

Background. Many neurologic syndromes are underpinned by infectious etiologies that are difficult to diagnose. Broad-range, universal PCR (uPCR), and metagenomic next-generation sequencing (mNGS) are emerging molecular techniques that may allow for enhanced pathogen detection in challenging cases. To date, their comparative clinical utility for pathogen detection in cerebrospinal fluid (CSF) has not been described.

Methods. We searched the electronic medical record at University of California, San Francisco for all patients who had mNGS and uPCR results available from the same CSF specimen. Using all available clinical information, patients' clinical episodes were categorized into one of four categories: (1) confirmed central nervous system (CNS) infection, (2) likely CNS infection, (3) confirmed/likely noninfectious etiology, (4) unknown etiology. We also determined whether mNGS and/or uPCR results changed clinical management.

Results. We identified 75 patients with 78 paired mNGS and uPCR results on CSF. 14/78 (17.9%) had a confirmed CNS infection underpinning their clinical presentation, 11 (14.1%) had a likely CNS infection, 33 (42.3%) had a likely noninfectious cause, and 20 (25.6%) had etiologies that could not be determined. Of the 14 patients with confirmed CNS infection, $n = 4$ (28.6%) were diagnosed by mNGS and $n = 1$ (7.1%) by uPCR (Table 1). Most diagnoses missed by mNGS and uPCR were made by CSF serology or from sites other than CSF. Overall, mNGS detected a pathogen in $n = 10/78$ (12.8%) cases, compared with $n = 4/78$ (5.1%) using uPCR (Table 2). Among those with a positive mNGS result, $n = 6/10$ represented a true or likely true positive result, while the remaining were likely contaminants. Of those with a positive uPCR result, $n = 1/4$ represented a true positive result, while $n = 3/4$ were likely contaminants. Clinical management was changed by the mNGS or uPCR result in two cases (Table 2).

Conclusion. mNGS appears to have superior clinical utility to that of universal PCR for pathogen detection in CSF samples, in large part because of additional ability to detect DNA and RNA viruses. Further studies are required to determine the clinical contexts in which mNGS is likely to have maximal diagnostic yield and to better define the utility of uPCR for CNS infections.

Table 1. Overview of cerebrospinal fluid mNGS and uPCR results in patients with a confirmed central nervous system infection (n=14)

#	Age	Sex	Presentation	CSF profile	CSF culture results	CSF mNGS result	CSF uPCR result	Additional positive CNS microbiology	Final diagnosis	How was diagnosis made?	Why was diagnosis missed?
1	50	F	Acute left-sided hemiparesis	WBC 1, protein 315, glucose 39	Bact/AFB/Fung neg	Neg	Neg	Candida albicans on fungal culture (brain biopsy)	Candida albicans brain abscess and arachnoiditis	Bacterial culture (brain biopsy)	Diagnosis by non-CSF (brain tissue)
2	31	F	Progressive headache	WBC 350 (52% lymph), protein 60, glucose 41	AFB/Fung neg	Neg	Neg	Cladophialophora bantiana on fungal culture and uPCR (brain biopsy)	Cladophialophora bantiana meningitis-encephalitis	uPCR (brain biopsy)	Diagnosis by non-CSF (brain tissue)
3	32	F	Progressive headache, incidental brain lesion	WBC 7 (96% lymph), protein 97, glucose 42	Propionibacterium sp. on bacterial culture	Neg	Neg	Staphylococcus epidermidis on bacterial culture (VP shunt)	Propionibacterium acnes, Staphylococcus epidermidis VP shunt infection	Bacterial culture (CSF)	CSF-based diagnosis (True miss)
4	54	F	Acute febrile illness with progressive weakness	WBC 112 (88% lymph), protein 55, glucose 53	Bact/Fung neg	West Nile virus	Neg	West Nile Virus-specific PCR (CSF)	West Nile virus	mNGS (CSF)	N/A
5	2	M	New seizure disorder	WBC 4 protein 45, glucose 68	Bact/AFB/Fung neg	Neg	Neg	Streptococcus pyogenes on bacterial culture (brain biopsy)	Streptococcus pyogenes brain abscess	uPCR (brain biopsy)	Diagnosis by non-CSF (brain tissue)
6	2	M	Daily fevers, gait ataxia	WBC 92 (47% lymph), protein 55, glucose 42	Bact/AFB/Fung neg	Neg	Neg	CSF Coxsackievirus complement fixation (titre: 1:32)	Coccidioides meningitis	Coccidioides complement fixation (CSF+serum)	Diagnosis by CSF serology
7	41	M	New seizure disorder, hydrocephalus	WBC 47 (87% lymph), protein 96, glucose 57	Bact/AFB/Fung neg	Neg	Neg	CSF cytotoxicity IgG by ILSA and immunoblot	Neurocysticercosis	Cysticercosis immunoblot (CSF)	Diagnosis by CSF serology
8	82	M	Acute fevers, chills, emesis, MRI with brain lesion, pulmonary cavitation on chest CT	WBC 47 (53% PMN), protein 203, glucose 39	Bact/AFB/Fung neg	Nocardia farcinica, Cytomegalovirus	Nocardia farcinica	N/A	Nocardia brain abscess	uPCR and mNGS (CSF)	N/A
9	35.6	M	Progressive left hand weakness	WBC 1, protein 35, glucose 49	None	JC virus + Epstein-Barr virus, Human	Neg	JC virus-specific PCR (CSF)	Progressive multifocal leukoencephalopathy	JC virus-specific PCR (CSF)	N/A

Table 2. Overview of clinical cases in which mNGS or uPCR was positive on cerebrospinal fluid

#	Age	Sex	Presentation	CSF culture results	CSF mNGS result	CSF uPCR result	Additional positive CNS microbiology	Final Diagnosis	How was diagnosis made?	mNGS Classification	uPCR Classification	Did mNGS or uPCR change management?
mNGS and uPCR positive for same organism												
1	82	M	Acute fevers, chills, emesis, MRI with brain lesion, pulmonary cavitation on chest CT	Bact/AFB/Fung neg	Nocardia farcinica, Cytomegalovirus	Nocardia farcinica	N/A	Nocardia brain abscess	uPCR and mNGS (CSF)	True positive (confirms diagnosis)	True positive (makes diagnosis)	Yes - stopped empiric, tuberculosis therapy and tailored antibiotic therapy after uPCR result
mNGS and uPCR positive for different organisms												
2	6	M	Encephalopathy, acute retinal necrosis	Bact/AFB/Fung neg	Bacteroides spp., Mycoplasma spp.	Aspergillus spp (not fumigatus)	VZV-specific PCR (CSF)	VZV meningitis w/focal involvement	Vancomycin-resistant zoster virus-specific PCR (CSF)	MW polymerase virus - a likely true positive (confirm clinical significance?)	Likely contaminant	No
3	72	F	Focal status epilepticus	None	Staphylococcus epidermidis	Eurotium sp.	N/A	Unknown	N/A	Likely contaminant	Likely contaminant	No
4	23	F	Recurrent encephalopathy	Bact neg	Staphylococcus saprophyticus, Corynebacterium, Acinetobacter, Streptococcus, Klebsiella, Bifidobacterium, Shewanella, and Micrococcus	Rhizobacter spp.	N/A	Unknown	N/A	Likely contaminant	Likely contaminant	No
mNGS positive only												
5	36	M	Sub-acute, progressive left-hand weakness	N/A	JC virus + Epstein-Barr virus, Human immunodeficiency virus (HIV)	Neg	JC virus on CSF PCR	Progressive multifocal leukoencephalopathy	JC virus-specific PCR (CSF)	True positive (confirms diagnosis)	N/A	No

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237. Adenovirus Types in Children with Acute Respiratory Illnesses in Nashville Over Two Respiratory Seasons

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Background. Human adenovirus (HAdV) types 1–7, 11, 14, 16, and 21 within species B, C, and E are commonly associated with acute respiratory illnesses (ARI) in children. We sought to compare demographics, clinical characteristics, and outcomes of HAdV types with children who presented with fever and/or respiratory symptoms.

Methods. Children < 18 years with fever and/or ARI seen at Vanderbilt Children's Hospital inpatient and emergency department settings from December of 2016 to October of 2018 were enrolled. Interviews and chart abstraction were conducted. Mid-turbinate nose and throat swab specimens were collected and tested by real-time RT-PCR for common respiratory viruses including HAdV. HAdV molecular typing was performed by type-specific real-time PCR assays for types 1–7, 11, 14, 16, and 21 targeting the hexon gene using published methods.

Results. Of 5111 ARI cases, 206 (4%) were HAdV-positive with a median age of 16 months (IQR 9–30); 57% male, 47% White, 40% Black, 33% Hispanic, 20% admitted, and 24% of hospitalized required oxygen support. Of the 206, 186 (90%) were able to be typed with more than one type detected in 13 (7%) cases. Distribution of HAdV types among single detections ($n = 173$) is shown in Figure 1; HAdV-1 and HAdV-2 were most common. Children with HAdV-2 were younger (median age 12 months vs. 15 months (HAdV-1) and 59 months (all other types), $P < 0.001$), and those with HAdV-1 were less likely to be male (44% vs. 65% for both HAdV-2 and other types, $P = 0.029$). Figure 2 displays HAdV detections over time, with winter and early spring peaks. Co-detection with other respiratory viruses occurred in 47% of cases; the most common among typable HAdV were rhinovirus/enterovirus in 30/186 (16%) and RSV in 19/186 (10%). Distribution among HAdV types is shown in Figure 3.

Conclusion. HAdV-1 and HAdV-2 were more prevalent than other HAdV types over two respiratory seasons in the Nashville area with peak cases in December-March. Children with HAdV-1 and HAdV-2 had some demographic differences. Further studies with a larger sample size for HAdV typing are needed in the pediatric population to determine whether additional clinically-relevant differences between HAdV types exist.

Figure 1. Distribution of HAdV Types Among Single Detections

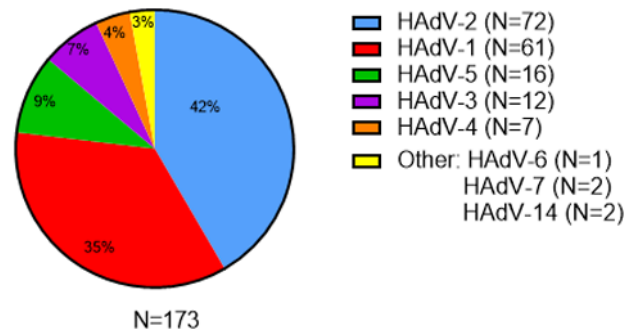


Figure 2. HAdV Type Detections by Month of Onset

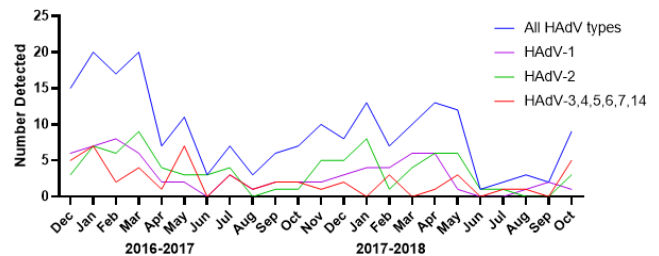
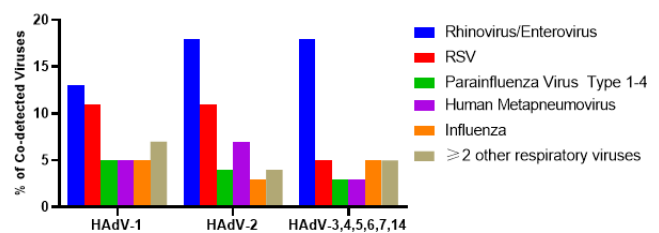


Figure 3. Co-detections of Other Respiratory Viruses Among HAdV Types



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