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RECURRENT ASEPTIC ENCEPHALITIS IN PERIODIC FEVER, APHTHOUS STOMATITIS, PHARYNGITIS AND ADENOPATHY (PFAPA) SYNDROME

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Abstract

An 11-year-old boy with episodes of periodic fever, aphthous stomatitis, pharyngitis and adenopathy (PFAPA) is reported. Two PFAPA episodes were associated with aseptic encephalitis and seizures. Recurrent acute aseptic encephalitis or seizures have never been reported during the febrile episodes of PFAPA. This possible association is discussed within the context of the etiology of PFAPA.

Keywords

aseptic encephalitis; recurrent encephalitis; PFAPA syndrome

Acute encephalitis is the most common cause of acute nonsuppurative neurologic disease in children.¹ The etiology remains undetermined in most cases. For example, an infectious agent accounted for 12% of the cases of acute encephalitis in California between 1998 and 2000. Noninfectious etiologies, including autoimmune, vascular, neoplastic, metabolic and psychiatric diseases and toxin ingestion, accounted for 10% of the cases.²

Recurrent aseptic encephalitis is uncommon in the immunocompetent child. Herpes simplex virus (HSV) is, by far, the most common infectious related etiology,³ but cases of Japanese encephalitis,⁴ lymphocytic meningoencephalitis⁵ and acute disseminated encephalomyelitis⁶ have been reported. Noninfectious inflammatory etiologies of recurrent encephalitis include Behcet's syndrome,⁷ Hashimoto's encephalitis⁸ and Sjogren's syndrome.⁹

PFAPA (periodic fever, adenitis, pharyngitis and aphthous stomatitis) is characterized by febrile episodes persisting for 4 to 6 days separated by afebrile periods lasting 4 weeks to 4 months.^{10,11} Nonclassic symptoms, such as arthralgia, chills, malaise, cough, coryza, headache, abdominal pain, nausea, vomiting, diarrhea, hepatosplenomegaly and rash, may occur during febrile periods.¹¹ Despite the fact that PFAPA was described almost 15 years ago, the etiology of this syndrome remains unknown.

This report describes a boy with a clinical course consistent with PFAPA who was hospitalized twice for acute aseptic encephalitis heralded by generalized seizures. This report documents one of the few cases of noninfectious recurrent aseptic encephalitis in a child. Since neither encephalitis nor seizures have been reported with PFAPA, this report widens the symptoms that may be associated with the febrile episodes of PFAPA.

CASE REPORT

An 11-year-old boy awoke disoriented and combative after 5 days of high fever (maximum 40°C), sore throat, adenopathy, myalgia and headache. In the emergency department (ED), two self-limiting, 1-minute, generalized tonic clonic seizures were observed. Fosphenytoin (20 mg/kg) was loaded. Cranial computed tomography scan was negative and cerebral spinal fluid (CSF) contained 24 leukocytes/mL with a differential of 82% lymphocytes, 17% monocytes, 1% polymorphonuclear neutrophilic leukocytes, 2 erythrocytes/mL, protein of 33 mg/dL and glucose of 67 mg/dL (serum glucose 106 mg/dL). Electrolytes, liver function tests and complete blood count were normal.

In the ED the boy was febrile (38.7°C) with tachycardia (140 bpm) and a normal respiratory rate (16 bpm) and blood pressure (117/75 mm Hg). His oropharynx was erythematous and contained aphthous ulcers on the anterior buccal mucosa and uvula. His neck examination was significant for a 1-cm soft mobile tender left anterior cervical lymph node and an absence of meningeal signs. Funduscopy, cardiovascular, pulmonary, abdomen and extremity examinations were normal. Dysmorphology, neurocutaneous stigmata and rash were absent.

Orientation was restored 5 hours after evaluation in the ED, but psychomotor slowing with reduced concentration and memory was observed. Cranial nerve and motor examinations were normal. Mild dysmetria, positional tremor, and ataxic gait were noted. Deep tendon reflexes were symmetrically brisk, toes were flexor, and Hoffman sign was present bilaterally. Elemental sensations were normal without extinction and Romberg was negative.

Birth history and developmental milestones were unremarkable. Since preschool, the boy suffered from recurrent febrile episodes, typically of 5 days' duration, characterized by oropharyngeal erythema, cervical adenopathy, aphthous ulcers and high fevers up to 40°C. Afebrile periods lasting 4 to 7 weeks separated the febrile episodes. Repeated bacterial throat cultures were negative.

The boy was hospitalized at 6 years of age for an episode similar to the current presentation. A 5-day prodrome of headache, high fever, nonspecific abdominal pain and greenish watery diarrhea heralded a brief (approximately 2 minutes), generalized tonic clonic seizure. Illness onset followed exposure to a sibling with gastroenteritis. CSF contained 18 leukocytes/mL with 66% lymphocytes, 13% monocytes and 21% atypical lymphocytes, 0 erythrocytes/mL, glucose of 82 mg/dL (serum glucose 139 mg/dL) and protein of 36 mg/dL. An electroencephalogram was negative, and a magnetic resonance imaging scan with gadolinium demonstrated meningeal enhancement. CSF HSV polymerase chain reaction (PCR) and bacterial and viral cultures were negative. A stool viral culture identified enterovirus.

The boy experienced varicella at 5 years of age. At 7 years of age, Kawasaki disease was suspected because of 6 days of high fever (40°C) associated with pharyngeal mucosa erythema and cervical adenopathy. Since the boy did not meet criteria for Kawasaki disease he was discharged with supportive treatment. An uncomplicated course of zoster along the left T8 dermatome developed at 8 years of age.

The boy excelled academically and athletically. The boy's father reported recurrent pharyngitis as a child, but these episodes were not as frequent or severe as his son's recurrent episodes. Family history was not significant for any immunologic or neurologic disease. The boy was fourth-generation American with ancestors originating from England and Scandinavia.

Treatment with ceftriaxone and acyclovir continued for approximately 48 hours until CSF bacterial and viral cultures and PCRs for HSV and enterovirus were negative. Nasopharynx, oropharynx, stool and rectal swab bacterial cultures demonstrated no abnormal organisms.

Nasopharyngeal aspirate demonstrated no adenovirus; HSV; influenza A or B; parainfluenza type I, II, or III or respiratory syncytial virus. Serum titers for Epstein-Bar virus, arboviruses including West Nile virus, *Borrelia* and *Mycoplasma* were negative. Urine drug screen on admission revealed no tricyclic antidepressants, aspirin, acetaminophen or ethanol. Antinuclear antibodies, antineutrophilic cytoplasmic antibodies and rheumatoid factor were normal.

An immunodeficiency workup was unremarkable. T-cell proliferation using tetanus and diphtheria antigens and phytohemagglutinin, concanavalin A and Pokeweed mitogen was normal. Antibodies levels to pneumococcus, tetanus and polysaccharide ribose phosphate antigens were normal. Serum alpha-1 antitrypsin, albumin, C3, C4, CH50, IgA, IgM, IgD, and IgG total and subclasses levels were normal. T-cell subsets were normal. CD19 B-cell were increased at 24% (normal, 5–10%).

A routine electroencephalogram that included sleep and magnetic resonance imaging without contrast, both on the second hospital day, were normal. The patient's mental status returned to normal approximately 48 hours after admission, and the patient was discharged 72 hours after admission. Phenytoin was discontinued 2 weeks after discharge.

A lumbar puncture performed 3 months after discharge was normal. The CSF contained 1 leukocyte/mL, 17 erythrocytes/mL, glucose of 57 mg/dL and total protein of 20 mg/dL. Bacteria, fungus, acid fast bacilli and virus cultures were negative. PCR for cytomegalovirus, EBV, HSV and varicella-zoster virus were also negative. Cytology, india ink preparation and cryptococcal latex antigen were negative.

One year after discharge, the patient continued to have monthly febrile episodes, but was otherwise developmentally and neurologically normal.

DISCUSSION

Recurrent acute aseptic encephalitis is exceedingly rare in children. Previously reported causes of recurrent aseptic encephalitis (see above) are unlikely in this case. Although enterovirus was identified in the stool during the first episode of encephalitis, enterovirus was not identified in the CSF. In addition, enterovirus has only been associated with recurrent neurologic changes in immunodeficient patients.¹² It is not known whether either occurrence of aseptic encephalitis was secondary to an infectious agent or a manifestation of a common underlying biologic mechanism causing both the symptoms of PFAPA and the aseptic encephalitis. Nevertheless, this is the first case documenting acute or recurrent encephalitis or seizures associated with PFAPA. This report demonstrates the wide variation of clinical symptomatology in the PFAPA syndrome and documents usually severe illnesses during febrile episodes in a patient with PFAPA.

The patient clearly fulfils the diagnostic criteria proposed by Thomas et al¹¹ for PFAPA: (1) a history of regularly recurring fevers since an early age; (2) fever episodes associated with constitutional symptoms, aphthous stomatitis, cervical lymphadenitis and pharyngitis without an upper respiratory illness; (3) cyclic neutropenia excluded; (4) asymptomatic between episodes; (5) normal growth and development. In addition, other disorders with clinical characteristics similar to PFAPA, such recurrent fever syndromes, inflammatory disorders and immunodeficiency, were ruled out.¹¹

Our patient appears to have several unusually severe illnesses associated with his febrile episodes. In addition to the two episodes of encephalitis, this patient developed an episode of zoster at an unusually young age. The episode of zoster in this patient at 8 years of age could possibly be associated with T-cell dysfunction. Previous reports have suggested that T-cell dysfunction or dysregulation may be the culprit in PFAPA since some patients respond to

cimetidine, a T-cell modulator, and since PFAPA syndrome is clinically similar to familial Mediterranean fever.¹⁰ A key diagnostic symptom of Behcet's disease, a chronic relapsing multisystem inflammatory disorder, like PFAPA, is recurrent aphthous stomatitis. A significant number of Behcet's disease patients have recurrent neurologic symptoms such as recurrent encephalitis, and Behcet's disease has been proposed to be related to abnormal T-cell function resulting in exaggerated immune reactivity to common infectious agents such as *Streptococcus* sp.⁷ The similarity between PFAPA and other periodic inflammatory disorders supports the notion that PFAPA may result from dysregulation of the immune system. As more reports about this disorder become available, the clinical spectrum and subtypes of PFAPA will become more evident and clinical correlations with other known disorders can be made.

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