Fluid Therapy, Diabetic Ketoacidosis, and Cerebral Injury in Children

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Sociedad Española de Urgencias de Pediatría
Bilbao, 16-18 de Abril de 2015
Case

- 11 y.o. girl presents with 3 weeks of polydipsia, polyuria
- 10 pound weight loss over 2-3 months
- 3 days of abdominal pain, nausea and vomiting
- In ED, ill appearing, pH 7.06, pCO₂ 10, positive urine ketones, serum glucose 900, BUN 40, sodium 128
- IV fluids, insulin drip, with gradual clinical and laboratory improvement
- Then 6 hours into therapy, sudden neurological decompensation, unresponsiveness....
- Initial CT normal; 5 hours later shows cerebral edema
Objectives

- Briefly describe the epidemiology of cerebral edema (CE) in children with DKA
- Debunk some myths about complications of DKA, particularly cerebral injury, given recent data
- The role of fluid Rx and the PECARN FLUID trial
DKA - epidemiology

- 64% of all deaths in children with diabetes are associated with DKA
- Of pediatric deaths due to diabetes, 83-97% are caused by DKA
- 62-63% of DKA-related deaths in children are the result of cerebral injury
Problem list and treatment considerations

<table>
<thead>
<tr>
<th>Problem:</th>
<th>Treatment:</th>
</tr>
</thead>
<tbody>
<tr>
<td>hyperglycemia</td>
<td>insulin</td>
</tr>
<tr>
<td>acidosis</td>
<td>insulin (bicarbonate?)</td>
</tr>
<tr>
<td>dehydration</td>
<td>iv fluids</td>
</tr>
<tr>
<td>electrolyte losses</td>
<td>replacement of Na, Cl, K, phos, (Ca, Mg)</td>
</tr>
</tbody>
</table>
Most important complication: *Cerebral edema (CE)*

- Most frequent cause of death in children with DKA
  - Death: 21-24%
  - Permanent neurological morbidity: 21-26%
Notable features of CE

- Although symptomatic CE occurs more commonly during treatment of DKA, symptomatic CE can occur at presentation, before any hospital treatment for DKA.
- Although symptomatic CE is rare, asymptomatic (subtle) CE is likely common, and is present both at presentation and during DKA treatment.
What causes cerebral injury in DKA? (traditional view)

- Cerebral edema occurs in a small minority of DKA episodes (~1%)
- Edema and increased ICP in these patients leads to cerebral injury
- Variations in DKA treatment likely play an important role in causing cerebral edema, particularly when DKA treatment leads to a rapid decline in osmolality
What causes cerebral injury in DKA?

How has our understanding evolved?

- Cerebral edema occurs in a small minority of DKA episodes (~1%)
- Clinically-apparent cerebral edema occurs in 0.3-0.9% of DKA episodes
- Sub-clinical or subtle cerebral edema occurs frequently (~50%)
Sub-clinical or subtle cerebral edema

- **Krane, 1985** *(6 children with DKA):* CT scans during Rx showed decreased ventricular size

- **Hoffman, 1988** *(9 children with DKA):* CT scans prior to, during and after Rx: both initial scans and those during Rx showed decreased ventricular size compared to after recovery
Figure 4. Representative Pairs of CT Scans from Patient e. The third ventricle (Panel A, arrows) and lateral ventricles (Panel B, arrows) are narrowed on the earlier scans (CT-1).
Lateral ventricle diameter during DKA treatment and after recovery (n=41)

Glaser/Kuppermann et al, Pediatric Diabetes, 2006
Mental status abnormalities in children with subtle CE

- 22 (54%) of 41 children had ventricular narrowing during DKA treatment
- 12/22 (55%) children with ventricular narrowing had abnormal mental status (GCS scores < 15) vs. 4/19 (21%) children without ventricular narrowing (p < 0.03)

Glaser/Kuppermann et al, Pediatric Diabetes, 2006
Subtle cerebral injury in DKA

- MR spectroscopy can be used as a non-invasive tool to evaluate cerebral metabolites.
- Ratio of N-acetyl aspartate/creatine measured by proton MRS is thought to be an indicator of neuronal health.
  - Decrease in NAA/Cr is seen in stroke, other brain injuries.
NAA/Cr ratios measured by proton MR spectroscopy during DKA and after recovery (n=29)

<table>
<thead>
<tr>
<th></th>
<th>during DKA treatment</th>
<th>after recovery</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal ganglia</td>
<td>1.68 ± 0.24</td>
<td>1.86 ± 0.28</td>
<td>&lt; 0.005</td>
</tr>
<tr>
<td>Peri-aqueductal gray matter</td>
<td>1.66 ± 0.38</td>
<td>1.91 ± 0.50</td>
<td>0.06</td>
</tr>
<tr>
<td>Occipital gray matter</td>
<td>1.97 ± 0.28</td>
<td>2.13 ± 0.18</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Wooton-Gorges et.al., Am J Neuroradiol 2006
MR spectroscopy during DKA and after recovery in a 13 year old girl

Wooton-Gorges et.al., Am J Neuroradiol 2006
What causes DKA-related cerebral injury?

*How has our understanding evolved?*

- Edema and increased intra-cranial pressure directly cause cerebral injury in children with DKA.
- Many children with DKA-related “cerebral edema” have no overt signs of edema on cerebral imaging.
Muir et al \textit{(Diabetes Care 2004)}

- Reviewed 23 children with profound neurological disturbances during DKA diagnosed with “cerebral edema”
  - 9 (39\%) had no abnormalities on initial CT
- Repeat imaging studies hours/days later showed development of edema, hemorrhage, infarction
Characteristics of DKA-related cerebral injury

How has our understanding evolved?

- Many children with brain injury during DKA have no radiological evidence of significant edema initially, suggesting that edema may be a consequence, rather than a cause of injury.

- DKA-related “cerebral edema” might more appropriately be termed “DKA-related cerebral injury”
Pathophysiology of DKA-related CE

- Previous hypotheses assumed that fluid shifts caused by osmotic changes were central to DKA-related CE.
- This assumption has not been well-supported by clinical data.
osmotic equilibrium

hyperosmolar stress

accumulation of intracellular osmolytes
rapid decrease in extracellular osmolality

osmotic swelling
## Risk factors for CE

**Case-control study of risk factors for cerebral edema**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted OR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>initial BUN</td>
<td>1.8</td>
<td>1.2, 2.7</td>
<td>0.008</td>
</tr>
<tr>
<td>initial pCO2</td>
<td>2.7</td>
<td>1.4, 5.1</td>
<td>0.002</td>
</tr>
<tr>
<td>change in Na during Rx</td>
<td>0.6</td>
<td>0.4, 0.9</td>
<td>0.01</td>
</tr>
<tr>
<td>bicarbonate Rx</td>
<td>4.2</td>
<td>1.5, 12.1</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Glaser/Kuppermann et al, NEJM, 2001
Risk factors for CE

No significant associations with CE for:

- Rate of change of serum glucose concentration
- Rate of insulin infusion
- IV fluid rate
- Rate or rate of sodium administration after adjusting for covariates
DKA-related cerebral injury

How has our understanding evolved?

- Variations in DKA treatment likely play an important role in causing cerebral edema, particularly when DKA treatment leads to a rapid decline in osmolality.

- Our large case-control study did not support.

- 5-19% of children with clinically-apparent DKA-related cerebral edema/injury are diagnosed at the time of ED presentation, *before initiation of treatment*. 
## Risk factors for DKA related cerebral injury

<table>
<thead>
<tr>
<th>authors</th>
<th>year</th>
<th>pts w/ CE (n)</th>
<th>control pts (n)</th>
<th>risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lawrence, et al</td>
<td>2005</td>
<td>21</td>
<td>42</td>
<td>higher initial BUN</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>lower initial bicarbonate</td>
</tr>
<tr>
<td>Edge, et al</td>
<td>2005</td>
<td>43</td>
<td>169</td>
<td>greater acidosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>lower initial Na</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>higher initial K</td>
</tr>
<tr>
<td>Glaser, Kuppermann, et al</td>
<td>2001</td>
<td>61</td>
<td>355</td>
<td>higher initial BUN</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>lower initial PCO₂</td>
</tr>
<tr>
<td>Mahoney, et al</td>
<td>1999</td>
<td>9</td>
<td>186</td>
<td>lower initial PCO₂</td>
</tr>
</tbody>
</table>
Insights into pathophysiology of CE

- Higher BUN likely indicative of greater dehydration
- Lower pCO₂ indicative of greater hyperventilation and possibly greater cerebral vasoconstriction
- Both higher BUN and lower pCO₂ would be expected to decrease CNS perfusion
- In previous studies, bicarbonate therapy in DKA also associated with decrease in CSF pH and pO₂
- Pathophysiology of CE may involve CNS hypoperfusion
Is DKA associated with neurocognitive dysfunction in children?

- Memory capacity is a particularly sensitive indicator of neurological injury in the setting of hypoxia/ischemia (e.g., high altitude climbing).
- Contextual memory: “Last time I saw my keys they were in my purse.”
- Children with diabetes with and without past history of DKA tested for contextual memory:
  - Color task
  - Spatial task
Memory capacity (contextual memory) in children with diabetes with DKA history (n=33) and without DKA history (n=29)

p<0.01 for both comparisons

Ghetti et al, J Pediatr 2010
Diffusion Weighted Imaging

- DWI measures the random motion (diffusion) of water molecules in cerebral tissues.
- Diffusion can be quantified as the “Apparent Diffusion Coefficient (ADC)”.
- Molecules of water in extracellular fluid diffuse freely (high ADC).
- Molecules of water in the intracellular space diffuse less freely due to interference by organelles, membranes (low ADC).
Diffusion Weighted Imaging

- Cytotoxic edema (ischemia, osmotic cellular swelling) – low ADC
- Vasogenic edema (tumors, reperfusion injury) – high ADC
Vasogenic edema – expansion of extracellular space

Cytotoxic edema – expansion of intracellular space

High ADC

Low ADC
DWI during DKA

- DWI cannot ethically be performed in children prior to treatment of DKA
- Rat model used to explore ADC values during DKA
ADC in rats with DKA vs. normal controls

p<0.01 for DKA vs. either control

Lam, Anderson, Glaser, O’Donnell. Diabetes; 2005
ADC changes during treatment for DKA with IV fluids and insulin

![Graph showing ADC changes]

- **Control rats**: ADC value
- **DKA**: ADC value
- **DKA after 6 hrs. treatment with fluids/insulin**: ADC value
Rat model of DKA

- Untreated DKA is associated with low ADC (suggests cytotoxic edema) and decreased CBF.
- MRS studies show high lactate and low NAA/Cr, consistent with cerebral hypoperfusion.
- ADC increases to above normal after DKA treatment suggesting vasogenic edema.
ADC values during DKA treatment and after recovery: mean of values for basal ganglia, thalamus and frontal white matter (n=26)

Glaser/Kuppermann et.al, J Pediatr, 2004
Summary of DWI in DKA

- Patterns of change in ADC are similar to those observed in various types of hypoxic/ischemic brain injury.
- ADC changes correlate best with acidosis/hypocapnia and with BUN, but not with degree of hyperglycemia or osmolality.
Implications of studies using DWI

- High ADC values during DKA treatment are not consistent with previous hypotheses attributing CE to osmotic shifts.
- Osmotic changes and rate of fluid infusion likely less important in the pathogenesis of DKA-related CE than previously hypothesized.
Hypothetical model of DKA-related cerebral injury

- Acidosis
- Hypocapnia
- Vasoconstriction
- Dehydration
- Hyperglycemia

↓ CBF

- Cerebral injury / cytotoxic edema
- Rehydration / reperfusion injury / vasogenic edema

Hyperglycemia
Characteristics of DKA-related cerebral injury

How has our understanding evolved?

- Both cerebral imaging and epidemiological studies suggest that dehydration, acidosis and hypocapnia correlate best with cerebral edema/injury in DKA.

- These findings suggest that cerebral hypoperfusion during DKA may be an important factor in causing cerebral injury.

- Osmotic changes during DKA treatment may be less important than previously hypothesized.
So... how do these data guide our care of children with DKA?

- The disappointing answer.... it’s unclear!
- Arguments both in favor of more rapid rehydration and slower rehydration could be made...
The fluid controversy

A randomized prospective trial of fluid therapies in DKA has been necessary for more than 25 years, but has never happened!

- Lack of ability to organize a study of adequate size
- Lack of expertise in emergency medicine research
- Lack of organizational structure to make a study of this complexity happen
- Dogmatic opinions and fear without good evidence
Arguments in favor of slower rehydration

- If vasogenic edema occurs later in DKA treatment, possibly with breakdown of the blood-brain barrier, slower rehydration might limit edema formation.

- If osmotic (glucose, sodium) changes play a minor role, limiting osmotic fluctuations might be of some benefit.
Arguments in favor of more rapid rehydration

- If cerebral hypoperfusion is occurring during untreated DKA, then it would make sense to correct hypoperfusion sooner / limit the time the brain is exposed to hypoperfusion.

- During DKA treatment, glucose declines and vascular volume declines (water moves into the tissues). More aggressive rehydration could limit this decline, preventing additional hypoperfusion / worsening of hypoperfusion during treatment.
Fluid therapies Under Investigation in DKA: “the FLUID trial”

Funded by grant 1R01HD062417-01 from the Eunice Kennedy Shriver NICHD.

PECARN is supported by the Health Resources and Services Administration (HRSA), Maternal and Child Health Bureau (MCHB), Emergency Medical Services for Children (EMSC) through the following grants: U03MC00008, U03MC00003, U03MC22684, U03MC00007, U03MC00001, U03MC22685, U03MC00006
Proposed PECARN Trial Protocol

- RCT to compare four DKA fluid treatment protocols using factorial design
- Enrollment target: 1400 children with DKA
- Study comparison groups:
  - More rapid rehydration vs. slower rehydration
  - 0.9% saline vs. 0.45% saline as rehydration fluid
Overview of FLUID study

Child diagnosed with DKA

Randomized to 1 of 4 fluid treatment protocols
(all other DKA treatment same as usual)

Child followed in hospital for mental status during treatment (GCS, digit span test), clinically-apparent CE and other DKA complications

DKA treatment finished

3 month follow up for long-term neurocognitive outcome (memory, IQ)
Current clinical implications

- Dehydration / CNS hypoperfusion may play a larger role than previously believed in DKA-related cerebral edema
- Under-hydration of children with DKA should be avoided
- Treat hypoperfusion/shock with fluid bolus(es)
Current clinical implications (cont’)

- Although aggressive hydration may play a (small) role in the development of DKA-related cerebral edema, do not “obsess” on this one factor – others are likely more important (severity of illness, bicarbonate therapy, etc.)

- Therefore, take a reasonable, balanced approach to hydration - correction of fluid deficits over 36-48 hours, no bicarbonate unless absolutely necessary

- Close monitoring for signs of neurological decompensation
DKA Summary

- DKA is an important cause of morbidity and mortality in children with diabetes
- Evidence-based approach to therapy when possible
- Cerebral injury is the most frequent major complication; etiology remains unclear
- Several important questions regarding risk factors for cerebral injury and ideal treatment regimens remain incompletely answered
Most debate on DKA treatment centers on avoidance of cerebral edema/cerebral injury.

Data suggest that subtle cerebral edema and cerebral injury occur in most children with DKA.

Whether injury can be minimized/avoided by optimizing DKA treatment (iv fluid therapy) is unknown – subject of the PECARN FLUID study.
## Treatment Arms

<table>
<thead>
<tr>
<th></th>
<th>A1</th>
<th>A2</th>
<th>B1</th>
<th>B2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Standard bolus</strong></td>
<td>10cc/Kg NS</td>
<td>10cc/Kg NS</td>
<td>10cc/Kg NS</td>
<td>10cc/Kg NS</td>
</tr>
<tr>
<td><strong>Additional bolus</strong></td>
<td>10cc/Kg NS</td>
<td>10cc/Kg NS</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td><strong>Assumed fluid deficit</strong></td>
<td>10% of body weight</td>
<td>10% of body weight</td>
<td>5% of body weight</td>
<td>5% of body weight</td>
</tr>
<tr>
<td><strong>Deficit replacement</strong></td>
<td>½ over 12 hrs, ½ over next 24 hrs (plus maintenance)</td>
<td>½ over 12 hrs, ½ over next 24 hrs (plus maintenance)</td>
<td>evenly over 48 hrs (plus maintenance)</td>
<td>evenly over 48 hrs (plus maintenance)</td>
</tr>
<tr>
<td><strong>Fluid for deficit replacement</strong></td>
<td>½ NS</td>
<td>NS</td>
<td>½ NS</td>
<td>NS</td>
</tr>
</tbody>
</table>