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Increasing age, diabetes mellitus and recovery from stroke

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Summary: In a prospective study of 200 patients with acute stroke, blood glucose and glycated haemoglobin (HbA_1) were measured within 72 hours of onset. Unrecognized hyperglycaemia as defined by a raised stable HbA_1 more than two s.d. above the mean reference value and no previous history of diabetes was present in 27%. No correlation existed between patient age and admission blood glucose or HbA_1 levels ($r = 0.1$).

Cumulative mortality and recovery of limb function was assessed in the first 136 patients with carotid distribution events. Admission blood glucose $\geq$8mmol/l was shown to be associated with a significantly greater mortality at 4 and 12 weeks ($P<0.05$). Multivariate analysis with age, glucose, HbA_1 as independent variables demonstrated that age was the only significant predictor for death at 4 weeks ($P<0.05$) but at 12 weeks both age and blood glucose were significant ($P<0.05$). In patients <65 years blood glucose was a significant predictor for death ($P<0.05$) but in patients $\geq$65 years HbA_1 and not glucose was significant ($P<0.05$). Patients $\geq$65 years with $HbA_1 \geq 7.5\%$ were significantly more likely to have a raised admission blood glucose. Hyperglycaemia on admission was not shown to influence recovery of limb function.

Increasing age is of greatest importance in predicting mortality although blood glucose is of prognostic value especially in the young stroke patient.

Introduction

The prevalence of stroke rises with increasing age.[1] This may be a direct consequence of prolonged exposure to previously recognized risk factors or the development of new risk factors arising as part of the ageing process.

Several studies have identified factors which predict survival or outcome, the most important of which is continuing presence of coma.[2-4] Large cerebral lesions as evidenced by a visual field deficit, gaze palsy, hemiparesis and depression of conscious level also carry a particularly poor prognosis.[3] There is, however, increasing evidence that there are other global and local factors which exert their influence at the time of stroke and thereby influence subsequent outcome for an individual patient. Furthermore, evidence indicates that increasing age is associated with a poor prognosis in acute stroke.[5-7]

It is generally accepted that glucose tolerance deteriorates with age.[8] There is evidence that a significant number of patients presenting with stroke have previously unrecognized glucose intolerance or diabetes mellitus, a factor known to confer a 2.5–3.5 times increased risk of stroke.[9] Earlier data from our own centre[10] and others[11] have demonstrated an association between neurological outcome and initial blood glucose levels. This study was undertaken to further determine the prevalence of glucose intolerance in stroke, to examine the influence of age upon such glucose intolerance, and to examine the influence of hyperglycaemia and glucose intolerance upon outcome from acute stroke.

Methods

All patients admitted to the Royal Victoria Infirmary and Freeman Hospital, Newcastle upon Tyne from February 1985 to September 1986 with a clinical diagnosis of stroke were identified and assessed as part of a single observer prospective study. An interim analysis of the first 86 patients recruited to the study and the study methods has been reported elsewhere.[10]

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Stroke was defined as a disturbance of focal neurological function with symptoms lasting more than 24 hours and thought to be due to infarction or haemorrhage.[12] Patients with subarachnoid haemorrhage and a neurological deficit lasting <24 hours were excluded as was any patient who was subsequently shown to have a deficit arising as a result of non-vascular cause. All patients admitted within 72 hours of onset of their stroke were included. Each patient was seen by the main assessor (CSG) and where the diagnosis was in doubt a second opinion was sought from another observer.

Patients were classified according to the arterial territory involved, i.e. carotid or vertebrobasilar. A previous history of diabetes mellitus was noted if patients satisfied one or more of the following criteria: (1) history of diabetes from the patient; (2) insulin or oral hypoglycaemic agent therapy; (3) previous dietary advice given for a diagnosis of diabetes mellitus.

Venous blood was taken on admission for blood glucose and stable glycated haemoglobin (HbA_1) estimations. All glucose estimations were performed more than 3 hours post-prandial. Blood glucose was measured using an automated glucose oxidase technique and HbA_1 was measured electrophoretically after removal of unstable adducts by semi-carbizide incubation.

An $HbA_1 \geqslant 7.5\%$ (normal range 5.0–7.5, i.e. above the 95% confidence limits for our reference range), was considered abnormal as was an arbitrary admission blood glucose estimation $\geqslant 8$ mmol/l. Patients were followed from the time of their stroke for a total of 12 weeks with neurological and functional assessments at 4 and 12 weeks.

Improvement (or worsening) of limb function was recorded at 4 and 12 weeks. Using simple hierarchical scales patients were graded according to best unassisted functional outcome. Upper limb: (1) normal, (2) fasten button, (3) hold cup, (4) no use. Lower limb: (1) normal, (2) stairs, (3) flat, (4) stand, (5) no use. For the purpose of this analysis only those patients who had attained full functional recovery, i.e. grade 1 were considered as having normal limb function at 4 and 12 weeks.

Statistics

Data were collected on a standard proforma and analysis performed using the SPSSX package on the Newcastle University's Multiple Access Computer (NUMAC). Significance was tested using the Mann-Whitney U (M-W U) test where indicated or Chi squared test with Yate's correction where appropriate. In addition where indicated multivariate analyses were performed to identify significant variables.

Results

Diabetes and hyperglycaemia in stroke

A total of 200 patients (99 males) were admitted to the study, with a mean age 70.5 years s.d. 10.8 (range 33–96). The prevalence of previously recognized diabetes in this group was 8.5% (17 patients), 15 (88%) of whom were non-insulin dependent diabetics.

HbA_1 was measured in all patients and raised ($\geqslant 7.5\%$) in 68 (34%), 54 (27%) of whom had previously unrecognized glucose intolerance (raised HbA_1 and no previous history of diabetes.)

Admission blood glucose and HbA_1 levels correlated ($r=0.5$ $P<0.01$) and patients with HbA_1 $\geqslant 7.5\%$ had significantly greater admission blood glucose levels when compared to those with a normal HbA_1 ($P<0.01$ M-W U test).

Age and glucose intolerance

There was no correlation between patient age and admission blood glucose ($r=0.1$) or HbA_1 levels ($r=0.1$). No significant relationship could be shown between patient age and admission blood glucose ($\geqslant$ or <8 mmol/l or HbA_1 ($\geqslant$ or $< 7.5\%$) (M-W U test).

Diabetes, hyperglycaemia and outcome from stroke

The first 136 consecutive patients with carotid distribution stroke were followed to determine the influence of diabetes, hyperglycaemia and age upon the outcome from stroke. Sixty four (47%) were male, 72 (53%) female and 10 had a previous history of diabetes.

There were 104 (76.5%) patients aged $\geqslant 65$ years and 32 (23.5%) <65 years. (Range 33–96 years, median 73 years). On admission 31 patients (22.8%) had a raised blood glucose ($\geqslant 8$ mmol/l) including 9 known diabetics. Forty six patients (33.8%) had a raised HbA_1 ($\geqslant 7.5\%$), 37 (80%) of whom had no previous history of diabetes.

Cumulative mortality

The influence of diabetes and hyperglycaemia on cumulative mortality was examined at 4 and 12 weeks. Cumulative mortality rates at 4 and 12 weeks were 29% (39 patients) and 37.5% (51 patients) respectively.

Admission HbA_1 levels were significantly higher in patients dying within 4 weeks ($P<0.5$) M-W U test. Median admission HbA_1 in patients dead at 4 weeks was 7.3% (range 4.8–12.6, mean 7.6) and in patients alive 6.9% (range 5.1–12.5, mean 7.2). No significant difference could be demonstrated between admission

blood glucose levels in patients alive or dead at 4 weeks. Median admission blood glucose in patients dead at 4 weeks, 6.7 mmol/l (range 4–17.8, mean 7.8), median glucose in patients alive, 6.3 mmol/l (range 3.5–17.9, mean 6.7)

Both admission HbA_1 and blood glucose levels were significantly greater in patients dead at 12 weeks ($P<0.05$ M-W U test). Median admission HbA_1 in patients dead at 12 weeks 7.3% (range 4.8–12.6, mean 7.6), median HbA_1 in patients alive 6.9% (range 5.1–12.6, mean 7.1). Median admission glucose in patients dead at 12 weeks 6.9 mmol/l (range 4–17.8, mean 7.8) median glucose in patients alive at 12 weeks 6.1 mmol/l (range 3.5–17.9, mean 6.5)

Patients with a past history of diabetes had no significant difference in cumulative mortality rates at either 4 or 12 weeks when compared with patients with no such past history. Cumulative mortality was significantly greater, however, in patients with admission blood glucose $\geqslant 8$ mmol/l at both 4 weeks ($P<0.01$), (95% confidence limits 6.2–44.8) and 12 weeks ($P<0.05$), (95% CL 2.7–42.1) (Table I). Cumulative mortality was not significantly influenced by the patient's admission HbA_1 status (Table I).

To examine mortality in relation to both admission blood glucose and HbA_1 levels the patients were grouped as in Table II. Patients with a raised blood glucose on admission and normal HbA_1 levels (Group 3) can be considered as having stress hyperglycaemia.[13] Cumulative mortality at 4 weeks was significantly greater in the hyperglycaemic groups ($P<0.05$) and, in particular, significantly greater in those patients with stress hyperglycaemia when compared with the rest of the population ($P<0.05$) (Table II). No significant differences in cumulative mortality could be demonstrated at 12 weeks.

Table I Admission blood glucose HBA_1 and cumulative mortality

		Cumulative mortality			
	Total no	*4 weeks*	*(%)*	*12 weeks*	*(%)*
Blood glucose					
<8 mmol/l	105	24	(22.9)	34	(32.4)
$\geqslant 8$ mmol/l	31	15	(48.4)*	17	(54.8)**
HbA_1					
$<7.5\%$	90	23	(25.6)	30	(33.3)
$\geqslant 7.5\%$	46	16	(34.8)†	21	(45.7)†

*$P = 0.005$; **$P = 0.02$; †NS = not significant.

Age hyperglycaemia and cumulative mortality

A significant increase in cumulative mortality can be demonstrated with increasing age both at 4 weeks ($P<0.05$) and 12 weeks ($P<0.05$, M-W U test). To examine the overall effect of the variables, glucose, HbA_1, sex and age on mortality at 4 and 12 weeks, multivariate analysis with death as the dependant variable was performed.

At 4 weeks, age was the only significant variable in predicting death ($P<0.05$); however, at 12 weeks both age ($P<0.05$) and admission blood glucose levels ($P<0.05$) were significant. Multivariate analysis on patients <65 years/$\geqslant 65$ years with death as the dependant variable and glucose, HbA_1 and sex as independant variables demonstrated that at 4 weeks admission blood glucose was significantly associated with increased mortality in patients <65 years ($P<0.05$). This was not found in patients $\geqslant 65$ years.

At 12 weeks' admission blood glucose was again significantly associated with an increased mortality ($P<0.05$) in patients <65 years. In patients $\geqslant 65$ years, HbA_1 was significantly associated with increased mortality ($P<0.05$).

If age is included as an independent variable in the above then in patients <65 years admission blood glucose is the only significant determinant of death at 4 weeks ($P<0.05$) although blood glucose and age are significantly associated with mortality at 12 weeks ($P<0.05$).

In patients $\geqslant 65$ years neither age, sex, admission blood glucose or HbA_1 significantly influence outcome at 4 weeks although at 12 weeks HbA_1 is significantly associated with an increased mortality ($P<0.05$).

Table II Glycaemic status and cumulative mortality

Glycaemic status (mmol/l) (%)	*Total no. patients*	*Cumulative mortality* 4 weeks (%)		12 weeks (%)		*Previous history of diabetes*
Glucose <8 HbA_1 <7.5	77	16	(20.8)	23	(29.8)	0
Glucose <8 HbA_1 $\geqslant 7.5$	28	8	(28.6)	11	(39.3)	1
Glucose $\geqslant 8$ HbA_1 <7.5	13	7	(53.8)*	7	(53.8)	1
Glucose $\geqslant 8$ HbA_1 $\geqslant 7.5$	18	8	(44.4)	10	(55.6)	8

*$P = 0.03$.

Hyperglycaemia and recovery of function

At the time of admission there was evidence of impaired upper limb function in 131 patients (grades 2–4) and impaired lower limb function in 127 patients (grades 2–5).

There were 85 patients still alive at 12 weeks, all of whom had impaired upper and lower limb function at the time of admission. Recovery of limb function in these 85 patients was compared with respect to admission blood glucose levels. No significant difference could be demonstrated in the numbers of patients who regained normal limb function at 4 or 12 weeks.

Discussion

The prevalence of previously recognized diabetes in acute stroke patients was 8.5% which is comparable to that previously reported.[14,15]

We have confirmed our earlier finding that a significant number of patients with acute stroke and no previous history of diabetes can be shown to have evidence of unrecognized hyperglycaemia or glucose intolerance preceding stroke as defined by a raised stable HbA_1.

The prevalence of stroke rises with age but no significant relationship could be demonstrated between the patient age and admission HbA_1 or blood glucose levels. A significant relationship, however, was demonstrated between blood glucose and HbA_1 levels primarily in the older patients (>65 years).

Earlier studies demonstrated that diabetes mellitus or hyperglycaemia in the acute phase is associated with increased morbidity and mortality following stroke,[11,16] although further clinical and experimental evidence suggests that it is the presence of stress hyperglycaemia and not diabetes or hyperglycaemia which confers a poor prognosis.[15, 17–19] Overall increasing age was the most important prognostic factor for death by 4 and 12 weeks. In patients less than 65 years of age admission blood glucose was the most important prognostic factor for mortality; however, in patients 65 years or over the most important prognostic factor was the admission HbA_1 level which was shown to be associated with raised admission blood glucose in the elderly. Our earlier data[10] demonstrated that early functional recovery was confined to patients with a normal blood glucose. In a large cohort of patients our final analysis has demonstrated that admission blood glucose levels did not significantly influence either early (4 weeks) or late (12 weeks) functional recovery. It would appear that any influence of blood glucose upon outcome in stroke is primarily upon death, this influence being maximal in the younger stroke patient.

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