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Sudden and Unexpected Deaths After the Acute Onset of Diabetes Mellitus

Sudden unexpected death after the acute onset of diabetes mellitus is relatively rare. Diabetes usually presents with the classical symptoms of polydipsia, polyuria, polyphagia, and loss of weight, but in some instances diabetic coma may be the initial symptom. If the cause of the coma is not diagnosed before death or if the individual dies without medical attendance, these instances may be referred to the medical examiner. Herein are presented four such deaths; three occurred at home while the fourth occurred in a hospital. In none of these cases was the diagnosis of diabetes mellitus made prior to demise.

Case Reports

Case 1

An 8-year-old female was found dead in bed at 7:00 a.m. On the previous day she had symptoms of nausea, vomiting, and a headache. Except for a number of bottles of soft drink, she had not consumed any nourishment that day. A younger sister had been sick a day earlier with similar symptoms. Neither child appeared seriously ill and the parents thought they had the "flu."

At autopsy, the only gross or microscopic finding was severe cerebral edema. Toxicologic analysis of the blood and organs, including plasma cholinesterase activity and heavy metals, was negative. The vitreous humor revealed a glucose level of 338 mg/dl. The free blood acetone level was 18 mg/dl. Additional diagnostic tests revealed a postmortem blood insulin level of 5.7 mU/ml and bile insulin level of 85.3 mU/ml.

In view of the elevated vitreous glucose and blood acetone, additional history was obtained from the parents. The mother stated that she had two brothers, both of whom had diabetes mellitus. The first brother had acute onset of diabetes at the age of 5 years after an episode of measles. At the time of this report he was 31 years of age and had diabetic retinopathy. The second brother developed insulin-dependent diabetes in his mid-twenties. The mother was aware of the classic symptoms of diabetes, but stated that to her knowledge the child never demonstrated them. The other sister was free of symptoms at the time of this report.

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Case 2

A 17-year-old white male presented to his family physician with a two-day history of nausea and vomiting. A diagnosis of gastroenteritis was made. He was treated with hydroxyzine hydrochloride (Vistaril®) and appeared improved. During the night, his symptoms returned, and the following morning he was given promethazine hydrochloride (Phenergan®) suppositories. His condition worsened and he was admitted to a hospital at 2:00 p.m., at which time he appeared dehydrated and confused with rapid respiration and a pulse of 120/min. He had neither fever nor diarrhea. The admitting diagnosis was "viral gastroenteritis with dehydration." Blood electrolytes on admission were sodium, 143 mEq/litre and chloride, 92 mEq/litre. The white blood count was 21 000/cm^3 with a differential of 83% neutrophils, 14% lymphocytes, 2% monocytes, and 1% eosinophils. Urinalysis revealed a specific gravity of 1.030, pH of 6, glucose strongly positive, and ketones reported as "some." (The results of the urinalysis did not reach the clinician until after the patient's death.) Blood was sent for Technicon SMA-12 analyses, but the quantity provided was insufficient and no tests were performed. The patient was started on 5% dextrose solution with promethazine hydrochloride. His temperature rapidly climbed to 104°F (40°C), and he was pronounced dead approximately 7 h after admission.

The autopsy revealed the deceased to be a well-developed but obese male. The liver was enlarged to 2820 g and microscopic examination revealed severe fatty metamorphosis. No other significant gross or microscopic findings were present. A sample of antemortem blood was obtained from the hospital and along with vitreous and postmortem blood underwent toxicologic and chemical analyses. The antemortem blood glucose was 1360 mg/dl and the vitreous glucose, 900 mg/dl. The postmortem blood acetone was 44 mg/dl, and the vitreous acetone was 36 mg/dl. Vitreous sodium was 173 mEq/litre; chloride, 144 mEq/litre; and urea nitrogen, 53 mg/dl, establishing a terminal hyperosmolar dehydration [*1*]. Analysis of both antemortem and postmortem serum revealed complete absence of insulin.

Additional information revealed a history of diabetes on the mother's side of the family involving several aunts and uncles. The deceased had gained approximately 100 lb (45 kg) over the past 2 years, and for a week prior to death had been drinking excessive quantities of soda pop and water. No one else was sick in the house and the deceased had not complained of being tired.

Case 3

The patient was a 10-year-old white female in apparent good health whose initial complaint was a sore throat. She appeared to have a fever, although the temperature was not taken. The following day the patient was taken to a private physician where a physical examination revealed evidence of an acute pharyngitis. A leukocyte count was 18 000 with 65% neutrophils. A throat culture was taken and the patient was given 600 000 units of penicillin intramuscularly and provided with oral penicillin to be taken at home.

Three days later the culture was read as positive for beta hemolytic streptococci, and the patient was requested to return to the clinic where she received 1.2 million units of benzathine penicillin G suspension (Bicillin®). The patient felt improved subjectively although a physical examination was not performed at that time. The next two days the patient continued to suffer from a sore throat and fever while also complaining of myalgia, arthralgia, and transient headaches. She returned to see her physician, and physical examination at that time revealed an oral temperature of 101°F (38°C). The pharynx appeared mildly inflamed while the chest and abdomen examinations were negative. The physician felt that the patient was somewhat dehydrated and suggested that special efforts be made to ensure good fluid intake. A slide test for infectious mononucleosis was drawn at that time.

After returning from her clinic visit the patient was described as being quite listless and was put to bed. The following morning, seven days after the onset of her symptoms, she was found dead in bed.

The autopsy examination revealed no significant gross or microscopic findings. Vitreous humor revealed a glucose of 924 mg/dl with a 4+ qualitative acetone. Vitreous sodium was 176 mEq/litre; potassium, 8.4 mEq/litre; chlorides, 134 mEq/litre; and urea nitrogen, 64 mg/dl, establishing a terminal hyperosmolar dehydration as in Case 2.

The physicians who had treated the patient indicated that a routine urinalysis was usually performed on their patients. However, it had not been done on any of the three occasions in which the deceased visited their clinic during her terminal illness. Upon review of the historical circumstances, the parents felt that there was some polyuria early in the illness but did not notice this on the final day. Further historical information indicated that an aunt of the decedent on the mother's side had diabetes mellitus and several cousins of the father had adult-onset diabetes mellitus.

Case 4

A 30-year-old obese white female was found dead on the floor of her apartment. There was no evidence of trauma. She had been treated for schizophrenia in the past. At autopsy there was a massively enlarged liver (4880 g) showing marked fatty metamorphosis. A toxicological analysis for acid, basic, and neutral drugs, volatiles, amphetamines, and propoxyphene was negative. No acetone was detected. Postmortem blood insulin was 2.7 mU/ml with a bile level of 26.5 mU/ml. The vitreous glucose was 1262 mg/dl. The electrolytes and urea nitrogen were within normal limits. No history of diabetes mellitus in the family could be elicited.

Comment

Diabetes mellitus is a metabolic disorder characterized by hyperglycemia and a failure to a greater or lesser extent to secrete insulin. There are some four million diabetics in the United States, only half of whom are diagnosed. In the juvenile-onset diabetic, the lack of insulin may be complete, while in a mild or mature-onset diabetic it may be only partial.

Approximately one third of diabetics are juvenile-onset type. The most important clinical difference between this group and the mature-onset diabetic is the tendency of the juvenile to develop ketoacidosis. While most juvenile-onset diabetics present with the classical symptoms of polyuria, polydipsia, polyphagia, and weight loss, approximately one third of affected children are initially seen in acidosis or coma, or both [*2*]. In a few cases, the onset of diabetes occurs with complete absence of symptoms and with an infective illness precipitating or at least preceding the acute onset of coma. A bacterial infection was established in Case 3, and viral causes were suggested in both Cases 1 and 2 of the present series.

In diabetic ketoacidosis the blood glucose elevations are seldom under 300 mg/dl or over 1000 mg/dl. The average blood level for 100 cases as reported by Oakley [*2*] was 736 mg/dl. The concentration of the blood glucose, however, is not a reliable guide to the severity of the illness.

The biochemical derangement in diabetic ketoacidosis is extremely severe. Increased metabolism of fatty acids results in formation of ketone bodies and acidosis. There is loss of large quantities of water, sodium, chloride, potassium, and nitrogen, but the hyperglycemia produces osmotic diuresis with hypertonic dehydration despite the electrolyte depletion. Clinically, blood electrolyte concentrations in ketoacidosis may appear normal or elevated depending on whether the electrolyte or fluid loss is the greatest. Breathing becomes deep and sighing (Kussmaul respiration), and acetone may be smelled on the

breath. Free acetone in the blood is elevated in cases of coma. Whereas levels of free acetone in normal individuals are generally less than 0.17 mg/dl, the levels in diabetic coma have been reported from 14.5 mg/dl to 74.95 mg/dl [3].

The aketotic form of diabetic coma, as demonstrated in Case 4, differs in several important respects from the classical coma of ketoacidosis. This type of coma has been reported with increasing frequency in recent years, often occurring in undiagnosed diabetics. While such patients tend to be older than those in the ketoacidotic group, it may occur in children. Blood glucose levels in this condition are extremely high, with Oakley [2] reporting an average level of 1949 mg/dl. The highest level to be found was 2500 mg/dl. Dehydration is particularly intense; however, Kussmaul breathing is not present and the urine contains either no ketones or only small amounts. Free blood acetone in four such cases examined had levels of up to 5.81 mg/dl [3]. Serum sodium and potassium are usually normal or high.

A sudden unexpected death caused by the acute onset of diabetes mellitus can present a major diagnostic problem to the forensic pathologist. Postmortem blood glucose levels are generally of no value because of the great fluctuation in the level of glucose after death. Elevated blood acetone, while suggestive of diabetes, is not diagnostic as it may occur in other conditions such as malnutrition. In addition, it may be absent in cases of aketotic diabetic coma. The presence of glucose in the urine is also not diagnostic since numerous conditions, including administration of intravenous glucose fluids, can cause it. The presence of glycogen in the proximal convoluted tubules of the kidney (Armanni-Ebstein lesion) is said to be diagnostic of uncontrolled diabetes but, unfortunately, glycogen is often absent, as it was in each of the above cases. The pancreas was autolyzed in all cases so that islet cell interpretation was impossible.

The recognition of vitreous humor as a reliable, easily obtainable fluid for analysis has made the postmortem diagnosis of diabetic coma relatively easy [4,5]. An elevated vitreous glucose is an accurate reflection of an elevated antemortem blood glucose. Fortunately, the conditions frequently associated with marked terminal rises in blood glucose levels do not manifest this rise in the vitreous glucose. In a recent study, Coe found 102 nondiabetics in whom postmortem peripheral blood glucose concentrations exceeded 500 mg/dl resulting from a terminal rise in blood sugar from a variety of causes [6]. However, the vitreous glucose in all of these cases was below 100 mg/dl. Even when intravenous glucose infusions have been administered for some time prior to death, the vitreous glucose levels in normal subjects are generally less than 200 mg/dl. Thus, glucose levels significantly above 200 mg/dl are considered diagnostic of diabetes mellitus. As the time between death and autopsy increases there tends to be a fall in the glucose level of the vitreous, but this decrease will be relatively gradual in the diabetic and significantly elevated levels of glucose will remain for prolonged periods after death [7].

Blood insulin levels were determined in Cases 1, 2, and 4. In the clinical laboratory at the University of Texas Health Sciences Center at Dallas, antemortem levels of insulin in normal subjects show a range of 6 to 26 mU/ml in plasma. Only the second case, the 17-year-old boy, demonstrated abnormally low values, insulin being absent in both antemortem and postmortem samples. Absence of insulin in postmortem samples, however, is probably of no significance. In a series of ten healthy individuals, ages 13 to 38 years of age, all of whom died suddenly and traumatically, four showed complete absence of insulin with the other individuals having levels ranging from 4.5 to 15 mU/ml.[4] In the case of the boy, only the absence of insulin in the antemortem blood sample makes the postmortem level significant. In contrast to low values of insulin, elevated levels of insulin postmortem are valid. The blood levels in cases of insulin overdose are in the high hundreds and low thousands. A study of insulin levels in the bile similarly demonstrated the increased

[4] W. Q. Sturner, unpublished observations.

reliability of interpreting markedly elevated concentrations in contrast to low levels and total absence [*8*].

Summary

Four cases of sudden and unexpected death caused by the acute onset of diabetes mellitus are reported. Three are examples of acute juvenile diabetes while the fourth demonstrated the aketotic form of diabetic coma. Such instances can present a diagnostic problem to the forensic pathologist. The usefulness of vitreous humor glucose analysis to diagnose such a condition is stressed.

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