HYPERGLYCEMIC NONKETOTIC COMA

Sunitaya Chandraprasert, M.D.*

Hyperglycemic nonketotic coma is characterized by marked hyperglycemia and hyperosmolarity in the absence of ketosis. The syndrome was first mentioned by Umber-Berlin in 1924[27], but is was Sament and Schwartz[24] who brought this condition of attention by detailed description of the syndrome in 1957. At present, over than one hundred cases have have been reported in the literature, and probably many more were unreported or unrecognised.

The purpose of this paper is to report three cases seen at the Chulalongkorn hospital during 1967–1969; and to review the mechanism and management of this syndrome.

Case. 1: A 10 year old woman was first admitted to the hospital in May, 1969 because of lethargy, somnolence, confusion and fever of two days duration. The patient was well until two weeks before admission when she developed polyuria, polydipsia and weakness. Four days later, she became drowsy, mentally confused and had a fever. She was seen by her private physician who made a diagnosis of diabetes mellitus with upper respiratory tract infection. She was given oral hypoglycemic drug (Diabenese) and tetracycline. The following day she became obtunded and was brought to the hospital. There was no history of diabetes mellitus in her family.

On admission, she was in semicoma and was moderately dehydrated. There was no stiffneck or any localizing neurological signs. The body temperature was 38.5 degree centigrade. Pulse and respiration rates were 90 and 26 per minute respectively. Fundoscopic examination was normal. No other abnormal findings were noted in systemic examination. The hemoglobin was 12 grams. The white cell count was 15100 with 88 per cent neutrophils and 12 per cent lymphocytes. The urine specific gravity was 1.041; the sediment contained 10–20 red cells and 10 white cells per high power field; and trace of acetone. The blood sugar was 684 mg. per 100 ml. with trace of plasma acetone. The sodium was 159, potassium 5.0, chloride 112, and carbon dioxide, 9.5 milliequiv per liter. The blood osmolarity was 403 milliosmol per kilogram. The patient recieved 2000 ml. of isotonic saline solution and 200 units of regular insulin within eight hours. The blood sugar then came down to between 150–200 mg.

* Department of Medicine Chulalongkorn Hospital, Faculty of Medicine, Chulalongkorn University, Bangkok.

(by dextrostix), and intravenous fluid was changed to isotonic glucose. Twelve hours after the beginning of therapy, the patient became more responsive and four hours later, regained consciousness. Her diabetes was subsequently controlled with 20 units of NPH insulin daily and then with oral agent alone (Chlorpropamide). She was discharged in good condition.

Case 2: A 45 year old single Thai woman was first admitted to this hospital on July 1. 1965 with complaints of polydipsia poly unia and weight loss for three years. Diabetes mellitus with peripheral neuropathy, urinary tract infection and immature cataracts were diagnosed. After one month in the hospital, she was discharged on chlorpropamide 500 mg. per day nad phenformin 25 mg. three times a day. After discharged, the patient failed to take medicine regularly, and thus, her diabetes was not well controlled. She lost more weight and became progressively weak. Prior to the second hospital admission in December, she was already bed-ridden for two months. At hospital, she was found to be cachectic, dehydrated, bed ridden with chronic ulcer at third toe of her left foot and pressure sore at right malleolus. The blood pressure was 120/80 mm. Hg., pulse rate was 73 per minute. The skin and mucous membranes were dry. Neck veins were flat. Auscultation of the heart and lungs disclosed no abnormalities. Deep tendon reflexes were absent. Peripheral pulses were strong. Ankle edema was not present. Pertinent laboratory studies were as follows; hemoglobin, 10.4 gm. White cell count was 23400/ with 92 per cent of neutrophils and 8 per cent of lymphocytes. The blood creatinine was 3.6 mg, BUN 106 mg. and fasting blood sugar, 355 mg. per 100 ml. The plasma acetone was negative, The serum albumin was 4.1 gm. and globulin 2.5 gm. per 100 ml. The total cholesterol was 237 mg. per 100 ml. Sodium was 143, potassium 5.2 and chloride 109 milliequiv. per litre. Urinalysis showed a specific gravity of 1024; sugar I plus with numerous white cells, The electrocardiogram was normal. After hospitalization, regular insulin was prescribed accordinlgy to positive urine sugar. Because of lack of urine test, regular insulin was given onty 40 units in 48 hours. The patient became weak, drowsy, and developed clonic convulsion of upper extremities and went into coma after the third convulsion. The result of blood chemistry while the patient was in coma were as follows; blood sugar was 1164 mg. per 100 ml. serum sodium was 137.5, potassium 5.2, chloride 104 and carbon dioxide 5.8 milliequiv. per liter. The blood calcium was 9.2 mg and phosphate was 7.1 mg. per 100 ml. Plasma acetone was negative. The blood osmolarity was 418 milliosmol per kilogram. The patient

was given regular, insulin hypotonic salt solution and sodium bicarbonate. Within the first four hours, she received 200 units of regular insulin, and 3,000 ml, fluid. The blood sugar came down to 425 mg. per 100 ml. but clinically there was on improvement. She was still in deep coma. Subsequently the patient developed hypotension and expired 6 hours after the treatment.

Case 3: A 40 year old man developed convulsion and coma and was brought to the hospital on April 6, 1969 by the owner of a restuarant where he had gone to have a dinner. No other information could be obtained at the time of admission. Physical examination revealed a blood pressure of 120/80 mm. Hg; pulse rate of 130 per minutes; body temperature of 40 degree centigrade. He appeared well nourished, not dehydrated and there was no jaundice. The heart and lungs were normal. Spleen was palpable 1 fingerbreath below the left costal margin. He was comatose; the pupils were fixed and did not react to light. Stiffneck was not present. Soon after hospitalization, the patient developed clonic convulsion of right arm, right leg, and twitching of eyelids for 15 minutes. Bilateral carotid angiogram was done and revealed no abnormalities. He continued having high fever, tachypnea, deep coma and hypotension and expired 36 hours after admission.

Additional information from a relative later revealed that he was a chronic alcoholic, known to have diabetes mellitus for 4–5 years and irregulary took oral hypoglycemic drug. The laboratory findings showed the urine specific gravity of 1012, with four plus sugar but no acetone was tested. The hemoglobin was 10 grams; white cell count was 17,500 with 65 per cent neutrophils and 35 per cent lymphocytes. No malarial parasites were found in the blood films. The urea nitrogen was 35 mg, blood sugar, 1,500 mg and serum albumin, 4.7 gm. per 100 ml. The sodium was 121 and potassium, 6.7 milliequiv. per liter. The autopsy findings showed no apparent cause of coma or convulsion. The changes in the brain were compatible with severe anoxia.

Dicussion:

After the first discription of hyperglycemic nonketotic coma by Sament and Schwartz in 1957 [24] Danowski and Nabarro[4] reviewed 32 cases. (1959). Since then additional cases have been reported by Maccario et al.[17] (1965), Dibenadetto et al.[6] (1965), Schwartz and Apfelbaum[25], Halmos et al.[11] (1966), Jackson and Forman[13] (1956).

It has also been found in association with pancreatitis,[5, 11] pancreatic carcinoma,[13] following peritoneal

and hemodialysis,[3, 19] severe burns,[1,22] administration of glucocorticoid,[2,16,20,26] large dose of dilantin[9] and administration of small amount of intravenous glucose during hypothermia.[28]

The onset of the disease may vary from several weeks to one day. Diabetes is sometimes undiagnosed until coma occurs. The predominent symptoms are polyuria, polydipsia, profound dehydration, mental confusion, precoma and coma. Various neurological manifestations have been reported, including both generalized and focal seizures, aphasia, hemiparesis hemianopsia, hyporeflexia, stiffneck and extensor plantar response.[17]

Blood sugar levels are almost always over 500, commonly between 1,000–2,000 mg. per 100 ml. Serum sodium, potassium and chloride are usually high or normal but occasionally they may be low[24] Carbon dioxide combining power is often normal but sometimes low. A mild degree of ketonemia is frequently found. Severe acidosis occure only in patients with coexistent lactic acid acidosis, probably resulting from hypotension and circulatory collapse.

Hyperosmolarity, common characteristic of this syndrome, is secondary to hyperglycemia or hypernatremia or both.

The pathogenesis of this syndrome has not been well defined. The absence of ketoacidosis indicates the existence of endogenous insulin activity, enough to inhibit lipolysis. The greater occurence of this syndrome in maturity rather than growth onset diabetes supports this theory, the former has elevated or normal insulin level[29].

During progressive hyperglycemia, increasing glycosuria will produce osmotic diuresis, thus resulting in greater loss of water than sodium, severe dehydration, hypernatremia, hyperosmolarity, and cellular dehydration. Cellular dehydration of the central nervous system is the most likely cause of neurological manifestations[17]. Severe dehydration, hemoconcentration and hypotension may predispose to intravascular clotting and produce arterial or venous thrombsois.[12] Heparinization may be useful in the initial treatment of such cases.

There was no correlation between the blood sugar concentration and the symptoms of the patient. Hyperosmolarity, dehydration and altered hemodynamic are better tolerated by young patients without significant vascular disease than by the older ones.

The mortality rate has been reported to be as high as 44 per cent by Di Benedetto[6]. Prompt diagnosis and treatment may improve the prognosis

Initial fluid therapy is still controversial. Many authors prefer hypotonic saline.[18, 25] While others.

use isotonic glucose[11] or isotonic saline.[10, 23] Those who suggested using isotonic glucose realized that 10 millicquiv. of sodium has an equivalent osmotic activity of 360 grams of glucose. Isotonic saline probably causes higher serum osmolarity, which may be harmful to the patient.

Those who were against initially using isotonic glucose feel that, since this syndrome already has severe hyperglycemia, additonal glucose would produce more hyperglycemis and excessive glycosuria, and more water loss and profound hypotension might develope before insulin, which was given initially, could exert its action.

Those who use isotonic saline in early treatment do so because they fear hemolysis from hypotonic solution. To avoid great hypotonicity, treatment has been suggested recently by Johnson, et al.[14], using a mixture of 0.45 per cent saline and 2.5 per cent fructose until blood sugar[19] below 300 mg. per 100 ml. when 5 percent glucose is used. (But mixture of 0.45 percent saline and 2.5 per cent glucos probably have the same effect).

Patients with this syndrome are considered to be more insulin sensitive than those with diabetic ketoacidosis. However, there is still a great variation in insulin requirment, ranging from no insulin up to 4,600 units.[13]

This syndrome differs from diabetic ketoacidosis in the following ways Clinically, it occurs mostly in mature noninsulin dependent diabetics. There is no Kussmaul respiration but focal seizures or other neurological symptoms are often present. Chemically, it can be differentiated by the lack of acidosis, ketonemia and marked hyperosmolarity. Therapeutically, it requires larger fluid replacement and much less insulin administration.

Summary :

Three cases of hyperosmolar hyperglycemic coma have been reported. Two of them had localizing neurological symptoms, which were diagnosed initially as hypoglycemic convulsion and cerebrovascular accidents. Unawareness of this syndrome and delay treatment probably were the cause of death in these two patients. Pathogenesis and treatment were briefly diecussed.

Reference

1. Bailey, B.N. : Hyperglycemia in burns. Brit. Med. J. 2 : 1783; 1960.

2. Boyer, M.H. : Hyperosmolarity in association with glucocrticoid therapy. JAMA. 202 : 1007; 1967.

3. Boyer, J., Gill, G.N., and Epstein, F.H. : Hyperglycemia and hyperosmolarity complicating peritoneal dislysis. Ann. Int. Med. 67 : 568; 1947.

4. Danowski, T.S. and Nabarro, J.D.N. : Hyperglycemic nonketotic

coma ; a review of 32 cases. Diabetes 14 : 162; 1965.

5. Davidson, A.I.G. : Diabetic coma without ketoacidosis in a patient with acute pancreatitis. Brit. Med. J. 1 : 356; 1964.

6. Di Benedetto, R.J. Crocco, J.A. and Soscia, J.L. Hyperglycemic nonketotic coma. Arch. Int. Med. 116 : 75 ; 1965.

7. Ehrlich, R.M. and Bain, H.W. : Hyperglycemia and hyperosmolarity in an eighteen month old child. New. England J. Med. 276 : 683; 1967.

8. Feagin, O.T. : Hyperosmolar coma in diabetes. Lancet 2 : 51; 1966.

9. Goldberg, E.M., Shafeek, S. and Sanbar, F. : Hyperglycemia nonketotic coma Following Administration of Dilantin. Diabetes 18 : 101; 1965.

10. Haapenen E. : Hyperomolar coma in diabetes. Lancet 1 : 1154; 1966.

11. Halmos, P.B. : Hyperosmolar nonketotic diabetic coma in patient with necrotizing pancreatitis. Bri. Med. J. 2 685; 1966.

12. Halmos, P.B., Nelson, J.K., and Lowry, R.C. : Hyperosmolar nonketotic coma in diabetes. Lancet 1 : 675; 1966.

13. Jackson, W.P, and Forman, R. : Hyperosmolar nonketotic diabetic coma. Diabetes 15 : 714: 1966.

14. Johnson, M.D , Conn, J.W., Dykman C.J.; Pek, S., and Starr, J.C. : Diabetes 18 : 111. 1965.

15. Kolodny, H.D., and Sherman C. : Hyperglycemic nonketotic coma in insulin dependent diabetic mellitus. JAMA 203 : 461; 1968.

16. Kumur, R.S. : Hyperosmolar nonketotic coma. Lancet 1 : 48; 1968.

17. Maccaric, M. and Messis, C.P., Focal seizures as the manifestation of hyperglycemia without ketoacidosis. Neurology 15 : 195; 1965.

18. Matz, R. and Drapkin, A. : Hyperosmolar coma. Lancet 1 : 1101; 1966.

19. Potter, D.J. : Death as a result of hyperglycemia without ketosis a complication of hemodialysis. Ann. Int. Med. 64 : 399; 1966.

20. Pyo "ra" la, K., Suhoven O. and Pentikacnar, P. : Steroid therapy and hyperosmolar nonketotic coma. Lancet 1 : 596; 1968.

21. Rosen, H., and Glick M.C. : Hyperosmolar coma in diabetes. Lancet. 1 : 1101; 1966.

22. 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 patiets convalescing from burns, New, England J. Med. 272 : 931; 1965.

23. Sament. S. : Hyperosmolar coma in diabetes. Lancent 1 : 1153; 1066.

24. Sament, S., and Schwartz, M.B. : Severe diabetic stupor without ketosis. South Africa Med. J. 31 : 893; 1957.

25. Schwartz, T.B, and Apfebaum : Nodketotic Diabetic coma, Year book of Endocrinology, (1965–1966) pp. 1195.

26. Spenncy, A.J.G., Eure, G.A. : and Kreisberg, R.A. : Hyperglycemic, Nonketoacidotic Diabetes. A Complication of Steroid and Immunosuppressive Therapy. Diabetes 18 : 107; 1969.

27. Umber–Berlin, F : Stoffwechselkrankheiten. II Der Diabetes mellitus. Munchen, Med. Wschr. 17 : 1324; 1924.

28. Wright. H.K., and Gaun, D.S. : Hyperglycemia hyponatremia in nondiabetic patients. Arch, Int. Med. 112 : 334; 1963.

29. Yalow, R.S., Glick, S.M., and Berson; S.A. Plasma insulin and growth hormone levels in obesity and diabetes. Ann. New York Acad. Sci 131 : 357; 1965.