

Case report

Hypoxic ischemic encephalopathy associated with neonatal seizures without other neurological abnormalities

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Abstract

We reported three term or near-term infants with parasagittal infarcts. Their Apgar scores were low and the amniotic fluid was meconium-stained. Resuscitation was necessary immediately after birth, but they were not stuporous and no neurological abnormalities were recognized on admission. They showed metabolic acidosis and transient hypoglycemia, and two showed hematoemesis. Seizures were observed between 2 and 15 h of age in all of them. Electroencephalography demonstrated moderate or severe depression, and CT demonstrated bilateral abnormal low densities in the border zones of the middle and posterior cerebral arteries. Two of them had mental retardation and epilepsy, although the other exhibited normal development. Our infants suggest that neonatal seizures can also occur in infants with hypoxic ischemic encephalopathy without apparent neurological abnormalities.

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1. Introduction

It is generally accepted that hypoxic ischemic encephalopathy (HIE) in term infants is usually associated with neurological abnormalities. Mild encephalopathy is characterized by hyperalertness, jitteriness and exaggerated primitive reflexes. Moderate encephalopathy is associated with lethargy, stupor, hypotonia and suppressed tendon reflexes. Severe encephalopathy is associated invariably with coma, and brainstem and autonomic dysfunction [1]. Seizures are seen in infants with moderate or severe HIE, who invariably have apparent neurological abnormalities. However, we experienced three term or near-term infants with seizures due to HIE without other neurological abnormalities. This report describes the clinical, laboratory, electroencephalographic and neuroimaging features of these infants.

2. Case reports

One hundred and forty-four term or near-term infants with asphyxia (1 min Apgar score <6 and/or the need for resuscitation in the delivery room) were admitted to our hospital during 1992 through 1999. Six of them had seizures confirmed by ictal electroencephalography (EEG). Severe neurological abnormalities such as coma and hypotonia were observed in three of them. The other three infants did not have neurological abnormalities other than seizures. The clinical courses of these infants are described below.

2.1. Case 1

A 1715 g girl was born at 35 weeks of gestation. Her mother was admitted to a regional hospital because of toxemia from 31 weeks of gestation. She was the second twin. No abnormalities were recognized in the first twin with a birthweight of 2360 g. Because of the non-reactive pattern on cardiotocography, induction of labor was performed. She was transvaginally delivered with breech presentation. Her Apgar score was 2 at 1 min. The amniotic fluid was meconium-stained and resuscitation with supplementary oxygen

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was necessary. She was transferred to our hospital at 1.5 h of age.

On admission, she was rather vigorous but no abnormalities were noted on physical examination. The Moro reflex, blink reflex and light reflex were present. The sucking reflex and doll's eye phenomenon were preserved, and the muscle tone of the trunk and extremities was normal. The anterior fontanel was flat and the cranial sutures were not widened throughout the neonatal course. Arterial blood gas analysis revealed metabolic acidosis with pH 7.19 and base excess -16.3 mmol/l. Acidosis was corrected by a single administration of sodium bicarbonate. The blood glucose level was 38 mg/dl. This was corrected by infusion therapy. The blood glucose level was 94 mg/dl at about 1 h after admission. The cultures and blood examination showed no signs of infection. Apneic spells were seen at 10 h of age. EEG showed paroxysmal discharges in the right central and temporal regions accompanied by apneic spells. Background EEG showed moderate depression according to the criteria proposed by Watanabe et al. [2].

The seizures disappeared on the administration of 10 mg/kg of phenobarbital. The urine output rate was 1.0 ml/kg per h during the first 48 h, and the peak blood urea nitrogen and creatinine values were 27 and 2.1 mg/dl, respectively. Echocardiography was normal during the neonatal period. Creatine kinase (CK) reached a peak value of 11245 IU/l on the second day of life, whereas the peak CK-BB isozyme value of 414 IU/l was observed on the first day of life. There was no evidence of clotting or thrombophilic abnormalities. Ultrasonography revealed widespread mild hyperechodensities in the bilateral cerebral hemispheres on the first day of life. The hyperechodensities had disappeared by the third day of life. CT at 40 weeks of conceptional age demonstrated low density areas in the bilateral parieto-occipital lobes (Fig. 1a). MRI at 5 years of age demonstrated atrophy in the bilateral parieto-occipital regions (Fig. 1b,c).

Her psychomotor development was mildly delayed,

although a motor deficit was not observed. Her development quotient was 70 at 3 years of age. Partial seizures with visual loss developed at 7 years of age and were controlled with clonazepam. EEG revealed spikes in the right occipital region.

2.2. Case 2

A 2550 g boy was born transvaginally after an uncomplicated gestation of 40 weeks. However, the amniotic fluid was meconium-stained and his Apgar score was 5 at 1 min. Resuscitation with supplementary oxygen was needed. He looked vigorous at 10 min of age. However, he was transferred to our hospital because of hypoglycemia (28 mg/dl).

No neurological abnormalities were noted on admission. The Moro reflex, blink reflex and light reflex were recognized. The sucking reflex and doll's eye phenomenon were preserved, and the muscle tone was normal. The anterior fontanel was flat and the cranial sutures were not widened throughout the neonatal course. Arterial blood gas analysis on admission revealed metabolic acidosis with pH 7.24 and base excess -12.4 mmol/l. The acidosis was corrected by a dose of sodium bicarbonate. The blood glucose level was 54 mg/dl on admission and remained within the normal range. Blood cultures showed no growth of pathogens. At 15 h of age, he exhibited seizures with apnea and tonic posturing. EEG showed paroxysmal discharges in the left frontal, bilateral central and right occipital regions. Background EEG showed moderate depression.

The seizures disappeared on the administration of 10 mg/kg of phenobarbital. He developed hematoemesis on the first day of life. This improved only with conservative treatment. The urine output rate during the first 24 h was maintained at 3.8 ml/kg per h, and blood urea nitrogen and creatinine remained within the normal ranges. CK reached a peak value of 1435 IU/l on the second day of life, whereas

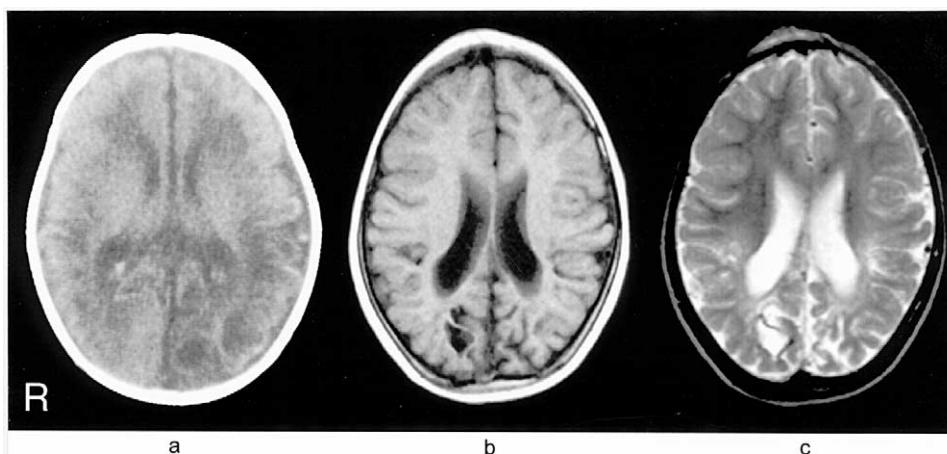


Fig. 1. CT and MRI findings in case 1. (a) CT at 40 weeks of conceptional age. Abnormal low density areas in the bilateral parieto-occipital regions were recognized. (b) A T1-weighted image (TR 450 ms, TE 14 ms) and (c) a T2-weighted image (TR 2000 ms, TE 120 ms) on MRI at 5 years of age demonstrated atrophy in the bilateral parieto-occipital regions.

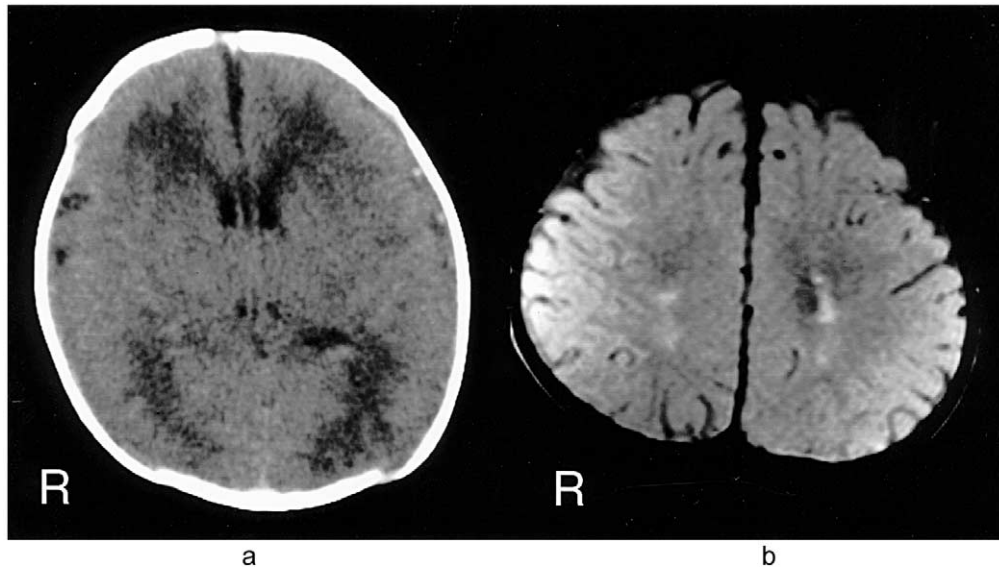


Fig. 2. CT and MRI findings in case 2. (a) CT on the eighth day of life. Widespread low densities in the white matter and occipital lobes were recognized. (b) A proton density image on MRI at 1 year of age demonstrated abnormal high signals in the bilateral parietal regions.

the peak CK-BB isozyme value of 79 IU/l was observed on the first day of life. There was no evidence of clotting or thrombophilic abnormalities. Echocardiography was normal during the neonatal period. Ultrasonography revealed widespread mild hyperechodensities in the bilateral cerebral hemispheres on the first day of life. The hyperechodensities had disappeared by the third day of life. CT on the eighth day of life demonstrated widespread low densities in the white matter and occipital lobes (Fig. 2a), and MRI at 1 year of age demonstrated abnormal high signals in the bilateral parietal regions without ventriculomegaly (Fig. 2b).

His psychomotor development was normal at the last follow-up at 2 years and 7 months of age. His developmental quotient was 95 at 18 months of age. He had not experienced epileptic seizures.

2.3. Case 3

A 2806 g boy was born at 39 weeks of gestation. He was delivered by emergent cesarean section because of massive vaginal bleeding. The amniotic fluid was meconium-stained, and the Apgar scores were 1 and 2 at 1 and 5 min, respectively. Resuscitation with transient endotracheal intubation was performed. He developed seizures and hypoglycemia (19 mg/dl). He was transferred to our hospital at 2.5 h of age.

He was vigorous but exhibited no neurological abnormalities on admission. The Moro reflex, blink reflex and light reflex were recognized. The sucking reflex and doll's eye phenomenon were preserved. The muscle tone was normal. The anterior fontanel was flat and the cranial sutures were not widened throughout the neonatal course. Arterial blood

gas analysis revealed metabolic acidosis with pH 7.20 and base excess -13.5 mmol/l. The acidosis was corrected by the administration of sodium bicarbonate. The blood glucose level was 22 mg/dl. The hypoglycemia was corrected by continuous intravenous infusion. Cultures and blood examination showed no signs of infection. Seizures recurred at 5 h of age without hypoglycemia. EEG showed paroxysmal discharges in the left central and occipital regions (Fig. 3a). Background EEG revealed marked depression (burst-suppression) (Fig. 3b).

The seizures were controlled by the administration of 10 mg/kg of phenobarbital. He developed hematoemesis, renal failure and thrombocytopenia. These problems improved only with conservative treatment. Anuria was seen in the first 24 h. The urine output rate was 1.0 ml/kg per h in the next 24 h. Blood urea nitrogen and creatinine reached peak values of 31 and 3.3 mg/dl, respectively, on the seventh day of life. Echocardiography was normal during the neonatal period. CK reached a peak value of 4318 IU/l on the second day of life, whereas the peak CK-BB value of 865 IU/l was observed on the first day of life. There was no evidence of clotting or thrombophilic abnormalities. Urine analysis did not indicate the presence of any inborn error of metabolism. Ultrasonography revealed no abnormalities throughout the neonatal course, but CT on the 18th day of life demonstrated a widespread low density area in the bilateral hemispheres (Fig. 4a). MRI at 10 months of age demonstrated atrophy in the bilateral occipital regions (Fig. 4b).

His mental development was severely delayed, although he exhibited no motor impairment. His development quotient was 28 at 3 years of age. Complex partial seizures associated with loss of consciousness and tonic posturing were observed from 9 months of age. EEG revealed bilateral frontal dominant spike-and-waves. No anticonvulsants

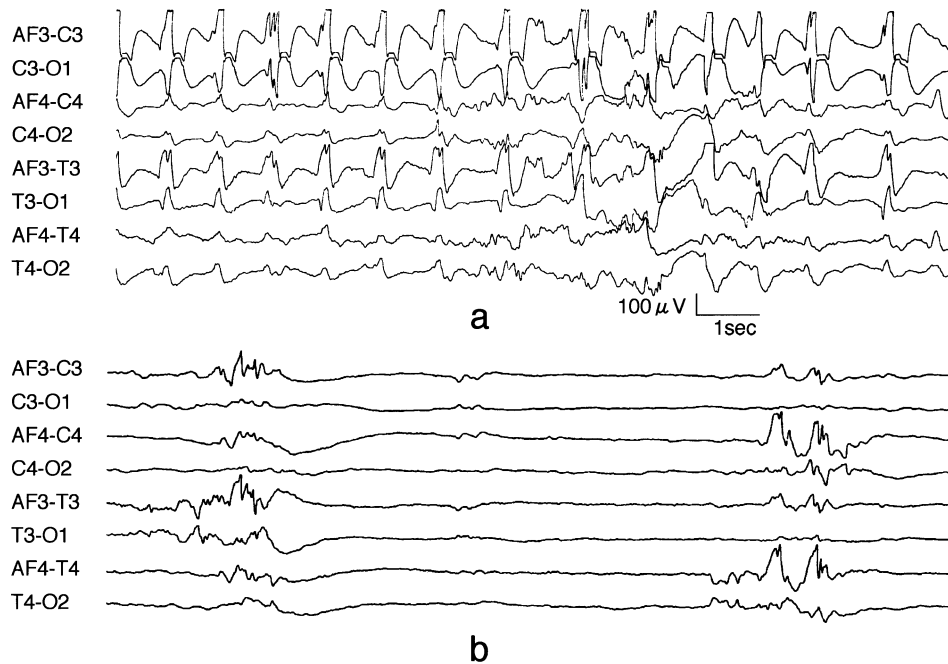


Fig. 3. EEG of case 3 on the first day of life. (a) Paroxysmal discharges were seen in the left central and occipital regions. (b) Background EEG demonstrated marked depression (burst-suppression).

were administered, because his family did not agree with the use of anticonvulsants.

3. Discussion

We consider that the seizures in our infants are attributable to HIE. Blood gas analysis on admission revealed mild but definite metabolic acidosis. The low Apgar scores, the

need for resuscitation immediately after birth, and the meconium-stained amniotic fluid indicate the occurrence of a hypoxic ischemic insult around birth. EEG on the first day of life demonstrated moderate or severe depression suggesting a suppressed brain function. Renal failure was seen in two infants and marked elevation of CK was recognized in all infants. These findings are consistent with HIE.

The neuroimaging findings in our infants are consistent with parasagittal infarcts, although the findings were mild in

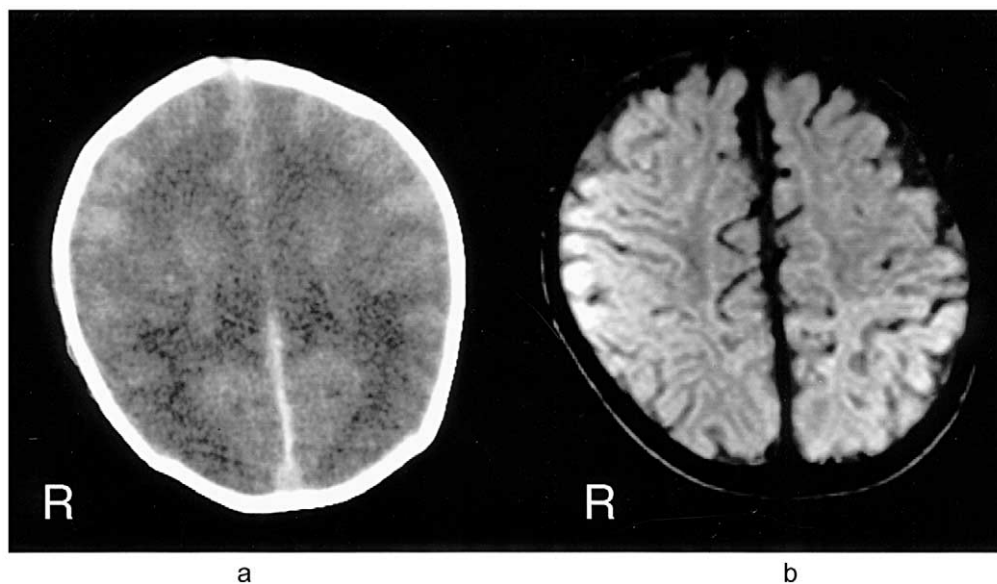


Fig. 4. CT and MRI findings in case 3. (a) CT on the 18th day of life. A widespread low density area in the bilateral hemispheres was recognized. (b) A proton density image on MRI at 9 months of age demonstrated atrophy in the occipital region.

cases 2 and 3. Parasagittal infarcts are characterized by atrophy and gliosis of the border zones of the anterior, middle and posterior cerebral arteries in the bilateral hemispheres [3,4]. Cerebral infarction can also cause neonatal seizures without apparent neurological abnormalities like in our infants [5]. Neuroimaging studies involving such as CT or MRI are useful for distinguishing parasagittal infarction from cerebral infarction. Infants with severe hypoglycemia also have occipital dominant widespread white matter lesions. It is difficult to differentiate the brain damage associated with HIE from that caused by neonatal hypoglycemia [6], although some authors stated that neuroimaging studies allow their differentiation [7]. Hypoglycemic cerebral lesions show a superficial distribution of the damage in pathological and neuroimaging studies. However, the involvement of the parasagittal watershed area is characteristic in infants with HIE. We consider that the distribution of the lesions was closer to that in HIE. In addition, the hypoglycemia seen in two of our infants was mild and quite transient, and seizures occurred even after the hypoglycemia had been corrected. Thus, hypoglycemia was less likely to be a cause of the seizures or brain lesions in our infants.

The prominent feature of our three infants is seizures without other neurological signs of HIE. The absence of apparent neurological abnormalities may not always exclude the occurrence of HIE. It is generally considered that neonatal seizures in HIE are observed in infants with moderate or severe cases [1]. Such infants are very likely to have stupor or coma. The muscle tone is usually reduced but may be increased in some cases. Primitive reflexes such as the Moro reflex are also attenuated. However, our three infants were not in the least stuporous before the seizures appeared. The muscle tone was normal and the primitive reflexes were completely preserved. These facts suggest that the HIE was relatively mild in our infants and that seizures can occur in infants with such HIE. In fact, neuroimaging demonstrated relatively mild changes and the developmental outcome was rather favorable. Another possible explanation is that these infants sustained earlier pre-partum brain damage with sufficient recovery before birth. As a result, the evidence of clinical encephalopathy could have been masked. The non-reactive pattern on cardiotocography in case 1 indicated the possibility of intrauterine brain injury. However, there was no evidence suggestive of fetal distress in cases 2 and 3.

It is interesting that our infants showed no clinical signs of increased intracranial pressure. The anterior fontanel remained flat and the cranial sutures were not widened. Studies have demonstrated that infant animals subjected to prolonged partial asphyxia develop brain swelling and cortex injury that is predominant in the parasagittal border zones [8]. Parasagittal infarcts are considered to be a consequence of reduced cerebral blood flow induced by brain edema and increased intracranial pressure [9]. This suggests that parasagittal infarcts can occur without profound brain

edema. In contrast, the basal ganglia and thalami remained intact in our infants. Infants with basal ganglia–thalamic lesions often have a history of near total asphyxia [8,10,11]. Therefore, the mode of brain insult in our infants will be similar to prolonged partial asphyxia rather than near total asphyxia.

Background EEG revealed remarkable abnormalities in our infants, although they did not exhibit apparent neurological abnormalities. The discrepancy between the EEG and clinical signs can be explained by the speculation that the participation of the cerebral cortex in movement or behavior is relatively little in newborn infants. When the brainstem remains intact, the muscle tone can be normal and the primitive reflexes can be preserved even if cortical dysfunction occurs. This indicates that detection of mild HIE without brainstem involvement is difficult without EEG recording. We consider that EEG is useful for determining the presence or absence of HIE.

In conclusion, our infants suggest that neonatal seizures can occur in infants with mild HIE without apparent neurological abnormalities. Neuroimaging studies have revealed parasagittal infarcts. EEG is useful for the diagnosis of mild HIE.

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