Brief Notes and Comments

Cerebral Edema, Diabetes Insipidus, and Sudden Death during the Treatment of Diabetic Ketoacidosis

Howard Taubin, M.D., and Robert Matz, M.D., New York

SUMMARY

A young diabetic patient with ketoacidosis responding to standard treatment abruptly developed pulmonary edema, apnea, coma, cardiac arrythmias and diabetes insipidus. At autopsy, cerebral edema and neuronal degeneration were present. In the hypothalamus many neurones were absent. Similar cases have been reported, but the pathogenesis of the syndrome is not understood. The present patient received large amounts of sodium bicarbonate, and significant potassium deficiency may have been present. DIABETES *17*: 108-09, February, 1968.

Coma and sudden death occurring despite adequate treatment of diabetic ketoacidosis has been reported sporadically in the past.[1,2] The descriptions of certain of these patients are sufficiently similar to suggest a common but inadequately explained pathogenesis.

CASE REPORT

B.H. (*M.C.H. No. 2099-67*) was a twenty-three-year-old woman with known diabetes for six months who was satisfactorily controlled with 40 U. NPH insulin daily. She was admitted to Morrisania City Hospital on March 6, 1967 in ketoacidosis, presumably precipitated by a viral gastroenteritis and cessation of insulin usage of two days' duration. She was lethargic and dehydrated with blood pressure 130/80 mm. Hg, pulse rate 100 per minute, Kussmaul respirations of 30 per minute and temperature 98.8° F. Her skin was warm and dry with mottled cyanosis of the lower extremities. The remainder of the physical examination was unremarkable except for the presence of a 1 × 1 cm. nodule in the right lobe of the thyroid and a liver edge palpable 2 cm. below the right costal margin.

Laboratory data on admission included: hematocrit 55 per cent, white blood count 22,450 per cmm, with 64 per cent polymorphonuclear leucocytes, 4 per cent bands, 30 per cent lymphocytes and 3 per cent monocytes. Urinalysis: specific gravity 1.022, 3+ protein, 4+ glucose, large acetone and 12 white blood cells per high power field. The blood glucose was greater than 500 mg./100 ml. The serum sodium was 132 mEq./L., carbon dioxide 4.5 mEq./L., chloride 89 mEq./L., urea nitrogen 17 mg./100 ml. and potassium 4.2 mEq./L. An electrocardiogram demonstrated a normal sinus rhythm with flattened T waves and prominent U waves. The serum acetone was strongly positive in 1:2 dilution and moderate in 1:4 dilution.

During the first eight hours of treatment she received 250 U. crystalline insulin subcutaneously and 5,000 ml. of intravenous fluids consisting of 2,000 ml. of sodium bicarbonate (88 mEq./L.) in distilled water, 1,000 ml. 5 per cent dextrose in 0.2 per cent saline, 1,000 ml. of 0.9 per cent saline and 1,000 ml. 5 per cent dextrose in water. With these solutions she received a total of 396 mEq. of sodium bicarbonate and 120 mEq. of potassium chloride. Her urine output during this time was 2,500 ml. At the eighth hour the following values were obtained: blood sugar 262 mg./100 ml., sodium 126 mEq./L., chloride 98 mEq./L., carbon dioxide 12.5 mEq./L., and potassium 2.9 mEq./L. The hematocrit had fallen to 49 per cent and serum acetone to a trace positive in a 1:2 dilution. The electrocardiogram was unchanged. The patient was more alert, taking sips of oral fluids and complaining of a headache.

By the ninth hospital hour increasing lethargy was observed and her headache persisted. While she was being prepared for a lumbar puncture, acute pulmonary edema developed which quickly responded to standard management. During this episode, she developed multiple supraventricular and nodal tachyarrhythmias with restoration of normal sinus rhythm following the rapid infusion of 80 mEq. of potassium chloride in 5 per cent dextrose in water.

Concomitant with this acute episode she became hypotensive, apneic and comatose with fixed dilated pupils. Intravenous metaraminol and colloid solution and assisted ventila-

From the Department of Medicine, Montefiore-Morrisania Affiliation, 168th Street and Gerard Avenue, Bronx, N.Y. Requests for reprints should be addressed to Robert Matz, M.D., Montefiore-Morrisania Affiliation, Bronx, N.Y.

tion were required to maintain respiratory exchange, blood pressure and urine output. Lumbar puncture at this time revealed clear fluid with a pressure of 180 mm. of CSF. No cells were present in the spinal fluid. Unfortunately, the sample sent for chemical analysis was lost in transit.

Two hours later her urine output increased to between 800 to 1,500 ml. per hour with specific gravities of 1.002 to 1.004. At this time, the serum sodium level was 136 mEq./L., chloride 95 mEq./L., potassium 3.8 mEq./L., and carbon dioxide 14 mEq./L. The blood sugar was 330 mg./100 ml. and serum urea nitrogen 17 mg./100 ml. Her hematocrit was 46 per cent and white blood count 14,000/cmm. The urine output was partially responsive to intravenous vasopressin and during the next twenty-four hours she received 18,000 ml. of intravenous fluids containing 800 mEq. of sodium and excreted 16,000 ml. of urine. During this time, she received an additional 150 U. regular insulin. Her electrocardiogram continued to demonstrate flattened and inverted T waves with prominent U waves despite the intravenous administration of greater than 800 mEq. of potassium chloride during her hospital course. Before death, thirty-two hours after the onset of therapy, her serum sodium was 140 mEq./L., chloride 116 mEq./L., carbon dioxide 19 mEq./L., blood sugar 918 mg./100 ml., potassium 4.9 mEq./L. and urea nitrogen 45 mg./100 ml.

An autopsy, severe pulmonary edema and passive congestion of the liver and spleen were present. A colloid goiter was present. In the heart there was edema of the fibers with interstitial infiltration of plasma cells and polymorphonuclear leucocytes. There were multiple foci of myocarditis with loss of cross striations and focal necrosis. In the kidneys the glomerular tufts and vessels were normal. The tubules had mild fatty vacuolization of the epithelial cells, primarily in the proximal tubules. Mild intertubular congestion was also present. The pituitary was normal, grossly and microscopically. The brain had narrowing of the sulci and broadening of the gyri, indicating diffuse bilateral cerebral edema. Further, there was bilateral uncal grooving and cerebellar tonsillar coning, the tonsillar cone extending to an elevation of 2 cm. On coronal section diffuse cerebral edema was manifested by almost complete obliteration of the ventricular system. Microscopically, prominent perineuronal spaces indicative of edema confirmed the gross appearance. Diffuse changes compatible with those of anoxia were evident throughout the brain, and in the hypothalamus many of the neurons were entirely absent.

DISCUSSION

This patient resembles those with sudden death in irreversible coma described by Fitzgerald et al.[1] and Young and Bradley.[2] In general these patients have been of a relatively young age, have had no evidence of underlying systemic disease, and unconsciousness has been delayed in onset with clinical evidence of severe central nervous system derangements including instability of blood pressure and respiration and the development of diabetes insipidus in two of the recorded patients. The postmortem descriptions of the brains have been similar, these being cerebral edema and neuronal degeneration.

Cerebral edema in patients dying with diabetic acidosis was described in detail some years ago by Dillon et al.[3] The pathogenesis is not understood, however. Young and Bradley have suggested that the edema and other findings may be related to anoxia,[2] the anoxia in turn being caused by ketosis[4] and decreased cerebral circulation.[5] The roles of potassium deficit[6] and possible spinal fluid acidosis resulting from administration of sodium bicarbonate[7] remain to be determined. It has been suggested also that a rapid decrease in extracellular fluid glucose concentration may release water to aggravate the edema.[8] In the present case it is possible that the administration of 396 mEq. of bicarbonate along with insufficient potassium (despite 800 mEq.) may have been deleterious.

The occurrence of diabetes insipidus in our patient and in Case 3 of Fitzgerald et al.[1] can probably be explained by the observed hypothalamic lesions. In the latter case, there was widespread necrosis of the hypothalamus and midbrain, while in ours the hypothalamus revealed diffuse anoxic changes with loss of many neurones. The cause of the myocardial lesions is not apparent.

ACKNOWLEDGMENT

The authors gratefully acknowledge the assistance of Drs. Paul W. Spear and Harold Rifkin in the preparation of this paper.

REFERENCES

[1] Fitzgerald, M. G., O'Sullivan, J., and Malins, J. M.: Fatal diabetic ketosis. Brit. Med. J. 1:247-50, 1961.

[2] Young, E., and Bradley, R. F.: Cerebral edema with irreversible coma in severe diabetic ketoacidosis. New Eng. J. Med. 276:665-69, 1967.

[3] Dillon, E. S., Riggs, H. E., and Dyer, W. W.: Cerebral lesions in uncomplicated fatal diabetic acidosis. Amer. J. Med. Sci. 192:360-65, 1936.

[4] Kety, S. S., Polis, B. D., Nadler, C. S., and Schmidt, C. F.: The blood flow and oxygen consumption of the human brain in diabetic acidosis and coma. J. Clin. Invest. 27:500-10, 1948.

[5] Shieve, J. F., and Wilson, W. P.: The changes in cerebral vascular resistance of man in experimental alkalosis and acidosis. J. Clin. Invest. 32:33-38, 1953.

[6] Meyer, J. S., Gotoh, F., Ehibara, S., and Tomita, N.: Effects of anoxia on cerebral metabolism and electrolytes in man. Neurology 15:892-901, 1965.

[7] Posner, J. B., and Plum, F.: Spinal-fluid *p*H and neurologic symptoms in systemic acidosis. New Eng. J. Med. 277: 605-13, 1967.

[8] Fulop, M.: Cerebral edema in severe diabetic ketoacidosis. New Eng. J. Med. 276:1445, 1967.