A Syndrome of Transient Encephalopathy Associated With Adenovirus Infection

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ABSTRACT. Background and Objective. Adenovirus is a common pathogen in the pediatric population. Respiratory, gastrointestinal, or renal systems are often involved in adenovirus infections. Several neurologic syndromes have been attributed to adenovirus, such as adenovirus aseptic meningitis, myelitis, subacute focal encephalitis, and Reye-like syndrome. The purpose of this study was to describe the clinical features and encephalography findings in 7 infants treated in our center for a syndrome of transient encephalopathy associated with adenovirus infection.

Study Participants. Three females and 4 males ages 7 to 34 months seen in our department between July 1983 and February 1984 and September 1998 and May 1999 presented with fever of at least 7 days' duration and a gradual decline in the state of alertness. Score on the Glasgow Coma Scale ranged from 9 to 12. Findings on lumbar puncture were normal. In all 7 patients, the encephalogram showed moderate to severe background slowing compatible with encephalopathy. All patients were catarrhal and had mild hepatomegaly with slight elevation of liver enzymes. Some had bronchopneumonia, diarrhea, and conjunctivitis either isolated or in combination.

Methods and Results. Adenovirus was isolated by immunofluorescence technique in all patients—from the sputum in 3 patients, nasopharynx in 5, conjunctiva in 4, and rectal swab in 5. In 5 patients, serotyping was performed by an antibody neutralization method. Adenovirus type 3 was ascertained from a nasal swab in 1 patient, sputum specimens in 3, throat swab in 3, and rectal cultures in 5. The clinical course was characterized by a progressive recovery of alertness. After several days, there was a complete reversal of neurologic findings.

Conclusion. We suggest that this syndrome of transient encephalopathy is a distinct entity and should be considered as another of the several neurologic syndromes known to be associated with adenovirus infection.

ADDITIONAL MATERIALS. EEG, electroencephalography; CNS, central nervous system; CSF, cerebrospinal fluid.

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herpes encephalitis. During drowsiness and deep sleep, sleep
or periodic lateralizing epileptiform discharges, which suggest
epileptic activity nor focal slowing. There were also no triphasic
activity in the range of 2 to 3 per second. There was neither
hydration and abdominal pain in 2 patients. The duration of this
symptom was 3 to 7 days. There was pneumonia in 6 and con-
junctivitis in 3 patients (Table 1). All 7 patients had been treated
with paracetamol by the local clinic pediatrician and 5 also re-
ceived antibiotics (amoxicillin, cefuroxime, 2). No sedatives or
other medications were prescribed.

The laboratory data are shown in Table 2. In addition to leu-
kopenia and mild elevations in aspartate aminotransferase levels,
ammonia and glucose levels were within normal range as were
serum electrolytes, pH, and blood gases, with no evidence of
dehydration or metabolic disturbances. Levels of urea, creatinine,
albumin, globulins, calcium, phosphorus, uric acid, bilirubin, cre-

TABLE 1. Clinical Characteristics of Children With Adenovirus-Associated Encephalopathy

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Age (Months)</th>
<th>Gender</th>
<th>Presenting Diagnosis</th>
<th>Duration of Fever (Days)</th>
<th>Level of Consciousness</th>
<th>Extra-CNS Manifestations</th>
<th>Hepatomegaly</th>
<th>Duration of Hospitalization (Days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>26</td>
<td>M</td>
<td>Pneumonia</td>
<td>7</td>
<td>Lethargy</td>
<td>Diarrhea</td>
<td>+</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>30</td>
<td>F</td>
<td>Pneumonia</td>
<td>14</td>
<td>Obtundation</td>
<td>Lethargy</td>
<td>Conjunctivitis</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
<td>F</td>
<td>Diarrhea</td>
<td>7</td>
<td>Lethargy</td>
<td>Diarrhea</td>
<td>Conjunctivitis</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>F</td>
<td>Pneumonia</td>
<td>7</td>
<td>Obtundation</td>
<td>—</td>
<td>—</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>5</td>
<td>15</td>
<td>F</td>
<td>Follicular tonsillitis</td>
<td>7</td>
<td>Stupor</td>
<td>Tonsillitis</td>
<td>+</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>6</td>
<td>13</td>
<td>M</td>
<td>Pneumonia</td>
<td>7</td>
<td>Stupor</td>
<td>—</td>
<td>—</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>7</td>
<td>34</td>
<td>M</td>
<td>Pneumonia</td>
<td>10</td>
<td>Lethargy</td>
<td>Diarrhea</td>
<td>+</td>
<td>Not mentioned</td>
</tr>
</tbody>
</table>

Pulse oximetry was normal, with no sign of hypoxemia in any of
the patients. Lumbar puncture showed protein and glucose
levels in the normal range with no pleocytosis. Cerebrospinal fluid
(CSF) culture for bacteria was negative. Viral cultures and routine
testing for encephalitis were not performed because of the
absence of leukocytes in the fluid. Four children were assayed
for Epstein-Barr virus and there was no evidence for acute infection,
so that the positive adenovirus culture in our cases shows a close
association between the clinical presentation and the isolation of
the virus. The rate of recovery of adenovirus during the same
time interval for hospitalized children with diagnosis unrelated to our
patients was low—in 3 patients the virus was isolated.

EEG was performed during states of arousal, drowsiness, and
deep sleep. In the aroused state, the background showed slow δ
activity in the range of 2 to 3 per second. There was neither
epileptic activity nor focal slowing. There were also no triphasic
waves, which usually indicate hepatic or uremic encephalopathy,
or periodic lateralizing epileptiform discharges, which suggest
herpes encephalitis. During drowsiness and deep sleep, sleep
spindles were seen together with the same diffuse slowing of the
background activity in the range of δ activity. In 3 patients, the
slowing was more prominent over the temporooccipital region.
This EEG pattern is compatible with encephalopathy attributable
to infectious, toxic, metabolic, or hypoxic factors.

Although there was evidence of involvement of several systems
(respiratory, gastrointestinal, and neurologic), the patients did not
seem to have a severe disseminated disease, and there were no
signs of multisystem organ failure or dysfunction on the labora-
tory tests. However, blood viral cultures and polymerase chain
reaction were not performed.

Six patients were treated with intravenous antibiotics for sus-
ppected pneumonia. Two were initially treated with intravenous
acyclovir because of suspected herpes encephalitis, with no effect
on the clinical manifestations. The clinical course was character-
ized by gradual improvement in signs and symptoms with pro-
gressive recovery of alertness and general well-being over a pe-
riod of up to 8 days. At discharge, the neurologic and physical
examination was normal in all children.

METHODS

Viral Isolation and Typing

Adenovirus was cultured on human kidney cells and was
identified by a modification of immunofluorescence technique
using the shell vial assay. It was isolated from all patients, from
the sputum in 3 patients, the conjunctiva in 4, rectal swab in 5, and
nasopharynx in 5. Serotyping was performed in 5 patients. In
these patients, the isolated viruses were identified by neutraliza-
tion assays, using rabbit hyperimmune serum prepared against
standard adenovirus strains types 1 to 7, provided by Dr Preira
(United Kingdom). They were tested for adenovirus antibodies of
the microcomplement fixation assay. The serotyping was per-
formed from a nasal swab in 1, sputum specimens in 3 patients,
throat swabs in 3, and rectal swabs in all 5. Type 3 was found in all
5 cases.

DISCUSSION

The Adenoviridae are DNA viruses and have a
worldwide distribution. In general, the subgenus B
adenoviruses, including types 3, 7, 14, 21, and 35, are
associated with more severe diseases. Outbreaks of
febrile respiratory disease have been attributed to
types 4 and 7, of severe pneumonia to types 3, 7, and
21, and of pharyngoconjunctival fever to type 3. Ac-
cording to reports from northern China and Korea,
adenovirus types 3 and 7 caused severe epidemics of
pneumonia in children with a mortality rate of 5% to
15%. In a more recent publication from Borneo, Mal-
aysia, during a fatal outbreak of enterovirus 71, sub-
group B adenovirus was isolated from 10 patients
who died and from 5 patients in whom the disease
was complicated by acute flaccid paralysis. The authors
suggest that adenovirus infection had a major
role in the morbidity and mortality of the disease.

Munoz et al described disseminated adenovirus dis-
ease with multiorgan involvement in 11 of 440 pa-

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nents (2.5%) with adenovirus infection. Serotypes 1, 2,
3, 5, and 7 were isolated. The mortality rate was
83% in the immunocompromised hosts (n = 6) and
60% in the immunocompetent hosts (n = 5).

Adenovirus may cause aseptic meningitis, although certain
strains, such as adenovirus type 7, are often responsible for a
meningoencephalitis with a rather severe course. Other
neurologic syndromes associated with adenovirus are myelitis,
subacute focal adenovirus encephalitis, fatal encephalitis in
transplanted patients, and Reye-like syndrome.

The association of adenovirus with CNS disease
was first reported in France in 1956. In this study, 5
children presented with neurologic symptoms during a serious outbreak of adenovirus respiratory disease. Adenovirus type 7 was isolated from the CNS tissue, thereby identifying the involvement as encephalitis.

Two years later, Chaney et al.17 isolated the same strain from the CSF and brain tissue of a patient with fatal pneumonia and encephalitis. Since then, there have been several sporadic reports of CNS disease associated with adenovirus infection.10,11,17-21 These patients had either pleocytosis in the CNS or a positive virus culture from CSF or brain tissue.

In 1979, Ladisch et al.15 described a fatal Reye-like disease in 3 children. The syndrome was characterized by antecedent upper respiratory infection, multiorgan involvement, lethargy progressing to coma, status epilepticus, and laboratory findings of elevated serum levels of muscle and liver enzymes and fatty infiltration of the liver. Disseminated intravascular coagulation was also present.

Recently, Ohtsuki et al.22 reported on 3 patients with acute encephalopathy related to adenovirus type 7 infection. In all cases, seizures appeared on days 8 to 10 of the disease. There was no CSF leukocytosis. Computed tomography showed mild brain atrophy. Steroid pulse was helpful in 1 patient, suggesting a pathogenesis of postinfectious encephalitis.

The patients in the present study seemed to have a milder form of CNS involvement with features compatible with transient encephalopathy. A similar syndrome caused by adenovirus type 7 in a pair of twins was described in 1983 by Kim and Gohd.23 In 1986, Levy et al.3 from our institution, described manifestations in 3 of 8 patients (patients 1, 5, and 8 in the original study) having adenovirus type 3 infection. These 3 are included among the 7 patients in the present series, as patients 5 to 7.

Clinically, the typical presenting symptoms of the syndrome are spiking fever of several days’ duration and a decline in the state of arousal to lethargy, obtundation, or stupor, but no seizures. Affected children are also catarrhal and some may have conjunctivitis and respiratory or gastrointestinal symptoms. Mild hepatomegaly may be characteristic. The patients all seem ill. This is the reason we performed lumbar puncture in our cases, although there were no meningeal signs. Laboratory workup shows mild leukopenia, mild elevation of liver enzymes; level of ammonia is normal, as are findings on lumbar puncture. The EEG tracing demonstrates diffuse background slowing. Some of our patients showed slowing in the temporocipital region. The neurologic and general state improves within several days. There is no need for brain biopsy.

The transient encephalopathy described in this article can be differentiated from adenovirus meningoencephalitis and adenovirus Reye-like syndrome based on the clinical and laboratory parameters. Adenovirus meningoencephalitis is characterized by pleocytosis in the CSF or the presence of the virus in brain specimens,16,17 indicating invasion of the CNS by the virus. Reye-like syndrome15 is characterized by status epilepticus. In our patients, there was neither peripheral leukocytosis nor elevation of creatine
phospho kinase. In addition, there was no evidence of disseminated intravascular coagulation. The clinical outcome was benign, in contrast to the downhill course in all the children reported by Ladisch et al.\textsuperscript{15}

The pathogenesis of this syndrome is unknown. We presume that in our patients, viral-induced host responses mediated the reversible encephalopathy. The presence of this clinical syndrome has been suspected in several other patients in our center. Owing to an incomplete workup, however, they were not included in the present article. Nevertheless, these cases contribute to our impression that the syndrome is not rare.

**CONCLUSION**

Transient encephalopathy associated with adenovirus infection may constitute a distinct entity. In contrast to the other neurologic syndromes associated with this virus, its outcome is benign.

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