Edwards

MEDICAL GRAND ROUNDS

PARKLAND MEMORIAL HOSPITAL

MAY 18, 1972

HYPERGLYCEMIC, HYPEROSMOLAR, NONKETOTIC COMA

HISTORY OF HNKC

1880 - It had been recognized by this time and earlier that some patients with diabetic coma, which was then attributed to acetone intoxication, could occur without ketonuria and Kussmaul respiration.

1883 - Frerichs (Z. Klin. Med. 6:1, 1883) describes the first case of HNKC in the world literature.

1886 - Dreschfeld (Brit. Med. J. 2:358, 1886) describes the second case--first in English literature.

1914 - Revillet - first case in French literature--attributes HNKC to renal inability to excrete ketones.

1915 - Rosenbloom, J. (N.Y. Med J 102:294) - First case in American literature.

1917 - HNKC is mentioned in Joslin's text.

1923 - A report to the British Medical Research Council on the first use of insulin in the treatment of the diabetic coma refers to three of the cases as being "not very serious diabetics - the blood sugar was very high, air hunger and dyspnea were not conspicuous features, little acetone in the breath and not much aceto-acetic acid in the urine." (Brit. Med. J. 1:737, 1923).

1925 - E. Warburg (Acta. Med. Scand. 61:301) - 4 cases of HNKC described. Since all 4 had renal disease, the Reville hypothesis, i.e. that ketonemia was really present but that a renal defect prevented ketonuria, was advocated. As a result no new syndrome was described, and HNKC as a clinical entity distinct from DKA disappeared from clinical awareness. This same year the first cure of HNKC was reported by Begg using subcutaneous water.

1957 - de Graef and Lips (Acts. Med. Scand. 157, 1957) and Sament and Schwartz (S. African Med. J. 31:893, 1957) rediscover HNKC. The latter are most often credited with discovering the syndrome. Actually, Evans and Butterfield had reported the syndrome in 1951 in a burn patient in the Annals of Surgery, and was widely ignored by internists throughout the world.

TABLE I

CHARACTERISTICTS OF HNKC VS DKA VS DKA

	HNKC	DKA
Age		
Mean	60	< 25
Range	<1 - >90	<1 - >90
Serum osm (mOsm/l)		
Mean	384	357±6 in 26 fatal cases
	290-594	323±1 in 287 non-fatal (Biegleman)
Serum Na (mEq/l)	144	132±2 spuriously low
	119-188	
Glucose (mg%)		
Mean	1120	400
Always	>600	250-1200
Usually	>900	
Highest	3000	
Se Ketones always <2+ at 1:1		always present (>4+ at 1:1)
Plasma FFA (μEq/l)		
Mean	727	2256
ISE	± 91	±250
Plasma Insulin (μU/ml)		
Mean	8	7
± SEM	± 2	± 2
	0 - 50	0 - 20
Plasma Glucagon (pg/ml) (not studied; probably always -100)		
Mean		540 (always ↑)
Plasma HGH (ng/ml)	0 - 12	2 - 215
Fluid deficit (%TBW)	15-20%	10%
Mean	7.3L	4L
Range	4.5 - 22	2-8 L
BUN	always increased	normal early, increased late
Insulin required to lower BS to <250		
Mean	350 U	>300 U
Range	30-500 U	300-3000 U

IMPORTANT QUESTIONS:

To understand HNKC and its relationship to DKA the following questions must be answered:

1. Why no ketoacidosis?

2. Why the extreme hyperglycemia?

3. Why coma?

QUESTION #1: Why no ketoacidosis?

The regulation of ketoacidosis in diabetes has been extensively reviewed (Krebs, 1961, ibid 1961a, ibid 1966; Bressler, 1966; Wieland, 1968; Williamson and Hems, 1970; McGarry and Foster, 1972). According to McGarry and Foster (Figure 1) ketoacidosis in diabetes is the result of

1. Increased FFA (a) released from fat cells because of insulin lack.

2. Increased hepatic FFA uptake and acyl CoA formation (b) because of hyperlipacidemia.

3. Increased FFA oxidation to acetyl CoA (e) despite increased esterification of acyl CoA to triglycerides(c).

4. The increased acetyl CoA pool generates more ketone bodies (f) because FFA resynthesis from acetyl CoA is insufficient.

5. Underutilization (g) of ketones may exaggerate the effects of increased ketone formation.

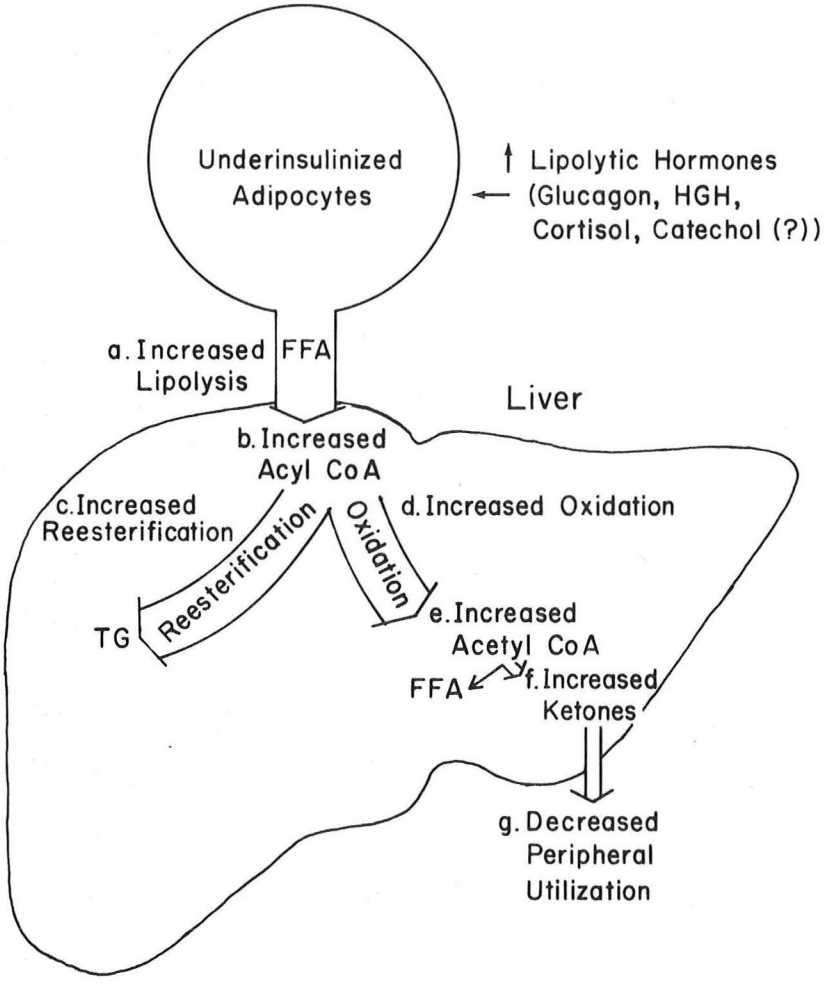

Figure 1: Mechanisms of diabetic ketoacidosis (after McGarry and Foster 1972).

HNKC could, therefore, result from a block at any point in Figure 1; there is, however, no real evidence of any block at either (b), (d), (e), or (f), or of enhanced peripheral ketone utilization. The difference appears to be at (a); in HNKC plasma FFA release is much less elevated than in DKA (Arieff and Carroll; Henry and Bressler, Gerich et al) averaging only 727 mEq/1, 30% of the average level in DKA (Table I). Everyone but Seftel (1967), who postulated a block at acetyl CoA $\longrightarrow$ ketones, agrees that the reason for the lack of ketoacidosis is the absence of marked hyperlipolysis. However, Vinik et al found 6 of 7 HNKC patients with 1437-4104 μEq/l FFA levels; they suspect either $\downarrow$ turnover or highly effective FFA metabolism into nonketogenic pathways - triglycerides and CO_2.

BEST ANSWER: Not as much hyperlipolysis

Possible reasons for insufficient hyperlipolysis in HNKC:

1. Sufficient insulin in HNKC to inhibit lipolysis via its direct antipolytic action but not enough for its glucose penetration action, which requires 10 times as much insulin so one sees hyperglycemia without hyperlipolysis.

NOTE: There is usually sufficient insulin to inhibit lipolysis directly in HNKC. (Zierler and Rabinowitz). But in many DKA patients insulin levels are just as high and yet ketoacidosis supervenes.

2. Sufficient glucose penetration to inhibit lipolysis. High glucose levels plus insulin levels in the basal range could theoretically cause just enough glucose penetration (Penetration index = [insulin] x [glucose] into fat cells to generate just enough α- glycerophosphate to esterify FFA and inhibit lipolysis in this way, while hepatic glucose production remains above the glucose outflow rate.

In other words:

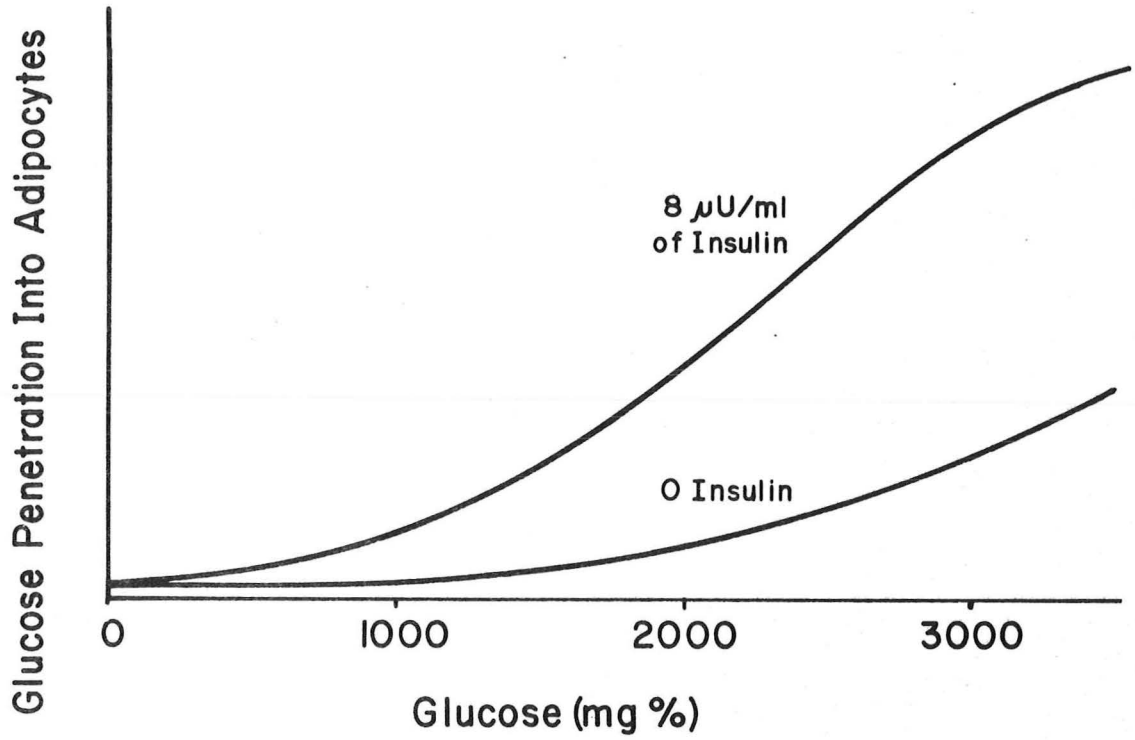

Figure 2, a theoretical experiment which has not yet been done, suggests that the insulin concentration alone is not the crucial antilipolytic factor--but that hyperglycemia with insulin is. In fact, Vinik et al observed HNKC in a man with 0 insulin. Brockman et al (1970) report a 29 year-old juvenile diabetic who, while in jail without insulin but with unlimited access to soft drinks, developed HNKC and was hospitalized; but in the hospital CHO intake was restricted and he developed DKA despite insulin.

3) Insufficient Lipolytic Hormones: Possibly the absolute hyperglucagonemia uniformly present in DKA is not present in HNKC (never measured). Hypersomatotropinemia, often seen in DKA, was absent (0-5 ng/ml) in the 7 patients of Vinik et al. However, HGH is not uniformly elevated in DKA. Measurements of catechols and other lipolytic hormones never reported.

4) Increased Antiketogenic Hormones: Cortisol and stressful illness can induce HNKC. Cortisol usually increased (25-77 μg%) in HNKC (Vinik et al, 1970) (Garces et al, 1968; Von der Nahmer et al, 1971) 29-75 μg%. But it is also increased in DKA.

CONCLUSION: High glucose (Explanation #2) seems the most reasonable explanation.

QUESTION #2: Why the extreme hyperglycemia? (If the above conclusion is correct, this now becomes the key question.

Obviously, extreme hyperglycemia requires that glucose inflow into ECF exceed glucose outflow from ECF. Glucose inflow and outflow from the ECF are depicted in Figure 3, and the factors which may alter them are listed.

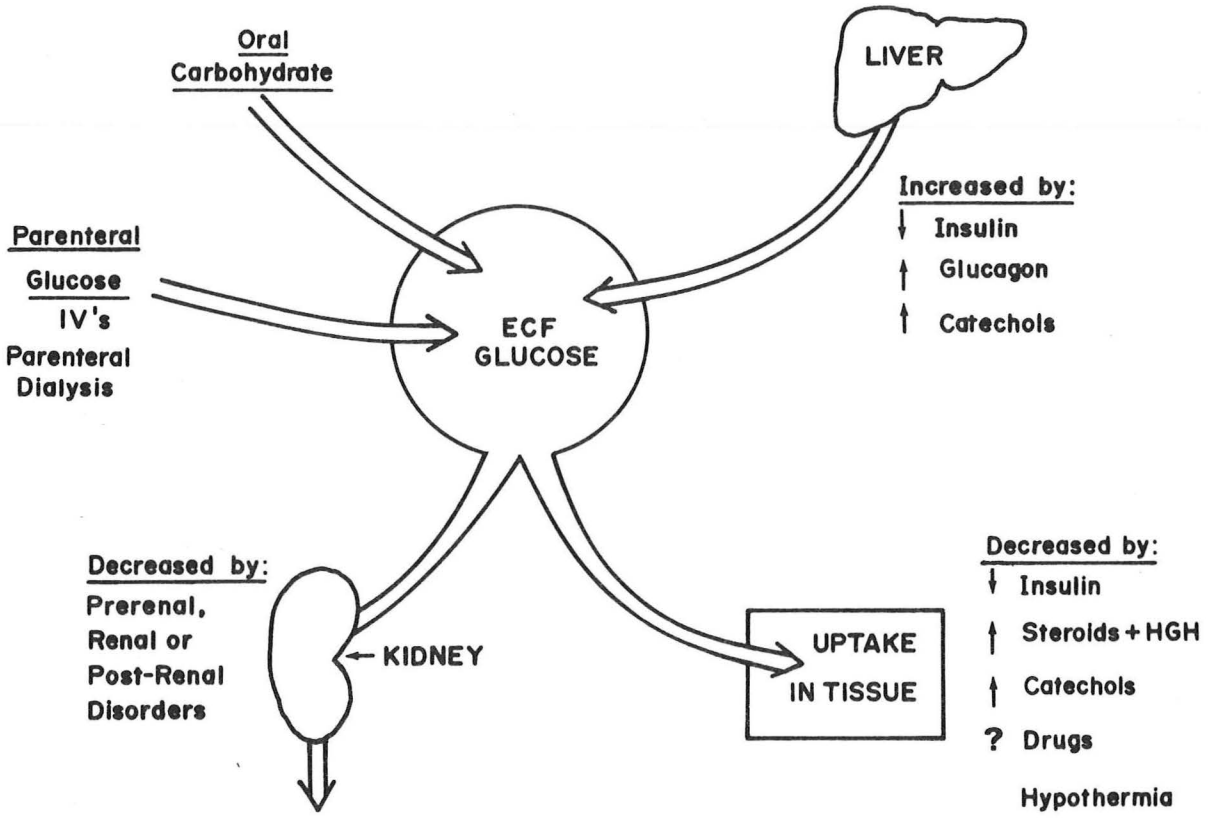

Figure 3 - Factors which determine ECF glucose concentration.

Analysis of the >200 case reports permits an estimate of the relative contribution of these factors. The following facts are apparent:

1. The sine qua non of the syndrome is an "outflow defect"-- apparent in practically every reported case.

2. The outflow defect is virtually always a "double outflow defect," involving both outflow pathways.

a. Outflow to tissues may be reduced to a variable degree by (1) relative insulin lack, i.e. inability of insulin secretion to increase appropriately with insulin need and thus prevent hyperglycemia through enhanced glucose uptake in insulin-dependent tissues (a normal person can dispose of >1 kg of glucose/24 hours) [insulin secretory defect may be caused by genetic diabetes, pancreatitis, pancreatic carcinoma, hypercatecholemia]; or, (2), by inability of tissues to respond to insulin and increase glucose uptake [this target tissue insensitivity could be due to HGH plus cortisol, tissue damage (e.g. hypothermia heat stroke)]. (Cf. cases of Monteleone and Keefe--heat stroke HNKC cured by rehydration without insulin.)

b. Glucose excretion is reduced; theoretically, if ECF volume remained undiminished the kidneys could eliminate 1.5 kg of glucose a day about as much as the maximal estimates of endogenous glucose production by the liver in the most severe total diabetic. It is probably next to impossible to develop "endogenous" HNKC if glucose excretion is unimpaired. (Of course, HNKC can occur on an exogenous basis with good renal function [Libertine et al, 1970].)

THEORETICAL SUPPORT FOR THE ESSENTIAL ROLE OF ↓GLUCOSE EXCRETION IN HNKC:

1. Insulin lack usually is not total (in most cases of HNKC in which insulin has been measured, it has been found in about the normal fasting concentration); it would appear that inability to increase its secretion in response to the rising glucose level is the main beta cell defect. Only once has 0 insulin been observed in HNKC (Vinik et al, 1970).

2. Since insulin lack is not total it follows that endogenous glucose production in HNKC is probably submaximal, less than in DKA and that glucose outflow block is not complete; some glucose outflow to insulin-dependent tissues (fat and muscle) probably occurs.

3. Therefore, theoretically, hyperglycemia should not be greater than in DKA on an endogenous basis unless glucose excretion is impaired.

FACTUAL SUPPORT FOR ↓ GLUCOSE EXCRETION IN HNKC

1. Even juvenile diabetics will develop HNKC, rather than DKA, if impaired glucose excretion is present at the time they begin to deteriorate. It may well be next to impossible to develop DKA despite total insulin lack unless

glucose excretion is seriously impaired at the time insulin lack commences, i.e. total pancreatectomy in a nephrectomized animal: extreme hyperglycemia would occur first and ketoacidosis would be inhibited (this experiment has never been done).

Case #1 of Spenney et al (1969), however, is similar to the above experiment. A 29 year-old white man, not a known diabetic, admitted because of rejection of a renal homograft, became hyperglycemic while on azothiaprine and steroids, and his blood glucose rose to 1400 mg%.

The case of Lotz (1968) and case #2 of Brockman (1970) in juvenile diabetics reveal that patients with repeated DKA episodes for 20 years can develop HNKC after Kimmelstiel-Wilson nephropathy appears.

The five cases of Rubin et al (1969) ranged in age from 6 weeks to 7 years; all had BUN elevation. The 13 year-old boy of Laugier et al (1969) had been polyuric when they began a sight-seeing tour in Tours, France, but his parents wouldn't let him drink water; he went rapidly into HNKC only from water restriction on a hot day. Had they permitted him to drink water it is assumed he would have developed DKA instead.

The key difference between DKA and HNKC: In DKA glucose outflow equals inflow for a length of time sufficient to develop ketoacidosis; HNKC glucose outflow must be less than inflow for a length of time sufficient to develop extreme hyperglycemia.

2. Only 3 of the >200 reported cases of HNKC had a normal BUN at the time of admission (Kolodny and Sherman [1968]; Gerich et al [1971]) and those three may have had an exogenous glucose source. According to Kreisberg (1968) no one with a BS >800 mg% has normal renal function.

CONCLUSIONS:

1. The extreme hyperglycemia is responsible for the lack of ketoacidosis.

2. Extreme hyperglycemia of HNKC cannot occur endogenously unless the ability to excrete glucose is seriously impaired.

3. Impaired glucose excretion prevents DKA and is the key to endogenous HNKC.

QUESTION #3 How does extreme hyperglycemia cause coma?

1. Not certain. Theory of Ohman et al (1971): Probably all diabetic coma, HNKC and DKA is a consequence of intracellular dehydration of certain brain cells by ECF hyperosmolarity, which characterizes DKA (Table I) as well as HNKC. Sotos et al (1966) report that any cause of hypertonicity, from NaCl, sucrose or glucose, lowers O_2 consumption and Krebs cycle activity in rat brain slices, and markedly raises brain sodium concentration. Shrinkage of the brain may tear dural blood vessels and cause dural and intracerebral bleeding (McCurdy, 1970), but in humans this is seen only in hypernatremic coma (shrunken cells, venous thromboses and hemorrhages [Dillon] et al, 1936, Am. J. Med. Sci. 192:360 Aireff and Kleeman (1972) find no loss of brain water. In uncomplicated diabetic coma infants, at least, show edema, capillary dilatation, and nerve cell degeneration (Finberg, Pediatrics 23:40, [1959]). Holliday et al (1968) claim that there are in the brain cells osmotically active particles normally inactivated by reversible binding to osmotically inactive large molecules; these are released during ECF hyperosmolarity enabling the brain to minimize shrinkage. But the formation of these idiogenic osmoles to protect against lethal loss of brain cell volume via breakdown of large organic molecules may interfere with cell function (McCurdy, 1970). Also, Sotos finds evidence of a breakdown of blood-brain barrier in hyperosmolality due to hypernatremia with ↑ intracellular NaCl.

In Favor of the Ohman Concept

1. Non-hyperglycemic hyperosmolar states are associated with a similar neurological picture.

2. CSF acetoacetate and pH are not sufficiently altered to account for DKA coma. CSF pH is normal or elevated in DKA (Ohman et al).

3. The argument that CNS cells are not insulin-requiring and that glucose is freely permeable, and, that an osmotic gradient across CNS cells could not result from hyperglycemia as it does from hypernatremia, can be countered as follows:

> Glucose transport into CNS cells through a non-insulin-requiring process may well involve a finite number of glucoreceptor sites; when these are saturated, as during hyperglycemia, glucose transport into CNS cells is insufficient to prevent an osmotic gradient. Geiger et al (1954) found that brain glucose in cats does not rise as rapidly as blood glucose. Ohman et al (1971) confirm this in man and believe that DKA, as must certainly be the case in HNKC, is due to cell dehydration.

4. CSF osmolality in DKA is sometimes greater than plasma (Ohman et al).

NEUROLOGY OF HNKC

A. Symptoms and Signs (Maccario et al, 1963)

1. Depression of consciousness always present. Ranges from mild drowsiness and confusion to stupor and profound coma--usually not deep.

2. Polypnea present in more than 50%--distinct from Kussmaul breathing.

3. Seizures (this is the big neurological difference between DKA and HNKC.)

a. May be focal or generalized--usually focal.

b. Usually associated with a loss of consciousness but some patients were aware of "shaking" and one described visual aura.

c. Seizures are resistant to dilantin (which can, by itself, precipitate HNKC).

d. EEG: Spike or paroxysmal delta bursts or seizure pattern.

e. Do not recur despite lack of anticonvulsive treatment once HNKC corrected.

f. Transitory focal post-ictal signs (aphasia, homonymous hemianopsia, hemiparesis, reflex asymmetry, hemihypalgesia) all clear within 10 days of correction of HNKC.

g. Hypothermia and hyperthermia.

4. In autopsied cases, no structural abnormalities noted. In adults shrunken brain is not described--in children it may have been noted. Nor have the hemorrhages which can be induced in animals with experimental HNKC, been reported in adults; in children generalized hemorrhages, edema are reported (Manigand, 1969).

CLINICAL EVOLUTION OF THE SYNDROME

The clinical events are as follows: A patient with either pre-existing or acute de novo impairment in insulin secretion (genetic diabetes, acute pancreatitis, hypercatecholemia, diazoxide, thiazides, dilantin) and/or target

tissue insulin unresponsive (high steroids, HGH, catechols or inability of tissues to metabolize glucose, as in hypothermia, heat stroke) develops either acutely or gradually, an inability to clear ECF glucose as fast as it enters the ECF.

Inability to clear glucose fast enough may be due to:

1. Prerenal factors:

a. Dehydration, a chronically negative water balance due either to increased external loss of fluids (glycosuric osmotic diuresis most common cause*, diuretic agents, renal concentrating defect pyelonephritis, "aging kidney" (Berenyi and Straus, 1969) , reduced cortical thirst center response to rising osmolality (cerebral disease), limited access to water, reduced ADH response.

b. Acute hypovolemia -- acute pancreatitis common, vomiting, diarrhea, surgical shock.

2. Renal Diseases: Only 6 of 24 patients studied by Arieff and Carroll (1972) had normal creatinine clearance after recovery from HNKC-- underlying renal disease common. Autopsy data supports this. Kimmelstiel-Wilson,arteriolar nephrosclerosis, chr. pyelo., chronic glomerulo, etc. Any renal disease can do it: acute tubular necrosis or ↓ GFR of shock, burns, and surgery, even rare situations like renal shutdown during a hypercalcemic crisis due to bone metastases (Kumar, 1968) and hyperuricemia due to rx of a lymphoma.

3. "Excessive" intake of carbohydrate: Normals can tolerate 1 kg of glucose daily without hyperglycemia (Kreisberg, 1968). Impaired outflow of glucose may make a far lower intake "excessive". For example, during

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*Osmotic diuresis interferes with H_2O reabsorption and thus increases urine flow rate, preventing maximal urine concentration even in presence of ADH; and increased urine flow rate prevents normal sodium reabsorption even if conservation is required. Even though urine (Na^+) is only in 10-50 mEq/l in HNKC, prolonged osmotic diuresis will lead to Na depletion unless intake is maintained, and ultimately hypovolemic, hypertonic dehydration. K^+ depletion also common -- unless K intake is maintained.

hypothermia 65-75 g of glucose iv may raise blood glucose to over 1000 mg% (Johnson et al, 1969).

a. ↑Oral Intake: HNKC attributed to high oral intake of solid CHO reported by Rosenberg et al (1965) and Halmos (1966). More commonly polydipsia causes increased intake of soft drinks; McConnell et al (1969) reports cases of patients in Belfast drinking CCDI, cokes (The more I drink the thirstier I became.") Markle and Sloan (1968) report a 33 year-old previously non-diabetic female who drank large quantities of soft drinks during 5 months of polydipsia and polyuria and developed coma with negative serum acetone and a blood glucose of 1470 mg%. Her serum P was 0.4 mg% which may be caused by osmotic diuresis (Pitts: Physiology of the Kidney) and could lead to 2, 3 DPG deficiency which, in turn with ECF ↓ could predispose to anoxia and lactic acidosis (the case of Markle had a pH of 7.26 without serum acetone.)

b. ↑Parenteral Intake: iv glucose, hyperalimentation, peritoneal dialysis. If long-standing dehydration is present in HNKC, both ECF and ICF contraction will have developed in parallel and serum sodium will be elevated unless unusually high sodium losses have occurred. But, if hyperglycemia develops acutely due, for example, to a rapid influx of glucose and/or to sudden reduction in glucose excretion or if ECF loss is isotonic as in pancreatitis or burns, ICF may contract disproportionately, thus protecting ECF volume, and serum Na^+ may be normal or low (cf. Case Report).

NOTE: Acute hyperosmolality due to IV glucose can, in elderly or cardiac patients, precipitate acute pulmonary edema (cf. Case Report) resulting from a rapid expansion of ECF at the expense of ICF--and this form of heart failure responds dramatically to insulin.

MORTALITY AND ASSOCIATED DISEASES

The high mortality of HNKC, 30-75%, is in large part due to the associated illness which may precipitate it or just coexist. In contrast to to the minor, benign illnesses which, at least in juvenile-type patients can precipitate DKA, HNKC is, in general, precipitated by potentially lethal diseases. In Arieff and Carroll's series (1972), gram-negative pneumonia, gram-positive sepsis, G-I hemorrhage, severe renal disease, CVA and MI were the most common associated illnesses in fatal cases of HNKC. Pancreatitis, surgery, burns are common. Hyperosmolality, itself, is a rare cause of death--death occurs despite its correction.

In children, HNKC is very often encountered in Down's disease--perhaps because of an inadequate response to thirst (?). Cerebral edema very rare in autopsied HNKC cases.

COMPLICATIONS

I. Thromboembolic Disese - Very common--MI, CVA, large vessel thrombosis and gangrene may complicate or precipitate HNKC.

II. Intravascular Thrombosis - Scharf et al (1971): A case of intravascular clotting with ↓ in platelets to 70,000, ↑ in PT to 30 sec., ↓ in fibrinogen, ↑ in fibrinogen split products on second day after HNKC in a mild untreated diabetic. On 6th day she suddenly died despite "cure" of HNKC--fresh infarctions of lungs with occlusion of main pulmonary arteries with clots were found at post; renal vein also thrombosed. Does DIC pose a problem in HNKC? Kwaan et al, 1972, report DIC in DKA shock. An increase in ADP-induced platelet aggregation (diabetic plasma and normal platelets) related to small vessel disease (nephropathy, retinopathy). Since endothelial damage appears to underly DIC, KW disease with capillary microangiopathy, ↑ viscosity may all coexist in HNKC as in DKA. And the high glucagon-low insulin state may increase platelet aggregation through cyclic AMP effect on platelets and can cause pulmonary capillary thrombosis. Halmos et al (1966) suggest prophylactic heparin. Gangrene common, even in babies (Belmonte et al, 1970). Infarction of liver reported.

III. Hypovolemic Shock* → acute tubular necrosis

Hypovolemic Shock* → tissue anoxia → lactic acidosis

IV. 2, 3 DPG deficiency (probably very rare but should be looked for when osmotic diuresis has been prolonged or if hyperalimentation is the cause of HNKC.

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*Shock may also be a hazard of insulin rx. Sudden hypovolemia may occur as water shifts back into cells. Case #1 of Halmos et al (1966) went into shock when treated and Case #6 developed acute tubular necrosis as a result. Probably common.

V. Acute Pulmonary Edema (very rare) - Ordinarily iatrogenic the result of a sudden hyperglycemic hyperosmolal state resulting from a rapid glucose overload in a patient in whom, because of insulin lack, glucose is osmotically active--e. g. when hypertonic glucose is mistakenly given to a semi-comatose with early HNKC or DKA. A rapid shift of ICF into ECF may cause acute pulmonary edema in patients with marginal cardiac function. (Cf. Case Report).

VI. Intravascular Hemolysis - Case #1 of Johnson et al (1969) developed dark brown urine soon after admission - SGOT, LDH, SHD, evidence of hemolysis, or since CPK rose too, muscle damage (EKG normal). Possible myoglobinuria and muscle damage vs hemolysis (very rare).

VII. Neurologic Residua

Quadriplegia reported twice (but one case was attributed to Guillain-Barré syndrome. The other exhibited amyotrophy involving lower extremities [Moulies et al, 1970] and adipsia for several weeks: loss of thirst required regular forced water ingestion to prevent hypernatremia.) Earlier, intense polydipsia had preceded the HNKC. Adipsia coincided with the quadriplegia.

Nystagmos (Portier et al, 1968).

IATROGENIC HNKC

HNKC may be an in-hospital occurrence in patients not previously known to be diabetic. Whether the HNKC represents a "pseudo-diabetes" or the "surfacing" of latent diabetes is unknown. The following circumstances are generally present when this syndrome is produced iatrogenically.

1. Increased parenteral glucose: hyperalimentation, peritoneal dialysis, hypertonic glucose for misdiagnosed hyperglycemia, or just the standard 5% glucose infusion. Case : 36 year-old healthy black man sustained 45% 3rd degree burn from a gasoline explosion. By 5th hospital day he was taking 4000 calories/d, mostly CHO. On 21st day he became lathargic and later unresponsive. Blood glucose was 1660, Na 160, BUN 68, and serum osmolality 459, 16,200 ml of fluid and 130 U of CZI. Mild CHO tolerance persisted after discharge. No FH of diabetes.

2. Severe stress, either endogenous (burns [Rosenberg et al, 1965], trauma, infection) or surgical stress, or exogenous"--cortisol rx , exp. in patients with diffuse skin disease (Ashworth et al, 1968)--or hypothermia or heat stroke.

3. Renal dysfunction and/or dehydration either spontaneous or from diuretics. (Portier et al, 1968, precipitated HNKC in a previously normoglycemic cirrhotic with renal disease and ascites by giving steroids, furosemide, benzothiadiazene and spironolactone--with rapid delivery of edema, the patient developed HNKC which cleared when anasarca was restored.)

4. Drugs - other than steroids and diuretics.

a. Dilantin (Goldberg and Sanber, 1969). Inhibits insulin release.

b. Thiazides - Impair carbohydrate tolerance and insulin release.

c. Chlorpromazine - Impairs carbohydrate tolerance (Gerich et al, 1970).

d. Immunosuppressive drugs (Spenny and Kreisberg, 1969) - Unknown effect.

e. Nalidixin

TREATMENT

1. Insulin: High doses unnecessary and may be dangerous. <400 U in first 24 hours. Beware of insulin-induced hypotension and oliguria. Of 9 patients given <100 U initially, 8 died (Arieff and Carroll, 1972), 5 because of hypovolemic shock during a rapid blood sugar fall. The higher the blood glucose, the greater the danger of rapid correction. Only 1 of 11 died in a group treated with 4-39 U per hour (McCurdy). Don't exceed 25 U per hour, and give less if hypovolemic shock is present on admission. Also this will avoid cerebral edema due to polyols or idiogenic osmoles; Arieff and Kleeman (1972) report that correction of extreme hyperglycemia by dialysis does not cause brain edema, but correction with insulin did--suggesting a specific insulin effect on idiogenic osmoles through Na^+ and K^+ transport. If CSF pressure rises, start osmotherapy immediately.

2. Fluids: Big controversy is here--hypotonic vs isotonic fluids. Average deficit 7-10 liters or 25% TBW. Arieff and Carroll (1972) calculate 70 mEq of monovalent cation with anion for each liter of water loss. Half of the estimated deficit should be replaced in first 8 hours (Kreisberg, 1968). Most agree that hypotonic fluids should be used unless shock or hyponatremia is present, since hypernatremic hyperosmolality may occur

after isotonic fluids plus insulin lower blood glucose and ECF water reenters cells. This is thought to be the big danger of isotonic fluids; a high mortality from physiologic saline according to Reville et al (1969). Flanigan et al (1970) calculate an average total Na deficit of 236 mEq in conjunction with a 7 l water loss; all of the Na deficit would be replaced by 3 l of half-normal saline, but only 40% of the water would be replaced.

But McCurdy (1970) disagrees strongly. She advocates, first, rapid repair of sodium deficit, which may be hard to estimate clinically in the absence of overt shock because of the protective effect of marked hyperglycemia. Because hypovolemia is, in her view, the most immediate threat to life, she advocates ECF support with normal saline; for example, if you give 1 liter of 0.03 normal saline to a patient with a Posm of 400, 700 ml will go into cells and the ECF will gain only 300 ml, all of which could be nullified by insulin-induced shift of ECF water into cells. Only after correction of Na deficits (diagnosed clinically) does she advocate repair of H_2O deficit with 0.25 - 0.5 normal saline with 10-30 mEq/l potassium. She gives at least 5 l of fluid in first 12 hours. She lowers Posm only to 325 to avoid water intoxication. Eg. a dehydrated man now weighing 60 kg with a Posm of 395 and TBW of 30 l needs 6.5 l of pure water to correct Posm to 325--a safe approximation. Finish up with oral fluids.

3. Potassium: Use it early unless hyperkalemia or acidosis is present. (10 mEq/hr) but with insulin. If hypokalemia is present in HNKC, severe deficit is present.

THERAPEUTIC APPROACH

I. Objectives:

a. Correct or prevent hypovolemic shock without causing fluid overload or hypernatremia.

b. Reduce hyperosmolality.

c. Prevent hypokalemia.

II. Fluid Therapy (This applies only when dehydration is present)

a. If hypovolemia is present, begin with isotonic saline, begin 1 liter in the first hour--until serum Na determination is available. If Na is elevated, then switch to hypotonic saline at a rate of 3 l the first two hours and at least 5 liters during the first 12 hours. If possible left ventricular failure is a worry, put in a Schwan-Ganz tube and pour in fluid until pressure reaches 12-15. If Na is low, continue isotonic saline, recalling that each 400 mg% reduction in blood glucose will mean a shift of about 2 liters of fluid, which should be replaced.

b. Give 10-15 mEq of K per hour on first day, unless hyperkalemia, acidosis or obvious renal insufficiency is present. Begin after the first insulin dose has begun to take effect. Monitor closely.

III. Insulin therapy

Give only 20-25 U per hour-- HNKC is usually sensitive to insulin and too rapid cataglycemia can (theoretically) cause cerebral edema and may induce shock as a consequence of too rapid a shift of ECF into cells. Occasionally insulin resistance is present and insufficient insulin may kill the patient as a result of prolonged cerebral hyperosmolality (rare).

NOTE: Don't overtreat hyperosmolity (325 mOsm/l is close enough), hyperglycemia (350 mg% is fine) and, when patient is conscious, try the oral route. If patient doesn't regain consciousness after several hours at this level, consider cerebral edema (rare) and other causes of unconsciousness (common).

CASE REPORT

A 68 year-old white male with a left hemiporesis was transferred from a nursing home to the Dallas VA Hospital at 4 a.m. because of fever, abdominal pain, disorientation and hypotension. On admission, the temperature was 104.4°, pulse 104 and irregular, B.P. 65/50. Abdomen was tender. Because of an estimated 10% dehydration 5% glucose infusion was begun. Three hours later, the admission laboratory data were received by the intern: Glucose 900 mg%, Na 131, BUN 111, CO_2 23, K 3.5. By now after about 75 g of glucose and 1500 ml of water, the patient was deeply comatose and dysnpeic and cyanotic. The lungs were full of rales and there was venous distension. A repeat glucose was 1600 mg%, Na 116, amylase 450. One hour later it was 1950 mg%, BUN 131, K 2.7, and CO_2 17. A central venous line was inserted and insulin was administered together with large volumes of fluid. As glucose fell, the venous pressure fell to normal despite 7,000 ml of fluid over the next 19 hours. He regained consciousness soon thereafter and was out of bed within a week.

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