Etiologies in a Cohort of Pediatric Patients Who Underwent CSF Metagenomic Next Generation Sequencing

Molly Wilson-Murphy, MD[1,2]; Gabriella S. Lamb, MD, MPH[2,3]; Asim A. Ahmed, MD[2,3]; Mark Gorman, MD[1,2]

1. Neuro-immunology Program, Department of Neurology, Boston Children's Hospital, Boston, MA; 2. Harvard Medical School, Boston, MA; 3. Division of Infectious Disease, Department of Pediatrics, Boston Children's Hospital, Boston, MA

Email: molly.wilson-murphy@childrens.harvard.edu
Phone: 857-218-4794

BACKGROUND

- Differential diagnosis for pediatric patients with central nervous system infections and autoimmune disease is broad.
- Even with advances in diagnostic testing, many patients remain undiagnosed.
  - Approximately 50% of pediatric patients with encephalitis do not have an identified etiology.
- Use of CSF metagenomic next generation sequencing (mNGS) may improve diagnostic yield.

METHODS

Design: Retrospective cohort study I
Inclusion Criteria: Pediatric patients (<21yo) hospitalized at a tertiary care center who underwent CSF mNGS.
Study Period: June 2017-February 2020.
Final Diagnosis: Assigned by two independent physician reviewers
- Pediatric Neurologist
- Pediatric Infectious Disease Doctor

Data abstraction: Boston Children's Hospital medical records

RESULTS

- Of 37 children evaluated, 26 (70%) had a diagnosis
  - 10 (27%) infectious – 4 of 10 (40%) infectious diagnoses were made by mNGS
  - 11 (30%) autoimmune/inflammatory
  - 5 (14%) other
- Eight (22%) had a positive result on CSF mNGS
  - Result was clinically significant in 7, diagnostic in 4
  - Result changed management in 5 (including one with a negative result)
- mNGS resulted mean 21.6 days (range 9-107) into stay & was often sent on a subsequent LP or as an add on
- Anti MOG antibody associated meningoencephalitis was single most common etiology (n=4; 11%)
- Powassan virus encephalitis was most common infectious etiology (n=3, 8%)
- Other infections:
  - Diagnosed via mNGS: EBV, rubella
  - Diagnosed via conventional testing: Lyme, EEE

RESULTS

Table 1: Demographics, diagnostics, therapeutics & outcomes (n=37)

Category	Variable	
Demographics	Age in years median (range)	9 (1-17)
	Female N (%)	23 (61%)
Diagnostics	LPs median (range)	1 (0-7)*
	MRIs median (range)	2 (0-9)*
Therapeutics	Antimicrobials N (%)	32 (86%)
	Immunotherapy N (%)	33 (89%)
Outcome	Recovered	11 (30%)
	Residual deficits	20 (54%)
	Deceased	2 (5%)
	Unknown	4 (11%)

*Multiple patients with LPs & MRI at outside facilities

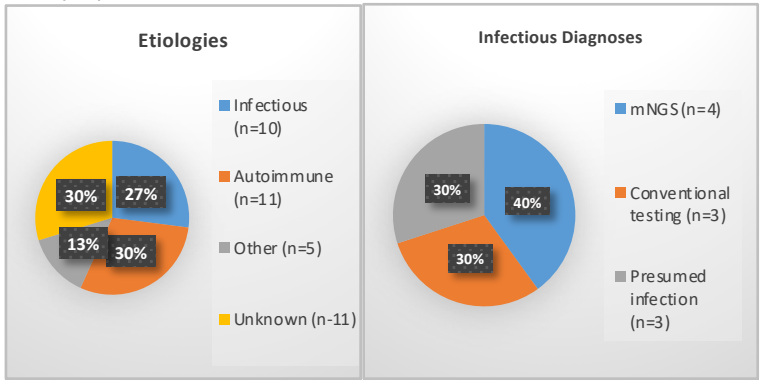

Figure 1a. Etiologies **Figure 1b.** Infectious Diagnoses **Figure 1c.** Mean Time to infectious diagnosis

Table 2: Patients with Positive CSF mNGS

Patient age & sex	mNGS	Conventional testing	Diagnosis	mNGS changed management
5 yo M	Powassan	Confirmed with serum serology after mNGS resulted	Powassan virus encephalitis	No further immunotherapy
17 yo M	Multiple bacterial genera found in soil & sludge (likely contaminant)		Presumed inflammatory internal capsule lesion vs tumor	
1.5 yo M	Rubella, HHV7, EBV	Confirmed: CSF Rubella PCR, NP Rubella PCR; CSF EBV PCR negative	CNS Rubella (vaccine strain) +/- EBV driven PTLD	Added weekly IVIg for rubella. (Already on EBV specific cytotoxic T cells for PTLD.)
4 yo F	HSV1	CSF HSV1/2 PCR negative	Orbital Inflammation (Infectious vs Autoimmune)	No – clinically felt not consistent with HSV
3 yo M	EBV	CSF EBV PCR positive (prior LP)	EBV driven PTLD vs fungal infection	Rituximab given
9 yo M	BK virus		Myelitis – infectious vs autoimmune	
11 yo F	Powassan	Confirmed with serum IgM after mNGS resulted	Powassan virus meningo-encephalo-myelitis	No further workup or treatment
11 to F	HSV1	CSF HSV1/2 PCR negative	Unknown – possible ingestion	No – clinically felt not consistent with HSV

CONCLUSIONS

- CSF mNGS provided a definitive infectious diagnosis in more cases than conventional testing in this cohort.
- Like conventional testing, CSF mNGS must be taken into clinical context; it was diagnostic in half of cases with a positive result.
- CSF mNGS has the potential to directly impact management, even when negative.
- Broad testing with a combination of CSF mNGS and conventional testing including for autoimmune etiologies may result in fewer undiagnosed patients (30% in this cohort vs about 50% typically in the literature).

ACKNOWLEDGMENTS

We would like to thank our colleagues at the Harvard Catalyst for their assistance with ongoing analysis.