

Neonatal Periventricular Leukomalacia due to Severe, Poorly Controlled Asthma in the Mother

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ABSTRACT

Background: We report a neonatal case of cystic periventricular leukomalacia (PVL) in which the hypoxia was considered to have been caused by severe asthma in the mother, who had not taken any medication during pregnancy because she was anxious about its possible effects on her unborn child.

Methods: After the mother had severe exacerbation of asthma for five days, the baby was born at 36 weeks in gestation, weighing 2100 g, and with moderate asphyxia. Although the baby had been aggressively treated in a neonatal intensive care unit, at birth, an ischemic area had been formed in the periventricular areas in the brain echogram. We suspected that she had severe brain damage due to prenatal hypoxia.

Results: The baby was found to have cystic PVL by ultrasonography at age 15 days, and diplegia at age 4 months.

Conclusions: The poorly controlled, persistent and severe asthma of the mother may have caused prenatal hypoxia, resulting in the cystic PVL and lower limb palsy. Pregnant patients with poorly controlled asthma should be advised of the great risk of this condition to the fetus. Also, patients should be assured of the safety of modern asthma treatments.

KEY WORDS

bronchial asthma, cerebral palsy, neonate, periventricular leukomalacia, pregnancy

INTRODUCTION

Poorly controlled asthma during pregnancy might lead have an adverse effect on the fetus, resulting in increased perinatal mortality, increased risk of prematurity, and low birth weight.¹ Acute exacerbation should be treated aggressively in order to avoid fetal hypoxia. It is more important to maintain good management in order to avoid exacerbation of asthma. These are spelled out in the Global Initiative for Asthma (GINA).²

In our Neonatal Intensive Care Unit (NICU), we treated a baby whose mother had a severe attack of bronchial asthma. Unfortunately, PVL was diagnosed in the baby: hypoxic necrosis had occurred in the periventricular area, and caused cerebral palsy.

CLINICAL SUMMARY

A pregnant 29-year-old Japanese woman with a gesta-

tional age of 35 weeks and 3 days was transferred to our emergency room in November 2004 because of status asthmaticus.

She had been treated for bronchial asthma from 4 years of age, and had been hospitalized several times for severe bronchial asthma attacks. After she was delivered of a baby for the first time, she was admitted to the hospital for asthma deterioration in 2003. Thereafter she had been treated for asthma with inhaled corticosteroid (fluticasone dipropionate), and oral theophylline. When she became aware of her second pregnancy, she unilaterally tried to discontinue all medications. However, she needed to use metered-dose inhalation of β_2 -stimulant frequently.

During the night, she suffered from asthma attacks leading to dyspnea and her symptoms gradually became worse. Thereafter she consulted a doctor in a local hospital. Although she was treated by inhalation therapy with oxygen and β_2 -stimulant again, she de-

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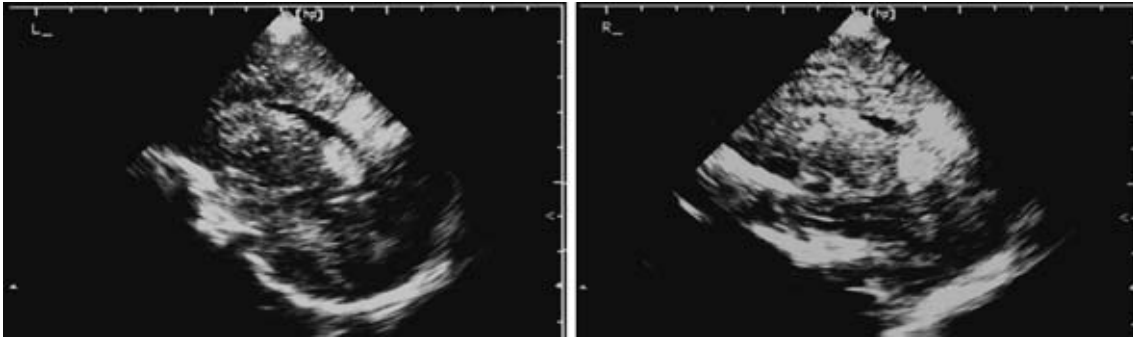


Fig. 1 Brain echogram at birth showing bilateral periventricular high-echoic lesions.

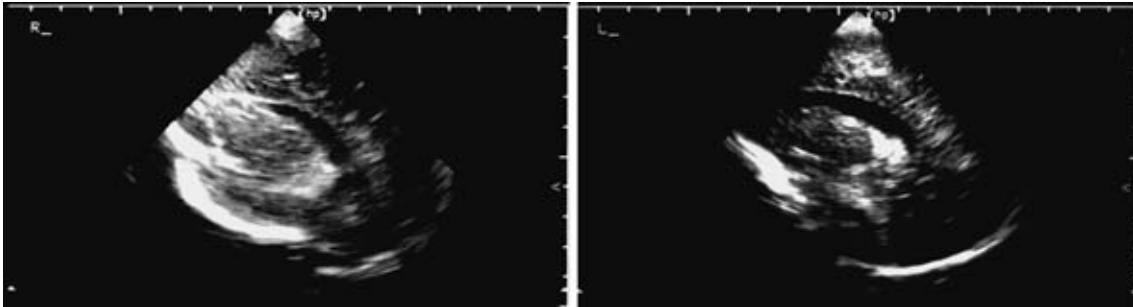


Fig. 2 Brain echogram on day 15: cystic lesions are seen bilaterally in the periventricular areas.

veloped respiratory failure. She was then intubated and transferred to our hospital for the care of her baby in the NICU.

PATHOLOGICAL FINDINGS

On admission, the mother's arterial blood gas analysis showed pH 7.033, PCO₂ 104.9 mmHg, PO₂ 144.6 mmHg, while FiO₂ was 0.6. After admission, she was transferred to our ICU, and was treated with intravenous methylprednisolone, an intravenous drip infusion of aminophylline, and salbutamol sulfate MDI for the asthma. She was also given mechanical ventilation, and sedated with midazolam, buprenorphine, and pentazocine. She improved gradually, and was extubated 2 days after admission. At this time, her fetal non-stress-test (NST) showed no acceleration, but the fetal heart rate was over 120 per minute. On the 5th day of hospitalization, she still needed supplemental oxygen, and her labor pains began. At that time, the fetal NST was partially reactive. Soon after the labor pains started, the baby was delivered.

The child was a girl, breech-delivered at 36 weeks of gestation, with a birth weight of 2100 g. During labor, the amniotic fluid was opaque, so the neonatologist immediately suctioned fluid from the baby's trachea. The Apgar score was 5/7 points. Meconium was suctioned from the trachea, which was then washed with diluted surfactant. Artificial ventilation was initiated to control the infant's respiration, and

monitored her PCO₂ and PO₂ by transcutaneously. At the time of admission to NICU, her venous blood gases showed no sign of acidosis (pH 7.368, PCO₂ 43.3 mmHg, PO₂ 44 mmHg, HCO₃⁻ 24.9, and BE 0), and her chest X-ray findings showed very mild infiltration as mild meconium aspiration syndrome. During artificial ventilation, we maintained her PCO₂ around 40 mmHg. Consequently, it was possible to wean the baby from artificial ventilation on the day after admission. After weaning, her clinical course was very satisfactory, and from 3 days after birth, she could suckle milk, though her sucking was sluggish.

Soon after birth, her brain echogram revealed periventricular high-echoic lesions bilaterally (Fig. 1), and so we followed these changes. On day 15, we found periventricular cystic lesions in the brain echogram appearing as cystic PVL (Fig. 2), and on day 16, brain magnetic resonance (MR) imaging revealed PVL. T1-weighted MR imaging showed high-signal lesions in both periventricular areas, and these findings extended into the parietal area (Fig. 3). T2-weighted MR imaging showed low-signal lesions on T1-weighted MR imaging (Fig. 4).

The auditory brainstem response was normal, and the clinical course was uneventful, so she was discharged from our hospital on day 22. After discharge, the baby was followed up in our outpatient division. At 2 months of age, we performed MR imaging again. T1-weighted MR imaging demonstrated high-signal

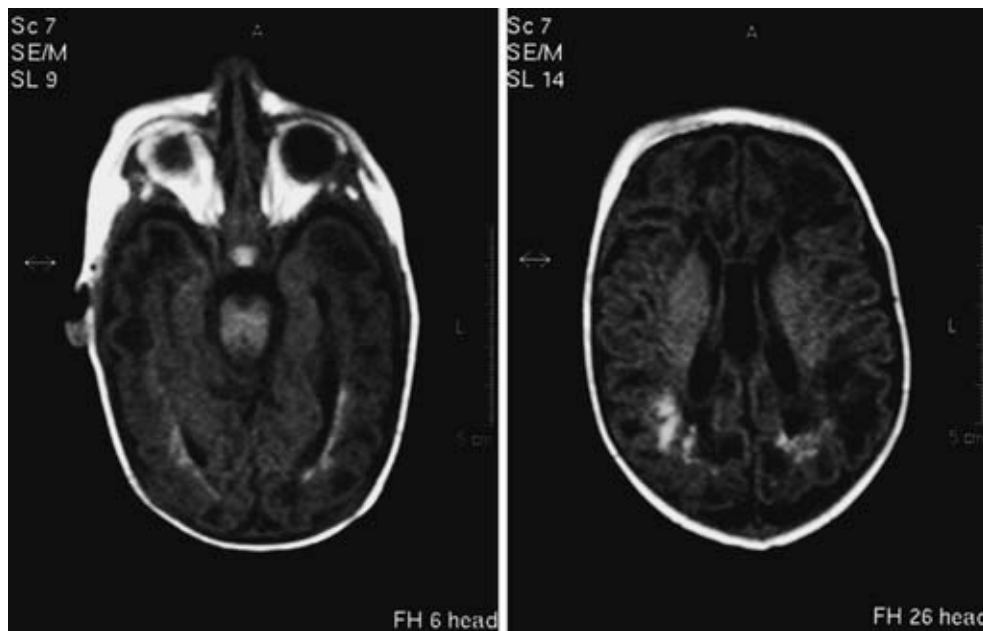


Fig. 3 T1-weighted brain MR imaging shows high-signal regions in the periventricular areas at day 16.

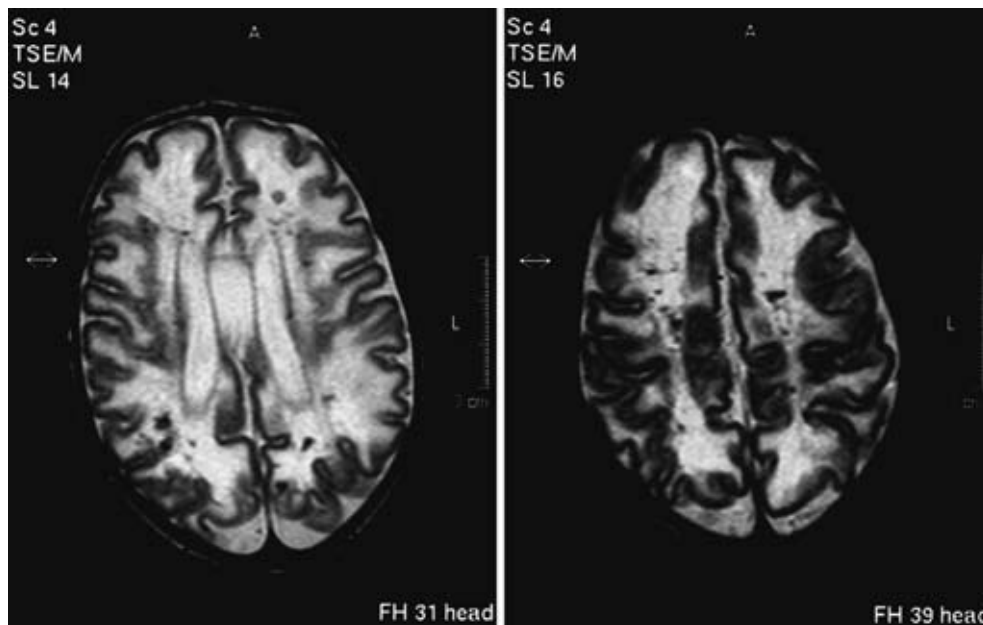


Fig. 4 T2-weighted brain MR imaging shows low-signal regions and cystic regions in the periventricular areas, which extended to the parietal area at day 16.

lesions in both periventricular area. The ventricular wall was serrated and the white matter of the brain was atrophic (Fig. 5). In the periventricular area, T2-weighted MR imaging showed low-signal lesions (Fig. 6).

A diagnosis of cerebral palsy with diplegia was

made at 4 months and she was treated with neurodevelopmental therapy.

DISCUSSION

We report a neonatal case of cystic PVL, due to fetal hypoxia. The hypoxia was caused by the mother's se-

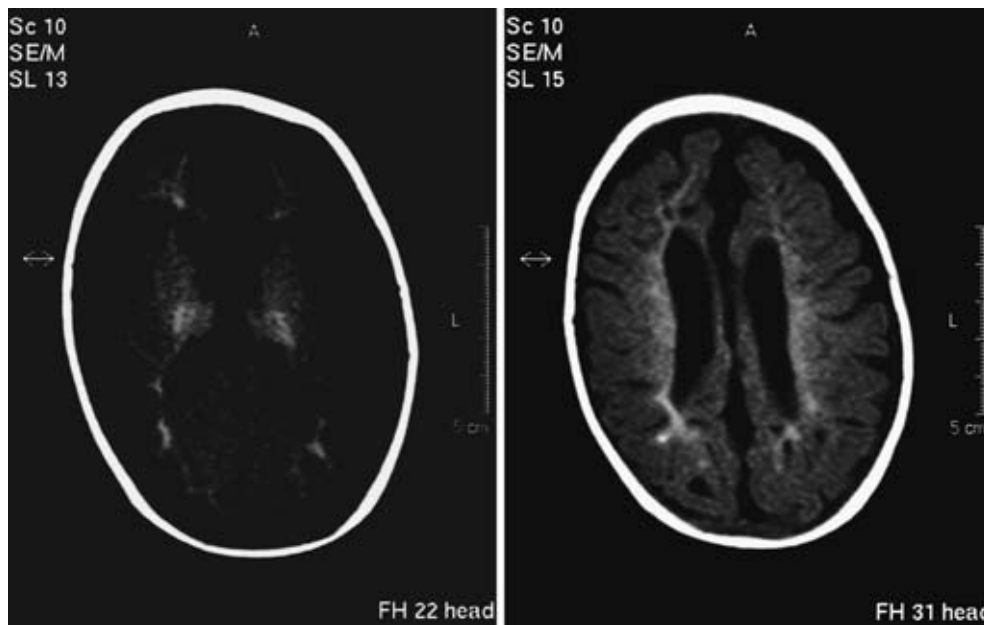


Fig. 5 At 2 months of age, T1-weighted brain MR imaging shows high-signal regions in the periventricular area, atrophy of the white matter and serrated ventricular walls.

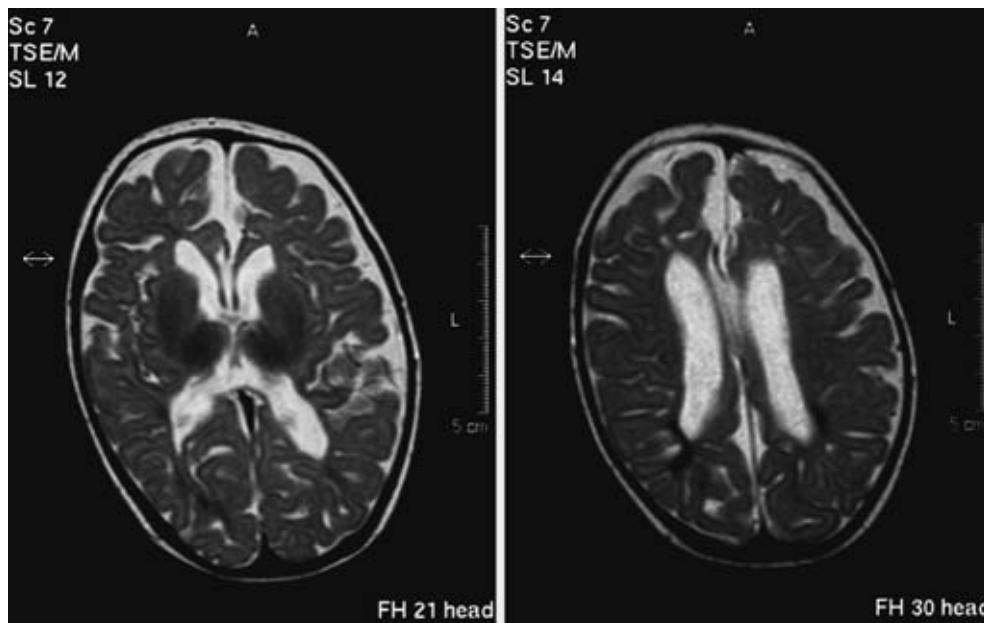


Fig. 6 At 2 months of age, T2-weighted brain MR imaging shows low-signal regions in the periventricular area, atrophy of the white matter and serrated ventricular walls.

vere asthma attacks. Although the mother needed controller medication and anti-inflammatory agents such as inhaled corticosteroids, she had stopped taking her controller medication, and status asthmaticus ensued. To the best of our knowledge, there are no previous report demonstrating a neonatal case of cys-

tic PVL in which the hypoxia was caused by severe asthma in the mother.

Bronchial asthma is a common complication of pregnancy, occurring in between 3.7 and 8.4 percent of pregnant women, according to United States national health surveys spanning 1997 to 2001.³ Asth-

matic women have a greater risk of complications during pregnancy, for example, perinatal mortality, pre-eclampsia, low-birth-weight infants, transient tachypnea of the newborn,^{4,5} meconium stain⁶ and preterm births, than non-asthmatic women. This is especially true in severely asthmatic women.^{1,7,8} However, when the asthma is well-controlled, the perinatal risk can be decreased.^{1,9,10}

Severe, life-threatening asthma or status asthmaticus occurs in 0.05 to 0.2%^{11,12} of all pregnancies. Gordon *et al.*¹¹ reported that some patients with severe asthma had neurologically abnormal infants, as in the present case. Another study reported that the incidence of newborn hypoxia was significantly higher in asthmatic mothers.¹³ Not only hypoxia but also hypercapnia in an asthmatic mother can result in fetal respiratory acidosis and in a shift of the fetal hemoglobin dissociation curve to the right, limiting the ability of fetal hemoglobin to bind to oxygen.¹⁴

PVL is a problem that causes neurological disabilities, for example, learning disabilities, cerebral palsy and mental retardation, and occurs most frequently in premature infants. The white matter of these fetuses is poorly vascularized and contains oligodendrocyte progenitors, which are sensitive to the effects of ischemia and infarction, and since PVL is an ischemic reperfusion injury of the white matter, it causes focal necrotic cystic lesions.¹⁵⁻¹⁷ Moreover, these cystic lesions formed about 14 days after ischemic injury. Once PVL has occurred, there is no effective treatment, thus prevention is important. In the present case, we found completely cystic areas on echography at 15 days after birth. Although muddy amniotic fluid was present, a skillful neonatologist was fortunately available to treat the infant, and the infant's trachea was quickly cleared and cleaned, so her respiration was soon well under control; but unfortunately, this was not soon enough to prevent the PVL that resulted from hypoxia during the mother's status asthmaticus.

In a population-based Norwegian study in low-birth-weight infants, with registration of cerebral palsy, 44% of the subjects had a perinatal etiology, most frequently intra- or periventricular hemorrhage, or PVL, or cerebral infarction.¹⁸ In Japan, Fujimoto *et al.* reported the incidence of PVL at one-third of cerebral palsy cases.¹⁹ In such cases, it is important for the medical staff to provide parents with adequate preparation and explanation, to offer to carry out rehabilitation on the baby, and to follow the case periodically. After the baby with cystic PVL was discharged, a neonatologist has been closely involved. She started early rehabilitation because she showed spastic palsy in the lower limbs.

In 2004, a NAEPP (National Asthma Education and Prevention Program) Expert Panel Report offered recommendations for pharmacologic asthma management during pregnancy. Fundamentally, asthma

treatment based on corticosteroid inhalation does not require modification even during pregnancy.²⁰ In the present case, PVL could probably have been avoided if the mother's asthma had been well controlled, but the mother was apprehensive about taking medications during pregnancy. Physicians and other medical staff should explain the necessity of well control in pregnancy to asthmatic women. If patients with asthma become pregnant, medical providers should explain the safety of inhalation corticosteroid therapy for both the pregnant woman and the fetus. These treatments and procedures are for the sake of the well-being of both mother and fetus. Pediatricians must also educate asthmatic children to maintain strict adherence to their asthma medication regimens.

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