

# 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. *Pediatrics* 2001;107(5). URL: <http://www.pediatrics.org/cgi/content/full/107/5/e69>; *encephalitis, adenovirus, encephalopathy.*

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

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Adenovirus is a common pathogen in the pediatric population causing acute respiratory diseases in 5% to 8% of infants.<sup>1</sup> The spectrum of adenovirus infections includes pharyngoconjunctival fever, follicular conjunctivitis, epidemic keratoconjunctivitis, myocarditis, hemorrhagic cystitis, acute diarrhea, intussusception, encephalomyelitis, bronchiolitis obliterans, and Reye-like syndrome.<sup>1</sup>

The term encephalopathy is used to describe a diffuse disorder of the brain in which at least 2 of the following symptoms are present: 1) altered state of consciousness; 2) altered cognition or personality; and 3) seizures.<sup>2</sup>

We have encountered several cases of a specific neurologic syndrome of adenovirus infection associated with reversible encephalopathy. The diagnosis of encephalopathy was established by the presence of the first 2 criteria and supported by the electroencephalography (EEG) finding of moderate to severe background slowing with no epileptiform activity. We believe that this syndrome constitutes a distinct clinical entity that should be included among the neurologic syndromes attributed to adenovirus. In the present article, we focus on the clinical features and describe the characteristic EEG findings observed in these patients.

## CLINICAL REPORT

The present article covers 7 infants treated in our department. Three (patients 5–7; Table 1) were encountered between July 1983 and February 1984 and were described in an earlier publication (patients 1, 5, and 8 in the original article).<sup>3</sup> A renewal of interest in this syndrome led to the present report of 4 additional patients, seen between September 1998 and May 1999. In all, there were 4 females and 3 males, ages 7 to 34 months (mean: 20 months). Their clinical features are summarized in Table 1.

All patients presented with fever of 38.8°C to 40.5°C that lasted at least 7 days. In 5 cases, the diagnosis of the referring primary physician was bronchopneumonia, based on the physical examination and chest radiograph findings, and in 2 patients, the referral diagnosis was acute diarrhea.

On admission to the ward, the patients appeared ill. The neurologic examination was notable for decreased level of consciousness ranging from lethargy (ie, difficulty in maintaining a state of arousal) in 3 patients, to obtundation (responsiveness to stimulation other than pain) only in 2 patients, stupor (responsiveness only to painful stimuli) in 2 patients. Scores on the Glasgow Coma Scale ranged from 9 to 12. None of the patients had seizures or signs of meningeal involvement. Cranial nerve functions, muscle tone, muscle strength, and sensation were normal. There were no pyramidal, cerebellar, or extrapyramidal signs.

Besides the central nervous system (CNS) manifestations, all patients were catarrhal with rhinorrhea/nasal congestions. There was pharyngitis in 1. Otitis media was not present. All had mild hepatomegaly. Diarrhea was present in 4 patients with mild de-

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

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

hydration and abdominal pain in 2 patients. The duration of this symptom was 3 to 7 days. There was pneumonia in 6 and conjunctivitis in 3 patients (Table 1). All 7 patients had been treated with paracetamol by the local clinic pediatrician and 5 also received antibiotics (amoxicillin, 3; cefuroxime, 2). No sedatives or other medications were prescribed.

The laboratory data are shown in Table 2. In addition to leukopenia 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, creatine phosphokinase, alkaline phosphatase, lactate dehydrogenase, and  $\gamma$ -glutamyltranspeptidase were also normal. Blood and urine cultures were negative. Coagulation studies were normal, with no evidence of disseminated intravascular coagulation. Chest radiograph examination disclosed bilateral bronchopneumonia in 6 patients; the seventh had experienced no signs or symptoms of respiratory tract disease.

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 screening tests 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 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  $\delta$  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 rhythm in the range of  $\delta$  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 laboratory tests. However, blood viral cultures and polymerase chain reaction were not performed.

Six patients were treated with intravenous antibiotics for suspected pneumonia. Two were initially treated with intravenous acyclovir because of suspected herpes encephalitis, with no effect on the clinical manifestations. The clinical course was characterized by gradual improvement in signs and symptoms with progressive recovery of alertness and general well-being over a period 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.<sup>4</sup> 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 neutralization 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.<sup>5</sup> The serotyping was performed 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.<sup>6</sup> 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. According 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%.<sup>1</sup> In a more recent publication from Borneo, Malaysia, during a fatal outbreak of enterovirus 71, subgroup B adenovirus was isolated from 10 patients who died and from 5 patients in whom the disease was complicated by acute flaccid paralysis.<sup>7</sup> The authors suggest that adenovirus infection had a major role in the morbidity and mortality of the disease. Munoz et al<sup>8</sup> described disseminated adenovirus disease with multiorgan involvement in 11 of 440 patients (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,<sup>9</sup> although certain strains, such as adenovirus type 7, are often responsible for a meningoencephalitis with a rather severe course.<sup>10,11</sup> Other neurologic syndromes associated with adenovirus are myelitis,<sup>12</sup> subacute focal adenovirus encephalitis,<sup>13</sup> fatal encephalitis in transplanted patients,<sup>14</sup> and Reye-like syndrome.<sup>15</sup>

The association of adenovirus with CNS disease was first reported in France in 1956.<sup>16</sup> In this study, 5

**TABLE 2.** Laboratory Data in Children With Adenovirus Infection

Patient Number	White Blood Cell Count/mm <sup>3</sup>	Aspartate Aminotransferase (U/L) ( <i>n</i> = <35)	Chest Radiograph	Lumbar Puncture	EEG	Positive Immunofluorescence for Adenovirus				
						Sputum	Nasopharynx	Conjunctiva	Rectal Swab	
1	6000	53	Bilateral bronchopneumonia	Normal	Diffuse slowing of activity		+	+	+	3
2	3400	401	Bilateral bronchopneumonia	Normal	Severe diffuse slowing with occipital accentuation			+	+	
3	9160	254	Not done	Normal	Diffuse slowing		+	+	+	3
4	5200	184	Bilateral bronchopneumonia	Normal	Diffuse slowing, especially temporooccipital		+	+	+	
5	3800	39	Bilateral bronchopneumonia	Normal	Generalized slowing of activity		+		+	3
6	8400	99	Bilateral bronchopneumonia	Normal	Temporooccipital slowing of activity		+			3
7	4600	197	Bilateral bronchopneumonia	Normal	Generalized slowing of activity		+	+	+	3

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<sup>17</sup> 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.<sup>10,11,17-21</sup> These patients had either pleocytosis in the CNS or a positive virus culture from CSF or brain tissue.

In 1979, Ladisch et al<sup>15</sup> 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<sup>22</sup> 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.<sup>23</sup> In 1986, Levy et al<sup>3</sup> 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 temporooccipital 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,<sup>16,17</sup> indicating invasion of the CNS by the virus. Reye-like syndrome<sup>15</sup> 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.<sup>15</sup>

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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