Regional Brain Water Content and Distribution During Diabetic Ketoacidosis

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Objective To characterize regional differences in brain water distribution and content during diabetic ketoacidosis (DKA) in children and determine whether these differences correlate with regional vascular supply.

Study design We compared changes in brain water distribution and water content in different brain regions during DKA by analyzing magnetic resonance diffusion weighted imaging data collected during DKA and after recovery in 45 children (<18 years of age). We measured the apparent diffusion coefficient (ADC) of water in the frontal and occipital cortex, basal ganglia, thalamus, hippocampus, and medulla. Brain water content was also measured in a subset of patients.

Results ADC values were elevated (suggesting vasogenic cerebral edema) in the frontal cortex, basal ganglia, thalamus, and hippocampus during DKA. In contrast, ADC values in the medulla and the occipital cortex were not increased during DKA, and ADC changes in the medulla tended to be negatively correlated with other regions. Regions supplied by the anterior/middle cerebral artery circulation had greater elevations in both ADC and brain water content during DKA compared with regions supplied by the posterior cerebral artery circulation.

Conclusions ADC changes during DKA in the brainstem contrast with those of other brain regions, and changes in both ADC and brain water content during DKA vary according to regional vascular supply. These data suggest that brainstem blood flow might possibly be reduced during DKA concurrent with hyperemia in other brain regions. *(J Pediatr 2017;180:170-6).*

Clinically apparent cerebral injury occurs in 0.7%-0.9% of diabetic ketoacidosis (DKA) episodes in children.[1,2] Signs and symptoms of this include a decline in mental status, often with other signs of neurologic dysfunction.[3] Notably, case reports of children with DKA-related brain injuries describe sudden onset of signs of brainstem dysfunction, such as respiratory depression, bradycardia, and hypotension.[4-6] This may suggest the occurrence of cerebral herniation. Imaging findings consistent with herniation, however, are infrequent and imaging studies may be normal in spite of these ominous clinical signs.[3,5] For example, among 25 children with severe DKA-related cerebral injury (resulting in death or permanent disability), 96% were unresponsive when DKA-related cerebral injury was diagnosed or suspected, 40% had abnormal respirations or suffered respiratory arrests, 56% had absent or abnormal pupillary reflexes, 64% had bradycardia without hypertension, and 12% had hypotension that could not be attributed to causes other than cerebral injury. Only 3 of these patients had imaging findings suggesting herniation or impending herniation.[3] An alternative explanation for the presence of clinical signs of brainstem dysfunction in these children must, therefore, be considered.

Subclinical cerebral edema occurs commonly in children with DKA. The cerebral ventricles are narrowed during DKA treatment,[7,8] and subtle cerebral dysfunction may be apparent.[7] Magnetic resonance imaging (MRI) studies demonstrate findings consistent with vasogenic cerebral edema, even in apparently asymptomatic children.[9-13] One previous study, however, showed that findings in the occipital cortex differ from those of other regions, suggesting that the brain's response to DKA may not be uniform and that regional differences in the brain should be investigated further.[9]

We hypothesized that clinical signs of brainstem dysfunction during severe DKA-related brain injury might result from alterations in brainstem perfusion. To investigate this hypothesis, we analyzed MRI data from children with DKA to compare regional alterations in brain water distribution (apparent diffusion coefficients

ADC	Apparent diffusion coefficient
CBF	Cerebral blood flow
DKA	Diabetic ketoacidosis
DWI	Diffusion-weighted imaging
GCS	Glasgow coma scale
GMRs	Geometric mean ratios
MRI	Magnetic resonance imaging
pCO_2	Partial pressure of carbon dioxide
RF	Radiofrequency
RGMRs	Relative GMRs

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[ADCs]) and brain water content. During vasogenic cerebral edema and hyperemia, ADC values are typically elevated, and brain water content is increased. In contrast, reductions in cerebral blood flow (CBF) are associated with decreased ADC values. In the current study, we determined whether regional changes in ADC values and brain water content vary according to differences in regional vascular supply and whether ADC changes in the brainstem suggest either hyperemia (elevated ADC) or hypoperfusion (decreased ADC).

Methods

We evaluated data from children with DKA (without overt signs of brainstem dysfunction) who underwent MRI as part of previous research protocols. The ADC data analyzed in this study were collected during 2 prospective studies (n = 27 and n = 18).[11,14] For the purposes of the current study, additional data were collected from the stored MRIs obtained in 1 previous study, including measurements of ADC values in brain regions not previously investigated and measurements of brain water content. Identical protocols were used to collect ADC data in both studies.

Database 1 (n = 27)[11] included (1) ADC measurements from children with uncomplicated DKA, 2-12 hours after beginning therapy and comparison ADC measurements after recovery, >72 hours after beginning therapy; (2) images obtained in frontal and occipital cortex, basal ganglia, and thalamus; (3) 3 clinical centers conducted imaging studies (78% at UC Davis Medical Center); and (4) no stored MRIs available for additional measurements.

Database 2 (n = 18)[14] included (1) ADC measurements from children with uncomplicated DKA 3-6 hours and/or 9-12 hours after beginning therapy with comparison measurements after recovery, >72 hours after beginning therapy; (2) images obtained in frontal and occipital cortex, hippocampus, basal ganglia, and thalamus; (3) all images obtained at a single center (UC Davis Medical Center); (4) brain water measurements recorded in an exploratory subset of patients (n=10); and (5) additional ADC data collected from stored images of the medulla (n = 16).

Both prospective studies enrolled patients who were younger than 18 years old, diagnosed with type 1 diabetes mellitus, and had DKA (serum glucose concentration >300 mg/dL, venous pH <7.25 or serum bicarbonate < 15 mEq/L, and a positive test for urine ketones or serum ketones > 3 mmol/L).

DKA Treatment Protocols

Patients enrolled in the prospective MRI studies were treated with DKA protocols in compliance with guidelines from the International Society for Pediatric and Adolescent Diabetes.[15] The only variation from these guidelines was that each patient received an initial intravenous fluid bolus of either 10 or 20 mL per kg of 0.9% saline, rather than administering fluid boluses at the discretion of the provider. Intravenous fluid infusions then replaced an estimated deficit of 70-100 cc per kg over 48 hours using 0.45%-0.9% saline. Insulin was administered intravenously (0.1 units per kg per hour) after completion of intravenous fluid bolus(es). Intravenous fluid treatment was continued until acidosis resolved (serum bicarbonate >18 mmol/L). Neurologic status was assessed hourly using Glasgow coma scale (GCS) scores[16] for all patients, and every 30 minutes or more frequently for patients with altered mental status (GCS scores below 14).

Diffusion-Weighted Imaging

Magnetic resonance diffusion-weighted imaging (DWI) data were collected 3-12 hours after beginning DKA treatment. Patients in the database underwent DWI at either 1 or 2 time points during the 3- to 12-hour window. DWI measures the ease of diffusion of water molecules in cerebral tissues, quantified as the ADC. Areas with cell swelling (cytotoxic edema) or tissue dehydration (reduced extracellular water content) are characterized by low ADC. Areas with increased extracellular water content (vasogenic edema) are characterized by elevated ADC. Comparison studies were obtained after recovery from DKA (>72 hours after beginning treatment). Methods for DWI were described previously.[11,14] ADC values were measured in the basal ganglia, thalamus, hippocampus, medulla, frontal cortex (gray and white matter), and occipital cortex (gray and white matter). ADC measurements were collected by 1 of 2 radiologists who were blinded to the patients' clinical data and to the study hypothesis. The means of ADC measurements on the right and left sides of the brain were used to determine regional values.

Brain Water Content Measurement

In a subset of patients (n = 10), brain water content was assessed using the following protocol. Brain water was measured on a 3.0T MRI system (Excite HDx, Ver.12x; GE Healthcare, Waukesha, Wisconsisn) with a 8-channel radiofrequency (RF) head coil (In-vivo, Inc, Gainesville, Florida) using 3-dimensional fast spoiled gradient echo scans (8.76 ms repetition time, 2.80 ms echo time, 24.0 cm field of view, 256 × 256 matrix, 2.0 mm thickness, 32 slices) with 5 different flip angles (3°, 6°, 9°, 12°, 15°, and 29°), followed by nonlinear curve fitting for generation of proton density (M0) and T1 maps, and finally by calculation of regional brain water by division of M0 map values by the reference average signal values in four 100% water reference vials attached to the RF coil. A fast spoiled gradient echo scan with 6° flip angle using the body coil for signal reception was also obtained, and postprocessing algorithms were developed to estimate the RF coil sensitivity and the B1 field (flip angle) spatial distributions to refine the curve fitting for M0 and T1 maps. Brain water content was recorded in 7 regions (basal ganglia, thalamus, hippocampus, occipital gray and white matter, and frontal gray and white matter) by 1 of 2 radiologists who were blinded to the patients' clinical data as well as to the study hypothesis. In both the frontal and occipital cortices, gray and white matter values were averaged to calculate brain water content. The brain water content protocol did not allow for measurements in the brainstem or any region caudal to the pontomidbrain junction.