

Prenatal Diagnosis of Fetal Encephalomalacia after Maternal Diabetic Ketoacidosis

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Am J Perinatol Rep 2014;4:e97–e100.

Abstract

Introduction Encephalomalacia in a developing fetus is a rare and devastating neurological finding on radiologic imaging. Maternal diabetic ketoacidosis (DKA) can lead to metabolic and vascular derangements which can cause fetal encephalomalacia.

Case We report the case of a 27-year-old pregnant woman with White’s Class C diabetes mellitus who presented in the 25th week of gestation with DKA. Four weeks after her discharge, marked fetal cerebral ventriculomegaly was noted on ultrasound. A subsequent fetal magnetic resonance imaging (MRI) demonstrated extensive, symmetric cystic encephalomalacia, primarily involving both cerebral hemispheres. The pregnancy was continued with close fetal and maternal surveillance. The patient underwent a repeat cesarean delivery in her 37th week. The infant had a 1 month neonatal intensive care unit stay with care rendered by a multiple disciplinary team of pediatric subspecialists. The postnatal course was complicated by global hypotonia, poor feeding, delayed development and ultimately required anticonvulsants for recurrent seizures. He died at the age of 9 months from aspiration during a seizure.

Discussion Although the maternal mortality from DKA has declined, DKA still confers significant neurological fetal morbidity to its survivors.

Keywords

- ▶ diabetic pregnancy
- ▶ diabetic ketoacidosis
- ▶ encephalomalacia

Encephalomalacia, from the Greek “brain softening,” refers to diffuse cerebral parenchymal volume loss. This typically occurs between the 20th and 30th weeks of gestation with the most common etiologies being maternal infection, trauma, or vascular insult.¹ Impaired brain perfusion leads to neuronal injury and cell death. Neuronal cell loss occurs in two phases: primary and delayed. The high rates of cellular metabolism in the developing fetal brain make neurons particularly sensitive to ischemia and lead to primary neuronal cell loss within 30 minutes of onset of hypoxia and/or ischemia. However, many neurons are spared during the initial insult.² Delayed loss results from free radical production. The cytotoxin-mediated apoptosis cascade usually oc-

curs in the days following the insult.¹ In contrast to porencephaly, or focal cystic white matter defects communicating with the ventricular system, encephalomalacia results in a global destruction of brain matter with symmetric bilateral effects. Because of neuronal cell death, diffuse brain atrophy results. In utero and postpartum outcomes are variable; however, this type of injury generally confers poor prognosis with neurodevelopmental delay, seizure disorders, and sensory and/or motor deficits.³

Diabetic ketoacidosis (DKA) during pregnancy can cause simultaneous metabolic and vascular insults and is a medical emergency for both mother and fetus. Although fetal mortality due to maternal DKA is well established, the mechanism of

received
June 28, 2014
accepted after revision
September 18, 2014
published online
November 18, 2014

DOI <http://dx.doi.org/10.1055/s-0034-1395990>.
ISSN 2157-6998.

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neurologic injury in the survivors is less well described. We report the first case, to our knowledge, of prenatal diagnosis of fetal encephalomalacia after an episode of maternal DKA.

Case

A 27-year-old woman, gravida 3, para 1011 with White's Class C diabetes mellitus was being comanaged by Endocrinology and Maternal Fetal Medicine. Previously, the patient had experienced three episodes of DKA at ages 16 and 18 years, and in the third trimester of her first pregnancy. During this second pregnancy, her first trimester hemoglobin A1C was 7.3%. She was receiving insulin via an aspart insulin pump. Her aneuploidy screening showed an increased risk for trisomy 21, but amniocentesis revealed a normal male karyotype. A second trimester obstetric ultrasound demonstrated normal fetal anatomy, and fetal echocardiogram confirmed a structurally normal heart.

At 25 weeks of gestation, the patient presented to an affiliated hospital with 24 hours of nausea and vomiting and was found to have a serum blood glucose of 402 mg/dL. She was hypotensive and mildly tachycardic with positive urine and serum ketones. Her arterial blood gas was significant for a pH of 7.1, with a compensated metabolic acidosis and base excess of 23.6 mEq/L. She was resuscitated with intravenous fluids and transferred to our hospital and was stabilized with intravenous dextrose and an insulin drip. From presentation to resolution, the episode of maternal acidosis lasted approximately 13 hours. After 3 days, her electrolytes and glucose levels were normalized. She was restarted on her insulin pump and later discharged home on hospital day 5.

At 29 weeks gestation, a fetal growth ultrasound revealed marked dilation of both the lateral and third ventricles (→**Fig. 1**). Subsequent fetal magnetic resonance imaging (MRI) demonstrated symmetric global cerebral white matter and deep gray matter atrophy with cystic encephalomalacia and enlarged extra-axial spaces (→**Fig. 2**). Maternal serum and amniotic fluid TORCH titers were negative for infection. The pregnancy was continued with close fetal and maternal surveillance. Based on fetal MRI findings, the patient was counseled regarding the overall poor neurologic prognosis by



Fig. 1 Fetal ultrasound at 29 weeks and 2 days, after episode of diabetic ketoacidosis at 25 weeks, demonstrating significant lateral ventricular dilatation. White matter loss and extra-axial fluid are not well visualized.

perinatology and neonatology. The remainder of her pregnancy continued without incident until intermittent insulin pump malfunctions led to worsening glycemic control at 36 weeks of gestation.

After an amniocentesis confirmed fetal lung maturity, the patient underwent delivery via a repeat cesarean delivery at 37 weeks. A 3410 g male infant with 1 and 5 minute APGAR scores of 8 and 9 and umbilical cord pH of 7.4 was delivered and admitted to the neonatal intensive care unit for respiratory distress. The infant was noted to be responsive but with microcephaly, poor muscle tone, and decreased reflexes, including the suck reflex.

A neonatal brain MRI showed diffuse, symmetric cerebral white matter and deep gray matter loss with microcephaly and ex vacuo hydrocephalus with a left-sided subdural hematoma (→**Fig. 3**). Postnatal evaluation included normal placenta pathology, normal sepsis screen, and workup by a multiple disciplinary team including pediatric neurology. The infant had a month-long neonatal intensive care unit stay and was discharged home with a gastric tube but without the need for respiratory support. While the infant surpassed initial expectations, he continued to have global hypotonia, poor feeding, delayed development, and ultimately required

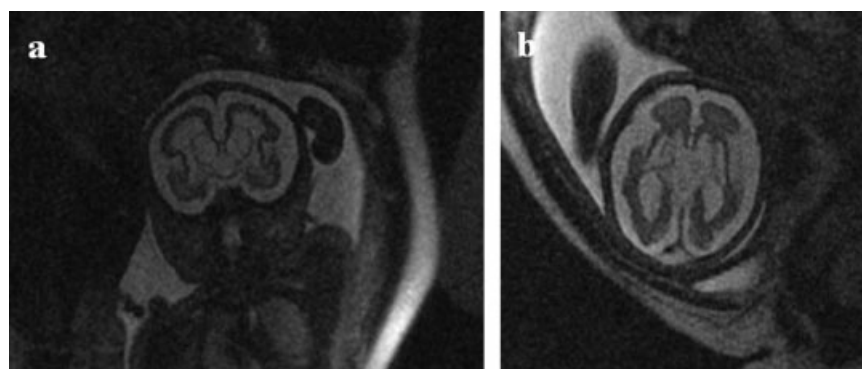


Fig. 2 Fetal magnetic resonance imaging performed at 31 weeks and 6 days of gestation. (a) and (b) Enlargement of the lateral and third ventricles due to atrophy of surrounding white matter and deep gray matter. A thin cortical rim of brain tissue remains. Increased extra-axial fluid is also present.

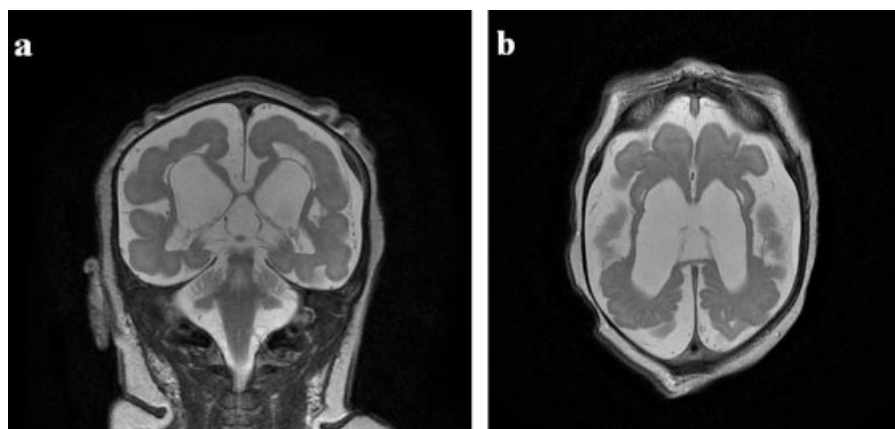


Fig. 3 Neonatal brain magnetic resonance imaging at 1 week of life. (a) and (b) Axial and coronal weighted sequence show progression of disease process with marked atrophy and loss of cerebral white matter and deep gray matter volume with continued ventriculomegaly and enlarged extra-axial spaces.

anticonvulsants for recurrent seizures. He died at the age of 9 months from aspiration during a seizure.

Discussion

Maternal physiology increases the susceptibility of pregestational and undiagnosed diabetes to DKA. The physiologic mildly compensated respiratory alkalosis makes the pregnant diabetic more vulnerable to DKA due to an inability to buffer ketones. Frequently triggered by cessation of insulin or infection, in DKA there is an extreme state of hyperglycemia and insulin deficiency that leads to the formation of ketone bodies and increased production of free fatty acids.⁴ The liver converts these fatty acids into acetoacetate, acetone, and β -hydroxybutyrate ketone bodies. Increases in hepatic glucose production with a concurrent decrease in glucose utilization result in a metabolic acidosis. The β -hydroxybutyrate ketone bodies have been shown in animal models to cross the placenta. This likely contributes to the fetal lactic acidosis and hypoxemia.⁵

Simultaneously, glucosuria causes an osmotic diuresis that results in profound dehydration and hypovolemia. Maternal hypovolemia leads to placental hypoperfusion and diminished fetal cerebral blood flow, which can result in global hypoxic-ischemic neurologic injury. In our patient, both of these potential mechanisms likely contributed to the fetal neurologic injury sustained during her DKA episode at 25 weeks. At that point in gestation, the fetus was especially susceptible to hypotension due to the immature cerebrovascular autoregulatory system.⁶ Anoxic brain injury results in neuronal cell death and consequent atrophy of the white matter, resulting in expansion of the cerebral ventricles, as seen in **Fig. 2**. Failure of further brain development affects skull formation and results in microcephaly and the likelihood of profound neurological impairment, as seen in our patient.

Although the maternal mortality from DKA has declined over the past several decades, the maternal disease nonetheless confers significant risk of neurological fetal morbidity to its survivors if hypoxemia and hypovolemia occur. We report

the first case to our knowledge of prenatally diagnosed fetal encephalomalacia after maternal DKA. These findings were evident on multiple imaging modalities, including obstetric ultrasound and fetal MRI. Early diagnosis and correction of the metabolic derangements may prevent delayed neuronal damage. Further research is needed to delineate the role of free-radical damage and to determine treatment that may halt the initiation of the pathological cascade. With improved understanding of the pathophysiology of neurologic injury due to DKA, it may be possible to prevent ongoing damage in neonates. Until then, it is imperative to maintain meticulous glucose control during pregnancy and counsel patients to recognize the signs and symptoms of DKA so that prompt treatment can be initiated.

Note

This article was presented at the American College of Obstetricians and Gynecologists Armed Forces District Annual Meeting, Baltimore, MD, October 2013.

Conflict of Interest

The authors report no conflict of interest.

Sources of financial support

No outside funding.

Disclaimer

Drs. Love, Lee, Matiasek, Carter, and Ylagan are military service members. The views expressed in this article are those of the author(s) and do not necessarily reflect the official policy or position of the Department of the Navy, Department of the Air Force, Department of Defense, or the U.S. Government. I am a military service member. This work was prepared as part of my official duties. Title 17 U.S.C. 105 provides that "Copyright protection under this title is not available for any work of the U.S. Government." Title 17 U.S.C. 101 defines a U.S. Government work as a work prepared by a military service member or employee

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