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Editorial

Hyperosmolar Coma

DURING the past dozen years nearly a hundred patients with a syndrome of coma associated with extreme hyperglycemia, with little or no acidosis or ketosis, have been reported. The great majority have had diabetes mellitus of the adult onset type. Although stupor has frequently been the initial manifestation of the diabetes, many patients have had acute illnesses or procedures at the time of or preceding the coma. The illnesses have been various but most characteristically have been severe infections, extensive burns, or problems involving the pancreas, usually pancreatitis or carcinoma.

In most of the cases reported the syndrome developed while the patients were under the care of a physician. Our failure to recognize the syndrome earlier in the history of diabetes mellitus may be related to a real paucity of such problems antecedent to our present day glibness in the administration of intravenous fluids, glucocorticoids and performance of peritoneal dialysis, hypothermia and extensive surgical procedures. Each of these has been associated with the development of this complication of diabetes.

A few words about the clinical character of the syndrome may allow us to understand its pathogenesis and thus to avoid precipitating the problem. Alarming symptoms may be preceded by a period of polyuria, severe thirst and gradually developing impairment of consciousness. Frequently these symptoms are overshadowed by those of an associated illness. As the process progresses, dramatic symptoms supervene which fall into two categories, hypovolemic and neurologic. Dehydration with volume depletion is universal and, not infrequently, shock and hypotension dominate the picture. In other patients the first serious symptom is the onset of convulsions. Many of these are focal, at least initially, but may progress to grand mal seizures with postictal depression. The preceding seizures complicate evaluation of the cause of the coma and of residual neurologic deficits. The physician may be misled into thinking he is dealing with a primary neurologic problem. Although hyperglycemia may follow acute central nervous system trauma (picûre diabetes), marked hyperglycemia in such circumstances is unusual even in the patient who is known to have diabetes. Actually there is no reason to believe that hyperosmolar coma might not be precipitated by a neurologic disaster. But if it were, the crisis of the metabolic disorder would have to take precedence because it threatens life acutely.

The most effective tool for recognition of hyperosmolar coma is the blood sugar determination. Not only are coma, seizures or neurologic deficit resulting from hypoglycemia thus excluded but also the finding of extreme hyperglycemia is in itself characteristic. Most of the patients with hyperosmolar coma have had blood sugar values between 600 and 3,000 mg. per 100 ml., levels infrequently observed even in diabetic ketoacidosis and essentially diagnostic of the syndrome. Ketosis is absent or mild, even as reflected in the extremely sensitive urinary nitroprusside test. None of the patients with hyperosmolar coma has had a positive serum

reaction for ketone bodies. Hypernatremia, hyperpotassemia and azotemia are usual but variable. The combination of marked hyperglycemia with total body water deficit results in extreme hyperosmolality.

When hypotension, oliguria, stupor or convulsion have developed the syndrome should be considered a medical emergency. Death has ensued in more than half of the patients in whom these features were observed. The reason for its malignancy is not superficially apparent. Two factors may make the main contributions. The first is the self-perpetuating character of the metabolic abnormalities. The second is inappropriate management because of failure to recognize the cause of the symptoms or lack of appreciation of the danger to life which it represents.

The progression to such extreme degrees of hyperglycemia, dehydration and hyperosmolality may be contributed to by a number of phenomena. In the presence of severe insulin deficiency (juvenile diabetes) ketosis usually develops and so dominates the picture of diabetic ketoacidosis that the hyperglycemia does not become as severe as in the patient with hyperosmolar coma. However, hyperosmolality may contribute to neurologic deficits in some patients with ketoacidosis also. The patient with hyperosmolar coma is protected from ketosis by a number of processes. The capability of a limited secretion of insulin may be a major factor. Glucocorticoid therapy, acute stressful illness, administration of large amounts of carbohydrate may not only contribute to hyperglycemia but also may protect against ketosis.

As the hyperglycemia becomes progressively more severe an osmolar diuresis results and increases. Because of the large osmolar load of glucose and loss of concentrating ability of the kidney in the face of such an osmolar load, water is lost in excess of electrolytes and urea, thus contributing to the hyperosmolality. As volume is depleted and renal blood flow impaired these problems are exaggerated. Thus, once the hyperosmolality reaches a certain level the process is self-perpetuating.

The mechanism of the coma and neurologic deficit is not entirely clear. Although hypovolemic shock with reduced blood flow is frequently present, the central nervous system manifestations are not those usually associated with hypovolemic shock. It seems probable that the hyperosmolality itself is a major factor contributing to the coma. With rising extracellular and intracellular osmolality it is easy to imagine that mechanical and biochemical disruption of cellular function might result. On the other hand such speculations cannot easily be confirmed. Among the recorded cases of the syndrome the correlation between absolute or estimated osmolality and the severity of the neurologic manifestations was not very good.

A rough estimation of osmolality (mEq. per L.) can be made as follows:

$$2[Na^+ + K^+] + \frac{\text{blood glucose (mg. per 100 ml.)}}{18} + \frac{\text{BUN (mg. per 100 ml.)}}{1.4}$$

In hyperosmolar coma the values are extraordinarily high, levels not commonly encountered in other circumstances. In diabetes insipidus, extreme hypernatremia may result in increased osmolality without the development of severe central nervous system symptoms. In these patients the hyperosmolality appears to develop gradually rather than acutely. Acute traumatic diabetes insipidus or acute thirsting also results in shock and stupor as well as hyperosmolality. Thus it may be that the rate at which hyperosmolality develops is at least as important as its degree in the induction of central nervous system symptoms.

The need for proper management of the syndrome is urgent and treatment must be planned carefully. The primary cause of the difficulty is hyperglycemia. Insulin is the most important need. Various doses have been used. Sometimes an amount only moderately above the patient's usual requirement has been effective in lowering the blood glucose level rapidly. Not all these patients appear to share the severe insulin resistance which frequently characterizes ketoacidosis. On the other hand sizeable doses of insulin have been relatively ineffective in a few patients. Just as in ketoacidosis there is no substitute for careful monitoring of the patient's response, both clinically and in terms of blood glucose level, to an initial insulin dose in determining the ensuing requirement. Fluid replacement is also critical in the treatment of the shock and hypovolemia. Several attempts have been made to use hypotonic solutions for replacement. If the patient is not too seriously ill or nauseated, fluids taken orally, particularly water, and insulin adminis-

tration may be all that are required. If the parenteral administration of fluids is required, solutions must have an osmolality of about 150 mEq. per L. if hemolysis of red blood cells is to be avoided. As an initial fluid 0.45 per cent sodium chloride without glucose seems to be the most judicious choice. In a number of instances this has resulted in prompt improvement in mental status as well as relief of hyperosmolality. Isotonic fluids may be needed before hypotonic saline solution can be obtained to relieve hypovolemic shock. They should not be given in excess of the required amount because in the presence of continuing hyperglycemia they tend to exaggerate the hyperosmolality by worsening the osmolar diuresis. Onset of deepening coma, seizures and death have been observed after such therapy. Total fluid deficits of 6 to 8 L. are not unusual but can be repaired after fluids can be taken orally and hyperglycemia is controlled. Initial intravenous therapy should be aimed at relief of shock and symptoms resulting from hyperosmolality *per se.*

Hyperpotassemia is usual as the patients are initially observed but just as in ketoacidosis some degree of total body potassium deficit is often present. A watch for development of hypopotassemia should be kept. Acidosis from lactate accumulation may be present but is usually not severe, although this additional but independent and unusual cause of coma in diabetic patients must be kept in mind.

Utmost care should be taken not to induce or contribute to the development of this frequently fatal syndrome in diabetic patients. Awareness of its characteristics and apparent pathogenesis will help both in its recognition and prevention.

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