

## Persistent Parvovirus B19 Encephalitis in a Paediatric Patient with B-Lymphoblastic Lymphoma

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**Abstract:** Parvovirus B19 is a small single-stranded DNA virus of the Parvoviridae family. Depending on host factors, it may produce a wide array of clinical disease states. Immunocompromised patients are generally affected more severely but rarely develop prolonged and persistent infections and can be life threatening. Acute Lymphoblastic Leukemia [ALL] is associated with significant immunocompromised state that can lead to reactivation of Parvovirus B19 infection and can be life threatening. Here, we describe a child who developed persistent fatal parvovirus infection in central nervous system during treatment for B- lymphoblastic lymphoma.

**Keywords:** Parvovirus B19; Acute Lymphatic Leukemia; Encephalitis.

**INTRODUCTION**

Parvovirus B19 is a small single-stranded DNA virus of the Parvoviridae family, and produces a wide array of clinical disease states ranging from self-limited asymptomatic state to severe life threatening infections. Immunocompromised patients are more likely to develop prolonged and persistent life threatening infections. Here, we describe a child who developed persistent fatal parvovirus infection while he was on treatment for B Lymphoblastic lymphoma during maintenance phase.

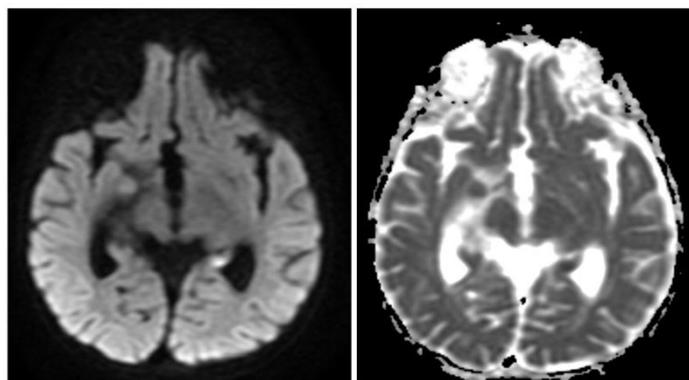
**CASE REPORT**

A 17 months old male child with B Lymphoblastic lymphoma of right orbit with intracranial extension was treated according to Modified BFM ALL 95 protocol. The initial intensive phases of chemotherapy were tolerated without any significant neutropenic complications. Maintenance phase consisting of monthly pulses of Vincristine at 1.5 mg/m<sup>2</sup> and Prednisolone at 60 mg/m<sup>2</sup> for 7 days along with daily 6-Mercaptopurine at 50 mg/ m<sup>2</sup> and Methotrexate tablets weekly at 20 mg/m<sup>2</sup> was initiated after completion of intensive phase. Five months into maintenance chemotherapy, child got admitted with febrile neutropenia and lower respiratory tract infection, requiring oxygen support and intravenous antibiotics. Contrast enhanced computed tomography (CT) of the thorax was suggestive of bacterial pneumonitis. On the fifth day of admission, child developed irritable cry along with an episode of tonic clonic seizures lasting 5 minutes which was controlled with anticonvulsants. After stabilisation of the child, lumbar puncture was done for Cerebrospinal fluid (CSF) analysis including work up for up for central nervous system (CNS) tuberculosis in view of history of contact with tuberculosis. CSF cytology and bacterial culture were negative. CSF virology panel Polymerase chain reaction (PCR) showed positivity for Parvovirus B19. Contrast enhanced CT imaging of brain did not show abnormal

meningeal enhancement. There was no significant history of anemia or history of recurrent transfusions. In view of his immunocompromised state, persistent pneumonia and contact history with tuberculosis, child was started on anti-tuberculosis drugs (Isoniazid, Rifampicin, Ethambutol, and Pyrazinamide). His condition improved and maintenance chemotherapy was restarted after an interval of 3 weeks. At the time of discharge from hospital child had no neurological deficits. Two months later child presented with pallor, hemoglobin concentration of 5 g/dL and platelet count of 22000/mm<sup>3</sup> and required multiple packed red cell transfusions. Blood report for qualitative parvovirus B19 PCR testing was positive. He also had hospital admission for acute respiratory syndrome with severe pneumonia requiring methylprednisolone and broad spectrum antibiotics. He recovered with treatment and anti-tuberculosis treatment and maintenance were continued. After two months, he was again admitted with severe pneumonia and respiratory distress, and was started on oxygen and antibiotics. During this admission, he developed vacant stare along with intermittent Myoclonus involving one upper limb, which soon progressed to involve all four limbs. CSF study showed normal biochemistry and negative cultures, and CSF Parvovirus B19 was positive. Magnetic resonance imaging of brain showed abnormal area of restricted diffusion noted in the left

parahippocampal region suggestive of encephalitis (Figure 1). The child's sensorium deteriorated along with worsening Glasgow Coma Scale (GCS), with persistent focal seizures for which child was ventilated. A diagnosis of Parvo virus B19 induced

meningoencephalitis was made and child was started on Intravenous Immunoglobulin [IVIG] (400mg/kg/day for 5 days). Child succumbed to death after five days on ventilator support.



**Fig-1: Magnetic resonance imaging of brain [Diffusion-weighted imaging and apparent diffusion coefficient images] of the patient showing abnormal areas of restricted diffusion in the left parahippocampal region suggestive of parvovirus B19 encephalitis**

## DISCUSSION

Parvovirus B19 (PVB19) was first identified as the cause of erythema infectiosum (fifth disease) by Anderson *et al.* in 1983 [1]. In addition to fifth disease and asymptomatic infection, it is known to cause anemia and pancytopenia in immunocompromised hosts, transient aplastic crisis in patients with hemoglobinopathies, non-immune hydrops-fetalis, chronic arthritis, myocarditis, hepatitis, vasculitis, renal disease, and idiopathic thrombocytopenic purpura [2, 3]. Up to 60% of children aged 6 to 19 years and more than 85% of the geriatric population have IgG antibodies against parvovirus.

In immunocompetent hosts, transient viremia is eliminated and neutralized by the intact immune system by formation of protective antibodies, whereas in immunocompromised patients due to weak antibody responses the ability to neutralize or eliminate the virus is limited [4]. Immunocompromised patients with parvovirus B19 infection may not manifest the characteristic immune mediated manifestations such as rash or joint symptoms, and are generally affected more severely but rarely develop prolonged and persistent infections. Although Parvovirus B19 is generally not regarded to be neurotropic, direct viral toxicity, dysregulated immune response with release of cytokines in the CSF, immune complex deposition on the endothelial cells, intracellular accumulation of toxic NS1 protein, and the virus acting as trigger for anti-N-methyl-D-aspartate receptor encephalitis are some of the proposed mechanisms of CNS manifestations of Parvovirus B19 [5]. Intravenous immune globulin (IVIG) in addition to red blood cell transfusion can be helpful in patients with chronic parvovirus B19 infection and anemia, which generally occurs in patients with immunodeficiency. Chronic infection may also

resolve with a decrease in immunosuppression or immune reconstitution, if possible. It is unclear if IVIG is beneficial in the setting of chronic parvovirus B19 infection without anemia.

In a study of 81 patients with neurological manifestations associated with Parvovirus B19, Miltiadis *et al.* [6] described that the most commonly found CNS disease was encephalopathy and/or encephalitis or meningoencephalitis. CSF PCR for Parvovirus B19 was positive in 81 % of these patients and the CSF positivity was unaffected by the immune status of the patient in this study. The median age for CNS manifestations was 8 years, with convulsions being the most common manifestation. The outcomes of encephalopathy and/or encephalitis or meningoencephalitis were often poor; 31% of such patients had persistent neurologic defects or died. In this study there were no statistically significant differences in the rates of sequelae or death between those who received IVIG and/or steroids and those who were treated without immunomodulatory therapy in patients with CNS manifestations. Another review by Barah *et al.* reports that there is insufficient evidence to support use of steroid or IVIG as treatment for parvovirus encephalitis, but patients with severe encephalitis may benefit from a combined regimen of IVIG and steroids [7].

Our case emphasizes that parvovirus infection in immunocompromised hosts can lead to prolonged and persistent infections which can be potentially life threatening. Other causes of chronic meningitis/encephalitis must be ruled out in such a setting. The exact reason for persistence of infection is not known, although the inability of the host to mount an adequate antibody response to neutralise and

eliminate the virus may be one of the reasons. This child had an initial symptomatic Parvovirus B19 CNS infection which resolved spontaneously with supportive care without any focal neurological deficit. Subsequently he developed Parvovirus B19 viremia resulting in anemia requiring multiple transfusions and possible recurrent pneumonia with doubtful Tuberculosis aetiology in view of history of contact. The second episode of symptomatic Parvovirus B19 CNS infection occurred 4 months after the first and was associated with significant neurological deterioration requiring ventilator support. In an immunocompromised patient the factors that determine the chronicity and reactivation of CNS symptoms appear unclear, whether intervention in the form of IVIG, steroids or combination will be beneficial is still not conclusively proven.

### CONCLUSION

In conclusion, parvovirus B19 is an important cause of anemia in patients with haematological malignancy. Diagnostic testing with standard parvovirus immunoglobulin titers and serum PCR for viral DNA is critical. Finally, our case report demonstrates that although rare, clinical reactivation of central nervous system parvovirus infection can be fatal in the setting of an immunocompromised host.

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