Adenovirus-Associated Central Nervous System Disease in Children

Kevin L. Schwartz, MD, MSc[1,2], Susan E. Richardson, MD[3], Daune MacGregor, MD[4,5], Sanjay Mahant, MD, MSc[4,6], Kamini Raghuram, MD[4,6], and Ari Bitnun, MD, MSc[4,7]

Objective To characterize the spectrum and salient clinical features of adenovirus-associated neurologic disease in immunocompetent children.

Study design Previously healthy children (aged 1 month-18 years) with central nervous system (CNS) disease associated with adenovirus infection were identified via the Encephalitis Registry (1996-2016) and Microbiology Database (2000-2016) at The Hospital for Sick Children, Toronto, and by systematic review of the literature. The data were pooled and analyzed to identify the spectrum of illness, clinical outcome, and risk factors for death or neurologic impairment.

Results Neurologic complications associated with adenovirus infection in our institution included febrile seizures, encephalitis, acute disseminated encephalomyelitis, and aseptic meningitis. A total of 48 immunocompetent children with adenovirus-associated CNS disease were included in the pooled analysis—38 from the literature and 10 from our institution. In 85% of cases, the virus was detected in the respiratory or gastrointestinal tract, but not the cerebrospinal fluid. Eighteen of the 48 (38%) patients either died or suffered permanent neurologic sequelae. Predictors of adverse outcome included younger age, coagulopathy, the absence of meningismus, serotype 2 virus, and the presence of seizures. After multivariable adjustment, only seizures remained a significant risk factor.

Conclusion Adenovirus is a rare cause of CNS disease in immunocompetent children. Disease spectrum is variable, ranging from mild aspetic meningitis and fully reversible encephalopathy to severe, potentially fatal, acute necrotizing encephalopathy. *(J Pediatr 2019;205:130-7).*

Adenovirus is a common pediatric infection typically manifesting as a febrile respiratory illness, gastrointestinal infection, or conjunctivitis. In contrast, central nervous system (CNS) disease due to adenovirus is rare. In 3 large prospective encephalitis cohorts involving 789 patients, who primarily were adults, no case was attributable to adenovirus.[1-3] However, in 1 pediatric study conducted in Finland, adenovirus was implicated in 5% of childhood encephalitis cases, suggesting a more significant role in children.[4] Meningitis and a transient adenovirus-associated encephalopathy also have been described in a small number of children.[5,6] In a retrospective pediatric study conducted in Taiwan and published in 2013, 3.3% (109 of 3298) of children with culture-confirmed adenovirus infections had symptoms or signs of neurologic dysfunction.[7]

The purpose of this study was to better characterize the spectrum and salient clinical features of CNS disease associated with adenovirus in previously healthy immunocompetent children. To do so, we combined data from The Hospital for Sick Children (SickKids) Microbiology Database and Encephalitis Registry with a systematic review of the literature.

Methods

Previously healthy children, aged 1 month to 18 years, with neurologic symptoms associated with adenovirus infection were identified from 3 different sources, the SickKids Microbiology Database, the SickKids Encephalitis Registry, and by systematic review of the literature. The SickKids Microbiology Database was used to determine the incidence and spectrum of neurologic complications, including febrile seizures, associated with adenovirus detections (January 1, 2000-December 31, 2016). The Encephalitis Registry Database was used to evaluate the role of adenovirus in acute childhood encephalitis and to describe the salient clinical features of adenovirus encephalitis (January 1, 1996-December 31, 2016). A systematic review of the literature, conducted in January 2017, was used to identify cases of adenovirus-associated neurologic disease, extract patient-specific clinical data where possible, and combine these data with those

CNS	Central nervous system
CSF	Cerebrospinal fluid
PCR	Polymerase chain reaction
SickKids	The Hospital for Sick Children

From the [1]Public Health Ontario; [2]Dalla Lana School of Public Health; [3]Division of Microbiology, Department of Paediatric Laboratory Medicine, The Hospital for Sick Children; [4]Department of Paediatrics, University of Toronto; [5]Division of Neurology; [6]Division of Paediatric Medicine; and [7]Division of Infectious Diseases, The Hospital for Sick Children, Toronto, Ontario, Canada

The authors declare no conflicts of interest.

https://doi.org10.1016/j.jpeds.2018.09.036

from our institution to further characterize disease spectrum, clinical outcome, and risk factors for death or neurologic impairment. The study was approved by the SickKids Research Ethics Board. Verbal guardian consent, documented in the patient record, was obtained for the case description of a child hospitalized at SickKids.

Inclusion and Exclusion Criteria and Definition of Neurologic Diagnoses

For cases identified in the SickKids Microbiology Database eligibility criteria included admission to SickKids, presence of neurologic symptoms, and detection of adenovirus in a sterile or nonsterile site by direct fluorescent antibody staining, culture, or polymerase chain reaction (PCR). Eligibility criteria for cases identified in the SickKids Encephalitis Registry included admission to SickKids, fulfillment of the inclusion criteria for the Encephalitis Registry as delineated below and detection of adenovirus as described for the Microbiology Database. Cases identified from the literature search were eligible for inclusion if they had a neurologic diagnosis other than febrile seizures and microbiologic or serologic evidence of acute adenovirus infection. Children identified in any of the 3 sources were excluded if they had a pre-existing noninfectious neurologic condition, a primary or secondary immune-compromising condition, or a plausible alternative infectious or noninfectious etiology.

For cases identified in the SickKids Microbiology Database or the Encephalitis Registry, encephalitis was defined by the presence of encephalopathy (depressed or altered level of consciousness persisting for >24 hours) plus 2 or more of the following: fever (>38.0°C), seizures, focal neurologic deficits, cerebrospinal fluid (CSF) pleocytosis (>5 cells/uL), electroencephalographic abnormalities, or diagnostic imaging abnormalities.[8,9] The diagnosis of isolated encephalopathy was reserved for children with encephalopathy who had fewer than 2 of the secondary criteria listed above. Other diagnoses were in accordance with those listed in discharge and follow-up medical records. For cases identified in the literature search, diagnosis was in accordance with that specified in the original publication.

SickKids Microbiology Methods

The presence of adenovirus was tested for in nasopharyngeal aspirates by direct fluorescent antibody staining, viral isolation, PCR, or combination of tests. Direct fluorescent antibody staining was performed using fluorophore-labeled monoclonal antibody against adenovirus (SimulFluor; Millipore, Temecula, California). Nasopharyngeal aspirate was inoculated into R-Mix shell vials (Diagnostic Hybrids, Athens, Ohio) and the coverslip stained with the same monoclonal antibody. Detection of adenovirus by PCR in respiratory specimens was performed using an in-house assay using primers targeting conserved segments bracketing the hypervariable region-7 of the hexon gene, until mid-2012. After this time, 1 of 2 real-time commercial assays—Adenovirus R-gene assay (Argene Inc, Verniolle, France or RealStar Adenovirus PCR Kit 1.0; Altona Diagnostics, Hamburg, Germany)[10] or a multiplex commercial assay on the Luminex platform (xTag-RVP Fast v2; Luminex Molecular Diagnostics, Toronto, Canada). Other specimens (eg, tissue biopsies, CSF and other sterile fluids except blood, urine, and eye swabs) were tested by PCR (in-house or commercial real time, as above) and virus isolation, until the latter was discontinued at the end of 2008. Stool was tested by electron microscopy. Serology was performed by complement fixation (antigen from Microbix Biosystems Inc, Mississauga, Canada) until October 2001, after which it was discontinued.

Literature Review

A systematic MEDLINE and EMBASE search was completed with the assistance of a senior hospital librarian. Search strategy included terms for 'adenoviridae,' 'adenovirus' or 'adenovirus infections' combined with 'encephalitis,' 'central nervous system viral disease,' 'viral/aseptic meningitis,' 'lymphocytic choriomeningitis,' 'central nervous system,' 'brain,' 'meninges,' 'arachnoid,' 'seizures,' or 'status epilepticus.' We restricted our search to the English language literature.

Statistical Analyses

For the purpose of describing the spectrum of adenovirus-associated CNS disease and the salient clinical features of these entities, the data for cases identified in our institution were combined with those identified from the literature review. Children with febrile seizures were excluded from this analysis. The clinical and microbiologic characteristics of those with and without adverse outcome, defined as death or neurologic sequelae, were compared. Data were analyzed using SAS Enterprise Guide v 7.1 (SAS Institute, Cary, North Carolina) for associations by χ^2 or Fischer exact test as appropriate for categorical variables, and by Wilcoxon Mann-Whitney test for continuous variables. Statistical significance was set at $P < .05$. Variables identified as significant risk factors for death or neurologic sequelae were evaluated in a multivariable logistic regression model.

Results

Case Description

A previously healthy 10-month-old female patient was brought to medical attention because of seizures and reduced level of consciousness following a prodromal illness of fever and diarrhea of 2 days' duration (case 1 in **Table I** and **Table II**). At the time of admission, she was profoundly encephalopathic and had a fixed and dilated left pupil. She was admitted to the intensive care unit and had an external ventricular drain placed because of raised intracranial pressure. Initial CSF analysis taken on the first day of illness showed a leukocyte count of 7 cells/uL, red blood cell count of 4473 cells/uL, and a protein of 339 mg/dL. She had evidence of hepatitis with peak serum alanine aminotransferase and aspartate aminotransferase of 258 U/L and 465 U/L, respectively. Magnetic resonance imaging on the day of admission showed extensive enhancement of the basal ganglia, midbrain, and periventricular areas bilaterally with extensive diffusion restriction of the thalami and periventricular areas, reflective of ischemia (**Figure 1**). A

Table I. Clinical characteristics of 8 children with adenovirus encephalitis at SickKids*

Patient no	Age/sex	Clinical		CSF findings			EEG findings	Imaging findings	Outcome (duration of follow-up)
		General	CNS	WBCs per uL (% lymph)	RBCs per uL	Protein mg/dL			
1	10 mo/F	Fever, vomiting, diarrhea, hepatitis	Decreased LOC, raised ICP, seizures	7	4773	339	Generalized slowing	CT: Diffuse hypoattenuation MRI: Bilateral symmetric increased T2 signal in cerebrum, thalamus, and cerebellum consistent with a diagnosis of ANE. Diffuse diffusion restriction. Elevated lactate peak on MRS	Profound impairment, GDD, refractory seizure disorder (8 mo)
2	5 y 7 mo/M	Rhinorrhea, fever	Decreased LOC, irritability, focal seizures, vomiting, parkinsonian movements	31 (85)	0	ND	Diffuse generalized slowing	CT: Normal MRI: Ischemia to the Substantia Nigra, lacunar infarct	Full recovery (10 mo)
3	14 y/M	Headache, vomiting, sore throat, fever. Diarrhea after admission	Lethargy, decreased LOC, difficulty speaking and writing, left arm hemiparesis	7	0	24	ND	CT: Normal	Full recovery (discharge)
4	10 mo/M	Diarrhea, fever	Lethargy, status epilepticus	0	0	32	Abnormal background with diffuse Beta activity. Repeat was normal	CT: subependymal heterotropia in occipital horn of right lateral ventricle MRI: ND	Seizure disorder, mild cognitive impairment (10 mo)
5	15 y/M	Headache, vomiting, fever	Combative, decreased LOC, seizures	9 (97%)	165	59	Normal	CT: Normal MRI: ND	Full recovery (1 mo)
6	5 mo/M	Rhinorrhea, fever, poor feeding	Lethargy, decreased LOC, generalized seizures with bicycling movements, CN VI palsy	750 (17%)	26 000	110	Generalized slowing	CT: hypodense lesion in left thalamus MRI: Diffuse bilateral symmetric increased T2/Flair signal in thalami and internal capsules consistent with a diagnosis of ANE.	Right sided Spasticity and paresis (3 mo)
7	20 mo/M	Rhinorrhea, diarrhea, fever	irritability, decreased LOC, refractory seizures	4	6	10	Generalized slowing	CT: Normal MRI: Prominence of folium, increased T2 in peritrigonal white matter and frontal regions bilaterally, volume loss in posterior fossa	GDD, seizure disorder prior, but worsened with developmental regression after encephalitis (9 y).
8	5 y/M	Cough, fever	Lethargy, decreased LOC, seizures, weakness, gait disturbance (glucose 0.1 mmol/L)	11 (8)	0	22	Generalized and focal slowing	CT: basal ganglia changes, loss of gray-white matter differentiation MRI: significant abnormal signal associated with diffusion restriction within the basal ganglia and cortex. Repeat 5 d later showed progression	Seizure disorder, dystonia (4 y). Etiology of hypoglycemia never identified

ANE, acute necrotizing encephalopathy; *CN VI*, cranial nerve VI; *CT*, computed tomography; *EEG*, electroencephalogram; *F*, female; *GDD*, global developmental delay; *ICP*, intracranial pressure; *LOC*, level of consciousness; *M*, male; *MRI*, magnetic resonance imaging; *MRS*, magnetic resonance spectroscopy; *ND*, not done; *RBC*, red blood cell; *T2/FLAIR*, T2-weighted-fluid-attenuated inversion recovery; *WBC*, white blood cell.
*Cases 1 and 6 were diagnosed with ANE; the remaining 6 had undifferentiated encephalitis.

Table II. Microbiology results in 8 children with adenovirus encephalitis at SickKids

Patient nos	Adeno PCR			Adeno viral culture		Stool EM adeno	Serology by CFT		Serotype
	NPA	Blood	CSF	NPA	Stool		Acute	Convalescent	
1	+	4521*	+	ND	ND	–	ND	ND	2
2	–	ND	ND	–	+	+	1:64	1:32	
3	+ (DFA)	ND	ND	+	+	–	1:16	1:256	
4	–	ND	ND	+	+	+	<1:8	1:32	
5	–	ND	–	+	–	–	ND	ND	
6	+	ND	–	ND	–	–	ND	ND	2
7	–	ND	ND	+	–	–	<1:4	1:64	
8	+ (DFA and PCR)	ND	ND	+	ND	ND	ND	ND	

CFT, complement fixation test; *DFA*, direct fluorescence antigen; *EM*, electron microscopy; *NPA*, nasopharyngeal aspirate.
*In-house assay, reported in copies per milliliter.

diagnosis of acute necrotizing encephalopathy was made. Adenovirus serotype 2 was detected by PCR in her nasopharynx, blood, and CSF. No other pathogen was identified, despite a comprehensive Encephalitis Registry investigation. The adenovirus load in the blood was measured at 4521 copies/mL. She survived the acute illness but suffered profound global neurologic impairment and seizure disorder.

Cases from Retrospective Review of SickKids Microbiology Database

Between January 2000 and December 2016 inclusive, 977 cases of adenovirus infection were identified from the Microbiology Database. Of these, 49 children had neurologic symptoms (5.0%). Seventeen of these 49 children were excluded, 11 because of a pre-existing neurologic disorder (isolated seizure disorder [n = 3], global developmental delay [n = 3], tuberous sclerosis [n = 2]), and 6 because of a clear noninfectious etiology identified during hospitalization (2 with episodic ataxia and 1 each with complex III deficiency, cortical dysplasia, severe hypoxic injury related to prolonged hypotension associated with ischemic bowel, cardiac arrest secondary to prolonged QT syndrome). Of the remaining 32 children (3.3%), 26 had febrile seizures (2.7% of all adenovirus infections), 4 had encephalitis (0.4% of all adenovirus infections), 1 had acute demyelinating encephalomyelitis, and 1 had aseptic meningitis (**Figure 2**).

The median age of the 26 children with febrile seizures was 1.5 years (IQR 1.2, 2.2 years); 65.4% were less than 2 years of age. In 20 of 26 patients, this was their first febrile seizure episode and in 24 of 26 the febrile seizures were classified as complex (16 with prolonged status epilepticus and 8 with 2 or more seizure in 24 hours). Eighteen required admission to the intensive care unit, including the 16 with status epilepticus. A preceding prodromal illness was recorded for 22 children (respiratory 21, gastrointestinal 1) with a median duration of 1 day prior to seizure onset (IQR 1, 2 days). Two of the 26 children with febrile seizures were later diagnosed with epilepsy.

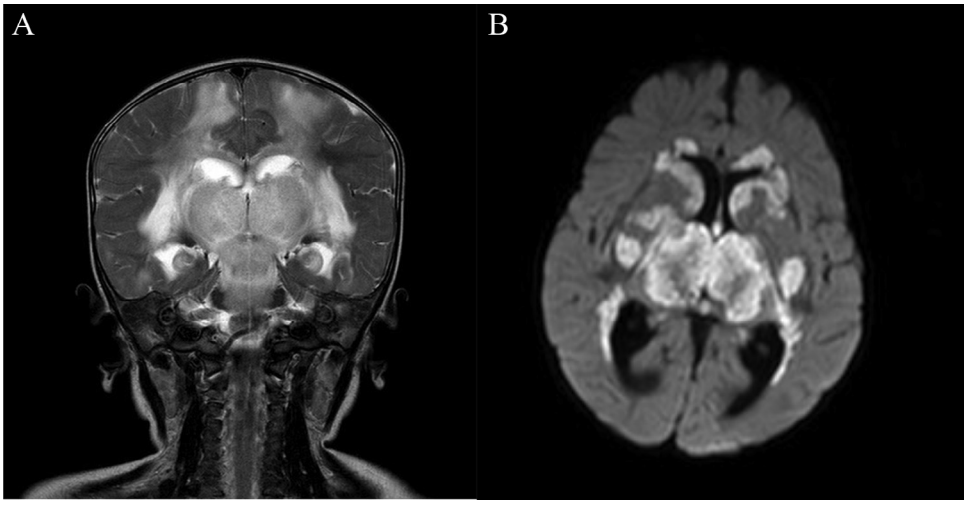

Figure 1. Magnetic resonance imaging from case 1 demonstrating typical features of acute necrotizing encephalopathy. **A,** Flair coronal image showing extensive, bilateral, symmetric enhancement of basal ganglia, midbrain, and periventricular areas. **B,** Extensive bilateral symmetric restricted diffusion of thalami and periventricular areas.

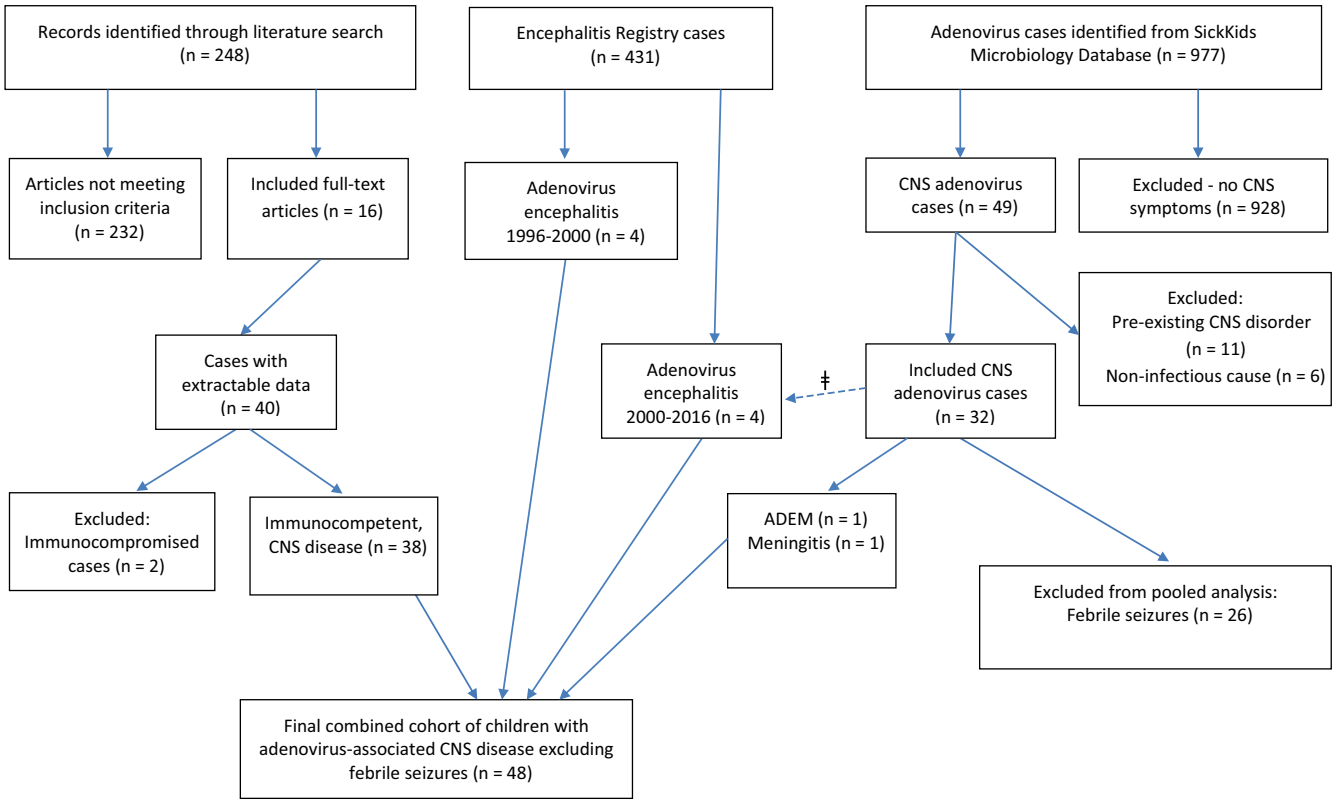

Figure 2. Flow diagram of case selection from SickKids Microbiology Database, SickKids Encephalitis Registry, and literature review for inclusion in pooled analysis. *ADEM*, acute disseminated encephalomyelitis.
‡ Four children with encephalitis were identified in both the Encephalitis Registry Database and the Microbiology Database.

Cases from Prospective SickKids Encephalitis Registry

Adenovirus was implicated as the likely cause of encephalitis in 8 of 431 (1.9%) children in the SickKids Encephalitis Registry between January 1996 and December 2016 inclusive. The 4 cases that were enrolled after the year 2000 also were identified from the Microbiology Database (**Figure 2**). The clinical and microbiology data for encephalitis cases are summarized in **Table I** and **Table II**. Two of 8 were diagnosed with acute necrotizing encephalopathy (cases 1 and 6 in **Table I** and **Table II**), the remaining 6 with undifferentiated encephalitis. Seven of 8 were male and 6 of 8 were less than 6 years of age. Prodromal manifestations included fever (n = 8), rhinorrhea/cough (n = 4), diarrhea (n = 4), and vomiting (n = 3). The median prodrome duration was 4 days (IQR 2, 5). Seizures (n = 7) and focal neurologic deficits (n = 2) were the predominant neurologic symptoms other than encephalopathy. The median CSF leukocyte count was 8 cells/uL (IQR 6.3, 16) and was predominantly lymphocytic in 50% of those with sufficient cells to perform a differential count. Neuroimaging was abnormal in 6 children, 3 of whom had thalamic or basal ganglia involvement. In 2 children with normal computed tomography scans, abnormalities were detected on magnetic resonance imaging. Three children, aged 15 years, 14 years, and 5.5 years recovered fully. One 5-year-old child and all 4 children who were less than 2 years of age suffered neurologic sequelae. There were no deaths.

Cases from Literature Review

A total of 248 publications on adenovirus-associated CNS disease were identified. Of these, 16 manuscripts published between 1958 and 2016 describing 40 children were relevant and contained adequate clinical information for further assessment.[5,6,11-24] Two of the identified cases were excluded due to documented immune deficiency (**Figure 2**).

Combined Analysis

A total of 48 children with adenovirus-associated CNS disease were included in this analysis, 38 from the literature review and 10 from the SickKids Encephalitis Registry and/or the SickKids Microbiology Database (**Figure 2** and **Table III**). The 26 children with febrile seizures from the SickKids Microbiology Database were excluded from this analysis. The median age of the 48 children was 2 years (IQR 1.3, 5.3); 19 (40%) were female. Fever was documented in 45 (94%) children. The most common prodromal symptoms were upper respiratory illness (23; 48%) followed by vomiting (11; 22%), and diarrhea (9; 19%). A diagnosis of pneumonia was made in 24 (50%). Hepatitis and coagulopathy developed during hospitalization in 19 (40%) and 7 (15%) children, respectively. Seven

Table III. Univariate and multivariable analysis of neurologic impairment or death in children with adenovirus-associated CNS disease (excluding children with febrile seizures)

Characteristics	Neurologic impairment or died	Full recovery	Crude		Adjusted*	
			P value	OR (95% CI)	*P* value	OR (95% CI)
Total (%)	18 (38)	30 (62)				
Age in y, median (IQR)	1.5 (1, 2)	2.7 (1.4, 6)	**.025**	—	.26	0.99 (0.97-1.01)
Female, n (%)†	5 (29)	14 (47)	.25	0.48 (0.13-1.69)		
Fever, n (%)†	16 (89)	29 (97)	.55	0.28 (0.02-3.28)		
Lower RTI, n (%)	8 (44)	16 (53)	.55	0.70 (0.21-2.26)		
Vomiting, n (%)†	2 (11)	9 (30)	.17	0.29 (0.06-1.54)		
Diarrhea, n (%)†	5 (28)	4 (13)	.27	2.5 (0.57-10.91)		
Hepatitis, n (%)†	8 (44)	11 (37)	.59	1.38 (0.42-4.54)		
Coagulopathy, n (%)	6 (33)	1 (3)	**<.01**	14.50 (1.57-133.68)	.20	4.95 (0.43-57.37)
Upper RTI, n (%)†	9 (50)	14 (47)	.82	1.14 (0.35-3.68)		
Meningismus, n (%)	0	9 (30)	**.02**	††		
Decreased LOC, n (%)	16 (89)	27 (90)	1.0	0.89 (0.13-5.90)		
Seizures, n (%)	13 (72)	6 (20)	**<.01**	10.40 (2.66-40.74)	**.01**	7.30 (1.69-31.45)
Focal neurologic findings, n (%)	3 (17)	3 (10)	.66	1.80 (0.32-10.05)		
CSF WBC ($\times 10^6$/L), median (IQR)‡	6 (0, 18)	0 (0, 17)	.47	—		
Abnormal EEG, n (%)§	10 (90)	17 (89)	1.0	1.18 (0.09-14.69)		
Abnormal imaging, n (%)¶	7 (100)	3 (60)	.15	††		
Respiratory AV detection, n (%)†	15 (88)	21 (70)	.28	3.2 (0.61-17.06)		
Stool AV detection, n (%)†	6 (35)	17 (57)	.16	0.41 (0.12-1.43)		
CSF or brain AV detection, n (%)†	4 (24)	3 (10)	.23	2.77 (0.54-14.23)		
Serotype 2, n (%)**	3 (17)	0	.05	††		
Serotype 3, n (%)	1 (6)	6 (20)	.23	0.23 (0.03-2.14)		
Serotype 7, n (%)	8 (44)	11 (37)	.59	1.38 (0.42-4.54)		

AV, adenovirus; *RTI*, respiratory tract infection.
Statistically significance results bolded if $P < .05$.
*To satisfy model convergence criteria only age, coagulopathy, and seizures could be included in the model. Model fit evaluated by Hosmer and Lemeshow test $P = .24$.
†1 missing.
‡CSF not obtained in 8 patients.
§18 EEG results not reported or performed.
¶36 imaging results not reported or performed.
**Other serotypes included: 12 (n = 2), 11 (n = 1), 6 (n = 1), 5 (n = 1).
††Unable to calculate ORs because of cells containing zero.

(15%) of the cases had isolation or detection of the virus in CSF or brain tissue.

Ten of the 48 (21%) died and 8 (17%) suffered permanent neurologic impairment, including 5 of the 8 cases of encephalitis from our institution. In univariate analysis, children who either died or suffered neurologic impairment were younger and were more likely to have coagulopathy and seizures than those who survived without sequelae (**Table III**). In the multivariable logistic regression model including age, seizure, and coagulopathy, only seizure remained significantly associated with a poor outcome (**Table III**).

A serotype was identified in 35 (73%) of the cases; 33 from the literature and 2 from our encephalitis registry (**Table III**). Serotype 7 was the most commonly reported serotype, followed by serotype 3, then serotype 2. Serotype 3 was more commonly associated with transient encephalopathy and milder disease, and serotype 2 was associated with severe encephalitis and poor outcome. Other serotypes reported in the literature included 2 cases of type 12, and 1 case each of types 11, 5, 6, and C.

Discussion

We combined 21 years of data from our institution and the literature to summarize the available evidence of adenovirus-associated CNS disease in children. The findings from our institution indicate a febrile (predominantly complex) seizure incidence of 3.3% and an encephalitis incidence of 0.4% among children with microbiologically confirmed adenovirus infection. The rate of neurologic complications among hospitalized children in our series is similar to the 3.3% observed in a large Taiwanese study.[7] The overall incidence of neurologic complications, however, is likely much lower, given that only a small proportion of children with adenovirus infections are hospitalized or seen in hospital emergency departments. Our Encephalitis Registry data suggest that 1.9% of childhood encephalitis is attributable to adenovirus, which is less than the 5% observed in a Finish study.[4] The observation that only 1 case of adenovirus meningitis was seen in our institution could have been due to adenovirus being a truly rare cause of meningitis, or a consequence of underdiagnosis, as testing for adenovirus would not routinely be performed for children with uncomplicated aseptic meningitis.

The combined results from our institution and the literature review suggest a spectrum of adenovirus CNS disease ranging from what has been labeled as a severe form of encephalitis at one end to a transient infection-associated encephalopathy, meningitis, and complex febrile seizures at the other. These findings are mirrored by the Taiwanese series in which the most common diagnoses were febrile seizure (48%),

encephalitis (26%), afebrile seizure (11%), and meningitis (8%).[7]

Most children with adenovirus-associated CNS disease do not have adenovirus detected in the CSF. This is exemplified by most children with a diagnosis of encephalitis from our institution, in whom adenovirus was detected in the respiratory or gastrointestinal tract but not the CSF. These cases also had indirect evidence of brain inflammation in the form of CSF pleocytosis or increased T2-weighted-fluid-attenuated inversion recovery (T2/FLAIR) signal of the brain parenchyma. The cases described by Straussberg et al as transient encephalopathy fulfill the encephalitis diagnostic criteria of both the SickKids Encephalitis Registry and the California Encephalitis Project.[3,5,8] Thus, it is often not possible to clearly distinguish encephalitis from infection-associated encephalopathy based on clinical criteria alone. The consensus statement of the International Encephalitis Consortium suggests a single set of diagnostic criteria for encephalitis and infection-associated encephalopathy.[25]

The presence of a classic encephalitis secondary to direct infection of the brain parenchyma is supported by the detection of the virus from CSF or brain tissue in 15% of those in our review and a mouse model showing certain adenovirus strains to be more neurotropic than others.[26] The possibility of a parainfectious pathogenesis is supported by brain pathology findings in 3 fatal cases of adenovirus type 7 that demonstrated diffuse cortical neuronal depletion and necrosis and detection of the virus in respiratory tract but not the CNS.[13] The authors postulated a toxic effect of the adenovirus penton antigen, a component of the viral capsid antigen known to be toxic to cells in tissue culture, or immunopathologic injury secondary to circulating antigen-antibody complexes. A mouse model of adenovirus encephalomyelitis demonstrating T-lymphocyte mediated perivascular edema, vascular wall degeneration and small numbers of inflammatory cells in the brain, suggests T-lymphocyte mediated immunopathology as a mechanism of brain injury.[21] The significance of the detection of adenovirus in the CSF of one of our cases is intriguing, but as blood was present in the CSF we cannot be certain that the result reflected presence of the organism in the CSF. It is important to keep in mind that the analytical sensitivity of various PCR assays for adenovirus differs, and some may not achieve the sensitivity necessary to detect all serotypes of the virus in CSF. This may be particularly relevant for older reports.

The strongest predictor of adverse outcome for the pooled cohort of adenovirus-associated CNS disease was seizures, followed by coagulopathy and younger age (**Table III**). It is noteworthy that most children who suffered neurologic sequelae were less than 2 years of age. It was not possible to reliably assess whether specific neuroimaging abnormalities were predictive of adverse outcome, as only a minority of the 48 children underwent neuroimaging. Among adenovirus-associated encephalitis cases at SickKids, 5 of the 6 children with neuroimaging abnormalities suffered neurologic sequelae, whereas those with normal neuroimaging made full recoveries. Meningismus was predictive of good outcome in the cohort as a whole, indicating that adenovirus meningitis is usually a benign condition in immunocompetent children.

It is noteworthy that 92.3% of adenovirus-associated febrile seizures identified through the SickKids Microbiology Database were classified as complex, and that 61.5% of affected children presented with status epilepticus requiring admission to the intensive care unit. However, the extent to which these findings reflect a propensity of adenovirus towards complex febrile seizures is uncertain due the higher probability of microbiologic investigations being performed in those with more severe disease at presentation. Thus, it is likely that many children with simple febrile convulsions associated with adenovirus infection could go undiagnosed as microbiologic testing would not be done.

The propensity for specific adenovirus serotypes to cause CNS disease is unknown and because of the small number of cases, overall firm conclusions cannot be drawn from this review. It is noteworthy, however, that serotype 7 was implicated in 19 (56%) children with CNS disease in whom serotype testing was performed.[11,13,18] Death or neurologic sequelae occurred in 40% of these children. Serotype 3 was implicated in 7 cases (21%), 6 of whom made full recoveries. Serotype 2 was found in 2 of our cases of severe necrotizing encephalopathy, and in 1 case from Japan of a 19-month-old boy with severe acute cerebral edema.[14] All 3 suffered adverse outcomes.

This study had several limitations. With respect to the retrospective data obtained from the SickKids Microbiology Database, the reasons for adenovirus testing in children without encephalitis were at the discretion of the treating physician and were likely influenced by severity of illness and degree of respiratory or gastrointestinal symptoms. Thus, it is likely, that mild forms of disease such as aseptic meningitis went undiagnosed. With respect to the literature review, there is an expected reporting bias skewing the results to a more severe spectrum and some studies had important patient data missing. Combining our data with those from the literature may have introduced some bias, but given the rarity of the condition we believed this was the most informative strategy. A related limitation was that individual patient data was not available in some relevant publications, precluding their inclusion in the statistical analysis. In addition, exposure of patients to potentially relevant medications, such as aspirin or nonsteroidal anti-inflammatory agents, was not known. Strengths of this study include the thoroughness of the literature review and the prospective nature of the SickKids Encephalitis Registry and comprehensive microbiology testing performed in patients with encephalitis.

In conclusion, adenovirus is a rare cause of CNS disease in immunocompetent children. Disease spectrum is highly variable, ranging from mild aspetic meningitis and fully reversible encephalopathy to severe, potentially fatal, acute necrotizing encephalopathy. Seizures (excluding febrile seizures), coagulopathy, and younger age are associated with adverse outcome. ■

We wish to thank Suganya Lee, the research coordinator for the SickKids Encephalitis Registry for her hard work and dedication.

Submitted for publication Jun 5, 2018; last revision received Aug 28, 2018; accepted Sep 12, 2018

Reprint requests: Ari Bitnun, MD, MSc, Division of Infectious Diseases, The Hospital for Sick Children, Rm 7301, 555 University Ave, Toronto, ON M5G 1X8, Canada. E-mail: ari.bitnun@sickkids.ca

References

1. Granerod J, Cunningham R, Zuckerman M, Mutton K, Davies NW, Walsh AL, et al. Causality in acute encephalitis: defining aetiologies. Epidemiol Infect 2010;138:783-800.
2. Mailles A, Stahl J-P, Committee botS, Group tI. Infectious encephalitis in France in 2007: a National Prospective Study. Clin Infect Dis 2009;49:1838-47.
3. Glaser CA, Honarmand S, Anderson LJ, Schnurr DP, Forghani B, Cossen CK, et al. Beyond viruses: clinical profiles and etiologies associated with encephalitis. Clin Infect Dis 2006;43:1565-77.
4. Koskiniemi M, Korppi M, Mustonen K, Rantala H, Muttilainen M, Herrgård E, et al. Epidemiology of encephalitis in children. A prospective multicentre study. Eur J Pediatr 1997;156:541-5.
5. Straussberg R, Harel L, Levy Y, Amir J. A syndrome of transient encephalopathy associated with adenovirus infection. Pediatrics 2001;107:E69.
6. Kelsey DS. Adenovirus meningoencephalitis. Pediatrics 1978;61:291-3.
7. Huang Y-C, Huang S-L, Chen S-P, Huang Y-L, Huang C-G, Tsao K-C, et al. Adenovirus infection associated with central nervous system dysfunction in children. J Clin Virol 2013;57:300-4.
8. Kolski H, Ford-Jones EL, Richardson S, Petric M, Nelson S, Jamieson F, et al. Etiology of acute childhood encephalitis at The Hospital for Sick Children, Toronto, 1994-1995. Clin Infect Dis 1998;26:398-409.
9. Amin R, Ford-Jones E, Richardson SE, MacGregor D, Tellier R, Heurter H, et al. Acute childhood encephalitis and encephalopathy associated with influenza: a prospective 11-year review. Pediatr Infect Dis J 2008;27:390-5.
10. Sarantis H, Johnson G, Brown M, Petric M, Tellier R. Comprehensive detection and serotyping of human adenoviruses by PCR and sequencing. J Clin Microbiol 2004;42:3963-9.
11. Gabrielson MO, Joseph C, Hsiung GD. Encephalitis associated with adenovirus type 7 occurring in a family outbreak. J Pediatr 1966;68:142-4.
12. Simila S, Jouppila R, Salmi A, Pohjonen R. Encephaloningitis in children associated with an adenovirus type 7 epidemic. Acta Paediatr Scand 1970;59:310-6.
13. Ladisch S, Lovejoy FH, Hierholzer JC, Oxman MN, Strieder D, Vawter GF, et al. Extrapulmonary manifestations of adenovirus type 7 pneumonia simulating Reye syndrome and the possible role of an adenovirus toxin. J Pediatr 1979;95:348-55.
14. Nikaido K, Doi T, Takayama R, Kobayashi T, Oka T, Tsutsumi H. Near-fatal cerebral edema associated with adenovirus type 2 infection in a previously healthy infant. Scand J Infect Dis 2004;36:701-3.
15. Pereira MS, Maccallum FO. Infection with adenovirus type 12. Lancet 1964;1:198-9.
16. Chatterjee NK, Samsonoff WA, Balasubramaniam N, Rush-Wilson K, Spargo W, Church TM. Isolation and characterization of adenovirus 5 from the brain of an infant with fatal cerebral edema. Clin Infect Dis 2000;31:830-3.
17. Chuang Y, Chiu CH, Wong KS, Huang JG, Huang YC, Chang LY, et al. Severe adenovirus infection in children. J Microbiol Immunol Infect 2003;36:37-40.
18. Sutton RN, Pullen HJ, Blackledge P, Brown EH, Sinclair L, Swift PN. Adenovirus type 7; 1971-74. Lancet 1976;2:987-91.
19. Krous HF, Chadwick AE, Miller DC, Crandall L, Kinney HC. Sudden death in toddlers with viral meningitis, massive cerebral edema, and neurogenic pulmonary edema and hemorrhage: report of two cases. Pediatr Dev Pathol 2007;10:463-9.
20. Huttunen L. Adenovirus type 7—associated encephalitis. Scand J Infect Dis 1970;2:151-3.
21. Chany C, Lepine P, Lelong M, Le TV, Satge P, Virat J. Severe and fatal pneumonia in infants and young children associated with adenovirus infections. Am J Hyg 1958;67:367-78.
22. Brendish NJ, Williams S, Faust SN, Tebruegge M. Respiratory tract infection associated with seizures. BMJ 2015;351:h4659.
23. Chen WX, Liu HS, Yang SD, Zeng SH, Gao YY, Du ZH, et al. Reversible splenial lesion syndrome in children: retrospective study and summary of case series. Brain Dev 2016;38:915-27.
24. Reyes-Andrade J, Sanchez-Cespedes J, Olbrich P, Falcon L, Sanchez-Ganfornina I, Tebruegge M, et al. Meningoencephalitis due to adenovirus in a healthy infant mimicking severe bacterial sepsis. Pediatr Infect Dis J 2014;33:416-9.
25. Venkatesan A, Tunkel AR, Bloch KC, Lauring AS, Sejvar J, Bitnun A, et al. Case definitions, diagnostic algorithms, and priorities in encephalitis: consensus statement of the international encephalitis consortium. Clin Infect Dis 2013;57:1114-28.
26. Guida JD, Fejer G, Pirofski LA, Brosnan CF, Horwitz MS. Mouse adenovirus type 1 causes a fatal hemorrhagic encephalomyelitis in adult C57BL/6 but not BALB/c mice. J Virol 1995;69:7674-81.