

Neonatal cerebral infarction presented with limb ischemia

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ABSTRACT

Cerebral infarction of newborn infants is a rare condition. It remains the least predictable etiology of neonatal seizures, and the appreciation of its occurrence among physicians needs to be re-addressed. The most common presenting feature is seizure. We report 2 full term newborn infants who developed middle cerebral infarction. These infants presented primarily with ischemic limbs for several hours before the evolution of seizures.

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Focal arterial infarction is an important cause of permanent brain injury in the perinatal period. Estimates from brain imaging suggest an incident of 0.2 per 1000 neonates which is 3-4 times higher than the results of studies in term infants who were diagnosed in later childhood. Aside from perinatal asphyxia, stroke is the most common cause of neonatal seizures at term. Hemiplegia may follow infarction in areas of the brain supplied by the entire middle cerebral artery.

Case Report. Patient One. A full term male infant, born by spontaneous vaginal delivery, was transferred at 10 hours of age from a local hospital because he was found to have a blue right arm at birth. At delivery, the umbilical cord was wrapped tightly around both the neck, and the right arm. The apgar scores were 6 and 9 at the first and the fifth minutes. The birth weight was 3.4 kilograms. The mother was 26 years old, gravida 4 para 3. All 3 other siblings were well. Family history was uneventful. At birth, the infant was found to have a blue, pulseless right arm. The infant was started on an intravenous infusion of unfractionated heparin (UFH), initiated by the referring physicians. On arrival, the infant was alert and quiet, with stable vital signs. There

was evidence of Erb's palsy of the right hand. The right arm was blue with no brachial and radial pulsation. Complete blood count revealed a hemoglobin level equal to 160 gram per liter (reference range is 130-200 gram per liter), and platelet count equal to 80,000 per millimeter (reference range is 90,000-35,000 per millimeter). Prothrombin time (PT) was 18 and partial thromboplastin time (PTT) of 150 per second (reference range is PT 12-20 and for PTT is 40-55 per second). At 12 hours of age, the infant was noticed to have frequent episodes of prolonged apnea and bradycardia. The cerebrospinal fluid (CSF) study showed no evidence of infection. Echocardiogram showed normal cardiac anatomy and no evidence of thrombi. Doppler scanning of both upper limbs showed normal arterial blood flow. This result was coinciding with the improvement of the color of the arm. At 24 hours of age, the infant developed frequent episodes of clonic seizures that started initially in the left arm then spread to the rest of the body. The seizures were controlled by intravenous phenobarbital. Magnetic resonance imaging (MRI) of the brain demonstrated a cerebral infarction of all the territories supplied by the right middle cerebral artery (**Figure 1**). Magnetic resonance angiography (MRA) of

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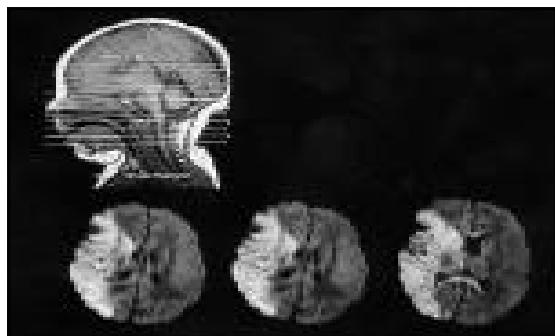


Figure 1

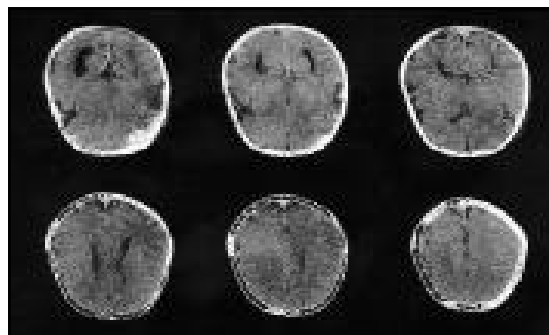


Figure 3

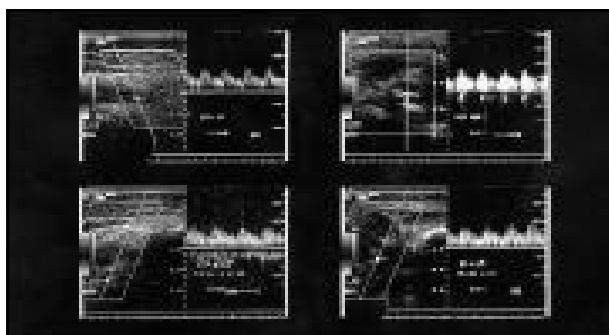


Figure 2

Figure 1 - Patient One. MRI brain scanning. The abnormal signal intensity area in the right cerebral hemisphere, grossly corresponding to extensive infarction in the vascular territory of the right middle cerebral artery.

Figure 2 - Patient 2. Lower limb doppler ultrasound scanning of the right femoral, popliteal anterior and posterior tibial artery. Note the very low flow within the femoral and popliteal arteries. The monophasic flow of the popliteal artery suggests proximal stenosis.

Figure 3 - Patient 2. CT scan of the brain, non-enhanced, showing diffuse subarachnoid hemorrhage. Mixed density areas within the right temporal lobe representing infarction. Note another intracranial hemorrhage within the left occipital lobe. Although such multiple hemorrhagic contusions may be related to traumatic event, clinical history did not suggest birth trauma.

the head, neck, and upper chest showed no evidence of thrombus formation. Unfractionated heparin was replaced with subcutaneous low molecular weight heparin (LMWH), to minimize the risk of bleeding inside the infarction for 2 weeks and, then replaced by warfarin, for family convenience before discharge. Serum protein C was 0.21 and serum protein S was 0.43 U/ml, while the reference range is 0.64-1.13 U/ml and 0.67-1.19 U/ml. Antithrombin III activity was 58% while reference range is 80-120%. Maternal and neonatal serum anticardiolipin, antinuclear, and anti DNA antibodies were not detected. The infant's right arm ischemia subsided completely and he regained a satisfactory brachial pulse at 48 hours of age. Apart from mild Erb's palsy of the right arm, the infant did well, and was discharged home after 2 weeks in hospital. At 6 months of age, in the outpatient clinic, the infant's neurological assessment demonstrated features suggestive of mild left sided spastic hemiplegia.

Patient 2. A full term, female infant, born by spontaneous vaginal delivery, was transferred at 12 hours of age due to ischemia of the right leg that was observed one hour after birth. The mother was 30 years old, gravida 3 para 2; with a history of gestational diabetes mellitus controlled by diet. The apgar scores

were 7 and 9, at the first and fifth minute. The birth weight was 3.8 kg. Family history was unremarkable. The infant was found at birth to have cold and pale entire right lower limb with poor femoral, popliteal, and posterior tibial artery pulsation (**Figure 2**). Unfractionated heparin infusion at rate of 50 unit/kilogram/hour was initiated by the referring physicians. On arrival, the infant was pale, her hemoglobin was 100 gram/L, with a platelet count of 35,000 /millimeter. Both PT and PTT times were prolonged (38 and 150 per second). The infant's CSF study showed normal values. The infant was transfused with packed red blood cells. At 18 hours of age, and after initiating mechanical ventilation to treat frequent episodes of apnea and shallow breathing, the infant experienced progressive clusters of focal seizures, which rapidly progressed to generalized clonic seizures. The seizures were controlled by intravenous infusion of both Phenobarbital and Phenytoin. Computerized axial tomography (CT scan) of the brain showed evidence of right cerebral infarction (**Figure 3**). Unfractionated heparin was replaced by subcutaneous LMWH, which lasted for 2 weeks then, replaced with oral warfarin. The lower limb perfusion improved significantly within 3 days and the infant was disconnected from the mechanical ventilator

at 3 days old. The serum level of protein C, S and antithrombin III activity were 0.34, 0.62U/ml and 70%. Maternal and neonatal serum anticardiolipin, antinuclear, and anti DNA antibodies were not detected. The infant was discharged home at 3 weeks of age with a concern about her neurodevelopmental outcome as she exhibited poor suckling ability, and poor muscle tone. At 6 months of age, in the neonatal outpatient clinic, the infant demonstrated early signs of moderate left side hemiplegia.

Discussion. Neonatal cerebral infarction has evolved as a recognized cause of neonatal seizures. The estimated incidence of cerebral infarction varies from 1.3 per 100,000 to 1 per 4000 in live birth, term infants. Several risk factors can lead to neonatal cerebral infarction.^{1,2} Prenatal insults are considered the most prevalent factor.^{2,3} In this case report, the timing of the diagnosis soon after birth nominated a perinatal insult as the most likely event. Birth trauma was reported in few studies.³⁻⁵ Günther et al demonstrated that 54% of patients had additional triggering factors like hypoxic-ischemic insult, septicemia, maternal diabetes, or perinatally acquired venous thrombosis.³ In addition, there was a higher rate of genetic prothrombotic risk factor, than those from healthy matched groups. He also described abnormal increase of serum lipoprotein level, and FV G1691A genotype as frequently observed risk factors during the prenatal period. Protein C deficiency was also a significant risk factor. Mercuri et al,⁵ in a series of 24 infants with perinatal cerebral infarction confirmed by post-natal magnetic resonance imaging, suggested that factor V leiden mutation, is significantly associated with a poor outcome after a perinatal cerebral infarction. In the first case in this report, the infant had established 2 predisposing factors. Serum protein C and S were significantly low and a history of birth trauma, as the infant was born with tightly wrapped cord around his neck and right arm. Antithrombin III level was also low. The second case had similarly low serum level of protein C, S and low antithrombin III activity that was combined with a maternal history of diabetes. These risk factors may contribute to the development of the infarction. Although, seizures were the most prevalent presenting sign in many reports, in these 2 cases, the trivial thrombotic ischemia of right arm and right leg were the initial clinical features. Sreenan et al,⁶ reported a series of cerebral infarctions, affecting the left cerebral hemisphere slightly more than the right. The thrombocytopenia that was noted can be explained by mild coagulopathy secondary to trivial thrombus formation in the affected limb that migrated to the corresponding middle cerebral artery branches and caused infarction. In these 2 cases, both infants were started on continuous heparin infusion immediately after diagnosis, which may cause a rapid dissemination of the thrombi or emboli. Although, trauma to the neck and

head is one of the predisposing factors for cerebral infarction, cerebral infarction secondary to distant arterial occlusion caused by thrombus and or embolus formation, vasculopathy or vasospasm are a well-recognized association.⁷ In that report, both cases had right-sided infarction while in the second case, the infarction was associated with subarachnoid hemorrhage. Magnetic resonance angiography was normal in the first case. The failure of the MRA to detect a thrombus formation in the first case, may suggest one of 3 scenarios. The first scenario is that the infarction was caused by multiple but small thrombi, difficult to be detected by the MRA.⁸ The second scenario is that the thrombi disappeared after using the heparin, hours before the MRA. Another scenario which may be worth mentioning is the occurrence of transient middle cerebral occlusion.⁹ Low molecular weight heparin is looked to as the finer alternative to UFH. The average molecular weight of these heparins is approximately 5000 Dalton. This new generation of heparin is unique, in that they bind to the anti-thrombin, inducing its conformational changes allowing more thrombin binding and reduced risk of thrombocytopenia with lower incidence of minor and major bleeding. Compared to older children, neonates and infants require more LMWH per body weight. Therapeutic doses of LMWH are based on anti-factor Xa levels following established guide-lines.^{10,11} The desired target of anti-Xa level is 0.50-1.0 mL in a sample taken 4 to 6 hours following a subcutaneous injection. Both cases were managed initially with UFH, and considering the potential risk of bleeding, we elected to re-start our patients on LMWHs. The dose was adjusted following the published normograms.¹¹ The authors believe that the combination of limb ischemia and seizures are strong indication for brain imaging to rule out cerebral infarction.

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