Hyperglycaemic, hyperosmolar, nonketotic coma

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Introduction

As mentioned in the previous article, the 'diabetic -related' comas listed in order of their probable frequency are

1 hypoglycaemia coma
2 diabetic ketoacidosis
3 hyperglycaemic hyperosmolar non-ketotic coma; and
4 lactic acidosis

A combination of disorders may be often seen, and it must also be appreciated that ketoacidosis can be met with in alcoholic individuals who are not necessarily diabetic, which alcoholic ketoacidosis might also be complicated by hypoglycaemia.

It must be remembered that a great variety of diseases that could induce coma can be present in diabetics as well as in non-diabetics, and hence one must avoid the pitfall of always equating a coma problem in a diabetic with one of the so-called 'diabetes-related' comas.

Among the commoner possibilities of coma-inducing conditions one finds alcohol, epilepsy, insulin (too much or too little), opium and narcotics, uraemia, trauma (head...), infections of the C.N.S., C.V.A., and shock.

In view of the relatively high incidence of type II diabetics in Malta, it could well be that a not insignificant number of hyperglycaemic hyperosmolar non-ketotic coma cases (especially in older persons) might be occassionally missed, diagnosed late or mis-diagnosed — this creating a potentially serious state, especially in view of the high frequency of both complications (including thrombosis) and mortality in this condition, especially in the elderly.

The following is an account of this important condition based on works by Arieff, Podolsky, Kozak and Rolla.

This is a life-threatening emergency with an extremely high mortality rate. It is a clinical syndrome with four major features:

(a) severe hyperglycaemia (blood glucose> 600mg/dl))
(b) lack of significant ketoacidosis (plasma Acetest <2 at 1:1 dilution)
(c) extreme hypertonic dehydration
(d) variable neurological signs - such as depressed sensorium or frank coma

Non-ketotic hyperosmolar coma with hyperglycaemia

Non-ketotic coma has been reported to occur in association with a wide variety of clinical situations, including: pancreatitis, severe infections, pulmonary embolism, burns,, myocardial infarction, dialysis (peritoneal &/or haemo-), hyperalimentation, hyper-thyrodism and chronic renal failure. In addition, different drugs, including thiazide diuretics, frusemide, propranolol, cimetidine, chlorpromazine, diphenylhydantoin, steroids and diazoxide and immuno suppressive agents have also been implicated.

The common denominator of all appears to be either (a) a decrease in insulin effect possibly via drugs or hormones that either antagonise insulin or interfere with insulin action and/or release and/or (b) excessive carbohydrate administration to a 'stressed' patient. The marked hyperglycaemia causes metabolic derangements leading to increasing loss of sodium salts and particularly water, in the urine. This, together with hyperglycaemia, increases extracellular hyperosmolality with consequent increasing thirst. Drinking water freely could for a while moderate the hyperosmolality, however when plasma osmolality reaches high levels, impairment of sensorium develops. This, eventually causes interference with the patient's ability to replenish water losses, and leads to a fall in glomerular filtration rate, azotemia and hyperglycaemia with further elevation of plasma osmolality, and rapid deterioration of mental function from somnolence to coma.

"The seriousness of the problem may not be apparent because of the relative paucity of symptoms. Thus, in contrast to patients with ketoacidosis, whose symptoms usually bring them to medical attention within a short period of time, patients with non-ketotic coma may exhibit a protracted course lasting several days to several weeks."

Non-ketotic coma occurs most frequently in elderly type II patients who have impaired pancreatic beta cell activity and who may be known to have mild diabetes. These patients could also often have an impairment in the ability of the liver to synthesise ketones from free fatty acid substrate, somewhat low

levels of growth hormone and cortisol, and frequently moderate to severe underlying cardiovascular or renal function impairment (this azotemia possibly playing a part in the development of oliguria that often ensues during therapy). In most patients there is a stressful event, such as a major illness. This syndrome also often develops insidiously in patients without previously diagnosed diabetes. Slightly more women than men are affected.

The typical patient is brought to hospital in a confusional (or comatose) state with a history of days or even weeks of polyuria and increasing thirst. Physical examination reveals a striking and profound dehydration, shallow respiration (and hyperventilation), but no odour of acetone in the breath. These patients often present with a variety of neurological signs including seizures, hemiparesis etc. suggesting diffuse cortical and subcortical damage. Not infrequently a cerebrovascular accident is suspected. Most of the localizing, neurological signs are completely reversed with successful treatment (involving mainly the correction of the dehydration and hyperglycaemia). There is a direct relationship between serum osmolality and impairment of consciousness, and comatose patients with hyperglycaemic, hyperosmolar non-ketotic coma most fequently have a serum osmolality above 340mOsm/kg.

(Plasma (serum) osmolality can be calculated from the following formula:

$$\text{mOsm/l} = 2(Na^{+}+K^{+}) + \frac{\text{blood glucose}}{18} + \frac{\text{Bld. urea Nitrogen}}{2.8}$$

normal plasma osmolality ranges from 285 to 300 mOsm/l).

Treatment

Some controversies exist as to the treatment recommended in hyperglycaemic, hyperosmolar non-ketotic coma. Irrespective of the exact amounts and types of insulin and fluids given, the key to recovery lies in the careful monitoring of these patients.

Therapy is directed towards

(a) correction of the extreme degree of volume depletion.
(b) correction of the hyperosmolar state.
(c) detection and correction of any underlying precipitating cuase, such as associated illness or drug administration.

Fluids

Various types of intravenous fluids have been advocated as the appropriate type of initial fluid therapy, but it now seems that $^1/_2$ Normal (0.45%) Saline is the fluid of choice. After confirmation of the diagnosis, circa 2 litres of hypotonic saline should be infused very rapidly i.e. within the first 2 hours. Some authorities however advise using 0.9 (rather than 0.45%) saline for this initial, immediate restoration of intravascular volume.

Thereafter infusion of hypotonic (0.45%) saline is administered, titrating according to the central venous pressure - on the average an addition 6 to 12 litres of fluid being required during the following 36 hours - (half the estimated water deficit being replaced in the first 12 hours and the remainder in the next 24 hours).

The infusion solution should be charged to 5% dextrose in water (or in half normal saline) when the blood glucose has fallen to 250mg/dl. — potassium supplements are often needed, and should be added if required, once the patient has an adequate urine output. Addition of at least 20 to 40 mEq of potassium chloride to each litre of parenteral fluid should be accomplished early — this is stopped if serum potassium levels rise above 5.0 mEq/l, or doubled if levels fall below 4.0 mEq/l. Since these patients often also have phosphate deficits, potassium phosphate 5 mM/l can be infused instead of potassium chloride.

Determinations of blood glucose, serum electrolytes, blood urea nitrogen and plasma osmolality at frequent (4-6 hrly) intervals will assist careful monitoring of the patient's response to treatment.

If hypotension or tachycardia is present, isotonic saline should be infused until the CVP begins to rise. Blood or plasma is indicated if the systolic blood pressure remains low (i.e. below 80 mm Hg.)

Insulin

Various regimens for insulin therapy have been recommended, the commoner being regular (short-acting) insulin administered in continuous i.v. infusion or i.m. similar to those used in D.K.A. The insulin needs in HNC are in general usually *less* than in D.K.A., however on certain occassions large amounts of insulin, similar to D.K.A. are necessary. Close monitoring of the patient and the blood glucose levels is essential.

It is recommended to start with a 'loading' dose of circa 20 units i.v., followed by 5 units i.m. per hour, until blood glucose levels drop to 300 mg/dl, when no additional insulin should be given. If this low dose method is used and the blood glucose does not respond adequately, the amount of insulin should be increased accordingly, (eg. doubling the dose). It cannot be overemphasized that adjusting the therapeutic regimen to the needs of the individual patient, with meticulous clinical care, the vigorous replacement of fluid and potassium and the correction of precipitating factors or associated illnesses are just as important as the details of insulin therapy. Finally, because of the propensity of these patients to develop arterial and venous thromboses, consideration should be given to early use of heparin therapy.

After recovery from the acute episode, the patient is transferred to a daily subcutaneous dose of Lente or NPH insulin, and many of these patients can be then gradually changed over to sulphonylurea therapy at, or after discharge from hospital.