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TEACHING FILES (GRAND ROUNDS)

AN INFANT WITH SEIZURES WITH POSITIVE HUMAN HERPES VIRUS 6 ON MULTIPLEX PCR AND POSITIVE HERPES SIMPLEX VIRUS 1 ON UNIPLEX PCR - HOW TO INTERPRET?

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Clinical Problem:

A 6 month old boy presented in May 2024 with fever, cough and cold for 10 days along with generalized tonic clonic convulsions on day 8 of fever followed by excessive irritability and refusal to feed. He was born at full term by vaginal delivery and birth weight was 3 kg. There were no antenatal or post-natal complication. He had gained his milestones appropriately for his age. On examination, weight was 8 kg (between 50th-75th centile according to WHO [World Health Organisation] growth charts), height was 69 cm (between 75th-85th centile according to WHO growth charts). There were no meningeal signs. Anterior fontanelle was normal. Other systemic examination was normal. MRI brain showed symmetrical diffusion restriction with T2 hyperintensity in bilateral corpus striatum, no abnormal brain parenchymal or meningeal enhancement was noted. Cerebrospinal fluid (CSF) analysis showed 1 cell/mm^3 with 100% lymphocytes, 55 mg/dl of sugar and 27 mg/dl of proteins. However, CSF multiplex Filmarray polymerase chain reaction (PCR) for meningitis/encephalitis panel detected human herpes virus 6 (HHV-6) and negative for herpes simplex virus 1 (HSV-1), for which patient was treated with intravenous (IV) acyclovir (20 mg/kg/dose 8 hourly). The child was also given anti-pyretics and anti-epileptics. CSF uniplex HSV-1 PCR was done after 2 days which was positive. Child was treated with IV acyclovir for 14 days. Repeat CSF HSV PCR done after 14 days was negative. The child subsequently recovered well, without any loss of attained milestones or complications.

Why did multiplex PCR not pick up HSV-1 and what is the significance of HHV-6 PCR on CSF with normal CSF findings?

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Discussion:

HHV-6 is a highly prevalent infection occurring in 90% of children till 3 years of age.[1] HHV-6 commonly causes exanthem subitem or roseola infantum in infants, a self-limiting febrile illness with a rash over the trunk and face.[2] HHV-6 is also a well-known cause of febrile seizures in children.[2] HHV-6 rarely affects immunocompetent patients, however there is an increased risk of encephalitis in immunocompromised patients.[2] HHV-6 exhibits tropism for the CD4 T-cells and undergoes latency mainly in macrophages and monocytes.[3] Latency is achieved by integration of HHV-6 genome with host chromosomal telomeric sites.[3]

HSV-1 is the leading cause of sporadic encephalitis with one-third cases occurring in children and adolescents.[4] Herpes simplex encephalitis (HSE) has a prodromal phase of fever, malaise and headache which precedes neurological symptoms.[4] HSE in children manifests as fever, lethargy, headaches, altered sensorium, seizures and focal neurological deficits.[4] Only 38% children present with neurological symptoms leading to a difficulty in diagnosis.[5] MRI is considered a good imaging tool with 90% sensitivity in detecting HSE abnormalities including temporal lobe involvement with white matter changes along limbic system to inferior frontal lobes and insular cortex.[4]

CSF findings in HSV and HHV-6 encephalitis are similar including minimal or absent pleocytosis with normal glucose and protein levels.[2,4] However, these findings are not specific, prompting the need for additional investigations. Diagnosis of HHV-6 and HSV-1 infections are primarily done by CSF uniplex or multiplex PCR assays.[2,4] The FilmArray Meningitis Encephalitis (ME) panel is a CSF based multiplex diagnostic PCR test for rapid detection of 14 common pathogens causing central nervous system (CNS) infections.[6] Herpes viruses are known to establish latency so detection may indicate a recent primary infection, reactivation without disease, latent infection or chromosomal integration in cells in the CSF.[7] Chromosomal integration of HHV-6 occurs in gametes in approximately 1% population resulting in inherited chromosomally integrated HHV-6 genome which is considered the leading cause of

congenital HHV-6 transmission.[3] Individuals with inherited HHV-6 genome have a copy in every nucleated cell resulting in a persistent high viral load, possibly leading to false positive results.[3] Immunocompetent children are reported to have lower viral load in the CSF, fewer than 100 copies/ml compared to brain, blood and hair follicles.[8] Hence, a positive qualitative multiplex PCR report should be done followed by a quantitative test to ascertain viral load.[2] Another cause for discrepant results could be due to contamination of CSF or presence of blood due to a traumatic tap.[7]

Discrepancies in ME panel are also reported to occur in patients with HSE, emphasizing the need to perform alternate testing in patients with high clinical suspicion despite a negative ME panel result.[9] A review done by Biofire Diagnostics® suggested that low viral load of HSV-1 can cause discordant results due to CSF collection during early course of infection or sample dilution.[10] HSV-1 replication mainly occurs within the neurons and hence it is poorly detected in CSF.[10] Differences in the HSV-1 strains due to sequence variants or rearrangements could contribute to decreased sensitivity.[10] As discussed earlier, latency established by HSV-1 like other herpes viruses, can lead to HSV-1 detection, especially by reactivation during a concomitant infection, immunocompromised state or raised cell counts.[10] According to the Infectious Diseases Society of America guidelines, in cases of high clinical suspicion of HSV-1 with negative HSV-1 PCR, acyclovir therapy should be continued and another CSF PCR should be repeated within 3-7 days.[4] In our case, initial CSF ME panel was negative for HSV-1, yet a repeat CSF sample after 2 days detected HSV-1. HSV infections in children are diagnosed with CSF PCR along with a blood PCR for HSV to ensure proper detection.[7] Therefore, careful interpretation of ME panel results should be made with regard of clinical history of the patient with the epidemiology of the detected pathogen.[7]

Compliance with Ethical Standards

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Conflict of Interest : None

References:

1. Cosme I, Ramírez MA, Peñata CA, et al. Human herpes virus 6 detection in children with suspected central nervous system infection. Pediatric Infectious Disease Journal. 2020 Sept 7;39(12).
2. Eliassen E, Hemond CC, Santoro JD. HHV-6-associated neurological disease in children: Epidemiologic, clinical, diagnostic and treatment considerations. Pediatric Neurology. 2020 Apr;105:10-20.
3. Pantry S, Medveczky P. Latency, integration and reactivation of human herpesvirus-6. Viruses. 2017 Jul 24;9(7):194.
4. AK AK, Bhutta BS, Mendez MD. Herpes simplex encephalitis [Internet]. U.S. National Library of Medicine; 2024 [cited 2024 Aug 2]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK557643/
5. Hosseini PS, Golfiroozi S, Hosseini PS, et al. Herpes simplex (HSV-1) encephalitis in an infant: A case report study. Annals of Medicine & Surgery. 2024 May 8;86(6):3674-8.
6. Messacar K, Breazeale G, Robinson CC, et al. Potential clinical impact of the film array meningitis encephalitis panel in children with suspected central nervous system infections. Diagnostic Microbiology and Infectious Disease. 2016 Sept;86(1):118-20.
7. Leber AL, Everhart K, Balada-Llasat J-M, et al. Multicenter evaluation of BioFire FilmArray meningitis/encephalitis panel for detection of bacteria, viruses and yeast in cerebrospinal fluid specimens. Journal of Clinical Microbiology. 2016 Sept;54(9):2251-61.
8. Yamanishi K, Mori Y. Human herpesvirus 6 and human herpesvirus 7. Clinical Virology. 2009 Feb 27;507-19.
9. Tansarli GS, Chapin KC. Diagnostic test accuracy of the biofire® FilmArray® meningitis/ENCEPHALITIS PANEL: A systematic review and meta-analysis. Clinical Microbiology and Infection. 2020 Mar;26(3):281-90.
10. HSV-1 detection by the biofire ® filmarray ® meningitis [Internet]. Technical Note BioFire Diagnostics, LLC [cited 2024 Aug 2]. Available from: https://www.biofiredx.com/wp-content/uploads/FLM1-PRT-0265-HSV-1-Detection-by-the-BioFire-FilmArray-ME-Panel-2.pdf