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Periventricular Leukomalacia and Prenatal Methamphetamine Exposure: A Case Report

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Abstract

Periventricular leukomalacia (PVL) is a complication of prematurity that carries a high risk of long-term neurologic morbidity. We report the first case, to our knowledge, of unexpected PVL associated with in utero methamphetamine exposure in a 30-week gestation premature infant with a benign hospital course, who subsequently developed cerebral palsy by 24 months of life.

Keywords

Periventricular leukomalacia; methamphetamine; prematurity; cerebral palsy; prenatal drug abuse

Periventricular leukomalacia (PVL) is a serious complication of prematurity with a high risk of long-term neurologic morbidity. The incidence of PVL has decreased over time from 8% in 1988 to 3% in 1994 in very low birth weight infants (<1500 g) as both our understanding of the pathophysiology and the care of premature infants has improved.¹ The primary concern with PVL is that it is a frequent antecedent of cerebral palsy in premature infants. Rogers et al² observed 26 infants who were born at less than 32 weeks who carried the diagnosis of cystic PVL. All 26 infants went on to develop cerebral palsy: 54% with quadriplegia, 42% with diplegia, and 4% with hemiplegia.

Premature infants have unique developmental characteristics that predispose them to PVL, including incomplete development of the vascular supply of the cerebral white matter, incomplete development of cerebral vascular autoregulation, and an increased vulnerability of the oligodendroglial precursor cells to ischemic injury.³ There are multiple risk factors for PVL, including premature delivery, premature rupture of membranes, intrauterine infection, intraventricular hemorrhage, cerebral ischemia, hypocarbia, hypotension, hypoglycemia, acidosis, and hypercoagulable states.⁴

In premature infants, prenatal exposure to methamphetamine has not been reported as a risk factor for PVL. However, prenatal methamphetamine exposure has been reported previously to be associated with fetal growth restriction, reduced head circumference, low birth weight, and cerebral hemorrhages. The National Toxicology Program Center for the Evaluation of Risks to Human Reproduction (National Institute of Environmental Health Sciences) recently published an extensive review on the reproductive and developmental toxicity of amphetamine

and methamphetamine.⁵ In this report, the expert panel found that there were no scientifically interpretable human data directly linking developmental toxicity with methamphetamine exposure. The human studies were difficult to interpret because of multiple factors, including the inability to control for potential confounding factors and issues of contamination of the methamphetamine that was being abused. Still, the expert panel, based on experimental animal work, concluded that there was concern for potential adverse perinatal outcomes and neurobehavioral alterations from prenatal methamphetamine exposure.⁵

Methamphetamine is a Schedule II stimulant with a chemical structure and vasoactive properties similar to amphetamine. Methamphetamine abuse has increased in Iowa and other Midwestern states, partly because methamphetamine can be synthesized from ingredients readily available in agricultural communities, including anhydrous ammonia. It is unknown how many fetuses are exposed yearly to methamphetamine and deliver prematurely. However, we report the first case, to our knowledge, of a preterm infant with no other known risk factors in whom PVL developed after in utero exposure to methamphetamine.

CASE REPORT

A 1080-g appropriate for gestational age male infant was born at 30 weeks gestation to a 23-year-old G4 P3 female who admitted to one episode of methamphetamine and marijuana use 3 days prior to delivery. She denied any other use during the pregnancy. The mother presented to her community hospital in preterm labor too far advanced for tocolysis. A cesarean section was performed because of preterm labor with breech presentation. There was artificial rupture of membranes at delivery with clear fluid. There was no history of fetal distress, chorioamnionitis, oligohydramnios, antepartum hemorrhage, preeclampsia, or maternal hypertension. The infant's Apgar scores were 6 at 1 minute and 7 at 5 minutes. At the local hospital, his initial capillary pH was 7.27, with PCO₂ 52 mm Hg, and base deficit -4. He was transferred because of respiratory distress and prematurity. Prior to transport, he was started on antibiotics, intubated for respiratory distress, and placed on intermittent mandatory ventilation.

On admission he had a mean blood pressure of 45 mm Hg and a capillary blood gas of pH 7.30, PCO₂ 37 mm Hg, base excess +1. He was changed to synchronized intermittent mandatory ventilation (peak inspiratory pressure of 16 cm H₂O, positive end-expiratory pressure of 4 cm H₂O, rate 30 breaths per minute, inspiratory time of 0.4 seconds). He did not require surfactant because his respiratory status quickly improved, and by 24 hours of life, he had been extubated to nasal cannula oxygen. His carbon dioxide tension was never below 35 mm Hg while ventilated, and his blood pressure was normal. He received 10 days of antibiotics for respiratory distress due to a presumed infection despite a negative blood culture. Meconium was sent for toxicological analysis because of the admitted maternal history of drug abuse. The drug screen was positive for both methamphetamine (850 ng/g of stool) and tetrahydrocannabinol (54 ng/g of stool).

The infant had a benign hospital course, requiring only one transfusion of packed red blood cells at 23 days of life for anemia of prematurity (hemoglobin 7.9 g/dl) and was weaned off nasal cannula oxygen by 6 weeks of age. He underwent head ultrasound (HUS) examinations at the ages of 1 and 6 weeks per unit routine for infants with a gestational age <32 weeks or a birth-weight <1500 g. The initial HUS examination was completely unremarkable, with no evidence of hemorrhages or cysts. However, the 6-week HUS examination was highly abnormal, with multiple small cysts bilaterally in the subependymal white matter anterior to the lateral ventricle consistent with the diagnosis of PVL (Fig. 1). The ophthalmologic examination at 6 weeks of age showed no retinopathy of prematurity and no evidence of any other abnormalities. He was discharged home at 8 weeks of age to the care of his father. At

discharge he had no significant neurological abnormalities. However, long-term follow-up at 24 months of life demonstrated severe developmental delay with spastic quadriplegic cerebral palsy requiring baclofen therapy.

DISCUSSION

We report a case of fetal methamphetamine exposure associated with PVL with subsequent development of cerebral palsy. This infant's course was not complicated by risk factors historically linked to the development of PVL. The only risk factor identified was prematurity at a relatively late gestation of 30 weeks. Other major risk factors associated with PVL in premature infants, including premature rupture of membranes, intrauterine infection, intraventricular hemorrhage, hypocarbia, hypotension, hypoglycemia, and acidosis, were not present. The absence of PVL on the first HUS at 1 week of life with the subsequent presence of cystic PVL at 6 weeks of life is consistent with the history of this infant being exposed to methamphetamine 3 days prior to birth rather than weeks before delivery. We postulate that this exposure to methamphetamine lead to cerebral ischemia, which in turn led to destruction of cerebral white matter and subsequent cyst formation 6 weeks later. The HUS is not capable of detecting early ischemia but will detect subsequent cyst formation.

There are limitations to our case report. It is not a controlled study and there may have been other confounding prenatal factors unknown to us that affected this fetus during development, including the possibility that the methamphetamine may have contained contaminants that could be potentially neurotoxic. The possibility of a coincidence always exists; however, our findings of cystic PVL in the absence of other known risk factors and the timing of the injury are consistent with the vasoconstrictive effects of an exposure to methamphetamine just prior to delivery.

An extensive review by an expert panel on the toxic effects of methamphetamine on development concluded that the available data on humans were difficult to interpret in terms of cause and effect, but animal data were sufficient to demonstrate neurobehavioral alterations with prenatal exposure.⁵ In uncontrolled studies, effects of in utero methamphetamine exposure on term infants have been reported, but its effects on preterm infants are not well known. Dixon and Bejar⁶ studied term infants exposed antenatally to cocaine and/or methamphetamine. Exposure was defined as a positive urine screen by immunoassay and confirmed by gas chromatography–mass spectroscopy.⁶ They compared HUS examinations from these infants with ultrasounds from infants who had not been exposed to illicit drugs. Of the 24 infants who had been exposed to methamphetamine, three had white matter densities and one had white matter cavities.

Oro and Dixon⁷ studied mother–infant pairs with positive toxicology screens and found that methamphetamine exposure altered behavioral patterns in infants, causing abnormal sleep patterns, poor feeding, tremors, and hypotonia. The drug-exposed group had higher rates of prematurity, in utero growth restriction, and smaller head circumferences when compared with drug-free controls. Smith et al⁸ found that methamphetamine use was associated with growth restriction in infants born at term.

Long-term detrimental effects of in utero methamphetamine exposure have also been reported. A group of Swedish children, evaluated 14 years after exposure to methamphetamine in utero, were found to have significantly lower performance in mathematics, language, and sports than their peers. A higher percentage of the methamphetamine-exposed children were also one grade lower than expected in school.⁹

Potential mechanisms by which maternal methamphetamine abuse resulted in PVL in the infant include maternal vasoconstriction with resulting fetal hypoxia, or cerebral vasoconstriction in

the fetus itself. Methamphetamine causes vasoconstriction by increasing levels of vasoactive neurotransmitters, such as norepinephrine, dopamine, and serotonin.¹⁰

Prenatal methamphetamine exposure should be considered as an additional potential risk factor for PVL in premature infants. The unexpected finding of PVL on a late HUS after an unremarkable early study in a low-risk premature infant with a benign hospital course suggests the need to screen actively for PVL with late ultrasounds (6 weeks or later) in premature infants exposed to methamphetamine.

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Figure 1.

The brain sonography at age 6 weeks shows multiple cystic areas (arrows) in the periventricular white matter of both hemispheres, predominantly in the trigonal region of the parietal lobe, in both the coronal and sagittal views.