Nonketotic hyperglycemic hyperosmolar coma

Report of neurosurgical cases with a review of mechanisms and treatment

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Seventy-eight critically ill patients who died while on the neurosurgical service were studied retrospectively to establish the prevalence of nonketotic hyperglycemic hyperosmolar coma (NHHC). All patients had been comatose before death, and all underwent necropsy. Criteria for the diagnosis of NHHC included moderate-to-severe hyperglycemia with glucosuria, absence of significant acetonuria, hyperosmolarity with dehydration, and neurological dysfunction. This study revealed seven cases of unequivocal NHHC (9%), and six of hyperosmolarity but with incomplete records. Five of the seven confirmed cases of NHHC demonstrated no evidence of cerebral edema, transtentorial herniation, or brain-stem damage, and showed central nervous system (CNS) lesions compatible with survival. Fatal complications of this syndrome, such as acute renal failure, terminal arrhythmias, and vascular accidents, both cerebral and systemic, were common in this series. The mechanism of coma in NHHC is believed related to shifts of free water from the cerebral extravascular space to the hypertonic intravascular space, with subsequent intracellular dehydration, accumulation of metabolic products of glucose, and brain shrinkage. It is uncertain whether injury to specific areas in the CNS is a predisposing factor to the development of NHHC. Factors documented to be significant in its development include nonspecific stress to primary illnesses, hyperosmolar tube feedings, dehydration, diabetes, and mannitol, Dilantin, or steroid administration.

KEY WORDS · nonketotic hyperglycemic hyperosmolar coma (NHHC) · hyperglycemia · hyperosmolar state · coma

In 1957, Sament and Schwartz described the entity of nonketotic hyperglycemic hyperosmolar coma (NHHC) as a severe and often fatal complication in diabetic patients. NHHC has since been observed as a complication of various primary diseases, both in diabetic and non-diabetic patients. Criteria for its diagnosis include moderate-to-severe hyperglycemia, 3+ to 4+ glucosuria in the absence of significant acetonuria or ketonemia, effective osmolarity greater than 330 mOsm/kg, dehydration with an osmotic diuresis during some phase of the illness, and central nervous system dysfunction, manifested by lethargy, seizure activity, or coma. Various predisposing factors to NHHC have been described: steroids, prolonged mannitol therapy, hyperosmolar tube feeding, Dilantin, and limited water replacement. Com-
TABLE 1

Summary of clinical and laboratory data in seven patients fulfilling all criteria of NHHC

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age</th>
<th>Sex</th>
<th>Diagnosis on Admission</th>
<th>Diabetes on Admission</th>
<th>Hosp. Day</th>
<th>Na mEq%</th>
<th>Glucose mg%</th>
<th>BUN mg%</th>
<th>HCO₃⁻ mEq/l</th>
<th>Serum Osmolarity mOsm/kg</th>
<th>pH</th>
<th>Urinalysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>43</td>
<td>F</td>
<td>metastatic breast cancer, to spine</td>
<td>yes</td>
<td>1</td>
<td>142</td>
<td>270</td>
<td>20</td>
<td>29</td>
<td>316*</td>
<td>3+ / neg</td>
<td>neg/neg</td>
</tr>
<tr>
<td>2</td>
<td>35</td>
<td>M</td>
<td>intracerebral hemorrhage</td>
<td>?</td>
<td>1</td>
<td>155</td>
<td>150</td>
<td>40</td>
<td>46</td>
<td>324</td>
<td></td>
<td>3+ / neg</td>
</tr>
<tr>
<td>3</td>
<td>50</td>
<td>F</td>
<td>rt cerebral infarction</td>
<td>yes</td>
<td>1</td>
<td>141</td>
<td>110</td>
<td>26</td>
<td>18</td>
<td>294*</td>
<td>neg/neg</td>
<td>3+ / neg</td>
</tr>
<tr>
<td>4</td>
<td>15</td>
<td>M</td>
<td>closed head injury &amp; basilar skull fracture</td>
<td>?</td>
<td>1</td>
<td>139</td>
<td>130</td>
<td>43</td>
<td>15</td>
<td>303*</td>
<td>neg/neg</td>
<td>3+ / neg</td>
</tr>
<tr>
<td>5</td>
<td>52</td>
<td>M</td>
<td>gunshot head wound</td>
<td>?</td>
<td>1</td>
<td>139</td>
<td>116</td>
<td>26</td>
<td>308</td>
<td>7.5</td>
<td>trace/neg</td>
<td>see comment</td>
</tr>
<tr>
<td>6</td>
<td>40</td>
<td>F</td>
<td>possible NHHC</td>
<td>yes</td>
<td>1</td>
<td>122</td>
<td>630</td>
<td>13</td>
<td>32</td>
<td>284*</td>
<td>4+ / neg</td>
<td>4+ / neg</td>
</tr>
<tr>
<td>7</td>
<td>61</td>
<td>F</td>
<td>dementia, seizures; possible CVA</td>
<td>yes</td>
<td>1</td>
<td>136</td>
<td>108</td>
<td>15</td>
<td>19</td>
<td>282*</td>
<td>3+ / neg</td>
<td>7.5 4+ / neg</td>
</tr>
</tbody>
</table>

* Calculated osmolarity.

Combinations of these factors are frequently used in the management of patients with neurological disorders and cerebral edema. Consequently, a higher prevalence of NHHC might be expected in these patients than has previously been recognized. A large series of such cases, together with necropsy correlations, has not been reported to date in the neurosurgical literature. Accordingly, a retrospective study of patients admitted to the Neurosurgical Intensive Care Unit during the years 1970 through 1972, all with autopsy examinations, was done to determine the prevalence of NHHC and its relation to the terminal course of the patient.

Case Reports

The clinical and necropsy records of 78 patients were reviewed. Seven patients fulfilled all criteria for a diagnosis of NHHC (Group A, Table 1); six others were hyperosmolar but lacked complete data to justify a definitive diagnosis (Group B). All patients had been in the Neurosurgical Intensive Care Unit and had been comatose at various intervals before death.

Group A

Case 1. This 43-year-old diabetic woman underwent transsphenoidal hypophysectomy...
Recognized Pertinent Autopsy Predisposing Comments
Clinically Findings Factors

suggested, but not treated
metastases to liver, spinal cord & calvaria; possible liver failure; no cerebral edema
cortisone, 300 mg/day IIV fluids
transphenoidal hypophysectomy on day 6 became somnolent on day 7 hypertensive for 6 days; died on day 14

no
intracerebral hemorrhage, rt basal ganglia; staph pneumonia; no cerebral edema or herniation
decadron, 36 mg/day glycercyl/NG tube IIV fluids
mild hypertension by history admitted in coma without improvement died on day 4

recognized terminally
infarction rt occiput, temporal lobe & basal ganglia; systemic emboli including pulmonary emboli; no cerebral edema or herniation
decadron, 8 mg/day tube feedings intermittent mannitol IIV fluids
It hemiparesis but responsive day 1; increasingly somnolent day 5; comatose followed by death day 11 & 12; serum acetone negative

no
encephalomalacia involving cortex & brain stem; no cerebral edema or herniation
decadron, 12-24 mg/day tube feedings intermittent mannitol IIV fluids
admitted in coma without improvement; died on day 6; no terminal urine available but pH 7.5, HCO$_3$ 24 mEq/l ruled out ketoacidosis

recognized to be hyperosmolar
destruction of rt parietal & temporal lobes & intracerebral hemorrhage; no cerebral edema or herniation
decadron, 24 mg/day mannitol Dilantin IIV fluids
admitted in coma without improvement; negative serum acetone on day 2; died on day 2

yes
astroblastoma of rt parietal cortex; cerebral edema and herniation observed Dilantin mannitol decadron 16 mg/day IIV fluids
hypokalemic at time of death (2.0) after aggressive insulin and fluid replacement

recognized to be hyperosmolar
ischemic infarct rt cerebral peduncl and cerebellum; no cerebral edema or herniation
mannitol tube feedings IIV fluids
symptoms progressed on day 4 after failure to receive insulin; died on day 13

† IIV = intravenous; NG = nasogastric.

for metastatic breast carcinoma. One day postoperatively, she became increasingly somnolent, progressing for 5 days to coma, although she had been alert and without signs of ketoacidosis preoperatively. On admission, laboratory tests had revealed the following: blood glucose 270 mg%, Na 142 mEq/l, HCO$_3$ 29 mEq/l, blood urea nitrogen (BUN) 20 mg%, 3+ glucosuria, and negative acetonuria (3+/negative). On the day of operation, her serum glucose rose to 450 mg%, with 4+/negative urine, progressing to a glucose of 534 mg%, and 4+/negative urines 3 days before death, and 5 days postoperatively. Serum osmolarity rose progressively from 330 mOsm/kg 5 days after operation to 353 mOsm/kg on the day of death, accompanied by a serum sodium of 151 mEq/l, and a rise in BUN to 44 mg%. The patient received steroids postoperatively. At autopsy, metastases to the ribs, liver, vertebral column, and calvaria were noted.

Case 2. This 35-year-old man, not known to be a diabetic, was admitted in coma with left hemiparesis. A diagnosis was made of intracerebral hemorrhage in the right basal ganglia. Serum glucose on admission was 150 mg%, Na 155 mEq/l, BUN 40 mg%, and serum osmolarity 324 mOsm/kg, with pH
greater than 7.5. By the second hospital day, the glucose had risen to 273 mg%. Further glucose determinations were not recorded, but at the time of death 2 days later, the patient had a serum osmolarity of 369 mOsm/kg, serum sodium of 163 mEq/l, and 3+/negative urines, with progression of his comatose state to total unresponsiveness. He had been treated with steroids, glycerol by nasogastric tube, and restricted fluids. Autopsy revealed bilateral staphylococcal pneumonia, and intracerebral hemorrhage confined to the right basal ganglia and parietal region. Evidence of significant cerebral edema or transtentorial herniation was not found.

Case 3. This 50-year-old woman was admitted with a left hemiparesis. She was a diabetic, well controlled on oral hypoglycemic agents. At the time of admission, the patient was both confused and dysarthric, with a mild left hemiparesis. Carotid arteriograms demonstrated a general mass effect without evidence of localization. Pertinent laboratory values on admission were glucose 110 mg%, Na 141 mEq/l, BUN 26 mg%, without glucosuria or ketonuria. On the fifth hospital day, the patient became increasingly somnolent, with Na 153 mEq/l, BUN 60 mg%, and 3+ glucosuria without ketonuria. A second arteriogram failed to reveal significant change. By the 11th hospital day, the patient was comatose with a glucose of 875 mg%, Na 138 mEq/l, BUN 141 mg%, osmolarity 375 mOsm/kg, and pH 7.5 with bicarbonate of 24 mEq/l. Autopsy revealed encephalomalacia of the cerebral hemispheres and brain stem, with basilar, and C-6 compression fractures.

Case 4. This 15-year-old youth without previous history of diabetes was admitted in coma with a closed head injury and basilar skull fracture. He was given mannitol, steroids, and hyperosmolar tube feedings. Laboratory values on admission were Na 139 mEq/l, glucose 130 mg%, BUN 43 mg%, and bicarbonate 15 mEq/l. During the next 5 days, the glucose progressively rose from 183 to 219, to 474 mg%; the BUN rose from 71 to 73 to 88 mg%, but the serum sodium remained normal. The physical findings, including coma with decerebrate response to noxious stimuli, remained unchanged. He died on the sixth hospital day with a glucose of 510 mg%, BUN 90 mg%, Na 165 mEq/l, negative acetonuria, osmolarity 390 mOsm/kg, and pH 7.5 with bicarbonate of 24 mEq/l. Autopsy revealed encephalomalacia of the cerebral hemispheres and brain stem, with basilar, and C-6 compression fractures.

Case 5. This 52-year-old man was admitted with a gunshot wound to the head, in coma with extensor responses to noxious stimuli. He was not known to be a diabetic. Laboratory values on admission were Na 139 mEq/l, glucose 116 mg%, osmolarity 308 mOsm/kg. He underwent craniotomy for debridement, and was treated with mannitol, steroids, Dilantin, antibiotics, and restricted fluid replacement. By the first day after admission, blood glucose was elevated to 405 mg%, with Na 163 mEq/l, and osmolarity 370 mOsm/kg. Follow-up studies on the same day revealed a glucose of 750 mg%, Na 156 mEq/l, BUN 19 mg%, bicarbonate 21 mEq/l, negative serum acetone, and osmolality 373 mOsm/kg. He died shortly thereafter on the second hospital day. Autopsy demonstrated destruction of the right temporoparietal cortex with intracerebral hematoma in the right anterior fossa. Cerebral edema or transtentorial herniation were not found.

Case 6. This 40-year-old diabetic woman was admitted with a sudden increase of lethargy after a 6-year history of progressively severe headaches and seizures. She had been receiving Dilantin intermittently during this period. Previous angiograms and pneumoencephalograms had been normal. Pertinent laboratory data on admission revealed a glucose of 630 mg%, Na 122 mEq/l, bicarbonate 32 mEq/l, glucose 4+ with negative acetonuria. Immediately after admission, the right pupil became fixed and dilated, and she became unresponsive to painful stimuli, followed by a respiratory arrest. She was given mannitol and steroids, with improvement. An emergen-
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cy right carotid arteriogram demonstrated an equivocal right to left shift of the internal cerebral vein. A diagnosis of nonketotic hyperglycemic hyperosmolar coma was considered on the basis of laboratory findings, and rehydration with insulin replacement was begun. She died, however, the next day after multiple respiratory arrests, without progression of neurological signs. She was noted to be hypokalemic (2.0 mEq/l), with a glucose of 1050 mg%, 4+ glucosuria without acetonuria, negative serum acetone, and osmolarity 333 mOsm/kg at the time of death. At autopsy, a 6 × 8-cm necrotic mass was found in the right parietal lobe, with evidence of transtentorial herniation. Histological examination revealed an astroblastoma.

Case 7. This 61-year-old known diabetic woman was admitted with a progressive 4-year history of dementia and a 1-month history of documented seizure activity. At the time of admission, she was confused, had a short attention span, truncal ataxia, and equivocal left-sided weakness. On the fourth hospital day, she did not receive her usual insulin dosage, and developed rapid obtundation with unequivocal left hemiparesis. A serum glucose determination 6 hours after insulin administration was 288 mg%, with negative serum acetone, 3+ glucosuria, and serum osmolality calculated at 320 mOsm/kg. The clinical impression was that she had osmotic diuresis coupled with dehydration leading to a cerebrovascular accident. Despite fluid replacement and insulin administration, she became progressively obtunded, and by the 10th hospital day had a blood glucose of 675 mg%, Na 143 mEq/l, elevation of BUN to 34 mg%, a pH of 7.5 with negative acetonuria and serum osmolarity of 344 mOsm/kg. The patient had received hyperosmolar tube feedings and a single dose of mannitol after the neurological deterioration on the fourth hospital day. Autopsy revealed ischemic infarction of the right cerebellar hemisphere and right cerebral peduncle, without evidence of transtentorial herniation or cerebral edema.

Group B

The six patients in this series had hyperosmolarity during the terminal phase of hospitalization, but because laboratory data were incomplete, they could not be included with certainty in the NHHC category. Significantly, all six had elevations in blood glucose values on admission (range 130 to 420 mg%), although none were known to be diabetic. The range of values of serum osmolarity in this group within 2 days before death was from 323 to 394 mOsm/kg, with a mean value of 351 mOsm/kg. Generally, absence of complete urinalyses and repeated blood glucose determinations precluded a definitive diagnosis of NHHC, although the hyperosmolar state was clinically suspected to be a contributing factor in the terminal phase of at least three of the six patients.

Discussion

Nonketotic hyperglycemic hyperosmolar coma (NHHC) probably occurs with greater frequency than is reported in the medical literature. The present retrospective study of seriously ill patients who died while in the Neurosurgical Intensive Care Unit during a 3-year period indicates a prevalence of verified NHHC approaching 10% (18% if Group B is included) as a complicating factor in the neurologically compromised patient. The reasons for this high frequency are clear. The cranial trauma or postcraniotomy patient often receives steroids and restricted fluids; mannitol may also be given if cerebral edema increases acutely. Dilantin is often used to prevent seizures. Tube feedings become necessary if the patient has inadequate oral intake. The stressed patient is therefore exposed to those very factors known to promote the development of NHHC. Similarly, nonspecific stress factors of a primary illness, initially unrelated to hyperglycemia, may also further the development of hyperosmolarity and dehydration. To this group of factors must now be added those associated with cranial trauma, intracerebral hemorrhage, and intracranial surgical intervention. Whether damage to specific areas in the central nervous system, such as the hypothalamus, may be important is not known at present.

Steroids have long been recognized for their diabetogenic potential. This effect is related to specific roles in: 1) increasing gluconeogenesis and hepatic glucose production; 2) increasing pancreatic beta cell function with subsequent exhaustion and degranulation of these cells; and 3) decreasing peripheral glucose utilization.

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Indeed, some investigators have noted a direct suppression of ketonemia after steroid administration, although other workers attribute the absence of ketonemia and ketonuria to a direct effect of increased blood glucose, associated with severe dehydration in some patients. Recent studies, however, produce convincing evidence that in NHHC, as opposed to ketoacidotic coma, there may be enough circulating insulin to inhibit lipolysis and mobilization of fatty acids, but not enough to suppress high levels of hyperglycemia.

The implication of hyperosmolar tube feedings in the pathogenesis of NHHC is primarily related to protein-induced hyponatremia secondary to extracellular water deficits of either an osmotic diuresis or diarrhea. A problem in the use of these feedings is the difficulty of determining the state of hydration in comatose patients. Six of the seven patients with unequivocal NHHC received tube feedings at some time during hospitalization.

Long-term, intermittent mannitol administration has also been responsible for several cases of NHHC. Renal function studies have confirmed that induced water diuresis during mannitol administration exceeds that of sodium loss, often adding to severe hyponatremia if treatment is prolonged. Severe intracellular dehydration attended by osmotic diuresis is then the rule.

In cases of prerenal azotemia, mannitol may be retained in the intravascular space. The osmotic gradient thus produced may account for normal or decreased serum sodium and chloride values occasionally found in some patients with NHHC. Four patients in Group A had normal or subnormal values of serum sodium; three of these had moderate to high elevations of BUN. These patients underscore the importance of "corrected" serum sodium values referable to elevations in blood glucose (or retained mannitol).

Dilantin has been implicated in the development of NHHC. Striking elevations of blood glucose after Dilantin administration have been observed in nondiabetic as well as in diabetic patients, particularly in those who are critically ill. A hypotensive effect of Dilantin has been observed on occasion, which leads to increased adrenergic response and secondary glucose mobilization. The drug has also been shown to decrease tissue uptake of glucose, and to increase glycogenolysis in the liver. Furthermore, the degree of hyperglycemia induced by Dilantin is greater in the severely ill patient than in those who were well before the onset of symptoms.

It is notable that none of the patients in Group A or B had seizures during hospitalization, a finding previously reported to be common in cases of NHHC. It has been suggested that various hyperosmolar states elicit epileptic activity in a cortex rendered susceptible by some pathological process such as hemorrhage. Our series is at variance with that concept.

Numerous investigators have questioned the significance of increased urea in the pathogenesis of NHHC. Poser noted that the osmotic contribution of urea is not significant because it moves freely between the intravascular and subarachnoid space, and recommends quantitating effective osmolality by the formula: 2(Na) + 18/glucose, rather than the usual formula: 2(Na) + 18/glucose + BUN/2.8. Excluding urea from osmolarity calculations in Group A, six of seven patients were still above the range of serum osmolarity (330 mOsm/kg) in which neurological manifestations become prominent, as defined by Plum and Posner. The seventh patient (Case 3) otherwise satisfied all criteria for the diagnosis of NHHC, and was the only patient in the series in which that diagnosis was made clinically.

The cause of coma in NHHC has been discussed at length in the medical literature. Intrinsic to its understanding is the fact that elevated blood sugars are often not paralleled by high brain and CSF glucose levels, leading to osmotic shifts of free water from the brain to the intravascular space. Prockop demonstrated the accumulations of metabolic products of glucose such as sorbitol, fructose, and inositol in the CNS, and subsequent interference with normal cerebral metabolism. Finally, the effects of pre-existing CNS lesions on cerebral metabolism, particularly those related to hypoxia, are known to arrest certain stages of intraneuronal enzyme activity and might further result in adverse effects of hyperosmolarity.

Many observers have noted a poor correlation between the progression of neurological signs and increased osmolarity, although osmolarities below 260 mOsm/kg, and above

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330 mOsm/kg, are likely to produce neurological symptoms. All patients in Group A had serum osmolarities greater than 330 mOsm/kg. Once coma developed, whether related to the primary illness or secondary to the development of NHHC, improvement was not noted in any of our patients. In Group A, five of seven patients had no morphological cause of death related to the CNS. Cerebral edema with herniation was noted in only one of the seven cases at autopsy.

Cases 2, 3, 5, and 7 demonstrated ischemic infarction, hemorrhagic necrosis, or intracerebral hemorrhage of various degrees, but all lesions in any one patient were confined to one hemisphere or the ipsilateral basal ganglia, and none had significant cerebral edema, transtentorial herniation, or brain-stem damage. Cases 3 and 7 are representative of a frequent complication in NHHC noted by others — the increased incidence of cerebrovascular accidents (CVA) and thromboembolic phenomena. The progression of a CVA coinciding with a rapid alteration in serum glucose was substantiated clinically in Case 3, and at autopsy multiple systemic emboli were found as well as recent hemorrhages in all areas of previous ischemic infarction. In Case 7, rapid deterioration of a left hemiparesis to hemiplegia followed the sudden onset of hyperglycemia secondary to relative insulin deficit. Necropsy 7 days later revealed recent ischemic infarction of the right side of the cerebellum and cerebral peduncle without significant cerebral edema or transtentorial herniation. Experimentally, Finberg, et al., have observed increased prevalence of hemorrhage in 23 of 27 animals made acutely hyperosmolar by intravenous administration of sodium.

The treatment of NHHC remains controversial, and no reliable methods for dealing with the problem in the neurologically compromised patient with pre-existing cerebral edema are available. Previous investigators recognized the need for rapid fluid and insulin replacement, but opinions varied concerning the content of the fluids given. Arieff and Carroll, in a series of 37 cases, advocated the use of 0.45% normal saline (NS) initially, followed thereafter by dextrose 5% in water, 0.45% NS, or 0.9% NS as determined by plasma osmolarity and electrolytes. The most useful end points for fluid and insulin replacement were found to be 1) serum glucose less than 250 mg%; 2) urine output less than 50 cc/hr; and 3) serum osmolarity less than 320 mOsm/kg. The mean value for total fluid given was 11.9 liters over 36 hours with one half the total given over the first 12 hours. The mean total units of insulin required was 350 units. Eight patients were evaluated with serial lumbar punctures for increased intracranial pressure during treatment, and no increase in CSF pressures were found in any of the eight. Significantly, of the seven patients in the series of 37 who died during correction, none showed findings of cerebral edema at autopsy.

McCurdy, in a review of the literature encompassing 84 cases, recommended the division of replacement into three stages: 1) rapid repair of sodium deficits; 2) rapid but incomplete repair of water deficits; and 3) a third phase of equilibrium establishment. The first is accomplished with 0.9% NS, if hypovolemic, until blood pressure and urine output are stable. Only when calculated osmolarities have confirmed total body water deficits, and the initial sodium deficit has been corrected, are hypotonic fluids indicated. The higher the plasma osmolarity, the more hypotonic the saline solution used. Once the plasma osmolarity reaches 325 mOsm/kg, less aggressive fluid therapy is indicated, as insulin replacements by this time have probably reduced glucosuria to the point that normal renal mechanisms can correct remaining imbalances. Few patients demonstrated insulin resistance, most requiring less than 400 units during the first 24 hours. McCurdy recommended not exceeding insulin dosages of 25 units/hour until sodium deficits have been replaced. Finally, if sodium is normal or increased in the presence of hyperglycemia, more hypotonic fluids were indicated in the early phase.

Gerich, et al., in a comparison of 20 patients with NHHC and 10 patients with severe ketoacidosis, recommended the use of 0.45% NS followed by isotonic saline as serum osmolarity and sodium fell. An average of 8.2 liters was required in the acute phase, restoring electrolyte balance and glucose levels below 300 mg% within an average period of 8 hours. A tendency toward insulin sensitivity was likewise noted in this series. The average patient with NHHC required 133 units of insulin, contrasting with
an average of 359 units in patients with ketoacidosis. If initial glucose values fell by 30% within 2 hours, insulin sensitivity was suggested, and often no more insulin was required.7

Although an established method for dealing with neurosurgical patients with NHHC has not yet been established, several points from the preceding review bear emphasis:

1. There is a paucity of patients with underlying intracranial disease in these series. Of a combined number of 141 patients studied, only eight cases with intracranial neurological disease were included. Six of these died during correction. This serves to underscore the fragility of the patient with an altered CNS blood-brain barrier and impending or established cerebral edema. For this reason, the use of normal saline is probably unwarranted, and the serial monitoring of CSF pressures appears essential. Furthermore, isotonic saline may impede the needed fall in serum osmolarity (10 mEq/l serum sodium is equivalent in osmotic activity to 360 mg%/glucose).11

2. Troublesome, and even fatal, induced hypotension may be encountered due to sudden glucose reductions secondary to rapid insulin administration. Before sodium deficits are repaired, hyperglycemia is responsible for an obligatory percentage of plasma volume still available.

3. The need for calculating serum osmolarity prior to the onset of therapy is emphasized, as cerebral symptoms may be initially related to water intoxication or cerebral edema, even in the face of severe hyperglycemia.

4. In several of our patients treated in the past, a relative insulin resistance has been encountered, which is contrary to the experience of others. It is not presently known whether this represents an idiosyncrasy in patients with significant intracranial disease who develop NHHC. For those who have demonstrated such resistance, however, the prognosis has been uniformly poor.

5. All investigators emphasize the need for early potassium replacement. Not only is the patient with NHHC generally alkalotic and tissue potassium depleted, but the intracellular movement of glucose and hemodilution during early fluid replacement may induce precipitous falls in plasma potassium levels.

6. Finally, it is emphasized that the degree of initial hyperosmolarity and hyperglycemia is not a reliable prognostic factor, as the rapid shift of serum osmolarity and glucose is more often the fatal common denominator.

References
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