Case Report

Herpes Simplex Virus Type-2 Encephalitis in Peripartum Period Preceded by Hepatitis

Apoorva Pauranik, Satish Jain and M C Maheshwari

Encephalitis by Herpes Simplex virus type-2 in adults is rare and has been described as part of a disseminated infection in settings of immunosuppression, pregnancy being one of them. The virus was isolated from CSF of a young female, who during puerperium, presented with hepatitis, encephalitis and subsequently developed persistent vegetative state. Case history of another woman at term pregnancy is described who had similar illness but virological proof could not be obtained.

Key Words: Herpes simplex virus, Encephalitis, Hepatitis

The pathobiological differences between the two strains of Herpes simplex virus (HSV) are well known but should not be considered absolute in terms of clinical presentation. This is more so with recognition of syndrome of disseminated HSV infection (mostly type-2), in states of altered host defence, including pregnancy. Encephalitis and encephalitis in adults are two of the important manifestations of this syndrome. HSV-2 encephalitis in non-pregnant adults is also rare and has been reported in situations like drug abuse and vaccination, renal transplantation and thymic dysplasia. The present communication reports case history of a young woman with HSV-2 encephalitis in puerperium preceded by hepatitis. Before the virological studies suggested the more definitive diagnosis, her clinical course raised a few interesting issues which have been discussed. Encounter with another patient (case 2) having many clinical similarities but without virological evidence, highlights vulnerability to systemic infections in peripartum period.

CASE REPORT: 1

A 20-year-old female had severe postpartum hemorrhage and shock after caesarian section for the delivery of her first child. Pregnancy had been normal. 1200 ml of blood was transfused and shock managed. Steroids were not used. Patient remained better for next one week but was depressed with tendency to weep and had a short episode of diarrhoea on 6th day, along with fever, anorexia, irritability, vomiting and pain in limbs. By this time icterus was noticed. Hepatitis-B surface antigen (HBs Ag) was detected in blood. Two days later her sensorium deteriorated rapidly and within 24 hours she was deeply comatose. A diagnosis of hepatic encephalopathy was made in a private clinic. Serum bilirubin was 100 $\mu$mol/l, SGPT 1500 IU/dl and prothrombin time 24 seconds against a control value of 12 sec. CSF was clear with 0.35 gm/l protein, 1.67 mmol/l glucose (blood glucose 3.5 mmol/l) and 3 lymphocytes/mm$^3$. She had one generalized tonic clonic seizure 2 days after lapsing into coma. Liver function tests improved significantly after one week but there was no change in her state of consciousness.

She was admitted with us 2 weeks after the onset of hepatic illness. On examination she was thin built, afebrile with a blood pressure of 126/82 mmHg. There was no icterus. Liver was palpable 1 cm below costal margin, soft and nontender. She kept her eyes open with normal rate of blinking. Sleep-wake cycles had resumed. There was no response to verbal commands. Deep painful stimuli did not result in any avoidance movements in limbs. Pupils and fundus were normal. Menace reflex was absent but oculocarpal and oculovestibular reflex were normal. There was mild spasticity in flexors of all limbs. Deep tendon jerks were normal and Babinski

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Sign was positive on both sides. There were short episodes of excessive autonomic activity in the form of sweating, flushing, tachycardia, tachypnea lasting for 10–15 minutes and occurring 2–3 times per day. Body temperature and blood pressure remained unchanged in these periods.

Investigations with normal results included hemoglobin, WBC counts, urine albumin, serum albumin and globulin, serum creatinine, alkaline phosphatase, serum sodium and potassium, blood sugar and urea. Serum bilirubin was 20 µmol/l, SGOT 41 IU/dl, prothrombin time 16 seconds as against 12 seconds of control value. HBs Ag was not detected in blood. CSF was clear with protein 1.16 g/1, sugar 3.34 mmol/1 and no cells. EEG revealed bilateral diffuse slowing (2–3 Hz) with frequent sharp wave discharges from both temporal regions. Plain and contrast enhanced CT scans showed moderate low attenuation at both temporal poles and medial temporal lobes.

Throat and rectal swab, blood and CSF were sent for virus isolation and antibody titers against Herpes simplex (Table 1). Inoculation of CSF into cultured Hela and Vero cells induced cytopathic changes characteristic of Herpes simplex type II virus, confirmed by type specific monoclonal antibody. The result was reproducible on reinoculation from the sample.

General supportive care and adenine arabinoside (Vira-A) in dose of 15 mg/kg I.V. for 10 days did not result in any change in her vegetative status. Patient was in same state for next one year before being lost to follow up.

Table 1. Virological Studies

<table>
<thead>
<tr>
<th></th>
<th>Case-1</th>
<th>Case-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virus isolation</td>
<td>HSV type II isolated</td>
<td>Negative</td>
</tr>
<tr>
<td>Complement fixing antibody against HSV</td>
<td>Serum 1: 16 on day 30</td>
<td>Serum 1: 8 on day 5</td>
</tr>
<tr>
<td></td>
<td>1: 64 on day 80</td>
<td>1: 32 on day 40</td>
</tr>
<tr>
<td></td>
<td>SF: 1: 1 on both occasions</td>
<td>SF: Negative</td>
</tr>
</tbody>
</table>

CASE REPORT: 2

A 20-year-old woman developed symptoms suggestive of hepatitis at 36th weeks of her first pregnancy. She had started improving after 3 weeks, while admitted to a hospital for delivery. No pedal edema, hypertension or urinary abnormality were detected. Mild icterus was present. Delivery was normal. Within 24 hours, she had sudden severe headache and restlessness, followed by loss of consciousness and generalized tonic-clonic seizures which culminated into status epilepticus lasting nine hours. She remained unconscious for next 10 days. Records from the district hospital revealed intermittent fever, absence of lateralizing signs, elevated proteins (1.1 gm/l) in a clear CSF. On admission to our institution about 15 days after the onset of illness she was found to be thin built, with blood pressure of 120/80 mmHg. She appeared awake, looking around vacantly. She tended to shirk away on loud verbal commands and made few semipurposeful avoidance movements on painful stimuli. Fundus was normal. Pupils were equal in size and reaction. Spontaneous and reflex eye movements were full but not volitional. Tone was variable with fixed attitudes for long periods. Tendon jerks were normal and symmetrical and plantars downgoing.

Investigations with results within normal range included hemoglobin, WBC counts, ESR, routine urinalysis, serum bilirubin, blood urea, blood sugar, serum sodium and potassium. CSF was clear and acellular, with 0.9 g/l protein and 1.39 mmol/l glucose (blood glucose 4.1 mmol/l). Derangement in liver functions was revealed by SGPT 890 IU/dl, serum alkaline phosphatase 414 IU/dl (normal upto 270 IU). EEG showed bilateral diffuse slow waves as 3 Hz delta. X-ray chest and CT-scan of head were normal. HBs Ag was negative and prothrombin time equal to control value.

Virological studies (Table 1) were negative except four fold rise in complement fixing antibody titers in serum at interval of 5 week. Cytological examination of cervical smear showed features characteristic of herpes virus infection including intranuclear eosinophilic inclusions. There had been no change in her level of responsiveness over next 6 months except occasional generalized tonic clonic seizures despite regular use of phenytoin 300 mg daily.

COMMENT

In the absence of history or physical signs of primary genital or cutaneous herpetiform infec-
tion, there was no initial lead to suspect the diagnosis which ultimately looked most probable. The onset with hepatitis compounded the differential diagnosis. The encephalopathic illness (in case-1) superimposed upon viral hepatitis was understandably diagnosed as hepatic encephalopathy (HE), though absence of evolution through precoma stage and lack of characteristic EEG changes were odd features. Blood and CSF ammonia levels were not obtainable. It has been rightly emphasized that any alteration of sensorium in the setting of hepatic dysfunction should not be diagnosed as HE, and CSF should be examined in cases with unexpected discrepancy between neurological manifestations and liver disturbances. Continued altered sensorium after recovery of liver function is also unusual for HE, and permanent neurological sequelae are not observed in HE unless hepatic dysfunction persists chronically or recurs. Severe brain damage, however, may take palce in fulminant hepatitis with encephalopathy, not due to hepatic failure per se but as a result of some intercurrent complication like hypoxia, shock, metabolic derangements and brain edema. The patients being reported apparently did not have these problems. Encephalitis by hepatitis virus was considered by us as an extremely rare possibility, because extrahepatic manifestations of viral hepatitis do include involvement of cranial and peripheral nerves, meninges and higher mental functions.

The diagnosis of HSV-2 encephalitis (case-1) rested on fairly firm ground after virus isolation from CSF. Low attenuation values in both temporal lobes on CT-scan, bitemporal sharp wave discharges in EEG and elevated CSF protein were consistent with the diagnosis, though absence of CSF pleocytosis is unusual. GSF hypoglycorrhachia may rarely occur in HSV encephalitis and was present in our both patients in mild

Table 2. Disseminated Herpes Simplex Virus infection in relation to pregnancy. Summary of cases described in literature.

<table>
<thead>
<tr>
<th>Year of publication and Ref.</th>
<th>Age yr.</th>
<th>Gest. wk.</th>
<th>Primary Infection</th>
<th>Hepatitis</th>
<th>Encephal (itis) opathy</th>
<th>Other organs/systems</th>
<th>Positive virus</th>
<th>Serology (C.F)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1965 2</td>
<td>33</td>
<td>26</td>
<td>Cervicitis</td>
<td>Severe</td>
<td>Brain edema Hepatic-encephalopathy</td>
<td>Multiple organ failure</td>
<td>Liver</td>
<td>Not reported</td>
<td>died</td>
</tr>
<tr>
<td>1969 3</td>
<td>24</td>
<td>28</td>
<td>Stomatitis</td>
<td>Severe</td>
<td>None</td>
<td>Thrombocytopenia</td>
<td>Mouth ulcer, Liver tissue</td>
<td>1: 256</td>
<td>Survived</td>
</tr>
<tr>
<td>1972 4</td>
<td>19 Term</td>
<td>Pharyngitis</td>
<td>None</td>
<td>Present</td>
<td>None</td>
<td>Brain tissue, CSF</td>
<td>Not reported</td>
<td>died</td>
<td></td>
</tr>
<tr>
<td>1974 5</td>
<td>23</td>
<td>28</td>
<td>Pharyngitis</td>
<td>Severe</td>
<td>None</td>
<td>Adrenals</td>
<td>Liver, Lung, Kidney, Blood</td>
<td>Not reported</td>
<td>died</td>
</tr>
<tr>
<td>1976 6</td>
<td>21</td>
<td>37</td>
<td>Vulvovaginitis</td>
<td>Mild</td>
<td>Disorientation and seizures</td>
<td>Pancreas, myo-cardium</td>
<td>Liver</td>
<td>1: 8</td>
<td>died</td>
</tr>
<tr>
<td>1979 7</td>
<td>19</td>
<td>30</td>
<td>Cervicitis vaginitis</td>
<td>Mild</td>
<td>Hepatic encephalopathy and seizures</td>
<td>Coagulopathy, On autopsy-atrophic thymus</td>
<td>Vagina, Liver, Blood Aseptic fluid</td>
<td>1: 8</td>
<td>died</td>
</tr>
<tr>
<td>1980 8</td>
<td>21</td>
<td>36</td>
<td>Cervicitis vaginitis</td>
<td>Severe</td>
<td>Hepatic &amp; Multifactorial metabolic encephalopathy, On autopsy-Encephalitis</td>
<td>Coagulopathy shock</td>
<td>Liver</td>
<td>1: 512</td>
<td>died</td>
</tr>
<tr>
<td>1983 9</td>
<td>18</td>
<td>28</td>
<td>Cervicitis vaginitis</td>
<td>Mild</td>
<td>None</td>
<td>Pancreas leukopenia</td>
<td>Vaginal ulcers, Liver</td>
<td>1: 64</td>
<td>Survived</td>
</tr>
<tr>
<td>1983 9</td>
<td>30</td>
<td>26</td>
<td>Cervicitis</td>
<td>Mild</td>
<td>None</td>
<td>Distant skin lesions, leukopenia</td>
<td>Cervix, urine, skin</td>
<td>1: 64</td>
<td>Survived</td>
</tr>
<tr>
<td>1983 10</td>
<td>33</td>
<td>26</td>
<td>Cervicitis</td>
<td>Severe</td>
<td>Hepatic encephalopathy, cerebral edema, seizures</td>
<td>Coagulopathy</td>
<td>Cervix, Liver</td>
<td>Not reported</td>
<td>died</td>
</tr>
<tr>
<td>Present case 20</td>
<td>2nd wk, post-partum</td>
<td></td>
<td>Mild</td>
<td>Deep coma &amp; seizures</td>
<td>Skin</td>
<td>CSF</td>
<td>1: 16</td>
<td>Persistent vegetative state</td>
<td></td>
</tr>
<tr>
<td>Present case 20</td>
<td>Term</td>
<td>Occultvaginitis</td>
<td>Mild</td>
<td>Deep coma &amp; seizures</td>
<td>None</td>
<td>None</td>
<td>1: 52</td>
<td>Persistent vegetative state</td>
<td></td>
</tr>
</tbody>
</table>
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grade. Lack of response to delayed therapy and persistence of vegetative state were not unexpected. Serological tests supported the diagnosis, but limitations of these tests are paramount, and particularly in pregnancy, virus isolation is most sensitive, specific and optimal test to which all other methods are compared.

The reasons for rarity of HSV-2 encephalitis in adults are not known. An analysis of five reported cases of HSV-2 encephalitis in adults stresses significance of immunosuppression but otherwise there are no contrasting clinical features from neurological point of view. Our patients bore resemblance to picture of akinetic mutism, and episodic diencephalic dysfunction in case-1 was similar to that of a patient with brainstem encephalitis due to HSV, seen earlier by authors.

It is most likely that HSV was responsible for initial hepatitis. Disseminated herpetic infections are being more frequently reported during pregnancy and analysis of 10 previously reported cases reveals hepatitis to be an important feature. Severe involvement almost always occurs during third trimester or at term. Onset of systemic illness during early puerperium as happened in case-1, has not been previously reported. The quiescence of primary infection in both patients of present communication was also exceptional, though non specific symptoms of dissemination were present in case-1. The occurrence of such widespread infection during pregnancy in an otherwise healthy person may be due to suppression of immune response which involves interaction of humoral and cellular systems.

The association between pregnancy and severe complications of other viral infections are well known.

Hepatic dysfunction during peripartum period followed by acute encephalitis with poor recovery of CNS function in two patients constitutes an interesting association. Disseminated HSV-2 infection may be one of the possibility and should be considered in differential diagnosis in similar situations, including absence of primary herpes infection and onset in puerperium.

REFERENCES