Thirty-two Fatal Cases of Severe Diabetic Ketoacidosis, Including a Case of Mucormycosis

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SUMMARY

There were thirty-two fatalities in 340 episodes of severe diabetic ketoacidosis occurring in 257 subjects during a three year period. Five patients expired within three hours of admission, before adequate therapy could be started. Causes of death were multiple and complex in certain patients—primary causes were classified as myocardial infarction in seven, pulmonary edema due to coronary arteriosclerosis in one, pneumonia or pneumonitis in eight, cerebrovascular accident in three, acute renal failure in two, gram-negative septicemia in two, acute pancreatitis in two, uncomplicated severe diabetic ketoacidosis in four, carcinoma of pancreas with metastases in one, hyperthyroidism (thyroid "storm") in one, and mucormycosis in one. This patient expired despite correction of the ketoacidosis and a course of amphotericin B therapy. Insulin resistance, pyelonephritis, gangrene of the leg, diabetic intracapillary glomerulosclerosis, and hepatic cirrhosis also contributed to fatalities in this series of cases. DIABETES 22:847-50, November, 1973.

Thirty-two fatal episodes of severe diabetic ketoacidosis (diabetic "coma") which occurred during three years, are analyzed in this communication. Any person admitted to the Los Angeles County-U.S.C. Medical Center with severe diabetic ketoacidosis who subsequently died is included, regardless of the time between admission and demise. Three hundred and forty sequential episodes in 257 patients, including the thirty-two deaths, that occurred during this period, were recently summarized.[1] Only four of the thirty-two fatalities were attributed to uncomplicated severe diabetic ketoacidosis; the remainder expired of "complications." Although numerous factors contribute to "coma" mortality, the so-called "complications," particularly cardiovascular disease and infections, have assumed increasing importance in recent decades. Rabinowitch et al.[2] noted an eightfold increase in mortality that was attributable to complications and also a direct relationship between the total mortality rate and the percentage of cases with complications.

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RESULTS

As indicated previously,[1] fatalities in men (19) outnumbered those in women (13). Degree of acidosis, as determined by serum HCO_3^- and blood pH, serum amylase level, and serum K^+, did not appear to be related to mortality. Serum ketone concentration—positive tests varying from 1:2 to 1:64 serum dilution—was not related to the fatality rate. The white blood cell count ranged from 3,700 to 24,000. Four of five cases with a WBC count below 9,000 had fatal infections. Five fatal cases entered with severe hypotension, with a diastolic blood pressure of 0. Maximum known duration of diabetes in this series of fatal cases was fifty years. Eight fatal episodes occurred in subjects who had no previous knowledge of their diabetes, the "coma" episode being the occasion of diagnosis. Three of four fatal cases with a definite history of alcoholism were in this category. Twenty-one of the fatal cases had a history of insulin therapy, the daily dose ranging from 13 to 300 U. Two subjects had been treated with oral sulfonylureas. One subject had known diabetes but had received no previous therapy.

The previously described association between mortality and higher admission serum glucose, urea nitrogen, and osmolality levels[1] does not appear simply to reflect the older age range in fatal episodes. Admission serum glucose values in nonfatal episodes of ketoacidosis were significantly lower in younger people (those below thirty years) than in older (those above fifty years), but the older fatal cases had significantly higher admission serum glucose levels than surviving older subjects (table 1).

As indicated in the previous communication[1] the time between admission and death varied from one and a half hours to thirty-one days. Five deaths occurred within three hours of admission—three due to acute myocardial infarction, one because of a cerebrovascular accident and arteriosclerotic heart disease, and one to uncomplicated ketoacidosis. Nine subjects expired four to thirty-one

TABLE 1

Admission serum glucose values compared in young and old (age > 50 years): comparison of fatal and nonfatal episodes

	No. of Episodes	Serum Glucose (mg./100 ml.) Mean ± S.E.M.*	P_1†	P_2‡
Nonfatal				
Age < 30	70	552 ± 33		
Age > 50	49	709 ± 39	<.01	
Fatal				
Age > 50	20	1,014 ± 88		<.01

* Standard error of mean.

† Probability of significance of difference between means of nonfatal episodes in ages below 30 compared to those above 50. "P" values from Fisher's Tables.

‡ Probability of significance of difference between means of nonfatal and fatal episodes in over-fifty age group. "P" values from Fisher's Tables.

days after successful therapy of their ketoacidotic episodes of causes probably unrelated to severe ketoacidosis, including lactic acidosis, myocardial infarction, gram-negative septicemia, hypoglycemia, pancreatic carcinoma with metastases, central nervous system destruction due to hemorrhage and mucormycosis, pneumonitis, pneumonia, and pancreatitis. The remaining subjects expired within three hours to three days after therapy was commenced.

As indicated in table 2, a major cause of mortality was acute myocardial infarction, which caused death in seven subjects (cases 1-7). In three cases, as mentioned previously, the onset of death was so rapid (within three hours) as to preclude sufficient time for institution of therapy.

The second major cause of death was infection, chiefly pneumonia (cases 9-16). Pneumonia was also a contributing factor in the demise of three other patients (cases 1, 19 and 26). There were two deaths due primarily to septicemia, one following surgery (case 17), and the second occurring in a subject with metastatic pancreatic carcinoma (case 18). A third case (case 1) also had septicemia, associated with pneumonia, although acute myocardial infarction was considered the prime cause of death. The case of mucormycosis (case 19) was characterized by an inexorable progression to death despite early correction of the ketoacidosis and active antifungal therapy with amphotericin B.

The deaths of two subjects with pancreatic carcinoma (cases 18 and 28) were attributed, in part, to metastases. There were three with cerebrovascular accidents (cases 20-22), and three subjects with presumed pancreatitis (cases 24-26). There was a fatal case of thyrotoxicosis with thyroid "storm" (case 27). Root reported that thyrotoxicosis is a hazardous complication of severe diabetic ketoacidosis.[3] There were four cases (cases 29-32) of uncomplicated coma.

CASE REPORT

R.S. PF no. 247-58-49 (case 19 in table 2)——*Mucormycosis*

Clinical summary: R.S., a forty-seven year old Negro female, was admitted because of fever, malaise, vomiting and irrationality extending three to five days. There was a ten year history of alcoholism, the last bout occurring one week before admission. There was no personal or family history of diabetes mellitus.

Physical examination: The patient was completely comatose upon admission—her blood pressure was 70/0 mm. Hg, respirations 30 per minute, pulse 120 per minute, and temperature 96.4° F. The left pupil was fixed, dilated, and unresponsive to light.

Admission laboratory findings: Hemoglobin was 13.4 gm. per cent, WBC count was 22,000 with a shift to the left, and urinalysis revealed 4 plus sugar and high acetone levels. Serum glucose was 1,290 mg. per 100 ml., urea nitrogen 91 mg. per 100 cc., HCO_3^- 6, K^+ 4.2, Na^+ 139 mEq. per liter, amylase 106 U., and acetone was positive at 1:4 dilution. The chest film showed multiple small calcified old granulomas. Skull series was negative. Lumbar puncture revealed slightly bloody fluid that cleared with successive samples.

Course: Within four hours of admission the blood pressure rose to 140/70 mm. Hg and serum glucose and urea nitrogen declined to 750 mg. per 100 ml., and 15 mg. per 100 ml. respectively; serum amylase was 106 U., HCO_3^- 15, K^+ 3.0 and Na^+ 141 mEq. per liter. At this time 300 U. of insulin and 3 L. of fluid were administered intravenously. The temperature rose to 103° F. ten hours after admission, at which time Keflin therapy (6 gm. per 24 hr.) was begun. She became responsive the following day but her condition slowly deteriorated as a large ecchymotic area appeared around the left eye. Pain and stiffness of the neck developed, the patient remained irrational and highly irritable, and a fever of 101 to 102° F. persisted despite vigorous intravenous antibiotic therapy. A repeat lumbar puncture disclosed cloudy spinal fluid with 1,100 cells per cubic millimeter and clumps of fungus-like material. The diabetes was easily controlled. Mucormycosis was suspected five days after admission, as her downhill course continued, and there was dark brown exudate of the nasal septum and turbinates, destruction of internal nasal architecture, and a large ulcer of the left palate. A wet mount of the lesion showed short segments of hyphae. Amphotericin B therapy (10 gm. intravenously in eight hours, and 0.25 mg. intrathecally) was begun, but she did not improve. Nine days after admission, the patient became comatose, the right pupil was nonreactive to light, and pallor of the right ocular fundus was noted. The patient died twelve days after admission.

Principal pathologic findings: Death was due to mucormycosis and bronchopneumonia. Mucormycosis involved the brain, tentorial vessels, and ethmoid and frontal sinuses. There was infarction of the right frontal lobe due to thrombosis and suppuration which involved the right anterior cerebral artery. Focal tubular nephrosis of the kidney was also present.

TABLE 2

Causes of death and major findings in thirty-two fatal cases of severe diabetic ketoacidosis

Case	Subject PF no.	Age	Sex	Primary Cause of Death	Other Major Pathologic Findings	Comments
1	C.W. 270-34-51	26	M	Acute myocardial infarction	Septicemia, bronchopneumonia, arteriosclerosis, pulmonary edema, intracapillary glomerulosclerosis (K-W lesion)	
2	P.M. 284-69-06	61	F	Acute myocardial infarction	Old myocardial infarction	
3	G.C. 229-82-86	32	M	Acute myocardial infarction	Acute coronary thrombosis, K-W lesion	
4	L.F. 258-83-79	30	F	Acute myocardial infarction	Pulmonary embolism, infarction, edema	Diabetes previously unknown
5	E.W. 254-22-43	84	F	Acute myocardial infarction	Arteriosclerotic heart disease, severe cerebral arteriosclerosis	
6	P.F. 233-23-48	35	M	Acute myocardial infarction	Severe coronary and cerebral arteriosclerosis	
7	W.P. 278-48-93	40	M	Acute myocardial infarction*		
8	B.B. 262-48-93	31	F	Pulmonary edema	Severe coronary arteriosclerosis	5-6 mo. intrauterine pregnancy
9	M.D. 271-97-87	52	M	Bronchopneumonia with suppuration	Chronic atrophic pancreatitis, fatty liver with fibrosis	Chronic alcoholism
10	F.M. 267-85-40	52	M	Chronic pneumonitis		Cardiac arrest at time of admission
11	V.C. 261-46-57	69	M	Bilateral bronchopneumonia	Renal arteriosclerosis	Diabetes previously unknown
12	G.S. 253-06-00	51	F	Bilateral bronchopneumonia	Hepatic fibrosis with fatty infiltration	Chronic alcoholism, diabetes previously unknown
13	F.B. 202-82-80	60	M	Bilateral bronchopneumonia	Generalized arteriosclerosis, K-W lesion	Psychotic, cardiac arrest at time of admission
14	W.O. 250-25-34	60	M	Pneumonia*		
15	I.P. 255-82-71	48	M	Bilateral bronchopneumonia*		
16	M.B. 078-44-97	73	M	Hypostatic pneumonia*		Endotoxic shock
17	L.B. 259-75-56	70	M	Post-operative septicemia	Gangrene of right leg, nodular K-W lesion	
18	J.M. 243-43-06	61	F	Gram-negative septicemia	Carcinoma of pancreas with metastases, arteriosclerosis, renal tubular necrosis, possible pyelonephritis	Surgery for pancreatic carcinoma 2 wk. earlier
19	R.S. 247-58-49	47	F	Mucormycosis involving brain, tentorial vessels, ethmoidal and frontal sinuses	Bronchopneumonia	Diabetes previously unknown
20	E.L. 099-10-63	57	F	Cerebrovascular accident*	Cerebral arteriosclerosis, acute pyelonephritis and pancreatitis	Serum amylase values of 400 and 2,840
21	P.C. 277-75-56	33	F	Cerebral hematoma		Diabetes previously unknown
22	M.N. 209-04-18	60	F	Cerebrovascular accident*	ASHD, old myocardial infarction	
23	L.B. 256-96-44	75	F	Acute renal failure*	Acute and chronic pyelonephritis	
24	H.G. 175-03-53	56	M	Acute renal failure*	Acute pancreatitis, possible cirrhosis of liver	Chronic alcoholism; amylase 1,206; diabetes previously unknown
25	J.S. 270-95-63	51	M	Acute pancreatitis*	Pulmonary congestion, subepicardial ischemia, pneumonitis	Amylase 590; WBC 3,700; chronic alcoholism; diabetes previously unknown

*No pathologic examination performed.

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TABLE 2 *(Continued from page 849)*
Causes of death and major findings in thirty-two fatal cases of severe diabetic ketoacidosis

Case	Subject PF no.	Age	Sex	Primary Cause of Death	Other Major Pathologic Findings	Comments
26	J.D. 258-72-53	50	M	Acute hemorrhagic pancreatitis*	Bilateral pneumonia	Diabetes previously unknown, insulin resistant (required 10,700 U. insulin), possible renal failure
27	G.A. 263-44-85	42	F	Thyroid "storm" due to hyperthyroidism*		
28	P.C. 223-36-76	53	M	Adenocarcinoma of pancreas with metastases		Surgery for pancreatic carcinoma
29	S.D. 208-04-35	36	M	Severe diabetic ketoacidosis*	Possible myocardial infarction	
30	W.R. 186-92-61	82	M	Severe diabetic ketoacidosis	Myocardial fibrosis, possible old myocardial infarction, pulmonary congestion, early bronchopneumonia	
31	F.M. 257-47-98	71	M	Severe diabetic ketoacidosis*		
32	G.H. 246-62-06	41	M	Severe diabetic ketoacidosis*	Pneumonia	

*No pathologic examination performed.

DISCUSSION

The association of complications with fatality in severe diabetic ketoacidosis has been recognized for many years. The importance of these complications, particularly cardiovascular disease and infection, has been emphasized repeatedly. Barnett et al. reported that four of six deaths in fifty-one cases of severe diabetic ketoacidosis (in subjects over sixty years of age) were caused by acute myocardial infarction.[4] In our series, also, particular attention is directed to the extremely grave prognosis of myocardial infarction associated with severe diabetic ketoacidosis—seven fatalities in eleven subjects.

Collen[5] and Dillon and Dyer[6] emphasized the important role of infections as a cause of diabetic ketoacidosis mortality in the pre-antibiotic era. The relationship between infection and fatality in severe diabetic ketoacidosis continues to be important, as indicated in this report. Pneumonia and pneumonitis remain the most common causes of death, but urinary tract infections, particularly when complicated by septicemia, are also important. The single case of mucormycosis in this series was fatal. Other reports also emphasize the relationship of mucormycosis to diabetic ketoacidosis and its ominous prognosis.[7-9] The absence of response to amphotericin B is not surprising. In a review of the subject,[9] Abramson et al. noted seven of fourteen deaths despite amphotericin B therapy.

In none of our thirty-two cases was there either clinical or pathologic evidence of fatal cerebral edema. As emphasized previously,[1] this supports the statement of Bradley and Young,[10] that the cause of this complication is not vigorous therapy.

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