The Clinical Course in the Periventricular Leukomalacia Complex

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ABSTRACT

Intraventricular hemorrhage (IVH) and classical periventricular leukomalacia complex are considered the two most common forms of perinatal anoxic-ischemic brain injury. However, recently, a third entity, the periventricular leukomalacia complex (PLC) was described and was seen in 31 percent of 61 premature infants coming to autopsy from the University of Connecticut Neonatal Intensive Care Unit (NBIC) and in several other centers. Periventricular leukomalacia complex consists of necrotizing lesions of the periventricular white and grey matter, hippocampus and subiculum, cerebellum and basis pontis. The clinical course of PLC is similar to that of IVH, but it is important to differentiate PLC as the widespread nature of these lesions may lead to a poor neurological outcome.

Introduction

Intraventricular hemorrhage and classical periventricular leukomalacia are considered the two most common forms of perinatal-hypoxic-ischemic brain injury. However, recently a third entity, the periventricular leukomalacia complex (PLC), has been described and has been seen more commonly than classical periventricular leukomalacia in several centers. In a recent autopsy study by the present authors of 61 neonates, six neonates (10 percent), were found who had the clinical picture of intraventricular hemorrhage (IVH) but who, at autopsy, were found to have moderate to severe periventricular leukomalacia complex (PLC) with no IVH or classical periventricular leukomalacia (PVL). Moreover, 13 (21 percent) other infants had pathological evidence of some degree of PLC as well as IVH without PVL. In this group of 61 infants, PVL was not seen. The periventricular leukomalacia complex (PLC) consists of necrosis of the basis pontis, hippocampus and subiculum, cerebellar folia, and periventricular grey and white matter with proliferation of macrophages and reactive astrocytes of varying degree. It is thought to be due to a combination of hyperoxia and hypotension. Infants who survive with even mild degrees of PLC could be expected to show more general neurological prob-
lems such as spasticity, incoordination, abnormal movements, and visual deficit than those with intraventricular hemorrhage or PVL alone because of the widespread nature of the lesions. Thus far, however, no infants with this disease who lived over 30 days have been examined.

Therefore, the clinical charts of the six neonates with PLC but no IVH were examined by the present authors and their clinical course was compared with four neonates who had IVH with no PLC to see if it was possible to differentiate infants with PLC from those with IVH. The few available computer assisted tomography scans (CT), ultrasound scans (US), and electroencephalographs (EEG) of these infants were also examined for clues to the diagnosis of PLC.

Materials and Methods

The gross and microscopic neuropathological findings in 61 consecutive premature neonates coming to autopsy from the University of Connecticut Neonatal Intensive Care Unit between 1980 and 1983 without central nervous system anomalies or infections were reviewed. All six neonates with PLC but without IVH were chosen for clinical chart review. Since neonates who have developed PLC lived a minimum of three days, it was attempted to age match the six PLC neonates with four infants with only IVH who lived three or more days. Age matching was difficult in that neonates with only PLC tended to live much longer than infants with only IVH. The charts, available CT and US scans, and EEG’s were reviewed to determine whether or not PLC had distinctive symptoms or signs which could differentiate it from IVH. Ultrasound scans, CT scans, and EEG’s were done only when the patients’ condition warranted it. The microscopic and gross neuropathological findings of these 10 neonates were reviewed as well. The neuropathological diagnoses of all 61 neonates are given in table I.

Results

The major feature of the clinical courses of three neonates with moderate PLC, three infants with severe PLC, and four infants with IVH are shown in table II.

Pathology: Babies 1 to 3 showed moderate PLC consisting of neuronal necrosis, nuclear pyknosis, and karyorrhexis with infiltration of foamy macrophages in the caudate nucleus, putamen, subiculum, Sommers sector of the hippocampus, the lateral thalamus, nuclei of the base of the basis pontis, internal granular cell layer of the cerebellum (figure 1), and periventricular white matter. The inferior olives showed moderate loss of neurons and reactive astrocytosis.

Babies 4 and 5 showed more extensive and severe changes. The nuclear pyknosis and karyorrhexis and spongy change extended throughout the white matter into the lower layers of the cortex, throughout all nuclei of the basis pontis into the lower pontine tegmentum, and into the external granular layer and Purkinje cell layer of the cerebellum.

Baby 6 showed more chronic changes of PLC. These included loss of neurons with astrocytosis in the caudate nucleus, putamen, thalamus, and hippocampus. The cerebral white matter was rarefied and showed reactive astrocytosis. The

| TABLE I                          |  
|----------------------------------|------------------------------|
| Diagnoses of Total Population    |------------------------------|
|                                  | Number | Percent |
| No lesions                       | 16     | 26      |
| PLC alone                        | 6      | 10      |
| PLC and IVH                      | 13     | 22 > 31 |
| IVH alone                        | 26     | 43      |
| PVL                              | 0      | 0       |

PLC = periventricular leukomalacia complex
IVH = intraventricular hemorrhage
PVL = periventricular leukomalacia
TABLE II  
Major Feature of the Clinical Courses of Neonates

<table>
<thead>
<tr>
<th>Moderate PLC Babies</th>
<th>Severe PLC Babies</th>
<th>Severe IVH Babies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestational age</td>
<td>28</td>
<td>28</td>
</tr>
<tr>
<td>Length of life</td>
<td>13</td>
<td>18.3</td>
</tr>
<tr>
<td>Bradycardic spells</td>
<td>5</td>
<td>15</td>
</tr>
<tr>
<td>Seizures, posturing</td>
<td>3</td>
<td>9.7</td>
</tr>
<tr>
<td>Decreased spontaneous respirations</td>
<td>1</td>
<td>12.3</td>
</tr>
<tr>
<td>Decreased spontaneous activity</td>
<td>3</td>
<td>10.7</td>
</tr>
<tr>
<td>Total Infants</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

PLC = periventricular leukomalacia  
IVH = intraventricular hemorrhage  

Bradycardia, apneic spells, and seizures were common in neonates with either PLC or IVH alone. Bradycardia, apneic spells, and seizures usually continued over a longer period of time for neonates with severe PLC than moderate PLC or IVH, although this was not true in individual cases. During the day or two prior to death, most of the neonates with either PLC or IVH had decreased spontaneous respiration and movements. One neonate with IVH only as well as two with PLC only developed renal failure and acidosis just prior to death.

Neonates with IVH often had bulging fontanelles and a drop in hematocrit whereas neonates with PLC alone did not show bulging fontanelle. One neonate in this group with PLC alone showed a drop in hematocrit secondary to a clinically evident pulmonary hemorrhage.

The average gestational age of neonates with PLC alone was somewhat greater than those with IVH alone, 28 weeks versus 27 weeks. In a larger series, gestational age of neonates with...
PLC, particularly when associated with IVH, was similar to those with IVH alone. The neonates with PLC alone lived significantly longer than neonates with IVH alone, 15 days versus five days.

One neonate with PLC alone and one with IVH plus PLC were subjected to EEG's. The neonate with PLC alone had an excessively discontinuous pattern for age with multifocal vertex sharp waves and spikes. The neonate with IVH and PLC showed severe background attenuation intermixed with high amplitude theta activity. This neonate also showed sharp waves in the central regions more prominent on the left.

The most severely affected neonate (Case 6) with a chronic stage of PLC alone had several ultrasound and CT scans. Early US scans showed hyper-echogenic regions about the ventricles with no increased echogenicity within the ventricles (figure 3). Later, both CT and US scans and autopsy brain examination showed moderately enlarged lateral ventricles and a cystic basis pontis.

Two other infants with PLC only showed a mild increase in periventricular echos on US scans one day prior to death.

Discussion

Portions of the periventricular leukomalacia complex have been described in other centers as pontosubicular necrosis by Friede, as hyperoxic brain necrosis by Barmada, and as massive necrosis of the newborn brain by Larroche. However, the clinical syndrome accompanying these lesions has not been described. Periventricular leukomalacia complex is an important diagnosis to make since the widespread lesions of this entity could lead to a poor neurological outcome.

In our present study and in a previous study, neonates with significant PLC showed spells of bradycardia and apnea, seizures, lethargy, unresponsiveness, poor tone, extensor rigidity and loss of spontaneous respirations and activity, but never developed a full fontanelle. In our previous series and in this series,
neonates with IVH had a very similar clinical course, although some neonates with IVH developed a full fontanelle, and all showed a drop in hematocrit. One infant with PLC alone in each series showed a drop in hematocrit associated with pulmonary hemorrhage.9 In the earlier series, the pulmonary hemorrhage was not clinically evident.

Cukier et al, and others described what they thought was a pathognomonic sign of IVH, namely Rolandic positive sharp waves.35 Subsequently, Rolandic sharp waves have been seen occasionally as single transients in small prematures, in hydrocephalous and in classical periventricular leukomalacia.11 Two of our infants with moderate to severe PLC, one of which also had IVH, showed positive sharp waves in the vertex or central regions, indicating that this sign may suggest PVL if IVH is not present on CT or US scan. Because of the small numbers of available EEG’s, the usefulness of the EEG in diagnosing PLC awaits further study.

On US scan and CT scan, the pathognomonic feature of the IVH is a hyper-density or hyperechogenicity within the lateral ventricles. The identification of PVL on US and CT scans is not clear.14 Recently, moderately hyperechogenic areas in periventricular regions have been seen in US scan which subsequently evolve to hypoechoic cystic areas. These have been interpreted as the lesions of classical periventricular leukomalacia.1,8 One neonate (Case 6) with the severe chronic PLC had several US scans which showed periventricular hyperechogenic areas but no evidence of IVH. Later, US and CT scans showed only enlarged ventricles and a cystic basis pontis which was also seen at autopsy. Two more of the infants who were found to have PLC without IVH had a mild increase in periventricular echos on US scan approximately one day prior to death as well. This suggests that CT and US scans may be helpful in differentiating PLC from IVH in neonates. Again, however, further study is needed to define the US and CT scan apperance of PLC.

In summary, an infant who has the clinical symptomatology of IVH and has vertex or central sharp waves along with other abnormalities but who has no intraventricular echogenicity on US scan should be suspected of having PLC.
Infants with both PLC and IVH will be difficult to diagnose clinically.

References