HUMAN ASTROVIRUS VA1 ENCEPHALITIS IN PEDIATRIC CANCER PATIENTS: REPORT OF TWO CASES AND REVIEW OF THE LITERATURE

Sakshi Bami[1], Jennifer Hidinger[1], Arshia Madni [1], Virginia Hargest[1], Stacey Schultz-cherry[1], Valerie Cortez[1], Shane Cross[2], Deborah Ward[2], Randall Hayden[1], Jeffrey Rubnitz[2], Ching-Hon Pui[2], Raja Khan[2], and Diego Hijano[2]

[1]St Jude Children's Research Hospital
[2]St. Jude Children's Research Hospital

April 05, 2024

Abstract

Novel human astrovirus (HAstV) strains have been recently shown to cause fatal encephalitis in immunocompromised patients. We report two cases from our institution. A 2-year old female undergoing treatment for acute lymphoblastic leukemia and a 9-year old male with refractory acute myeloid leukemia. Both were found to have HAstV-VA1 in the cerebrospinal fluid (CSF) by metagenomics next generation sequencing (m-NGS) after the initial evaluation did not reveal any etiology. Patient 1 remains alive, in remission, showing gradual neurological improvement after treatment with steroids, intravenous immunoglobulin, ribavirin, nitazoxanide and Peg-INF-alpha 2b. Patient 2 died 7 weeks later while receiving palliative care.

INTRODUCTION

Encephalitis is characterized by brain dysfunction due to inflammation of the brain parenchyma and is associated with significant morbidity and mortality. Despite significant advances in diagnostic methods, the etiology remains unknown in about 60% of cases.[1-3]

Immunocompromised patients with encephalitis pose unique diagnostic and therapeutic challenges. They are more likely to have atypical presentations from common pathogens and are at higher risk of infections by novel agents.[4]

Classical human astroviruses (HAstV) are gastrointestinal pathogens responsible for approximately 10% cases of acute, non-bacterial gastroenteritis in children.[5-7] Recently discovered, divergent strains of HAstV, MLB and VA1, also cause self-limited diarrheal illnesses.[6,8] However, HAstVs have also been reported to cause fatal encephalitis, primarily in immunocompromised hosts. To date, 10 cases of HAstV central nervous system (CNS) infection have been reported.[9-17] The most frequently identified strain has been VA1.[9,11-14] We report 2 cases of HAsV-VA1 encephalitis in children with cancer at our institution and perform a literature review of previously published cases.

METHODS

Demographic and clinical information was abstracted. We performed ELISAs to identify and quantify HAstV-1 and HAstV-VA1 specific antibodies in 9 polyvalent IVIG lots. In addition, we performed neutralization as described elsewhere. [18] (Supplemental methods) The study was approved by St Jude's Institutional Review Board. Consent from parents of Patient 2 was waived and verbal consent from parents of Patient 1 was obtained.

CASE REPORT

PATIENT 1

A 2-year-old female with standard risk B-cell acute lymphoblastic leukemia (B-ALL) and CNS leukemia at diagnosis developed myoclonic twitching during week 22 of continuation chemotherapy. She became increasingly somnolent, irritable, and developed bouts of agitation, difficulty in walking, inability to communicate, and dysphagia. A magnetic resonance imaging (MRI) of the brain demonstrated cerebral volume loss and a nonspecific ill-defined FLAIR hyperintensity in the cerebral white matter. Electroencephalogram (EEG) showed diffuse slowing. CSF bacterial and fungal cultures were negative (Supplemental Table 1). PCR panel did not detect micro-organisms, autoimmune panel resulted negative, and cytology showed no evidence of leukemia. For presumed autoimmune encephalitis, she was treated with intravenous immunoglobulin (IVIG) with no improvement. CSF m-NGS resulted positive for HAstV-VA1. Management was based on a previously published case[11] and included ribavirin, methylprednisolone, IVIG and Peg-INF-alpha 2b. In addition, we added oral nitazoxanide due to its efficacy in vitro against HAstV-VA1.[19,20] Due to side effects, Peg-INF-alpha 2b was discontinued after 3 doses. (Supplemental Fig 1)

To further optimize her treatment, we tested 9 lots of IVIG for HAstV antibodies and did not find any significant difference (Supplemental Fig.2A). None showed significant viral neutralization (Supplemental Fig.2B, 2C).

MRI demonstrated T2 prolongation in thalami and restricted water diffusion consistent with acute necrotizing encephalitis that improved over time. (Fig.1) She was discharged after 108 days of hospitalization on PO ribavirin, nitazoxanide and IVIG. Her chemotherapy was held and restarted 15 days after astrovirus treatment initiation. Dexamethasone and vincristine were omitted from therapy to prevent further CNS damage. She was treated for astrovirus infection for approximately 8 months (Supplemental Fig.1) and has shown gradual yet significant neurologic improvement. At her most recent follow up, 16 months after diagnosis, she could socially interact but was minimally verbal, remained without seizures with improving hypertonia, and demonstrated clinical improvement even after stopping astrovirus directed therapy.

PATIENT 2

A 9-year-old male with KMT2A-rearranged relapsed refractory acute myeloid leukemia developed respiratory syncytial virus (RSV) infection and was admitted for neutropenic fever.

Shortly after admission he developed altered mental status, including periods of agitation and confusion alternating with being overly sedated. Head CT showed cerebral volume loss. EEG showed diffuse slowing consistent with encephalopathy. CSF evaluation showed negative bacterial and fungal cultures. PCR panel was negative for micro-organisms, and cytology showed no leukemia involvement (Supplemental Table 1). He was treated with broad spectrum antibiotics for neutropenic fever, acyclovir for presumed herpes simplex virus encephalitis and PO ribavirin for RSV infection. He received IVIG (1g/kg/dose x 2 days) for presumed autoimmune encephalitis with no benefit. CSF m-NGS was positive for HAstV-VA1.

Because of his incurable leukemia, he remained inpatient for palliative care. Treatment for astrovirus infection was aligned with his goals of care with IVIG (1 g/kg/dose thrice weekly for one week then weekly thereafter) and oral nitazoxanide (250 mg orally twice daily). He had progressive neurologic deterioration, developed renal and respiratory failure and died 7 weeks after diagnosis. Family refused autopsy.

DISCUSSION

Divergent strains of astroviruses are known to cause infection in humans, including classical HAstV (types 1-8), MLB and VA1 viruses.[5] Studies show 90% and 65% seropositivity against classical HAstV and VA1 and close to 100% seropositivity in adulthood for MLB1 suggesting that viral exposure is common and frequent throughout life.[21-24] These pathogens have recently been found to cause CNS infection mostly in immunocompromised hosts, especially VA1. Astrovirus encephalitis was first described in 2010. Since then, a total of 10 cases of astrovirus CNS infection have been reported (Table 1).[9-17]

All five patients with HAstV-VA1 infection were immunocompromised[9,11-14] and were diagnosed with m-NGS; in only 2 cases the virus was identified before the patient died.[11,13]One patient was treated with ribavirin, steroids, IVIG and Peg-INF survived but recovered with cognitive and movement sequelae.[11] Two of three cases with MLB encephalitis recovered fully, one was an immunocompetent host.[10,15]One patient with classical strain (HAstV-4) died while the other was an immunocompetent host and recovered.[16,17] Hence, there seems to be variability, not only on the host characteristics but also on the virulence among strains.

We report two children who developed encephalitis with HAstV VA1 strain while undergoing treatment for leukemia. In both patients, traditional diagnostic tests were negative, and the virus was identified using m-NGS on the CSF. This unbiased technique, not limited by specific targets, enables the identification of novel pathogens.[25]Despite its potential, m-NGS is not routinely utilized. Considerations of costs, reimbursement, turnaround time, and regulations remain major hurdles.[25] Interpretation of m-NGS can be difficult and discerning between a contaminant, colonizer or pathogen can be challenging.[25]

Patient 1 was managed based on the treatment outlined by Frémond et al[11] which resulted in the only surviving case of VA1 encephalitis to date. Our patient was treated for about 8 months and survived. She remains with significant neuropsychiatric sequelae and dependent for activities of daily living. The extent to which she will recover neurologically remains unknown. Given the paucity of information in treating this severe infection, we attempted to optimize her treatment by including nitazoxanide, based on in vitro data[19,20] and analyzing commercially available IVIG. While we observed VA1 and HAstV-1 antibodies in all IVIG lots, there was no significant differences in neutralizing activity. These results show that commercially available IVIG lots have HAstV antibodies but their role in this setting remains to be determined.

HAstV should be considered in the differential of acute encephalitis in immunosuppressed patients. m-NGS is not routinely accessible but can be vital in yielding a definitive diagnosis when conventional tests are inconclusive. We emphasize the importance of early diagnosis due to high morbidity and mortality associated with HAstV encephalitis, with potential improved outcomes with the therapy described in surviving patients. The true extent of the pathogenesis of HAstV among immunocompromised patients is unclear and needs to be elucidated with further studies.

CONFLICT OF INTEREST

Shane J cross is a consultant for Lexicomp. Randall T Hayden serves on the advisory board for Roche molecular, Quidel and Inflammatix. The other authors have no relevant conflict of interest.

ACKNOWLEDGEMENTS

None

REFERENCES

1. Khetsuriani N, Holman RC, Anderson LJ. Burden of encephalitis-associated hospitalizations in the United States, 1988-1997. *Clin Infect Dis.* 2002;35(2):175-182.

2. Glaser CA, Honarmand S, Anderson LJ, et al. Beyond viruses: clinical profiles and etiologies associated with encephalitis. *Clin Infect Dis.* 2006;43(12):1565-1577.

3. Glaser CA, Gilliam S, Schnurr D, et al. In search of encephalitis etiologies: diagnostic challenges in the California Encephalitis Project, 1998-2000. *Clin Infect Dis.* 2003;36(6):731-742.

4. Saylor D, Thakur K, Venkatesan A. Acute encephalitis in the immunocompromised individual. *Curr Opin Infect Dis.*2015;28(4):330-336.

5. Bosch A, Pintó RM, Guix S. Human astroviruses. *Clin Microbiol Rev.* 2014;27(4):1048-1074.

6. Finkbeiner SR, Li Y, Ruone S, et al. Identification of a novel astrovirus (astrovirus VA1) associated with an outbreak of acute gastroenteritis. *J Virol.* 2009;83(20):10836-10839.

7. Glass RI, Noel J, Mitchell D, et al. The changing epidemiology of astrovirus-associated gastroenteritis: a review. *Arch Virol Suppl.* 1996;12:287-300.

8. Kapoor A, Li L, Victoria J, et al. Multiple novel astrovirus species in human stool. *J Gen Virol.* 2009;90(Pt 12):2965-2972.

9. Brown JR, Morfopoulou S, Hubb J, et al. Astrovirus VA1/HMO-C: an increasingly recognized neurotropic pathogen in immunocompromised patients. *Clin Infect Dis.* 2015;60(6):881-888.

10. Cordey S, Vu DL, Schibler M, et al. Astrovirus MLB2, a New Gastroenteric Virus Associated with Meningitis and Disseminated Infection. *Emerg Infect Dis.* 2016;22(5):846-853.

11. Frémond ML, Pérot P, Muth E, et al. Next-Generation Sequencing for Diagnosis and Tailored Therapy: A Case Report of Astrovirus-Associated Progressive Encephalitis. *J Pediatric Infect Dis Soc.*2015;4(3):e53-57.

12. Lum SH, Turner A, Guiver M, et al. An emerging opportunistic infection: fatal astrovirus (VA1/HMO-C) encephalitis in a pediatric stem cell transplant recipient. *Transpl Infect Dis.*2016;18(6):960-964.

13. Naccache SN, Peggs KS, Mattes FM, et al. Diagnosis of neuroinvasive astrovirus infection in an immunocompromised adult with encephalitis by unbiased next-generation sequencing. *Clin Infect Dis.*2015;60(6):919-923.

14. Quan PL, Wagner TA, Briese T, et al. Astrovirus encephalitis in boy with X-linked agammaglobulinemia. *Emerg Infect Dis.*2010;16(6):918-925.

15. Sato M, Kuroda M, Kasai M, et al. Acute encephalopathy in an immunocompromised boy with astrovirus-MLB1 infection detected by next generation sequencing. *J Clin Virol.* 2016;78:66-70.

16. Koukou G, Niendorf S, Hornei B, Schlump JU, Jenke AC, Jacobsen S. Human astrovirus infection associated with encephalitis in an immunocompetent child: a case report. *J Med Case Rep.*2019;13(1):341.

17. Wunderli W, Meerbach A, Güngör T, et al. Astrovirus infection in hospitalized infants with severe combined immunodeficiency after allogeneic hematopoietic stem cell transplantation. *PLoS One.*2011;6(11):e27483.

18. Janowski AB, Wang D. Infection and Propagation of Astrovirus VA1 in Cell Culture. *Curr Protoc Microbiol.* 2019;52(1):e73.

19. Hargest V, Davis AE, Tan S, Cortez V, Schultz-Cherry S. Human Astroviruses: A Tale of Two Strains. *Viruses.* 2021;13(3).

20. Hargest V, Sharp B, Livingston B, Cortez V, Schultz-Cherry S. Astrovirus Replication Is Inhibited by Nitazoxanide In Vitro and In Vivo. *J Virol.* 2020;94(5).

21. Burbelo PD, Ching KH, Esper F, et al. Serological studies confirm the novel astrovirus HMOAstV-C as a highly prevalent human infectious agent. *PLoS One.* 2011;6(8):e22576.

22. Holtz LR, Bauer IK, Jiang H, et al. Seroepidemiology of astrovirus MLB1. *Clin Vaccine Immunol.* 2014;21(6):908-911.

23. Koopmans MP, Bijen MH, Monroe SS, Vinjé J. Age-stratified seroprevalence of neutralizing antibodies to astrovirus types 1 to 7 in humans in The Netherlands. *Clin Diagn Lab Immunol.*1998;5(1):33-37.

24. Kriston S, Willcocks MM, Carter MJ, Cubitt WD. Seroprevalence of astrovirus types 1 and 6 in London, determined using recombinant virus antigen. *Epidemiol Infect.* 1996;117(1):159-164.

25. Chiu CY, Miller SA. Clinical metagenomics. *Nat Rev Genet.*2019;20(6):341-355.

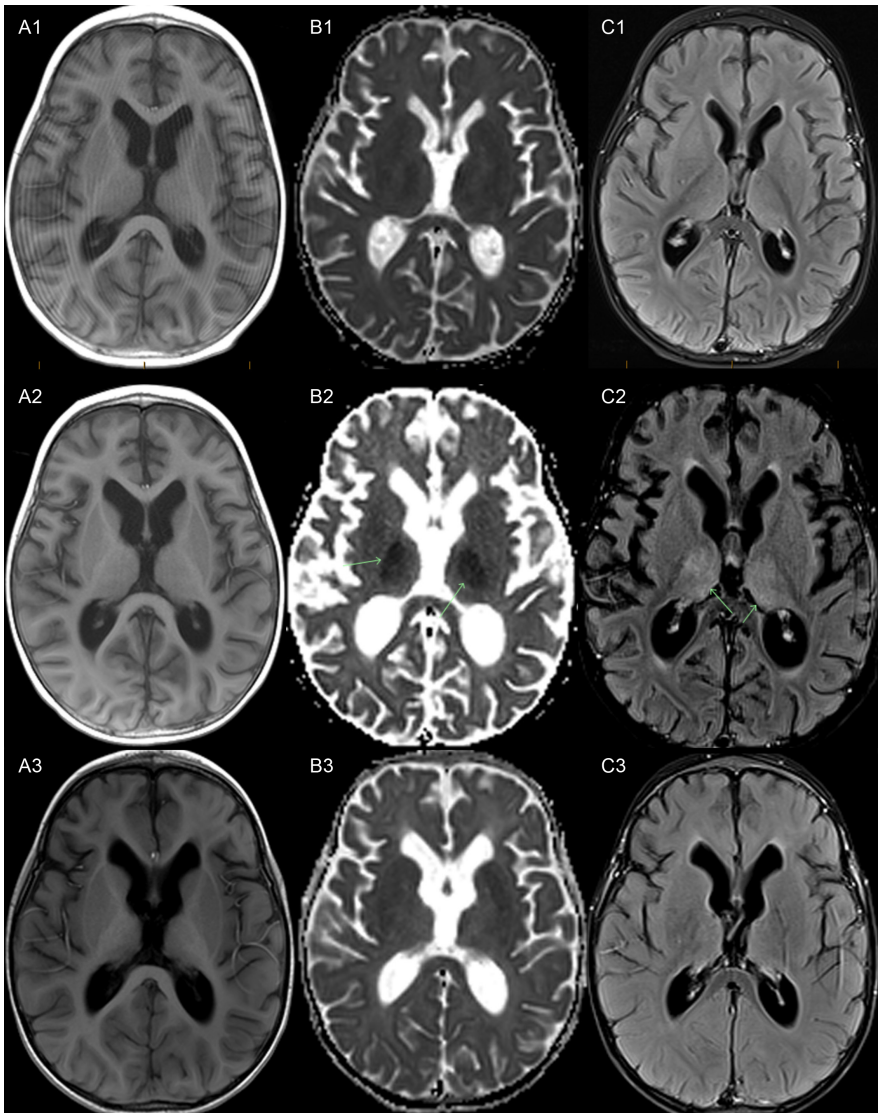
LEGENDS

Figure 1

MRI images at the beginning of illness (A1, B1, C1), end of 2nd week of illness (A2, B2, C2) and 8-weeks after onset of illness (A3, B3, C3). A1-3 are T1 weighted images showing no abnormality except increased generalized atrophy 2-weeks into the illness (A2) and some recovery by 8-weeks (A3). Diffusion weighted imaging (ADC map) showing restricted diffusion in bilateral thalami (arrows) 2-weeks into the illness (B2) and no diffusion restriction early in course (B1) and at recovery (B3). FLAIR imaging showing a hint of increased signal in thalami early in the disease (C1), more pronounced increased signal 2-weeks into the illness (C2), and recovery by 8-weeks (C3). Note increased generalized brain atrophy 2-weeks into the illness (A2, B2, C2) with some recovery by 8-weeks (A3, B3, C3).

Table 1

Cases of astrovirus central nervous system infection reported in the literature



Hosted file

TABLE 1 Final 6_30_21.docx available at https://authorea.com/users/733565/articles/711179-human-astrovirus-va1-encephalitis-in-pediatric-cancer-patients-report-of-two-cases-and-

review-of-the-literature