TREATMENT OF HYPOPITUITARY COMA

BY

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Any patient with severe hypopituitarism is liable to have episodes of a particular type of coma. She may recover from the first few attacks, but ultimately one of them proves fatal. A detailed description of this coma has already been given (Sheehan and Summers, 1949), and only the main aspects need be summarized here. To save space, the recent literature will not be analysed in the present paper.

The coma does not usually develop until the hypopituitarism has been present for several years, though occasionally it has been reported as occurring within a few weeks after the destruction of the gland. In many cases it follows some minor infection, or attacks of vomiting and diarrhoea, or some surgical operation. The patient gradually becomes drowsy, and, within a day or so, stuporous. She then passes into deep coma, which is sometimes preceded by one or two convulsions. During the stage of coma she may lie in a rigid, curled-up position and resist interference, or she may be flaccid and unresponsive to stimuli. In many cases there is no pulse at the wrist, and the heart sounds are almost inaudible. The nose and extremities are cold to the touch, the face is pale, and there is no sweating. Occasional cases have pyrexia. Ketonuria is common.

The exact cause of the coma is unknown. Despite the relative uniformity of the clinical picture, there may be several different types of functional disturbance. Some of the patients are in severe hypoglycaemia, with blood sugars of 15 to 30 mg. per 100 ml.; others have blood sugars in the range of 50 to 70 mg., which is a common level in uncomplicated hypopituitarism. Some patients have normal blood electrolytes; a few have a large reduction in sodium and chloride levels. The functional disturbance in these latter cases can be interpreted either as evidence of acute adrenal insufficiency or merely as the result of the preceding attack of vomiting and diarrhoea. A third group of patients have pronounced hypothermia and bradycardia, and their condition is in many ways analogous to hibernation.

The degree of hypothermia can easily be overlooked in routine hospital practice where the temperature is taken with a clinical thermometer. The mercury column has rarely been shaken down below the lowest graduation, and, when the thermometer has not "registered," the patient is recorded by the staff as having merely a low normal temperature. The significance of this point was emphasized by two recent observations on patients with myxoedema (not hypopituitarism) who were admitted in coma to the hospital. They were reported to have normal temperatures as observed with a clinical thermometer. The rectal temperature was then taken by a thermometer from a bacteriological incubator, and was found to be 77° F. (25° C.) in one case and 83° F. (28.3° C.) in the other.

It is not easy to assess the value of treatment of hypopituitary coma, because if the patients are left without treatment some of them recover from the coma spontaneously and some die. Thus the only indications of the efficacy of any particular treatment are the rapidity of the clinical response and the proportion of patients treated in this way who do show a rapid response. At present there is little or no information about the real effect of each line of treatment, and the opportunities of obtaining this information are not frequent. The usual method of treatment in cases erported in the literature has been to give a stock combination of all therapeutic agents which might theoretically be of use. Our plan was to give each patient a single line of treatment, and then to leave her for a few hours so that any response could be observed. In the cases in which no improvement resulted, a second line of treatment was tried. Clearly this method would not reveal synergistic effects of different treatments, but such synergy is quite hypothetical.

Present Observations

Nine examples of hypopituitary coma have been studied in eight patients during the past four years. All the patients had the typical syndrome of severe hypopituitarism due to post-partum necrosis of the anterior lobe. The duration of the illness was from 6 to 21 years. In all the cases the clinical diagnosis was made before any treatment was given for the coma. Two of the patients died, and the clinical diagnosis was confirmed pathologically. These patients were usually admitted as emergencies at times when full laboratory facilities were not available, so that treatment had in most cases to be begun without prior information of any biochemical disturbance which might be present.

The methods investigated in these patients were: (1) no therapy; (2) the administration of large doses of glucose, to treat any possible hypoglycaemia; (3) the administration of cortisone, with the object of correcting a possible acute deficiency of corticosteroid hormones; (4) the administration of sodium chloride and deoxycortone, in order to correct disturbances of electrolyte metabolism; and (5) direct treatment of the hypothermia.

Cases Having No Therapy

Two of the patients who were not very deeply comatose were left without any specific therapy but under careful observation. With rest in a warmed bed they gradually recovered in the course of two to three days. The possibility that the warmth may have contributed to their recovery must be seriously considered in view of the results obtained by active treatment of hypothermia.

Glucose

In one patient, in whom a severe hypoglycaemic coma had been produced by insulin, the intravenous administration of 100 ml. of 25% glucose solution produced a dramatic and complete recovery within a few minutes. This is a special case, but the literature contains several reports of patients with hypopituitarism who spontaneously developed coma associated with severe hypoglycaemia, and whose coma responded equally rapidly to intravenous glucose.

Four patients with spontaneous coma were given 1 to 2 litres of 10% glucose solution intravenously in the course of two hours. Two of these showed some improvement within a few minutes. Instead of lying flaccid they began to make spontaneous movements and resisted interference; when attempts were made to rouse them they became noisy but incoherent. With continued administration of glucose during the next two days both patients gradually returned to full consciousness. One of these patients had a blood sugar of 70 mg. per 100 ml. before the administration of the glucose; the blood sugar in the other patient is not known. In contrast to these beneficial results, two other patients were given intravenous glucose in similar large doses, but the coma remained quite unaffected. One of these had been under observation for two days before she

became comatose. During that period she had been given very large amounts of glucose, so that she had a blood sugar of 110 mg. per 100 ml. at the time the coma developed. The initial blood sugar of the other patient was not ascertained.

When any patient with hypopituitarism has been given a large amount of intravenous glucose she is liable to become seriously hypoglycaemic within a few hours after stopping the treatment. It is therefore important, in cases of coma treated with intravenous glucose, to continue this treatment for a couple of days and subsequently to keep a careful watch on the blood-sugar level.

Cortisone

As it is sometimes considered that the coma is due to a deficiency of the adrenal hormones which control glucose metabolism, two of the patients were given large doses of cortisone intravenously. The preparation used was the standard suspension of cortisone acetate in saline "for intramuscular injection only." It contains some unknown suspending agent and 1.5% of benzyl alcohol. The intravenous administration of particulate suspensions has well-known dangers, but the circulatory state of the patients was so poor that rapid absorption from an intramuscular injection could not be expected. The suspension was therefore given by an intravenous needle, and followed by about 50 ml. of glucose–saline in order to carry the hormone from the arm to the right side of the heart. The amount of suspension given in each injection was 5 ml., with a content of 125 mg. of cortisone acetate. This was repeated at half-hourly intervals; in one case the total dose was 375 mg. and in the other case 750 mg. There was no recognizable effect, either good or bad, on the coma or on the general clinical condition. One of the patients subsequently recovered after the use of a different treatment; the other remained in coma and died 24 hours later. At necropsy there were no lesions, such as thrombosis in small pulmonary vessels, to indicate that the intravenous injection of the particulate suspension had in fact had any harmful effect.

As yet there is no information to indicate whether cortisone would have any prophylactic effect if given during the few days before the onset of coma.

Testosterone

As testosterone is of considerable value in the treatment of uncomplicated hypopituitarism, the question arises whether it would be of any use in the treatment of coma. This particular application has not yet been studied. Testosterone does not seem, however, to have any prophylactic effect. One of the present patients had received intramuscular injections of 100 mg. of testosterone propionate once a week for five weeks before the onset of coma, the last dose being given 36 hours before the coma began.

Saline and Deoxycortone Acetate

One patient was given an intravenous injection of one litre of normal saline containing 30 mg. of deoxycortone, without any other treatment for the first three hours after admission in coma to hospital. This did not have any effect on her clinical condition, but she responded subsequently to intravenous glucose.

Another patient, who was in fact developing a hypothermic coma, had been given 30 mg. of deoxycortone daily for three days before the onset of the coma. There was no apparent prophylactic effect.

Treatment of Hypothermia

A recent case of hypopituitarism admitted in coma was investigated from the aspect of hypothermia. She was of the clinical type which is characterized by much facial oedema and which shows similarities to myxoedema. During the previous few months her general condition had responded to cortisone but not to testosterone. As the clinical thermometer did not register, the rectal temperature was measured with a bacteriological thermometer and was found to be 87° F. (30.5° C.). The mouth temperature was the same. There was no pulse, the heart sounds were almost inaudible, and the heart rate was 41 a minute. Respiration and skin circulation were similarly depressed, and the general picture was in some ways similar to that of the late stage of severe shock.

It was decided to raise the patient's temperature to normal. Any attempt to do this by means of hot-water bottles or electric blankets would probably have produced blistering, in view of the very sluggish skin circulation. The patient was therefore immersed to the chin in a bath of water at a temperature of 93° F. (33.9° C.), and the temperature of the water was gradually raised to 102° F. (38.9° C.) in the course of one and a half hours. During this period the mouth temperature gradually increased and the heart rate became more rapid. When the mouth temperature reached 95° F. (35° C.) and the heart rate 65 a minute the pulse returned at the wrist and the colour of the face became less ashen. When the mouth temperature reached 97° F. (36.1° C.) and the pulse rate 75 the patient began to show signs of returning consciousness; she made active movements and muttered incoherently. When the temperature reached 98.6° F. (37° C.) and the pulse rate 92 she had returned to full consciousness and spoke short coherent sentences. Her physical condition at this time appeared good. She was dried quickly and returned to a warm bed, where she fell asleep. During the next few days her temperature remained at levels of 97 to 98° F. (36.1 to 36.7° C.) without any artificial aids such as hot-water bottles. She remained mentally rather dull for two days, but then began to respond satisfactorily to the short course of cortisone therapy which was instituted.

On a subsequent occasion this patient was readmitted to hospital in an almost identical hypothermic coma, with a rectal temperature of 89° F. (31.6° C.). The same treatment was given, and she was fully conscious again within two hours.

Summary

The coma which complicates, and often terminates, hypopituitarism is associated sometimes with hypoglycaemia, sometimes with low plasma sodium and chloride, and sometimes with a severe degree of hypothermia which may not be recognized. In theory the treatment should be varied to suit the particular functional disturbance, but in practice it has usually to be begun on an empirical basis before the results of biochemical investigations are available.

Intravenous glucose seems to be of moderate value in some cases, even with normal blood-sugar levels.

A patient with very low temperature recovered rapidly and dramatically from the coma when her temperature was raised to normal by means of a warm bath. This treatment was employed successfully in a subsequent attack of coma. It seems to hold promise in cases with hypothermia.

Intravenous administration of cortisone, and of saline solution with deoxycortone, produced no recognizable improvement in the few cases in which they were tried.

In individual cases no prophylactic value was observed from testosterone given during five weeks before the onset of the coma, deoxycortone for three days, and large quantities of glucose for two days.

The present conclusions are based on a small number of cases, and can therefore only be tentative.

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REFERENCE

Sheehan, H. L., and Summers, V. K. (1949). *Quart. J. Med.*, **18**, 319.