

Evaluation of patients admitted with hypoglycaemia to a teaching hospital in Central Anatolia

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Summary

Hypoglycaemia is one of the most common endocrine emergencies in practice. We analysed retrospectively the incidence and causes of hypoglycaemia in patients admitted to Erciyes University Medical School in Turkey between January 1991 and June 1998 because of hypoglycaemia. Charts were reviewed according to multiple variables including age, sex, blood glucose levels, renal and liver functions, diagnoses, symptoms, drugs, complications, sequelae, and survival status. During this period, 13 500 patients were hospitalised and hypoglycaemia was reported in 126 (0.9%) patients. The most common causes were diabetic treatments in 54 cases (42%), endocrine deficiencies in 25 cases (20%), and malignancy in 15 cases (12%), respectively. The leading endocrine deficiency was panhypopituitarism. Sheehan's syndrome was the most common cause of panhypopituitarism (44%). No underlying cause was diagnosed in seven cases. Nine patients died (7%) and neurological sequelae were observed in one patient with diabetes mellitus. We conclude that hypoglycaemia accounts for about 1% of hospital admissions. Although the hypoglycaemia could be attributed to hypoglycaemic agents in the treatment of diabetes mellitus in the majority of cases, Sheehan's syndrome was also found to be an important cause of hypoglycaemia in our hospital.

Keywords: hypoglycaemia; Sheehan's syndrome; endocrine emergency; insulinoma

Hypoglycaemia is defined as the occurrence of a wide variety of symptoms in association with a plasma glucose concentration of 50 mg/dl (2.8 mmol/l) or less.¹ It appears to be a relatively common problem among hospitalised adult patients, with a reported incidence of approximately 1.2%.² It is well known that many drugs, endocrine disorders, malignancies, malnutrition and renal insufficiency can cause hypoglycaemia, however, hypoglycaemic agents used in diabetes mellitus are the most common cause.²⁻⁵ The causes of hypoglycaemia may also depend on the medical facilities in the region, and on the sociocultural and economic status of the population.

A high morbidity and mortality are still associated with hypoglycaemia, and accurate diagnosis and early treatment may improve the prognosis.⁶⁻⁸ We attempted to analyse the incidence and causes of hypoglycaemia in patients admitted to our hospital for this condition.

Patients and methods

This study was carried out between January 1991 and June 1998 in the Department of Internal Medicine of Erciyes University Medical School in Kayseri. The population of the city centre is about 550 000 but the hospital has a 5 million hinterland. Kayseri is a rapidly developing city and its economic status is high. All patients hospitalised because of hypoglycaemia in the Department of Internal Medicine were included in the study. The diagnosis of hypoglycaemia was made either in the Casualty Department or in the Outpatient Clinic. Patients who had hypoglycaemic episodes during hospitalisation were not included in the study.

Patient charts were reviewed according to multiple variables, including age, sex, blood glucose levels, renal and liver function, diagnoses, symptoms, drugs, number of hypoglycaemic episodes, complications, sequelae, and survival status. We defined hypoglycaemia as a serum glucose concentration <50 mg/dl (2.8 mmol/l). In the Casualty Department blood glucose was measured simultaneously by a glucometer in capillary blood and by the glucose oxidase method in venous plasma in the laboratory. In patients seen in Outpatient Clinics, blood glucose was measured only by the glucose oxidase method, which was therefore taken as the reference method. Laboratory analysis of the samples was done in as short a time as possible. Renal insufficiency was defined as a serum creatinine level above 3 mg/dl (265 µmol/l), or a need for long-term dialysis. Liver disease was diagnosed by clinical and biopsy findings, serologic and biochemical analysis, and prolonged prothrombin time. Endocrine deficiencies were diagnosed by the basal levels of hormones and stimulation tests. The diagnosis of Sheehan's syndrome was based on the medical history, physical examination, basal hormone levels, dynamic pituitary tests including thyrotropin-releasing hormone and luteinising hormone-releasing hormone stimulation tests, insulin tolerance test, L-dopa stimulation test, and computed

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tomography (CT) or magnetic resonance imaging (MRI) of the pituitary gland. Plasma insulin and C-peptide levels were measured and a prolonged fasting test was applied for diagnosis of insulinoma. Sepsis was defined by a positive blood culture.

Results

During the study period, 13 500 patients were hospitalised and hypoglycaemia was detected in 126 (0.9%) patients. Of these 126 patients, 76 were female, median age 51 years (range 18–80), and 50 were males, median age 55 years (20–81). Mean glucose levels were 36.0 ± 12.6 mg/dl (2.0 ± 0.7 mmol/l).

The causes of hypoglycaemia are presented in the table. The most common causes were insulin and oral anti-diabetic agents in 54 patients with diabetes mellitus (42%), endocrine dysfunctions in 25 patients (20%), and malignancies in 15 patients (12%), respectively. The leading cause of endocrine deficiency was panhypopituitarism. Multiple episodes of hypoglycaemia occurred in 32 patients, 14 of whom had diabetes mellitus, while seven had insulinoma, three had chronic renal failure and were on insulin therapy, two had Sheehan's syndrome, one had Addison's disease, one had hemangiopericytoma, and four had reactive hypoglycaemia.

All the patients in whom a diagnosis of Sheehan's syndrome was made (11 patients) gave a medical history of postpartum haemorrhage, failure of lactation (except one patient), and amenorrhoea, and CT or MRI of the pituitary gland showed empty sella.

Table Causes of hypoglycaemia in the patients

	Number (%)
Diabetes mellitus	54 (42)
Insulin therapy	32
Sulfonylurea	22
Liver disease	3 (2)
Fulminant hepatitis	2
Cirrhosis	1
Insulinoma	7 (6)
Endocrine deficiencies	25 (20)
Panhypopituitarism	14
Hypophysectomy	3
Sheehan's syndrome	11
Withdrawal of chronic steroid therapy	1
Addison's disease	10
Chronic renal failure	6 (5)
Malignancies	15 (12)
Lymphangioma	1
Gastric carcinoma	1
Hypernephroma	1
Lymphoma	3
Oesophagus carcinoma	1
Cervix carcinoma	1
Leukaemia	2
Nasopharynx carcinoma	1
Rectum carcinoma	1
Gastric lymphoma	1
Hemangiopericytoma	1
Hepatocellular carcinoma	1
Miscellaneous	9 (7)
Malnutrition (anorexia nervosa)	2
Reactive	4
Pregnancy	1
Sepsis	1
Alcohol intoxication	1
Unknown	7 (6)
Total	126 (100)

Nine patients (7%) died. Causes of death were fulminant hepatitis (one case), disseminated intravascular coagulation due to sepsis (six cases), hyperkalaemia due to chronic renal failure (one case), and alcohol intoxication (one case). Neurological sequelae, such as aphasia and paresis, were observed in one patient with diabetes.

Discussion

Hypoglycaemia is one of the most common endocrine emergencies in practice.⁹ Early diagnosis of hypoglycaemia and determination of the underlying cause is necessary for appropriate diagnosis.¹ One study dealt with patients in whom hypoglycaemia developed in hospital.² There are few data on the aetiology of hypoglycaemia in patients admitted with hypoglycaemia.

Hypoglycaemia is most commonly seen in diabetic patients, in whom it is commonly due to overdose of anti-diabetic agents, low calorie intake, malnutrition, excessive exercise, prolonged starving, and development of either renal or hepatic failure.^{3–5, 10} Fischer *et al*² reported that 64 hypoglycaemic episodes were due to low calorie intake and inappropriate insulin therapy in 42 diabetic patients. In 20 of these 42 patients, hypoglycaemia was due to chronic renal failure.² We have found that hypoglycaemia in 54 (42%) patients was due to inappropriate insulin use in 32 patients and to oral anti-diabetic drugs (sulfonylureas) in the remainder. Of the 32 cases who had more than one hypoglycaemic episode, nine cases were due to insulin therapy. These values do not reflect the real frequency of hypoglycaemia among diabetic patients which is much higher; the majority of such cases are treated at home, since the symptoms of hypoglycaemia are well known by the patients and/or their relatives.

It has been reported that 50% of episodes of hypoglycaemia in hospitalised patients are due to chronic renal failure.² Our study showed that hypoglycaemia in six (5%) patients was related to renal failure. Hypoglycaemia in such patients generally develops due to insulin treatment, additional hepatic and renal failure, or dialysis.¹¹ Spontaneous hypoglycaemia in patients with renal failure is related to decreased calorie intake, decreased insulin clearance and gluconeogenesis in kidney, decreased glucose synthesis and the delayed activity of counter-insulin hormone response.¹² The duration of the hypoglycaemia is variable. The episode may be single or recurrent.¹¹ Dialysis also predisposes to hypoglycaemia in uraemia, possibly because of the chronic state of malnutrition.^{2, 9, 11}

Mesenchymal or neuroendocrine tumours, carcinomas, or haematologic malignancies can also cause hypoglycaemia, which may develop due to either overuse of glucose by the tumour, or to impaired release of glucose from the liver. While carcinoid tumours and fibrosarcoma cause hypoglycaemia via hyperinsulinaemia, other tumours such as hepatoma, adrenal carcinoma, or lymphomas, secrete IGF-2. Malnutrition is also an important factor.^{2, 9, 13} We found

malignancy as a cause of hypoglycaemia in 15 patients (12%).

Hypoglycaemia due to endocrine disorders is known to be rare.¹⁴ However, endocrine disorders were the second most common cause of hypoglycaemia in our patients (25 patients, 20%). Hypopituitarism in 14 patients (11 due to Sheehan's syndrome, and three due to another causes), Addison's disease (10 cases), and sudden withdrawal of steroid treatment (one case) were diagnosed as causes of hypoglycaemia. Adrenal failure causes a defect in gluconeogenesis and decreases glycogen stores. Starvation and alcohol intake may cause hypoglycaemia in such patients.¹⁴ Sheehan's syndrome, which is due to postpartum pituitary necrosis caused by severe vaginal bleeding, is extremely rare in developed countries. Toogood and Shalet reported only one case of Sheehan's syndrome among 404 patients with pituitary disorders.¹⁵ There were no patients with Sheehan's syndrome in a Swedish series of 333 patients with pituitary failure.¹⁶ However, it is still an important problem in developing countries.¹⁷ Although obstetrical care and medical facilities have been remarkably improved in central Turkey in recent years, we still see patients with Sheehan's syndrome, not uncommonly because of inadequate medical management in the past. Newly developed Sheehan's syndrome is very rare. Hypoglycaemia was the first finding in some of the patients with Sheehan's syndrome. Our findings have shown Sheehan's syndrome to be the second most common cause of hypoglycaemia after treated diabetes mellitus. The causes of hypoglycaemia clearly differ from one country to another.

Insulinoma was detected in seven patients. This relatively rare disease must be kept in mind in patients who have no overt cause for hypoglycaemia. Solitary adenoma is the most

common cause of insulinoma. Insulinoma may be seen in 9% of patients with multiple endocrine neoplasia-type I.¹⁸ All the patients in the present study had solitary adenomas.

Fischer *et al* observed hypoglycaemia in 18 patients with liver disease.² The liver has great importance for glucose homeostasis. Injuries involving more than 80% of the liver cause hypoglycaemia, due to the loss of enzymes and hormones which synthesize glycogen. The use of alcohol and hypoglycaemic agents also enhances the hypoglycaemic effect.^{2,19} Nouel *et al* reported hypoglycaemia in 50% of patients with cirrhosis and sepsis.¹⁹ We found hypoglycaemia in three patients (2%); in two cases due to fulminant hepatitis and in the other due to liver cirrhosis.

Hypoglycaemia can also be seen in pregnancy, due to low calorie intake, several drugs and additional diseases. In one series, the incidence of hypoglycaemia related to pregnancy was reported to be 9.6%.² In this study, pregnancy was detected in only one patient.

Mortality in hypoglycaemia was reported to change from 4% to 27%.^{2,19} We found a mortality rate of 7%, which is due to the underlying disease rather than hypoglycaemia *per se*. Palsy, behavioural disorders, persistent neurologic sequelae, and psychiatric problems may be seen after hypoglycaemia.^{1,6,20,21} Persistent aphasia and paresis developed in one patient.

In conclusion, we found the frequency of hypoglycaemia to be about 1% in patients who were admitted to our hospital. The most common cause was insulin or oral anti-diabetic therapy in the patients with diabetes mellitus. It is interesting to find that the second most frequent cause of hypoglycaemia was Sheehan's syndrome. It seems that the causes of hypoglycaemia can vary from one country to another.

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