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Prenatal Ischemic Stroke as a cause of Neonatal Seizure Diagnosed by Magnetic Resonance Diffusion-Weighted Imaging

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Perinatal ischemic stroke is a serious complication of pregnancy that may be attributed to certain specific risk factors associated with either some maternal or some infantile characteristics. While the occurrence of perinatal stroke may develop during the prepartum, intrapartum, or postpartum period, it is difficult to determine the exact time of occurrence because of obscure clinical manifestations in newborn babies. Here, we present the case of a neonate suffering from focal clonic seizure 24 hours after birth. The neonate was diagnosed as having perinatal ischemic stroke, which may have been caused by prenatal ischemic insult, as judged from the characteristic features in magnetic resonance (MR) diffusion-weighted imaging (DWI) performed a week after his birth. Finally, we strongly suggest that neonatal focal seizures be immediately investigated by MRI, especially with MR DWI. This image modality provides not only early diagnosis of perinatal ischemic stroke, but also assists to clarify the specific time (prepartum, intrapartum, or postpartum period) of the stroke's occurrence.

Key words: perinatal ischemic stroke, magnetic resonance diffusion-weighted imaging, neonatal seizure

INTRODUCTION

Perinatal ischemic stroke is a serious complication of pregnancy leading to subsequent neurological disabilities including cerebral palsy, epilepsy, and cognitive impairment in the child[1-8]. The etiology of perinatal stroke has been considered to be related to some risk factors in terms of maternal and infant characteristics as well as prepartum and intrapartum complications. However, the clinical manifestations of perinatal stroke are variable and obscure. Thus, in numerous cases of perinatal ischemic stroke it is difficult to clarify the exact time of the stroke's occurrence, which may distress both obstetricians and pediatricians. Magnetic resonance imaging (MRI) has been proven an effective imaging modality for the evaluation of neonatal cerebral infarction. Moreover, magnetic resonance diffusion-weighted imaging (DWI) is capable of differentiating acute from chronic infarcts. Here, we demonstrate a case of prenatal ischemic stroke in a newborn with seizure diagnosed one week subsequent to his birth by characteristic DWI features. To conclude, DWI shows great potential in clarifying the specific time of a stroke's occurrence so that further investigations of various prepartum, intrapartum, or postpartum events can be considered.

CASE REPORT

A full-term male newborn was admitted to our neonatal intensive care unit (NICU) 30 hours subsequent to his birth, under the impression of partial seizure with rhythmic clonic twitch of his left-side limbs. According to his medical record and parents' statements, the antenatal examinations all proved to be normal. His parents also denied any systemic disease, significant illness or need for medication by the mother during pregnancy. From the family history, his mother's elder sister had suffered from an unpredictable spontaneous abortion. The newborn's mother was admitted to our hospital four days prior to the delivery due to regular uterine contraction; consequently, an elective cesarean delivery was performed at that time. After delivery, no perinatal insults, in terms of perinatal asphyxia, delay of initial crying, maternal fever, or prolonged rupture of the membrane were found and the neonate's Apgar score proved to be eight and nine at the first and fifth

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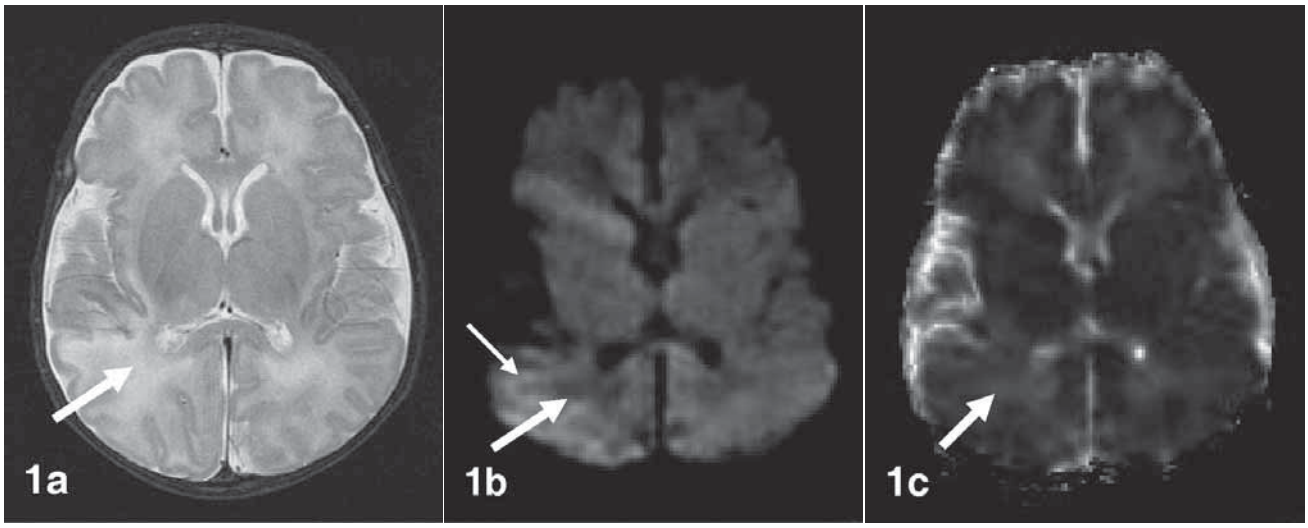

Fig. 1 **1a-c Brain MRI images performed 7 days subsequent to birth**. (a). From the T2-weighted image, the infarcted area (white arrow) appears hyperintense. (b). This diffusion-weighted image (DWI) shows mild hypointensity in the infarcted area (large white arrow) of the brain, indicating infarcted immature brain in the subacute stage. The hyperintensity of the DWI in the peripheral infarcted area (small white arrow) was due to T2 shine-through effect. (c). In this ADC map, the mild hyperintensity apparent in the infarcted area (white arrow) confirmed ischemic stroke in the subacute phase.

minutes respectively. The gestational age was 38 1/7 weeks with normal birth weight, body length, and head circumference. At first, no significant abnormalities of the neonate were noted by initial physical, neurologic examinations, and general condition. However, the neonate, around 24 hours subsequent to his birth, developed an episodic focal clonic twitch involving both left upper and lower limbs without loss of consciousness. He was later transferred to our NICU under the impression of neonatal seizure, with the consequent physical and neurological examinations revealing no significant abnormal findings, except for a mild increased DTR (deep tendon reflex) of the left-knee jerk. Then, he underwent a series of laboratory evaluations including cerebral spinal fluid (CSF) analysis , blood culture, CBC, arterial blood gas analysis, glucose, BUN, Cr, AST, ALT, NH_3, C-reactive protein, Na^+, K^+, Cl^-, free Ca^{2+}, Mg^{2+} and total IgM, all of which revealed unremarkable findings. Even cranial ultrasound revealed no significant findings. Nevertheless, an abnormal electroencephalogram (EEG) demonstrated an ictal discharge over the neonate's right-side parietal region, which was consistent with his left-side focal clonic seizure. Thereafter, the neonate's seizure was kept under control after receiving treatment with phenobarbital. To our surprise, MRI of the newborn's brain with gadolinium, acquired at the age of seven days, revealed a high signal region on a T2-weighted image over the posterior portion of the neonate's right parietal lobe with both cortical and medullary involvement (Figure 1a), a result that was consistent with the EEG findings in the neonate. In addition, the lesion showed mild hypointense signal on DWI (the peripheral mild hyperintense signal of the lesion was due to a T2-shine-through effect) with mild enhancement of the apparent diffusion coefficient map (ADC); Figures 1b-c, showing that subacute ischemic stroke occurred at the posterior branch of the right middle cerebral artery and the estimated time of occurrence would be eight to ten days prior to the MRI. In other words, this implies that the stroke developed prior to delivery. In order to rule out mitochondrial encephalopathy and vascular disorder, a brain MRI was repeated incorporating MR spectrum (MRS) and high-resolution magnetic resonance angiography (MRA), revealing entirely negative findings for both disorders. Moreover, the risk factors for coagulopathy, including prothrombin time (PT) and partial thrombin time (PTT), serum level of protein C, protein S, and anti-thrombin III were all evaluated, with no significant findings disclosed. We followed up the patient for one year and he was within the range of normal development without any detected significant neurological sequelae, although mild residual encephalomalacia was revealed by the follow up MRI study (data not shown).

DISCUSSION

Perinatal ischemic stroke, with an incidence of about one in 4,000 term neonates, represents focal arterial infarction of the brain and contributes to a substantial share of cerebral palsy and other neurologic disabilities such as epilepsy and cognitive impairment in children[1-8]. In contrast to stroke in adults and older children, perinatal stroke often presents characteristically with seizures, but not with focal neurological deficits[9]. Transfontanel ultrasound is the primary imaging modality to evaluate neonatal seizure during this period due to its wide availability and sensitivity for intracranial hemorrhage, however, the value of ultrasound for the diagnosis of perinatal ischemic stroke is limited[10]. Alternatively, EEG plays a diagnostic role in perinatal stroke, particularly when the patient experiences focal seizure disorder during the neonatal period.

Moreover, MRI incorporating diffusion-weighted image sequences has been found to be an effective imaging modality in evaluation of neonatal cerebral infarction[11]. Recently, a typical signal pattern of ischemic infarction in the immature brain has been demonstrated to feature a very characteristic time course for the associated diffusion abnormalities[12-17], which was different from the corresponding pattern for adults suffering from stroke. Accordingly, retrospectively diagnosing and differentiating between prepartum, intrapartum, or postpartum ischemic stroke in the newborn period by different corresponding patterns of MRI sequences might be available. MRI has a role in the diagnosis of ischemic infarction in adolescent and adult patients, in whom the tentative diagnosis is achieved clinically and the role of imaging is principally 1) to rule out hemorrhage as a differential diagnosis, 2) to locate the ischemic brain parenchyma, 3) to evaluate the extent of the lesion, and 4) to gain insight into the etiology of the stroke for the treatment of predisposing lesions. However, alternatively, perinatal ischemic stroke is difficult to diagnose clinically due to its obscure clinical presentation and requires further image analysis to make an exact diagnosis. Recently, advanced DWI allows clear visualization of cytotoxic edema, a hallmark of ischemic cell damage, indicating that a diffusion abnormality is the first sign of ischemic brain damage. The imaging method with the highest accuracy is MRI incorporating DW sequences; such a modality can clarify the kinetic course during ischemic stroke[18] and thus provide a vital role in early diagnosis of perinatal ischemic stroke disorders.

A systematic survey of the temporal behavior of the diffusion abnormality after stroke has been undertaken in adults and in animal experiments[19,20]. A signal abnormality typically occurs within minutes of an ischemic event due to a net shift of water from the fast-diffusion compartment of the extracellular spaces to the slow-diffusion compartment of the intracellular spaces. This results in a net slowing of the water diffusion from extracellular to intracellular spaces. In the chronic stage of the infarction, there is a tendency toward an increased diffusion rate. In the infarcted area, the cell walls break down, and the restriction of water diffusion by the cellular walls diminishes. During this process, the rate of water diffusion passes a stage of "pseudonormalization", when the diffusion characteristics of the damaged tissue are equal to those of the healthy brain tissue. In adults, this usually occurs several weeks subsequent to the stroke, whereas "pseudonormalization" tends to occur one week after stroke in the newborn, which is much faster than in the adult brain[16,17]. This may be due to various factors including the neonatal distribution and regulation of cerebral blood flow, incomplete myelination, and the existence of an immature blood-brain barrier and brain metabolism. Nevertheless, the reasons for the rapid changes in ADC values in neonatal stroke remain incompletely understood.

According to Kuker et al.[12], the DWI of ischemic stroke lesion becomes isodense (pseudonormalization) at around one week after stroke, and hypodense at around two weeks after stroke. Mader et al.[17] also demonstrated two cases of perinatal ischemic stroke in which both individuals underwent DWI of the brain ten days after stroke, and both showed a mildly hypodense signal intensity. In the case of the perinatal stroke we described here, the event developed during the prepartum perinatal period, and was diagnosed by the characteristic features of diffusion-weighted MR imaging one week after the birth. A table showing the period subsequent to stroke and corresponding characteristic MRI features has been prepared following the results from the studies of Kuker et al.[12] and Mader et al.[17] (see Table 1). Based on this table, the specific ischemic stroke event in our case occurred more than one week prior to the

Table 1 Characteristic signal intensity changes of Diffusion weighted MR Image and T2-Weighted Image in neonatal ischemic stroke

Time after stroke / Sequence	Within 72 hrs	Around 5 days	Around 7 days	After one week
DWI	Hyperintense	Mild hyperintense	Isointense	Hypointense
T2-weighted	Isointense (white matter)	Hyperintense	Hyperintense	Hyperintense

(Summarized from Kuker W et al. Childs Nerv Syst. 2004;20(10):742-748.; and Mader I et al. Stroke 2002;33:1142 — 1145.)

MRI examination performed one week after the birth. Therefore, we suggest that the ischemic stroke event in our patient developed several days prior to his birth.

Perinatal stroke is due to thromboembolism from an intracranial or extracranial vessel, the heart, or placenta. Commonly the source is undetermined, but a placental origin is suspected in many cases[21]. The risk factors predisposing a fetus to prepartum ischemic stroke include placental disorders (placental thrombosis, placental abruption, placental infection, fetomaternal hemorrhage); blood, homocysteine, and lipid disorders (polycythemia, disseminated intravascular coagulopathy, factor-V Leiden mutation, protein-S deficiency, protein-C deficiency, prothrombin mutation, homocysteine, lipoprotein (a), factor VIII); vasculopathy (vascular maldevelopment); cardiac disorders (congenital heart disease, patent ductus arteriosus, pulmonary valve atresia); infectious disorders (CNS infection, systemic infection); and maternal disorders (autoimmune disorders, coagulation disorders, anticardiolipin antibodies, twin-to-twin transfusion syndrome, in utero cocaine exposure, and infection)[2]. After reviewing the clinical presentation, images, and laboratory findings of our patient, the possible etiology of his prepartum ischemic stroke might have been placental thrombosis, factor-V Leiden mutation, lipoprotein (a) disease, factor VIII disorders, maternal autoimmune disorders, maternal coagulation disorders or maternal anticardiolipin antibodies; only one or multiple factors might contribute to the prepartum ischemic stroke. Further studies to rule out or rule in these possible factors may further clarify the exact etiology of his stroke, however, the placenta pathology to confirm placenta disorders was not possible.

CONCLUSION

By using the characteristic signal features for perinatal ischemic infarction from MR DWI scanning, we are able to diagnose prepartum, intrapartum, or postpartum ischemic stroke during the newborn period retrospectively and thus more precisely define the pre-, intra-, or postpartum factors that contribute to perinatal ischemic stroke. Consequently, when the exact time of the occurrence of the stroke can be delineated and clarified, both obstetricians and pediatricians are provided with an important reference for tracing the underlying risk factors of perinatal stroke.

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