Grand Rounds Review

Enteroviruses in X-Linked Agammaglobulinemia: Update on Epidemiology and Therapy*

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X-linked agammaglobulinemia (XLA) has been associated with a broad range of infections, but enteroviral disease represents one of the most damaging infections. The risk of enteroviral infection in XLA is lower now than in the setting of intramuscular immunoglobulin or in patients without immunoglobulin replacement, but the rate of infection has not declined significantly in the era of intravenous immunoglobulin replacement. Enteroviruses can cause inflammation of nearly every organ, but in XLA, infections often manifest as dermatomyositis or chronic meningoencephalitis. Difficulty and delay in recognizing symptoms and lack of specific therapy contribute to the poor outcomes. Furthermore, cerebrospinal fluid detection of enteroviruses is not very sensitive. Reluctance to perform brain biopsies can lead to significant delays. The other feature compromising outcomes is the lack of specific therapy. High-dose peripheral and intraventricular immunoglobulin have been used, but failure is still common. New antienteroviral drugs are in development and show promise for immunodeficient patients with life-threatening infections with enterovirus. © 2016 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2016;■:■-■)

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CASE REPORT

The patient is a now a 4-year-old boy. Family history was significant for 2 male maternal cousins who died from infections (diarrhea and Bacillus Calmette-Guerin) during childhood, and a maternal uncle with X-linked agammaglobulinemia (XLA) who died from a progressive encephalopathy that developed after a dermatomyositis-like syndrome at age 12 years. The patient was admitted at 8 months for dehydration and culture-negative sepsis. His laboratory studies included the following: IgG = 325 mg/dL (after first infusion of intravenous immunoglobulin [IVIG]), IgA < 7 mg/dL, and IgM < 4 mg/dL; CD19 was undetectable (<1%), CD3 = 4758 cells/mm^3 (89%), CD4 = 3418 cells/mm^3 (64%), and CD8 = 1228 cells/mm^3 (23%). His white blood cell count was 830 cells/mm^3, with an absolute neutrophil count of 16 cells/mm^3. He was hospitalized for 20 days in the intensive care unit. A diagnosis of XLA was confirmed via genetic testing: c.763C>T resulting in a truncated protein R255X with a loss of 61% of Bruton tyrosine kinase protein. The patient was started on IVIG therapy and initially did well. At 1 year, he experienced ataxia, attributed to aseptic meningitis. He improved somewhat but never regained full lower-limb function. At 15 months, he developed a slowly progressive encephalopathy and regression of previously acquired motor milestones. Lumbar puncture showed a lymphocytic pleocytosis, but PCR testing for multiple viruses (including the John Cunningham virus, human herpesvirus 6, herpes simplex virus 1 and 2, varicella-zoster virus, EBV, cytomegalovirus, and enterovirus) was negative from cerebrospinal fluid (CSF). Magnetic resonance imaging (MRI) showed progressive white matter changes followed by the development of large subdural collections (Figure 1). Enteroviral encephalitis was suspected despite negative CSF studies. He began receiving IVIG 1 g/kg every 15 days and IFN-α 2b 1,000,000 U 3 times a week. He also briefly received cidofovir. He continued to decline. At 29 months, the patient had a brain biopsy that confirmed the diagnosis of enteroviral meningoencephalitis by standard PCR from brain tissue and from subdural fluid. Concomitant brain and CSF samples sent for novel pathogen discovery demonstrated PCR positivity for enterovirus using consensus PCRs (5′-untranslated region and VP4/2 regions) from brain tissue and CSF. Amplification of the VP1 region indicated that the virus shared 89% at the nucleotide acid level with human coxsackievirus B5 (GenBank accession KT963010). Because of continued progressive decline, the patient was treated under a compassionate-use protocol with the novel small-molecule antienteroviral drug pocapavir. The patient completed a 30-day course of pocapavir, followed by stabilization of neurologic status and gradual improvement in cognitive and motor function. CSF inflammation resolved, and MRI changes stabilized. The patient is

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* Results are reported from the United States Immunodeficiency Network, the Latin American Society for Immunodeficeincies, and the European Society for Immunodeficiencies registries in this article.

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Abbreviations used
CEMA- chronic meningoencephalitis in agammaglobulinemia
CSF- cerebrospinal fluid
IVIG- intravenous immunoglobulin
KREC- κ-deleting recombination excision circle
MRI- magnetic resonance imaging
XLA- X-linked agammaglobulinemia

currently almost 2 years out from completion of therapy with pocapavir and is stable and improving, though he continues to have significant motor and cognitive deficits (Table I).

There are several important lessons from this case.

- Testing for an immune deficiency was pursued after a single severe infection.
- Sepsis is the presenting manifestation in 10% of patients with XLA.[1]
- Neutropenia is seen in 10% to 25% of patients with XLA and is most often found at the time of diagnosis.[2,3]
- The clinical presentation of enteroviral disease in XLA is subtle initially and progression can be slow.
- PCR detection of enterovirus in CSF is relatively insensitive.[4]
- Enteroviral disease is still seen in patients with XLA, and a high degree of suspicion is required to establish the diagnosis.

This review will cover the clinical features, virologic features, new detection strategies, and new treatments.

ENTEROVIRUSES AND DISEASE

Enteroviruses form a diverse genus within the virus family *Picornaviridae* (small RNA virus). The *Enterovirus* genus currently consists of 12 species, 7 of which are viruses that infect humans: *Enterovirus A*, *B*, *C*, *D*, and *Rhinovirus A*, *B*, and *C*[5] (Table II). There appears to be a core group of about 15 serotypes consistently found in the United States that account for approximately 84% of reports to the Centers for Disease Control and Prevention, all of which are *Enterovirus B* viruses.[6] Periodically, minor or new serotypes may predominate in a given season, as exemplified by the enterovirus-D68 outbreak of 2014.[7-9]

In the United States, there are 10 to 15 million enteroviral infections each year, predominately in the summer and fall.[10] In a normal host, most infections last 2 to 3 weeks and are either asymptomatic or present as a mild febrile illness although myocarditis, pancreatitis, myopathy, and meningitis occur. In newborns and individuals with weakened or deficient immune systems, more serious disease may occur, including neonatal enteroviral sepsis, myocarditis, pericarditis, meningitis, encephalitis, acute flaccid myelitis or paralysis, and poliomyelitis. Some serotypes are often associated with particular diseases. For example, echovirus 6, echovirus 9, and echovirus 30 are associated with aseptic meningitis; echovirus 11 with enteroviral sepsis presenting as hepatitis-hemorrhage syndrome; and coxsackievirus B5 with myocarditis. However, each virus can be associated with several disease presentations and each can be neurotropic.[6]

CHRONIC ENTEROVIRAL MENINGOENCEPHALITIS IN AGAMMAGLOBULINEMIA

Historical aspects

Almost from the time of the description of XLA, cases of enteroviral meningoencephalitis have been described.[11] Although described in other types of immune deficiencies such as CD40 ligand deficiency, common variable immune deficiency, and severe combined immune deficiency, the occurrence of enteroviral infections is much higher in XLA and this review will focus on that association. In the 1970s, prominent reports identified enteroviruses as a specific and often lethal concern in XLA.[12,13] Early literature on XLA found 15% to 20% of patients with XLA infected and fairly dismal outcomes.[14,15] Of 90 immune-deficient patients identified in one series, only 5 were completely well after infection.[15] Although improved diagnosis and management of patients with XLA has led to fewer cases, it is clear that this infection still arises. Patients can have enteroviral infections that occur before diagnosis, and lack of immunoglobulin replacement for various reasons can lead to susceptibility after diagnosis. Although immunoglobulin products have detectable titers to many enteroviruses, coverage is not universal and, therefore, infection could occur even in the presence of adequate doses of immunoglobulin.[16,17] Registries give a minimal estimate of the frequency of chronic meningoencephalitis in agammaglobulinemia (CEMA). A 2006 XLA registry report found that 2 of 6 deaths from enterovirus occurred before intravenous formulations of immunoglobulin, but the other 4 deaths occurred in the modern era.[18] In the United States Immunodeficiency Network registry of patients with immune deficiencies in the United States, there were 390 patients with XLA registered with 26 cases of meningoencephalitis and 12 cases (3%) of confirmed enteroviral meningoencephalitis. Only 1 case occurred in a patient born after 1995 for a rate of 3.6% in cases with birth years 1995 or earlier and 1.1% for those born 1996 or after. In the European Society for Immunodeficiencies registry, there were 827 registered patients with XLA and 1% had reported enteroviral meningoencephalitis (0.9% with birth year 1995 or earlier and 1.4% with birth year 1996 or after). The Latin American Society for Immunodeficeincies registry was examined and of 214 patients with XLA, 3.7% had meningoencephalitis (4.8% with birth year 1995 or earlier and 3% with birth year 1996 or later). Therefore, enteroviral disease in XLA is not common but is still seen.

One patient with XLA survived wild-type polio in 1951,[19] but the first descriptions of clear CEMA began to appear in the 1970s.[12,13,20,21] These early patients either exhibited a classic poliovirus presentation of acute flaccid paralysis related to live vaccine administration or the more typical meningoencephalitis seen with nonpolio enteroviruses. In the meta-analysis of 90 immunodeficient patients in 2003, there was a striking predominance of echovirus 11. The age of onset was anywhere from infancy to 50 years. Most of the patients had classic CEMA; however, arthritis, hepatitis, dermatomyositis, polyradiculitis, and myocarditis were seen. Among the non-meningoencephalitis phenotypes, dermatomyositis and hepatitis were the most frequent. Most of the cases exhibited paralysis, convulsions, cognitive decline, deafness, or coma. A critical observation from these early cases was that low serum IgG levels were found in most of the patients with CEMA. In some cases, patients were not on treatment but the average among treated patients was only 300 mg/dL. A subsequent study also suggested that risk is highest before therapy.[22] Other settings with low B cells and low immunoglobulin levels can also be associated with CEMA.[16-18,23,24]