MEDICAL GRAND ROUNDS

Parkland Memorial Hospital
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CEREBRAL EDEMA COMPLICATING THE TREATMENT OF DIABETIC KETOACIDOSIS

(FitzGerald, O'Sullivan and Malins - Brit. Med. J. 1961)

"In the 35 episodes of ketoacidosis in age group 10-19 years three patients died, a mortality rate of 8.6%. All three cases were quite unexceptional in respect of the severity of the ketosis. The mode of death was so similar and so unlike the other fatal cases in the series that they merit more detailed description.

..."Of the 19 deaths in the series the three in adolesence followed a pattern not hitherto described...

..."Three deaths occurred in adolesence owing to progressive cerebral damage at a time the ketosis was improving. In one there was massive destruction of the hypothalamus and mid-brain which gave rise to diabetes insipidus..."

Case I - [redacted]

This 15 year old [redacted] adolescent with known diabetes of one years duration entered the E.R. in diabetic ketoacidosis with a history of increasing polyuria of 2 weeks duration plus nausea, vomiting and lethargy of one days duration. On admission he was lethargic, dehydrated, and showed Küssmaul respirations at 28-30/min. His urine was 4+/large and initial chemistries revealed a CO_2 of 4 mEq/L, pH of 7.10; pCO_2 12, glucose 590, K. 4.5, Na 123 with a grossly lipemic serum.

During the initial 12 hours of therapy he received 1000 u of regular insulin, 3000 ml of 1/2 normal saline and 1000 ml of D_5W. No bicarbonate was administered. Within 3 hours blood glucose declined from 590 to 300 mg% and blood glucose was subsequently maintained between 300-375 mg% by IV glucose. By 10 hours his CO_2 increased 12 mEq/L and by 14 hours to 21 mEq/L. On admission his B.P. was 120/80. After 7 hours of therapy it was recorded at 160/100. By 12 hours he complained of severe headache and was noted to be more somnolent. Neurological examination including eyegrounds was negative. By 16 hours his B.P. rose to 170/110 and a spinal tap revealed an opening pressure of 440 mm H_2O. The spinal fluid was otherwise negative. Treatment for cerebral edema was started with 12 mg of Decadron and 25 gms of Mannitol. Within the next 12 hours he had complete resolution of all signs and symptoms of cerebral edema. B.P. stabilized at 120/70. Spinal tap before discharge was normal.

Case II - [redacted]

This 16 year old [redacted] adolescent was in good health until 1 month prior to admission when he developed increasing polyuria, polydypsia and polyphagia with a 20 pound weight loss. During the week prior to admission he vomited frequently and became progressively weaker. On admission he appeared volume depleted, had KUssmaul respirations but was not stuporous. Neurological examination was negative. Urine was 4+/large. Blood sugar was 400, Na 134, K 4.0, CO_2 5, pCO_2 13, pH 7.18, BUN 25, Cr. 1.6. No mention was made of lipemia.

During the first 8 hours he received 400 u of regular insulin, 1 liter of 1/2 N saline, 500 cc R/L and 3 L of D_5W containing a total of 132 mEq of $NaHCO_3$ and 60 mEq/K. CO_2 rose progressively and in 2 hours was 13 mEq/L and in 5 hours 15 mEq/L. Serum Na fell progressively and at 8 hours was 125 despite an unchanged glucose (402 mg%).

Four hours after start of treatment he complained of severe headache. The neurological examination was negative. By 10 hours he was unconscious and could not be aroused. The respirations were Cheyne-Stokes, discs were clear. L.P. was cautiously performed and pressure allowed to rise to 300 mm H_2O then stopped. The spinal fluid was negative. He was given Decadron and IV Mannitol. Later he became apneic. Neurosurgeons drilled a hole in the right occipitoparietal region and inserted an 18 gauge needle which revealed CSF at a high pressure. The patient died shortly thereafter.

Autopsy revealed widening of the gyri with obliteration of the sulci. No uncal or cerebellar tonsillar herniation was present. Sections of the cerebral cortex, hypothalamus, cerebellum and brain stem showed cerebral edema.

Case III - [redacted]

This 37 year old [redacted] man, a known heroin addict, was brought to the hospital in a comatose state, with Küssmaul respirations and an odor of ketones on his breath. On a previous admission blood sugars were 174 and 186 mg%. A diagnosis of diabetic ketoacidosis was made. He was treated with insulin, IV fluids and recovered.

Time	pH	pCO_2	$BHCO_3$	Gluc.	$BHCO_3$ Admin.
0	6.87	17	>3.0	650	
1	7.11	23	6.8	588	
2	7.04	19	5.3	510	440 mEq
3	7.11	16.5	5.4	390	
4	7.35	16	9.0	390	
6	7.41	15	9.2	372	
8	7.45	15	10.0	336	
12	7.58	19	17.5	314	
18	7.57	23	21	360	

TABLE I

OUTLINE

CEREBRAL EDEMA COMPLICATING THE TREATMENT OF DIABETIC KETOACIDOSIS

I Clinical Picture, Occurrence, Pathology (ref 1 - 9)

II Pathophysiology of Cerebral Edema in Diabetic Ketoacidosis

A) The Importance of Hyperglycemia: The Role of the Polyol Pathway (ref 10-21): The Role of a Rapid Drop in Blood Glucose (ref 7, 8, 14)

B) The Role of Ketoacidosis: Cerebral Hemodynamics and Metabolism in Diabetic Ketoacidosi

1. Normal Control of CBF (ref 22, 23)
2. Cerebral Blood Flow and Metabolism in Ketoacidosis (ref 24)
3. Cerebral Anoxia and Cerebral Metabolism & Electrolytes (ref 25)
4. The Luxury Perfusion Syndrome - its Probably Occurrence in Diabetic Ketoacidosis with Coma (ref 26, 27, 24)

C) The Role of Red Blood Cell 2,3-Diphosphoglycerate (2,3-DPG) in the Regulation of Oxygen Release from Hemoglobin.

1. Normal Control (ref 29-35)
2. Effects of Acidosis on 2,3-DPG and its Consequences (ref 28, 36)

III The Rational Use of $NaHCO_3$ in the Treatment of Ketoacidosis

A) Dangers of Acidosis per se

1. Slight ↓ in bicarb. when buffer capacity is low can cause great change in pH.
2. Pulmonary edema during fluid replacement (ref 37)
3. Susceptibility to vascular collapse (ref 38-40)

B) Propensity for the Development of Alkalosis with $NaHCO_3$ Administration (ref 41-43)

C) Dangers of Alkalosis

1. Worsening of Hypokalemia (ref 44, 45)
2. Production of Cerebrospinal Fluid Acidosis (ref 46)
3. Shift in Oxygen Dissociation Curve and Decrease in P_{50}. Worsening of Cerebral Hypoxia (ref 47)

IV The Treatment of Cerebral Edema

A) Hypertonic Mannitol (ref 48, 49)

B) Steroids (ref 49, 50)

C) The Use of Passive Hyperventilation (ref 51, 52)

D) 100% O_2 administration as soon as diagnosis suspected

TABLE II

SUMMARY OF PATHOPHYSIOLOGICAL DEFECTS IN DIABETIC KETOACIDOSIS

I Dehydration - Hypertonicity with high, low or normal serum sodium

II ECF volume deficit - with ECF volume partially sustained by hyperglycemia

III POtassium deficiency with high, normal or low serum K

IV Ketoacidosis with potential bicarbonate

TABLE III

Ref.	Age/Sex	State of Mentation on Admission	Onset of Symptoms or Signs of Cerebral Edema	Changes in Blood Glucose and Electrolytes			Outcome
				B.S.	Na	CO_2	
#1	13/F	Drowsy but not unconscious	10 hrs - sudden coma	A)530	-	-	Died in few minute
				6 hr)260	-	-	
	15/M	Consciousness not impaired	6 hrs - sudden coma-periodic breathing	A)540	-	-	Died
				6 hr)288	130	12.1	
	16/M	Drowsy but rational	8 hrs - sudden coma, Babinskis lg unequal pupils	A)546		9.5	Diabetes Insipidus
				8 hr)200	150	22	Died
#4	14/?	Drowsy but responsive	Progressive loss of consciousness	A)640	134	9	Death
				4 hr)360		13	
			3 hrs - deep coma	11 hr)148	142		
			12 hrs - deep coma				
			15 hrs - papilledema				
			CSF = 600 mm H_2O				
	9/F	Semicomatose	6 hr - deep coma	A)580	-	11	Died
			pupils sluggish	3 hr)420	-	7.2	
			Papilledema	8 hr)120	-	7.0	
#6	23/F	Lethargic	8 hr - Alert but headache	A)>500	132	4.5	Diabetes Insipidus
			9 hr - Increasing lethargy	8 hr)262	126	12.5	Death
			Headache - then sudden apnea, pul edema, coma, fixed pupils				
PMH	15/M	Lethargic	7 hrs B.P. 160/100	A)590	123(L)	4.0	Recovered
			12 hrs - severe headache	3 hr)300			
			† Somnolence	>4 hr)300			
			16 hrs - B.P. 170/110	370			
			CSF = 440 mm H_2O	10)300-370	125	12.0	
	16/M	Lethargic	4 hrs - severe headache	A)400	134	5.0	Died
			10 hrs - unconscious	2 hr)		13.0	
			Cheyne Stokes	5 hr)		15.0	
			CSF = 300 mm H_2O	8 hr)400	125		

TABLE IV

SIGNS AND SYMPTOMS SUGGESTIVE OF IMPENDING CEREBRAL EDEMA DURING Rx OF KETOACIDOSIS

1. Expected return of consciousness fails to occur within a reasonable number of hours after institution of therapy whilst biochemical improvement continues.
2. When light stupor or lethargy advances to coma at a time when biochemical improvement is occurring i.e. an unexplained worsening of mentation.
3. Onset of severe headache during therapy.
4. Progressive elevation of blood pressure to hypertensive levels.
5. Development of hypotension and tachycardia at a time when fluid replacement should have prevented collapse.
6. Fever of unknown cause appearing after several hours of treatment.

TABLE V

POSSIBLE PROGNOSTIC TESTS FOR EARLY DETECTION OF THE DEVELOPMENT OF CEREBRAL EDEMA

1. Frequent observations of the fundi for early papilledema. Absence does not rule out cerebral edema.
2. Increasing intraocular tension to abnormal levels (Tonometer).
3. Electroencephalographic tracing for early detection of high voltage Delta waves or diffuse theta waves.

TABLE VI

PREVENTION OF CEREBRAL EDEMA DURING DIABETIC KETOACIDOSIS

1. Prevent a too rapid fall in blood glucose and thereby an osmotic dysequilibrium.

2. Prevent too much free water administration and the danger of a rapid change from hypertonicity to hypotonicity.

3. Administer $NaHCO_3$ cautiously and only when indications are present. Always monitor pH and do not increase pH above 7.25.

4. Administer O_2 - heated mist off wall outlet (40% O_2 → pO_2 250 and increase O_2 content by 3/4 vol%). If there is any evidence of impending cerebral edema use mask with reservoir bag or IPPB.

5. ? Return to use of balanced phosphate solutions to increase resynthesis of red blood cell 2,3-DPG.

TABLE VII

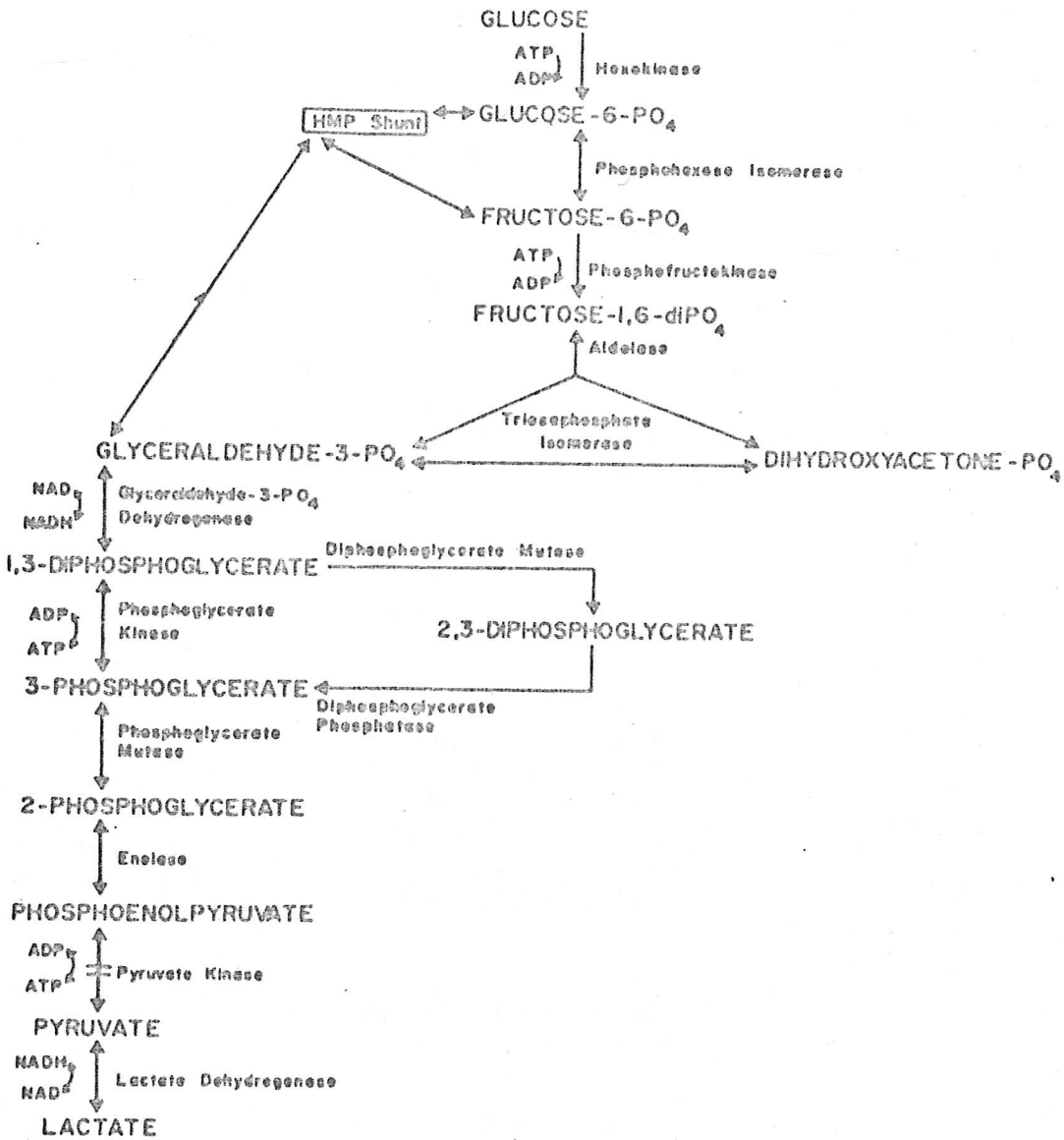
THE TREATMENT OF CEREBRAL EDEMA

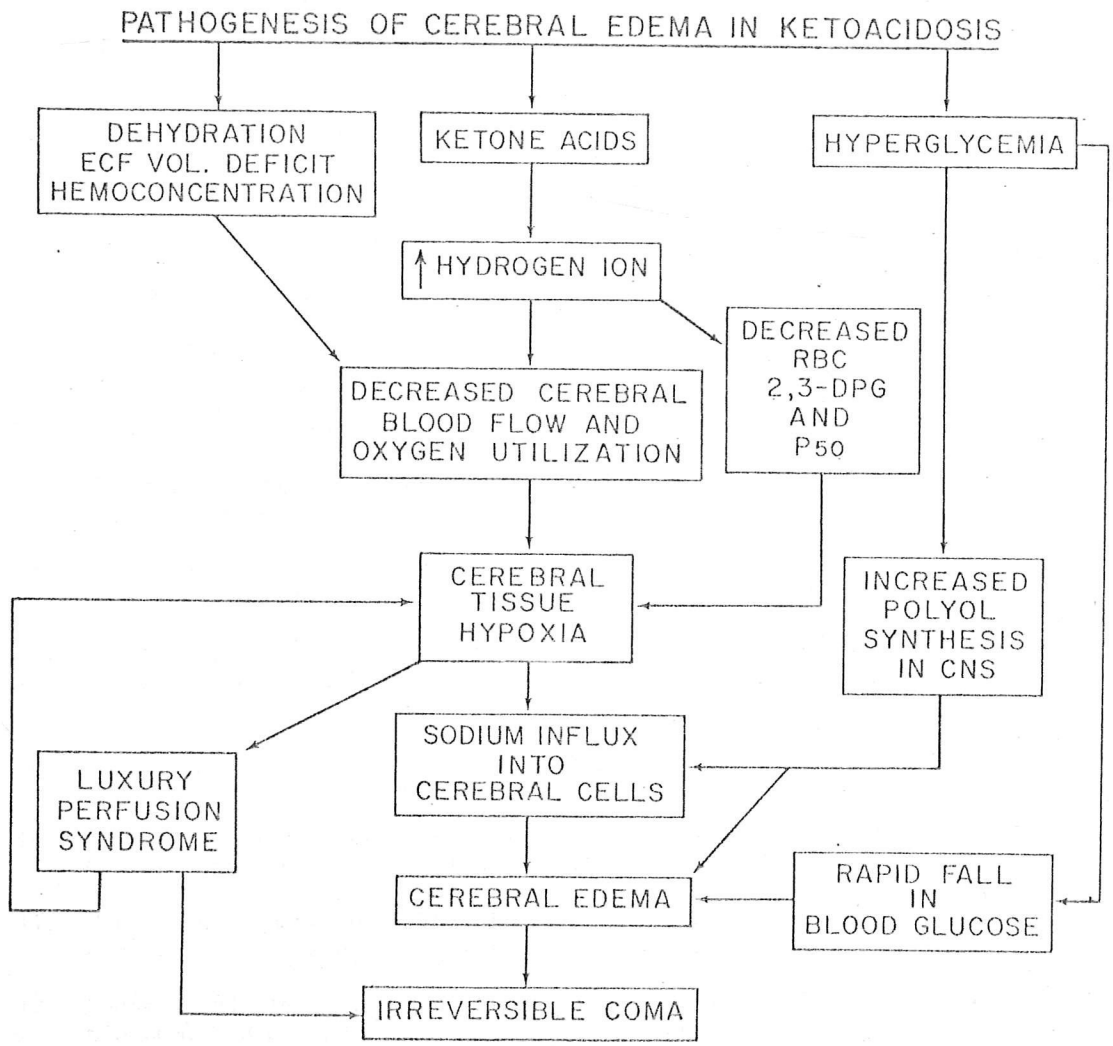
1. 100% O_2 administration - Raise O_2 dissolved in plasma and increase PO_2 and CDO_2.

2. Hypertonic mannitol 20% solution. 1.5 to 2.0 gms/Kg body weight.

3. Glucocorticoids 10 mg Dexamethasone I.V. repeat 4 mg q 6 hours.

4. ? Passive hyperventilation to reduce pCO_2 and increase pO_2.


GLUCOSE
ATP
ADP
Hexokinase
HMP Shunt
GLUCOSE-6-PO4
Phosphohexose Isomerase
FRUCTOSE-6-PO4
ATP
ADP
Phosphofructokinase
FRUCTOSE-1,6-diPO4
Aldolase
Triosephosphate Isomerase
GLYCERALDEHYDE-3-PO4
DIHYDROXYACETONE-PO4
NAD
NADH
Glyceraldehyde-3-PO4 Dehydrogenase
1,3-DIPHOSPHOGLYCERATE
Diphosphoglycerate Mutase
ADP
ATP
Phosphoglycerate Kinase
2,3-DIPHOSPHOGLYCERATE
3-PHOSPHOGLYCERATE
Diphosphoglycerate Phosphatase
Phosphoglycerate Mutase
2-PHOSPHOGLYCERATE
Enolase
PHOSPHOENOLPYRUVATE
ADP
ATP
Pyruvate Kinase
PYRUVATE
NADH
NAD
Lactate Dehydrogenase
LACTATE


PATHOGENESIS OF CEREBRAL EDEMA IN KETOACIDOSIS
DEHYDRATION
ECF VOL. DEFICIT
HEMOCONCENTRATION
KETONE ACIDS
HYPERGLYCEMIA
↑ HYDROGEN ION
DECREASED
RBC
2,3-DPG
AND
P50
DECREASED CEREBRAL
BLOOD FLOW AND
OXYGEN UTILIZATION
CEREBRAL
TISSUE
HYPOXIA
INCREASED
POLYOL
SYNTHESIS
IN CNS
SODIUM INFLUX
INTO
CEREBRAL CELLS
LUXURY
PERFUSION
SYNDROME
CEREBRAL EDEMA
RAPID FALL
IN
BLOOD GLUCOSE
IRREVERSIBLE COMA

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