How Do Viruses Really Cause Neuropathology?: Is There More to the Story

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Abstract

Our work has focused over the years on Primate Erythroparvovirus 1 [more commonly known as parvovirus B19 (B19)]. B19 is a human pathogen that is the causative agent of erythema infectiosum, the common rash disease of childhood. In addition to several other human diseases, B19 has also been associated with multiple brain diseases. Those brain diseases include, but are not limited to, encephalitis, encephalopathy, meningitis, meningoencephalitis, ataxia, seizures, and stroke. To date, the association has grown, but causation has not been determined. Several possible mechanisms of pathogenesis including direct infection, indirect/epigenetic, reactivation, and autoimmune/inflammatory cytotoxicity, as well as effects due to infection of other organs have been suggested. We will also offer other hypotheses.

Keywords: Parvovirus B19; Brain; Autoimmunity; Inflammation; Reactivation; Epigenetic

Introduction

Primate Erythroparvovirus 1 [more commonly known as parvovirus B19 (B19)] is a small, non-enveloped, single-stranded DNA virus [1]. Particle sizes are approximately 23 nm in diameter. The viral genome is 5,596 nucleotides in length. The genome encodes 2 major protein types: the nonstructural (replication) protein (NS1) and the viral capsid proteins (VP1/2), as well as some other more minor proteins. B19 is a human pathogen that is a known cause of several human diseases [1,2] including, but not limited to, aplastic crisis, erythema infectiosum (fifth disease), arthritis, thrombocytopenia, hydrops fetalis, and myocarditis. B19 infection has been associated with multiple brain diseases [1-3] such as encephalitis, encephalopathy, meningitis, meningoencephalitis, ataxia, seizures, and stroke. Herein we discuss possible mechanisms by which B19 and possibly other viruses may cause brain disease.

Direct Infection/Persistence

We have shown in large-scale (N>100 subjects) studies that B19 DNA can be detected in two different regions of the brain: dorsolateral prefrontal cortex [4] and cerebellum [5]. In a smaller-scale (N=30 subjects) study, Manning et al. also detected B19 in frontal and occipital lobes [6]. Therefore, B19 infection and persistence in the brain are strongly supported.

Replication of B19 in general leads to expression of its NS1 protein. B19 NS1 has been shown to induce apoptosis in permissive and non-permissive cell types [7-10]. NS1-induced cytotoxicity was suspected as early as 1994 to play a role in neuropathology [11]. NS1-induced cytotoxicity is likely a major mechanism by which B19 could cause neuropathology.

Reactivation and Interaction with Other Viruses

B19 has been proven to actively replicate in erythroid progenitors [1-2]. Although the virus has been detected (via DNA) in different areas of the CNS [4-6], it has not yet been shown to fully replicate in any other cells, including the brain. Our group, as well as others, has shown that B19 gene expression, albeit at a low level, occurs in several other organs including bone marrow, heart, liver, skin, and thyroid.
[19,20]. We speculate that this persistent virus may be reactivated within the brain, and when this replication process is stimulated it may lead to neurological symptoms via direct cytotoxicity, due to NS1 expression, as described above. In addition, the possibility of interactions with other latent/reactivating viruses is also intriguing.

In our studies [4,5], B19 was not the only virus detected in the brain. Up to 21% of our study cohort was double-positive for B19 and adeno-associated virus (AAV). In the Manning et al. study [6], some of the subjects were also infected with the human immunodeficiency virus (HIV), also known to infect the brain. Many viruses, such as the herpes simplex virus and retroviruses, can infect and persist in the brain. The question is whether we really understand how all of these viruses interact, especially at the cellular level in the brain.

Autoimmunity/Inflammation

Suspicion of an immunological mechanism for B19 infection that may lead to neurological disorders was proposed as early as 1994 [21]. There have been numerous reports documenting B19 DNA within the brain, but some have proposed a theory suggesting that the brain may be an incomplete host for the virus and therefore stimulates an autoimmune response as opposed to direct NS1 cytotoxicity causing brain cell death [22].

The other most often discussed theory is the stimulation of the immune system by NS1. During the acute and convalescent phase of B19 infection, NS1 upregulates expression of cytokines TNF-alpha and IL-6 leading to an autoimmune process [23,24]. TNF-alpha is known to play an important role in cell apoptosis associated with B19 infection [25]. This could lead to a host immune response with the release of NS1 protein during cell death [26]. Also auto-antibodies such as antinuclear antibody (ANA) and rheumatoid factor (RF) have been found during and after a B19 infection [27,28]. This autoimmune response via NS1 protein may lead to brain damage, due to cell death, which in turn could manifest in specific neurological symptoms and disorders.

Infection of Other Organs and its Resulting Effect on Brain

B19 is known to cause diseases in other organs. These disease states could potentially affect brain pathology. A study found that B19 grew better under hypoxic conditions [29,30]. During a B19-induced anemia, the decreased oxygen circulation and delivery to the brain could lead to neurological manifestations. In myocarditis, fluctuating blood volumes delivered to the brain could lead to similar neurological disorders. Rheumatic disease caused by B19 can lead to vascular disorders that could cause stroke as well as hypoxia within the brain [31]. An infection of the liver with B19 can cause hyperammonemia and jaundice [32]. Bilirubin deposition in the brain and high levels of ammonia may lead to encephalopathy as well as other brain abnormalities.

The thyroid has also been implicated. There have been 3 case studies and a fourth group study linking thyroid diseases with B19 [33-36]. Our laboratory and others have shown that B19 infects the thyroid [37-39]. The thyroid's critical role in early neurological development may be altered by B19 infections [40].

Closing Remarks

There are likely many possible mechanisms, both direct and indirect, by which viruses such as B19 may contribute to neuropathology. It is very likely that there are multiple mechanisms at play, not just one. Another thing to keep in mind is that there are many emerging or undiscovered viruses that either already have or will infect and persist in the brain. Zika virus is a prime and more recent example. How these viruses affect the brain is still not completely understood. The full extent of their contribution to neuropathology is not known. We do not fully understand how they interact with known viruses. There is also so much we do not understand about the brain.

We have a great deal to learn about virus contribution to brain disease. It is important to keep studying individual viruses and their interactions with the brain. However, we must broaden our hypotheses to incorporate an awareness of how to take into account the effects of multiple viruses on the brain.

References


