Neuroinflammation-Related Encephalopathy in an Infant Born Preterm Following Exposure to Maternal Diabetic Ketoacidosis

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A pregnant woman with new-onset type 1 diabetes and ketoacidosis delivered an infant at 28 weeks of gestation who died with multiple organ failure and severe cerebral vasculopathy with extensive hemorrhage, diffuse microgliosis, and edema. This illustrates that antenatal metabolic and inflammatory stressors may be associated with neonatal encephalopathy and cerebral hemorrhage. *(J Pediatr 2018;■■:■■-■■).*

In 1861, William J. Little implicated events during the birth process as potential etiologies of cerebral palsy, whereas in 1897, Sigmund Freud suggested that prenatal factors may be responsible. This debate remained unresolved until 1984, when the Collaborative Perinatal Project provided evidence that only a small proportion of cerebral palsy stemmed from events arising during labor and delivery.[1] Several smaller subsequent studies supported this conclusion.[2-5] Furthermore, the failure of cerebral palsy incidence rates to decline despite advances in perinatal medicine[6] supports the concept that underlying disorders occurring before birth mediate the majority of abnormal neurodevelopmental outcomes in children,[2-5] in agreement with Freud's hypothesis.

Intrauterine pathophysiological factors that may contribute to cerebral palsy include hypoxic–ischemic injury, inflammation, and immunologic and coagulation abnormalities.[7-15] Inflammation is now recognized as an important contributor to pregnancy-related complications[13,16] and is at the core of both type 1 and type 2 diabetes. Type 1 diabetes is an autoimmune disorder,[17,18] whereas type 2 diabetes is an insulin resistance disease. Type 1 or type 2 diabetes during pregnancy exposes the fetus to a hyperglycemic inflammatory milieu.

In this report, we present an infant born to a mother who developed new-onset type 1 diabetes during pregnancy and presented with severe diabetic ketoacidosis in the perinatal period. The infant died shortly after birth from extensive brain injury and multiorgan failure. This case illustrates that neonatal brain injury can result from prenatal maternal metabolic, inflammatory, and immune pathophysiological factors.

Report of a Case

The mother was a 19-year-old G3, P0111 woman who presented at 28 weeks and 4 days of gestation with flu-like symptoms, including a sore throat, body aches, nausea, vomiting, and abdominal pain but without chills or diarrhea. The pregnancy was associated with recurrent urinary tract infections. However, routine prenatal blood and urine studies were normal and fetal movements were positive. A level II prenatal ultrasound scan was interpreted as showing multiple choroid plexus cysts, but subsequent ultrasound examinations were normal.

Maternal admission physical examination was notable for tachypnea, tachycardia, and a body mass index of 31.6 kg/cm.[2] The arterial pH was 7.21; pCO_2: 15 mm Hg; base excess: −18.9 mEq/L; serum sodium: 139 mEq/L; serum glucose: 335 mg/dL; hemoglobin A1C: 8.3% and C-peptide: 3.8 ng/mL. The metabolic panel revealed an anion gap with acidosis and 2+ urinary ketones. The patient was diagnosed with diabetic ketoacidosis secondary to adult-onset type 1 diabetes mellitus. The fetal heart rate was <60 beats/minute, prompting an emergency cesarean delivery and deferral of further maternal medical workup.

The female infant had an initial Apgar score of 0. The infant was intubated, and positive pressure ventilation and chest compressions were initiated 2 minutes, 44 seconds after birth due to inadequate response to previous resuscitative efforts. After intubation, the first epinephrine dose was administered via the endotracheal tube, and 2 subsequent intravenous doses were given via an umbilical venous catheter. After 16 minutes of resuscitation, heart rate improved, chest compressions were discontinued, and the infant was admitted to the neonatal intensive care unit with a fraction of inspired oxygen (FiO_2) of 0.90. Arterial cord pH was 6.67, venous pH was 6.91, and the base excess was −22.7 mEq/L.

The initial examination in the neonatal intensive care unit revealed a normal-appearing female infant born premature with a birth weight of 1450 g (90th percentile). The infant had profound, diffuse hypotonia, no spontaneous activity, myoclonus, and fixed dilated pupils. Clinical interventions included synchronized intermittent mandatory ventilation

CRP	C-reactive protein
FiO_2	Fraction of inspired oxygen
GFAP	Glial fibrillary acidic protein

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(FiO_2 0.40-0.90) for respiratory depression, administration of 2 doses of surfactant and 1 dose of caffeine, and dopamine infusion for hypotension. Initial laboratory studies revealed a pH of 6.94, PO_2 of 49.5 mm Hg, PCO_2 of 128.7 mm Hg, base excess of −20 mEq/L, serum glucose of 229 mg/dL, serum bicarbonate of 12 mEq/L, sodium of 139 mEq/L, creatinine of 1.36 mg/dL, and a normal complete blood count. Ketones, lactate, and insulin levels were not measured. At 3 hours, a postnatal cranial ultrasound scan revealed normal midline structures and cerebral ventricles, cerebral echogenicity, and no evidence of intraventricular hemorrhage.

Despite aggressive support, the infant remained ventilator-dependent with persistent metabolic acidosis, high FiO_2 requirements, bradycardia, and anuria. Laboratory findings included serum creatinine (1.71 mg/dL), aspartate aminotransferase (410 U/L), alanine aminotransferase (59 U/L), and alkaline phosphatase (599 U/L) levels. A second cranial ultrasound examination performed at 18 hours demonstrated diffusely heterogeneous echogenicity throughout the cerebrum, most likely reflecting severe ischemic injury. In light of the increased demands for respiratory support, multiorgan failure, and high likelihood of a poor neurologic outcome, consent was obtained from the family to redirect care. The infant died at 24 hours of age, shortly after she was extubated. Consent was obtained to perform a full autopsy.

General Autopsy Examination

The postmortem examination revealed a normally developed female infant weighing 1475 g (>90th percentile). Evidence of multiple organ failure was manifest by cardiomegaly with left ventricular hypertrophy, hepatomegaly with massive congestion, diffuse bilateral renal intramural hemorrhages, and serous body cavity effusions. Thymic involution with petechial hemorrhages reflected responses to stress. The pancreas had normal acinar development, islet distribution, and islet architecture and showed no evidence of fibrosis or inflammation, including insulitis and peri-insulitis. In addition, immunohistochemical staining for insulin confirmed the absence of islet cell hyperplasia.

The placenta weighed 327 g (75th-90th percentile), had characteristic preterm histologic features with superimposed pathologies reflecting maternal vascular malperfusion, manifested by hypertrophic-type decidual vasculopathy with focal fibrinoid necrosis of vessel walls, accelerated villous maturation, basal plate multinucleated trophoblast, and multifocal villous edema.

Postmortem Neuropathologic Examination

The brain weighed 196 g and its development was appropriate for gestational age. The brain exhibited diffuse edema with early encephalomalacia, extensive symmetrical hemorrhage, with early cavitation throughout cerebral white matter and subcortical nuclei, leaving a thin rind of cortical parenchyma intact. Less severe hemorrhage symmetrically involved all levels of brainstem. Of note is that the germinal matrix zone, ventricular cavities, choroid plexus, and cerebellum were spared (**Figure 1**).

Formalin-fixed, paraffin-embedded sections of the hippocampus, neostriatum including germinal matrix, frontal, parietal, and occipital cortex and white matter, periventricular white matter, choroid plexus, brainstem (all levels), cerebellum, and spinal cord stained with Luxol fast blue stain and hematoxylin and eosin revealed 3 main pathologic processes: (1) extensive acute multifocal, predominantly perivascular hemorrhages, bilaterally distributed in cerebral white matter and subcortical nuclei and less severe involvement of the midbrain, but relative or complete sparing of the middle and lower brainstem and cerebellum, ie, structures supplied by posterior circulation vessels, as well as the germinal matrix, ventricles, and choroid plexus (**Figure 1**); (2) severe diffuse microgliosis with prominent involvement of white matter, subcortical nuclei, and cerebral cortex; and (3) acute to subacute hypoxic–ischemic and metabolic encephalopathy.

The extensive acute hemorrhages in basal ganglia and white matter had mainly perivascular distributions. In many areas, focal attenuation or disruption of vessel and endothelial cell apoptosis or necrosis was associated with transmural egress of erythrocytes (**Figure 2**; available at www.jpeds.com). Diffuse cerebral white matter and subcortical nuclear microgliosis was associated with edema (**Figure 3**; available at www.jpeds.com). Acute hypoxic–ischemic-metabolic encephalopathy was associated with diffuse pericellular and microvesicular edema, increased metabolic (type 2) astrocytes, apoptosis or nuclear pyknosis of oligodendrocytes, and cytoplasmic eosinophilia and nuclear pyknosis in neurons (**Figure 4**; available at www.jpeds.com). Related subacute injury was associated with loss of neurons, proliferation of reactive hypertrophic astrocytes, re-endothelialization of previously damaged ependymal linings, and gliotic microinfarcts (**Figure 4**).

Immunohistochemical staining revealed extensive glial fibrillary acidic protein (GFAP) immunoreactivity in central white matter and moderate labeling of periventricular white matter and germinal matrix zones (**Figure 5**, A-D). GFAP immunoreactivity reflects gliosis that would have taken longer than 24 hours to become established. Immunostaining for CD34, which detects endothelial cells, demonstrated markedly reduced labeling of vessels surrounded by recent hemorrhage, and robust labeling of intact vessels that were unassociated with hemorrhage (**Figure 5**, I-L). CD68 immunostaining demonstrated diffuse infiltration of white matter and subcortical nuclei by individual, small clusters, or large aggregates of macrophages/microglia (**Figure 5**, E-H).

Discussion

Pregnancy with type 1 diabetes mellitus is associated with obstetric complications and increased risk of congenital malformations, perinatal mortality, and neonatal morbidity.[19-24] High rates of fetal morbidity and mortality occur with maternal ketoacidosis[25] due to rapid transfer of ketoacids and glucose across the placenta.[26,27] Diabetic ketoacidosis–induced fetal distress is mediated by (1) decreased uteroplacental blood flow due to osmotic diuresis and attendant volume depletion;

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