CASE REPORT
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Combined Treatment of Progressive Encephalitis in an X-linked Agammaglobulinemia Patient

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ABSTRACT

Most patients with X-linked agammaglobulinemia are susceptible to infections, while some cases also suffer from inflammatory or autoimmune complications. We describe a patient with progressive encephalitis who improved after the use of immunomodulatory treatment with corticosteroids, fluoxetine, and nitazoxanide. In most of the cases the evolution of the progressive encephalitis is complicated and catastrophic. Based on our experience and the review of the literature, we propose the use of this combined treatment to control this devastating complication.

Keywords: Agammaglobulinemia; Immunomodulators; Primary immunodeficiency diseases; Neuroinflammatory diseases; Therapy

INTRODUCTION

X-linked agammaglobulinemia (XLA) is characterized by a low number of B cells, agammaglobulinemia, and increased susceptibility to infections by encapsulated bacteria and certain bloodborne viruses. Patients with XLA are generally considered to have a low risk of autoimmune or inflammatory disease compared to other errors of innate immunity cohorts. However, data from a national registry indicated that a significant proportion of patients with XLA have symptoms consistent with the diagnosis of an inflammatory condition.[1] A number of patients with XLA have been reported to have progressive encephalitis of uncertain etiology.[2] We present a patient with XLA who developed progressive encephalitis and showed improvement with a combined treatment with fluoxetine, nitazoxanide, and corticosteroids.

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CASE PRESENTATION

A 14-year-old boy was diagnosed at 4 years of age with XLA (hypogammaglobulinemia, no CD19 cells, no expression of Bruton Tyrosine Kinase (BTK) by Western Blot), and monthly intravenous immunoglobulin (IVIG) at 800 mg/kg/dose was started. At 4 years old, he had his first episode of seizures, and at 10 years old, he was diagnosed with focal epilepsy and treated with magnesium valproate. During his initial neurological evaluation, he was diagnosed with a mild intellectual disability. In December 2018, at the

age of 12, he had an increase in the frequency of seizures, and was subsequently switched to oxcarbazepine. He developed progressive neurological deterioration characterized by the loss of cognitive abilities such as dyscalculia, anomic dysphasia, and a decline in language skills. He also had dysgraphia and tremors. The patient had problems with social interaction and irritability, and stopped attending school. A mini-mental state examination (MMSE) revealed a score of 3 points (normal > 24 points).

Magnetic resonance imaging (MRI) of the brain revealed extensive multifocal changes in the white matter, characterized by a hyperintense signal in T2 in the frontoparietal and temporal regions. Additionally, cortical and subcortical atrophies were observed. The cerebral spinal fluid (CSF) showed 5 cells/mL and a protein concentration of 24 mg/dL. Microbial cultures and specific polymerase chain reaction (PCR) for viruses (including JC and BK viruses) and bacteria were negative.

In July 2019, a brain biopsy was performed. During the surgical procedure, a dose of dexamethasone (0.15 mg/kg every 6 hours) was administered, after which he had an improvement in neurological status with the disappearance of tremors and started to talk coherently. A brain biopsy revealed chronic perivascular lymphocytic infiltration without intracytoplasmic inclusions. No special stains or PCRs were performed. He received anti-inflammatory therapy with prednisone (10 mg/day) because of the lymphocytic infiltration, and he also began taking fluoxetine (20 mg/day) and nitazoxanide (500 mg/day), which have been reported to have antiviral effects in the literature. The patient had clinical improvement in neurological symptoms, and a follow-up MRI 10 months later showed similar findings of atrophy and leukoencephalopathy compared with the initial MRI. At the last neurological evaluation, there was an objective improvement in higher brain functions such as memory, attention, calculation, speech, and language, with a recent MMSE of 8. The patient is still on low-dose prednisone, fluoxetine, and nitazoxanide and continues to remain stable.

DISCUSSION

XLA patients can present with viral chronic meningoencephalitis as well as progressive multifocal leukoencephalopathy.[3] There are a few cases in the literature of XLA patients presenting with progressive encephalitis of uncertain etiology. All of them had a negative infectious disease assessment, had neurological deterioration after IVIG treatment, brain biopsies demonstrated lymphocytic infiltration, and most of them had a fatal outcome (Table 1).[2,4-9]

Gall et al, reported a 29-year-old male with XLA and progressive neurodegenerative disease without an identifiable infectious etiology who was treated with IVIG and interferon-alpha without improvement.[4] In other patients, intrathecal immunoglobulin and pleconaril have been used without evidence of benefit.[2] In all these patients that present with chronic encephalitis of uncertain etiology, it has been speculated that this may result from an autoimmune reaction against brain tissue, an undefined infectious agent, or a complication of intravenous immunoglobulin therapy.

Frequently, it is challenging to distinguish between infectious diseases and this progressive encephalitis of uncertain origin when considering clinical, laboratory, imaging, and histopathological aspects. Recently, in patients with XLA suffering from unidentified progressive encephalitis, new diagnostic tests allowed the identification of new viruses as the possible etiology of the neurological disease.[10.11] Fremond et al. reported a 10-year-old boy who presented with progressive encephalitis, and only after next-generation sequencing (NGS) of the brain biopsy specimen was an astrovirus documented. He responded to a combined treatment of steroids, interferon-alpha, and ribavirin.[10] Wilson et al. reported an XLA patient with Cache Valley Virus, a mosquito-borne orthobunyavirus detected by NGS of the CSF and brain tissue, as the cause of fatal progressive encephalitis.[11]

Although an infectious etiology was not identified in our case, we cannot rule out a viral etiology that causes the inflammatory process of the CNS. High-dose corticosteroids have been recommended in viral encephalitis to improve disturbances of consciousness.[12] Of note, in the cases of XLA, complicated with non-infectious chronic encephalitis, corticosteroids were avoided due to concerns of exacerbating an underlying infection (Table 1). Importantly, our patient has not had an infectious complication since corticosteroid treatment was started. We believe that corticosteroids could be beneficial as an add-on treatment to stabilize progressive encephalitis in XLA.

Table 1. Comparative features of previously reported XLA patients with non-infectious encephalitis and our case.

Author (Year)	Tuzankina (2011)	Tuzankina (2011)	Mohammadzadeh (2012)	Sag (2014)	Domingo (2014)	Gall (2019)	Kasahara (2020)	Kasahara (2020)	Saini (2021)	Our case
Age at presentation	6 years	4 years	14 years	20 years	19 years	20 year	6 years	15 months	2 years	13 years
Origin	NR	Russia	Iran	Turkey	Philippines	USA	Japan	Japan	India	Mexico
Clinical manifestations	Difficulty walking, weakness, difficulty swallowin, mental and motor capabilities fade	Difficulty walking, deterioration of speech	Headache, irritability, regression in language skills, weakness in lower extremities	Progressive cognitive decline, involuntary movements, gait disturbance	Hearing impairment at 2 years of age, dystonia and progressive neurodegeneration at 19 years of age	Tremor, anhedonia, poor memory, ataxia	Hearing disturbance progressive intellectual disability at 9 years of age seizures and decorticate rigidity	Ptosis progressive neurological deterioration	Seizures, hemiparesis fever, progressive lethargy	Progressive cognitive decline, seizures, dyscalculia, the ability to oral expression, regression in language skills, anomia, dysgraphia
CSF	NR	Negative	Normal	Negative	Negative	Normal	NR	Pleocytosis, 67 cells/µL, 78% mononuclear $CD4^+$ and $CD8^+$ T cells	Elevated protein	Negative
Image	NR	MRI: diffuse cerebral atrophy, focal lesions with high signal intensity on T2w and FLAIR in periventricular and subcortical regions	MRI: brain atrophy	MRI: cerebral and cerebellar atrophy, hyperintensities in the mesial temporal regions	MRI: atrophy of the caudate nuclei	MRI: severe global atrophy	CT: cerebral atrophy	MRI: inflammatory changes in the basal ganglia, hypothalamus, midbrain, and pons, multiple nodular lesions	MRI: frontal subcortical white matter lesions	MRI: cortical and subcortical atrophy, hyperintensities in T2w, and FLAIR in frontal and temporal regions.

Biopsy	NR	Massive perivascular $CD8^+$ lymphocyte infiltration in the cerebral cortex and leptomeninges	NR	NR	NR	NR	Diffuse neuronal loss and gliosis in the cerebral cortex, perivascular infiltration of lymphocytes and macrophages in leptomeninges and brain parenchyma	NR	Autopsy: perivascular $CD3^+$ lymphocyte infiltration, microglial proliferation with nodule formation	Perivascular lymphocyte infiltration
Treatment	NR	NR	NR	NR	NR	Interferon -alpha-2B, IVIG	NR	Intraventricular immunoglobulins	Acyclovir, high-dose IVIG	Steroids, nitazoxanide, fluoxetine
Outcome	NR	NR	NR	Lost to follow-up	Alive at follow-up	Alive at follow-up	Deceased	Deceased	Deceased	Improvement

Fluoxetine and nitazoxanide were added due to their reported antiviral properties.[13-17].Nitazoxanide inhibits the replication of a broad range of RNA and DNA viruses, including astrovirus and Japanese encephalitis virus.[16,17] Nitazoxanide and its active circulating metabolite, tizoxanide are active in vitro against a broad range of anaerobic gram-positive and gram-negative bacteria, as well as certain *Mycobacterium tuberculosis* strains.[17] Fluoxetine, an antidepressant drug that acts as a selective serotonin reuptake inhibitor, reduces the synthesis of enteroviral RNA and has been used in chronic enterovirus encephalitis.[13-15]

Chetty et al. report an 8-month-old patient with SCID (severe combined immunodeficiency) and enterovirus encephalitis who was treated successfully with a combination of favipiravir, fluoxetine, and IVIG.[14] Gofsgteyn et al, reported that fluoxetine, IVIG, and corticosteroids halted the progression of enteroviral encephalitis in an XLA patient.[13] The diagnosis of enterovirus encephalitis was made through direct tissue real-time PCR testing for enterovirus RNA.[13] Electron microscopy in search of virus particles and PCR or NGS techniques should be considered in all patients with chronic progressive encephalitis in XLA when routine infectious tests are negative.

XLA has symptoms consistent with the diagnosis of an inflammatory disease, including inflammatory bowel disease, arthritis, enthesitis, membranoproliferative glomerulonephritis, Kawasaki disease, and hemophagocytic lymphohistiocytosis.[18-23] Inflammatory conditions associated with an infectious trigger (echovirus dermatomyositis-like disease and pyoderma gangrenosum due to Helicobacter species) have also been described.[1,23]

Diverse mechanisms may underlie these manifestations; XLA patients present a dysregulated TLR (Toll-like receptors) signaling in the absence of BTK. BTK has been found to function as a physiologic inhibitor of NLRP3 (NLR Family Pyrin Domain Containing 3), favoring inflammasome activation.[24,25] Ray et al. reported a patient with Good's syndrome presenting with a combination of autoimmune and viral encephalitis.[26] In XLA, in the absence of a positive autoantibody serology, autoimmune encephalitis can't be entirely excluded. Neuropathological features of autoimmune encephalitis overlap with that of viral encephalitis.[26] In both documented infectious progressive encephalitis and undetermined progressive encephalitis, $CD4^+$ and $CD8^+$ lymphocytic infiltration are observed. In the case that we present, the decision to continue corticosteroids was made based on the presence of central nervous system inflammatory reaction with lymphocytic infiltration on brain biopsies and previous reports in both infectious and unidentified etiology progressive encephalitis of the presence of elevated proinflammatory cytokines in CSF.[2,13]

In conclusion, we propose that in progressive encephalitis of uncertain etiology in XLA, the combination of fluoxetine, nitazoxanide, and corticosteroids could stabilize the disease.

STATEMENT OF ETHICS

The parents have provided informed consent for the publication of the case. Since this is a single case report, ethics approval was not required.

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CONFLICT OF INTEREST

Dr. M.A.Y.N has received lecture fees from Shire, CSL Behring, and Octapharma. The rest of the authors declare no conflict of interest.

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REFERENCES

1. Hernandez-Trujillo VP, Scalchunes C, Cunningham-Rundles C, Ochs HD, Bonilla FA, Paris K, et al. Autoimmunity and inflammation in X-linked agammaglobulinemia. J Clin Immunol. 2014;34(3):627-32.
2. Kasahara Y, Imamura M, Shin C, Shimizu H, Utsumi J, Hosokai R, et al. Fatal Progressive Meningoencephalitis Diagnosed in Two Members of a Family With X-Linked Agammaglobulinemia. Front. Pediatr. 2020;8:579.
3. Teramoto T, Kaneko H, Funato M, Sawa H, Nagashima K, Hirose Y, et al. Progressive multifocal leukoencephalopathy in a patient with X-linked agammaglobulinemia. Scand J Infect Dis. 2003;35(11-12):909-10.
4. Gall T, Hawley J, May Y. Progressive neurodegeneration in X-linked agammaglobulinemia (meeting abstract). Neurology 2019;95(15 Suppl):P1.7-005.

5. Tuzankina I, Kobeleva Y, Kiseleva N, Bolkov M, Reuter G, Maródi L. Cytotoxic T Lymphocytes Mediate Neuronal Injury in Patients With X-linked Agammaglobulinemia and Progressive Neurodegenerative Disease. Allergy. 2011;66:1617-8.
6. Domingo A, Schmidt TG, Barcelon E, Lukban M, Westenberger A, Klein C. X-linked agammaglobulinemia with hearing impairment, dystonia-parkinsonism, and progressive neurodegeneration. J Neurol. 2014;261:2225-7.
7. Sag AT, Saka E, Ozgur TT, Sanal O, Ayvaz DC, Elibol B, et al. Progressive Neurodegenerative Syndrome in a Patient With X-linked Agammaglobulinemia Receiving Intravenous Immunoglobulin Therapy. Cogn Behav Neurol. 2014;27:155-9.
8. Mohammadzadeh I, Yeganeh M, Khaledi M, Salehiomran MR, Aghamohammadi A, Rezaei N. Debilitating Progressive Encephalitis in a Patient With BTK Deficiency. Acta Microbiol Immunol Hung. 2012;59:335-42.
9. Saini AG, Radotra BD, Bhattarai D, Rawat A, Bhatia V. X-Linked Agammaglobulinemia With Chronic Meningoencephalitis: A Diagnostic Challenge. Indian Pediatr. 2021.15;58(2):169-173.
10. Frémond ML, Pérot P, Muth E, Cros G, Dumarest M, Mahlaoui N, et al. Next-Generation Sequencing for Diagnosis and Tailored Therapy: A Case Report of Astrovirus-Associated Progressive Encephalitis. J Pediatric Infect Dis Soc. 2015;4:e53-7.
11. Wilson MR, Suan D, Duggins A, Schubert RD, Khan LM, Sample HA, et al. A Novel Cause of Chronic Viral Meningoencephalitis: Cache Valley Virus. Ann Neurol. 2017;82(6):105-114.
12. Nakano A, Yamasaki R, Miyazaki S, Horiuchi N, Kunishige M, Mitsui T. Beneficial effect of steroid pulse therapy on acute viral encephalitis. Eur Neurol. 2003;50(4):225-9.
13. Gofshteyn J, Cárdenas AM, Bearden D. Treatment of Chronic Enterovirus Encephalitis With Fluoxetine in a Patient With X-Linked Agammaglobulinemia. Pediatr Neurol. 2016;64:94-98.
14. Chetty K, Cheng I, Kaliakatsos M, Gonzalez-Granado LI, Klapsa D, Martin J, et al. Case report: Novel treatment regimen for *enterovirus* encephalitis in SCID. Front Immunol. 2022;13:930031.
15. Sham L, Bitnun A, Branson H, Hazrati LN, Dell SD, Yeung RSM, et al. Treatment of rituximab-associated chronic CNS enterovirus using IVIg and fluoxetine. Neurology. 2019;92(19):916-18.
16. Hargest V, Sharp B, Livingston B, Cortez V, Schultz-Cherry S. Astrovirus Replication Is Inhibited by Nitazoxanide In Vitro and In Vivo. J Virol. 2020;94(5):e01706-19
17. Shakya A, Bhat HR, Ghosh SK. Update on Nitazoxanide: A Multifunctional Chemotherapeutic Agent. Curr Drug Discov Technol. 2018;15(3):201-13
18. Sukumaran S, Marzan K, Shaham B, Church JA. A Child With X-Linked Agammaglobulinemia and Enthesitis-Related Arthritis. Int J Rheumatol. 2011;2011:175973.
19. Han SP, Lin YF, Weng HY, Tsai SF, Fu LS. A Novel *BTK* Gene Mutation in a Child with Atypical X-Linked Agammaglobulinemia and Recurrent Hemophagocytosis: A Case Report. Front Immunol. 2019;10(2):1953.
20. Rivas-Larrauri F, Aguilar-Zanela L, Castro-Oteo P, Rosales-Hernandez LA, Otero-Mendoza F, López-Herrera G, et al. Kawasaki disease and immunodeficiencies in children: case reports and literature review. Rheumatol Int. 2019;39:1829-1838.
21. Barmettler S, Otani IM, Minhas J, Abraham RS, Chang Y, Dorsey MJ, Ballas ZK, et al. Gastrointestinal Manifestations in X-linked Agammaglobulinemia. J Clin Immunol. 2017;37(3):287-94.
22. Lavrador V, Correia F, Sampaio R, Candido C, Sameiro-Faria M, Marques L, Mota C. Membranoproliferative Glomerulonephritis and X-Linked Agammaglobulinemia: An Uncommon Association. Case Rep Pediatr. 2014;2014:480947.
23. Tan Q, Ren FL, Wang H. Pyoderma Gangrenosum in a Patient with X-Linked Agammaglobulinemia. Ann Dermatol. 2017;29(4):476-8.
24. Mao L, Kitani A, Hiejima E, Montgomery-Recht K, Zhou W, Fuss I, Wiestner A, Strober W. Bruton tyrosine kinase deficiency augments NLRP3 inflammasome activation and causes IL-1β-mediated colitis. J Clin Invest. 2020;130(21):1793-1807.
25. González-Serrano ME, Estrada-García I, Mogica-Martínez D, González-Garay A, López-Herrera G, Berrón-Ruiz L, et al. Increased proinflammatory cytokine production after lipopolysaccharide stimulation in patients with X-linked agammaglobulinemia. J Clin Immunol. 2012;32(15):967-74.
26. Ray S, Kathuria H, Chakravarty K, Rawat A, Takkar A, Mehta S, et al. Seronegative panencephalitis complicated by viral encephalomyelitis in a case of Good's syndrome - a neuropathological report. Int J Neurosci. 2020:1-6.