Hyperglycemic, Hyperosmolar, Nonketoacidotic Diabetes

A Complication of Steroid and Immunosuppressive Therapy

J. G. Spenney, M.D., C. A. Eure, M.D., and
R. A. Kreisberg, M.D., Birmingham, Alabama

SUMMARY

Two cases of hyperglycemic, hyperosmolar, nonketoacidotic diabetes are reported. Both had renal disease and were receiving corticosteroids and azathioprine. A third patient with hepatitis receiving corticosteroids alone and developing ketoacidosis is described also. The syndrome of hyperglycemic coma is discussed and speculations on the role of steroids and azathioprine are made. DIABETES *18*: 107-10, February, 1969.

Over one hundred cases of hyperglycemic, hyperosmolar, nonketoacidotic coma have been reported. Despite the diabetogenic properties of corticosteroids and their wide use in modern medical treatment, they have rarely been associated with this serious syndrome. Indeed, we are aware of only eleven cases in the literature in which steroids have been implicated.[1-8] Although the pathogenesis of hyperglycemic, hyperosmolar, nonketoacidotic coma is not understood, its rare occurrence during corticosteroid therapy suggests that factors in addition to the administration of steroids may be concerned. Recently two patients at the University of Alabama Medical Center developed hyperglycemic nonketotic coma and one patient ketoacidosis while receiving steroid treatment. The fact that the two patients without ketoacidosis and two of the above mentioned eleven cases[7,8] received antimetabolite therapy suggested that this combination of therapy may favor the production of the syndrome."

From the University of Alabama at Birmingham, The Medical Center, Birmingham, Alabama 35233.

Address reprint requests to Dr. Robert A. Kreisberg, University of Alabama Medical Center, 1919 Seventh Avenue South, Birmingham, Alabama 35233.

CASE REPORTS

Case I

A twenty-nine-year-old white man, admitted to the University of Alabama Medical Center in April, 1968, had chronic glomerulonephritis, malignant hypertension, chronic renal failure, and peripheral neuropathy. After bilateral nephrectomy and preparatory hemodialysis, a renal homograft was inserted on June 19, 1968, and he was started on azathioprine (275 mg./day) and prednisone (120 mg./day). He was discharged on prednisone 100 mg., azathioprine 200 mg., hydralazine 100 mg., and hydrochlorothiazide 100 mg. daily. During a subsequent admission for a rejection reaction, he noted a slight polyuria, polydipsia, and polyphagia which was not mentioned to the medical staff until he returned one week later. During that week he had noted progressive polyuria, polydipsia, blurred vision, and a dry mouth; however, he remained alert and oriented and had no weight loss. The patient appeared Cushingoid and was alert and oriented. The temperature was 98.6° F.; pulse, 112/min.; respirations, 24/min.; and blood pressure, 170/90 mm Hg. The retina revealed arteriolar narrowing, exudates, and resolving hemorrhages but no microaneurysms. During the first thirty-six hours, he voided 10 liters of urine which was strongly positive for glucose but negative for acetone. The blood sugar was 1,400 mg./100 ml.; serum Na^+, 150 mEq./L.; K^+, 4.9 mEq./L.; Cl^-, 100 mEq./L.; HCO^-_3 25 mEq./L.; BUN 55 mg. per cent and creatinine 1.7 mg. per cent. Therapy consisted of water by mouth and 70 U. of Regular insulin. The blood sugar fell to 180 mg./100 ml. in sixteen hours. He was subsequently controlled with a diabetic diet and 90 U. of NPH insulin daily.

CASE II

A twenty-three-year-old white woman, admitted to the University of Alabama Medical Center on June 29, 1968, had the nephrotic syndrome. Prednisone (60 mg./day) was initiated two weeks prior to admission. She was grossly edematous and had obvious ascites. Her blood pressure was 160/85 mm. Hg. and there was no retinopathy. There was a Grade II/VI holosystolic apical murmur and the liver was palpated 1 centimeter below the right costal margin. The WBC was 12,600/mm.^{3} and the hematocrit was 40 vol. per cent. Urinalyses revealed 4+ protein, numerous RBC's,

WBC's/hpf and doubly refractile fat bodies. Twenty-four-hour urinary protein was 5-7 grams. Serum electrolytes were normal and the BUN 46 mg. per cent. The creatinine clearance was 32 ml./min. The serum albumin was 1.33 gm. per cent and $beta_1$ C globulin was absent. Blood sugars during a glucose tolerance test were: fasting, 121 mg./100 ml.; 30 min., 161 mg./100 ml.; 60 min., 157 mg./100 ml.; 120 min., 168 mg./100 ml.; 180 min., 168 mg./100 ml. A renal biopsy was read as showing severe focal glomerulonephritis with fibrinoid necrosis. Following informed consent, a clinical trial with azathioprine and steroids was initiated. She was discharged to the medical clinic for continuing care. Two and one-half weeks later she complained of blurred vision, thirst, and polyuria; although she had lost four pounds, edema and ascites persisted. Protein and formed elements in the urine were unchanged, but there was 2+ glycosuria without acetonuria. Prednisone was reduced from 60 to 30 mg. per day and azathioprine was increased to 200 mg. per day. Over the next three days she became worse and returned on August 19, 1968, at which time she was moderately dehydrated and lethargic but oriented and easily aroused. There was no peripheral edema and her ascites was markedly reduced. Her temperature was 98.6° F.; pulse, 130/min.; respirations, 16/min.; and blood pressure, 135/90 mm Hg. There was 4+ glycosuria, moderate acetonuria, but only a trace of serum acetone. The blood sugar was 1,950 mg./100 ml.; serum Na^+, 127 mEq./L.; K^+, 4.5 mEq./L.; Cl^-, 86 mEq./L.; HCO^-_3 22 mEq./L.; and BUN 79 mg. per cent. Arterial blood pH was 7.42, and the serum osmolality was 380 mOsm./L. In the first twenty-four hours, she received 310 U. of Regular insulin and 5 liters of 0.45 per cent saline. Her blood sugar decreased to 250 mg./100 ml. and her weight increased from 105 to 115 pounds. Despite a fall in serum osmolality to 288 mOsm./L., her mental state did not clear for forty-eight hours. Prednisone was tapered to the 20 mg./day and azathioprine was continued at a dose of 200 mg./day. Her diabetes was controlled on 1.5 gm. of tolbutamide daily.

CASE III

A fifty-eight-year-old Negro woman, admitted to the University of Alabama Medical Center on December 13, 1966, had a three-day history of general malaise, anorexia, nausea, vomiting, and dark urine. One month previously she received 3 units of whole blood during a vaginal hysterectomy. She was a mildly hypertensive, moderately obese woman with icteric sclera. There was no diabetic retinopathy. The right upper quadrant of the abdomen was tender but neither the liver nor spleen was palpable. Initial laboratory studies revealed a normal CBC and urinalysis. The total bilirubin was 9.5 mg. per cent; SGOT, 865 units (normal 25 units); and alkaline phosphatase, 4.2 Bessey-Lowry units (normal 0.8-2.5 units). A diagnosis of hepatitis was made. Despite clinical improvement on a high carbohydrate diet, the total bilirubin rose to 19.5 mg. per cent and the SGOT to 1,165 units during the next ten days. Dexamethasone (2.24 mg. daily) was initiated, and within six days, the total bilirubin decreased to 5.8 mg. per cent and the SGOT to 42 units. Four days after dexamethasone was reduced to 1.5 mg./day, she became semicomatose and dehydrated. Her temperature was 105° F.; pulse, 124/min.; respirations, 48/min.; and blood pressure, 110/90 mm. Hg. A blood sugar was 1,450 mg./100 ml., the serum acetone was strongly positive at 1:2 dilution, and arterial blood pH was 7.32. Serum electrolytes were Na^+, 120; K^+, 7.0; Cl^-, 88; HCO^-_3 12 mEq./L. respectively; BUN, 105 mg. per cent; and SGOT, 43 units. The serum osmolality was 380 mOsm./L. She was treated with 8 liters of 0.45 per cent saline and 150 U. of Regular insulin. Within eighteen hours, she was alert and the blood sugar was 73 mg./100 ml. Her diabetes, initially requiring insulin therapy, was controlled with tolazamide (250 mg./day) after dexamethasone was discontinued.

DISCUSSION

The hyperglycemic, hyperosmolar syndrome occurs primarily in middle aged and older patients with or without previously diagnosed diabetes mellitus.[9] However, it has also been observed in the very young,[10] in insulin dependent diabetes,[11] as a complication of severe burns,[12-15] following peritoneal and hemodialysis[16,17] pancreatitis,[18,19] pancreatic carcinoma,[20] corticosteroid therapy,[1-8] and lymphoma treated with antimetabolites and/or corticosteroids,[1,8] To our knowledge, this is the first reported case occurring in a patient with a renal homograft.

The pathogenesis of this syndrome has not been defined, but an explanation may be inferred from the work of Zierler.[21] In the human forearm, the amount of insulin necessary to promote glucose transport is ten times that which inhibits fat mobilization. Since fat mobilization is required for ketone body production, it is possible to have a concentration of insulin which would allow dissociation of ketosis and hyperglycemia. The greater prevalence of this syndrome in maturity rather than growth onset diabetes would be predicted since insulin levels are normal or elevated in the adult diabetic.[22] Patients developing diabetes on corticosteroid therapy also have increased insulin levels,[23] secondary either to peripheral insulin resistance[23] and/or increased gluconeogenesis,[24] so that deterioration of carbohydrate tolerance would be more likely to occur in the absence of ketosis.[25]

There was no correlation between the blood sugar concentrations of our patients and their symptoms. Although the level of consciousness in patients with this syndrome varies from lethargy to frank coma,[11] factors in addition to hyperglycemia must be responsible for producing the central nervous system symptoms. Hyperosmolality, dehydration, and altered hemodynamics may be better tolerated by young patients without significant vascular disease. With alterations of consciousness and impairment of thirst, older patients are unable to maintain their fluid intake and hyperosmolality and de-

hydration intensify.

Blood sugar concentrations have been recorded as high as 2,760 mg. per 100 ml.,[25] and the serum sodium, though generally elevated, may be normal or low.[9] A mild degree of ketonemia is frequent but acidosis is seldom severe[9] unless there is accompanying lactic acidosis.

The liberal use of fluids and insulin is the keynote of therapy. The magnitude of the volume deficit in individuals with the full-blown syndrome is often large, and aggressive replacement must be undertaken. Although the fluid of choice for repairing the deficit has been controversial, most authors have preferred hypotonic saline.[8,27,30] A few have suggested that glucose and hypotonic saline[31-33] is preferred because, in their opinion, precipitous falls in blood glucose levels have been associated with a deterioration in central nervous system status. Recently there has been some experimental evidence to support this contention.[34] We have used hypotonic saline in these patients and in others with this syndrome until the blood sugar has decreased to 250 mg. per 100 ml. We have noticed no deterioration of central nervous system function with this approach although there was a delay in recovery in the patient mentioned in Case II. Hydration and re-establishment of renal perfusion allows dissipation of glucose by the kidney and may be as important as insulin in lowering the blood sugar.

Patients with hyperglycemic, hyperosmolar, nonketoacidotic diabetes are considered to be more insulin sensitive than those with diabetic ketoacidosis. However, because there is considerable variation in insulin sensitivity, the guidelines for insulin dosage are not as well-defined and initial insulin therapy is not as aggressive. Patients have been described in which as little as no insulin[3] and as much as 4,600 U. of Regular insulin[20] have been required for recovery. This disorder represents one extreme of a spectrum of insulin deficiency syndromes which range from only hyperglycemia to hyperglycemia with ketoacidosis depending upon the relative or absolute degree of insulin deficiency. Therefore, it could be expected that there would be patients with varying degrees of hyperglycemia, hyperosmolality, ketoacidosis, and insulin sensitivity, as demonstrated by the patient in Case III.

The role of steroids in producing this syndrome in our patients is not clear. None of the patients had a positive family history for diabetes; however, all three had disorders associated with abnormal glucose tolerance.[35,36] The patient with the nephrotic syndrome had an abnormal glucose tolerance test on steroids alone, which could represent unmasking of either genetic diabetes or the carbohydrate intolerance associated with chronic renal disease. Because of the high prevalence of the gene(s) for diabetes in the general population, all of our patients may have been genetic diabetics made manifest by steroid therapy. Alternatively, it is possible that none of these patients were genetic diabetics and that diabetes was precipitated by very large doses of steroids alone or in combination with immunosuppressive therapy.

We know of no studies on the effect of azathioprine on glucose metabolism in animals or in man, so that one can only speculate about its role in the development of this syndrome in our patients. Azathioprine's initial metabolic product in the body, 6-mercaptopurine,[37] decreases the uptake and oxidation of glucose by sarcoma tissue but not normal tissue.[38] However, since there is evidence that its biologic action is not due only to conversion to 6-mercaptopurine,[37] studies with the latter drug may not be representative. Inhibition of the synthesis of either insulin or the enzyme(s) which regulate glucose utilization might be expected due to its effects on RNA-dependent protein synthesis. Underutilization of glucose would then be added to the overproduction produced by steroids, creating conditions more favorably suited for the development of this syndrome.

ACKNOWLEDGMENT

This study was supported by USPHS Grants T1 AM 5053-13, 2 MO1 FR 32-08 and AM 09722-03.

REFERENCES

[1] Kumur, R. S.: Hyperosmolar non-ketotic coma. Lancet *1*:48, 1968.

[2] Boyer, M. H.: Hyperosmolar anacidotic coma in association with glucocorticoid therapy. JAMA *202*:1007, 1967.

[3] Hayes, T. M., and Woods, C. J.: Hyperosmolar nonketotic coma. Lancet *1*:209, 1968..

[4] Pyörälä, K., Suhonen, O., and Pentikäinen, P.: Steroid therapy and hyperosmolar non-ketotic coma. Lancet *1*:596, 1968.

[5] Mach, P. R. S., and DeSousa, R. C.: Coma avec hyperosmolalité et deshydratation chez des malades hyperglycémiques sans acidocétose. Schweiz Med. Wschr. *36*:1256, 1963.

[6] Plauchu, M.: Paliard, P., Malluret, J., Noel, P., and DeMontgolier, R.: Un nouveau cas d'etat d'hyperosmolarité plasmatique ou de coma hyperosmolaire déclenché par les corticoïdes chez un diabetique latent, porteur dúne lympose. Lyon Med. *217*:1921, 1967.

[7] Brocard, H., Akoun, G., and Grand, A.: Diabète stéroïde compliqué d'un coma de type hyperosmolaire. Bull. Soc. Med. Hop. Paris *116*:353, 1965.

[8] Schwartz, T. B., and Apfelbaum, R. I.: Non-ketotic diabetic coma. Yearbook of Endocrinology *172*: 1965-1966.

[9] Danowski, T. S., and Nabarro, J. D. N.: Hyperosmolar and other types of nonketoacidotic coma in diabetes. Diabetes *14*:164, 1965.

[10] Ehrlich, R. M., and Boin, H. W.: Hyperglycemia and hyperosmolarity in an eighteen-month-old child. New Eng. J. Med. *276*:683, 1967.

[11] Kolodny, H. D., and Sherman, L.: Hyperglycemic nonketotic coma in insulin dependent diabetes mellitus. JAMA *203*:461, 1968.

[12] Rosenberg, S. A., Brief, D. K., Kinney, J. M., Herrera, M. G., Wilson, R. E., and Moore, F. D.: The syndrome of dehydration, coma and severe hyperglycemia without ketosis in patients convalescing from burns. New Eng. J. Med. *272*: 931, 1965.

[13] Evans, E. I., and Butterfield, W. J. H.: Stress response in the severely burned: interim report. Ann. Surg. *134*:588, 1951.

[14] Arney, G. K., Pearson, E., and Sutherland, A. B.: Burn stress pseudodiabetes. Ann. Surg. *152*:77, 1960.

[15] Bailey, B. N.: Hyperglycemia in burns. Brit. Med. J. *2*: 1783, 1960.

[16] Boyer, J., Gill, G. N., and Epstein, F. H.: Hyperglycemia and hyperosmolality complicating peritoneal dialysis. Ann. Int. Med. 67:568, 1967.

[17] Potter, D. J.: Death as a result of hyperglycemia without ketosis—a complication of hemodialysis. Ann. Int. Med. *64*: 399, 1966.

[18] Halmos, P. B.: Hyperosmolar non-ketoacidotic diabetic coma in a patient with necrotizing pancreatitis. Brit. Med. J. *2*:685, 1966.

[19] Davidson, A. I. G.: Diabetic coma without ketoacidosis in a patient with acute pancreatitis. Brit. Med. J. *1*:356, 1964.

[20] Jackson, W. P. U., and Forman, R.: Hyperosmolar nonketotic diabetic coma. Diabetes *15*:714, 1966.

[21] Zierler, K. L., and Rabinowitz, D.: Roles of insulin and growth hormone, based on studies of forearm metabolism in man. Medicine *42*:385, 1963.

[22] Yalow, R. S., Glick, S. M., and Berson, S. A.: Plasma insulin and growth hormone levels in obesity and diabetes. Ann. N.Y. Acad. Sci. *131*:357, 1965.

[23] Berger, S., Downey, J. L., Traisman, H. S., and Metz, R.: Mechanism of the cortisone-modified glucose tolerance test. New Eng. J. Med. *274*:1460, 1966.

[24] Ashmore, J., and Morgan, D.: Metabolic effect of adrenal glucocorticoid hormones. *In* The Adrenal Cortex, A. B. Eisenstein, ed., Boston, Little, Brown, and Co., 1967, p. 249.

[25] Scott, J. L., and Engel, F. L.: The influence of the adrenal cortex and cold stress on fasting ketosis. Endocrinology *53*:410, 1953.

[26] Maccario, M., Messis, C. P., and Vastola, E. F.: Focal seizures as a manifestation of hyperglycemia without ketoacidosis. Neurology *15*:195, 1965.

[27] Matz, R., and Drapkin, A.: Hyperosmolar coma in diabetes. Lancet *1*:1101, 1966.

[28] Sament, S.: Hyperosmolar coma in diabetes. Lancet *1*: 1153, 1966.

[29] Haapanen, E.: Hyperosmolar coma in diabetes. Lancet *1*:1154, 1966.

[30] Rosen, H., and Glick, M. G.: Hyperosmolar coma in diabetes. Lancet *1*:1101, 1966.

[31] Halmos, P. B., and Nelson, J. K.: Hyperosmolar nonketoacidotic coma in diabetes. Lancet *1*:675, 1966.

[32] Harding, T., and Turck, W. P. G.: Hyperosmolar diabetic coma. Lancet *2*:746, 1966.

[33] Tovey, J. E.: Hyperosmolar coma in diabetes. Lancet *1*:1324, 1966.

[34] Clements, R. S., Prockop, L. D., and Winegrad, A. I.: Acute cerebral oedema during treatment of hyperglycemia. An experimental model. Lancet *2*:384, 1968.

[35] Hampers, C. L., Soeldner, S., Doak, P. B., and Merrill, J. P.: Effect of chronic renal failure and hemodialysis on carbohydrate metabolism. J. Clin. Invest. *45*:1719, 1966.

[36] Megyesi, C., Samols, E., and Marks, V.: Glucose tolerance and diabetes in chronic liver disease. Lancet *2*:1052, 1967.

[37] Chalmers, A. H., Knight, P. R., and Atkinson, M. R.: Conversion of azathioprine into metcaptopurine and mercaptoimidazole derivatives in vitro and during immunosuppressive therapy. Aust. J. Exp. Biol. Med. Sci. *45*:681, 1967.

[38] Mihich, E., Clarke, D. A., and Phillips, F. S.: Effects of 6-mercaptopurine on respiration, anaerobic glycolysis and succino-dehydrogenase activity in normal and tumor tissues. Proc. Soc. Exp. Biol. Med. *112*:758, 1963.