Cerebral infarcts in full term neonates

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Cerebral infarcts are an important cause of neonatal convulsions. We report the etiologic factors, and clinical and neuroradiologic findings of four full term neonates who presented with neonatal convulsions and had cerebral infarct.

In our patients the risk factors for the cerebral infarct were perinatal asphyxia, sepsis, dehydration and catheter application. All had convulsions as the initial sign of infarct and had cranial imaging which revealed the definitive diagnosis. The patients underwent an extensive evaluation for hereditary causes of cerebral infarct that included anticoagulant factors (Proteins C and S, antithrombin III, antiphospholipid antibodies), factor V Leiden and prothrombin gene mutations, blood and urine amino acid and urine organic acid levels. The results were found to be within normal limits.

In conclusion, neonatal convulsions can be the first sign of cerebral infarct. For this reason it seems preferable to include cranial imaging by computed tomography or magnetic resonance imaging (MRI) in the work-up of cases with unexplained neonatal convulsions.

Neonatal cerebral infarcts, relatively common conditions with a prevalence of 1 in 4,000 live births, usually present with neonatal seizures alone or together with various neurologic findings[1]. With the advent of neuroimaging techniques and diagnostic methods, the nature, etiology, and clinical findings of neonatal cerebral infarcts have been clarified[2]. Although a great number of causes including cardiac, hematologic, metabolic, and primary vascular abnormalities may lead to neonatal cerebral infarct, the etiology remains unclear in nearly half of the patients[3]. Similarly, limited data exist regarding the neurological outcome of infants with neonatal stroke. In this report we aimed to discuss the clinical and radiological findings and outcome of four full term neonates with cerebral infarct, and evaluated the etiologic factors.

Case Reports

Demographic and clinical features of the patients are presented in Table I, and the results of

Table I. Clinical Features

Patient no.	Birth weight	Route of delivery	Apgar scores*	Clinical symptom	Risk factors	Treatment
1	2900	vaginal	2/3/7	HIE** Generalized convulsion	– Perinatal asphyxia – Multiorgan failure – DIC	– Mechanical ventilation – Antiepileptics
2	3500	vaginal	8/9	Focal convulsion (right)	– Central catheterization – Enterobacter	– Antibiotics – Antiepileptics
3	3800	vaginal	6/9	Focal convulsion (left)	– Hypernatremic dehydration – Sepsis	– IV rehydration – Antibiotics – Antiepileptics
4	3300	vaginal	8/9	Focal convulsion (right)	– Sepsis – Meningitis	– Antibiotics – Antiepileptics

DIC: disseminated intravascular coagulation.
* Apgar scores are given for the first, fifth and tenth minutes where indicated.
** HIE: Hypoxic ischemic encephalopathy.

Table II. Biochemical, Neuroradiologic and EEG Findings of Patients with Cerebral Infarct

Patient no.	Anticoagulant factors	Cranial ultrasound	Cranial computed tomography	Magnetic resonance imaging	EEG	Others
1	Protein C: 74% Protein S: 70% Antithrombin III: 111mg/dl	Normal	Subdural hematoma Left temporoparietal infarction	Letf MCA[1], PCA[2] infarction	Irregular background activity at the left hemisphere	Echocardiography N
2	Protein C: 92% Protein S: 87% Antithrombin III: 31 mg/dl	Normal	Not performed	Left parietal cortical and subcortical infarction	Normal	Echocardiography N
3	Protein C: 90% Protein S: 75% N Antithrombin III: 28 mg/dl N	Normal	Right occipitoparietal infarction and edema	Right occipito parietal infarction, right transverse sinus thrombosis[3]	Slow background activity at the right occipital area	Echocardiography N Urine organic acids Blood amino acid
4	Protein C: 100% Protein S: 150% N Antithrombin III: 24 mg/dl	Not performed	Left temporoparietal and occipital infarction	Left PCA infarction	Irregular background activity	Echocardiography N Urine organic acids Blood amino acid N

laboratory investigations in Table II.

Case 1

The infant was born at term to a 26 year old, gravida 3, para 2 mother vaginally after induction of labor. Birth weight was 2900 g Apgar scores were 2, 3 and 7 at 1,5 and 10 minutes, respectively. After a successful neonatal resuscitation which includeden dotracheal intubation in the delivery room, the infant was admitted to the neonatal intensive care unit. The patient had irregular respiration, poor peripheral perfusion and hypotension. She presented encephalopathy and exhibited decerebrate posturing after tactile stimulation. Brain stem reflexes were normal, but all newborn reflexes were absent. No other neurologic abnormality was detected. The laboratory evaluation showed severe metabolic acidosis and biochemical markers of multiorgan failure. She had recurrent seizures which were treated by phenobarbital and phenytoin. After a week of mechanical ventilation and supportive treatment of multiorgan failure, she began to improve clinically. Cranial magnetic resonance imaging (MRI) showed left middle cerebral artery (MCA) and posterior cerebral artery (PCA) infarction (Fig. 1). At three weeks of age she was discharged from the hospital with phenobarbital therapy. The neurologic examination at discharge revealed truncal hypotonia. The patient was followed at the pediatric neurology department. The current neurologic examination at 14 months of age revealed right hemiparesis and mild psychosocial delay.

Case 2

The patient was transferred to our neonatal intensive care unit for the treatment of hyperbilirubinemia secondary to ABO incompatibility at 27 hours of age. He was treated with phototherapy and intravenous immunoglobulin. Because of the rapid increase of bilirubin, isovolumetric double volume exchange transfusion was performed as well. Enterobacter cloacae grew in the blood cultures obtained during the exchange transfusion. Investigation of cerebrospinal fluid did not reveal meningitis. Intravenous meropenem and amikacin were started. At 48 hours of age the infant had a clonic convulsion on the right side and was treated with phenobarbital.

(a) (b)

Fig. 1. Cranial MRI examinations of patient 1:

a) T1-weighted sequence, coronal section, showing infarction in the territories of left middle cerebral artery (MCA) and posterior cerebral artery (PCA).

b) T2-weighted sequence, axial section, showing subacute left MCA and PCA infarcts (3 weeks after admission).

Fig. 2. Cranial MRI of patient 2: T2-weighted sequence, coronal section, showing left parietal cortical and subcortical

Cranial MRI results were compatible with left parietal cortical and subcortical infarctions (Fig. 2). When he was discharged after 14 days intravenous antibiotic treatment, the neurologic examination was normal. The family did not bring the child for follow-up, but when contacted by phone approximately one year later, stated that the child had achieved age-appropriate developmental milestones.

Case 3

The patient was referred to our hospital for difficulty in feeding, lethargy and jaundice starting at 24 hours of age. Upon referral to our hospital the infant had a convulsion characterized by deviation of eyes to left and apnea. At that time serum glucose level was 25 mg/dl. On exam the infant looked moderately dehydrated, hypoactive and icteric. His weight was 15% lower than the birth weight and he was diagnosed to have hypernatremic dehydration. He had a negative sepsis work-up and cerebrospinal fluid examination was normal. The patient was treated with antibiotics as well as intravenous fluids and phototherapy. Despite the correction of dehydration and hypoglycemia, the infant continued to be lethargic and had 2 to 3 convulsions a day which were treated with phenobarbital. Cranial MRI and MR venography showed right occipito-parietal infarction and right transverse sinus thrombosis (Fig. 3). The patient was discharged after 3 weeks of hospitalisation with phenobarbital therapy. The neurologic examination at discharge showed no asymmetry, but preferential deviation of the eyes to the right was noted. He was followed up in pediatric neurology and physical therapy departments. At 12 months of age his neurologic findings consisted of microcephaly, left hemiparesis, mild psychosocial and language delay. He had mixed type of seizures including infantile spasms. Cranial MRI revealed right occipitotemporoparietal atrophy. MR venography was normal.

Case 4

At 30 days of age the patient had irritability, poor feeding and convulsions and was admitted to the hospital. Despite treatment with IV antibiotics (ampicillin and netilmicin) with presumptive diagnosis of sepsis and meningitis, there was no clinical improvement after 3 days and he was transferred to our hospital for further evaluation. On admission the infant was hypoactive and hyperthermic and had depressed newborn reflexes. He had increased tonus at the lower

(a) (b)

Fig. 3. Neurodiologic examinations of patient 3:

a) Cranial CT showing hypodense area at the right occipitoparietal region.

b) Cranial MRI (T2-weighted sequence, axial section) showing right occipitoparietal infarction.

extremity and clonus on the right side. He continued to have multifocal clonic convulsions. Left temporoparietal and occipital infarctions were detected on cranial MRI. After four weeks of hospitalisation, he was followed up as outpatient and physical therapy was continued. At four years of age, the paitent had mild right hemiparesis, but his psychosocial development was normal.

Discussion

Cerebrovascular disorders (CVDs) are medical emergencies in term newborns with variable clinical presentation and high mortality and morbidity rates[3]. Hemorrhagic or ischemic disorders of the brain may be seen in the newborn period, however focal ischemic infarction is much less common in neonates than intracranial hemorrhage[4]. Ischemic cerebral infarct implies a focal cerebral necrosis resulting from a vascular insufficiency usually caused by thromboembolism and vascular malformations[2]. Cerebral infarcts may have prenatal or perinatal onset. Prenatal cerebral infarcts present as porenphalic cysts or hydrencephaly after birth[5]. A great number of causes classified as cardiac, intravascular (metabolic and hematologic) and vascular abnormalities may result in ischemic cerebral infarct[6]. Thrombotic stroke is usually the result of either a de novo thrombus or an endothelial abnormality resulting in clot formation. Risk factors for neonatal cerebral thrombosis include systemic infections, polycytemia, dehydration, asphyxia, catheter application, placental dysfunction, fetal growth retardation, feto-fetal transfusion, maternal eclampsia,birth trauma, or maternal drug abuse[3,7]. Neonates with congenital heart disease and infants of diabetic mothers are at increased risk of thrombotic complications. Genetic conditions that predispose to cerebral infarcts are inherited prothrombotic disorders including protein C and S deficiency as well as other physiologic anticoagulant deficiencies, and inborn errors of metabolism such as homocystinuria, organic acidemias, and congenital disorders of glycosylation[8]. Even with the recent advances in diagnostic methods, etiological factor cannot be identified in half of the newborns with ischemic cerebral infarct[7].

Neonates with cerebral infarcts should be screened for inherited thrombophilia[9-13]. The clinical manifestations of inherited thrombotic disorders occur in less than 5% of affected children, but neonates are at the greatest risk of childhood thromboembolic complications[7]. All of our patients were investigated for hereditary thrombophilia and none had deficiency of proteins C or S or antithrombin III. Patients 1, 3 and 4 were screened for factor V Leiden and prothrombin gene mutations but none was present.

Sepsis was the cause of cerebral infarcts in three of four newborns in our study. Disseminated intravascular coagulation (DIC) together with perinatal asphyxia, central catheter application, and dehydration were the other risk factors. Catheter-related thromboses have been reported in 2-20% of the neonates with central catheters[14]. Although neonatal thromboses related to central venous catheters tend to occur particularly in very sick preterm neonates[14,15], term newborns who have central catheter should be carefully observed for possible risk of cerebral thrombosis. Septicemia is among the most commonly listed causes in the reported series[15]. It has been reported that infection can potentially increase the risk for thrombosis and cerebral ischemia by several pathogenic pathways[16-20]. Fever and reduced fluid intake during infection may cause hemoconcentration and decreased cerebral blood flow. Plasma viscosity may increase because of high fibrinogen levels[16]. High leukocyte count and increased activation of leukocytes may cause microvascular flow disturbances[18-20]. Increased elastase release by activated granulocytes and activation of the coagulation system may plan an important role in the pathogenesis of infection-associated stroke[20]. During inflammation, anticoagulant pathways, including the protein C/protein S system and antithrombin III, may be inhibited. Cerebral vascular endothelium is activated by inflammatory cytokines including IL-1 and tumor necrosis factor (TNF), and these cytokines stimulate procoagulant properties while inhibiting the anticoagulant and fibrinolytic systems[20]. All newborns with septicemia are at great risk for cerebral infarct, thus clinical findings during management of these infants indicating a cerebral infarct (seizure etc.) should be carefully evaluated.

Neonates with cerebral infarcts most commonly present with seizures that can be in focal type or associated with apnea, alteration of conscious

ness and hypotonia[21]. Whereas, it was reported that cerebral infarct was detected in 12-18% of term newborns with seizures[1,22]. All the newborns in this report had seizures, and in three of them the type of seizure was focal clonic. Major focal motor deficits are usually uncommon even in large infacts[1]. If the appropriate cranial imaging technique is not used in newborns with risk factors for cerebral ischemia or in babies with unexplained seizures as well as unexplained neurological findings, cerebral infarct will be missed. Thus, all newborns with unexplained seizures need to have cranial imaging by computerized tomography (CT) or MR[1,23].

Although periventricular and subcortical infarcts may be visualized by cerebral ultrasound, it has a limited value for cortical lesions[1,22]. All three of our patients who had a normal ultrasound result were diagnosed to have a cerebral infarct later by MRI. The cranial CT findings of newborns with cerebral infarct are similar to that of the older children or adults[4]. However, on cranial MRI, which is the best available method to demonstrate injured regions of the brain in acute and chronic phase, the appearance of infarcts is different and may be subtle[4,24]. The acutely edematous infracted cortex becomes isointense with the underlying unmyelinated white matter on routine spine echo sequence. In subacute phase, regions of infarct show hyperintensity on T1-weighted images and hypointensity on T2-weighted images[4]. The middle cerebral artery territory is affected more often than anterior or posterior artery territories; rarely is more than one artery involved in a given patient[2]. The left carotid artery has a straighter course than the right artery, thus infarcts on the left side are more common. Similarly, the localization of infarcts was on the left side in three of the four presented patients.

The management of newborns with CVD is still questionable. In the newborn period, the CVD is usually a self-limited condition with low risk of recurrence, and the possible side effects of anticoagulant drugs may be life-threatening[21,25,26]. Most of the authors have not recommended anticoagulation in cerebral thrombosis[21,26]. None of the presented patients received anticoagulation therapy nor had a recurrence.

Limited data exist regarding the neurological outcome of infants with neonatal stroke and the prognostic value of clinical and laboratory findings[21,26-28]. Three of four patients were followed up and all of them had hemiparesis of various degree, two patients had psychosocial developmental delay, and one patient had microcephaly and developed West syndrome. In one series of 16 term newborns with cerebral infarct, 11 of 15 survivors had an apparently normal outcome, although detailed evaluations were not done[27]. In another study, five of nine infants with neonatal stroke involving the corticospinal tract developed hemiparesis[28]. It has been reported that severe disabilities following neonatal cerebral infarct are not the rule, however, careful neurodevelopmental testing is needed to detect possible language and perceptual abnormalities[29]. The prognostic value of clinical features, EEG and neuroradiologic findings is controversial[2,30].

Three of our patients who developed hemiparesis had abnormal findings on neurologic examination at discharge. Sreenan et al.[29] have reported the association of abnormal findings on neurologic examination at discharge with long-term disability. Irregular background activity at the site of the infarct was observed in three of the presented cases who developed hemiparesis later. The patient with cerebral venous thrombosis associated with large hemorrhagic infarct (patient 3) developed microcephaly, hemiparesis, psychosocial developmental delay and infantile spasms; however, the prognosis of three patients with arterial infarct was better. Patients with larger infarcts or infarcts involving functionally important regions of the cerebral cortex have larger residual deficits than those with smaller infarcts involving less important regions[4]. Because of the plasticity of immature neonatal brain, some functions normally performed by the injured regions of brain are taken over by other regions that have been spared, particularly in patients with small infarcts[4].

In conclusion, neonatal seizures alone or in addition to any unexplained neurologic symptoms may be the clinical presentation of a cerebral infarct in neonates with or without any risk factors for thrombosis. Therefore, neuroimaging studies should be performed in these newborns.

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