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AN UNEXPECTED CAUSE OF HEPATITIS

Michael Croix, MD
University of Rochester School of Medicine & Dentistry

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[video transcript]

00:08
Alright. So this is about an unexpected cause of Hepatitis. Just to start off we have our accreditation statements, no disclosures by the rest of the panel, and no disclosures by myself either. I do not have a case to go along with this particular unusual cause. As you can see here, it's going to be HSV Hepatitis, and you'll see kind of as we go through the objectives here why I probably do not have a case, but why it is something that is important for you to consider as well. So we'll go over the epidemiology, what the clinical presentation is, discuss the associated mortality, and then the management for this as well.

00:55
So starting off with just the epidemiology of HSV in general. So periodically, the World Health Organization updates the prevalence of several infections, among them is HSV. And in 2020, they published a bulletin updating the global prevalence of both HSV 1 and 2. And as you can see here, the global prevalence is 67% of individuals have HSV 1, 63% oral and then 5% genital with a couple of percent overlap, and this is in individuals who are aged 0 to 49, or 15 to 49 for genital. And then for HSV 2, the estimated prevalence was 13.2%. Also here you can see the incidence for both of them, so new cases in 2016, there were an estimated 120 million newly infected individuals with HSV 1, and then 24 million individuals, or 0.6%, of the population with HSV 2. WHO divides the world into several different regions of which we fall into the Americas region, where we have the lowest prevalence of oral HSV 1, but the highest prevalence of genital HSV 1, and then the second highest prevalence of HSV 2 for regions.

02:27
This is just a review of the cycle for HSV. So you get your initial penetration into mucosal or epithelial cells, which leads to a local lytic reaction, which leads to your initial inflammation and ulcerations, and then the viral particles then travel in a retrograde fashion along sensory neurons back to the dorsal root ganglia. And from there, you can either get spread to the CNS where you can get meningitis or encephalitis. But certainly HSV as we know, once you have acquired it, it is a lifelong infection because it establishes latency, and then either through stress or trauma or immune suppression, you get local reactivation and travel back down the sensory neurons to roughly the same distribution as the primary infection, and this is where individuals can get recurrent episodes of HSV.

03:33
HSV has several manifestations for both primary and reactivation. Most primary infections are asymptomatic in 70 to 80% of individuals, which is why most of the population does not know they have it. But you can certainly have cutaneous presentations in the form of Herpetic Whitlow, Eczema Herpeticum. Wrestlers can get Herpes gladiatorum. And then of course, you can have oral pharyngeal manifestations including esophagitis, pharyngitis, genital infections, of course, we're all familiar with. Neurologic, as I mentioned, you can get encephalitis or recurrent meningitis known as Mollaret's meningitis, and then rarely you can get pneumonitis. But particularly in this talk, we're going to focus on Hepatitis which is quite a rare manifestation.

04:40
So HSV associated with Hepatitis. This is a figure from 2008, publication in Hepatology from the Acute Liver Failure Study group. And as you can see here, you do not see HSV when they looked at patients over a 10 year period. And this is an 1100 adult patients with acute liver failure. But for viral Hepatitis, you predominantly see Hepatitis A and Hepatitis B. This is out of North America as opposed to Africa and Asia, where you may see more in the way of Hepatitis E as well. But at least out of the patients that they had during this study, they did not have any individuals with HSV. But on the pediatric side, they just grouped things into viral, but with 339 pediatric cases of acute liver failure there were 11 cases of herpes simplex being the cause of viral Hepatitis.

05:39
So how common is it overall? There's not great estimates, because of the rarity, so about 2 to 4% is the expected estimate of the cause of acute viral Hepatitis. But it also contributes to an estimated 1% of acute liver failure. So, of course, not all patients with acute viral Hepatitis will go on to have liver failure. But based off of this, you can estimate that 25 to 50% of individuals with HSV Hepatitis will actually develop liver failure from it. And why is it such a problem even though it's so rare? And it's because the mortality estimates exceed 70%. And we will go through the limited literature that's available. In particular, this study down here we'll go through, is a review from 2007 of the 137 cases that were available at the time. And it can be associated with both HSV 1 as well as HSV 2.

06:51
So this is from that review of the literature from 2007, looking at the 137 cases, showing the demographic data. And you can see that there may be a slight predominance for females looking at gender. But more importantly is who actually gets HSV Hepatitis? And you can see, you find it in both individuals who are immunocompetent, but there is quite a predominance of individuals who are immunosuppressed, which makes sense. We don't routinely see this, you know, in our patients who have HSV infections, and people who are immunosuppressed are more prone to disseminated type and more severe infections. But what's also interesting to note is that 23% of the patients, or 40% of the female patients, were pregnant. So this is another particular risk group to keep in mind as we talk about things later, for who you should keep this in the back of your mind as a potential cause of liver failure and Hepatitis.

08:08
So what are the clinical findings associated with it? In the 100 patients they had available vitals data for, almost everyone had a fever when they presented. What is perhaps not expected is that these individuals, most of them did not have visible herpetic lesions, either at the onset of symptoms or during their hospitalization. So nearly 60% of individuals will not have an identifiable rash, but those who do will either have mucocutaneous or potentially more disseminated lesions. As to be expected with individuals who have viral Hepatitis, their LFT abnormalities are quite profound. So the mean ALT and AST were in the upper 4000s, around 5000, but you can see there's quite a bit of variability here too. So most of these individuals will tend to be at least above 1000. They may have an elevated bilirubin, but not everyone does,

and not everyone has jaundice. And then other lab findings to look for are individuals who have leukopenia, and then other signs of liver failure. So as to be expected with liver failure when you have issues creating your appropriate clotting factors, you can see thrombocytopenia in nearly all these patients. Many of these patients have coagulopathy, many of them actually end up developing renal failure as well. And they often have hepatic encephalopathy as you would expect, you know, perhaps with a decompensated cirrhosis. And then as I mentioned, you can see this in individuals with both HSV 1 and HSV 2, with really no particular predominance of one or the other.

10:07
So how do you make the diagnosis? That's a little bit of a challenge, as we'll see here, as well as in the next slide. So the clinical findings are somewhat nonspecific, they'll point you to an abdominal cause. But you can see that most of the patients presented with fever, nausea, vomiting, abdominal pain. And even though rash was only present in about 40% of the patients, still important to do a comprehensive skin exam, including both an oral skin exam and then a pelvic exam as well to look for any genital ulcers. Laboratory studies will primarily point you towards evidence of acute viral Hepatitis. So again, your significant elevations of ALT and AST, some abnormalities in your clotting factors, and then as I mentioned with the CBC, you may look for leukopenia and thrombocytopenia. There's interesting information regarding HSV serology, looking for antibodies, and in general these are unlikely to be useful other than saying potentially whether or not someone has been exposed to HSV. If this is someone who has a new primary infection and develops Hepatitis, you may not actually have IgM antibodies present. And then IgG antibodies will tell you that certainly the patient has been exposed to HSV, but as I mentioned, this is prevalent in over 60% of the population. And so in and of itself doesn't necessarily give you the diagnosis. There have been some case series that have looked at HSV PCR that I will mention, particularly in pregnancy, this may suggest that there's at least active viral replication and that something is going on. But again, doesn't necessarily give you a definitive diagnosis, but should raise your suspicion.

12:17
And then I'll show a couple of images here of CT findings. So you can see on the left is a pre contrast CT. This is in a 25 year old pregnant female who was diagnosed with HSV Hepatitis. But then on the right, if you are able to see, there are several of these small one to three millimeter hypo dense lesions. And these are actually areas of focal necrosis. So this doesn't necessarily tell you that the diagnosis is HSV Hepatitis. This can also be seen in VZV, this can be seen in fungal infections. But in someone who has acute liver failure, who doesn't have other findings suggestive of another infectious etiology or non infectious etiology, you should at least consider HSV Hepatitis, if you are seeing these punctate areas of necrosis.

13:23
And this is another CT scan from a 21 year old female who was postpartum that again has these innumerable punctate lesions. And actually, when you move over to the left lobe here, you can see there's more confluent hypo density, suggesting more extensive necrosis. And then this is just the coronal film showing the same sort of punctate lesions and necrosis here. So

something to keep in mind with someone who's coming in with acute liver failure, if you see abnormalities on imaging.

14:01
As I mentioned, you know, you can look at the clinical findings as being suggestive, but unfortunately, the actual diagnosis in this case series, nearly 60% of people were diagnosed at autopsy. And the other primary diagnostic method was actually liver biopsy. The problem of course, being with obtaining a liver biopsy in someone who has liver failure, is you already have an organ that is prone to bleeding, and now is someone who has coagulation abnormalities as well, makes it quite a risky procedure.

14:39
They included 11 patients in this study who they diagnosed based off of clinical criteria. And this was based off of either serology or biopsy of non liver tissue that was consistent with an HSV infection. So again, they've used serology before. Elevated transaminases over 500 and then no other attributable cause. Perhaps what's also interesting is that out of these 137 patients, only 31 were suspected to have HSV Hepatitis, which then leads down to the primary concern is whether or not individuals get started on treatment. So because only 31 individuals had clinical suspicion, the number who received Acyclovir was only 49 out of 134 at this point, or less than 40%. And as I mentioned, the overall mortality was over 70%, at 74%. And seven of these individuals ended up getting liver transplants.

15:55
So they performed a univariate analysis of the 137 cases. Again, you know, it's a limited dataset, so take it with a grain of salt. But older individuals who are male had higher odds ratio for mortality. And unsurprisingly, individuals who had findings suggesting more severe liver failure, so coagulopathy, encephalopathy, elevated ALT, low platelets, had the highest risk of mortality. The only thing that showed any protective factor was actually treatment with Acyclovir. So they compared individuals treated with Acyclovir to those who are not, the only actual statistically significant difference in their demographics were individuals who were treated were younger. But again, you know, there's potentially bias, this is non randomized. But you can see looking down here at the mortality, or liver transplant, that only 25 of the 49 individuals who were treated died, so 51%, compared to 88% of individuals who were not treated.

17:25
And I will come back to that momentarily, but I do want to mention again, HSV Hepatitis and pregnancy. So there was a separate review. This is more recent, from 2019, of 56 cases from 36 different articles. So all of the literature is primarily cases or case series. But the pregnant patients tend to be young. It tends to occur later during the pregnancy. But as you can see, the number of pregnancies does not affect who is at risk here. And particularly in pregnant patients, the clinical features may be less obvious. Only 50% of the pregnant patients had fever, compared to the nearly 100% of the rest of the population. And then they were more likely to have abdominal tenderness or fundal tenderness, although they didn't actually provide numbers regarding this. Also, what's striking is a vesicular rash was even less common in these individuals. As I mentioned previously, 44% had a rash when you looked at all comers. But in

this series, only 18% of pregnant patients actually had a rash. You still see the same laboratory abnormalities regarding leukopenia, thrombocytopenia, and LFT abnormalities. And then they actually ended up having HSV cultures on 28 of the patients and then 24 of them had positive cultures, but they don't really specify if these were just taken from ulcers or if there were other areas where they had taken cultures. And then 12 of the patients had PCR performed and all 12 of them had positive PCR.

19:24
But what makes pregnancy a little bit difficult is that there are several other potential etiologies. In particular Hellp syndrome where you already have elevated liver enzymes, you can have low platelets, you can have anemia, which may be present if you're having active bleeding as well. And then several other causes of, you know, potential lower LFT abnormalities due to backup of bile, such as colilithiasis and intrahepatic cholestasis. And then of course, acute viral Hepatitis, primarily in adults, B and C in the United States, but again, elsewhere in the world you may also see more in the way of A and E.

20:12
So, going back to Acyclovir now, really the primary treatment is early initiation of IV Acyclovir. That review of 137 patients, although they didn't have this in any of their tables or figures, it did in their results mention that those who survived and were treated with Acyclovir, they were treated at mean of hospital day 3.5. Whereas those who received Acyclovir, but still died, were treated with a mean of hospital day 4.7. So the earlier you initiate treatment, the more likely you are to have a better outcome for these individuals. And so based off of that, there's been some discussion on which groups should you start Acyclovir on. And some studies have suggested anyone that comes in with an undifferentiated acute liver failure, so you don't see evidence of, you know, Tylenol toxicity, alcohol toxicity, or other viral Hepatitis, that you should consider starting Acyclovir. And some people would push back against this because of the rarity of HSV Hepatitis, but others have suggested that, in particular, pregnant patients or immunocompromised patients who do not have an identifiable cause of acute liver failure should be started on IV Acyclovir until a diagnosis is determined. There's also debate on whether or not they should be treated entirely with IV, should they be transitioned to oral, how long do you treat for. There has been a case report of a 28 year old female who was treated for HSV Hepatitis for 43 days with Acyclovir and then switched to Valacyclovir, and four days later she returned to the hospital with multi organ failure. And while the multi organ failure was due to other organisms, they did find on autopsy that she had HSV 2 resistant to Acyclovir. And whether or not that was residual HSV or if that was due to development of resistance because of inappropriate treatment is unclear.

22:48
Other considerations, Foscarnet has been used before in an individual who had HSV Hepatitis that had encephalopathy that was not improving on Acyclovir alone. But again, there's no comparison to know whether or not that individual would have improved on just Acyclovir and whether or not Foscarnet was necessary. And finally, there was one pregnant patient who was treated with three days of plasma exchange that had resolution of LFT abnormalities from HSV 2 Hepatitis. But unfortunately, because of the small number of individuals, most of these

therapies, particularly Foscarnet, Cidofovir, and plasma exchange, there is no great data for. So really, the important thing to remember is if you're suspecting HSV Hepatitis in a patient to start IV Acyclovir early. Any questions?

[End]