Meningoencephalitis in Children with Primary Antibody Deficiency: A Single-Center Experience From Northwest India and Review of Literature

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Abstract

Patients with primary antibody deficiency (PAD) are predisposed to develop meningoencephalitis that is often considered to be enteroviral. However, there is a paucity of literature on this subject, and there are no studies from developing countries. We analyzed our cohort of children with PAD who developed meningoencephalitis. This complication was observed in 11/135 (8.1%) patients with PAD - 4 patients had X-linked agammaglobulinemia (XLA), and 7 had common variable immunodeficiency (CVID). The mean age at onset of neurological illness was 8.6 years (range: 2-28 years). Presenting features included seizures (n=7), neurodevelopmental delay (n=2), regression of milestones (n=1), and acute flaccid paralysis (n=1). Trough IgG levels were found to be low in 9 (81.8%) patients at the time of development of neurological symptoms. Herpes simplex virus (HSV), cytomegalovirus (CMV), and Streptococcus pneumoniae were isolated in 1 patient each. No etiological agent was identified in cerebrospinal fluid of 8 patients. Eight (72.7%) patients had altered signal hypointensities in gray matter and deep white matter on magnetic resonance imaging (MRI), while 3 patients showed global cerebral atrophy. All patients were treated with high-dose intravenous immunoglobulin (IVIg). Fluoxetine was given to 2 patients. Eight (72.7%) patients in the present series have succumbed, while three have recovered with varying degrees of neurological sequelae. To conclude, meningoencephalitis is an uncommon complication in patients with PAD and is associated with high morbidity and mortality in our setting. Early diagnosis of immune deficiency and initiation of replacement immunoglobulin therapy may prevent the development of neurological complications.

Introduction

Primary antibody deficiencies (PADs) (such as X-linked agammaglobulinemia [XLA] and common variable immunodeficiency [CVID]) are inborn errors of immunity (IEI) caused by a predominant defect in the humoral arm of the adaptive immune system[1, 2, 3]. The most common clinical presentation of PADs is recurrent sinopulmonary infection. Pyogenic meningitis is also a common infection in patients with PAD[2]. In addition, these patients are predisposed to develop viral infections and non-infectious autoimmune complications[4]. Although meningoencephalitis (often caused by enteroviruses) has been reported in patients with PADs, most published literature pertains to anecdotal clinical reports. There is a paucity of data from large patient cohorts studied over extended periods of time, and no information is available on this subject from developing countries. We report herein our experience on meningoencephalitis in patients with PADs.

Patient And Methods

We carried out a review of records of all patients who were diagnosed to have XLA or CVID and were registered at the Pediatric Immunodeficiency Clinic, Advanced Pediatrics Centre, Postgraduate Institute of Medical Education and Research, Chandigarh, India. Our center is a not-for-profit tertiary care referral teaching institute in northwest India. Patients with XLA or CVID who were also diagnosed to have meningoencephalitis were analyzed in detail. For the purpose of this study, the terms’ XLA’ and ‘CVID’ were defined as per criteria given by the European Society of Immunodeficiencies[5, 6]. Patients who had pyogenic meningitis without any evidence of encephalitis (clinical or radiological) were excluded from this analysis. Clinical details, laboratory and imaging findings, treatment, and outcome of these patients were recorded. A pan-enterovirus reverse transcriptase-polymerase chain reaction (RT-PCR) targeting the highly conserved 5’ untranslated region of enterovirus genome was performed at the Department of Neurovirology, National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, for identification of enteroviruses from the cerebrospinal fluid (CSF).

Results

In this study, we retrieved clinical details of 70 patients with XLA and 65 patients with CVID. Of these, 11 were diagnosed to have meningoencephalitis.

Case 1

A 7-year-old boy presented with complaints of headache, 1 episode of generalized tonic-clonic seizure, and two episodes of transient loss of consciousness for 1 week. He had had a history of recurrent ear discharge and chronic diarrhea since the age of 1 and one episode of pyogenic meningitis at 6 years.

On examination, he had absent tonsils, and lymph nodes were not palpable. CSF examination was normal. Magnetic resonance imaging (MRI) of the brain revealed altered signal intensities in parieto-occipital regions. Investigations are summarized in Table 1. He was diagnosed to have XLA with possible viral encephalitis. He was empirically treated with intravenous acyclovir (60 mg/kg/day) and one dose of intravenous immunoglobulin (IVIg) (1 g/kg). He showed clinical improvement. Acyclovir was continued for 21 days. Over 77 months of follow-up, he is clinically well without any neurological sequelae and is being treated with high-dose intravenous immunoglobulin (IVIg) and cotrimoxazole prophylaxis (5mg/kg/day of trimethoprim component).

Case 2

A 4-year-old boy presented with fever and diarrhea. He had had a history of molluscum contagiosum over his face and legs since the age of 1. On examination, he had hypoplastic tonsils and non-palpable lymph nodes. Laboratory investigations are summarized in Table 1. A clinical possibility of CVID was considered, and he was given cotrimoxazole prophylaxis and IVIg replacement therapy (0.4g/kg/month).

A month later, he started developing left focal seizures and weakness of the left lower limb. On examination, he was noted to have Epilepsia partialis continua, hypotonia, and decreased power in the left lower limb. CSF examination is shown in Table 2. Trough IgG at this time was 3.72 g/L. MRI brain was suggestive of altered signal intensities in the right paracentral lobule, right thalamus, and right internal capsule (Figure 1). He was initiated on high dose IVIg (1 g/kg every 3 weeks) and fluoxetine (initially 0.5 mg/kg/day, and gradually hiked to 2.5 mg/kg/day). He showed some clinical improvement, and seizures were controlled. Fluoxetine and antiepileptic drugs were gradually tapered and discontinued over the next 2 years. He continued to receive cotrimoxazole prophylaxis and monthly IVIg replacement therapy. At 6 years, he developed acute onset, painless loss of vision in both eyes (visual acuity restricted to finger counting at 1-
A 16-year-old boy was symptomatic since infancy when he developed fever, severe pallor, hepatosplenomegaly, and pancytopenia. Bone marrow examination revealed a marked reduction in erythroid precursors and fibrosis (Figure 5). He was being followed up under pediatric hematology services and was treated with intravenous methylprednisolone pulse (30mg/kg/day for 5 days) followed by tapering doses of oral prednisolone (2mg/kg/day initial dose). He showed some clinical improvement but developed anemia every time an attempt was made to taper prednisolone. On follow-up, he was also noted to have short stature and skeletal abnormalities such as pectus carinatum, small head, hallux valgus, and pes planus. Low-dose prednisolone (0.5mg/kg/day) was continued till 5 years of age and later tapered and stopped. He was re-hospitalized at the age of 17 with complaints of generalized seizures following a short febrile illness. On examination, he was drowsy, had papilledema, signs of meningeal irritation, raised intracranial pressure, and hepatosplenomegaly. Laboratory investigations revealed anemia (hemoglobin: 86g/L) and a positive PCR for HSV in CSF (Table 2). MRI brain revealed non-enhancing mild diffusion restricted T2 hyperintensities involving bilateral frontal and periventricular white matter, along with mild hydrocephalus (Figure 4). He was empirically initiated on acyclovir, high dose IVlg (1g/kg/3 weeks), and fluoxetine (initially 0.5mg/kg/day, gradually hiked to 1mg/kg/day). He showed some improvement in sensorium. However, he developed an episode of pneumonia one month later. He was hospitalized at a nearby health care facility, where he succumbed to this illness.

Case 6

A 16-year-old boy was symptomatic since infancy when he presented with red eyes and was noted to have hypertonia, brisk deep tendon reflexes, and vascular tortuosity in the peripapillary region of the retina with mild optic atrophy. Laboratory investigations showed hemoglobin: 106 g/L, total leucocyte count 10.3X10^9/L, and platelet count 356X10^9/L. The trough IgG level was 2.95g/L. MRI brain revealed areas of encephalomalacia with gliosis in the bilateral frontal lobes with a prominence of frontal horns of lateral ventricles that suggested a sequel of old ischemic insult. CSF opening pressure was 60 cm H2O. However,
the CSF examination was normal. A clinical possibility of benign intracranial hypertension was considered. He was continued on IVIg replacement therapy, but there was progressive neurological deterioration. One month later, he developed an episode of pneumonia and died at a hospital elsewhere.

Case 7

A 5-year-old boy had intermittent fever, recurrent ear discharge, and progressive abdominal distension. He also had a global developmental delay. He was born to a third-degree consanguineously married couple with a history of death of two siblings and two cousins (all because of some infections during the neonatal period). Examination showed generalized lymphadenopathy, splenomegaly, hepatomegaly, frontal bossing, long slender fingers and toes, pectus carinatum, and multiple joint contractures. Laboratory investigations are summarized in Table 1. A radiograph of the arms showed exostosis of the right humerus. Investigations suggested a clinical possibility of CVID. MRI brain was normal. He was initiated on monthly IVIg replacement therapy (0.4g/kg/month), following which his cytopenias started improving, and there was gradual regression in hepatosplenomegaly. There was, however, no improvement in his neurological status. A year later, he developed a short febrile illness requiring hospitalization and succumbed soon thereafter.

Case 8

A 4-year-old boy presented with recurrent pneumonia and ear discharge since early infancy. He was born to a second-degree consanguineously married couple. On examination, he had wasting, stunting, absent tonsils, small lymph nodes, tachypnea, diffuse crepitations in bilateral lung fields, and mild hepatomegaly. Investigations are summarized in Table 1. He was initiated on monthly IVIg replacement therapy (0.4g/kg/month) and cotrimoxazole prophylaxis. He was re-hospitalized at the age of 6 with complaints of subacute ascending paralysis of all four limbs that appeared two weeks after an acute upper respiratory tract infection. Examination showed proximal muscle weakness in all limbs, upper motor neuron type left-sided facial nerve palsy, a retinal scar in the left eye, and brisk deep tendon reflexes. CMV PCR in CSF was positive. CMV viral load in blood was 946 copies/mL. MRI brain showed diffuse cerebral atrophy with T2 hyperintense signals in the tegmental tract on both sides. He was treated with high dose IVIg (1g/kg every 2 weeks), ganciclovir (5 mg/kg/day for 3 weeks) followed by oral valganciclovir (5 mg/kg/day for 4 weeks), and intravenousceftriaxone (0.1g/kg/day) for 2 weeks. He was given IVIg 1g/kg every 2 weeks (6 doses) followed by monthly replacement doses of 0.4 g/kg/month and showed gradual improvement. He is doing well with no breakthrough infections and no evidence of muscle weakness at 11 months of follow-up.

Case 9

A 5-year-old boy had had an acute febrile illness with left-sided tonic-clonic convulsions and altered sensorium. Examination showed encephalopathy, nuchal rigidity, left hemiparesis, and brisk deep tendon reflexes. He was also found to have bilateral tympanic perforation and profound hearing loss in both ears. Computed tomography (CT) head showed ill-defined hypodense lesion in the right frontal cortex and bilateral thalami posteriorly and mild hydrocephalus. Details of the CSF examination are given in Table 1. He was treated with intravenous ceftriaxone and amikacin for 14 days and showed gradual improvement in sensorium. However, he continued to have recurrent sinopulmonary and ear infections thereafter and developed bilateral lower motor neuron facial nerve palsy at 12 years that needed middle ear exploration and tympanoplasty.

Meanwhile, his nephew had been diagnosed to have XLA and was initiated on IVIg replacement therapy. After the diagnosis of XLA in his nephew, the index patient was brought to our clinic at the age of 18, evaluated (Table 1), and diagnosed with XLA. He showed poor compliance to IVIg replacement therapy, developed an episode of pneumonia at the age of 20, and succumbed to the illness.

Case 10

A 13-year-old boy presented with recurrent pneumonia, loose stools, and skin infections since the age of three. He was the second-born child of a non-consanguineously married couple. His elder sibling had expired at 8 months because of pneumonia and diarrhea. He developed progressive regression of his milestones, paucity of movements, ataxia, and lost partial control of his bowel and bladder at 13 years. Examination revealed supranuclear gaze palsy, hypertonia, rigidity, bradykinesia, exaggerated deep tendon reflexes, and clinical signs suggestive of cerebellar dysfunction. MRI brain showed diffuse cerebral and cerebellar atrophy with the widening of sulci and folial spaces (Figure 6). Investigations are summarized in Tables 1 and 2. Whole-exome sequencing showed no pathogenic variants. A clinical possibility of CVID was considered, and he was given one dose of IVIg (1g/kg), cotrimoxazole prophylaxis, fluoxetine (0.5mg/kg/day), and levodopamine. He is being continued on IVIg replacement therapy (0.4g/kg/month). At 4 months of follow-up, there have been no further breakthrough infections. However, he is continuing to be neurologically impaired.

Case 11

A 28-year-old male was diagnosed to have CVID (Table 1). Chest CT showed changes suggestive of bronchiectasis. He was initiated on IVIg replacement therapy and cotrimoxazole prophylaxis. He developed multiple episodes of generalized seizures 2 months after initiation of IVIg. The trough IgG level at this time was 6.81g/L. MRI brain showed T2 weighted hyperintensities in bilateral centrum semiovale, peri-Rolandic white matter in the right cerebral hemisphere, and temporo-occipital lobe in the left cerebral hemisphere, right midbrain, and thalamus. He was continued on replacement IVIg (0.4g/kg every month), antiepileptics, and cotrimoxazole. He remained seizure-free thereafter but had progressive neurological worsening. At the age of 29, he developed acute chest pain, for which he was taken to a nearby health care facility and died within a few hours. The exact cause of death could not be ascertained.

Discussion

Patients with PADS are predisposed to develop a spectrum of neurological complications[8]. Bacterial meningitis (commonly caused by Streptococcus pneumoniae, N. meningitidis, S. aureus, and Pseudomonas sp.) is the most common CNS infection[9,10]. Meningoencephalitis is usually caused by
enteroviruses (e.g., echovirus, coxsackievirus, and poliovirus). There is a paucity of published literature on large patient cohorts followed up over extended periods and there are no studies from developing countries.

Under the National Immunization Program in India, oral poliovirus vaccine is still being used routinely, and most patients with PADs in India would have received this vaccine prior to their diagnosis getting confirmed. This further predisposes them to develop neurological complications related to the vaccine strain of poliovirus. Our center was part of a Jeffrey Modell Foundation (JMF) funded study on poliovirus excretion in patients with PADs. However, the vaccine strain of poliovirus in the stool sample was not detected in any of the patients with PAD who were screened for it from India.

The incidence of meningoencephalitis in XLA has been reported to be 1.1% in the registry of United States Immunodeficiency Network, 1% in the ESID registry, and 3% in the registry of Latin American Society for Immunodeficiencies. In a recent multicenter experience on patients with XLA from India, 23% were reported to develop pyogenic meningitis, while 4.8% of patients had evidence of encephalitis (likely viral).

In the present study, we report our experience of meningoencephalitis in patients with PAD. We also reviewed all previously published reports on meningoencephalitis in patients with XLA or CVID (Table 2). We observed meningoencephalitis in 11/135 (8.1%) patients - 4 with XLA and 7 with CVID. One patient had low CD40L expression with low IgG, low IgA and high IgM suggesting a possibility of Hyper-IgM syndrome. Whole exome sequencing, however, failed to identify any pathogenic variant in that patient. Low CD40 ligand expression has also been reported in patients with CVID.

The mean age of diagnosis of primary illness (hypogammaglobulinemia) in our cohort was 9.36 years (range: 2-28 years), and the mean age of onset of CNS illness was 8.6 years (2-28 years). Children with XLA were diagnosed earlier, except for one patient (case no 9) whose diagnosis was made at the age of 18. These results are similar to what has been reported previously.

In five patients (case 1, 6, 7, 9, 10) the diagnosis of PAD was made while they were being investigated for the neurological illness. The remaining six patients developed this complication while they were receiving replacement IVIg. It is important to note that all patients who developed meningoencephalitis while on replacement IVIg did so within the first two years of initiation of therapy. As compared to reports from the West (Table 2), the diagnosis of PAD was delayed in this series. Whether this delay has any direct bearing on the occurrence of meningoencephalitis, remains conjectural. Although commonly used immunoglobulin preparations usually have detectable titers of antibodies to many enteroviruses, coverage is not universal. Viral infections have been shown to occur even with adequate IVIg replacement therapy.

In the present study, trough IgG levels were found to be low in 9/11 patients at the time of development of neurological symptoms despite replacement immunoglobulin therapy. American Academy of Allergy, Asthma & Immunology recommends maintaining a trough level of at least 5 g/L in patients with agammaglobulinemia. In our published experience on serial serum IgG trough levels in patients with XLA at Chandigarh, the median trough IgG level was 3.97 g/L. This was found to be protective against the development of serious infections in our setup. It has been suggested that higher doses of IVIg and higher trough IgG levels are needed for protection against enteroviral encephalitis due to the presence of low levels of antibodies against prevalent enteroviruses in commercial IVIg preparations. Because of lack of universal insurance coverage in India, access to replacement immunoglobulin therapy is a challenging task. In the past few years, the cost of replacement immunoglobulin therapy for some patients is being supported by a few state governments and philanthropic organizations in our country. However, despite this support, the dose of replacement immunoglobulin remains suboptimal, and therefore, it is difficult to maintain an adequate trough IgG level in most of our patients.

Identification of causative organism for meningoencephalitis is challenging, especially in resource-limited settings. Laboratory evaluation is limited due to high costs and low reliability of currently available diagnostic tests. Serological tests are erratic in presence of hypogammaglobulinemia. Viral infections can be identified by isolating the virus in cell lines or in laboratory animals or by detection of viral nucleic acids by PCR in CSF samples (latter has higher sensitivity for virus detection). No etiological pathogen was identified in 8 (72.7%) patients in our study. Enteroviruses could not be isolated in any patient. This may be due to low sensitivity of enteroviral detection in CSF samples. While the specificity is high (92–100%), sensitivity of PCR based assays for detection of enteroviral RNA in CSF varies from 31–95%. Sensitivity of the test can be increased by performing PCR in stool, throat swabs and urine samples. A PCR can also be performed on brain biopsy in settings of high clinical suspicion. Metagenomic next-generation sequencing is a novel approach that allows unbiased detection of any microbial nucleic acid present in a biological specimen, including divergent and novel pathogens. This can provide enhanced detection of etiological agents, when used in conjunction with conventional microbiological testing.

Neuroimaging may be normal in up to 25% of patients with viral encephalitis within the first few days. In the present series, MRI brain was performed in 10 and CT head in 1. Nine patients had altered signal hyperintensities in gray and deep white matter, while 3 showed global cerebral atrophy. Neuroimaging in patients with enteroviral encephalitis often shows symmetric bilateral T2 weighted hyperintense lesion in the dorsal brainstem, cerebellum and spinal cord while it may show cerebral atrophy in later stages. Neuroimaging findings in the present series, however, did not show the characteristic findings of enteroviral encephalitis.

Management is guided by the identification of causative organism. Most patients are initially managed empirically using broad-spectrum antimicrobials. High-dose IVig therapy has been found to be useful. Ten patients needed high-dose IVig therapy (1 g/kg every 2 weeks). Intrathecal immunoglobulin has also been reported to be beneficial in treating enteroviral encephalitis. However, this therapy was not administered to any of our patients. Selective serotonin reuptake inhibitor, fluoxetine, has been shown to have antiviral effects and may be useful in enterovirus encephalitis. Two of our patients also received fluoxetine. However, the use of fluoxetine did not result in significant clinical improvement. Several antiviral drugs (e.g., pleconaril, vapendavir, enviroxime, ViroD7000 and pocapavir) are undergoing clinical trials for their therapeutic use in these cases. However, none of these drugs could be used in the present series because of lack of availability.
Eight (72.7%) patients in the present series have died. Three patients are on replacement IVIg, and the mean follow-up duration is 29.6 months (Table 2). Two amongst these (case 1 and 8) have shown complete neurological recovery, while one patient has shown some clinical improvement at follow-up of 3 months (case 10). Viral encephalitis in patients with PAD has been reported to have a poor prognosis. Rudge et al reported 13 patients with encephalomyelitis, and all patients succumbed to neurological illnesses[8]. McKinney et al. reported 23 deaths in their series of 41 patients with chronic enteroviral meningoencephalitis, while 6 patients improved with a combination of IVIg and intraventricular IgG therapy[41]. Halliday et al. reviewed 90 patients with primary immunodeficiencies and enteroviral infections. Of these, only 5 patients were reported to be well on follow-up[42]. Of the 117 cases reported so far with hypogammaglobulinemia and meningoencephalitis, only 52 (44.4%) patients survived (Table 2), and a large majority of these patients continued to have neurological deficits.

The strengths of this study are that diagnosis and treatment of all patients were done at a single center, thereby bringing uniformity to patient management. This is the largest single-center cohort of patients with meningoencephalitis in patients with PADs from India. Limitations include a limited diagnostic armamentarium for identification of pathogenic organisms, especially enteroviruses.

To conclude, patients with PADs may present with a spectrum of neurological manifestations. Identification of a causative organism is extremely difficult in resource-limited settings such as ours. Treatment is largely limited to high doses of IVIg, and prognosis remains guarded in most patients. Early diagnosis and initiation of replacement immunoglobulin therapy (maintaining a trough IgG >5 g/L) may prevent the occurrence of neurological complications.

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Author's contribution:

AKJ: Writing of initial draft, patient management, editing of manuscript at all stages of its production, review of literature
HC: Writing of initial draft, patient management, editing of manuscript at all stages of its production, review of literature
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KI/OO/SN/LM/KWC/YLL: Editing of manuscript, laboratory investigations, review of literature
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Tables

Table 1: Clinical details and immunological workup in the present cohort of patients with primary antibody deficiency and meningoencephalitis
| Case no. | Type of disease | Age at diagnosis(years) | Clinical features at diagnosis | Immunoglobulin profile at diagnosis | Lymphocyte subsets at diagnosis | Other immunological tests | Genetic abnormality |
|---------|----------------|------------------------|-------------------------------|----------------------------------|---------------------------------|--------------------------|---------------------|
| 1       | XLA            | 7                      | Recurrent diarrhea, ear discharge, headache, seizures, transient ischemic attacks | IgG: 3.1 g/L (normal range: 5.4-16.1 g/L) | CD19+B lymphocytes: 0.1% (normal: 10-31%), IgM: <0.12 g/L (normal: 0.5-1.8 g/L) | Btk protein expression on patient’s monocytes (20.5%, MFI: 1.28) when compared to control (90.5%, MFI: 1.6) | Missense pathogenic variant detected in exon 17 of BTK (c.1732T>C, p. Ser578Pro) |
| 2       | CVID           | 4                      | Fever, diarrhea, molluscum contagiosum | IgG: 0.39 g/L (normal range: 5.4-16.1 g/L) | CD19+B lymphocytes: 9.56% (normal: 14-44%), IgM: <0.23 g/L (normal: 0.5-1.8 g/L), IgA: <0.17 g/L (normal: 0.7-2.5 g/L) | Antibody response to vaccinations against diphtheria: 0.03 IU/ml (protective: ≥0.1 IU/mL) | Not done |
| 3       | XLA            | 2                      | Recurrent infections          | IgG: 0.92 g/L (normal: 3.7-15.8 g/L) | CD19+B lymphocytes: 0.07% (normal: 14-33%), IgM: <0.25 g/L (normal: 0.5-2.2 g/L), IgA: <0.17 g/L (normal: 0.3-1.3 g/L) | Btk protein expression on CD14+ monocytes in patient: 11.5%; MFI: 1.89; Btk protein expression on CD14+ monocytes in control: 87.4%; MFI: 5.84 | BTK (c.310-8C>A [Splice-site acceptor variant]) |
| 4       | CVID           | 2                      | Recurrent episodes of fever, oral ulcers and sinopulmonary infections | IgG: 0.39 g/L (normal range: 4.9-16.1 g/L), | CD19+B lymphocytes: 16% (normal range: 14-44 %), CD3+T lymphocytes: 58.6% (normal: 43-76%), IgM: <0.25 g/L (normal: 0.5-2.0 g/L) | Naive B lymphocytes: 66.3% (normal: 43-83%), and Unswitched memory B lymphocytes: 19.9% (normal:7.4-32.5%) | Not done |
|         |                |                        |                               |                                  |                                 |                                |                     |
| 5   | XLA | 4 | Recurrent sino-pulmonary infections, 1 episode of pyogenic meningitis and global development delay |
|-----|-----|---|----------------------------------------------------------------------------------------------|
| IgG | 0.39 g/L (normal range: 4.9-16.1 g/L) |
| IgA | <0.17 g/L (normal: 0.4-2 g/L) |
| IgM | <0.25 g/L (normal: 0.5-2.0 g/L) |
| IgA | <0.17 g/L (normal: 0.4-2 g/L) |

| 6   | CVID | 16 | Fever, severe pallor, hepatosplenomegaly, pancytopenia |
|-----|------|-----|------------------------------------------------------|
| IgG | <0.95 g/L (normal: 5.4-16.1 g/L) |
| IgA | <0.17 g/L (normal: 0.8-2.8 g/L) |
| IgM | <0.25 g/L (normal: 0.5-1.9) |

| 7   | CVID | 5  | Intermittent fever, ear discharge since infancy and progressive abdominal distension |
|-----|------|----|------------------------------------------------------------------------------------------------|
| IgG | 0.49 g/L (0.49-1.6 g/L) |
| IgM | <0.25 g/L (normal: 0.5-2.0 g/L) |
| IgA | <0.36 g/L (normal: 0.4-2 g/L) |
| Case | Primary Antibody Deficiency | Clinical Presentation | IgG | CD19+ B Lymphocytes | IgM | CD3+ T Lymphocytes | CD56+ NK Lymphocytes | CD40L Expression on Activated Helper T Lymphocytes | CD40L Ligand Expression on CD4+ T Lymphocytes |
|------|----------------------------|-----------------------|-----|---------------------|-----|------------------|-------------------|---------------------------------------------|-----------------------------------------------|
| 8    | CVID                        | Recurrent pneumonia and ear discharge since early infancy | 3.89 g/L (normal: 4.9-16.1 g/L) | 13.5% (normal: 14-44%) | 1.13 g/L (normal: 0.5-2.0 g/L) | 81% (normal: 43-76%) | 0.08% (normal: 4-23%) | Switched memory B lymphocytes 0.82% (normal: 6.5-29.1%) | CD40 ligand expression on CD4+ T lymphocytes 82.34% as compared to 96.25% in control |
| 9    | XLA                        | Recurrent pneumonia and bilateral ear discharge | <0.93 g/L (normal: 5.4-16.1 g/L) | 0.1% (normal: 6-23%) | <0.11 g/L (normal: 0.5-1.9 g/L) | 0.1% (normal: 6-23%) | 0.18 g/L (normal: 0.8-2.8 g/L) | CD40L expression on activated helper T lymphocytes: 8.3% (control: 47.1%) | BTK gene (intron B~intron 9 deletion) |
| 10   | HIGM                       | Recurrent pneumonia, loose stools and skin infections | 0.12 g/L (normal: 5.4-16.1 g/L) | 7.71% (normal: 6-23%) | 2.17 g/L (normal: 0.5-1.9 g/L) | 74.05% (56-84%) | CD56+ lymphocytes: 2.57% (normal: 3-22%) | Switched memory B lymphocytes 0.57% (normal: 6.5-29.1%) | Not done |
| 11   | CVID                        | Recurrent pneumonia, diarrhea, ear discharge and sinusitis since early childhood | 5.0 g/L (normal: 9.77-15.19) | 0.1% (normal: 6-19%) | 0.81 g/L (normal: 0.85-1.13 g/L) | 45.4% (normal: 55-83%) | CD56+ NK lymphocytes: 56.5% (normal: 7-31%) | Regulatory T lymphocytes: 2.17% (control: 4.14%) | Btk protein expression on monocytes normal |

**Abbreviations used:** XLA: X-linked agammaglobulinemia, CVID: common variable immunodeficiency, HIGM: Hyper IgM syndrome, Btk protein: Bruton tyrosine kinase protein, MFI: Mean fluorescent intensity, Hb: hemoglobin, TLC: total leucocyte count, CD40L: CD40 ligand

Due to technical limitations, table 2 is only available as a download in the Supplemental Files section.

Table 3: Review of previously reported cases with primary antibody deficiency and meningoencephalitis
| Study, country, year [reference] | No of patients | Type of disease | Neurological manifestations | Age at diagnosis(in years) | Age at time of illness(in years) | Organism isolated | Treatment |
|--------------------------------|----------------|----------------|----------------------------|---------------------------|------------------------------|-------------------|------------|
| Linnemann et al, USA, 1973[43] | 2              | XLA            | Encephalitis               | 1                         | 1.5                          | Herpes simplex virus, Echovirus 2 | None       |
| Ziegler, USA, 1975[44]         | 1              | XLA            | Viral meningoencephalitis  | 14                        | 14                           | Echovirus 30      | Intramuscular gamma globulin |
| Wilfert et al, USA, 1977[45]   | 5              | 3 XLA, 2 hypogammaglobulinemia | Chronic meningoencephalitis; 4; dermatomyositis: 3 | Mean age: 2.4(1.5-3.5) | Mean: 10.8(3.5-24) | Echovirus 9, 19, 30, 33 | Steroids; immune serum globulin |
| Bardelas et al, USA, 1977[46]  | 1              | Hypogammaglobulinemia | Meningoencephalitis, polymyositis, edema | Echovirus 24 | Specific serum anti-Echovirus 24 plasma |
| Webster et al, England, 1978[23] | 2              | XLA, Hypogammaglobulinemia | Encephalitis: 2 dermatomyositis:1 | 1.5, 2 | 11, 2 | Echovirus 11, Echovirus 25 | Hyper-immune plasma, steroids |
| Weiner et al, USA, 1979[47]    | 1              | XLA            | Chronic myositis, meningoencephalitis | 3                         | 5                             | Echovirus 5        | Hyperimmune plasma |
| Bodenstein et al, USA, 1979[48] | 1              | X linked Hypogammaglobulinemia | Chronic meningoencephalitis | 17                        | Echovirus 5          | High-titer, specific plasma |
| Mease et al, USA, 1981[33]     | 1              | XLA            | Meningoencephalitis, myositis | 22                        | 32                           | Echovirus 11       | IVlg       |
| Erlendsson et al, USA, 1985[34]| 1              | XLA            | Chronic meningoencephalitis | 6                         | 6                             | Enterovirus        | IVlg, intraventricular Ig |
| Johnson et al, USA, 1985[49]   | 1              | XLA            | Chronic meningoencephalitis | 11                        | Echovirus 11       | IVlg, intraventricular Ig |
| Crennan et al, USA, 1986[32]   | 1              | XLA            | Meningoencephalitis, dermatomyositis | 4                        | 28                           | Coxsackievirus B3 | Cyclophosphamide, Steroids |
| McKinney et al, USA, 1987[41]  | 42             | 18 XLA, 20 CVID, 4 acquired hypogammaglobulinemia | Chronic enteroviral meningoencephalitis | Mean age: 14.2(3 mo-35 years) | Mean age: 20.1(2-42 years) | Enterovirus | IVlg, intraventricular Ig |
| Kondoh et al, Japan, 1987[21]  | 1              | XLA            | Meningonecephalitis       | 7                         | 12                           | Echovirus type 11  | IVlg, intraventricular Ig |
| Dwyer et al, Australia, 1988[35] | 3              | XLA            | Chronic enteroviral meningoencephalitis | 7                        | 3 months | 7 | 4 | 9 | Enterovirus | IVlg, intraventricular Ig |
| Roberton et al, Australia, 1989[50] | 1              | XLA            | Chronic enteroviral meningoencephalitis | 3                        | 9                             | Pirocavirus        | IVlg, intraventricular Ig |
| Maldergem et al, Belgium, 1989[51] | 1              | XLA            | Chronic enteroviral meningoencephalitis | 6 months | 8.5 | Echovirus type 13. | High dose IVlg |
| Misbah et al, UK, 1992[30]     | 1              | XLA            | Chronic enteroviral meningoencephalitis | 4                        | 8                             | Echovirus         | High-dose IVlg (2.5 to 7.5 g) |
| Rudge et al, USA, 1996[8]      | 13             | 7 XLA, 6 CVID    | Myelopathy: 5/13 Encephalopathy: 12/13 Myositis: 3/13 Hearing loss: 2/13 Retinopathy: 3/13 | 13.4(0.5-56) | 31.4(6-62) | Echovirus 3: 1 Echovirus 11: 1 JC virus: 2 | Immunoglobulin: 12 Plasma: 2 IFN-µ: 1 |
| Authors                  | Country, Year | Immunodeficiency | Disease Description                                      | Treatment | Other Treatments |
|--------------------------|---------------|------------------|----------------------------------------------------------|-----------|-----------------|
| Wense et al              | Germany, 1998 | XLA              | Chronic enteroviral meningoencephalitis                  | Echovirus type 6 | IVIG, 1 g/kg/week |
| Bezrodnik et al          | Argentina, 1998 | XLA              | Progressive Multifocal Leukoencephalopathy               | JC virus | Cytosine arabinoside |
| Cunningham et al         | USA, 1999     | XHIGM            | Enteroviral meningoencephalitis                          | Echovirus 14 Enterovirus | IVIG, 1.5 g/kg per week |
| Plebani et al            | Italy, 2002   | XLA              | Meningitis, meningoencephalitis                          | Neisseria meningitidis in 1 | IVIG, 1 g/kg/week |
| Cucchiara et al          | USA, 2003     | Good syndrome    | Encephalitis                                             | Cytomegalovirus | Foscarnet |
| Halliday et al           | USA, 2003     | XLA, CVID,HIGM   | Chronic encephalitis and meningitis                      | Enterovirus | High dose IVIg, intrathecal immunoglobulin |
| Shiroma et al            | Japan, 2004   | XLA              | Progressive Encephalitis                                 | IVlg, IFN-µ | |
| Ansari et al             | India, 2010   | CVID             | Herpes simplex encephalitis                              | HSV-1     | Ayclovir, IVlg |
| Borish et al             | USA, 2011     | CVID             | Herpes simplex encephalitis                              | HSV-1     | Ayclovir, IVlg |
| Sempere et al            | Spain, 2011   | CVID             | Bilateral optic neuritis                                 | Steroids, IVlg | |
| Bakri et al              | Jordan, 2013  | CVID             | Encephalitis                                             | BK virus   | IVlg, ganciclovir |
| Khair et al              | Qatar, 2015   | CVID             | Autoimmune encephalitis                                  | 1         | IVIG |
| Nguyen Et al             | USA, 2016     | CVID             | Left monoparesis, enhancing lesions of the left cerebellar hemisphere with mass effect, optic neuritis | Steroids, rituximab and azathioprine | |
| Najem et al              | USA, 2017     | CVID             | Intracranial granulomatous disease                       | Steroids 4/19 | |
| Gofshrey et al           | USA, 2018     | XLA              | Chronic Enterovirus Encephalitis                         | Enterovirus | High dose IVIg, fluoxetine |
| Shribman et al           | England, 2018 | CVID             | Encephalomyelitis with retinopathy                       | Teenage   | IVlg |
| Slade et al              | Australia, 2019 | CVID           | Chronic lymphocytic meningoencephalitis                  | Enterovirus | High-dose IVIG (2 g/kg) and methylprednisolone 2 mg/kg, cyclophosphamide |

Abbreviations used: XLA: X linked agammaglobulinemia, CVID: common variable immunodeficiency, Ig: Immunoglobulin, IVIg: intravenous immunoglobulin, †
Figures

**Figure 1**
Axial T2-weighted (A and C) and FLAIR (B and D) MRI images at 4-years of age showing hyperintense lesion in the right thalamus and internal capsule (arrow). No diffusion restriction or susceptibility changes seen. Similar lesion is also seen in the right paracentral lobule involving cortex and white matter. At 6-years of age, axial T2-weighted (E and G) and FLAIR (F and H) MRI images showing hyperintense lesion in the central part of pons (arrow) and left lateral thalamus. The right thalamic lesion seen in the previous MRI is no longer visible.

**Figure 2**
Fundus examination of case 2 showed necrotizing retinitis involving posterior pole in both eyes (a and b). Optical coherence tomography (OCT) showed hyporeflective spaces in retinal layers, suggestive of tissue loss, with sparing of the internal limiting membrane (c and d).
Figure 3

Axial T2 (A, D, and G), FLAIR (B, E, H and J to L), and T1-weighted (C, F and I) MR images of a child with chronic progressive meningoencephalitis. The first MRI shows a right frontal cortical-subcortical lesion (A-C, arrows). MRI after 2 months (D-I) shows progression with mild gliosis in the frontal lesion, and there is the involvement of bilateral occipital lobes as well (arrows in G). Subsequent MRI (J-L) demonstrated multiple new lesions involving the cortex of bilateral cerebral hemispheres and deep grey matter involving thalami and basal ganglia.
Figure 4

MR Axial T2 (A and D), FLAIR (B and E), and T1-weighted (C and F) images showing mild diffuse cerebral atrophy. There is ventriculomegaly with periventricular white matter changes. Multiple small white matter lesions are seen in bilateral cerebral hemispheres (arrows).

Figure 5

A) Peripheral blood smear showing decreased red blood cell density with an admixture of normocytic and few microcytic red cells (May Grunwald-Giemsa stain, original magnification 1000x); B) bone marrow aspirate smear showing myeloid series of cells in varying stages of maturation with a marked reduction in erythroid precursors (May Grunwald-Giemsa stain, original magnification 1000x); C) bone marrow trephine biopsy section at low magnification showing cellular marrow spaces (Hematoxylin & Eosin stain, original magnification 100x); D) bone marrow trephine section at high magnification showing predominance of myeloid series of cells along with few lymphocytes (arrows) and scattered megakaryocytes (arrowheads) and near absence of erythroid precursors (Hematoxylin & Eosin stain, original magnification 400x); the inset shows increased reticulin fibrosis of bone marrow (reticulin stain, original magnification 200x)
Figure 6

Axial T2 (A and D), FLAIR (B and E), and T1-weighted (C and F) MR images showing diffuse cerebral atrophy with prominent ventricles and extra-axial spaces. Multifocal small white matter lesions are seen in bilateral cerebral hemispheres (arrows).

Supplementary Files

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