Late Onset Neonatal Herpes Encephalitis: A Case-Based CNS Complication and Neurological Outcome

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Abstract

Individual neurological complication caused by Herpes simplex viruses in neonates is well-known. We report neonatal Herpes encephalitis that caused multiple neurological complications in the same patient during acute phase of illness. Our patient differs from previously reported cases in the following ways: 1) Late onset neonatal presentation; 2) Development of multiple neurologic complications during acyclovir therapy; 3) Cesarean-section did not prevent perinatal transmission of Herpes simplex virus; and 4) Our patient’s acute hydrocephalus was managed conservatively and he had no reoccurrence of seizure, hydrocephalus, and no motor deficits. A high degree of suspicion, timely needed supportive medical and surgical care, and prompt initiation of intravenous acyclovir offer the best chance for neurological outcome in neonates with Herpes encephalitis.

Keywords

Neonatal Herpes Encephalitis, Central Nervous System Complication, Acute Hydrocephalus, Intracranial Hemorrhage, Opsoclonus or Dancing eye, Cerebral Palsy

Subject Areas: Neurology

1. Introduction

Clinical signs associated with neonatal herpes simplex viral (HSV) infection are variable and its course tends to...
be rapidly progressive [1]. Neonates usually present with seizure with or without fever preceded by undetermined lethargy. In such scenario, their cerebrospinal fluid (CSF) is examined by polymerase chain reaction (PCR) for HSV DNA. An urgent magnetic resonance imaging (MRI) is indicated during early course of the illness. The MRI identifies the predilection of the HSV for temporal and extra-temporal gray matter leading to hemorrhagic encephalitis [2].

The individual neurological complications in isolation such as intracerebral or intraventricular hematoma, hydrocephalus, ischemic stroke, opsoclonus with and without myoclonus, Wallenberg’s lateral medullary syndrome, acute retinal necrosis, and uncal herniation have been reported in the past [3]-[9].

Authors report late onset neonatal Herpes encephalitis in a single patient who developed multiple neurological complications in acute phase of his illness. Authors provide evidence-based cases review of central nervous system (CNS) complications and outcome in neonates with Herpes encephalitis.

2. Case Report

An 8-week-old boy was brought to a tertiary University Children’s Medical Center Emergency Department (ED) for continued fever (39°C), poor feeding, and being “fussy” for the past five days. His birth history was complicated by early rupture of the membrane and cesarean section (C-section). He had multiple seizures without regaining consciousness. Emergency management of status epilepticus was initiated with intravenous (IV) lorazepam (0.14 mg/kg in two divided doses) and phenobarbital (20 mg/kg). The emergency medical interventions terminated the status. IV ampicillin, cefotaxime, and acyclovir (60 mg/kg/day) were started in the ED. Four days prior to admission, past medical history included inpatient medical care with empirical treatment for bacterial meningitis.

Examination in pediatric intensive care unit revealed a lethargic child with stable vitals. Head circumference was 39 centimeter (50th percentile) and anterior fontanel was open and soft. There were no mucocutaneous lesions. His pupils were equal and reactive to light. The eye movements were in full.

The routine blood tests, serum biochemistry, and coagulation profile, all were normal. Initial brain computerized tomography (CT) demonstrated a normal ventricular size and preservation of white matter-gray matter junction (Figure 1(a)). CSF studies revealed a white blood cell count of 160/mm³ (predominantly lymphocytes), red blood cells of 2900/mm³, protein of 186 mg/dl, and glucose of 35 mg/dl. Serum glucose was 83 mg/dl (normal 65 - 110). CSF culture revealed no bacterial growth. Polymerase chain reaction (PCR) was positive for HSV-2 DNA and it was negative for HSV-1 DNA. Nasal swab culture for Enteroviruses was negative. The electroencephalogram and brain magnetic resonance imaging (MRI) findings were consistent with the right temporal-frontal encephalitis. His ophthalmic examination was normal.

On day six, he developed chaotic eye movements of varying amplitudes (opsoclonus) without facial movements (myoclonus). A stat follow-up brain CT scan revealed hydrocephalus, intraparenchymal and intraventricular hemorrhages. They were monitored clinically with the use of head ultrasound. His hydrocephalus was treated conservatively. A follow up brain CT, two weeks after acyclovir therapy, is shown in Figure 1(b).

He completed a 21-day course of IV acyclovir therapy. He was discharged on phenobarbital. During the first two years of follow-up, his eye movements returned to normal. There was no reoccurrence of seizure, HSE, or hydrocephalus. He had no motor deficits.

3. Discussion

Neonatal Herpes simplex encephalitis (HSE) is most commonly (70%) caused by HSV-2. By contrast, virtually all adults HSE are caused by HSV-1. The fetus acquires HSV-2 infection through shedding of the virus during vaginal delivery [10]. An elective C-Section is usually performed to prevent transmission of virus in suspected mothers. In our case, the mother was asymptomatic. Because of non-progressive labor for 21 hours, the child was delivered by C-Section. But this did not prevent the transmission of the virus. We believe that the patient acquired an ascending infection in the presence of an early rupture of the membrane prior to C-section.

Like this case, an early diagnosis remains a significant problem. This may relate to the rarity of the condition. Non-specific CSF pleocytosis, the finding suggesting partially treated bacterial meningitis, and a false negative CSF PCR in the early course of the disease may delay the diagnosis [11]. Additionally, lack of abnormality on initial brain CT and delay in obtaining MRI of the brain could further delay the diagnosis.
Figure 1. Computerized tomography of the brain axial cross-sectional images at third ventricle. (a) Prior to start antiviral therapy shows a normal ventricular size, a normal cerebrospinal fluid signal, and the preservation of frontal white matter-gray matter junctions; (b) Two weeks after acyclovir therapy at one level above (a) shows loss of white matter-gray matter differentiation, hyperdense right frontotemporal, right frontal horn and both occipital horns suggesting intraparenchymal and intraventricular hemorrhage, respectively. Note: A global enlargement of ventricles, including fourth which is not seen at this level.

The pathogenesis of multiple complications, intracerebral and intraventricular hemorrhage and communicating hydrocephalus may have been caused by a combined effect of an initial delay in diagnosis and intracerebral hemorrhage leading to intraventricular hemorrhage. Compromise in cerebrovascular (arterial and venous circulation) would result in an impedance or inability to absorb CSF efficiently by arachnoid villi at the superior sagittal sinus. Such functional blockage has been reported to occur after intracranial hemorrhage.

Opsoclonus-myoclonus-syndrome is usually associated with diseases of the brainstem and cerebellum. This has been reported, but it is not limited to neuroblastoma, varicella-zoster, West Nile and Enteroviruses in adult and pediatric populations. This is thought to be a result of an autoimmune response directed against cross-reactive proteins of offending agents and neuronal cells. The cause of an isolated opsoclonus without myoclonus in our case remains speculative. Contrary to Kroczek S et al. (2003), description of opsoclonus as a possible early sign of HSV-2 CNS infection, our patient opsoclonus developed during acyclovir therapy [12].

4. Literature Search and the Results

We performed PubMed online search for English literature for infants and neonatal herpes encephalitis. We used terms “Herpes simplex virus 1 and 2”, “Herpes Encephalitis”, “hydrocephalus”, “CNS complication”, neurological outcome in isolation or combination with either neonate or infant. Bibliography of the reports was searched for additional information.

The results of our search are shown in Table 1 [12]-[26].

Combined CNS complications occurred in 32/48 (67%) neonates. In HSV-1 group, 6 neonates (40%) and HSV-2 group, 26 (79%) had neurological complications. In HSV-1 group; 9 (64%) and in HSV-2 group; 7 (21%) had no neurologic sequelae. No deaths were reported in neonates with HSV-1. Two patients with hypertonicity were excluded in the graph. Neonates with no HSV typing done were excluded from the study.

Why our patient had good neurological outcome despite multiple complications? Probably, this relates to severity of the infection and maturity level of the brain, as our patient presented at age 8 weeks. The literature search revealed age ranges of neonatal Herpes encephalitis between births to a maximum of 26th days.

5. Conclusions

In conclusion, awareness of these complications together with previously reported entities will allow acting in timely manner. Acute hydrocephalus is a potentially life-threatening and a treatable surgical complication of
Table 1. Shows combined summary of the reports clinical demography for central nervous system complications in 48 neonates with Herpes simplex encephalitis type 1 and 2.

<table>
<thead>
<tr>
<th>Clinical presentation</th>
<th>Antiviral initiation</th>
<th>HSV type</th>
<th>Acute CNS complication</th>
<th>Neurologic outcome [reference]</th>
</tr>
</thead>
<tbody>
<tr>
<td>At birth/boy</td>
<td>Mucocutaneous lesions</td>
<td>4 days/yes</td>
<td>2</td>
<td>NA</td>
</tr>
<tr>
<td>At birth/boy</td>
<td>Lethargy, mucocutaneous vesicles</td>
<td>15 days/no</td>
<td>2</td>
<td>Necrotizing retinitis</td>
</tr>
<tr>
<td>At birth/girl</td>
<td>Skin lesions and severe jitteriness</td>
<td>NA</td>
<td>2</td>
<td>Seizures, apnea, abnormal posture</td>
</tr>
<tr>
<td>At birth/boy</td>
<td>Generalized seizures, Lethargy, Full anterior fontanelle</td>
<td>NA</td>
<td>2</td>
<td>Large and tiny hemorrhages in cerebellar hemispheres</td>
</tr>
<tr>
<td>2 hours/boy</td>
<td>Focal seizures and Apnea</td>
<td>18 hours/yes</td>
<td>2</td>
<td>Encephalomalacia</td>
</tr>
<tr>
<td>2 days/boy</td>
<td>Lethargy, Apnea, and hypopnea</td>
<td>4.5 hours/yes</td>
<td>2</td>
<td>NA</td>
</tr>
<tr>
<td>7 days/girl</td>
<td>Clonic jerking of right side</td>
<td>2 days/yes</td>
<td>1</td>
<td>Recurrent Obstructive hydrocephalus</td>
</tr>
<tr>
<td>9 days/girl</td>
<td>Vesicles on occipital and parietal scalp</td>
<td>&lt;1 day/yes</td>
<td>1</td>
<td>None</td>
</tr>
<tr>
<td>9 days/girl</td>
<td>Apnea, bradycardia, and encephalitis</td>
<td>&lt;1 day/yes</td>
<td>1</td>
<td>Left parietal Encephalomalacia with hemorrhagic component</td>
</tr>
<tr>
<td>9 days/girl</td>
<td>Seizures</td>
<td>4 days/yes</td>
<td>2</td>
<td>NA</td>
</tr>
<tr>
<td>10 days/girl</td>
<td>Pustular rashes over the eyelid and encephalitis</td>
<td>&lt;6 hours/yes</td>
<td>2</td>
<td>NA</td>
</tr>
<tr>
<td>10 days/girl</td>
<td>Apnea, lethargy, encephalitis</td>
<td>5 days/yes</td>
<td>2</td>
<td>Recurrent Herpes simplex virus encephalitis</td>
</tr>
<tr>
<td>13 days/girl</td>
<td>Generalized myoclonic seizures, lethargy</td>
<td>7 days/yes</td>
<td>2</td>
<td>Cerebral malakoplakia</td>
</tr>
<tr>
<td>14 days/girl</td>
<td>Seizures, flaccid paralysis, left ptosis.</td>
<td>2 days/yes</td>
<td>2</td>
<td>Spastic right hemiplegia, chorioretinitis, homonymous hemianopia</td>
</tr>
<tr>
<td>15 days/girl</td>
<td>Focal seizures, apneic episodes</td>
<td>3 days/yes</td>
<td>2</td>
<td>Megacystic encephalomalacia, Cortical atrophy and Subdural effusions</td>
</tr>
<tr>
<td>15 days/girl</td>
<td>Seizures</td>
<td>&lt;1 day/yes</td>
<td>1</td>
<td>NA</td>
</tr>
<tr>
<td>16 days/girl</td>
<td>Lethargy, Facial diplegia, and Hypotonia</td>
<td>1 day/yes</td>
<td>2</td>
<td>Hypotonia, and Hyperreflexia</td>
</tr>
<tr>
<td>17 days/girl</td>
<td>Focal clonic upper limb seizures</td>
<td>2 days/yes</td>
<td>1</td>
<td>Acute retinal necrosis</td>
</tr>
<tr>
<td>17 days/girl</td>
<td>Seizures and mucocutaneous lesions</td>
<td>2 days/yes</td>
<td>2</td>
<td>NA</td>
</tr>
</tbody>
</table>
Continued

<table>
<thead>
<tr>
<th>Age (days)</th>
<th>Condition</th>
<th>Duration</th>
<th>Seizures</th>
<th>Sequelea</th>
<th>Description</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>18/day</td>
<td>Seizures</td>
<td>2/day</td>
<td>yes</td>
<td>2</td>
<td>NA</td>
<td>[13]</td>
</tr>
<tr>
<td>20/day</td>
<td>Generalized seizures</td>
<td>7/day</td>
<td>1</td>
<td>Oro-glosso-phaalgeal paralysis</td>
<td>Epilepsy, opercular syndrome, and cerebral palsy</td>
<td>[25]</td>
</tr>
<tr>
<td>20/day</td>
<td>Seizures</td>
<td>2/day</td>
<td>yes</td>
<td>2</td>
<td>NA</td>
<td>[13]</td>
</tr>
<tr>
<td>23/day</td>
<td>Generalized seizures</td>
<td>5/day</td>
<td>2</td>
<td>Severe bilateral Encephalomalacia, and chorioretinitis</td>
<td>Severe developmental delay and epilepsy</td>
<td>[17]</td>
</tr>
<tr>
<td>26/day</td>
<td>Lethargy and opsoclusus</td>
<td>4/day</td>
<td>2</td>
<td>Seizures</td>
<td>No sequela</td>
<td>[12]</td>
</tr>
<tr>
<td>1 - 15/day</td>
<td>Lethargy, poor feeding, cutaneous lesions</td>
<td>3-8/day</td>
<td>1</td>
<td>Unknown</td>
<td>Eight neonates had no sequela</td>
<td>[26]</td>
</tr>
<tr>
<td>0 - 10 days</td>
<td>Lethargy, poor feeding, cutaneous lesions</td>
<td>2-6/day</td>
<td>2</td>
<td>Unknown</td>
<td>Four neonates had no sequela</td>
<td>[26]</td>
</tr>
<tr>
<td>NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NA, data not available. Foot note: our patient differs from previously reported cases in the following ways: 1) a late neonatal presentation; 2) a C-section did not prevent perinatal transmission; 3) Multiple CNS complications, opsoclusus, intraparenchymal and intraventricular hemorrhage, and acute hydrocephalus in the same patient. Additionally, our case required an emergent neurosurgical intervention. Two neonates, one neonate was diagnosed by positive serology testing [27] and another by PCR but no HSV typing [28], both were excluded from the Table 1 and Graph 1.

Graph 1. Is showing neurologic outcome of neonates with combined herpes simplex encephalitis type 1 and 2. Combined CNS complications occurred in 32/48 (67%) neonates. In HSV-1 group, 6 neonates (40%) and HSV-2 group, 26 (79%) had neurologic complications. In HSV-1 group, 9 (64%) and in HSV-2 group; 7 (21%) had no neurologic sequelae. No deaths were reported in neonates with HSV-1. Two patients with hypertonicity were excluded in the graph. Neonates with no HSV typing done were excluded from the study.
Herpes encephalitis. These actions alone may not prevent the CNS complication. For this reason, primary prevention of perinatal transmission of herpes by considering an elective C-section remains important.

A high degree of suspicion, timely needed supportive medical and surgical care, and prompt initiation of intravenous acyclovir offer the best chance to improve morbidity and mortality of neonatal herpes encephalitis.

**Conflict of Interest**

None.

**References**


**Abbreviations**

CNS: central nervous system;  
CSF: cerebrospinal fluid;  
CT: computerized tomography.
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