and intercellular spread, ER stress pathways, 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