X-Linked Agammaglobulinemia With Chronic Meningoencephalitis: A Diagnostic Challenge

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X-linked agammaglobulinemia (XLA) is a primary disorder of humoral immunity characterized by *Bruton tyrosine kinase* gene mutations resulting in a primary antibody deficiency. While an intact T-cell function largely protects against majority of viral infections, enteroviruses are notorious for infecting these patients due to impaired mucosal immunity. Although the incidence of enteroviral meningoencephalitis in XLA is only 1-5%, yet the mortality is quite high. A typical presentation of enteroviral encephalitis in XLA is a subacute to chronic nervous system infection. A progressive loss of motor and cognitive milestones, spastic quadriplegia, coma, and death are common presentations. The histopathological features reflect gliosis, gradual neuronal loss, neuronophagia, and microglial proliferation. We describe the clinical and brain histopathological findings in a 2-year-old boy with XLA and progressive encephalitis, possibly due to an enteroviral infection.

Keywords: *Central nervous system infection, Enterovirus, Encephalitis, Epilepsia partialis continua, Immunodeficiency.*

A 3-year-old boy was admitted with recurrent febrile illnesses and neurological symptoms. The first illness, at 21 months of age, manifested as a high-grade fever with non-paroxysmal cough, respiratory distress, and a generalized macular rash, present over one week. The perinatal period and development were normal. Computed tomography scan of the chest showed nodules in the bilateral lower lobe with necrotic conglomerating mediastinal lymph nodes suggestive of infective etiology. A clinical diagnosis of probable measles with pneumonia was considered. At 24 months of age, he again presented to our center with a febrile illness. Examination showed the absence of tonsils and peripheral lymph nodes, and presence of a BCG scar. Family history revealed that two of his maternal uncles had died in early childhood due to an undiagnosed infection. A clinical diagnosis of X-linked agammaglobulinemia (XLA) was considered and confirmed by specific investigations as per the diagnostic criteria proposed by European Society for Immuno-deficiencies [1]. Monthly intravenous immunoglobulin (IVIg) (400 mg/kg) was initiated, and he showed symptomatic improvement. At 26 months of age, he developed left-sided focal motor status epilepticus and left-sided hemiparesis without associated fever, altered sensorium, cranial nerve involvement, or features of raised intracranial pressure. Investigations are shown in **Table I**. Magnetic resonance imaging (MRI) of the brain showed focal signal changes (details in the section on investigations). A clinico-radiological diagnosis of XLA with probable focal enteroviral encephalitis was considered. Intravenous acyclovir (30 mg/kg/d for 15 days) and high-dose IVIg (1g/kg) were given. He recovered with residual left hemiparesis. He was readmitted a month later with persistent vomiting, intermittent lethargy, redness of eyes with watery discharge, and brief intercurrent seizures over the past one week. He had been on regular monthly IVIg replacements, and trough IgG level was 600 mg/dl. He continued to have altered sensorium and residual left hemiparesis with radiological progression of the focal encephalitic changes (details in the section on investi-gations). He had two further admissions, one and six months later, with persistent left-sided, focal seizures and residual left hemiparesis. By 34 months of age, he developed subacute neurological deterioration (progressive lethargy and reduced interaction), visual deterioration, and recurrent right-sided focal tonic-clonic seizures followed by right hemiparesis. At this time, examination showed weight 10 kg (-2 to -3 *z*), length 90 cm (-1 to -2 *z*) and head circumference 48 cm (-1 to -2 *z*). His Glasgow Coma Scale was 11 ($E_3M_5V_{3-4}$), and pupils were 2mm bilaterally equal and reacting to light. He had chronic left-sided motor weakness with lower limb spasticity, acute-onset right-sided weakness with diminished tone, brisk deep tendon reflexes and bilateral extensor plantar response. Rest of the systemic examination was unremarkable.

Table I Relevant Investigations During Multiple Hospitalizations

Investigations	*First admission*	*Subsequent admissions*	*Last admission*
Platelets (10^9/L)	179	504	565
TLC (10^9/L)	16	95	76.3
DLC (%)	$N_{32}L_{38}M_{28}E_2$	$N_{49}L_{35}M_9E_6$	$N_{53}L_{31}M_8$
ANC (cells/mm^3)	512	4655	4043
Serum galactomannan[a]	0.4	0.18	0.3
Microbiological and radiological investigations			
Blood, urine and CSF cultures	Sterile	Sterile	Sterile
Toxoplasma PCR	Negative	-	Negative
Mycoplasma serology	Negative	Negative	Negative
HIV serology	Non-reactive	-	-
Cerebrospinal fluid	No cells, glucose 59 mg% protein 21 mg%	No cells, glucose 61 mg% protein 21mg%	No cells, glucose 183 mg% protein 438 mg%
Cryptococcal antigen	Negative	Negative	Negative
Herpes PCR	Negative	-	Negative
Enterovirus	Negative by PCR and cultures		
Electroencephalogram	Right-sided centro-parietal periodic lateralized epileptiform discharges		Encephalopathic pattern with interictal discharges
Immunological investigations			
Immunoglobulin G (mg/dL)	<92 (370-1580)		
Immunoglobulin A (mg/dL)	<17 (30-130)		
Immunoglobulin M (mg/dL)	<25 (50-220)		
CD3+ T-lymphocytes	83.93% (56-75%)		
CD20+ B lymphocytes	0.07% (14-33%)		
CD56+ natural killer cells	9.74% (4-17%)		
CD3+/56+ natural killer T-cells	3.35 (normal)		
Btk protein expression on CD14+ monocytes	11.5% positive; Median Fluorescence Intensity (MFI): 1.89 (Control 87.4% positive; MFI: 5.84)		

HSV: herpes simplex virus; PCR: polymerase chain reaction; TLC: total leucocyte count; DLC: differential leucocytes count; ANC: absolute neutrophil count; [a]Serum galactomannan index normal <0.5.

Investigations (**Table I)**: XLA being a prototype primary humoral immunodeficiency disorder, T cells and their subsets were not tested in the blood or on the brain sections at autopsy. Stool sample was negative for both polio and non-polio viruses. Baseline MRI of the brain at the onset of seizures showed presence of a right-sided, frontal, subcortical white matter lesion, which showed gliosis later. New lesions appeared in bilateral occipital and parietal subcortical white matter, and the thalamus, suggesting a progressive, subcortical, multifocal involvement (**Fig. 1A-H)**. MR spectroscopy revealed reduced NAA with a small lactate peak.

Course and Management: Multiple anti-epileptic drugs (phenytoin, valproate, levetiracetam, phenobarbitone, midazolam infusion) were sequentially given for right-sided epilepsia partialis continua. He was intubated and ventilated for worsening sensorium. Intravenous acyclovir and high dose IVIg (2g/kg total dose) were restarted. Brain biopsy was deferred due to the poor general condition of the patient. Newer therapies such as pleconaril and pocapavir were considered but could not be tried due to resource-constraints. The patient further developed high-grade fever secondary to nosocomial infection and/or aspiration pneumonia. Intravenous antimicrobials were sequentially upgraded (ceftriaxone, meropenem, vancomycin). He suffered a cardiac arrest on day 19 of hospital stay and could not be revived.

Unit's Final Diagnosis

X-linked agammaglobulinemia with recurrent seizures and encephalopathy probably due to chronic enteroviral encephalitis complicated with nosocomial pneumonia.

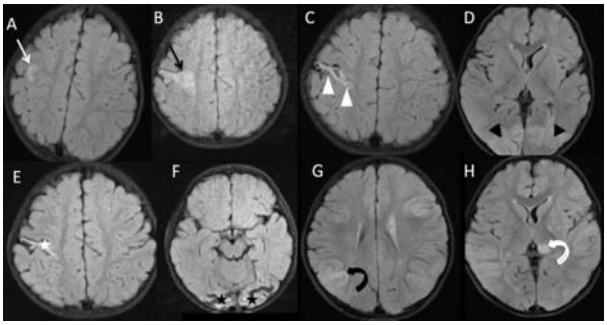

Fig. 1 Sequential axial flair MR images of the patient: Baseline MRI *a*) shows the presence of frontal subcortical white matter lesion (white arrow). MRI after 24 days *b*) shows the progression of frontal subcortical white matter lesion (black arrow). Interval MRI after one month, *c,d*) shows gliosis in the right frontal subcortical lesion (white arrowheads) and appearance of bilateral occipital subcortical lesions (black arrowheads). Interval MRI after 1.5 months (e,f) shows gliosis in the frontal (white star) and occipital (black stars) subcortical lesions. Interval MRI after five months (g,h) shows the appearance of new parietal subcortical (curved black arrow) and thalamus (curved white arrow) lesions. No evidence of any diffusion-weighted abnormality, susceptibility-weighted abnorma-lity, contrast enhancement, or angiographic abnormality was noted in all the MRI examinations.

DISCUSSION

Clinical discussant: We had a 34-month-old boy with recurrent sinopulmonary infections, absent tonsils, lymph nodes and peripheral B-cells, pan hypogammaglobulinemia, reduced Btk protein expression on CD14+ monocytes and progressive neurocognitive decline. The family history supported an X-linked inheritance pattern. Based on the standard diagnostic criteria, a diagnosis of underlying XLA is beyond doubt [1].

Regarding the central nervous system (CNS) manifestations, the patient had an acute CNS event, which progressed both clinically and radiologically over the subsequent 12-14 months with intermittent exacer-bations. CNS manifestations in children with XLA can be either due to an inability to clear the opportunistic infections, or due to a dysregulated immunity, or both. XLA is a prototype of humoral immunodeficiency disorders with B-lymphocyte differentiation arrest, resulting in recurrent infections with encapsulated bacteria like pneumococcus and *H. influenza*, gastrointestinal infections with giardia and chronic enteroviral infections [2]. However, the chronic and indolent clinical course, presence of significant neutropenia and absence of fever during all episodes of clinical deterioration make bacterial infection unlikely. Moreover, the patient being on regular IVIg replacement therapy had adequate trough level (>600 mg/dL) to control the bacterial infections [3]. Although there are anecdotal reports of fungal and mycobacterial infections causing primary CNS manifestations in XLA patients, overall, these infections primarily concern the cell-mediated immunity, which is intact in XLA patients.

In the index case, toxoplasma serology (IgG and IgM) and PCR were negative. In neuroimaging toxoplasmosis lesions usually appear as hypointense (on T1- weighted) with high or mixed signal intensity (on T2-weighted and FLAIR images) signals, typically in basal ganglia, cortico-medullary junction, white matter, and the periventricular regions [4]. Few case reports of toxoplasmosis in acquired immunodeficiency syndromes have shown hyperintense lesions involving basal ganglia, thalamus and cerebral hemispheres [5,6]. However, in our case, neuroimaging was not in favour of toxoplasmosis.

Enteroviral infections are known to cause difficult, persistent CNS disease in children with XLA. As opposed to other viruses, which are dealt with by cell-mediated immunity, the host response to enteroviral infections in XLA is by forming neutralizing antibodies. In one of the largest series of 36 patients of XLA seen over two decades, CNS infections constituted a significant proportion (25%) of all infections [7] with enteroviral infections including echo, polio and coxsackie being the most problematic [8]. As seen in our case, enteroviral encephalitis in XLA are described as insidious onset, slowly progressive loss of motor and cognitive milestones over 2-3 years, followed by spastic quadriplegia, coma with mortality in nearly 44% of cases [9, 10]. CSF samples remained negative for all enteroviruses, tested both by PCR and by viral cultures in the index case, which may be falsely negative and does not exclude the infection. Though adequate trough levels by IVIg replacement therapy may prevent bacterial infections it protect against enteroviral infections [3].

Besides enteroviruses, astrovirus, measles and herpes viruses need to be considered in XLA [11, 12]. Though, the index case had a measles-like past illness, and had been immunized with a live vaccine, measles inclusion body encephalitis was unlikely, because it is a disease of patients with depressed cell-mediated immunity with a rapid and fatal course. The clinical and radiological presentation in the index case did not favor subacute sclerosing pan-encephalitis. Moreover, the measles serology was negative and measles virus inclusion bodies were absent on the histopathology. Other than these, clinical presentations described in the anecdotal reports of other viruses such as adenovirus, influenza virus, cytomegalovirus, and John Cunningham (JC) virus [13] did not fit into our clinical scenario. Progressive multifocal encephalopathy, reported with XLA was also unlikely [14,15]. Dysregulated immunity leading to autoimmune encephalitis, abnormal immune response to

drugs [2] or IVIg therapy induced progressive, chronic neuro-regression [3] were other differential diagnosis, but unlikely in this case.

Pediatric immunologist 1: In the present case, the trough level of immunoglobulins being well above 600 mg/dL, he was protected against the common bacterial pathogens, thus making bacterial infection of CNS unlikely. The most common CNS pathology in such patients is an enteroviral infection, which can occur even when the patient is on regular IVIg therapy. Therefore, this is consistent with a case of chronic enteroviral infection with XLA.

Neurologist 1: The diagnosis of chronic enteroviral infection with XLA seems most likely in this case. The early onset of gliosis in the MRI brain of this patient suggests a vascular invasion. As pointed rightly by the clinical discussant, measles inclusion body encephalitis is a fulminant infection that does not follow such a chronic indolent course. Additionally, there is no contrast enhancement in any of five sets of MRIs probably due to the lack of immunity to mount an inflammation. JC virus could be another possibility.

Virologist: Enterovirus is the most common etiology for this clinical presentation. Astrovirus, as the discussant highlighted, is also being reported. Sensitivity of detection of enterovirus by CSF PCR ranges from 75-100%. It would be ideal to take a throat swab along with CSF samples. Studies have shown that sensitivity has improved when throat swab is being examined along with CSF PCR.

Pediatric pulmonologist: Although the case strongly points towards a viral infection, yet the presence of necrotic lymph nodes in computed tomogrpahy chest and persistent mastoiditis might be suggestive of other infectious agents such as fungus or an invasive hospital-acquired infection. As the autopsy was done for brain only, infection elsewhere in the body could not be identified.

Pediatric hemato-oncologist 1: One could consider granulomatous amoebic infections such as *Balamuthia*, which have been previously reported from the center, although the MRI picture does not conform to it.

Pediatric immunologist 2: The patient received 4-5 doses of oral polio vaccine in routine immunization schedule, along with a dose on the national immunization day, 15 days prior to the onset of illness. Live viral vaccines are contraindicated in such patients as well as in siblings and their surroundings.

Physician: Measles seems more likely in the index case than enteroviruses as the posterior parts of the brain are more involved. The absence of enhancement and cells in the CSF and the presence of high protein and gliosis in the brain are described in measles. However, the clinical course in measles is shorter for 1-3 months, as compared to the chronic course in the index lasting nearly 12 months.

Clinical discussant: Measles inclusion body encephalitis is primarily a disease of cell-mediated immunity, seen more commonly in adult patients, and follow a rapid fulminant course. Subacute-chronic measles virus infection could not be completely excluded. Serological testing for measles virus was not feasible as B-cells are deficient in XLA. JC virus infection would be unusual as the virus is carried to the brain by B-cells, which are deficient in XLA patients. Polioviruses are also a type of enteroviral infections. XLA patients are prone for atypical manifestation of enteroviruses, which includes fulminant polio encephalitis as well as paralytic poliomyelitis. The abnormal chest findings on computed tomography described the lung pathology at the time of first illness when the child was admitted with a viral prodrome, bacterial pneumonia and neutropenia suggestive of an acute bacterial necrotizing pneumonia. Additionally, investigations for tuberculosis and fungal infections had been non-corroborative at that time. It would be very unusual for a mycobacterial or fungal infection to present with such CNS manifestations over several months. However, systemic infection with pneumocystis carinii is described in patients with XLA.

Pediatric hemato-oncologist 2: As progressive multifocal leukoencephalopathy secondary to JC virus infection is common in hematological conditions treated with rituximab, a similar mechanism may be proposed for XLA patients also. The patient also had persistent microcytic, hypochromic anemia with thrombocytopenia, which could be due to an enteroviral inflammatory bowel disease or an intestinal giardiasis, which is common in XLA patients.

Pediatric immunologist 1: As part of an international collaborative study, 32 children of the institute, with XLA were screened for poliovirus. None of them had poliovirus infections. In Iran, 4% of children with XLA had poliovirus infection [16]. The negative stool samples for poliovirus make this infection unlikely in the case.

Pediatric neurologist 1: Chronic herpes encephalitis type 1 and human herpes virus-6 infection may be additional possibilities.

PATHOLOGY PROTOCOL

A partial autopsy was performed in this case. The external

examination of the brain weighing 1142 grams, showed slightly congested meninges, without any exudate. A mild tonsillar herniation was noted. Blood vessels of circle of Willis and brainstem appeared normal. Bilateral parieto-occipital and temporal lobes were discolored, collapsed and soft (**Fig.2**). The coronal sectioning of the brain revealed softening, shrinkage and thinning of the cortical ribbons of left inferior frontal, left frontal, paramedian area above cingulate gyrus and right middle and inferior frontal gyrus (**Fig. 2**). Both temporal lobes and bilateral parietal cortices had similar changes with a shrunken left temporal lobe. The right occipital lobe showed cystic encephalomalacia. While the left putamen and adjacent internal capsule showed necrosis explaining his right hemiparesis, the right lentiform nucleus was normal (**Fig. 2**). The affected areas of the brain corresponded to the anterior, middle, and posterior cerebral artery territories indicating global hypoxia. The hippocampi, thalami and midbrain appeared normal grossly. The white matter was mostly spared. The brainstem axial cuts revealed mild congestion of the dorsal parts of the pons, with unaffected medulla and cerebellum.

Microscopic examination revealed sparse meningeal infiltrates, predominantly lymphocytic (**Fig. 2**). The grossly affected cortical areas showed laminar and transcortical necrosis, replaced by large number of foamy macrophages admixed with few lymphocytes, accompanied by reactive glial proliferation (**Fig. 2**). The adjacent cortical areas showed evidence of hypoxic changes, more marked at the base of the sulci than the crests. Hippocampi showed diffuse hypoxic damage and patchy neuronal loss. The posterior parts of the occipital cortex showed extensive neuronal loss, cyst formation and calcium deposits indicating chronicity (**Fig. 2**). Therefore, the cerebral cortex, in nutshell, showed presence of hypoxic damage and varying degree of cortical necrosis, explained by recurrent seizures. Histological examination of the dorsal pons demonstrated neuronal loss, neuronophagia and microglial proliferation with nodule formation, highlighted by CD68 immuno-staining. The perivascular lymphocytic infiltration consisted of CD3-positive T-cells without any CD20-positive B-cells. Similar changes were noted in the midbrain, dentate nucleus of the cerebellum and grey matter around 4th ventricle with cerebellar folia being unremarkable. The dorsal motor root of vagal nucleus and the anterior horn cells of the cervical segment of the cord were affected. Immunohistochemistry for herpes simplex virus 1 and 2, cytomegalovirus, simian virus 40 (SV40), Epstein Barr and parvovirus were negative. In addition, PCR for enteroviruses was negative in the brain tissue. The post-mortem biopsy samples of brain, lung and liver tissues did not contribute any significant information.

The topography of the lesions in this brain namely the involvement of dorsal pons, dentate nucleus, medulla, part of the hypothalamus and sparing of thalamus and cortical zone favours enteroviral infection, even though PCR was negative. PCR positivity depends on multiple factors and at best gives 50% positive results. The lesions and the histological features favour a chronic enteroviral infection over JC virus. SV40 antibody, which recognizes both JC virus and BK polyoma virus failed to show any positivity. The final autopsy diagnosis was XLA with probable enteroviral encephalitis and cystic cerebral encephalomalacia.

Open Forum

Pediatric neurologist 2: Considering a remarkably similar case of XLA with seizures reported by the CDC, where RNA separation method detected astrovirus, infection with other single-stranded RNA viruses could be a possibility. The presence of hemorrhage and calcification in the occipital lobe could also suggest Posterior reversible encephalopathy syndrome-like changes.

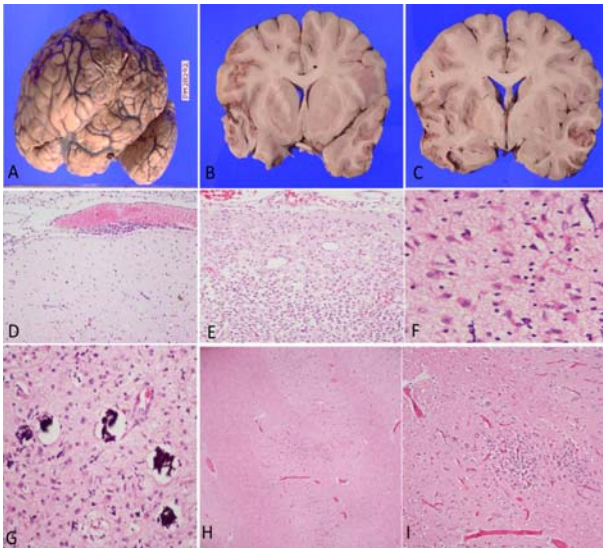

Fig. 2 *a*) The parietal convexity is discolored and collapsed due to softening of underlying cortex of the brain; *b*) Coronal section of the brain shows shrinkage and softening of the cortical ribbons affecting left inferior frontal gyrus and both temporal lobes. The white matter is relative spared, *c*) The left putamen and internal capsule are soft and necrotic in this coronal slice. The right basal ganglia and both thalami are spared. Note that left temporal is affected more than right temporal lobe; *d*) Sparse lymphocytic inflammation is seen in the cortical leptomeninges; *e*) The affected cortical areas showed neuronal loss and necrosis and replacement by macrophages and lymphocytes; *f*) Reactive hypertrophied astro-cytes. The occipital cortex demonstrated foci of micro-calcification and microglial proliferation, *g-h*) The dentate nucleus of the cerebellum shows neuronal loss, microglial proliferation, and vascular congestion.

Neurologist 2: As none of the viral studies yielded an etiological agent, autoimmune encephalitis could be a possibility. The response to ongoing IVIg therapy could also be a pointer toward an underlying autoimmune process.

Pathology discussant: The case has been a clinical and histopathological challenge. While Posterior reversible encephalopathy syndrome mostly involves the white matter, gray matter involvement was seen in this case. Autoimmune encephalitis should only be considered when infectious causes have been excluded. A negative PCR does not exclude an enteroviral infection. Enterovirus A71 infection has been prevalent in India, Bangladesh, Malaysia, and Taiwan. Enterovirus D68 can present similarly in an XLA patient. Other uncommon enteroviruses and single-stranded RNA viruses also remain a possibility. In the presence of normal limbic organs, cingulate gyrus, and amygdala on histopathology, a limbic encephalitis is most unusual. Other forms of autoimmune encephalitis such as anti-NMDAR and anti-AMPAR need specific testing. The California encephalitis project has reported that 63% of the probable encephalitis cases remain unknown despite extensive investigations for infectious causes. The hypoxic changes in the brain in the case were probably due to recurrent seizures.

Pediatric immunologist 3: The histopathology shows typical features of viral encephalitis with infiltration by CD3 lymphocytes alone, CD20 lymphocytes being absent, as expected in XLA patients. The diagnosis of astrovirus infection in the CDC case alluded to in the previous discussion was based on highly advanced pyro sequencing PCR technique which is not routinely available.

DISCUSSION

The case highlights the unique presentation of a child with XLA and recurrent infections. A simple throat examination for the presence of tonsils is a vital bedside clue and helps clinch the diagnosis. CNS infections are tough to treat and constitute a significant cause of mortality in these children as seen in the index case [17]. Although the presence of good T-cell functions protects the patients from common childhood viral infections, yet enteroviruses notoriously cause chronic infections [18,19]. The brain pathology was not consistent with the diagnosis of JC virus-related multifocal leukoencephalopathy, where multifocal discrete white matter demyelination occurs initially, progressing to form confluent large demyelinating lesions appearing as granular soft discolored plaques. As mentioned in the pathology description, the white matter was spared in this case with a predominantly grey matter disease. No demyelination is seen in the index case. There were no oligodendroglia inclusions or bizarre astrocytes and anti-SV40 antibody on immunohistochemistry did not show any viral antigen in brain tissue. The typical involvement of brainstem nuclei, dentate nucleus of cerebellum and hypothalamus showing neuronal loss, microglial hyperplasia is characteristic of an enteroviral infection [19]. Although JC virus could not be tested in the CSF, SV40 antibody used for immunostaining on the brain sections did not show any positivity for the same. The collections of foamy macrophages with a few lymphocytes on histopathology are from multiple infarcts involving various regions of the cerebral cortex. This is the second pathology in brain, which occurred due to severe hypoxia in this child because of repeated seizures. The cerebral infarcts were of different durations.

Hence, with the available investigative work-up possible in a resource-limited setting, we could conclude that the case was a probable enteroviral meningoencephalitis. The topography of the lesions, the peculiar preponderance of enteroviral infections in children with XLA, the histological features and immunohistochemistry favour an enterovirus over JC virus, although the virus could not be demonstrated by PCR in the brain tissue. This is a common scenario in several pediatric centers in India and needs to be brought out, even if an organism could not be identified. Prevalence of enteroviral encephalitis in XLA is reported between 1% and 3% [8]. Echovirus, poliovirus, coxsackievirus and several uncommon enteroviruses may cause chronic progressive encephalitis with neuroregression [17,20] with enteroviruses being one of the most common causes of meningoencephalitis in patients with XLA [21]. The sensitivity of CSF PCR-based assays for enteroviruses ranges from 75%-80%. Combining the CSF PCR with a throat swab may increase the sensitivity of detection [22, 23]. Regular IVIg therapy with adequate trough levels protects against severe bacterial infections [3]. However, the role of high dose peripheral and intraventricular immunoglobulin for enteroviral encephalitis is debatable [9,17].

Contributors: AGS: Concept and design of the study, data collection and interpretation, drafting manuscript data interpretation, editing of draft, critical revision, Clinical discussant of CPC; BDR: Design of the study, drafting manuscript, acquisition of data and data analysis; pathology discussant of CPC; DB: Concept and design of the study, patient care, data collection and interpretation, drafting manuscript data interpretation, editing of draft, critical revision; AR: Acquisition of immunological data and data analysis, critical revision of manuscript; VB: Acquisition of radiological data and data analysis, critical revision of manuscript, radiology discussant of the CPC.

REFERENCES

1. Conley ME, Notarangelo LD, Etzioni A. Diagnostic Criteria for Primary Immunodeficiencies. Representing PAGID (Pan-American Group for Immunodeficiency) and ESID (European Society for Immunodeficiencies). Clin Immunol. 1999;93:190-7.
2. Hernandez-Trujillo VP, Scalchunes C, Cunningham-Rundles C, et al. Autoimmunity and inflammation in X-linked agammaglobulinemia. J Clin Immunol. 2014;34:627-32.
3. Suri D, Bhattad S, Sharma A, et al. Serial serum immunoglobulin G (IgG) Trough levels in patients with X-linked agammaglobulinemia on replacement therapy with intravenous immunoglobulin: Its correlation with infections in Indian children. J Clin Immunol. 2017;37:311-8.
4. Osborn AG, Jhaveri MD, Salzman KL, editors. Diagnostic imaging. Brain. Third edition. Elsevier; 2016.
5. Hofmann A, Zaharatos G, Miller M. Case report and review of the literature: Toxoplasma gondii encephalitis in a 40-Year-Old woman with common variable immunodeficiency and a new diagnosis of large granular lymphocytic leukemia. Can J Infect Dis Med Microbiol. 2008;19: 309-10.
6. Holtkamp M, Okuducu AF, Klingebiel R, Ploner CJ. Cerebral toxoplasmosis in a patient with common variable immunodeficiency. Neurology. 2004;63:2192-3.
7. Singh S, Rawat A, Suri D, et al. X-linked agammaglobulinemia: Twenty years of single-center experience from North West India. Ann Allergy Asthma Immunol. 2016;117:405-11.
8. Winkelstein JA, Marino MC, Lederman HM, et al. X-linked agammaglobulinemia: Report on a United States registry of 201 patients. Medicine (Baltimore). 2006;85: 193-202.
9. Bearden D, Collett M, Quan PL, Costa-Carvalho BT, Sullivan KE. Enteroviruses in X-linked agammaglobulinemia: Update on epidemiology and therapy. J Allergy Clin Immunol Pract. 2016;4:1059-65.
10. Halliday E, Winkelstein J, Webster ADB. Enteroviral infections in primary immunodeficiency (PID): A survey of morbidity and mortality. J Infect. 2003;46:1-8.
11. Conley ME, Dobbs AK, Farmer DM, et al. Primary B cell immunodeficiencies: comparisons and contrasts. Annu Rev Immunol. 2009;27:199-227.
12. Dropulic LK, Cohen JI. Severe viral infections and primary immunodeficiencies. Clin Infect Dis. 2011;53:897-909.
13. Chun J-K, Lee TJ, Song JW, Linton JA, Kim DS. Analysis of clinical presentations of Bruton disease: A review of 20 years of accumulated data from pediatric patients at Severance Hospital. Yonsei Med J. 2008;49:28-36.
14. Teramoto T, Kaneko H, Funato M, et al. Progressive multifocal leukoencephalopathy in a patient with X-linked agammaglobulinemia. Scand J Infect Dis. 2003;35:909-10.
15. Zerbe CS, Marciano BE, Katial RK, et al. Progressive multifocal leukoencephalopathy in primary immune deficiencies: Stat1 Gain of function and review of the literature. Clin Infect Dis. 2016;62:986-94.
16. Mamishi S, Shahmahmoudi S, Tabatabaie H, Teimourian S, Pourakbari B, Gheisari Y, Yeganeh M, Salavati A, Esteghamati AR, Gooya MM, Nategh R, Parvaneh N. Novel BTK mutation presenting with vaccine-associated paralytic poliomyelitis. Eur J Pediatr. 2008;167(11):1335-8
17. Sag AT, Saka E, Ozgur TT, et al. Progressive neurodegenerative syndrome in a patient with X-linked agammaglobulinemia receiving intravenous immunoglobulin therapy. Cogn Behav Neurol. 2014;27:155-9.
18. Suri D, Rawat A, Singh S. X-linked agammaglobulinemia. Indian J Pediatr. 2016;83:331-7.
19. Sanna PP, Burton DR. Role of antibodies in controlling viral disease: Lessons from experiments of nature and gene knockouts. J Virol. 2000;74:9813-7.
20. Wong KT, Ng KY, Ong KC, et al. Enterovirus 71 encephalomyelitis and Japanese encephalitis can be distinguished by topographic distribution of inflammation and specific intraneuronal detection of viral antigen and RNA. Neuropathol Appl Neurobiol. 2012;38:443-53.
21. Misbah SA, Spickett GP, Ryba PC, et al. Chronic enteroviral meningoencephalitis in agammaglobulinemia: Case report and literature review. J Clin Immunol. 1992;12:266-70.
22. Jain S, Patel B, Bhatt GC. Enteroviral encephalitis in children: clinical features, pathophysiology, and treatment advances. Pathog Glob Health. 2014;108:216-22.
23. Plebani A, Soresina A, Rondelli R, et al. Clinical, immunological, and molecular analysis in a large cohort of patients with X-linked agammaglobulinemia: An Italian multicenter study. Clin Immunol. 2002;104:221-30.