Hyperemia and impaired cerebral autoregulation in a surgical patient with diabetic ketoacidosis

[L'hyperémie et l'autorégulation cérébrale altérée chez un patient de chirurgie atteint d'acidocétose diabétique]

Monica S. Vavilala MD,* Michael J. Souter MB CHB FRCA,† Arthur M. Lam MD FRCPC‡

Purpose: We describe cerebral hyperemia and impaired cerebral autoregulation documented with transcranial Doppler (TCD) ultrasonography in an adult patient with diabetic ketoacidosis (DKA) and sepsis presenting for surgery.

Clinical features: Middle cerebral artery flow velocity was increased relative to PaCO₂ (Vmca 52 cm·sec⁻¹; PaCO₂ 22 mmHg) and the autoregulatory index (ARI) was 0 prior to surgery. Twenty hours after admission and treatment, cerebral hyperemia resolved (Vmca 52 cm·sec⁻¹; PaCO₂ 35 mmHg) and cerebral autoregulation returned to normal (ARI 0.91).

Conclusion: To our knowledge, this is the first description of impaired cerebral autoregulation in adult DKA. Our observations suggest a relationship between cerebral hyperemia and impaired cerebral autoregulation in DKA.

Objectif: Décrire l'hyperémie cérébrale et l'autorégulation cérébrale altérée documentées par le Doppler transcrânien (DTC) chez un adulte atteint d'acidocétose diabétique (ACD) et de septicémie admis pour une intervention chirurgicale.

Éléments cliniques : La vitesse du flux de l'artère cérébrale moyenne a augmenté en relation avec la PaCO₂ (Vmca à 52 cm·sec⁻¹; PaCO₂ de 22 mmHg) et l'index d'autorégulation (IAR) était de 0 avant l'intervention chirurgicale. Vingt heures après l'admission et le traitement, l'hyperémie cérébrale était stoppée (Vmca à 52 cm·sec⁻¹; PaCO₂ de 35 mmHg) et l'autorégulation cérébrale revenue à la normale (IAR de 0,91).

Conclusion : Selon nous, c'est la première description d'autorégulation cérébrale altérée chez un adulte atteint d'ACD. Nos observations suggèrent une relation entre l'hyperémie cérébrale et l'autorégulation cérébrale altérée en cas d'ACD.

DIABETIC ketoacidosis (DKA) is a common complication of insulin dependent diabetes mellitus type I (IDDM). Cerebral complications related to DKA include altered mental status, cerebral edema, cerebral infarction, coma, and brain herniation.¹⁻⁵ We describe cerebral hyperemia and impaired cerebral autoregulation documented with transcranial Doppler (TCD) ultrasonography in a patient with DKA and sepsis presenting for surgery.

Case report

A 21-yr-old male presented for incision and drainage of a large posterior *sc* abscess with surrounding cellulitis (dermatome T2-T6 distribution). The patient's past medical history was significant for a 12-yr history of IDDM, multiple hospital admissions for DKA, one-week history of emesis, and elevated blood glucose (range 16.7–27.8 mmol·L⁻¹). On admission, the patient was confused and complained of back pain and thirst. His vital signs were: temperature 36°C, pulse 140 beats·min⁻¹, respiratory rate 40 breaths·min⁻¹, and blood pressure 120/80 mmHg [mean arterial pressure (MAP) 90 mmHg]. Notable laboratory results included: white blood count 30 G·L⁻¹, hematocrit 60%, Na⁺ 63.5 mmol·L⁻¹, K⁺ 2.3 mmol·L⁻¹, HCO₃⁻ 4.5 mmol·L⁻¹, positive serum and urine ketones, and hyperglycemia (22.9 mmol·L⁻¹). Arterial blood gas on room air revealed: pH 7.24, PaCO₂ 24 mmHg, PaO₂ 100 mmHg, and HCO₃⁻ 4.5 mmol·L⁻¹. The patient received 16 U of *ip* insulin (0.05 U·kg⁻¹·hr⁻¹), and 7 L of normal saline (1 L·hr⁻¹) during the seven hours prior to surgery.

From the Departments of Anesthesiology,*†‡ Pediatrics,* and Neurological Surgery,‡ University of Washington, Seattle, Washington, USA.

Address correspondence to: Dr. Monica S. Vavilala, Department of Anesthesiology, Harborview Medical Center, 325 Ninth Avenue, Box 359724, Seattle, Washington 98104, USA. Phone: 206-731-3059; Fax: 206-731-8009; E-mail: vavilala@u.washington.edu

Accepted for publication August 5, 2004.

Revision accepted December 10, 2004.

TABLE Cerebral autoregulation testing at eight and 20 hr following hospital admission

	<i>Supine</i>	<i>Tilted</i>	<i>ARI</i>	<i>Supine</i>	<i>Tilted</i>	
PaCO ₂ (mmHg)	22			35		
eMAP (mmHg)	90	73		90	73	
Vmca (cm·sec ⁻¹)	52	41	0.0	52	50	0.91

ARI = autoregulatory index; eMAP = mean arterial pressure at the external auditory meatus; Vmca = middle cerebral artery flow velocity. ARI < 0.4 indicates impaired cerebral autoregulation.

On arrival at the operating room, the patient was lethargic, and complained of dizziness upon standing. His vital signs were: temperature 36°C, pulse 100 beats·min⁻¹, respiratory rate 24 breaths·min⁻¹, and blood pressure 122/85 mmHg (MAP 97 mmHg). Laboratory results at this time (eight hours after admission) included hematocrit 45%, Na⁺ 68 mmol·L⁻¹, K⁺ 1.7 mmol·L⁻¹, HCO₃⁻ 4.8 mmol·L⁻¹, and glucose 12.4 mmol·L⁻¹. Invasive arterial and central venous pressures were monitored. Arterial blood gas, while breathing room air, revealed: pH 7.24, PaCO₂ 22 mmHg, PaO₂ 110 mmHg, HCO₃⁻ 5 mmol·L⁻¹.

To aid blood pressure and PaCO₂ management relating to cerebral perfusion, middle cerebral artery flow velocity (Vmca) was measured using TCD ultrasonography and cerebral autoregulation was tested using the tilt test methodology, prior to induction of general anesthesia. Vmca was measured continuously using a 2-MHz ultrasound probe. Measurements were first recorded in the supine position. The patient was then tilted 13.6 cm head-up to effect a 10-mmHg decrease in MAP (assuming a decrease in MAP of 1 mmHg for each 1.36 cm increase in vertical height). Invasive MAP was measured at the level of the external auditory meatus. Cerebral autoregulation was quantified by the autoregulatory index (ARI):⁶

$$\text{ARI} = \Delta - [\text{eCVR}] / \Delta \text{MAP}$$

where eCVR (estimated cerebrovascular resistance) = Vmca/MAP (ARI ≥ 0.4 represents preserved cerebral autoregulation, ARI < 0.4 represents impaired autoregulation and ARI = 0 reflects completely absent cerebral autoregulation).⁶ The Vmca was 52 cm·sec⁻¹, suggesting cerebral hyperemia (relative to PaCO₂) and the ARI was 0, indicating absent autoregulation (Table).

Following preoxygenation with 100% oxygen, rapid sequence induction of general anesthesia was

performed with *iv* etomidate 14 mg, and rocuronium 50 mg. The patient's trachea was intubated and general anesthesia was maintained using sevoflurane (end-tidal concentration 1.2–2.1%) with mechanical ventilation. The patient was placed in the prone position. MAP was maintained within 20% of baseline using *iv* infusion of a balanced salt solution. Arterial blood gases (30 min after incision) on 50% FiO₂, revealed a respiratory accentuation of metabolic acidosis with pH 7.19, PaCO₂ 35 mmHg, PaO₂ 250 mmHg and HCO₃⁻ 5 mmol·L⁻¹. Mechanical ventilation was adjusted to restore the baseline PaCO₂ of 22 mmHg and to increase pH. After an uneventful two-hour procedure, the patient's trachea was extubated and he was admitted to the intensive care unit.

Twelve hours later (20 hr following hospital admission), repeat TCD examination and cerebral autoregulation testing revealed normal Vmca of 51 cm·sec⁻¹ [MAP 93 mmHg, PaCO₂ 35 mmHg, glucose 10.4 mmol·L⁻¹, and intact cerebral autoregulation (ARI 0.91)]. The patient was discharged home on postoperative day four.

Discussion

DKA occurs in 43,000 hospital admissions per year in the 20 to 44 yr age group⁷ and is the leading cause of death in diabetic patients less than 24 yr of age.² The age adjusted death rate for DKA in the USA is 1.0 per 100,000.⁷ Cerebral edema occurs in 1% to 5% of DKA episodes and carries a mortality rate ranging from 45 to 80% in young patients.^{1,8,9} The cause of cerebral edema is controversial but an ischemic etiology has been proposed.^{1,9} Children with DKA may have cerebral hyperemia, with a consequent increase in intracranial pressure (ICP).¹⁰ We describe cerebral hyperemia and impaired cerebral autoregulation in an adult patient with DKA presenting for surgery.

Normal adult cerebral blood flow (CBF) averages 50 mL/100 g·min⁻¹ at a PaCO₂ of 40 mmHg and is maintained by a homeostatic process, cerebral autoregulation, whereby cerebral arterioles dilate and constrict in response to decreases and increases in MAP respectively.¹¹ TCD ultrasonography is a non-invasive clinical tool widely used to estimate changes in CBF. Although TCD does not directly measure CBF, changes in CBF correlate with changes in Vmca.^{12,13}

In pathological states, CBF may be increased, decreased or unchanged relative to metabolic need^{14–17} and cerebral autoregulation may be impaired.^{17–19} The implication for patients with impaired cerebral autoregulation is that even modest hypotension or hypertension can lead to cerebral

ischemia or hyperemia respectively. CBF also changes with PaCO_2 ; hypocapnia causes cerebral vasoconstriction and hypercapnia results in vasodilation. This CO_2 response can be altered physiologically with either a decrease in sensitivity to CO_2 or by a shift of the CO_2 response curve in response to changes in acid-base metabolism. Hyperemia can, subsequently, lead to vasogenic cerebral edema and increased ICP. Additionally, $\text{PaCO}_2 > 55$ mmHg has been shown to impair cerebral autoregulation in healthy adults²⁰ rendering CBF dependent on MAP. The presence of hyperemia has also been associated with impaired cerebral autoregulation in brain-injured patients.¹⁷

In the only report of TCD assessment of intracranial hemodynamics in DKA, Hoffman and colleagues reported vasoparalysis and suggested the presence of increased ICP that resolved when PaCO_2 returned to normal. In their series of five children nine to 13.5 yr, TCD measurements were made prior to treatment, at six, 24, 48 hr of treatment and on day six of admission.¹⁰ Although the cerebrovascular changes in DKA have not yet been clearly elucidated, and the effect of DKA on cerebral autoregulatory capacity and CO_2 reactivity in adults is largely unknown, our observation of vasoparalysis and cerebral hyperemia support the findings of Hoffman *et al.*¹⁰ Most recently, Glaser and colleagues reported increased apparent diffusion coefficients on magnetic resonance imaging in children with DKA, also suggesting a vasogenic mechanism for the development of cerebral edema.²¹

Since hyperventilation decreases CBF, we were concerned about intraoperative cerebral ischemia, and considered increasing PaCO_2 to prevent cerebral ischemia. However, a decrease in alveolar minute ventilation could increase PaCO_2 and CBF and worsen the patient's acidosis. Hypotension in the context of disordered autoregulation could predispose to cerebral ischemia, but paradoxically, volume resuscitation may itself result in cerebral edema. To solve this clinical dilemma and to guide the ventilation and hemodynamic management of this patient, we measured Vmca and examined cerebral autoregulation preoperatively. Unexpectedly, Vmca was within normal physiologic range but high relative to the low PaCO_2 . Correction of this hypocarbia might have increased CBF and cerebral blood volume, with an increase in ICP and risk of edema, and we therefore maintained the pre-existing hypocarbia. Impaired autoregulation mandated tightly controlled MAP, and was accomplished satisfactorily with fluid administration. Given the abnormal perioperative observations, we re-examined Vmca and cerebral autoregulation during recovery. Twenty hours following admission, the patient's

metabolic condition improved, hyperemia resolved (Vmca 51 $\text{cm}\cdot\text{sec}^{-1}$, PaCO_2 35 mmHg) and cerebral autoregulation normalized.

These observations suggest a metabolic etiology for this patient's cerebrovascular abnormalities. Classically metabolic acidosis is considered of minor relevance in determining CBF but the combination of acidemia, and hyperglycemia may override the vasoconstrictive effect of hyperventilation and cause hyperemia.¹⁰ In liver transplantation, metabolic acidosis has been shown to impair cerebral autoregulation.²²

Clinically apparent cerebral edema is relatively infrequent but several studies suggest subclinical cerebral edema to be common.^{23,24} Proposed mechanisms for cerebral edema include osmotic disequilibrium between brain and plasma, intracellular acidosis, overhydration and hyponatremia, and cerebral ischemia.²⁵ Suspected clinical risk factors include high admission serum urea nitrogen concentrations, bicarbonate treatment, metabolic acidosis and hypocapnia.^{8,26,27} Although this patient did not have clinical evidence of cerebral edema, no imaging studies were performed and we cannot exclude its presence. Our physiologic observations are important because they suggest that cerebrovascular changes in DKA may derive from cerebral hyperemia rather than cerebral ischemia. It can be theorized that cerebral ischemia is a consequence of hyperemia related cerebral edema in DKA.

In conclusion, to our knowledge, this is the first description of impaired cerebral autoregulation in an adult patient with DKA. Our observation suggests a relationship between cerebral hyperemia and impaired cerebral autoregulation in DKA. These changes may be related to DKA related metabolic alterations and may be of importance to clinicians managing patients with DKA. The presence of DKA in the surgical patient may constitute an indication for TCD ultrasonography to exclude impaired cerebral autoregulation during the perioperative period.

References

- 1 Glaser N. Cerebral edema in children with diabetic ketoacidosis. *Curr Diab Rep* 2001; 1: 41–6.
- 2 Dunger DB, Sperling MA, Acerini CL, *et al.* European Society for Paediatric Endocrinology. Lawson Wilkins Pediatric Endocrine Society. European Society for Paediatric Endocrinology/Lawson Wilkins Pediatric Endocrine Society consensus statement on diabetic ketoacidosis in children and adolescents. *Pediatrics* 2004; 113: e133–40.
- 3 Brown TB. Cerebral oedema in childhood diabetic ketoacidosis: is treatment a factor? *Emerg Med J* 2004; 21: 141–4.

- 4 Ertl-Wagner B, Jansen O, Schwab S, Sartor K. Bilateral basal ganglion haemorrhage in diabetic ketoacidotic coma: case report. *Neuroradiology* 1999; 41: 670–3.
- 5 Roe TF, Crawford TO, Huff KR, Costin G, Kaufman FR, Nelson MD Jr. Brain infarction in children with diabetic ketoacidosis. *J Diabetes Complications* 1996; 10: 100–8.
- 6 Strebel S, Lam AM, Matta B, Mayberg TS, Aaslid R, Newell DW. Dynamic and static cerebral autoregulation during isoflurane, desflurane, and propofol anesthesia. *Anesthesiology* 1995; 83: 66–76.
- 7 Center for Disease Statistics Surveillance. The Public Health Burden of Diabetes Mellitus in the United States. 1999. <http://www.cdc.gov/diabetes/statistics/survl99/chap1/ketoacidosis.htm>. Accessed April 6, 2004.
- 8 Glaser N, Barnett P, McCaslin I, et al. The Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics. Risk factors for cerebral edema in children with diabetic ketoacidosis. *N Eng J Med* 2001; 344: 264–9.
- 9 Marcin JP, Glaser N, Barnett P, et al. American Academy of Pediatrics. The Pediatric Emergency Medicine Collaborative Research Committee. Factors associated with adverse outcomes in children with diabetic ketoacidosis-related cerebral edema. *J Pediatr* 2002; 141: 754–6.
- 10 Hoffman WH, Pluta RM, Fisher AQ, Wagner MB, Yanovski JA. Transcranial Doppler ultrasound assessment of intracranial hemodynamics in children with diabetic ketoacidosis. *J Clin Ultrasound* 1995; 23: 517–23.
- 11 Paulson OB, Strandgaard S, Edvinson L. Cerebral autoregulation. *Cerebrovasc Brain Metab Rev* 1990; 2: 161–92.
- 12 Larsen FS, Olsen KS, Hansen BA, Paulson OB, Knudsen GM. Transcranial Doppler is valid for determination of the lower limit of cerebral blood flow autoregulation. *Stroke* 1994; 25: 1985–8.
- 13 Hughson RL, Edwards MR, O'Leary DD, Shoemaker JK. Critical analysis of cerebrovascular autoregulation during repeated head-up tilt. *Stroke* 2001; 32: 2403–8.
- 14 Bruce DA, Alavi A, Bilaniuk L, Dolinskas C, Obrist W, Uzzell B. Diffuse cerebral swelling following head injuries in children: the syndrome of "malignant brain edema". *J Neurosurg* 1981; 54: 170–8.
- 15 Bouma GJ, Muizelaar JP, Fatouros P. Pathogenesis of traumatic brain swelling: role of cerebral blood volume. *Acta Neurochir Suppl (Wein)* 1998; 71: 272–5.
- 16 Zwienenberg M, Muizelaar JP. Severe pediatric head injury: the role of hyperemia revisited. *J Neurotrauma* 1999; 16: 937–43.
- 17 Vavilala MS, Lee LA, Boddu K, et al. Cerebral autoregulation in pediatric traumatic brain injury. *Pediatr Crit Care Med* 2004; 5: 257–63.
- 18 Junger EC, Newell DW, Grant GA, et al. Cerebral autoregulation following minor head injury. *J Neurosurg* 1997; 86: 425–32.
- 19 Sahuquillo J, Munar F, Baguena M, Poca MA, Pedraza S, Rodriguez-Baeza A. Evaluation of cerebrovascular CO₂-reactivity and autoregulation in patients with post-traumatic diffuse brain swelling (diffuse injury III). *Acta Neurochir Suppl (wien)* 1998; 71: 233–6.
- 20 McCulloch TJ, Visco E, Lam AM. Graded hypercapnia and cerebral autoregulation during sevoflurane or propofol anesthesia. *Anesthesiology* 2000; 93: 1205–9.
- 21 Glaser NS, Wootton-Gorges SL, Marcin JP, et al. Mechanism of cerebral edema in children with diabetic ketoacidosis. *J Pediatr* 2004; 145: 164–71.
- 22 Doblar DD, Frenette L, Poplawski S, et al. Middle cerebral artery transcranial Doppler velocity monitoring during orthotopic liver transplantation: changes at reperfusion – a report of six cases. *J Clin Anesth* 1993; 5: 479–85.
- 23 Krane EJ, Rockoff MA, Wallman JK, Wolfsdorf JL. Subclinical brain swelling in children during treatment of diabetic ketoacidosis. *N Engl J Med* 1985; 312: 1147–51.
- 24 Hoffman WH, Steinbart CM, El-Gammal T, Steele S, Cuadrado AR, Morse PK. Cranial CT in children and adolescents with diabetic ketoacidosis. *AJNR Am J Neuroradiol* 1988; 9: 733–9.
- 25 Silver SM, Clark EC, Schroeder BM, Sterns RH. Pathogenesis of cerebral edema after treatment of diabetic ketoacidosis. *Kidney Int* 1997; 51: 1237–44.
- 26 Mahoney CP, Vlcek BW, DelAguila M. Risk factors for developing brain herniation during diabetic ketoacidosis. *Pediatr Neurol* 1999; 21: 721–7.
- 27 Edge JA. Cerebral oedema during treatment of diabetic ketoacidosis: are we any nearer finding a cause? *Diabetes Metab Res Rev* 2000; 16: 316–24.