HYPOTHERMIA—A DIAGNOSTIC AID TO HYPOGLYCAEMIA

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The manifestations of hypoglycaemia are well known. Depending on the level of the blood sugar, various clinical phases may be exhibited.[1] These phases are not always present but when they occur they may be linked to neuronal function. The sequence of responses is as follows:

1. *Parasympathetic,* consisting of hunger, nausea, eructation and occasionally bradycardia and mild hypotension. This phase is not always present in every patient.
2. *Cortical,* comprising diminished cerebral function which occurs in most patients and is characterized by lethargy, lassitude, frequent yawning, loss of spontaneous conversation and at times inability to do simple calculations or to repeat number sequences.
3. *Sympathetic,* characterized by increase in the systolic blood pressure, the pulse pressure and heart rate,

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and by hyperventilation, profuse sweating, blanching of circumoral area and dilatation of pupils.

4. *Mesencephalic*, in which phase convulsions may occur followed by coma.

In the absence of definite signs and symptoms, or if these are minimal, the diagnosis of hypoglycaemia may be unsuspected. In these circumstances patients may be wrongly diagnosed as having hysteria, neurosis or organic disease of ominous prognosis. Any diagnostic aid is therefore of considerable value. A sign which is seldom emphasized is hypothermia; while not always present, its recognition has helped to detect the presence of a low blood glucose and allow of appropriate therapy.[3] An example of its importance is afforded by the following case which also demonstrated some of the peculiar autonomic responses which may occur in a chronic alcoholic during a hypoglycaemic attack. The possible association between the mechanism of the hypothermia and the autonomic nervous system is also discussed.

CASE REPORT

A 48-year-old African male was admitted to the Edenvale Hospital in a stuporose state. He was sweating and cold. His nutrition was poor and showed tegmentary and other changes seen in chronic alcoholism. Examination was conducted by artificial light and the presence of jaundice was suspected. There was no anaemia, cyanosis or foetor hepatis. Abdominal examination showed the liver to be enlarged 5 fingerbreadths below the costal margin in the mid-clavicular line with a large mass protruding from the anterior surface of the right side There was no splenomegaly. The pulse rate was 48 beats per minute and the blood pressure 124/80 mm.Hg. The oral temperature was 94°F and the respiratory rate 18 per minute. There was no evidence of any endocrine dysfunction and the rest of the examination was unremarkable.

A provisional diagnosis of pre-hepatic coma was made and intravenous therapy with dextrose water was commenced. He was observed 15 minutes later and was noted to be fully lucid, rational and cooperative. He admitted to being a heavy drinker and it was assumed that his symptoms were due to hypoglycaemia which had been induced by alcohol. This association of hypoglycaemia with alcoholism is a not uncommon occurrence observed in our wards.

The patient was advised to remain in hospital to determine the nature of the hepatic enlargement. The investigations revealed a haemoglobin level of 16·3 G/100 ml. and a normal appearance of the red blood cells and platelets. The leucocyte count was 8,000 with a relative neutrophilia and a monocytosis. The indirect bilirubin level was 0·4 mg./100 ml. and total bilirubin 0·8 mg./100 ml. Moderate disturbances in liver function were revealed by a colloidal red test of 4+ positive, a zinc sulphate turbidity of 21·8 units, an alkaline phosphatase level of 25·6 KA units and a cholinesterase value of 55% of the average normal activity. The serum glutamic oxalacetic transaminase was 57 units, serum glutamic pyruvic transaminase 26 units, lactic dehydrogenases 320 units and leucine aminopeptidase 553 units. The urine analysis and serum electrolyte levels were completely normal. Radiological examination of the abdomen revealed no abnormality but the chest radiograph revealed erosion of the second left rib. A provisional diagnosis of carcinoma of the liver with metastatic deposit to the thoracic cage was made but until the prothrombin index had reached a satisfactory level (80%), a liver biopsy was not performed. He was treated with high doses of vitamin K and a high-carbohydrate diet. No other drugs were administered.

While undergoing ward investigation he was occasionally reported to exhibit short episodes of mental confusion, lethargy and lassitude. This was especially prominent in the early mornings but by the time medical aid could be summoned, his signs and symptoms had usually disappeared. On several occasions during periods of disorientation he was violent and once sustained an injury to his mouth. In between attacks he was rational and cooperative and exhibited no neurological signs or other physical abnormalities. His blood pressure was 120/80 mm.Hg and his pulse rate varied between 60 - 70 beats/min.

Three weeks after admission a lumbar puncture was performed shortly after an episode of confusion. This revealed a cerebrospinal fluid sugar content of 34 mg./100 ml. The abnormal states of consciousness were therefore considered to be hypoglycaemic in origin. This was proved one morning when he was found cold and sweating and in a state of stupor. The blood sugar was 50 mg./100 ml. and he responded dramatically to 50% glucose administered intravenously. The hypothermia during this episode was particularly prominent and was recorded as 94°F on the oral thermometer. It rose to 97·8°F 20 minutes after the administration of the glucose. There was little alteration in the pulse rate, which was in the vicinity of 70 beats/min. during and subsequent to the attack.

Review of the temperature chart revealed previous periods of hypothermia in which the oral temperature had been recorded as 94°, 95°, and 96°F and the pulse rates between 60 - 70 beats/min. The respiratory rate was usually 18/min. These periods occurred invariably in the mornings and could in retrospect be correlated with the periods of confusion. Three days later the triad of hypothermia, hypoglycaemia and mental confusion was conclusively demonstrated when in an episode of disorientation the blood sugar was 33 mg./100 ml. and the oral temperature 95·4°F (Table I). Shortly after

TABLE I. CORRELATION OF HYPOGLYCAEMIC AND HYPOTHERMIC ATTACKS

Date	*Pulse*	*Temperature (°F)*	*Blood pressure (mm.Hg)*	*Blood sugar (mg./100 ml.)*	*Sweating*	*Clinical condition*
31/12/64	48	94	124/80	—	Profuse	Mental confusion, lethargic
1/1/65	62	94	—	—	—	Violent
2/1/65	60	95	—	—	—	Confused, dull
24/1/65	70	96	—	34 (CSF)	Moderate	Confused
27/1/65	70	94	120/80	50	Profuse	Confused, restless
2/2/65	68	95·4	115/80	33	Profuse	Confused, aggressive
12/2/65	78	97·2	—	140	Nil	Well orientated, placid
2/3/65	98	97·6	—	112	Nil	No symptoms or complaints
3/3/65	115	98·2	120/82	56	Mild	Lethargic, dull*
6/3/65	116	96	—	—	—	Weak, dull*
9/3/65	96	95	—	—	—	Lethargic*

* = Infection of the urinary tract present.

the intravenous administration of glucose the temperature rose to 97·4°F. During this episode he sweated profusely and the pulse rate and blood pressure were 68 beats/min. and 115/80 mm.Hg respectively.

The attacks of hypoglycaemia were considered to be hepatic in origin. However, hypoglycaemia could also be a manifestation of hypothyroidic or other endocrine dysfunction. Although there was no clinical evidence of endocrine disease, investigation of the endocrine system was nevertheless undertaken. The following were the results obtained from 24-hour urine estimations: 17-ketosteroids 6·0 mg., total 17-hydroxycorticosteroids 6·1 mg. and vanillyl mandelic acid 1·4 mg. The serum protein-bound iodine level was 12·0 μg./100 ml. but since he had been taking a multivitamin preparation which probably contained iodine, the result was not valid. The serum cholesterol level was 70 mg./100 ml. No abnormality in the radiological examination of the pituitary fossa was observed.

The patient was treated with 2-hourly glucose drinks and a liberal supply of glucose foods. Attacks of hypoglycaemia, hypothermia and mental confusion were then experienced only on rare occasions. In order to prevent the hypoglycaemia it was found convenient to regulate the patient by means of the oral temperature. Whenever this was in the vicinity of 96°F, the oral consumption of glucose was increased with excellent response. He felt better and more alert and the temperature rose. Two weeks after intensive glucose therapy the temperature assumed the character of a low-grade pyrexia as is frequently observed in cirrhosis of the liver.[4] Random blood sugar samples estimated during this period were always above 100 mg./100 ml. (Table I).

Four weeks after admission a percutaneous liver biopsy was performed. The report read as follows: 'Sections of the

liver biopsy show the presence of an anaplastic carcinoma in parts having an acinar arrangement. The features could be consistent with a malignant hepatoma but the possibility of a metastatic tumour cannot be entirely excluded.'

The patient gradually deteriorated. Ten weeks after admission a urinary tract infection developed. He was unable to void urine spontaneously and had to be catheterized frequently. He developed a flaccid paralysis of the lower limbs, which, in the absence of a definite cause, was attributed to anterior horn cell destruction following repeated attacks of hypoglycaemia. He became too ill to maintain his oral supply of glucose and although attacks of hypoglycaemia ensued, hypothermia was observed only infrequently. There was also a rise in the pulse rate which was usually in the region of 100 beats or more per minute. This was attributed to the presence of pyrexia which was associated with the urinary tract infection. A blood sample during this period revealed a sugar content of 56 mg./100 ml.; the pulse rate was 115 beats/min., the temperature 98·2°F and the blood pressure 120/80 mm. Hg. He was lethargic when these observations were made and was unable to respond to simple questions. Eleven weeks after admission he suddenly collapsed and died before medical aid could be summoned. Permission for autopsy was refused.

DISCUSSION

The occurrence of hypothermia in profound hypoglycaemia has been described with involvement of the myencephalic area of the brain.[5] This is associated with deep coma, shallow respiration, atonia, bradycardia and meiosis. Loss of consciousness is however not necessarily a feature and the presence of hypothermia has also been noted in moderate or asymptomatic forms of hypoglycaemia.[3] The hypothermia may occur in association with a low blood sugar due to a wide variety of causes.[6]

The skin eliminates heat by conduction, convection, insensible water loss and sweating. Sweating is a prominent manifestation of sympathetic discharge and may have been responsible for the hypothermia in our patient. However, it would appear that the mechanism is more obscure. There are reports of the frequent occurrence of a lowered body temperature without any sign or symptom of hypoglycaemia and with blood sugar levels only moderately decreased.[3] In our patient the absence of tachycardia and systolic hypertension in the presence of profuse sweating is significant. This would suggest that there was an inappropriate response to sympathetic stimulation or an imbalance of the autonomic nervous system.

Experimentally, hypothermia associated with hypoglycaemia has been produced in chronic alcoholics by the intravenous administration of alcohol.[7] Detailed simultaneous monitoring of blood sugar and rectal temperature has shown the drop in temperature to parallel the reduction in blood sugar, although on occasion it may occur after the hypoglycaemia has been induced. During this procedure the pulse rate was not elevated above 90 beats/min. in any subject and in some instances profound reduction in blood sugar was effected without any alteration in cardiac rate. The diastolic and systolic blood pressures were usually lowered. Our patient was also a chronic alcoholic. He displayed many unusual physiological responses not unlike those seen in the above experiments. The patho-physiology has not been elucidated but various suggestions have been advanced.

Autonomic Nervous System

It would appear that the mechanism of the hypothermia may be linked to the autonomic nervous system and is influenced by pharmacological agents which affect its neurohumoral aspect.[10] In the presence of hypoglycaemia and profuse sweating a normal pulse rate occurred. However, in the pyrexial phase a tachycardia supervened as was observed with a blood sugar of 56 mg./100 ml. This would suggest that the hypoglycaemia could be dissociated from the previously normal pulse rate and the hypothermic component by an agent, infection, which influences autonomic mechanisms. Experimentally in alcohol-induced hypoglycaemia, when neuronal transmission was interrupted, a comparable situation was observed: with the subcutaneous administration of atropine the pulse rate rose to levels above 90 beats/min. and the temperature to above 98°F. The hypoglycaemia was maintained.[7]

Systolic hypertension was never observed throughout the course of the patient's illness. Hypothermia therefore was not associated with its occurrence. Similarly published experimental data would suggest that the mechanism of the hypothermia may be dissociated from simultaneous changes in systemic blood pressure.[8]

Localization of Defect

The autonomic nervous system is intimately connected with heat regulation. Many of the physiological responses observed in our case are compatible with a disturbance of autonomic function. A disorder of the hypothalamic heat-regulating centre has been suggested, producing increased heat dissipation through dilated capillaries.[5]

The defective manifestations of sympathetic discharge observed in our case have also been observed in other chronic alcoholics during hypoglycaemia induced by insulin. That this lack of autonomic reactivity was not due to impaired responsiveness of target tissues was shown by the administration of exogenous epinephrine.[7]

The unusual autonomic responses may have been due to impoverished counter-regulatory measures. Alcohol can effect the acute release of catecholamines and serotonin from preformed tissue stores. Repletion of such stores is not immediate and it is possible that mobilizable neurohumors could be compromised by chronic ethanol addiction.[7] In our case the urinary catecholamines were normal, but no facilities were available for the quantitative estimation of serotonin. The possibility that it was depleted cannot be ruled out.

The Endocrine System

There was no endocrinopathy. In view of the normal hydroxycorticoid content of the urine it is unlikely that gluconeogenesis was defective. It would appear that the mechanism need not be abolished by cortisone administered in pharmacological doses.[8] During hypoglycaemia plasma-free fatty acids are usually elevated;[1,8] it is therefore unlikely that decreased calirogenic substrate in the absence of glucose would be responsible for the mechanism.

Spontaneous Hypoglycaemia and Hypothermia

Much has been written about the physiological and metabolic adjustments which occur during hypothermia. In 1941 Talbott suggested that it was possible that some patients develop spontaneous hypoglycaemia and shivering was subsequently inhibited.[11] In 1942 it was stated

that during hypothermia the blood sugar tended to drop, the average being between 80 - 90 mg./100 ml., suggesting a possible resting state of the liver.[12] Studies also indicate that hypoglycaemia develops in prolonged hypothermia at 26°C and is more apt to occur in starved hypothermic animals.[9] However, current concepts of the blood sugar in hypothermia do not regard hypoglycaemia as a prominent metabolic derangement. If the blood sugar does not remain normal, then it is usual for hyperglycaemia to ensue because of decreased glucose metabolism.[13,14]

The hypothermia was not spontaneous. It was not considered to be the prime factor in our patient because of the presence of an obvious cause for the low blood glucose (a probable carcinoma of the liver[15]), and by elevation of the temperature following the administration of glucose. It is postulated that the liberal intake of glucose increased the content of stores previously depleted of this substance by the patient's illness. The blood sugar returned to normal, further attacks of hypoglycaemia were prevented until the terminal phase, and the temperature assumed the character of a low-grade pyrexia.

Not all cases of hypoglycaemia are associated with hypothermia. In the febrile state this relationship was seldom present although attacks of hypoglycaemia were known to occur. Review of records from patients suffering from hypoglycaemia in this hospital has not revealed a constant relationship. That the mercury column had not been shaken down to hypothermic values is a possibility, but other factors, e.g. the rate of development of the hypoglycaemia, the influence of drugs, particularly those affecting the autonomic nervous system, infection, associated illnesses, etc., should also be considered.

Clinically the occurrence of a lowered body temperature as a sign of hypoglycaemia is of paramount importance. It may provide a clue to the diagnosis in the absence of the more familiar signs or in obscure illnesses. Field and Kedes observed the phenomenon in a variety of situations.[3] It was the only sign in a diabetic of a blood sugar less than 25 mg./100 ml. and recognition of its significance avoided a serious threat to life. These authors also reported hypothermia in a case of carcinoma of the liver and in a patient with alcohol-induced hypoglycaemia. The temperature in their cases varied from 95 to 96°F and the blood sugars from 14 to 26 mg./700 ml. No definite explanation for the phenomenon was advanced.

SUMMARY

The importance of the occasional occurrence of hypothermia with hypoglycaemia is stressed. A case illustrating this association is described. The physiological and clinical observations are compared with data published from experiments with alcohol-induced hypoglycaemia in chronic alcoholics. The mechanism of the hypothermia is obscure; there was no endocrine dysfunction and a defective autonomic nervous system is considered. The phenomenon was modified in the presence of infection. Attention is drawn to the importance of the recognition of hypothermia as a valuable bedside sign in cases of hypoglycaemia.

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