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**Acute encephalitis and encephalopathy associated with human parvovirus B19 infection in children**

Watanabe T *et al*. Parvovirus B19 encephalitis and encephalopathy

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**Abstract**

Reports of neurologic manifestations of human parvovirus B19 (B19) infection have been on the rise. Acute encephalitis and encephalopathy is the most common, accounting for 38.8% of total B19-associated neurological manifestations. To date, 34 children with B19 encephalitis and encephalopathy have been reported, which includes 21 encephalitis and 13 encephalopathy cases. 10 (29%) were immunocompromised and 17 (39%) had underlying diseases. Fever at the onset of disease and rash presented in 44.1% and 20.6% of patients, respectively. Neurological manifestations include alteration of consciousness occurred in all patients, seizures in 15 (44.1%) patients, and focal neurologic signs in 12 (35.3%) patients. Anemia and pleocytosis in cerebrospinal fluid (CSF) occurred in 56.3% and 48.1% of patients, respectively. Serum Anti-B19 IgM (82.6%) and CSF B19 DNA (90%) were positive in the majority of cases. Some patients were treated with intravenous immunoglobulins and/or steroids, although an accurate evaluation of the efficacy of these treatment modalities cannot be determined. 19 (57.6%) patients recovered completely, 11 (33.3%) patients had some neurological sequelae and 3 (8.8%) patients died. Although the precise pathogenesis underlying the development of B19 encephalitis and encephalopathy is unclear, direct B19 infection or NS1protein of B19 toxicity in the brain, and immune-mediated brain injuries have been proposed.

**Key words:** Human parvovirus B19; Neurological manifestation; Encephalitis; Encephalopathy; Pathogenesis; Complication

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**Core tip**: Reports of acute encephalitis and encephalopathy associated with human parvovirus B19 (B19) infectionhave recently increased. B19 DNA has been detected in cerebrospinal fluid samples in approximately 4% patients with etiologically undiagnosed encephalitis. Some patients were treated with intravenous immunoglobulins and/or steroids. More than half of the patients with B19 encephalitis and encephalopathy recovered completely, but some patients developed severe neurological sequelae or died. Although the precise pathogenesis underlying the development of B19 encephalitis and encephalopathy is unclear, direct B19 infection or NS1 protein of B19 toxicity in the brain, and immune-mediated brain injuries have been proposed.

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**INTRODUCTION**

Human parvovirus B19 (B19) is a member of the erythrovirus genus in the family Parvoviridae, first discovered by Cossart *et al*[1,2] in 1975. B19 is a small, single-stranded DNA virus that binds the cellular receptor P antigen on erythrocytes[3]. The viral genome encodes only three proteins of known function, including nonstructural protein 1 (NS1), and two viral capsid proteins, viral protein 1 (VP1) and viral protein 2 (VP2)[1]. NS1 promotes multiple replicative functions and is cytotoxic to host cells[1].Since Shneerson and Mortimer reported the first symptomatic febrile patients with B19 infection in 1980[4], various clinical manifestations of B19 have been identified. These include erythema infectiosum (EI)[5], arthropathy, non-immune hydrops fetalis and congenital anemia, thrombocytopenia, hepatitis, myocarditis and neurologic diseases in healthy hosts, chronic pure red cell aplasia in immunodeficient hosts, and transient aplastic crisis in patients with increased red cell turnover[1,6]. Of these, neurologic manifestations of B19 infection have been increasingly reported, especially in children[7,8].

B19-associated neurologic manifestations include encephalitis, encephalopathy, meningitis, cerebellar ataxia, transverse myelitis, stroke, and peripheral neuropathy[7,8]. Of these, encephalitis and encephalopathy are the most common with 38.8% of total B19-associated neurological manifestations[8]. Furthermore, recent reports reveal that specific forms of encephalopathy also are associated with B19 infection, which include chorea encephalopathy[9-11], mild encephalitis/encephalopathy with reversible splenial lesion (MERS)[12] and posterior reversible encephalopathy syndrome (PRES)[13]. The following is a review of B19 associated encephalitis and encephalopathy (B19 encephalitis and encephalopathy) in children.

**DEFINITION OF B19 ENCEPHALITIS AND ENCEPHALOPATHY**

Because encephalitis is defined as inflammation of the brain parenchyma, pathologic examination of brain tissue (brain biopsy) is necessary for its diagnosis. However, brain biopsy is rarely done premortem with its potential risk for patients[14]. In this review, we used the Pillai encephalitis definitions[15], as follows. Encephalopathy was defined as an altered or reduced level of consciousness and a change in personality or behavior or confusion lasting ≥ 24 h. Encephalitis was defined as an acute encephalopathy with 2 or more of the following: fever ≥ 38 °C, seizures or focal neurologic signs, cerebrospinal fluid (CSF) pleocytosis (≥ 5 white blood cells/μL), electroencephalographic (EEG) findings consistent with encephalitis, and neuroimaging suggestive of encephalitis[15]. B19 infection was based on the detection of either B19 DNA or anti-B19 IgM specific antibodies in serum or CSF[8]. Two patients with encephalitis and encephalopathy without laboratory tests confirming B19 infection were included in this review on the basis of clinical presentation of EI[16-17].

**EPIDEMIOLOGY**

Balfour *et al*[16] reported an 8-year-old boy who developed encephalitis associated with EI in 1970. Seven years later, Hall *et al*[17] reported a 9-month-old boy with severe encephalopathy during the course of EI who developed permanent neurologic sequelae. In the era of molecular and serological diagnostics for B19 infection, cases of encephalopathy and B19 DNA in sera and in CSFare accruing[18-19]. To date, 34 patients less than 19 years of age with B19 encephalitis or encephalopathy have been reported (Table 1)[9-11,16-31]. This includes 21 patients with encephalitis, five with encephalopathy, four with chorea encephalopathy, three with MERS and one with PRES. Eleven patients have been reported from United Kingdom, eight from Japan, six from Jamaica, three from United States, two from Italy, two from Brazil, one from Germany and one from Turkey. The age of patients ranges from 1 to 15 years (mean of 6.7 years, median of 7 years). Fifteen patients were male, and the male to female ratio was 0.79. 24 (71%) were immunocompetent individuals, and 10 were immunodeficient. Seventeen (39%) patients had underlying diseases, including sickle cell disease, hereditary spherocytosis (HS), congenital heart diseases, acute lymphocytic leukemia, Crigler-Najar syndrome, Cockayne syndrome, Turner syndrome, and post-renal transplantation for nephropathic cystinosis[20,23-26,28]. One patient suffered from ulcerative colitis eight years after B19 encephalopathy[12,29].

Although the prevalence of B19 infection for all encephalitis and encephalopathy is unknown, two studies reported that B19 DNA has been detected in CSF samples in 2 of 43 (4.7%) and 7 of 162 (4.3%) patients with etiologically undiagnosed encephalitis[22,23].

**CLINICAL MANIFESTATIONS**

Fever at the onset of diseases presented in 15 of 34 (44.1%) patients (Table 2). Rash was reported in seven (20.6%) patients[13,16,17,19,21,29,31]. Rash developed before the onset of CNS manifestations in two patients, simultaneously with the onset in two patients, and after the onset in three patients. All patients with rash had normal immune function. 3 (8.8%)patients complained of arthralgia.

Acute kidney injury occurred in three patients with sickle cell disease, and in one patient with Cockayne syndrome as a part of multiple organ failure[23-25]. Patients experiencing acute B19 infection sometimes develop renal complications[32,33]. These include acute glomerulonephritis, thrombotic microangiopathy and Henoch-Schönlein purpura nephritis, probably due to direct cytopathic effects on glomerular epithelial cells and endothelial cells, and an immune complex mediated mechanism[32,33].

One of the neurological manifestations was a reduced level of consciousness, which occurred in all patients. Seizures developed in 15 (44.1%) patients and two had statue epilepticus[19,27]. 12 (35.3%) patients exhibited focal neurologic signs (Table 2), which included neurogenic bladder, chorea[, loss of vision, ataxia[, dysarthria, hemiparesis, and focal seizures[16,9-11,13,22,23,25,30,31].

**LABORATORY DATA**

B19 infection causes various blood diseases and cytopenias affecting several blood cell lineages, such as red cell aplasia, pancytopenia and hemophagocytic lymphohistiocytosis (HLH)[34]. In patients with B19 encephalitis and encephalopathy, anemia developed in 18 of 32 (56.3%) patients (Table 3). Aplastic crisis was recorded in five patients with sickle cell disease and three patients with HS. Pancytopenia and HLH occurred in 4 patients and 2 patients, respectively.

Cerebrospinal fluid (CSF) examination showed pleocytosis in 13 of 27 (48.1%) patients and increased protein levels in 8 of 20 (40%) patients (Table 3).

Anti-B19 IgM antibodies and B19 DNA were detected in the sera of 19 out of 23 (82.6%) patients and 12 out of 20 (60%) patients, respectively. Anti-B19 IgM antibodies and B19 DNA were detected in the CSF of two out of 11 (18.2%) patients and 18 out of 20 (90%) patients, respectively (Table 3). These results suggest that serum anti-B19 IgM and CSF B19 DNA examinations are useful tools for diagnosing of B19 infection in patients with encephalitis and encephalopathy.

**IMAGING STUDIES AND EEG**

6 of 13 (46.2%) patients had abnormal brain computed tomography (CT) findings, which included an enlarged ventricle, brain edema, frontal and occipital vasogenic swelling, and lesions in right parietal, temporal or occipital areas[13,22,23,25]. Brain magnetic resonance images showed abnormal findings in 10 of 15 (66.7%) patients. These findings included high signal intensity in the white matter[13,23,26,30], basal ganglia, and cerebellum in T2 weighted images, high signal intensity in the splenial lesion of corpus callosum in diffusion-weighted images or T2 weighted images, and enlarged ventricles[12,23,26,29,31].

EEG revealed abnormal findings in 15 of 19 (78.9%) patients, which included diffuse or focal slowing of the background activity, encephalopathic changes or epileptic abnormality[10,12,16,17, 24,26,27,29,30] .

**TREATMENT**

As discussed elsewhere, direct B19 infection or NS1 toxicity in the brain, and immune-mediated brain injuries have been proposed as pathogenic causes that result in the development of B19 encephalitis and encephalopathy[7,8,35]. Some patients with B19 encephalitis and encephalopathy were treated with intravenous immunoglobulin (IVIG) and/or steroids (Table 3). IVIG and steroids are often used in post-infectious or immune-mediated encephalitis as immuno-modulatory therapies[36]. In addition, IVIG is used for many clinical conditions associated with B19 infection such as chronic anemia, because immunoglobulin preparations are a good source of neutralizating antibodies against B19[6].

Both IVIG and steroids were administrated to three patients[10,25,30], two of them showing neurologic sequelae (epilepsy and cerebellar syndrome) Three patients were treated with IVIG only, and they all recovered completely. Steroids only were administered to two patients, one of whom exhibited neurological sequelae (cerebellar syndrome)[12,23,26,31]. Since there have been only a few reports of B19 encephalitis and encephalopathy with IVIG and/or steroids, an accurate evaluation of the efficacy of these treatment cannot be determined. However, due to the lack of other effective treatments for B19 encephalitis and encephalopathy, Baraf *et al*[8] recommended that treatment of severe cases might benefit from a combined regimen of IVIG and steroids.

**OUTCOME**

19 of 33 (57.6%) patients recovered completely from neurologic disturbances, whereas 11 (33.3%) patients had some neurological sequelae and three (8.8%) patients died (Table 2). Patients with B19 encephalitis had worse prognosis (8 of 20 patients had neurological sequelae, and 3 patients died) than patients with B19 encephalopathy, MERS or PRES (2 of 13 patients had neurological sequelae, and no patient died). Neurological sequelae included psychomotor retardation[11,17,19], cognitive deficit, epilepsy, cerebellar syndrome, hemiparesis and spastic quadriplegia[16,19,22,23,27,31]. All of the patients that died were immunodeficient (two neonates and one patient with Cockayne syndrome)[23].

**SPECIFIC FORMS OF B19 ENCEPHALOPATHY**

Recent reports have revealed that specific forms of encephalopathy are associated with B19 infection, which include chorea encephalopathy, MERS and PRES[9-13].

***Chorea encephalopathy***

Chorea encephalopathy is characterized extrapyramidal features in the context of self-limiting neurological illness with CSF oligoclonal IgG bands, probably caused by immune-mediated (possibly autoantibody) pathogenic mechanisms[37]. Four patients with B19 associated chorea encephalopathy have been reported to date[9-11]. Grillo *et al*[38,39]pointed out the clinical similarity between chorea encephalopathy and anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis, which is an autoimmune encephalitis caused by autoantibodies against the NR1 subunit of NMDAR, and suggested that some cases of anti-NMDAR encephalitis could be triggered by B19.

***Clinically mild encephalitis/encephalopathy with reversible splenial lesion***

Clinically mild encephalitis/encephalopathy with reversible splenial lesion (MERS) is clinically mild encephalitis/encephalopathy characterized by an MRI finding of a reversible lesion with reduced diffusion in the corpus callosum, first proposed by Tada *et al*[41] in 2004. Delirious behavior, impaired consciousness and seizure often occur as neurological symptoms, all of which completely recover within a month[40]. Although a majority of patients with MERS are associated with viruses or bacteria[40], some cases of Kawasaki disease associated with MERS have been reported[42]. The precise pathogenesis of MERS is unknown, intramyelinic edema, interstitial edema in tightly packed fibers and transient inflammatory infiltrate have been postulated[40].

Three patients with B19-associated MERS have been reported[12,29]. Oshima *et al*[29] reported a 9-year-old girl with HS developed MERS and aplastic crisis. They followed the plasma and CSF concentrations of B19 by real-time polymerase chain reaction and found that the symptoms of encephalopathy had occurred at the peak viral load, suggesting that B19 MERS might occur as a result of direct B19 invasion. Suzuki *et al*[12] also reported that two brothers with HS developed B19 MERS and HLH. HLH is due to dysregulated lymphocyte activation, which leads to macrophage hyperactivation and over-expression of pro-inflammatory cytokines, including IL-6[43]. HLH has been reported in 28 patients with B19 infection, most of whom had HS as an underlying disease[43]. Moreover, increased IL-6 levels in CSF have been reported in patients with MERS[44,45]. These findings suggest that B19-induced IL-6 overproduction may lead to MERS and HLH in patients with HS[12].

***Posterior reversible encephalopathy syndrome***

Posterior reversible encephalopathy syndrome (PRES) is characterized clinically by headaches, impaired consciousness, visual disturbances and seizures, and radiologically by posterior (parieto-occipital) imaging changes predominantly occurring in the sub-cortical white matter[46]. Although the pathophysiology underlying the development of PRES is multifactorial, hypertension plays a major role in the development of PRES through disruption of autoregulation in cerebral blood vessels[46].

Cugler *et al*[13] reported a 9-year-old girl with severe acute glomerulonephritis and PRES associated with B19 infection mimicking systemic lupus erythematosus. Only adequate control of blood pressure and diet led to complete resolution of the patient’s symptoms.

**PATHOGENIC MECHANISMS**

Although the precise pathogenesis underlying the development of B19 encephalitis and encephalopathy is unclear, direct B19 infection or NS1 toxicity in the brain, and immune-mediated brain injuries that include cytokine dysregulation and autoantibody production directed against brain antigens, have been proposed[7,8,35].

***Direct B19 infection or NS1 toxicity***

Only erythroid progenitor cells are permissive for B19 replication because these cells have both high concentrations of P blood type antigen, the receptor for B19[3] and α5β1 integrin, the co-receptor for B19[47]. P antigen is also expressed on other cell types including megakaryocytes, granulocytes, lung, heart, liver, kidney, endothelium, and vascular smooth muscle[48]. However, P antigen is necessary for B19 binding but not sufficient for virus entry into cell, which requires α5β1 integrin as a cellular co-receptor[47]. Because non-erythroid progenitor cells with P antigen do not have α5β1 integrin, B19 can bind, but cannot infect them. However, the NS1 exerts a cytotoxic effect on the cells it binds without any B19 replication or virion accumulation[49,50]. Therefore, NS1 may directly damage the cerebrovascular endothelium during B19 infection.

B19 DNA has been detected in the brain of two intrauterine deceased fetuses in mothers with recent B19 infection[51,52]. Hobbs and colleagues reported that B19 DNA was detected in 42% of dorsolateral prefrontal cortex and in 100% of cerebella, of postmorten samples taken from 104 subjects without recent acute B19 infection[53-54]. Manning *et al*[55] also reported that B19 DNA was detected in 69% of frontal or occipital lobe of postmortem brain tissue samples taken from 29 subjects without recent acute B19 infection.

Although B19 DNA was frequently detected in the CSF of children with B19 acute encephalitis and encephalopathy, B19 detection in the brain has never been reported in children[35]. Kerr *et al*[24] reported that postmortem brain tissue from a child with B19 acute encephalitis was negative for B19 in using in situ hybridization method. Skaff *et al*[56] also reported negative immunohistochemistry results for detecting B19 in brain biopsy tissue taken from an immunocompetent adult patient with B19 encephalitis. Meanwhile, B19 DNA was detected in brain biopsy tissues taken from adult patients with B19 encephalitis by PCR[57,58]. There is still controversy regarding whether B19 has direct infection or NS1 toxicity in the brain cells or not[59].

***Cytokines dysregulation***

B19 infection induces cytokine dysregulation. Wagner *et al*[60] studied concentrations of interleukin (IL)-1β, and IL-6 concentrations and interferon (INF)-γ messenger RNA (mRNA) in peripheral blood mononuclear cells (PBMC) from patients with acute B19 infection and reported that these cytokine genes were activated in PBMC, suggesting systemic monocyte and T cell activation. Moffatt *et al*[61] demonstrated that IL-6 production caused by the B19 NS1 protein was mediated by an NF-κB binding site in the IL-6 promotor region. Kerr *et al*[62,63] reported that serum IL-6, tumor necrosis factor (TNF)-α, IL-1β, IL-4, IL-8, INF-γ, macrophage chemoattractant protein-1(MCP-1), granulocyte-monocyte colony stimulating factor (GM-CSF) levels were increased during acute B19 infection.

Kerr *et al*[24] reported that increased levels of TNF-α, INF-γ, IL-6, INF-γ, GM-CSF and MPC-1 in the serum and CSF of patients with B19 encephalitis and suggested that over-production of inflammatory cytokines might play a role in B19 encephalitis.

***Autoantibody production***

B19 infection often develops clinical features similar to autoimmune disease and has been associated with the production of antibodies against self-antigens, including nuclear antigens, rheumatoid factor, neutrophils cytoplasmic antigens, and phospholipids[64,65]. Molecular similarities between host and B19 proteins and the induction of inflammatory cytokine production encourage the development of autoimmune reactions during B19 infection[64,65]. B19 chorea encephalitis has been suggested to be caused by autoimmune reactions against brain autoantigens[38].

**CONCLUSION**

Acute B19 encephalitis and encephalopathy are the most common B19-associated neurological manifestations. Some patients were immunocompromised or had underlying diseases. Impaired consciousness, seizures and focal neurologic signs are the main neurological features. Serum Anti-B19 IgM and CSF B19 DNA examinations are useful tools for diagnosing B19 infection in patients with B19 encephalitis and encephalopathy. Two studies reported that B19 DNA has been detected in CSF samples in approximately 4% of patients with etiologically undiagnosed encephalitis. Serum Anti-B19 IgM and CSF B19 DNA should be examined in patients with etiologically undiagnosed encephalitis and encephalopathy. Some patients with B19 encephalitis and encephalopathy were treated with IVIG and/or steroids; however, an accurate evaluation of the efficacy of these treatment modalities cannot be determined. Although more than half of B19 encephalitis and encephalopathy patients recovered completely, some patients developed severe neurological sequelae or died. While the precise pathogenesis underlying the development of B19 encephalitis and encephalopathy is unclear, direct B19 infection or NS1 toxicity in the brain, and immune-mediated brain injuries have been proposed.

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| --- | --- | --- | --- | --- | --- | --- | --- |
| **Table 1 Basic characteristics of children with B19 encephalitis and encephalopathy** | | | | | | |  |
| Case | Reference | Age | Gender | Diagnosis | | Underlying disorders | Immunodeficiency |
| No. |  |  |  |  | |  |  |
| 1 | 16 | 8 yr | M | Encephalitis | |  | - |
| 2 | 17 | 9 mo | M | Encephalitis | |  | - |
| 3 | 19, 20 | 5 yr | F | Encephalitis | |  | - |
| 4 | 23, 24 | 2 mo | F | Encephalitis | |  | - |
| 5 | 23, 24 | 2 yr | M | Encephalitis | | Acute lymphocytic leukemia | + |
| 6 | 23, 24 | 2 yr | F | Encephalitis | |  | - |
| 7 | 23, 24 | 6 yr | F | Encephalitis | | Cockayne syndrome | + |
| 8 | 23, 24 | 9 yr | M | Encephalitis | |  | - |
| 9 | 23, 24 | 13 yr | F | Encephalitis | | Crigler-Najar syndrome | - |
| 10 | 23, 34 | 13 yr | M | Encephalitis | |  | - |
| 11 | 23, 34 | 15 yr | F | Encephalitis | |  | - |
| 12 | 23, 24 | 1 d | F | Encephalitis | | Necrotizing enterocolitis Patent ductus arteriosus Respiratory distress syndrome | + |
| 13 | 23, 24 | 1 d | F | Encephalitis | | Ventricular septal defect Atrial septal defect Patent ductus arteriosus Turner syndrome Obstructive jaundice | + |
| 14 | 25 | 8 yr | F | Encephalitis | | Sickle cell disease Nephrotic syndrome | + |
| 15 | 25 | 8 yr | M | Encephalitis | | Sickle cell disease Nephrotic syndrome | + |
| 16 | 25 | 12 yr | F | Encephalitis | | Sickle cell disease Aplastic crisis | + |
| 17 | 25 | 14 yr | M | Encephalitis | | Sickle cell disease Aplastic crisis | + |
| 18 | 27 | 10 yr | F | Encephalitis | |  | - |
| 19 | 28 | 9 yr | M | Encephalitis | | Nephropathic cystinosis Renal transplant | + |
| 20 | 30 | 4 yr | F | Encephalitis | |  | - |
| 21 | 31 | 5 yr | F | Encephalitis and cerebellitis | |  | - |
| 22 | 18 | 8 yr | F | Encephalopathy | |  | - |
| 23 | 19 | 5 yr | F | Encephalopathy | |  | - |
| 24 | 21 | 5 yr | M | Encephalopathy | |  | - |
| 25 | 22 | 4 yr | M | Encephalopathy | | Prader-Willi syndrome | - |
| 26 | 26 | 13 yr | F | Encephalopathy | | Sβ+thalassemia | + |
| 27 | 9 | 8 yr | F | Chorea encephalopathy | |  | - |
| 28 | 10 | 1 yr | M | Chorea encephalopathy | |  | - |
| 29 | 11 | 1 yr | M | Chorea encephalopathy | |  | - |
| 30 | 11 | 1yr | F | Chorea encephalopathy | |  | - |
| 31 | 29 | 9 yr | F | MERS | | Hereditary spherocytosis | - |
| 32 | 12 | 11 yr | M | MERS | | Hereditary spherocytosis | - |
| 33 | 12 | 10 yr | M | MERS | | Hereditary spherocytosis | - |
| 34 | 13 | 9 yr | F | PRES | | Acute glomerulonephritis | - |
| yr: year; mo: month; d: day  MERS: Clinically mild encephalitis/encephalopathy with reversible splenial lesion  PRES: Posterior reversible encephalopathy syndrome | | | | | | | |
|  | | | | |

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Table 2 Clinical manifestations of children with B19 encephalitis and encephalopathy** | | | | | | | |  |  |
| Case | B19 related symptoms | | |  | Neurological manifestations | | | Complications | Sequelae or death |
| No. | Fever | Rash | Arthralgia |  | Unconsciousness | Seizure | Focal neurologic signs |  |  |
| 1 | + | + | + |  | + | - | +Neurogenic bladder |  | Left weakness and clonus |
| 2 | + | - | - |  | + | + | - |  | Psychomotor retardation |
| 3 | + | + | - |  | + | + | - | Status epilepticus | Epilepsy Mental retardation |
| 4 | + | - | - |  | + | + | - |  | - |
| 5 | + | - | - |  | + | - | - |  | Cognitive deficit |
| 6 | + | - | - |  | + | - | +Ataxia |  | - |
| 7 | - | - | - |  | + | - | - | Multiple organ failure Acute renal failure | Died |
| 8 | - | - | - |  | + | + | - |  | Cognitive deficit Epilepsy |
| 9 | - | - | - |  | + | - | - |  | Not determined |
| 10 | - | - | - |  | + | - | + Right hemiparesis Ataxia |  | - |
| 11 | - | - | - |  | + | - | - |  | Cognitive deficit |
| 12 | - | - | - |  | + | - | - |  | Died |
| 13 | - | - | - |  | + | - | - |  | Died |
| 14 | - | - | - |  | + | + | + Right hemiparesis Transient blindness | Acute renal failure Aplastic crisis Acute chest syndrome | - |
| 15 | - | - | - |  | + | + | + Cortical blindness | Acute renal failure Aplastic crisis Acute chest syndrome | - |
| 16 | + | - | - |  | + | + | + Focal seizures | Acute renal failure Acute chest syndrome | - |
| 17 | + | - | - |  | + | + | - |  | - |
| 18 | + | - | - |  | + | + | - | Status epilepticus | Epilepsy |
| 19 | - | - | + |  | + | + | - |  | - |
| 20 | + | - | - |  | + | + | + Cerebellar syndrome |  | Cerebellar syndrome |
| 21 | + | + | - |  | + | + | - |  | Cerebellar syndrome |
| 22 | - | - | + |  | + | + | - |  | - |
| 23 | - | + | - |  | + | + | - |  | - |
| 24 | - | - | - |  | + | - | - | Pancytopenia Liver dysfunction | - |
| 25 | - | - | - |  | + | - | - |  | Spastic quadriplegia |
| 26 | + | - | - |  | + | - | - | Aplastic crisis | - |
| 27 | - | - | - |  | + | - | + Chorea |  | - |
| 28 | - | - | - |  | + | - | + Chorea |  | - |
| 29 | - | - | - |  | + | + | + Left hemiparesis  Athetosis |  | - |
| 30 | - | - | - |  | + | + | + Left hemiparesis Choreo-athetosis |  | Global developmental delay |
| 31 | + | + | - |  | + | - | - | Aplastic crisis Pancytopenia | - |
| 32 | + | - | - |  | + | - | - | Aplastic crisis HLH Pancytopenia | - |
| 33 | + | - | - |  | + | - | - | Aplastic crisis HLH Pancytopenia | - |
| 34 | + | + | - |  | + | + | + Loss of vision | Transient SLE symptoms Hypertension | - |
|  |  |  |  |  |  |  |  | HLH: Hemophagocytic lymphohistiocytosis;  SLE: Systemic lupus erythematosus. | |

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Table 3 Laboratory data and treatment of children with B19 encephalitis and encephalopathy** | | | | | | | | | | | |  |
| Case | Anemia | Serum B19 markers | | |  | CSF B19 markers | | |  | CSF | | IVIG |
| No. |  | IgM | IgG | DNA |  | IgM | IgG | DNA |  | Pleocytosis | Increased protein | and/or steroids |
| 1 | - |  |  |  |  |  |  |  |  | + | - | - |
| 2 | - |  |  |  |  |  |  |  |  | - | + | - |
| 3 | - | + | + | + |  |  |  | - |  | + | + | - |
| 4 |  | - | - | - |  | - | - | + |  | - |  | IVIG |
| 5 |  |  |  |  |  | + | - | - |  | - | - | - |
| 6 | + |  |  |  |  | - | - | + |  | - | - | - |
| 7 | - |  |  |  |  | - | - | + |  |  |  | - |
| 8 | + | + | - | + |  | - | - | + |  |  |  | - |
| 9 | - |  |  |  |  |  |  | + |  |  |  | - |
| 10 | - |  |  |  |  |  |  | + |  | - |  | - |
| 11 | - |  |  |  |  |  |  | + |  | + |  | - |
| 12 | + | + | - | + |  | + | - | + |  |  |  | - |
| 13 | + | - | - | - |  | - | - | + |  |  |  | - |
| 14 | + | + | + | + |  |  |  |  |  | + |  | - |
| 15 | + | + | + | + |  |  |  |  |  | + |  | - |
| 16 | + | + | + | + |  |  |  |  |  | + |  | - |
| 17 | + | + | + | + |  |  |  |  |  | + |  | - |
| 18 | - | + | - |  |  | - | - |  |  | + | + | IVIG and steroids |
| 19 | + | + |  | + |  |  |  |  |  | + | + | - |
| 20 | - | - | - | + |  | - | - | + |  | + | - | IVIG and steroids |
| 21 | - | + | + | + |  |  |  | + |  | + | + | Steroids |
| 22 | + | + |  | + |  |  |  | + |  | - |  | - |
| 23 | - | + | + | + |  |  |  | + |  | - | + | - |
| 24 | + | + | + | + |  |  |  | + |  | - | + | - |
| 25 | - | + | + | + |  | - | - | + |  | + | + | - |
| 26 | + | + | + | - |  | - | - |  |  | - | - | Steroids |
| 27 | + |  |  | + |  |  |  | + |  | - | - | - |
| 28 | - | + | + |  |  |  |  | + |  | - | - | IVIG and steroids |
| 29 | - | + | - |  |  |  |  |  |  |  |  | - |
| 30 | + | + | - |  |  |  |  |  |  | + | - | - |
| 31 | + | - | + | + |  |  |  | + |  | - | - | Steroids |
| 32 | + |  |  |  |  |  |  |  |  | - | - | IVIG |
| 33 | + |  |  |  |  |  |  |  |  | - | - | IVIG |
| 34 | + | + | + | + |  |  |  | + |  | - | - | - |
|  |  |  |  |  |  |  |  |  |  |  | IVIG: Intravenous immunoglobulin;  CSF: Cerebrospinal fluid. | |