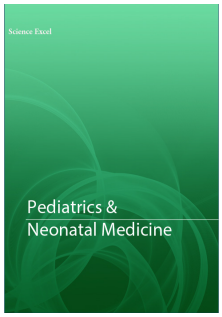
Pediatrics and Neonatal Medicine

Case Report



Unusual Presentation of Herpes Simplex Virus Hepatitis in Pregnancy leading to severe Maternal Morbidity and Sadly Neonatal Death: A Case Report and Review

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Abstract

We present the unusual case of HSV Hepatitis in pregnancy in a previously healthy young woman who contracted herpes simplex virus presumably through partner contact, which progressed to fulminant hepatitis, severe morbidity and sadly neonatal death. A 32-year-old (Gravida 5; Para 3) woman presented with fever, tachycardia and lethargy followed by severe hepatitis in the 3rd trimester of pregnancy. Progressive deterioration obliged an emergency cesarean section at 35+3 weeks of gestation. Following the review which took account neonatal death, the information from the post-mortem, placental histology and other investigations the cause of death of the baby was determined to be: Disseminated neonatal herpes type 2 virus. There was history of herpes simplex infection in partner and mother also had herpes but unfortunately confirmed once neonatal herpes was diagnosed at postmortem.

Background

The incidence of fulminant herpes simplex virus hepatitis is extremely low, and the diagnosis is often missed due to the lack of specific signs or symptoms. [1] Fulminant hepatic dysfunction in the third trimester of pregnancy accompanied by fever may result from disseminated herpes simplex virus. In 1969, the first case was reported. To our knowledge, only 30 cases have been reported [2]. Mucocutaneous lesions are present in only half of cases [3]; therefore, suspicion for diagnosis of this disease is low. Twenty-five percent of cases were not diagnosed until autopsy. Maternal and perinatal mortality are high, approaching 39 percent for both mother and fetus. Early recognition with initiation of antiviral therapy appears to be most important in maximizing survival [4].

Hepatitis is an unusual manifestation of herpesvirus infection. Herpes simplex virus hepatitis is a difficult diagnosis to establish, and the infection is often fatal [5].

Case presentation

A 32-year-old lady (Gravida 5; Para 3) was admitted to our unit at 35+1 weeks of pregnancy with high grade fever, feeling lethargicandunwell.Onphysicalexamination Maternity Observation Early warning score was 5. Her BP was 108/66 mmHg, temp was 38.1 and HR was 144bpm. Fetal heart rate was 152bpm. She had normal cardio-respiratory and neurological examination. Urine dipstick showed; Leucocytes positive, Nitrates positive, Ketones4+, Protein 2+. MSSU was sent which came back as normal. Patient mentioned that her partner had a recent flare-up of genital herpes. Her family, medical, surgical and drug history were not significant. On local examination there was no sign of genital herpes. A speculum examination showed multiparous cervical os and HVS (high vaginal swab) was taken that came back normal as well. (for investigations refer to Table 1). She was managed via the sepsis pathway with IV Antibiotics; Amoxicillin 1gram 6 hourly and Metronidazole 500mg 8 hourly. Regular paracetamol was given, oral hydration encouraged and thromboprophylaxis prescribed in form of TED stockings and LMWH.

Looking back at her background history: She had a booking visit with the CMW at 11 weeks. She was G6P3+2 with a BMI of 24.2, 2 previous Normal vaginal deliveries and a previous CS at 34 weeks due to Antepartum Haemorrhage. She was subsequently booked for consultant led care at 14 weeks, and an antenatal plan for serial growth scan due to

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previous SGA baby was in place. Her mid trimester scan and serial growth scans were normal with growth at 50th centile. Fetal heart rate monitoring was normal throughout.

On day 2, patient was still febrile and appeared lethargic. Her blood tests showed: Hemoglobin 85g/L, Platelets 98 (decreasing) and ALT 70 (increasing). Further investigations were requested. A Chest x-ray and Renal USS was normal. CTG's (fetal monitoring) was normal. Urine specimen for legionella and a throat swab were sent both of which came as normal. Plan was made to continue IV antibiotics. Microbiology opinion was sought and antibiotics escalated to Meropenem.

On day 3, the patient's general condition declined further with rising ALT and falling platelets. However, urea and electrolytes were within normal ranges. The results of liver function tests were grossly abnormal (Table 1). A Medical review was requested and the case discussed with a Gastroenterology specialist who advised EMV & CMV serology, a blood film, USS liver, and careful monitoring of platelets, LFT's, haptoglobin and coagulation. Liver Ultrasound was normal and Ultrasound Kidney showed a focal hypodense area in the mid to upper pole of the right kidney which may have represented focal pyelonephritis. A working diagnosis of HELLP /Urosepsis was made, and treatment with intravenous antibiotics continued. A decision to deliver by Emergency LSCS made. A live male infant was delivered in good condition, 2.4 kg APGARS 9/1 9/5. The infant was transferred to NNU for observation.

Patient remained in HDU care for 4 days. From days 3 to 6 after CS the patient's condition continued to deteriorate. She remained pyrexic and hypoxemic, and had a steadily deteriorating liver function (Figure 1). The prothrombin time ratio was normal. Blood cultures and urine cultures were negative. Cytomegalovirus and Epstein-Barr virus IgM and IgG antibody titers were negative as well. Her MEOWS deteriorated to 8 on Day8 of admission and a decision was made to transfer from AMU to ITU where the patient stayed for 10 days. On D11 of ITU a decision was made to transfer to Liver unit at QEHB in view of worsening hepatic failure where the patient stayed for 5 weeks.

Baby was initially admitted in NNU at GHH where he was managed for respiratory distress (CPAP for 1 day and ventilated for 2 days) and septic shock of unknown origin with IV antibiotics. As his condition continued to deteriorate, the baby was transferred to BHH NNU (on D7) where treatment for septic shock continued. Diagnosis of hepatic failure, DIC, sub-ependymal, germinal and intraventricular hemorrhage was made, palliation initiated and NND happened on Day 7 post-delivery. Aciclovir was started for the patient since partner had history of genital herpes after transfer to QEHB on day 6 postnatal. On Day 8 postnatal (1 day after neonatal death,) baby's serum HSV2 -PCR came back positive.

Discharge & follow up: Patient was stepped down to ward after discharge from liver unit, liver functions were monitored for a few months and she received input from bereavement midwife.

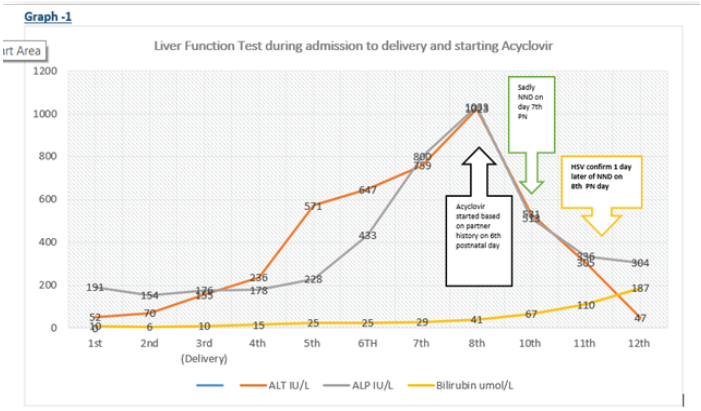

Figure 1. *Liver Function Test during admission to delivery and starting Acyclovir*

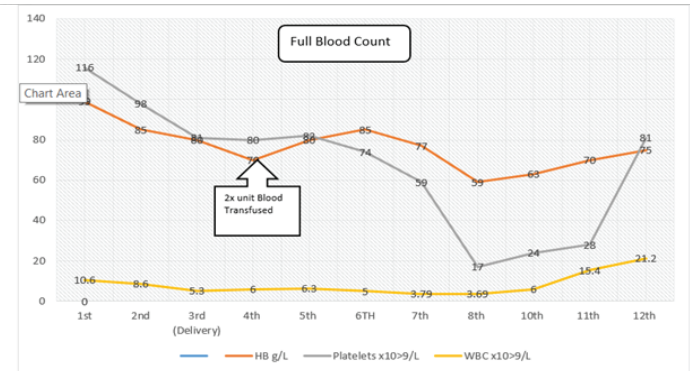

Figure 2. *Full Blood Count*

Investigations

Table 1. *Investigations*

Investigation	1st Day of admission	2nd	3rd (Delivery)	4th	5th	6th	7th	8th	9th (Acyclovir)	10th	11th	12th
Hemoglobin	99	85	80	70(2un)	80	85	77	59	Transfer to QEH	63	70	75
INR	1	1	1.1	1	1	1.3	1.8	2.2		1.3	1.7	1.0
APTT ratio	1.2	1.2	1.2	1.2	1.2	1.4	1.8	2.6		1.2	1.2	1.0
Fibrinogen	No result available					1.63	1.57	0.85				
Platelets	116	98	81	80	82	74	59	17		24	28	81
White Cell	10.6	8.6	5.3	6.0	6.3	5	3.79	3.69		6.0	15.4	21.2
ALT IU/L	52	70	155	236	571	647	759	1023		531	305	47
ALP IU/L	191	154	176	178	228	433	800	1033		513	336	304
Bilirubin umol/L	10	6	10	15	25	25	29	41		67	110	187
Coagulation	N	N	N	N	N	N						
Creatinine	62	N	52	55						144	46	176
LDH							3828	13790				
CRP	150	-	-	-	-	186				163	131	350
AKI	0	0	0	0						1	N/A	3
S.Lactate	0.6	0.8		1.6	1.3	-				1.6	3.1	2.6
PCR	--	-	N	-	-	-						
ASP. AMINO-TRANSPARSE	-	-	-	-	2134	-						

Hb: Hemoglobin,INR: international normalized ratio,.ALT: alanine aminotransferase, ALP: alkaline phosphatase, LDH: lactate dehydrogenase, CRP: c-reactive protein,AKI: acute kidney injury, PCR: polymerase chain reaction

Differential diagnosis

1. Sepsis in pregnancy
2. Pyelonephritis / Uro-sepsis
3. HELLP syndrome
4. Viral Infection

Treatment

IV Antibiotics for sepsis? pyelonephritis, IV antibiotics escalated to Meropenem in view of no response. Emergency LSCS in view of deteriorating LFT and possible diagnoses of HELLP syndrome. Transfer of care of woman to QEH in view of worsening hepatic failure. Institution of acyclovir treatment in mother.

Outcome and follow-up

1. Emergency CS
2. ITU care
3. Liver failure
4. Neonatal death: A post-mortem and placental histology was carried out. Following the review which took into account the information from the post-mortem, placental histology and other investigations the cause of death of the baby was determined to be: Disseminated neonatal herpes type 2 virus. After he died herpesvirus was identified on blood samples. Mum also had herpes: confirmed once neonatal herpes was confirmed.

Method of Research

TWhen pregnant women present with fever, raised LFTs & thrombocytopenia, urgent investigations are required to identify common diagnoses, such as Sepsis & HELLP syndrome. Nevertheless, viral Hepatitis is a very treatable cause of this presentation with potentially serious complications if missed, and may be more common in later stages of pregnancy. Hepatitis should not be discounted for if the patient is without skin lesion or eruptions and jaundice. Most cases show elevated transaminases and low to normal bilirubin, thus getting the name of “anicteric hepatitis” [6].

The most commonly affected individuals are immunosuppressed patients and females in the third trimester of pregnancy. Although, HSV hepatitis can occur in immunocompetent patients. [7] Typically, herpes hepatitis is identified by fever, leucopenia, and elevated transaminases (about 100 - to 1000-fold above normal with AST predominance [8]. Most patients who develop herpes hepatitis are immunocompromised (pregnant, newborn, on oral steroids, burn victims, organ transplantation, malignancy, or AIDS)

The diagnosis is frequently made at postmortem examination due to the nonspecific clinical presentation and lack of awareness [7]. Herpes hepatitis mortality is estimated to be 40 - 50% in pregnancy and more than 80% for all herpes associated hepatitis [9].

In our case a diagnosis was possible only in retrospect as there was no history or presentation of mucocutaneous lesions to suggest herpes infection. The limited evidence for a diagnosis of systemic herpes infection was virus isolation from body fluids of baby on postmortem and evidence of maternal liver infection recovery following acyclovir treatment. Patient recovered 2-3 months after the acute illness.

Risks to mother

Management of Genital Herpes in Pregnancy (BASHH/ RCOG 2014): The maternal mortality associated with this condition is high. Disseminated herpes is a rare condition in adults but more commonly reported in pregnancy, particularly in the immunocompromised. It may present with encephalitis, hepatitis, disseminated skin lesions or a combination of these conditions.

Neonatal Herpes [10] is a rare but serious infection with a high morbidity and mortality. 70% of infants with neonatal herpes have disseminated and/or CNS infection and approximately 60% of infants with local CNS and/or disseminated disease will present without skin, eye and/or mouth infection. 5-8% is congenital. Transmission from the mother to fetus is dependent on: the type of maternal infection (primary or secondary) and transplacental maternal neutralizing antibodies. Disseminated herpes is more common in preterm infants and occurs almost exclusively as a result of primary infection in the mother.

Early recognition and treatment are imperative as it is highly responsive to acyclovir treatment, preventing the progression to fulminant liver failure. Review of literature also suggests the initiation of empirical therapy in patients with progressive hepatic failure with no underlying cause. We recommend keeping disseminated HSV hepatitis as a differential diagnosis in any patient who presents with elevated aminotransferases and fever of unknown etiology in the presence or absence of skin lesions [2].

Learning points/take home messages

- Unusual presentation of primary Herpes in the mum leading to severe maternal morbidity and sadly neonatal death. Diagnosis of HSV hepatitis is often complicated by its rarity and nonspecific signs and symptoms. For this reason, clinicians should be aware of this condition and maintain it as a differential diagnosis in any patient who presents with elevated aminotransferases of unknown etiology.
- Could we have thought of Herpes?
- Should we ask regarding partner's sexual health at booking? The Sexual Health of the partner at booking was not known
- Think Herpes in a scenario of liver failure with unremitting sepsis not responding to usual antibiotics. .
- The history of acute genital herpes flare ups in partner should be consider to treat patient and baby .
- Sepsis and HSV guideline should be updated to add Importance of partner history of HSV at booking and subsequent visit if any concern.
- Involve Infectious Disease consultant/GU physicians in unusual cases of sepsis/ STI: it is unclear if microbiology were asked again when the patient was not responding to an escalated antibiotics regime..
- Clinical Information to go with PM or placenta requests. Mum wanted to know whether she transmitted herpes to her baby trans-placentally.

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