

## Neonatal Herpes Simplex Virus-2 Encephalitis

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Of the two virologically distinct types of *Herpes simplex* viruses *i.e.*, types 1 and 2, *Herpes simplex* virus-2 [HSV-2] is the predominant cause of neonatal disease, and is almost always acquired from an infected maternal genital tract. Perinatally transmitted HSV-2 infection in the neonate may have either a localized, disseminated or encephalitic pattern of presentation. The encephalitic form often remain undiagnosed as 40-60% of neonates with central nervous system infection have no skin lesion at the time of clinical presentation(1). The outcome of the disease is largely dependent on a prompt diagnosis, which is difficult to make and adequate treatment, which is expensive. We are reporting the management of a neonate with HSV-2 encephalitis, which to our knowledge has not been documented earlier in Indian pediatric literature.

### Case Report

A 21 day term vaginally delivered female neonate with a birth weight of 2700 g was referred as a case of non-responsive pyogenic meningitis with

multiple focal clonic seizures since day seven of life. She had been treated with several parenteral antibiotics including aminoglycosides and third generation cephalosporins with -no significant improvement in cerebrospinal fluid (CSF) parameters. On admission to our neonatal nursery, the vital parameters were normal, no mucocutaneous vesicles were noted, there was mild hepatosplenomegaly, fundoscopy revealed no evidence of chorioretinitis. The multiple focal clonic seizures were difficult to control despite full therapeutic doses of intravenous phenobarbitone, phenytoin sodium and diazepam. Systemic examination revealed a few crusted skin lesions on the trunk. Nervous system examination revealed an increase in the tone of all the extremities and exaggerated deep tendon reflexes. Maternal genital tract showed no herpetic lesions.

A non-traumatic lumbar puncture revealed xanthochromic CSF with 2 polymorphonuclear cells, 1155 red blood cells/cu mm and 1150 mg/dl proteins with a normal glucose level. Smear and culture were negative for bacteria. A hemogram, liver function tests and coagulation profile were normal. In view of a hemorrhagic CSF report, crusted skin lesions and no response to adequate treatment for pyogenic meningitis, a diagnosis of HSV-2 encephalitis was entertained.

The first electroencephalogram (EEG) on admission showed an isoelectric pattern (*Fig. 1*). HSV-2 specific serum immune titres were as follows; (i) HSV-2 IgM of neonate: 1.013 U/ml (positive >0.229 U/ml); (ii) HSV-2 IgG of mother: 62.9 U/ml (positive >20 U/ml);

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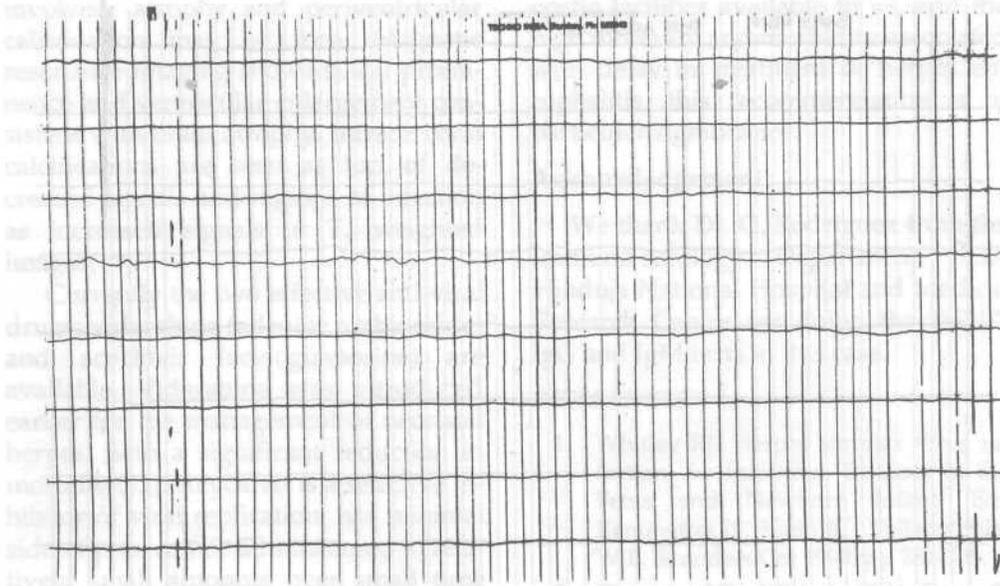


Fig. 1. Electroencephalogram; pre-acyclovir therapy showing an iso-electric pattern.

and (Hi) IgM of mother: 0.249 U/ml (positive >0.208 U/ml). CSF HSV-2 immune titres were not available to us. Radionuclide brain scan and cranial ultrasonography were normal. Computed tomography and magnetic resonance imaging could not be performed.

The patient was treated with intravenous acyclovir 10 mg/kg/dose as an infusion over one hour, three times a day for 14 days and then maintained on oral acyclovir 30 mg/kg/day for 14 days(2).

Clinically, the crusted lesions healed, multiple focal seizures ceased and the child accepted breast feeds; however, the EEC continued to remain isoelectric (Fig. 2). CSF analysis at the end of three weeks of treatment was normal.

### Discussion

According to Western data, the incidence of newborn infection due to

*Herpes simplex-2* is estimated to be between 1:2000 to 1:5000 live births(1). Neonatal herpes infection is classified into three categories: (i) Infection localized to the skin, eye and/or mouth; (ii) Encephalitis with/without localized muco-cutaneous disease; and (iii) Disseminated infection with multiple organ involvement including the CNS, lung, liver, adrenal, skin, eye and mouth. Each of these three presentations has an almost equal incidence of between 30-35%(3). Localized CNS disease has a mortality of 50%(1).

CSF abnormalities typically consist of xanthochromia, consistent with the release of blood into the subarachnoid space secondary to the necrotizing nature of the disease, RBCs ranging from 0-500/mm<sup>3</sup>, moderate pleocytosis(50-200 WBCs/mm<sup>3</sup>), an elevation of protein levels (60-200 mg/dl) with normal levels of glucose and cultures which are

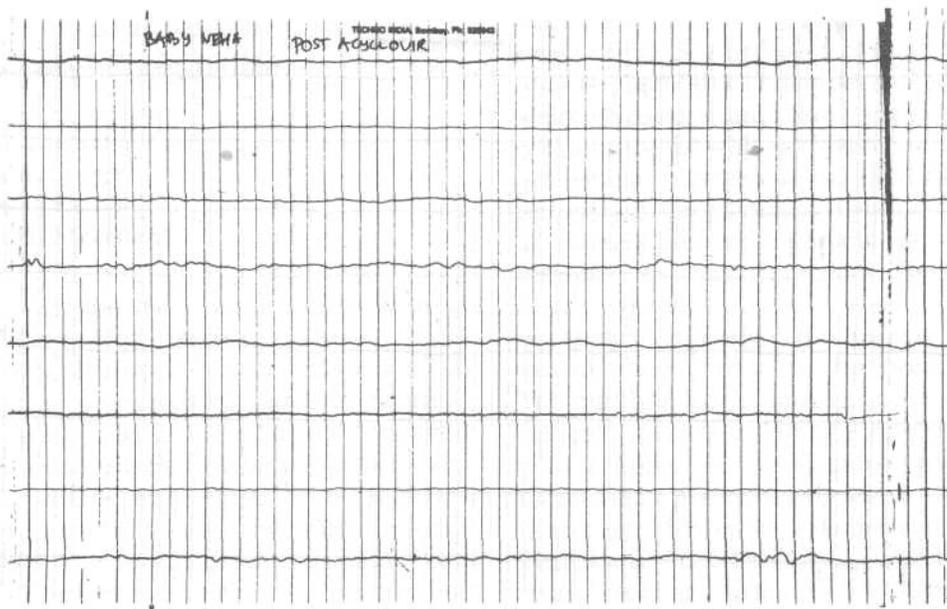


Fig. 2. Electroencephalogram: post-acyclovir therapy continues to show an iso-electric pattern.

negative, for bacteria(4). This typical picture was present in our case.

The EEG in herpes encephalitis shows a diffuse slow wave background with periodic complexes, sharp and slow waves over the frontal and temporal lobe indicative of the site of cerebral insult. These findings are only present in 50% of cases(5). A low voltage, flat tracing or isoelectric pattern as seen in our patient (*Figs. 1 & 2*), occurs in neonates with severe brain insult, due to hypoxia, intra-ventricular hemorrhage, meningitis, subdural hemorrhage and profound dysgenetic malformations. This pattern carries a poor prognosis(6,7).

The most definitive diagnosis of HSV infection entails recovery of the virus from visible lesions or throat, stool, conjunctiva, urine and CSF. However, this requires the specimen to be frozen at  $-70^{\circ}\text{C}$  and shipped in dry ice or to be transported in ambient temperatures us-

ing Stuart medium(8). Facilities for virus isolation are not routinely available in our country. Analysis of infants IgM specific antibody response is the most rapid and suggested means of establishing the infection(9). This antibody appears two weeks following onset of infection and persists for 6-12 months. The rarity of HSV-2 infection in infants less than 6 months of age, makes finding of the IgM antibody in this age group highly suggestive of perinatal infection. This diagnostic facility is available only in a few centres in our country. Newer techniques for rapid diagnosis of herpes simplex encephalitis include the nested polymerase chain reaction assay of CSF(10). Characteristic though not pathognomic features have been described for neonatal herpes simplex virus encephalitis in brain imaging techniques. On computed tomography, the temporal lobes are most commonly

involved, atrophy and periventricular calcification may be seen. Magnetic resonance imaging shows sulcal prominence and ventricular enlargement consistent with brain atrophy. Intracerebral calcifications are seen as foci of decreased signals and regions of infection as increased signals in T<sub>2</sub> weighted images(H).

Currently the two effective anti-viral drugs; vidarabine (adenine arabinoside) and acyclovir (acycloguanosine) are available. Vidarabine was introduced earlier for the management of neonatal herpes, with a significant reduction in mortality(12). Acyclovir is a selective inhibitor of viral replication, has minimal side-effects, can be administered in relatively small amounts over small time periods and is the favored drug in treatment at present. However, studies have shown no significant differences in the final outcome with either drug(13). The recommended dose of acyclovir is 10 mg/kg/q8h with each dose infused over 1 hour and of Vidarabine is 15-30 mg/kg/day given as an infusion over 12 hours. Both drugs are given for 10-14 days(1). Controlled studies have shown that antiviral therapy leads to an impressive reduction in mortality and morbidity. However, non administration of anti viral therapy or a delay in its institution is associated with a high mortality and complications such as; microcephaly, hydranencephaly, porencephalic cysts, spasticity, chorioretinitis, blindness, learning disabilities and seizures(14). Low incidence of side-effects with acyclovir led to the recommendation that in highly suggestive situations a specific diagnosis of herpetic infection before treatment is no longer required(15). In view of limited diag-

nostic facilities available to us, and the high mortality and morbidity associated with delay in treatment of herpes encephalitis, this recommendation is of particular significance.

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## Complicated Anophthalmos

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Holoprosencephaly is an early developmental defect of the brain in which there is a failure to form paired cerebral hemispheres. The cerebrum is made up

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of an unpaired Sphere and the lateral ventricles are represented by a single mid line cavity. Usually there is an associated arhinencephaly-absence of olfactory bulbs and tracts, cleft lip and microphthalmia or cyclopia. Affected children rarely survive past infancy(1). Complete failure of development of the primary optic vesicle results in anophthalmos(2). Complicated anophthalmos is a syndrome comprising of anophthalmos associated with craniofacial malformation, harelip, polydactyly, cardiac malformations and mental retardation(3). We report a similar case. This condition is extremely rare.

### Case Report

A 21-day-old infant was admitted with facial abnormality, small eyes and inability to open the eyes. The baby was 3rd in order delivered at term normally. There was a history of antenatal drug