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ORIGINAL ARTICLE

Causes and Clinical Presentation of Hypoglycemia in Patients with Low Blood Glucose Admitted to the Emergency Ward

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Hypoglycemia is a medical emergency with nonspecific symptoms and severe side effects. We determined causes and symptoms of hypoglycemia in patients with low blood glucose admitted to the emergency ward; approaches for the prevention in hypoglycemia and side effects are also proposed.

Materials and Methods: All patients with symptoms of hypoglycemia and blood glucose levels below 45 mg/dL admitted to the emergency ward, between 2002-2003, were included in this survey. Initially a questionnaire on demographic information, coexisting disorders and drug history was completed; physical exam was done and then 10 ml of venous sample were obtained for CBC, liver and renal function tests; if indicated, hormonal assay and 72 hour fasting test were done.

Results: Eighty-nine patients with mean age of 66.73 ± 14.91 years were included; 53% female and 47% male (P= NS). 86.5% were diabetic and 13.5% nondiabetic (P< 0.001). Common causes of hypoglycemia were: drugs (36.3%), renal failure (23%), sepsis (14.3%) and medical mismanagement (11%). The most common symptoms in diabetic and nondiabetic patients were adrenergic + neurglycopenic 50.6% and 58.3% , neurglycopenic 46.8% and 41.7% , and adrenergic 2.6% and 0% respectively (P=NS).

Conclusion: Drugs were the most common cause of hypoglycemia, although medical mismanagement was observed in 11% of patients. Education not only for patients but also for medical groups is the basis of prevention. High percentage of patients had neurglycopenic symptoms due to long duration of diabetes and also old age as an independent risk factor; drugs should hence be used cautiously in old patients, and training physicians especially for geriatric groups is also recommended.

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Introduction

Maintenance of the plasma glucose concentration within a relatively narrow range of roughly 70 to 150 mg/dL is critical for normal function of different organs; besides plasma glucose is the predominant fuel used by the central nervous system.[1-2] Because hypoglycemia is dangerous, the body has glucoregulatory mechanisms to protect against low glucose level, these include inhibition of insulin secretion and activation of counter regulatory systems (stimulation of glucagons, epinephrine, cortisol and growth hormone secretion) as the plasma glucose level falls, ini-

tially neuroadrenergic and then neuroglycoenic symptoms appear, and by prolongation of this process, irreversible brain damage and death could result.[3-6] A retrospective study of patients admitted for hypoglycemia in the emergency ward revealed that more than two thirds of them had diabetes mellitus, and nearly one fourth were septic.[7-8] Drugs, insulin in particular, are the most common cause of hypoglycemia in hospitalized patients; critical illnesses, renal or hepatic failure and sepsis are also common but hypoglycemia resulting from hormonal deficiencies is uncommon etiology.[9-11] Clinical manifestations of hypoglycemia differ widely among between patients. Cryer et al showed that sometimes neuroglycopenia or neuroadrenergic disturbances may be the only presenting symptoms indicating age to be an effective factor.[12] The aim of this study was to evaluate the causes and clinical presentation of hypoglycemia in patients with low blood glucose levels admitted to the emergency ward, in order to determine an appropriate preventive method and reduce later complications.

Materials and Methods

Between March 2002 to Feb 2003, all patients aged above 12 years, admitted in the emergency ward of Loghman Hakim general hospital for clinical presentation of hypoglycemia and simultaneous plasma glucose <45 mg/dL, were enrolled. After stabilization of patient status, a questionnaire was completed including personal demographic information, past medical history, dug history, alcohol consumption, addiction, clinical manifestations relevant to hypoglycemia and records of a systemic examination; 10^{cc} of venous blood sample was also obtained for laboratory examination. Tests was conducted for prothrombin time (Normal <14 second) by thromboplastin method, serum albumin (3.5–5 g/dL) and protein (6-8 g/dL) using calorimetric assay, plasma glucose concentration (70–110 mg/dL) by the enzymatic method, plasma urea (10–20 mg/dL) and creatinine level (0.5–1.4 mg/dL) using the Jaffe method. Complementary tests were carried out if no obvious etiology was defined for hypoglycemia including hormonal assay, with thyroid function tests (TFT), rapid ACTH test and the 72 hour-fasting test. Clinical presentations of hypoglycemia were classified as neuroadrenergic (fatigue, tremor, hunger, blurred vision, palpitation and sweating) and neuroglycopenic (headache, diplopia, disorientation, stupor, convulsion and coma) presentations. Hypoglycemic patients, recently diagnosed as diabetics based on FBS below 160 mg/dL and using more than 5 mg of glibenclamide tablet daily, were classified as the prescription error or the mismanagement group.

Statistical analysis: Quantitative variables are introduced by mean±SD. Data analysis was done using student t-test and chi 2 and statistical analysis carried out using SPSS version 11 software. $p<0.05$ was considered significant.

Results

In this study, 89 hypoglycemic patients, 47 (53%) females and 42 (47%) males, aged between 20 and 90 years (66.7±14.9), admitted to the emergency room, were enrolled; of these, 77 (86.5%) patients were known cases of diabetes mellitus and 12 (13.5%) patients had no history of diabetes. Duration of diabetes mellitus was between 1 week and 45 years (10±8.1 year). None of the cases consumed alcohol. Mean plasma glucose was 34.5±3 and 29.2±4 mg/dL in the diabetic versus the non-diabetic subgroups respectively (P=NS); 75.3% of diabetic patients had been treated with glibenclamide, 20.8% with insulin and 3.9% with glibenclamide and insulin concommitantly. The most common cause of hypoglycemia in the study group was iatrogenic drug misuse (36.3%) the other frequent etiologies included renal failure (23%), sepsis (14.3%), and prescription error by physician (11%). Moreover complementary examination and laboratory tests revealed that in most patients more than one etiology can be recognized for hypoglycemia (Table 1).

Table 1. Causes of hypoglycemia in patients admitted to emergency ward (n=89)

Etiology	Percent
Anti-diabetes drug overdose	22%
Anti-diabetes drug overdose (suicide)	3.3%
Anti-diabetes drug overdose + renal failure	7.7%
Anti-diabetes drug overdose + malnutrition	3.3%
Renal failure	10%
Renal failure + malnutrition	5.3%
Renal failure + opium overdose	3.3%
Renal failure + severe sepsis	4.4%
Malnutrition + severe sepsis	14.3%
Mismanagement	11%
Poor feeding due to stroke	7.7%
Gastroenteritis	5.5%
Severe heart failure	1.1%
Opium overdose	1.1%

Iatrogenic hypoglycemia was the most common cause in diabetic patients (n=77), (36.8%) followed by renal insufficiency (21%) prescription error (13%) and severe sepsis (11.5%), (Table 2).

Table 2. Causes of hypoglycemia in diabetic (n=77) and non diabetic (n=12) patients admitted to emergency ward

Etiology	Diabetic patients	Non diabetic patients
Anti-diabetes drug overdose	36.8%	25%
Renal failure	21%	33%
Mismanagement	13%	--
Severe sepsis	11.5%	33%
Poor feeding due to stroke	8.6%	9%
Gastroenteritis	6.5%	--
Opium overdose	1.3%	--
Severe heart failure	1.3%	--

In the subgroup of patients, with no previous history of diabetes mellitus (n=12), three cases had used glibenclamide or insulin for suicidal purposes (25%); severe sepsis was the main etiology in four patients (33%), with four other patients having renal insufficiency (33%) plus in one old patient (9%), the inanition and inability to feed due to stroke was observed. The main cause of low plasma glucose could not be determined precisely in two patients, although a complementary hormonal assay including 72 hour-fasting were done for them; it is suggested that poor feeding related to severe heart failure and opium overdose may be responsible for hypoglycemia in these patients.

The most frequent clinical manifestations of hypoglycemia were neuradrenergic followed by neurglycopenic symptoms in 51.7% of episodes, while 41.6% of patients had only neurglycopenic manifestations and 2.2% of the cases were admitted with neuradrenergic symptoms per se. More specific neuradrenergic plus neurglycopenic presentations were determined in 50.6% and 58.3% of diabetic versus non-diabetic patients, neurglycopenic symptoms in 46.8% and 41.7% and neuradrenergic presentation in 2.6% and 0% of these subgroups respectively (P=NS) (Fig. 1) .

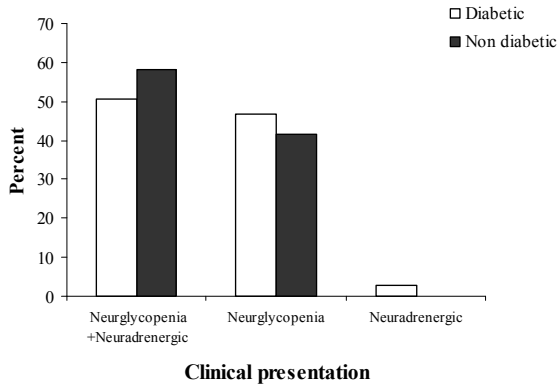

Fig. 1. Comparison of clinical manifestations between diabetic and non diabetic patients

Previous hypoglycemia attacks were reported by 27% of diabetic patients; 33% of diabetic cases used beta blockers, all having neurglycopenic presentation per se. In patients with renal insufficiency, the mean serum creatinine concentration was 2.5±0.5

mg/dL. Three cases (3.3%) of our study group died due to severe septicemia and renal failure.

Discussion

Hypoglycemia is not a simple disease but the sign of a glucose metabolism disturbance with several different causes. In this project we studied the etiologies and clinical manifestations of hypoglycemia in patients admitted to the emergency ward of a general hospital during two years; 89 inpatients with mean age of 66 years were evaluated. No differences were determined between female and male cases for occurrence of hypoglycemia. More than 86% of our patients were diabetic, which is in agreement with the results of the other studies.[13-16] Malouf et al studied one series of patients treated in an emergency room for hypoglycemia and reported that more than two thirds of them were know cases of diabetes mellitus.[7] Misuse of anti-diabetic agents by patients was the most common cause of low blood glucose (36.3%) i.e. glibenclamide (75.3%) , insulin (20.8%) and both of these (3.9%); three cases used these drugs for suicidal purposes. In 27% of them previous episodes of hypoglycemia had occurred. The other frequent causes included: renal failure, severe sepsis and prescription error by physicians. Evidently the most common cause of hypoglycemia reported in almost all studies has been drugs.[17–20] A review by Seltzer on a series of hypoglycemic inpatients, from 1940 to 1988, revealed that insulin, sulfonylurea and alcohol were responsible for more than 70% of hypoglycemia episodes in the USA.[11] Fischer et al also reported that drugs, especially insulin, were the most frequent cause of hypoglycemia in hospitalized patients, followed by renal, hepatic and heart failure and severe sepsis; in contrast, hormone deficiencies were infrequent etiology.[8]

Hence proper education of diabetic patients for drug usage and enhancing knowledge about hypoglycemic symptoms is a cornerstone for prevention of this dangerous condition.

The results of our study revealed, in most instances, that more than one effective etiology can be determined for occurrence of hypoglycemia (Table 1). Considering that the mean age of our population was 66 years, it should be mentioned that, most metabolic disturbances which can easily be tolerated by younger patients, may be dangerous or even life threatening for aged patients with severe decrease of plasma glucose levels. On the other hand, old age and long term diabetes mellitus significantly influence the trend of hypoglycemia, not only by lowering the threshold of counter regulatory hormones defense response, but also by promotion of autonomous neuropathy. Moreover utilization of drugs like nonselective beta blockers or angiotensin–converting enzyme inhibitors are concomitant risk factors for lowering blood glucose.[21-24] Of our diabetic cases, 33% used beta blockers, all of them being admitted in the emergency room with only neurglycopenic presentations. Although mismanagement by physician is a subgroup of iatrogenic hypoglycemia in most studies, we classified this as an independent etiology, because it was responsible for about 11% of our hypoglycemic events, including 10 patients although recently diagnosed as new case of diabetes mellitus with F.B.S not higher than 160 mg/dL, but treated with glibenclamide 5 mg/dL or more by their physicians prescription, and consequently were admitted in the emergency room for hypoglycemia because of mis management. In fact, for aged diabetic patients, ideal blood glucose and goal of therapy is qualite different from younger ones, and decision making for initiation of beginning an oral hypoglycemic agent must be clearly justified. It should be mentioned that aged people need to be the under observation of expert physicians trained for this specific subgroup of patients. Indeed in most developed countries, not only has a new branch of medicine, named geriatric medicine, been

defined but geriatric wards have also been established in general hospitals.[25–27]

The most common clinical manifestations were neuradrenergic (51.7%) followed by neurglycopenic symptoms 46%. We need to point out more than 95% of patients had neurglycopenic symptoms at the time of admission, about half of them were totally unaware of neuradrenergic symptoms, something that would not only be due to disturbance in the autonomous system and hypoglycemia unawareness, but could also be attributed to old age and individual differences in attitude and explanation of symptoms.[28–29] A comparative study by Shilo et al of 60 hypoglycemic patients mean age 65 years, in the geriatric ward, revealed that only 38.4% of them could actually explain hypoglycemic symptoms.[30] Moreover there was no significant difference for clinical presentation between diabetic and non diabetic cases, showing that old age, as a factor independent of diabetes, can deeply influence the clinical presentation; some known reasons for this are first, with increase of age, not only does total body water significantly decrease, indirectly influencing drug metabolism, but counter regulatory hormone and protective defense mechanisms against drug side effects also progressively decrease. Orthostatic hypotension due to utilizing anti-hypertensive drugs, electrolyte imbalance secondary to diuretics, gastrointestinal side effects of non steroidal anti-inflammatory drugs and hypoglycemia secondary to diabetes treatment, are some frequent examples. Drug prescription for geriatric patients must be made under close observation and with special caution, because of changes in body metabolism in aged people.[31,32]

From the results of the study it appears that for reduction of recurrent hypoglycemic events and the later complications, proper education of patients afflicted by diabetes mellitus, and training of expert physicians for geriatric patients are recommended. Geriatric care in general hospitals will also help to enhance our health care system.

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