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Disseminated Herpes Simplex Virus-1 in Previously Healthy Child Without Skin Rash

A case report and review

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Abstract

Disseminated Herpes Simplex Virus (HSV) is a known fatal condition in neonate and immunocompromised patients. However, very few cases have been reported in immunocompetent host. We report a one year old child who was previously healthy, presented with febrile illness associated with decrease conscious level. Child has been found to have marked elevated liver enzymes. Ultimately diagnosed with disseminated. HSV (encephalitis/ hepatitis) based on Cerebrospinal fluid (CSF) polymerase chain reaction (PCR) finding of HSV as well as positive HSV Immunoglobulin M (IgM) serology. She received acyclovir course and follow up for 1 year showed excellent developmental outcome.

Keywords: HSV, Encephalitis, Hepatitis.

Introduction

Herpes Simplex Virus (HSV) virus is a type of Deoxyribonucleic acid (DNA) virus that is enveloped and belongs to the Herpesviridae family. HSV can have lifelong effects, although it typically does not result in severe illnesses for individuals with strong immune systems. A recent study conducted in Saudi Arabia revealed that there

is a high seroprevalence of HSV among children in the country. It has been found 60% of children between the ages of 6-13 years tested positive for the infection in a local study.[1] This percentage is significantly higher than reported seroprevalence of HSV in the United States for example, which has been documented at 31% for children of the same age range.[2] Previously reported cases of children with disseminated HSV were mainly in neonates or immunocompromised children and very rarely reported in healthy children. So it is important to consider immunodeficiency as there are reported severe HSV infection in cases with interferon pathway defect and other immunodeficiency.[3]

Hence, we report the case of a healthy immunocompetent child, who presented with disseminated/visceral HSV without, skin involvement.

Case Report

Our team has reviewed the case of a 12-month-old female child who was transferred to the Children's Hospital in Riyadh at 2022 due to acute liver injury and suspected viral encephalitis. Prior to her transfer, the child had been in good health with no prior surgical or medical history. She was admitted to the referral hospital after experiencing high-grade fever, poor oral intake, and reduced activity for four days.

The patient was admitted with a high-grade fever of 39 ºC and appeared lethargic with decreased activity levels. Skin and mucous membranes showed signs of dehydration, but no rash was observed. Neurological examination showed weakness in all extremities, while abdominal examination revealed hepatomegaly 3 cm below the costal margin and diffuse abdominal tenderness with no guarding or rebound tenderness. Cardiovascular and chest examinations were normal. Initial liver function tests (LFT) revealed markedly elevated liver enzymes (Alanine transaminase ALT: 1413 IU/L, Aspartate transaminase AST: 2404 IU/L) and a mild derangement [prothrombin time PT: 19 seconds, (normal reference; 11-15), international normalized ratio INR: 1.5 seconds, (normal reference; 0.9-1.1)] of the coagulation profile (Table 1). Complete blood count CBC and renal function were normal. Due to a rapidly declining level of consciousness, the patient was transferred to the pediatric intensive care unit and commenced empirical therapy with cefotaxime, vancomycin, and acyclovir respectively.

The tests for viral serology for hepatitis viruses HAV, HBV, and HCV came back negative, but the cerebrospinal fluid (CSF) polymerase chain reaction (PCR) for HSV-1 and serum HSV IgM antibodies were both positive. Interestingly, despite having received high doses of acetaminophen before presentation, the serum level of the drug at the time of presentation was rather low (4.4 microgram/ml). Nonetheless, the patient's condition progressively improved following the commencement of medications, with gradual normalization of the liver enzymes and clotting profile. By the 20th day of acyclovir therapy, the patient's ALT had reduced to 40 IU/L, AST was 47 IU/L, PT was 12.8 seconds, while the INR was 0.95 seconds. By the 21st day of acyclovir therapy, the child had become fully conscious and had resumed premorbid activities. Magnetic resonance imaging (MRI) brain and electroencephalogram (EEG) has been performed late in the course of illness. MRI showed pachymeningeal enhancement, however it did not show characteristic HSV features. EEG was abnormal due to generalized background slowing for age which represents mild encephalopathy.

The patient was subsequently discharged, and an out-patient follow-up at the clinic was scheduled. After a year of follow up child is doing fine, and her developmental milestones are appropriate for her age. It is worth mentioning that immune investigations were not done as immunodeficiency was not suspected.

Informed consent was obtained from parents for the case report publication purposes while ensuring the strict confidentiality of the patient’s identity. Ethical approval (IRB) was obtained.

Discussion

It is worth noting that HSV is not commonly associated with acute liver failure in children. Only 2% of viral-related acute liver failure cases in the general population are caused by HSV, and these cases often have a poor outcome.[4] A study conducted in Saudi Arabia that reviewed the viral causes of hepatitis in children did not find any cases of HSV-related hepatitis, with Hepatitis A virus being the most common etiology.[5] Moreover, research has shown that over 70% of adults with HSV-related liver failure were immune compromised, and less than half of the affected cases had

skin manifestations.[6] Interestingly, our index case did not exhibit any cutaneous manifestation.

Most of the previously reported cases of disseminated HSV infection were among neonates and immunocompromised children.[7] Disseminated HSV likely 2nd to viremia as demonstrated in viral blood culture in one study.[8] It has significant mortality.[9,10] Data is sparse on the occurrence of disseminated or visceral HSV among previously healthy children beyond the neonatal period. An old study has reported severe non-neonatal HSV infection in 93 children, majority had measles or malnutrion.[11]

Other reported cases have varying manifestations but generally had good outcomes. Very few cases have been documented in the literature where healthy children suffer from acute liver failure and encephalitis. For instance, a five-year-old was reported to have acute liver failure and encephalitis in addition to renal failure and disseminated intravascular coagulopathy, which was not present in our case report.[12] Similarly, a nine-year-old had hepatitis, herpetic rashes, and fever, but had relatively lower liver enzymes (ALT and AST were around 300 IU) and no clotting issues.[13] Another nine-year-old had herpetic stomatitis and liver transaminases as high as our index case, with ALT peaking at 2,400 IU and AST at 4,000 IU.[14]

It has been observed in the literature that children diagnosed with HSV hepatitis have shown positive outcomes upon initiation of acyclovir treatment in earlier mentioned cases, unlike adults who suffer from HSV-associated acute liver failure. A previous review had indicated that many adults with HSV acute liver failure succumbed to the disease or underwent liver transplantation. Additionally, the review inferred that a significant proportion of 74% of cases of HSV-related liver failure were identified through autopsy.[6]

Our patient also had HSV encephalitis, which is a more common form of disseminated/visceral HSV in affected children and, which generally responds favorably to IV acyclovir but long term sequela has been reported frequently.[15] The diagnosis of HSV encephalitis may be relatively more straightforward, due to the characteristic features of viral encephalitis on CSF analysis and the widespread availability of PCR.

Although, viral causes of acute liver failure, including HSV, should be proactively investigated in children with fever and features of hepatic dysfunction, another important consideration in such children is acetaminophen toxicity. Our index cases had received high doses of acetaminophen before presentation, however, the serum level of the drug at the time of presentation was rather low (4.4 microgram/ml) and, the identification of CSF fluid PCR for HSV-1 and serum HSV Immunoglobulin M IgM antibodies in our patient makes HSV infection the more plausible diagnosis.

Disseminated HSV is a treatable condition, following the prompt commencement of acyclovir. Hence, we suggest the routine workup for HSV in children with acute liver failure of unknown etiology and early initiation of acyclovir in such cases. This has the potential to reduce the need for liver transplantation and preserve liver function in affected children.

Conclusion

In conclusion, this case report highlights the occurrence of disseminated HSV infection in a previously healthy immunocompetent child without cutaneous involvement. This case is significant because HSV is not commonly associated with acute liver failure in children, and most reported cases of disseminated HSV infection are in neonates or immunocompromised individuals. The prompt initiation of acyclovir therapy led to the gradual normalization of liver enzymes and clotting profile, as well as the improvement the overall patient's condition. This emphasizes the importance of considering HSV as a potential etiology in children presenting with acute liver failure of unknown origin. Further research and awareness are needed to enhance the routine evaluation and early recognition of HSV in such cases, which has the potential to prevent the need for liver transplantation and preserve liver function in affected children.

Authors' Contribution

IAA, AA, ASA and FA were responsible for writing the manuscript. AA and MA revised the manuscript. All authors approved the final version of the manuscript.

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Table 1: Laboratory results

Laboratory	At presentation	After 3 weeks	Normal reference
ALT	1413	40	4-36 IU/L
AST	2404	47	15-60 IU/L
PT	19	12.8	11-15 seconds
INR	1.5	0.95	0.9-1.1 seconds
Paracetamol level at presentation	4.4		Toxic level >25 mcg/ml
HAV, HBV, HCV	Negative		Negative
HSV PCR in CSF	Positive		Negative
HSV IgM in serum	Positive		Negative

**ALT Alanine transaminase, AST Aspartate transaminase, PT prothrombin time, INR international normalized ratio, IU/L international units per liter, mcg/ml micrograms in one mL, umol/L micromoles per liter, HAV, HBV, and HCV hepatitis viruses, HSV Herpes simplex virus, CSF cerebrospinal fluid, PCR polymerase chain reaction, IgM Immunoglobulin M.*