

Neurotropic Astrovirus VA Strain Detected by CSF Metagenomic Sequencing in Immunocompromised Hosts: A Multicenter Case Series



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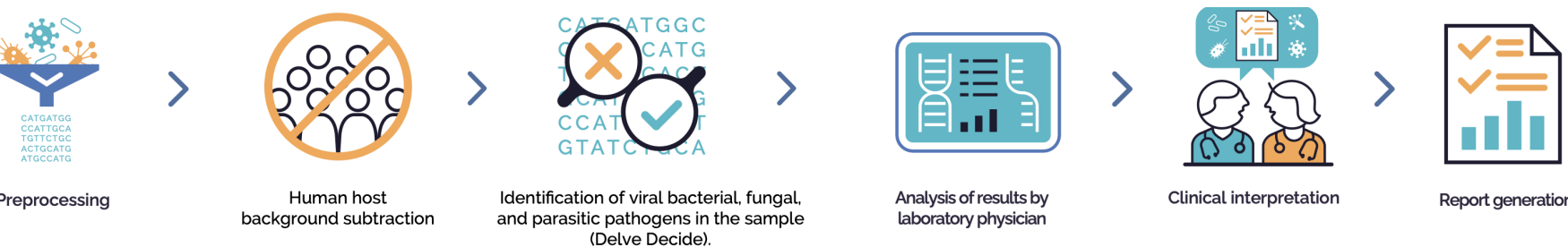
Background & Objectives

- Background**
- Human astroviruses typically cause gastroenteritis, but HASTV-VA1, a divergent neurotropic strain, can cause severe CNS infection in immunocompromised hosts.
 - These strains are not routinely detected by conventional CSF or GI PCR panels.
 - Their clinical significance, optimal treatment, and outcomes remain poorly defined.
- Objectives**
- Characterize the clinical spectrum, immune risk factors, treatments, and outcomes of HASTV-VA1 cases.
 - Assess the diagnostic and clinical implications of CSF mNGS detection.

Methods

- Multicenter case series across 5 U.S. centers
- Cases identified through Delve clinical consultation program (Clinical Microbial Sequencing Board)
- Clinical data obtained via retrospective chart review
- CSF mNGS: ≥10 million reads per sample, analyzed against a curated microbial database

Pathogen Detection Through mNGS



Curated Pathogen Database

Filtered from NCBI NT for CNS-relevant organisms

Deduplicated, high-quality references

>68000 organisms

Bacteria

>26,000 species

Viruses

>10,000 species

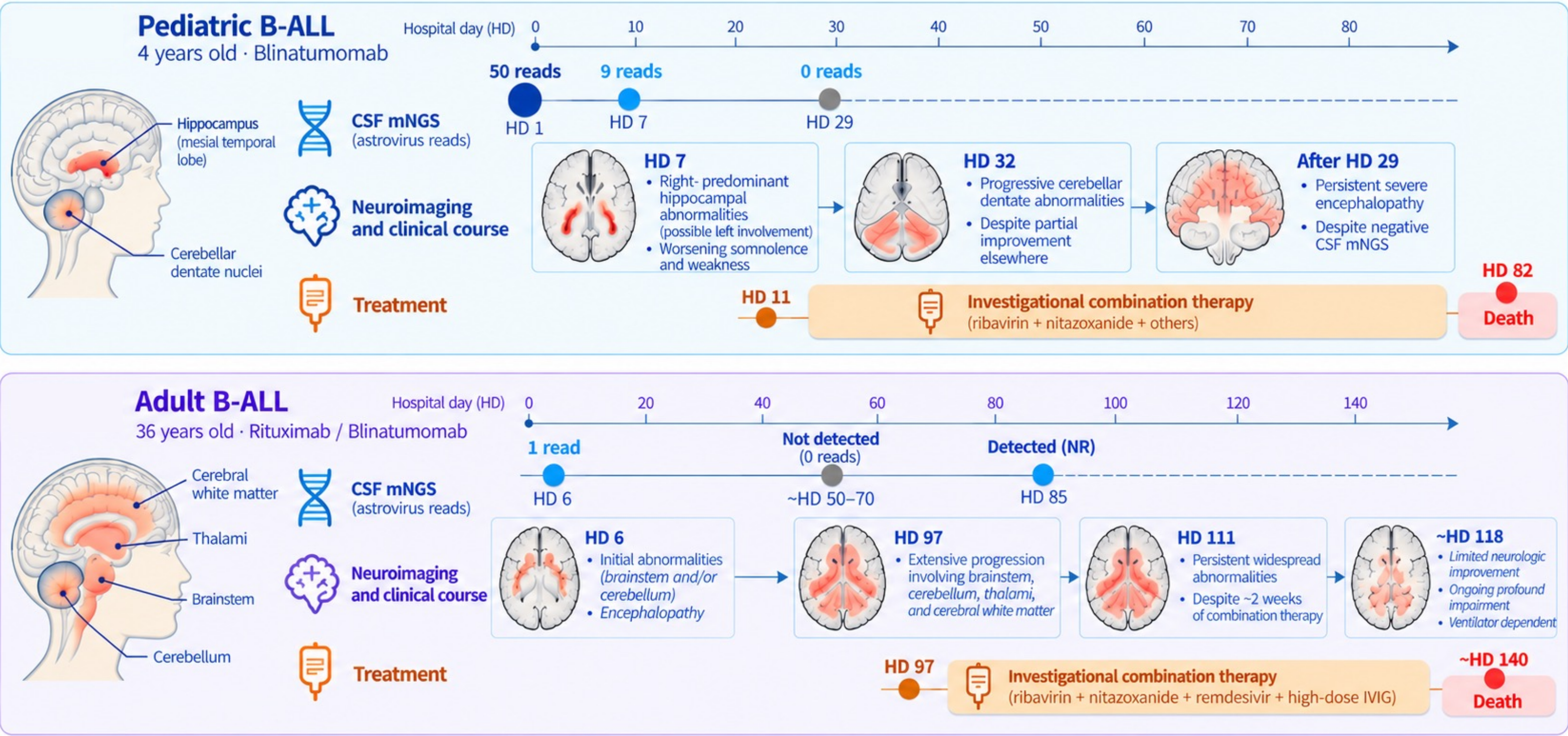
Fungi

>16,000 species

Parasites

>15,000 species

Longitudinal Clinical Timelines in Two Fatal Cases of HASTV-VA1



Case Histories, Treatment & Outcomes

CASE	CLINICAL PRESENTATION	mNGS READS	MANAGEMENT	OUTCOME
Case 1 4y M B-ALL	Progressive encephalitis; neurologic deterioration	50→9→0	IVIG; ribavirin; nitazoxanide; peginterferon alfa-2a	Fatal; CSF read clearance without clinical recovery
Case 2 2y F B-ALL	Fever, somnolence, later seizures and progressive WM changes; CSF GBS PCR+	49	Cefepime for possible GBS meningitis; IVIG; corticosteroids for suspected inflammation	Survived; role of astrovirus uncertain
Case 3 4y M B-ALL	Progressive encephalopathy; CN/dentate MRI findings	2→0→0	IVIG; ribavirin; nitazoxanide; remdesivir; PLEX; virus-specific CTLs	Survived with residual deficits; improving
Case 4 36y M B-ALL	Severe progressive encephalitis w/ extensive neuro deficits	1 initially; later pos. at UCSF	IVIG; ribavirin; nitazoxanide; remdesivir	Fatal
Case 5 63y F MM	Acute bilateral retrobulbar optic neuropathy	4→0	No astrovirus-directed therapy	Survived; clinical significance uncertain

B-ALL, B-cell acute lymphoblastic leukemia; MM, multiple myeloma; GBS, group B Streptococcus; IVIG, intravenous immunoglobulin; PLEX, plasma exchange; CTLs, cytotoxic T lymphocytes.

Host Immune Profiles

UNDERLYING CONDITION	IMMUNE-MODIFYING THERAPIES	IMMUNE FINDINGS
B-ALL	Blinatumomab	IgG 41 mg/dL; B-cell aplasia
B-ALL	CD19 CAR-T; αβ T-cell-depleted allogeneic HCT	CD19 ⁺ cells 1/μL; IgG 315 mg/dL
B-ALL	Haploidentical αβ T-cell-depleted allogeneic HCT	CD4 ⁺ cells 123/μL; IgG ~1,000 mg/dL
B-ALL	Rituximab; blinatumomab	Hypogammaglobulinemia
Multiple myeloma	Prior autologous HCT; CAR-T; elranatamab	IgG 376 mg/dL

B-ALL, B-cell acute lymphoblastic leukemia; CAR-T, chimeric antigen receptor T-cell therapy; HCT, hematopoietic cell transplantation. Immune parameters were obtained at different times and may not coincide with CSF mNGS sampling.

Clinical Implications

- Consider neurotropic HASTV-VA1 in immunocompromised patients with unexplained neurologic syndromes.
- Routine CSF and gastrointestinal PCR panels do not detect divergent astrovirus strains.
- Low-level or intermittent CSF mNGS detection requires interpretation in the context of immune status, neurologic findings, and alternative diagnoses.
- No established antiviral regimen exists; treatment remains individualized and investigational.

Conclusions

- CSF mNGS identified HASTV-VA1 across five immunocompromised patients with heterogeneous neurologic presentations and outcomes.
- Two patients experienced fatal progressive encephalitis despite investigational combination therapy.
- CSF mNGS enables detection of uncommon neurotropic viruses that may be missed by conventional diagnostics, providing critical insights into challenging CNS infections and informing clinical management.