BANGLADESH J CHILD HEALTH 2021; VOL 45 (1) : 55-58

X-linked Agammaglobulinemia (XLA) Associated with Progressive Neurodegenerative Syndrome: A Case Report

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Abstract:
Primary immune deficiency disorders (PIDs) are not an uncommon entity, but the diagnosis is often delayed or even missed due to lack of awareness. Central nervous system involvements due to various reasons are documented in patients with PIDs. This case report describes a 10- year old boy, diagnosed as X-linked agammaglobulinemia (XLA) who developed progressive encephalopathy. He had severe cognitive impairment along with cerebellar and pyramidal dysfunction. MRI of the brain showed generalized cerebral and cerebellar atrophy. Therefore, this boy was diagnosed as a case of XLA with progressive neurodegenerative syndrome.

Keyword: *Primary immune deficiency disorders (PIDs)*

Introduction:

Primary immune deficiency disorders (PIDs) are genetic diseases that affect the development, and/or function of the immune system. In addition to recurrent infections, these patients are also prone to autoimmune diseases, allergies and lympho-proliferative disorders.[1] The most common PIDs are humoral deficiency, followed by combined defect (both T lymphocytes and defective antibody response), phagocyte deficiencies and, complement deficiencies.[2] XLA is one of the common primary immunodeficiency disorders (PIDs) caused by mutations in the Bruton tyrosine kinase (BTK) gene that result in defective B-lymphocytes development. Reduced serum immunoglobulins, absence of circulating B cells, small to absent tonsils and non-palpable lymph nodes are the essential features of this defect.[3] Absence of B cells causes failure to produce IgG. IgM, IgA and IgE.[4] As a result, XLA is characterized by increased susceptibility to recurrent bacterial infections from 6 months of age when protective IgG from mother gradually weaned off.[5] Besides sinopulmonary infections (sinusitis, pneumonia, otitis media) and other bacterial infections; septicemia, osteomyelitis, diarrhea and meningitis are usual patterns of the recurrent infections.[6]

Central nervous system (CNS) involvement in PIDs causes severe disability and can eventually be fatal. Pyogenic or viral (enterovirus) infections due to lack of neutralizing antibodies and some PID related syndromes, or autoimmune process are responsible for the CNS involvment.[7-9] Recent studies have identified that a growing number of XLA patients developed unexplained CNS deterioration without evidence of infection.[6,10] There is little information about progressive neurodegenerative disorders associated with PIDs available in the literature. To disseminate the clinical presentations of this uncommon syndrome and also to raise the awareness about PIDs, we report here, a case of progressive neurodegenerative disorder in a child with Bruton Agammaglobulinemia, also called XLA.

Case Report:

A 10- year old immunized boy only issue of healthy non-consanguineous parents had been suffering from recurrent infections since 3 years of age and was admitted several times in different hospitals. Several episodes of pneumonia, ear infection, sinusitis and skin infections were the reasons for his repeated hospitalization. Most of the time, he needed injectable antibiotics followed by oral antibiotics for a prolonged period. There was no history of recurrent or severe infections or immunodeficiency in his family.

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Received: 22/11/2020 **Accepted:** 3/03/2021

At eight years of age, he was admitted to the department of paediatrics, Bangabandhu Sheikh Mujib Medical University (BSMMU) and based on history, physical findings and laboratory profile, a diagnosis is of XLA was made. His laboratory profile showed normal complete blood count, liver function tests, renal function tests, and septic screenings. Quantitative immunoglobulin analysis found pan-hypogammaglobulinemia having low Ig A (0.25 gm/L), IgG (1.39 gm/L), and Ig M levels (1.69 gm/L). Flow cytometry showed that CD19 B-cell was absolutely absent and CD3 T cell, CD4 T cell and CD8 T cell counts were within normal limit. Genetic analysis of BKT gene could not be done due to non-availability.

The boy was treated with IVIG (400 mg/kg) 4 weekly and prophylactic antibiotic-cotrimoxazole (TMP- 5 mg/kg) orally once daily 3 days/week. With these treatments, the boy became symptom-free. He was gaining weight, maintaining good health and regularly attending the follow-up clinic. After 18 months of treatment, he suddenly developed progressive cognitive impairment, involuntary movements and gait disturbance. He had tremor of hands while reaching toward objects, could not stand, and get up from sitting and lying positions. His speech and writing skills gradually deteriorated and were not able to feed and dress up himself. The slowness of all activities and deterioration of school performance were the characteristics findings of his presentations. No history of seizure, vomiting, headache, and trauma was found in this patient. On neurologic examination, the boy was disorientated, tone was spastic and all refexes were exaggerated. Bilaterally Planter response was extensor and ankle clonus was present. He had features of cerebellar dysfunction and involuntary movements like; dyssynergia, dysdiadochokinesia, dysmetria and tremor (Fig:1).

Laboratory findings, including blood count, urine examination and septic screenings were normal. Antinuclear antibody (ANA) titers, compliments level (C3,C4), thyroid hormone status, blood lactate, serum ceruloplasmin, and 24-hour urinary copper excretion were also normal. CSF study, serologic markers for the human immunodefciency virus (HIV), hepatitis virus and TPHA assay were also negative. Polymerase chain

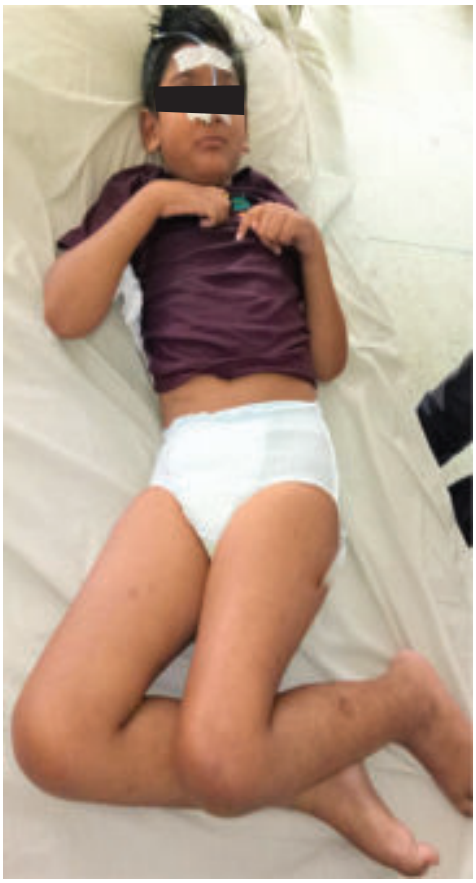

Fig.-1: Showing posture of the boy

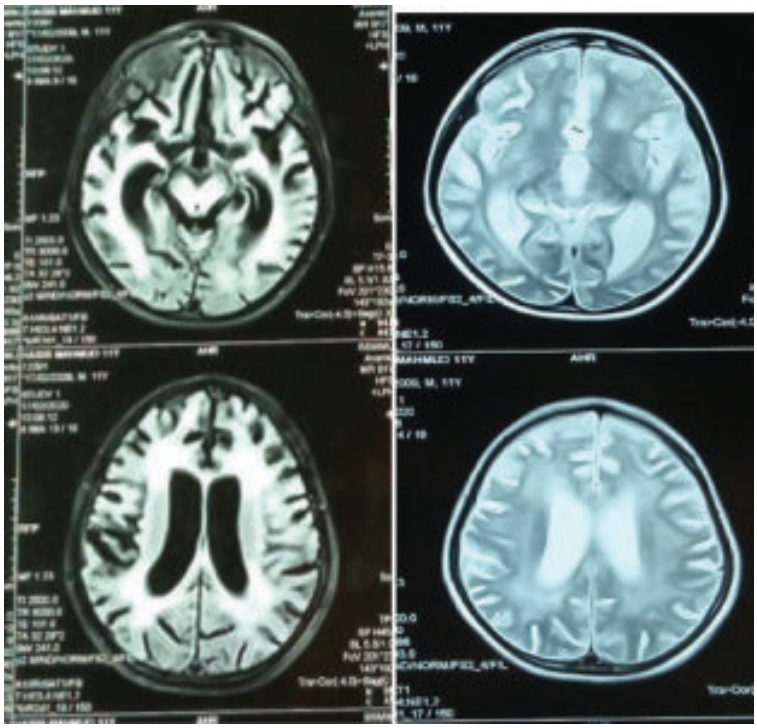

Fig 2: ***A:*** MRI of brain, FLAIR image showing diffuse hyperintense signal changes in periventricular and subcortical white matter of both cerebral hemisphere with generalized cerebral atrophy. ***B:*** MRI of brain T2 image showing diffuse hyperintense signal changes in periventricular and subcortical white matter of both cerebral hemisphere with generalized cerebral atrophy

reaction (PCR) assay for tuberculosis and viral screening (e.g. enteroviruses, herpes simplex virus, cytomegalovirus, Epstein-Barr virus, varicella-zoster virus, adenovirus, measles virus) were negative. An electroencephalogram (EEG) was unremarkable.MRI of the brain showed generalized cerebral and cerebellar atrophy with microvascular deep white matter chronic ischemic changes. T2-weighted (Fig: 2A) and FLAIR images showed diffuse hyperintensity signals in the periventricular and subcortical white matter of both cerebral hemispheres (Fig: 2B).

From the history, clinical features, laboratory, and imaging fndings, we could probably exclude other disorders that can produce rapidly progressive neurodegenerative disease, such as chronic bacterial or viral infections, Wilson disease and leukodystrophy. Our patient's main clinical features were cognitive impairment, extrapyramidal and cerebellar signs that progressed over more than one year leading to spasticity and walking disability. He ultimately lost his speech and motor function and became bedridden. This boy was finally diagnosed as a case of XLA with progressive neurodegenerative disorder and treated with IVIG, prophylactic antibiotics like co-trimoxazole and tizanidine, trihexyphenidyl hydrochloride for reducing the rigidity, dyskinesia and involuntary movements. With these above treatments, rigidity and involuntary involvement improved slightly, but cognitive impairment is still persisting.

Discussion:

XLA has defective humoral immunity caused by the mutation in the gene coding for BTK. Most of the XLA patients have severely reduced or absent peripheral blood B cells and below normal levels of all serum immunoglobulins isotypes. The expression or function of BTK is crucial for the maturation of B cell lineages at pro-B and Pre-B cell stages. So, there is failure of B cells to develop from pro-B to mature state.[11]

Autoimmunity is an important association and it was found in 20% of PID patients.[2] XLA is a hereditary immunodefciency disorder that also has a high risk of autoimmune manifestations.[12] Lack of antibody is commonly caused by dysregulated immune responses in the autoimmune conditions.[6] Chronic infammation resulting from subclinical infections, also could be an important contributor to the immune dysregulation in XLA patients.[13]

Ziegner et al. reported progressive neurodegenerative disorder in a cohort of PID patients including, four XLA patients who have received IVIG therapy.[10] They have observed that the interval between start of the IVIG treatment and the onset of the neurological symptoms was 2.5 years to 13 years. Dementia with loss of language skills, memory defcits and cognitive decline were common presentations in their study. Some of the patients showed ataxia, incoordination, spasticity, and choreo-athetoid movements. XLA patients in that cohort, had reduced number of B lymphocytes and low serum immunoglobulins. CT and/or MRI revealed brain atrophy with prominent sulci and enlarged ventricles.[10] These findings were very similar to our study findings. In one case report of an XLA patient, John Cunnigham (JC) virus infection was confirmed by brain biopsy.[14] We were unable to do brain tissue biopsy but viral screening by PCR assay were done to exclude the identifiable viral causes.

Papapetropoulos et al. in their study found that XLA patients who had received IVIG therapy for 13 years, subsequently developed neurodegenerative syndrome in the form of behavioral changes, speech difficulties and involuntary movements and MRI showed bilateral atrophy and nonspecific T2 hyperintensity.[15] In another study, Sag et al. also found similar findings where an XLA patient who was diagnosed at 2 years of age, received regular IVIG therapy and at the age of 20 years, began to develop progressive neurodegenerative syndrome.[16] So it may happen that chronic IVIG therapy may have relation with progressive neurodegenerative syndrome.

Our patient received IVIG for more than a year, and the predominant features were extrapyramidal symptoms and cognitive impairment. So perhaps, it was not due to IVIG therapy. This boy was investigated meticulously not only for identifiable infectious causes but also for genetic and metabolic diseases. None of the tests could provide any significant clues. We believe that an autoimmune mechanism or an infectious agent or IVIG therapy may be the cause of this severe complication of this boy.

Conclusion:

The frequency of progressive neurodegenerative syndrome associated with PID patients is scarce and the exact mechanism of the underlying syndrome is also unknown. So, we should carefully observe the clinical presentations, treatment response, and progression of disease in any PID patients to minimize the complications and to improve the quality of life.

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