Outbreak of Enteroviral Infection in a Pediatric Hematology-Oncology Unit

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We review the clinical courses and outcomes of an outbreak of enteroviral infection that occurred in 5 children with acute lymphoblastic leukemia during a 2-month period in a hematology-oncology unit. Three patients presented with encephalitis and 2 with parotitis. Three of the 5 patients recovered uneventfully and 2 died, 1 of chronic encephalitis and 1 of acute brain stem encephalitis.

Enteroviral infections occur throughout the year. The majority of enteroviral infections in children are asymptomatic. The most common symptomatic manifestations include febrile illness, with or without rash, accompanied by upper respiratory symptoms; hand, foot, and mouth disease; and aseptic meningitis or encephalitis. Immune deficient patients with hereditary or acquired defects in B cell function (such as patients with leukemia) may develop persistent enteroviral infection, which almost always includes encephalitis. Enteroviral encephalitis in immunodeficient patients has a broad spectrum of clinical manifestations and outcomes. Chronic enteroviral infection may result in a fatal outcome [1, 2].

Patients and methods. We assessed clinical courses and outcomes for an outbreak of enteroviral infection that occurred in the hematology-oncology unit of “Agia Sophia” Children’s Hospital, which is an 800-bed university tertiary-care hospital in Athens, Greece. The outbreak occurred in November and December 2000, and 5 children with acute lymphoblastic leukemia (ALL) were affected. The hematology-oncology unit consists of 16 rooms (single and double) and has a playroom for children and parents.

Enterovirus was detected in samples of blood and/or CSF by reverse-transcriptase PCR (RT-PCR). Enteroviral cultures could not be performed in our laboratory. Table 1 presents details of clinical findings and results of laboratory tests for each patient (in the order that the cases occurred). Results of tests for antibodies against Mycoplasma pneumoniae, mumps virus, and Toxoplasma gondii were negative. Furthermore, no genetic material from herpesviruses (e.g., cytomegalovirus, Epstein-Barr virus, herpes simplex virus, or human herpesviruses 6, 7, or 8) was detected by PCR in plasma or CSF specimens obtained from any of the patients. After enteroviral infection was diagnosed, all children received a single dose (400 mg/kg) of intravenous immunoglobulin (IVIG) as prophylaxis.

Patient 1 presented with vomiting and mild upper respiratory illness at the time of admission to the hospital. Bilateral swelling of the parotid gland, headache, and seizures progressively developed. Findings of an electroencephalogram (EEG) were normal. Spontaneous recovery from symptoms was observed within a week.

Patient 2 presented with mild fever, rash, somnolence, irritability, suppressed consciousness, and status epilepticus. The findings of an EEG were indicative of encephalitis. Laboratory tests revealed neutropenia (WBC count, 200 cells/mm3). Clinical findings and results of laboratory tests for each patient are presented in Table 1.

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Table 1. Clinical features, laboratory findings, and the time line of the outbreak for enteroviral (EV) infections in 5 patients with acute lymphoblastic leukemia (ALL).

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age in years, sex</th>
<th>Time to onset of EV infection</th>
<th>Day of onset of EV infection</th>
<th>Diagnosis</th>
<th>Protein level in CSF, mg/dL</th>
<th>Site where EV detected</th>
<th>Neuroimaging method, findings</th>
<th>Patient outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4, M</td>
<td>15 months</td>
<td>Day 0</td>
<td>Parotitis</td>
<td>ND</td>
<td>Blood</td>
<td>CT, normal</td>
<td>Survived</td>
</tr>
<tr>
<td>2</td>
<td>8, F</td>
<td>15 days</td>
<td>Day 8</td>
<td>Chronic encephalitis</td>
<td>At onset, 25; at 1st rel, 65; at 2nd rel, 75</td>
<td>Blood and CSF</td>
<td>CT, normal; MRI, abnormal; 2nd MRI, abnormal</td>
<td>Died</td>
</tr>
<tr>
<td>3</td>
<td>3, F</td>
<td>6 months</td>
<td>Day 28</td>
<td>Parotitis</td>
<td>ND</td>
<td>Blood</td>
<td>ND</td>
<td>Survived</td>
</tr>
<tr>
<td>4</td>
<td>10, F</td>
<td>12 months</td>
<td>Day 30</td>
<td>Encephalitis</td>
<td>25</td>
<td>CSF</td>
<td>CT, normal</td>
<td>Survived</td>
</tr>
<tr>
<td>5</td>
<td>4, F</td>
<td>25 days</td>
<td>Day 40</td>
<td>Pancreatitis, brain stem encephalitis</td>
<td>ND</td>
<td>Blood</td>
<td>ND</td>
<td>Died</td>
</tr>
</tbody>
</table>

**NOTE.** ND, not done; rel, relapse of encephalitis.

* Time between diagnosis of ALL and onset of EV infection.

* During the outbreak, relative to onset of infection in patient: day 0 was the day of admission to the hospital.

* By reverse-transcription PCR

Figure 1. Initial MRIs of an 8-year-old girl (patient 2) with acute lymphoblastic leukemia and enteroviral encephalitis. T1-weighted images obtained after intravenous administration of a paramagnetic substance demonstrating "pinhead"-sized lesions that enhance, both in gray and white matter, in a diffuse and periventricular distribution.
developed. Findings of electrocardiography (ECG) monitoring remained normal, but the patient had cardiac arrest 20 min after the onset of pupil dilation. Chest radiography performed at the time of death revealed normal findings. Resuscitation efforts were unsuccessful. The fact that the patient had mydriasis and had normal ECG and chest radiograph findings indicates that death was most likely due to a rapid viral invasion of the CNS that caused brain stem encephalitis, rather than due to myocarditis.

**Results.** These 5 immunocompromised children with enteroviral infection presented with parotitis or severe encephalitis. Three patients had fever, and 2 of these 3 also had rash. It should be noted that clinical manifestations were different in all patients and that multiple organs were involved. With respect to treatment for leukemia, the 2 patients who died (patients 2 and 5) were in the induction phase of chemotherapy, and the other 3 patients (patients 1, 3, and 4), who recovered, were in the maintenance phase of chemotherapy. Patients in the induction phase of chemotherapy were isolated in single rooms and were not allowed to go to the playroom. None of the health care providers in the hospital unit developed symptoms or signs indicative of enteroviral infection. On the other hand, parents and hospital staff were moving throughout the rooms and playroom. Enterovirus genetic material was detected in the CSF of the children with encephalitis (patients 2 and 4) and in the plasma of all children but 1 (patient 4). Parents and health care workers on the unit were not screened by RT-PCR to identify asymptomatic carriers.

**Discussion.** Enteroviruses are among the most common causes of acute viral illness in childhood and account for approximately 10%–20% of cases of encephalitis of proven viral etiology [3]. Encephalitis can present as either acute viral encephalitis due to direct infection of neural cells with perivascular inflammation of the gray matter or as postinfectious encephalomyelitis following viral infection with demyelination of the white matter [4]. Enteroviruses are cleared from the host by an antibody-mediated mechanism; therefore, immunocompromised patients may have more-devastating acute disease and long-term sequelae. Patients with agammaglobulinemia may have chronic meningoencephalitis with poor outcome. The immunological deficits of our patients probably had a major effect on the clinical course and the outcome of the disease. Patients 2 and 5 had severe immunodeficiency due to their underlying disease and the intensive chemotherapy, and they presented with chronic encephalitis and acute brain stem encephalitis, respectively, both of which had a fatal outcome. In contrast,
patient 4, who was in the maintenance phase of chemotherapy, presented with serious encephalitis that had a shorter duration and a favorable outcome.

Severe brain stem involvement has been found in children without specific neurologic signs, as in patient 5 [5]. Enteroviruses have also been associated with severe clinical syndromes, such as acute flaccid paralysis mimicking paralytic poliomyelitis, brain stem encephalitis, Guillain-Barré syndrome, acute transverse myelitis, and amyotrophic lateral sclerosis [6–8]. The fatality rate is significantly higher among children <5 years old [9].

Results of CSF analysis are normal in one-third of patients with encephalitis, but, in the majority of cases, mild pleocytosis with an elevated protein level is found. The absence of CSF pleocytosis in our patients might be explained by the myelosuppression that occurred secondary to chemotherapy. Although enterovirus genetic material was detected in the CSF of patients with enteroviral encephalitis, results of RT-PCR may, on rare occasions, be negative intermittently during the course of chronic enteroviral encephalitis [10]. For patient 2, the results of RT-PCR of CSF samples were positive for enterovirus at both the onset and the first relapse of encephalitis. Later, RT-PCR results were negative for enterovirus, perhaps due to local replication of the enterovirus, and they were again positive at the second relapse, which had a fatal outcome.

Individual serotypes of enteroviruses have tropism for certain tissues, but this tropism is neither unique nor specific. Infections with a single serotype may present in different ways, as was the case in our patients, and different serotypes can cause similar clinical syndromes [11].

Treatment of encephalitis with corticosteroids has been widely used, but the beneficial effect of these drugs is controversial. Immunoglobulins have been used prophylactically and therapeutically against enteroviral infections in immunodeficient patients [10]. Before the introduction of IVIG therapy for immunodeficient patients, chronic encephalitis was considered fatal. The prophylactic use of IVIG can ameliorate the clinical course of encephalitis but cannot always eliminate the enteroviral infection. There is evidence that, despite ongoing IVIG therapy, the virus can persist (as detected by PCR) and lead to progressive neurological deterioration in many patients [1]. High amounts of immunoglobulins could penetrate a damaged blood-brain barrier and reduce viral replication [12]. It has been reported that such treatment of enteroviral meningoencephalitis has been successful in 2 children with X-linked agammaglobulinemia [10]. On the basis of this report, for patient 2, after the second relapse of encephalitis, we administered IVIG every week.

The natural history of the disease can include periods of improvement in clinical and virological parameters. In patient 2, relapse occurred each time acyclovir therapy was discontinued. We do not have an explanation for the association between acyclovir and the relapse of the infection.

These case reports suggest that enteroviral infections should be included in the differential diagnosis of a variety of illnesses, such as parotitis, pancreatitis, and encephalitis, in children with leukemia. Patients who were in the induction phase of chemotherapy and who were <5 years of age had a poor outcome. Chronic encephalitis due to enterovirus can develop in patients with leukemia. It has been emphasized that a high degree of awareness is necessary for children with leukemia, if there is clinical suspicion of enteroviral infections. The incorporation of new molecular biology techniques for the detection of viral infection may allow for early diagnosis of disease and may prevent it from spreading in the health care facility.

References