MULTICYSTIC ENCEPHALOMALACIA IN AN UNCOMPLICATED TWIN PREGNANCY

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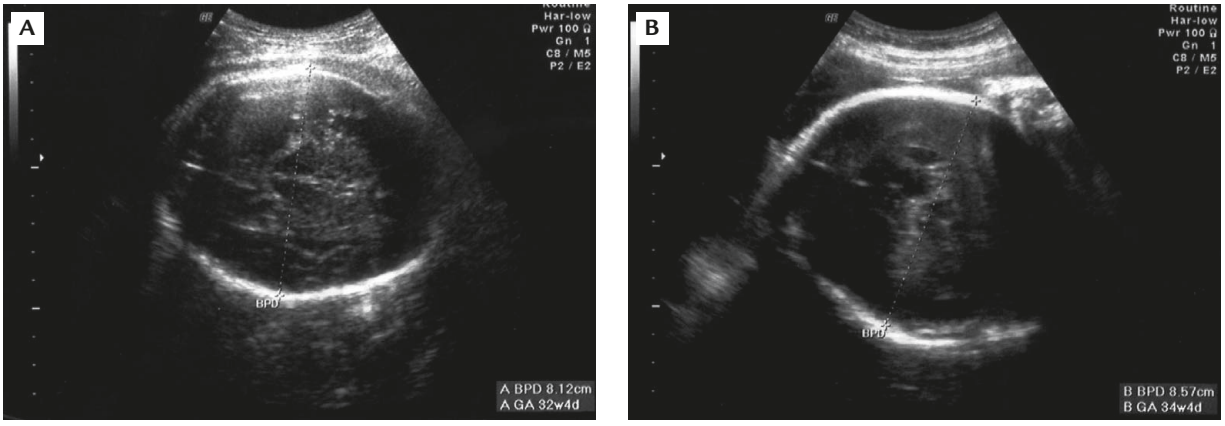

Figure 1. Prenatal ultrasound at 36 weeks of gestation. (A) The normal brain structures can be identified clearly in twin A. (B) Relatively diffuse lower echogenicity is seen in twin B.

A 24-year-old female, gravida 1, para 0, had monozygotic twins conceived spontaneously. She occasionally smoked cigarettes before marriage but quitted before pregnancy. Laboratory examination revealed that she had beta-thalassemia minor and her husband had alpha-thalassemia minor. There was no other maternal systemic disease. The maternal serum Down screening result was 1/23,764. No discomfort was complained of during pregnancy, except for one episode of vomiting and poor appetite for several days but without fever at 31 weeks of gestation. Conservative treatment for acute gastritis was provided, and she recovered well. Prenatal ultrasounds prior to 36 weeks of gestation were all relatively normal. However, at 36 weeks of gestation, the fetal brain ultrasound of twin B revealed relatively diffuse lower echogenicity (Figure 1). Since twin B was lying obliquely just behind twin A, the brain tissue visualization was limited. Further prenatal examinations, such as biophysical profiles, cord blood analysis and magnetic resonance imaging (MRI), were not performed, because there was no discordance found between the twins, including fetal abdominal circumference, estimated body weight, amniotic fluid amount and fetal umbilical artery velocities. The patient did not complain of any decrease in fetal movements.

Cesarean section under spinal anesthesia was performed because of malpresentation at 38 weeks of gestation. Fetal cardiotocography performed before birth showed reactive fetal heart rates for both twins (Figure 2). Two female babies weighing 2,230 g (twin A) and 2,180 g (twin B), with Apgar scores of 9 (twin A)/8 (twin B) and 10 (twin A)/9 (twin B) at 1 and 5 minutes, respectively, were delivered. The respiratory effort of twin B was slow and irregular without spontaneous crying. She later turned completely pink in skin color, with active movements and vigorous crying when stimulus was applied. She was sent to the baby room later without any additional observation. The surgery procedure was smooth without subsequent maternal complications, and the blood loss, including amniotic fluid during operation, was 400 mL. Upon gross examination, the

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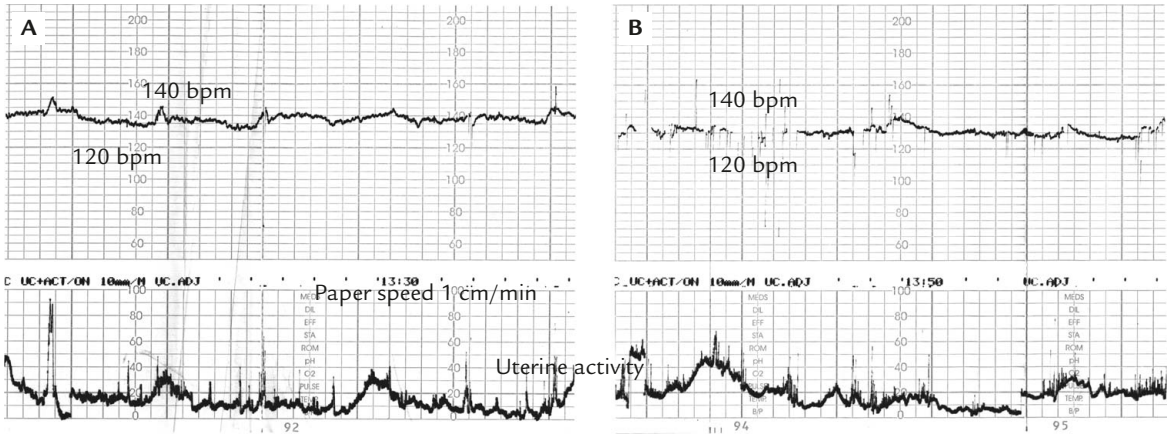

Figure 2. Fetal cardiotocography performed before birth shows reactive fetal heart rates for both (A) twin A and (B) twin B.

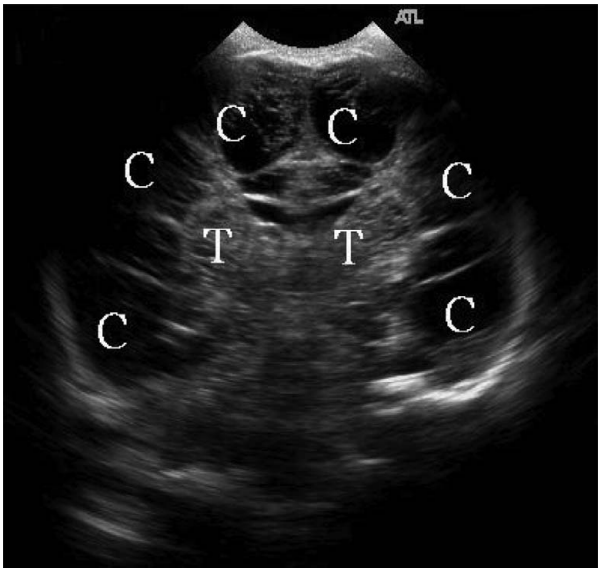

Figure 3. Ultrasound of the brain of twin B at 5 days old (coronal view). Diffuse multiple cystic formations over cortex are seen. C = cystic formations; T = thalamus.

placenta was monochorionic and diamniotic without obvious vascular anastomosis. The postpartum period of the mother was uneventful.

Twin B was sent to the intensive care unit for further observation at 2 days old because of poor response to stimulation. The results of a complete blood count showed: white blood cell (WBC) 12,600/mm^3, hemoglobin 17.6 g/dL, mean corpuscular volume (MCV) 102.7 μm^3, platelets 344,000/mL, and neonatal erythrocytes 3%. The arterial blood analysis showed pH 7.341, PaO_2 82.4 mmHg and $PaCO_2$ 40.7 mmHg. The brain ultrasound at 5 days old revealed abnormal echogenicity with diffuse multiple cystic formations (Figure 3), and some hyperechoic lesions over the central semiovale, periventricular and basal ganglia areas were also noted. Further, diffuse low blood flows were found over the middle cerebral arteries and anterior cerebral arteries. Series examinations were performed for twin A later. Results of her complete blood count were: WBC 8,200/mm^3, hemoglobin 14.0 g/dL, MCV 94.4 μm^3, and platelets 397,000/mL. Ultrasound examination showed normal brain structures in twin A.

MRI of twin B at 10 days old confirmed the diagnosis of multicystic encephalomalacia (MCE) (Figure 4). There was a membranous structure in the bilateral cerebral hemispheres, with little cerebral parenchyma and relatively intact thalamus and posterior fossa structures. Magnetic resonance angiography revealed that the bilateral internal carotid arteries and vertebrobasilar arteries were patent, but the bilateral middle cerebral arteries, anterior cerebral arteries, and posterior cerebral arteries were poorly visualized. There were neither epileptiform discharges nor asymmetries found on the electroencephalogram. The related laboratory data, including toxoplasma, rubella, cytomegalovirus (CMV), herpes simplex virus (HSV), antinuclear antibody, C3, C4, anti-β2 glycoprotein 1 IgG, anticardiolipin antibody, protein S, protein C and antithrombin III, were within normal limits, except for a mild elevation of IgG to CMV (238.30 Au/mL). The blood and urine cultures showed negative findings.

At the time of writing, twin B was 8 months old. She had few social smiles and showed little visual contact, poor response to sound, and some seizure-like movements. Her prognosis was poor because of expected spastic quadriplegia, hearing loss, blindness and microcephaly.

MCE is a rare disease, presenting with destruction and cystic changes in the cortical areas of the brain. Its pathophysiologic mechanism is intrauterine severe partial hypoxic–ischemic damage, instead of asphyxia [1]. Therefore, central structures, such as the basal ganglia, thalami and posterior fossa structures, remain relatively unaffected [1]. As in our case, the central nervous system-regulated biophysical activities, including

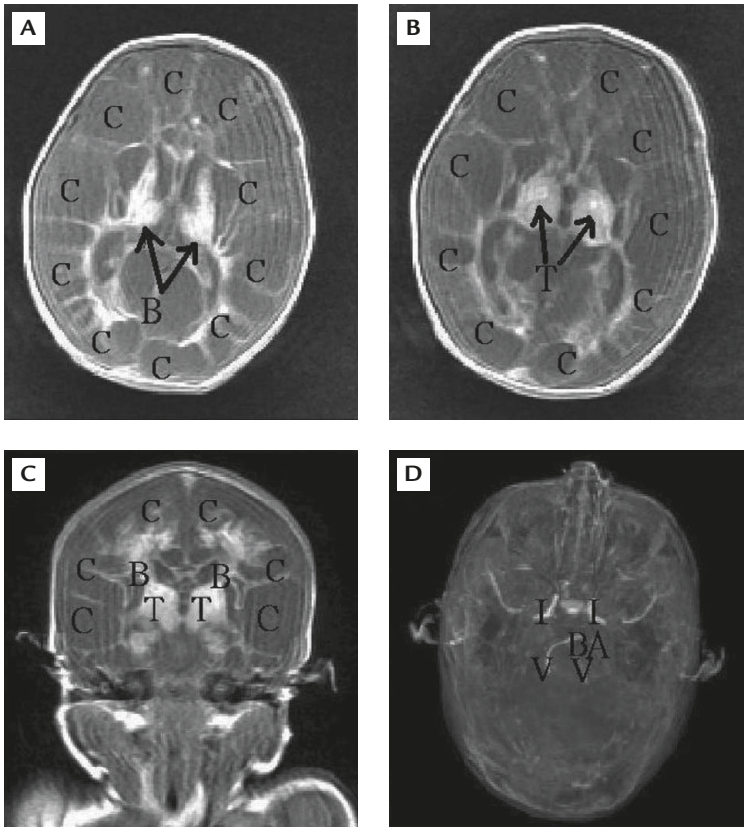

Figure 4. Magnetic resonance imaging of the brain of twin B at 10 days old. (A, B) Transverse and (C) coronal T1-weighted sections. Diffuse multiple cystic formations over the cortex and membranous structure in the bilateral cerebral hemispheres with little cerebral parenchyma. (D) Magnetic resonance angiography reveals that the bilateral internal carotid arteries and vertebrobasilar arteries are patent, but the bilateral middle cerebral arteries, anterior cerebral arteries and posterior cerebral arteries are poorly visualized. B = basal ganglia; C = cystic formations; T = thalamus; BA = basilar artery; I = internal carotid arteries; V = vertebral arteries.

the reactivity of fetal heart rate, gross body movements and fetal tone, were not affected. Although twin B's respiratory effort was slow and irregular without spontaneous crying at birth, there was no cyanosis, hypoxia or acidosis after birth. Another pathogenesis of fetal neurologic damage, i.e. asphyxia, may result in fetal brain death [2]. Although it is rare, profound asphyxia lasting more than 20 minutes can cause destruction and cystic change in both the brain stem and brain cortex [1,2].

Intrauterine severe partial hypoxic–ischemic damage causing MCE may result from a variety of etiologies. In reviewing the published literature, the reported suspected reasons for MCE are: (1) co-twin demise in monochorionic twins [3,4]; (2) twin-to-twin transfusion syndrome [5]; (3) alloimmune thrombocytopenia or trauma [6]; (4) maternal anaphylactic shock [7]; (5) perinatal infections [5,8], such as Group B streptococcus and HSV types 1 and 2; (6) maternal cardiac arrest [5]; (7) maternal gene mutation; and (8) neonatal cerebral vasoconstriction [9]. Although ours was a case of monochorionic twins, neither fetal demise occurred nor twin-to-twin transfusion syndrome developed. There was no maternal trauma, maternal shock or maternal cardiac arrest during pregnancy. The surveys of thromboplastin effects and alloimmune thrombocytopenia revealed normal findings. Concerning the etiology of perinatal infections, no infections were found on urine and blood cultures. There was no HSV infection. The only abnormal finding was the positivity of CMV IgG, although it was not proved that twin B was infected with CMV. She did not have typical CMV infection symptoms/signs at birth. Further, asymptomatic CMV excretion can be shown in up to 10% of pregnant women, and the majority have recurrent infections with low fetal risk. Most infected newborns have no clinical findings. In a symptomatic infected fetus, typical sonographic findings are bilateral periventricular hyperechogenicities. To our knowledge, no published literature has shown the correlation of CMV with MCE. Rather, CMV was not detected in the MCE cases reviewed [8]. CMV may not be the insult that caused MCE in our case.

Most brain injuries diagnosed in a newborn represent several hours or days of intrauterine damage before the final days of pregnancy. The total time span

of this process of hypoxic–ischemic damage leading to permanent cortical brain tissue loss is presumed to be 4–6 months [1]. Therefore, MCE is often diagnosed in infants. However, the shortest possible time during which this mechanism can operate and cause significant brain damage is not known, and it depends on the degree and length of the hypoxia, as well as the maturity of the brain at the time of the insult. MCE cases have been reported in the survivor within 30 minutes of co-twin demise [3]. In our case, the relative diffuse lower echogenicity of the ultrasound picture at 36 weeks of gestation may have indicated the beginning of the process of cerebral edema instead of poor visualization due to poor fetal position.

The outcome of MCE is poor, because the common clinical consequences are severe mental retardation, microcephaly, spastic tetraplegia, epilepsy, and spastic hemiplegia [1,5,6,8]. In our case, we predicted that spastic quadriplegia, hearing loss, blindness, and microcephaly will occur in twin B, and she will need long-term rehabilitation.

Sonography is the diagnostic tool for early detection of MCE [5]. A general increase in echogenicity and compression of the ventricles can be found. However, false-negative examinations are common [1]. Computer tomography is a better diagnostic tool when the edema is at its maximum, around 72 hours after the insult [1]. MRI may be more sensitive for acute or small ischemic lesions and can identify abnormal intracerebral anatomy more precisely [1,10]. For pregnant women, MRI is a better choice. Diffusion-weighted MRI provides very early prenatal diagnosis of acute hypoxic–ischemic cerebral lesions, i.e. acute infarction, and may influence the management of the pregnancy [10].

Compared with singletons, multiple gestations are at greater risk of mortality, severe morbidity and congenital malformations. Monozygotic, especially monochorionic, twins are at greater risk than dichorionic twins. The major morbidity is neurologic impairment. The incidence of adverse neurodevelopmental outcome in twin-to-twin transfusion syndrome survivors is high, especially after the intrauterine fetal demise of a co-twin. A severe complication, such as MCE, occurs in approximately 20% of surviving twins after second- and third-trimester intrauterine co-twin demise in monochorionic pregnancies [4]. In twins without co-twin demise, fetal neurologic damage is rare but may also occur in those with elevated antiphospholipid antibodies, elevated lipoprotein(a) and elevated factor VIIIc [11]. In our case, MCE of unclear etiology developed in an uncomplicated twin pregnancy. Prenatal consultations of twin pregnancy should be undertaken with great care.

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