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Primate Erythroparvovirus 1 (*Parvovirus B19*): An Etiologic Agent of Ataxia and Cerebellar Disease?

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Abstract

Ataxia, a gross lack of motor control, is symptomatic of broader neurological disorder, typically of the cerebellum. A few case reports have documented the association of primate erythroparvovirus 1 [more commonly known as human *parvovirus B19* (B19)] with ataxia. Parvoviruses are small DNA viruses that infect many different species. B19 is a well-known cause of erythema infectiosum, a common rash disease of childhood. B19 is also a cause of hydrops fetalis, a severe anemia of the fetus. Is it possible that the human *parvovirus B19* is a cause of ataxia?

Keywords: *Parvovirus B19*; Cerebellum; Cerebellar; Ataxia

Summary of Case Reports

In a 1999 report [1], a 2-year-old boy developed acute truncal ataxia and horizontal nystagmus that prevented him from walking or maintaining a sitting position. These symptoms were followed four days later by erythema infectiosum. B19 infection was confirmed by genomic DNA and anti-B19 antibodies (IgM and IgG) in serum. The ataxia and nystagmus dissipated within one week, and there were no neurological sequelae in this case. A vascular reaction to the B19 infection in the cerebellum was hypothesized to contribute to the ataxia.

Two more cases of ataxia were reported by Barah, et al. [2,3]. Ages were 27 months (female) and 13 years (male). B19 DNA was positive in the CSF. Both children died and were found to have cerebellar pathology at autopsy.

A fourth case, reported in 2004 [4], documented a 16-month-old girl who presented with bone marrow abnormalities, progressive ataxia, tremor, and nystagmus. Serum was positive for anti-B19 IgM antibody indicative of acute infection (IgG seroconversion was later documented). She recovered gradually over two years. No further discussion of the ataxia was offered as neurologic findings were not the main focus of the report.

A fifth case, from 2008 [5], documented a 4-year-old female who developed a cerebellar syndrome of severe ataxia, nystagmus, hypotonia, head and trunk tremors, dysmetria, and dysarthria. Serum and CSF were positive for B19 DNA by polymerase chain reaction (PCR); serum was positive for anti-B19 IgM and IgG. Symptoms persisted at 4 month follow up.

A sixth case, from 2014 [6] documented a 70-year-old male with a history of chronic lymphocytic leukemia and bone marrow evidence of B19 infection by immunostaining. Neurologic exam was significant for dysarthric/scanning speech, severe dysmetria, intention tremor, wide-based gait and truncal ataxia. Serum and CSF were positive for B19 DNA by PCR. Some symptoms of ataxia improved with intravenous immunoglobulin (IVIG) treatment.

Evidence of B19 Infection of Cerebellum

In 115 cerebellum tissues from unique individuals, we showed that greater than 70% were positive by nested PCR for B19 DNA [7]. In a small sub-cohort (N=10), serum anti-B19 IgG was confirmed in 80%. The number of B19-positive cerebellum samples was nearly double that found in the dorsolateral prefrontal cortex from the same cohort [8] suggesting that the cerebellum is a favored target than other areas of the brain for B19 infection.

What does the Animal Literature Tell us?

Case reports are instructive and very interesting, but difficult to determine causation. Animal, both natural and experimental, models can provide further support. Several studies, many performed decades before the first human case report, have shown that infections with animal parvoviruses lead to cerebellar hypoplasia and cerebellar ataxia in various feline [9,10], rodent (mice, rat, and hamster) [11-14] and ferret [15] models. The specific viruses are feline panleukopenia virus, rat virus, minute virus of mice I, and mink enteritis virus. The exact cerebellar cell target, granular or Purkinje, is dependent on the virus and host. Early neurodevelopment appears to be the window of susceptibility.

B19 and Ataxia: Possible Mechanisms of Action

The exact mechanism by which B19 may cause cerebellar disease, particularly ataxia, is not known. One mechanism is by direct cytotoxicity of cerebellar neurons due to viral replication during early neurodevelopment which has been shown in the animal studies noted above as well as more directly by Ohshima et al. who showed that the H-1 parvovirus induces apoptosis in the cerebellum [16]. Another possibility is that the virus may exert epigenetic effects by modifying cellular gene expression. Though there have been no studies linking B19 to cerebellar ataxia via epigenetic effects, there has been one report

of B19 association with a DNA methylation pattern in B cells of subjects with acute lymphoblastic leukemia [17]. In one form of hereditary ataxia, Friedreich ataxia (FRDA), a genetic mutation within the first intron of the Frataxin (FXN) gene has been identified as the cause [18]. In studies of FRDA-associated cells, tissues, and mouse models, it has been found that epigenetic alterations, especially DNA methylation, might be involved in the silencing of FXN in FRDA [19-21]. Therefore, aberrant expression of the enzymes that are required for either establishment or maintenance of DNA methylation, including DNA methyltransferases and histone methyltransferase G9a/GLP [22,23], might lead to the occurrence of FRDA. The question remains as to whether B19-induced DNA methylation or other epigenetic processes may play a role in any form of ataxia. Interestingly, inactivation of G9a has been demonstrated to result in resistance to RNA viruses by increasing type I interferon production [24]. B19, via its nonstructural protein NS1 blocks this interferon signaling so that it theoretically could still play a role in human ataxia.

Final Remarks

Animal model data is highly supportive of parvoviruses as causes of cerebellar disease, including ataxia. B19 has been detected in a large-scale study in the human cerebellum. There are still less than a dozen human case reports associating B19 and ataxia. The mechanism of B19-induced ataxia is likely direct cytotoxicity of developing cerebellar neurons, but an epigenetic or other role could contribute especially once beyond early neurodevelopment. Much more work needs to be done to "catch up" with the animal data. However, the basic science data is very compelling. Gathering further case studies/series as well as prospective clinical studies on ataxia and B19 are highly warranted.

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