

Hyperglycemic Hyperosmolar Nonketotic Syndrome and Diabetic Ketoacidosis

I. Epidemiology and Mortality

- HHNS
 - 1 in every 1000 hospital admissions
 - usually elderly, type II diabetics, frequently patients who are unable to maintain adequate fluid intake because of stroke, dementia, neglect, etc
 - mortality as high as 12-45%, increases with age and higher level of serum osmolality
 - no significant decrease in the incidence of HHNS or associated morbidity/mortality in the last 15-20 years
- DKA
 - in 1995, 4.6-8 episodes per 1000 diabetic patients
 - usually younger type I diabetics
 - overall mortality in developed countries 2-10 %
 - >64 mortality exceeds 20%, compared to 2-4% for younger adults
- Patients do not usually die as a result of hypertonicity or acidosis, but most commonly from a concurrent disorder that may have precipitated HHNS or DKA

II. Etiology/Pathophysiology

- Two abnormalities necessary for both- insulin deficiency and glucagon excess
- Decreased tissue utilization alone will produce only postprandial hyperglycemia; increased gluconeogenesis is required to maintain severe fasting hyperglycemia seen in both HHNS and DKA
- Both are frequently precipitated by various stresses (infection, surgery, MI, emotional stress, etc) which increase the secretion of glucagon and other hormones that can promote ketone and glucose production
- HHNS
 - increased ratio of glucagon/insulin results in accelerated gluconeogenesis and reduced glucose clearance, leading to the development of hyperglycemia and hyperosmolality
 - hyperglycemia pulls fluid from the intracellular to extracellular space (transiently maintaining adequate perfusion), resulting in a profound diuresis and electrolyte depletion
 - pre-renal azotemia ensues and further impairs glucose disposal, worsening hyperglycemia and hyperosmolality; depressed GFR in many older, diabetic patients contributes to the process
 - total body water deficit at presentation is usually 8-10L
 - severe ketoacidosis is *usually* absent; likely due to a differential in the sensitivity of fat and glucose to the effects of insulin (the concentration of insulin required to suppress lipolysis is one-tenth that required to promote glucose uptake)
 - mild ketoacidosis is not uncommon
- DKA
 - insulin deficiency and glucagon (and other counterregulatory hormone) excess leads to the promotion of lipolysis, increasing FFA delivery to the liver where they are converted by free fatty acyl CoA into ketones
 - osmotic diuresis ensues as in HHNS (with the additional action of ketones exerting a strong osmotic effect) with volume and electrolyte depletion (urinary ketones also promote excretion of positively charged ions); total body water deficit at presentation is usually 5-7 L

III. Presentation

- HHNS
 - onset is usually insidious, over days-weeks
 - several days of deteriorating glycemic control, polyuria, polydipsia, are followed by increasing lethargy and decreased mental status; 25% present in coma
 - predominant signs are those of dehydration, volume depletion, and mental status changes (depression of sensorium correlates directly with the degree and rate of development of hyperosmolality)
 - orthostasis, hypotension, tachycardia, cool extremities, poor turgor
 - focal neurological signs are common, and numerous, usually a reflection of cerebral dehydration
 - partial or generalized complex seizures, myoclonus, chorea, aphasia, ballism, central hyperpyrexia, hallucinations, acute quadriplegia
 - may mimic a focal neurological event, such as CVA
 - nausea, vomiting, abdominal pain occur less frequently than with DKA
- DKA
 - duration of symptoms is relatively short; hours to a day or two
 - often present with abdominal pain, vomiting, weakness, altered sensorium, and evidence of volume depletion.
 - focal neurological signs are rare

IV. Laboratory Evaluation

Lab Criteria of DKA and HHNS

| | DKA | HHNS |
|--------------------------|------|------------|
| Glucose, mg/dL | >250 | >600 |
| Arterial pH | <7.3 | >7.3 |
| HCO ₃ , mEq/L | <15 | >20 |
| BUN, mg/dL | <25 | >30 |
| Osmolality, mOsm/kg | <320 | >320 |
| Ketones | | |
| urine | >3+ | - or small |
| serum | + | - or small |

- hyperosmolality is more severe in HHNS than DKA
 - patients with DKA likely present earlier with other symptoms (SOB, abdominal pain)
 - patients with DKA tend to be young with high GFR, having a greater capacity to excrete glucose than an older patient with HHNS
- electrolyte depletion is common to both
 - sodium:
 - lost in the osmotic diuresis
 - tubular reabsorption is decreased in the absence of insulin
 - because losses are proportionately less than water losses, hypernatremia may occur
 - remember to correct for blood glucose
 - potassium:
 - total body depletion, though presenting level may be normal to high; hypertonicity, insulin deficiency, acidosis (if present) will cause a shift of potassium out of cells, which in the presence of osmotic diuresis results in a significant loss
 - magnesium, phosphate
 - as with potassium, total body stores are depleted, but serum concentrations may not initially be representative
- patients with HHNS do not usually have a significant ketoacidosis caused by DM, but may have an anion gap metabolic acidosis due to a combination of lactic acidosis, starvation ketoacidosis, and retention of inorganic acids from renal hypoperfusion
- in DKA:
 - creatinine levels may be falsely elevated in DKA as ketones interfere with automated creatinine measurements
 - Acetest positive
 - reacts with acetone and acetoacetate, but not β -hydroxybutyrate (75% of circulating ketones in DKA)

- false positives are produced in the presence of therapy with sulfhydryl drugs (captopril, penicillamine, mesna)
- elevated amylase/lipase age often seen in patients with DKA but without pancreatitis, the mechanism remains unclear

V. Therapy

- fluid replacement
 - should precede insulin therapy 30-60 minutes in markedly hypovolemic patients to allow the administration of 1-2 L of saline, avoiding the “latent shock of dehydration”
 - initially attempt to correct the circulatory volume deficit (0.9% NaCl), followed by correction of the whole-body water deficit (0.45% NaCl)
 - 1-2 L in first 1-2 hours, then 1 L/hr for 3-4 hours depending on response; once stable attempt to replace ½ the water deficit in first 12 hours, remainder in next 24
 - be wary of renal failure-insulin may be all that’s necessary
- correct hyperglycemia and acidosis
 - insulin doses generally are similar in DKA and HHNS
 - loading dose regular insulin 0.1 to 0.2 U/Kg; then 5 to 10 U/hr, with a goal decline in plasma glucose 75-90 mg/dL/hr
 - any dose of insulin that corrects hyperglycemia will also normalize ketone metabolism
 - bicarbonate use is controversial; bicarbonate is generated by the metabolism of ketoacids in the presence of insulin
 - in general should not be given unless acidemia is severe (pH<6.9) or other indications are present
 - add D5 to fluids when glucose reaches 250
- electrolyte replacement
 - potassium
 - already depleted total body stores will fall even further with hydration, improved acid-base status, and insulin-mediated entry into cells
 - amount and rate of replacement should be guided by serum concentration and renal function
 - initially, hold off on replacing unless <4-5 mEq/L; once adequate urine output is established add 20-40 mEq per liter, with the goal being 4-5 mEq/L
 - magnesium
 - should be routinely replaced
 - phosphate
 - routine phosphate replacement has not been proven to be beneficial
- search for underlying causes
 - empiric antibiotics
 - EKG, cardiac enzymes
 - evidence of noncompliance
- treat complications
 - seizure control requires normalization of osmolality and glucose; standard antiepileptics are ineffective, and phenytoin can inhibit the release of insulin
 - cerebral edema is rare and thought secondary to rapid correction of the hyperosmolar state after CNS adaptation to intracellular dehydration by the generation of idiogenic osmols
 - more often seen in kid with DKA
 - typically treated with hyperventilation, mannitol, ICP monitoring
 - vascular occlusions, more common with HHNS
 - hyperosmolality/hyponatremia may alter factor VIII and contribute to a hypercoagulable state already produced by increased viscosity
 - prevented by adequate treatment of hypovolemia
 - prophylactic anticoagulation may be considered

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