Disorders of Glucose Metabolism in Acute Stroke Patients

An underrecognized problem

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OBJECTIVE — To determine the prevalence of disturbances in glucose metabolism in patients with acute stroke.

RESEARCH DESIGN AND METHODS — Consecutively admitted acute stroke patients ($n = 286$) were screened for glucose tolerance according to the standardized World Health Organization protocol in the 1st and 2nd week after the stroke event. In addition, we repeatedly measured fasting capillary blood glucose during the first 10 days.

RESULTS — Measurements were not performed or cancelled if patients were not fully conscious or had severe dysphagia or early complications that made transfers to other hospitals necessary ($n = 48$). Of the remaining 238 patients, 20.2% had previously known diabetes; 16.4% were classified as having newly diagnosed diabetes, 23.1% as having impaired glucose tolerance (IGT), and 0.8% as having impaired fasting glucose; and only 19.7% showed normal glucose levels. Another 47 patients (19.7%) had hyperglycemic values only in the 1st week (transient hyperglycemia) or could not be fully classified due to missing data in the oral glucose tolerance test. Patients with diabetes compared with nondiabetic subjects had more severe strokes (National Institutes of Health Stroke Scale [NIHSS] on admission: 7.2 ± 6.6 vs. 4.6 ± 3.1, 4.2 ± 4.4, and 3.7 ± 3.6 for IGT, transient hyperglycemia, and normoglycemia, respectively; $P < 0.001$), a worse outcome (modified Rankin scale 0–1 at discharge: 40.2 vs. 54.4, 63.8, and 72.3% for IGT, transient hyperglycemia, and normoglycemia, respectively; $P < 0.001$), and a higher rate of infectious complications (35.6 vs. 12.3, 21.2, and 4.2% for IGT, transient hyperglycemia, and normoglycemia, respectively; $P < 0.001$). In the multivariate analysis, NIHSS on admission, female sex, and the occurrence of urinary tract infection were independently associated with newly diagnosed diabetes.

CONCLUSIONS — The majority of acute stroke patients have disorders of glucose metabolism, and in most cases this fact has been unrecognized. Diabetes worsens the outcome of acute stroke. Therefore, in the post–acute phase, an oral glucose tolerance test should be recommended in all stroke patients with no prior history of diabetes.

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The prevalence of disturbances of glucose metabolism in acute stroke has hitherto not been properly investigated in a Western population. By a Chinese study (1), diabetes and impaired glucose tolerance (IGT) were diagnosed by performing an oral glucose tolerance test (OGTT) within 3–6 months after stroke in 33.5 and 21%, respectively, of patients. Of individuals with diabetes, 40% were previously undiagnosed. In the cohort of the Glucose Insulin in Ischemic Stroke Trial (GIST) (2) patients without previously known diabetes, 21% had diabetes, 37% had IGT, and 42% had normal glucose values 3 months after stroke. However, only 44% of randomized patients underwent the OGTT protocol in this study. In a study of patients with acute coronary syndromes (3), two-thirds had disturbances of glucose metabolism. In a recent study (4), more than half of the patients with previous stroke or transient ischemic attack had IGT or diabetes.

Diabetes is a proven risk factor for stroke (5–7), with a two- to threefold increased risk for diabetic patients compared with nondiabetic patients. The population attributable risk lies between 18 and 54% (8). According to a Finnish study, diabetes causes 16% of stroke mortality among men and 33% among women (9). Compared with the rates in the normoglycemic population, IGT carries a higher incidence of coronary heart disease (10), cardiovascular diseases (11,12), and total mortality (13). Its role as a risk factor for stroke is less well documented, but recently, a prospective cohort study showed an increased risk for ischemic stroke or transient ischemic attack in patients with the metabolic syndrome (14). In a recently published study (15), insulin resistance was found to be independently associated with the risk of stroke even if adjusted for glycemic control. Up to 50% of people with IGT develop manifest diabetes within 10 years (16), but lifestyle changes such as diet, weight control, and regular physical activity can substantially reduce this progression (17). Thus, screening the high–vascular risk group of stroke patients for disturbances of glucose metabolism may yield a significant potential for secondary prevention.

Furthermore, the early recognition of disorders of glucose metabolism in stroke patients is important because hyperglycemia during the acute phase worsens the outcome (18), probably by reducing the salvage of penumbral tissue mediated by high lactate levels in brain tissue (19).

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Abbreviations: IGT, impaired glucose tolerance; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; OGTT, oral glucose tolerance test.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Baseline characteristics and stroke subtypes in stroke patients with diabetes, IFG/IGT, transient hyperglycemia, and normoglycemia*

	Diabetes*	IFG/IGT	Hyperglycemia	Normoglycemia	*P*
n	87	57	47	47	—
Characteristics					
Age (years)	74.4 ± 11.2	72.8 ± 11.2	71.5 ± 15.2	65.9 ± 15.2	0.005
Female sex	54 ± 62.1	27 ± 47.1	29 ± 61.7	19 ± 40.4	0.048
BMI (kg/m^2)	27.6 ± 5.3	27.1 ± 4.5	27 ± 4.5	26.3 ± 5.3	NS
Waist circumference (cm)	103.2 ± 17.5	103.8 ± 16	99.6 ± 13.3	102.2 ± 15.4	NS
NIHSS at admission	7.2 ± 6.6	4.6 ± 3.1	4.2 ± 4.4	3.7 ± 3.6	<0.001
A1C (%)	6.7 ± 1.6	5.6 ± 0.4	5.6 ± 0.4	5.6 ± 0.4	<0.001
Vascular risk factors					
Hypertension	73 (83.9)	43 (76.8)	31 (66)	26 (55.3)	0.004
Atrial fibrillation	24 (27.6)	13 (23.2)	10 (21.3)	6 (12.8)	NS
Coronary heart disease	19 (21.8)	8 (14.3)	5 (10.6)	7 (14.9)	NS
Previous stroke	23 (26.4)	13 (23.2)	11 (23.4)	7 (14.8)	NS
Hypercholesterolemia	39 (44.8)	30 (53.6)	19 (40.4)	23 (48.9)	NS
Cigarette smoking	14 (16.1)	10 (17.9)	8 (17)	16 (34)	NS
Alcohol abuse (two or more beverages per day)	11 (12.6)	10 (17.9)	12 (25.5)	3 (6.4)	NS
Stroke subtype					
TIA	15 (17.2)	8 (14)	9 (19.1)	12 (25.5)	NS
Minor stroke	27 (30)	25 (43.9)	18 (38.3)	20 (42.6)	NS
Major stroke	37 (42.5)	19 (33.3)	19 (36.2)	12 (25.5)	NS
Intracerebral hemorrhage	8 (9.2)	5 (8.8)	3 (6.4)	3 (6.4)	NS

Data are means ±SD or *n* (%) unless otherwise indicated. Minor stroke was defined as stroke with mild, usually quickly resolving, symptoms of mostly lacunar syndromes; major stroke was defined as completed territorial infarcts with severe symptoms. *Known and newly diagnosed diabetes.

RESEARCH DESIGN AND METHODS

— A total of 300 consecutive patients with a suspected acute (defined as symptom onset within 24 h preceding admission) ischemic or hemorrhagic stroke event were ascertained for the study, of whom 14 had to be excluded because their neurological deficit proved to be of nonischemic origin, leaving 286 patients for the screening program. Patients not fully conscious and patients with unstable severe dysphagia or with medical complications that made transfer to other hospitals necessary were excluded from analysis, as were patients on corticosteroid therapy or with high serum creatinine levels (>177 mmol/l) ($n = 48$), leaving 238 patients for the study protocol. The excluded patients were clinically heterogeneous, and it was not possible to obtain a history of diabetes or to perform standard fasting plasma glucose measurements in a comparable way. However, the mean HbA_{1c} (A1C) value (5.8 ± 0.8%) of these patients did not significantly differ from that of the nondiabetic patients who underwent the protocol (Table 1). Patients with known diabetes or with admission blood glucose levels >11.1 mmol/l were excluded from oral glucose tolerance testing and considered diabetic. The OGTT was performed according to the World Health Organization protocol (20): after overnight fasting, patients drank 250 ml of a solution of 75 g glucose within 3 min. Immediately before administering the drink and after 60 and 120 min, venous blood samples were taken in sodium fluoride tubes. Blood samples were cooled and analyzed immediately (by Hitachi Laboratory Systems). The first OGTT was performed on day 4 after stroke onset and the second during the following week (days 7–10). During the first 10 days, we also repeatedly measured fasting capillary blood glucose. Results of plasma glucose levels were classified according to the World Health Organization (20) and American Diabetes Association guidelines (21). Diabetes was diagnosed if results of either the OGTT or fasting capillary blood glucose measurements exceeded the cutoff values for the diabetic metabolic state on at least two different occasions in the 1st and 2nd week. If patients had at least two raised values, but only in the measurements of the 1st week, they were classified as having transient hyperglycemia.

We recorded data about the following known vascular risk factors: hypertension (repeatedly elevated blood pressure readings above 140/90 or concurrent drug treatment), coronary heart disease (history of angina, myocardial infarction, coronary artery bypass surgery, angioplasty, or stenting), previous stroke (either by clinical signs or by a documented history of a previous stroke), peripheral arterial disease (history of claudication, acute arterial occlusion, bypass surgery, angioplasty, or stenting of extremity arteries), dyslipidemia (any elevation of either total cholesterol or triglycerides or LDL cholesterol), smoking, and alcohol consumption. Documented parameters of stroke severity and outcome were the National Institutes of Health Stroke Scale (NIHSS) (22) and the modified Rankin scale (mRS) (23).

Additionally evaluated laboratory values were A1C and serum creatinine. All patients had fundoscopy to screen for diabetic retinopathy or maculopathy. If indicated, patients had an MRI scan (Siemens 1.0 T) of the brain including diffusion weighted imaging.

Statistical analysis

Dichotomous variables were tested with the χ^2 test and continuous variables with variance analysis. To look for interdependency regarding the classification of newly diagnosed diabetes, the covariates age, sex, NIHSS on admission, hypertension, and occurrence of stroke-associated complications including infections were entered into a logistic regression model. Conversely, a similar logistic regression

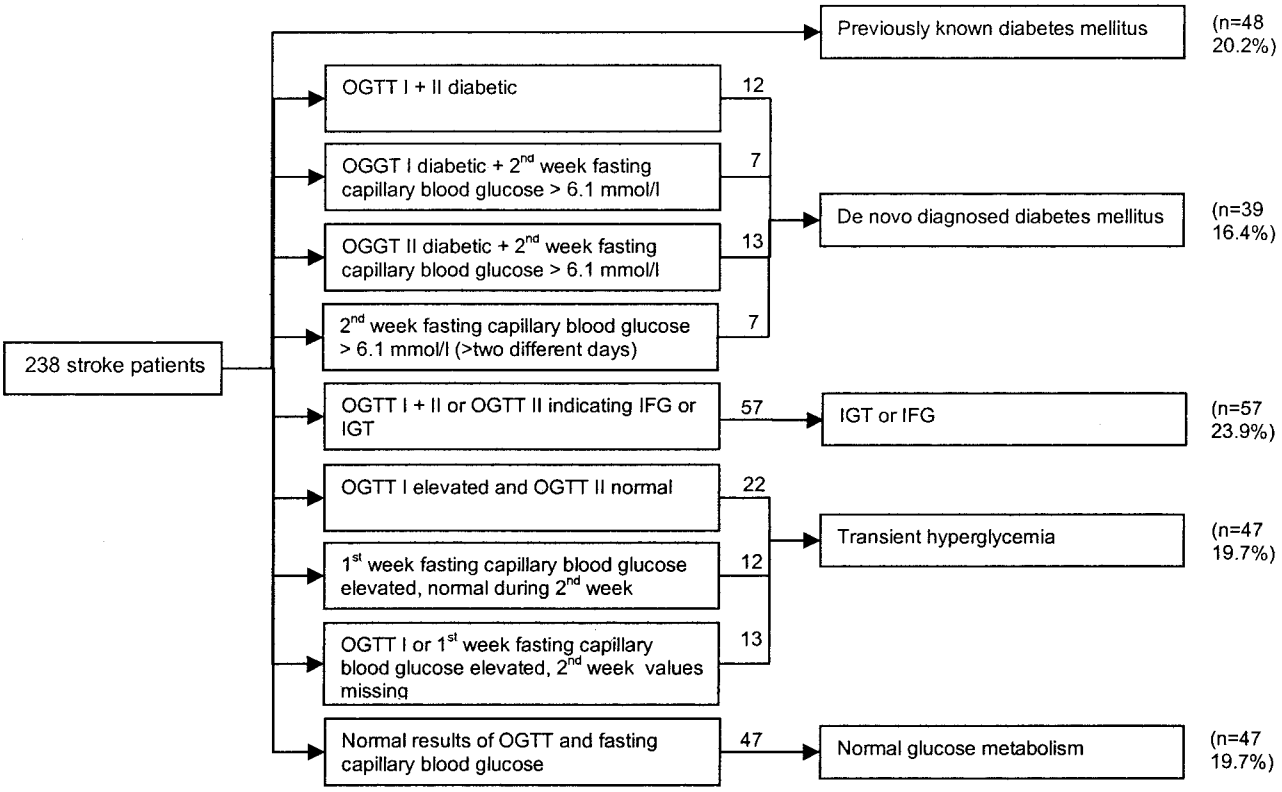

Figure 1—*Flow chart displaying the mode of classification of different groups of disturbances in glucose metabolism according to the OGTT and fasting capillary blood glucose. OGTT I was performed at day 4; OGTT II was performed from days 7 to 10 after the stroke event. IFG, impaired fasting glucose.*

model was applied for the classification of normal versus disturbed glucose regulation.

RESULTS — Of the 238 subjects analyzed, 48 (20.2%) had previously known diabetes; 39 (16.4%) were classified as having newly diagnosed diabetes, 55 (23.1%) as having IGT, 2 (0.8%) as having impaired fasting glucose; and only 47 (19.7%) were normoglycemic (Fig. 1). Another 47 (19.7%) subjects had hyperglycemic values only in the 1st week after stroke, suggesting transient stress hyperglycemia, or could not be classified into any category because of missing data in the OGTT (13 patients). One-quarter of the 1st week's OGTT results were classified as diabetic values (17.5% of the results of the 2nd week). Overall, 68.5% of the OGTT results of the 1st week after the event implied disturbed glucose regulation, as did 62.5% of the results of the 2nd week (Fig. 2). In only 19 patients (8%), previously undiagnosed diabetes would have been diagnosed if considering fasting plasma or capillary glucose levels alone, whereas elevated 2-h values in the OGTT led to the diagnosis of diabetes in an additional 20 patients (8.4%). Furthermore, the best receiver-operator characteristic curve for diagnosing diabetes was obtained with the 2-h OGTT values of the 2nd week: area under the curve 0.925 (95% CI 0.869–0.982) for 2-h OGTT in the 2nd week, 0.829 (0.736–0.922) for 2-h OGTT in the 1st week, 0.801 (0.7–0.902) for the fasting value of the 2nd week, 0.803 (0.7–0.905) for the fasting value of the 1st week, and 0.565 (0.475–0.655) for A1C.

Patients with normal glucose regulation were more often men (more women among diabetic patients) and significantly younger than patients classified as having abnormal glucose regulation (Table 1). Hypertension was the only vascular risk factor significantly more prevalent in the diabetic patients; reported family history of diabetes or cerebrovascular disease, BMI, and waist circumference did not differ between the glucose categories (Table 1).

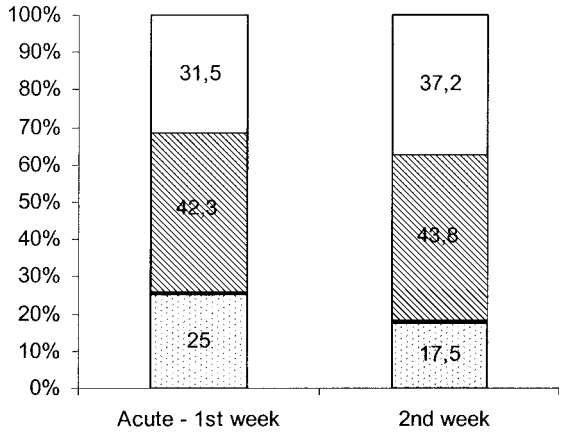

Figure 2—*Distribution of diagnostic groups according to the results of the OGTT performed in the 1st and 2nd week after stroke. □, Normoglycemic values; ▨, IGT; ■, IFG; ▩, diabetic values.*

Table 2—*Logistic regression model for the classification of newly diagnosed diabetes*

	Newly diagnosed diabetes (n = 39)	Other diagnostic groups (n = 199)	OR	95% CI	P
Age ≥70 years	29 (74.4)	125 (62.8)	1.02	0.39–2.65	0.97
Female sex	29 (74.4)	100 (50.3)	3.26	1.33–8.0	0.01
NIHSS on admission	9.4 ± 7.2	4.5 (4.2)	1.16	1.09–1.24	<0.001
Hypertension	31 (79.5)	142 (71.4)	1.5	0.57–3.95	0.41
Complications					
Pneumonia	10 (25.6)	23 (11.6)	0.64	0.19–2.16	0.47
Urinary tract infections	10 (25.6)	7 (3.5)	5.86	1.93–17.8	0.002

Data are means ±SD or *n* (%) unless otherwise indicated.

A1C was the only laboratory marker significantly higher in the group of diabetic patients. None of the newly diagnosed diabetic patients had diabetic retinopathy or maculopathy, indicating microvascular complications, whereas among the subjects with previously known diabetes, 12 had diabetic retinopathy.

Patients with diabetes (known and newly diagnosed) had more severe strokes (NIHSS on admission: 7.2 ± 6.6 vs. 4.6 ± 3.1, 4.2 ± 4.4, and 3.7 ± 3.6 for IGT, transient hyperglycemia, and normoglycemia, respectively; $P < 0.001$), a higher rate of pneumonia and urinary tract infections during the admission (35.6 vs. 12.3, 21.2, and 4.2% for IGT, transient hyperglycemia, and normoglycemia, respectively; $P < 0.001$), and a worse outcome at discharge (mRS 0–1 at discharge: 40.2 vs. 54.4, 63.8, and 72.3% for IGT, transient hyperglycemia, and normoglycemia, respectively; $P < 0.001$) than nondiabetic patients. Although the number of deaths in this patient material was quite small and the case fatality did not differ among the glucose categories, all seven deaths occurred in patients who had some kind of hyperglycemia and none occurred in normoglycemic patients. The occurrence of any other complication of acute stroke (recurrent stroke, symptomatic cerebral bleeding, cerebral edema, seizure, cardiac arrhythmia, heart failure, and extracerebral bleeding) did not differ between the groups.

In the multivariate logistic regression model, NIHSS on admission ($P < 0.001$, odds ratio [OR] 1.16, 95% CI 1.09–1.24), female sex ($P = 0.01$, 3.26, 1.33–8.0), and urinary tract infections ($P = 0.002$, 5.86, 1.93–17.8) were independently associated with the classification of newly diagnosed diabetes (Table 2). Age <70 years ($P = 0.014$, 2.34, 1.19–4.6) and normotension ($P = 0.014$, 2.38, 1.19–4.76) were factors associated with normal glucose values in OGTT.

CONCLUSIONS — In concordance with previous studies (1,2,4), we found a high proportion of disorders of glucose regulation, including newly discovered diabetes, in our study population. To what extent these hyperglycemic states were contributing to the risk of the stroke event remains unknown. There is a lack of data on the potential role of asymptomatic hyperglycemia for the stroke risk, whereas diabetes is an established risk factor (7,8). We found that the vast majority of patients suffering acute stroke had abnormal glucose regulation. In addition, diabetic patients had more severe strokes and a higher rate of infectious complications.

In a logistic regression analysis, stroke severity, urinary tract infection, and female sex were independently associated with previously unrecognized diabetes. This left the possibility that the test results of diabetic patients were influenced by inflammation or stroke-associated stress reaction (24). On the other hand, patients with diabetes tend to have more severe strokes and are generally prone to infections; therefore, the causal direction of this association cannot be decided. For lesser degrees of glucose intolerance (IGT and impaired fasting glucose), this may also be true, but the sample size of our study cohort was too small to detect these presumably small influences. The association with female sex was unexpected and cannot be interpreted by our data, leaving the possibility of a chance finding. It may also reflect the fact that women lose their relative advantage regarding cardiovascular risk compared with men when they have diabetes (25). Recently, a prospective cohort study found that women with metabolic syndrome have a 1.5 higher risk for ischemic stroke or transient ischemic attack than men (14).

One of the important results of this study was that the 2-h postchallenge glucose value during the OGTT was essential in identifying the majority of cases with newly diagnosed diabetes and, naturally, all cases with IGT. This is in keeping with the recent findings from the EuroHeart Survey among patients hospitalized with acute myocardial infarction or elective consultation for coronary heart disease (26). It is also known that the diagnostic value of 2-h glucose level is more predictive for vascular events and mortality in middle-aged and elderly subjects compared with the fasting glucose level (27–30).

There were limitations in our study. First, the OGTT could not be performed in all patients with acute stroke because of disease-associated complications such as dysphagia; therefore, we could not completely screen our hospital cohort for diabetes. Second, fasting capillary blood glucose and plasma glucose values during the OGTT were higher and more often hyperglycemic in the 1st week after stroke than in the 2nd week. This may indicate stress hyperglycemia during the acute phase of the illness, but part of it is due to the regression to the mean. Therefore, it is possible that patients with this transient hyperglycemia would be classified as normal if they are not tested during the acute phase of stroke.

The outcome assessment at discharge is not completely standardized because the time of assessment from the onset of stroke varies considerably and is influenced by various factors, such as concurring complications, the necessity of further investigations, and patient compliance. Nevertheless, we consider the lower proportion of independency at dis-

charge (mRS 0–1 40.2 vs. 62.9%) in diabetic patients versus nondiabetic patients to be a good indicator for a more severe disease course in diabetic patients. This finding contrasts with previous studies that did not find an influence of diabetes on stroke outcome (31,32). However, in these studies, diabetes was defined as history of clinically diagnosed diabetes, and therefore among nondiabetic patients, many subjects had asymptomatic hyperglycemia as shown by the present study. The negative influence of hyperglycemia in nondiabetic stroke patients is quite well documented (18,23,33). Moreover, there is evidence that hyperglycemia is associated with reduced penumbral salvage and worse functional outcome in diabetic and nondiabetic patients (19).

As several studies have demonstrated (34,35), it is important to detect diabetes early and to control blood glucose levels and other risk factor parameters carefully. Effective antidiabetic drug treatment may improve the prognosis of diabetic patients with stroke, but thus far, there are no data from randomized controlled trials that would indicate that newly diagnosed diabetic patients would benefit from such treatment, either in the acute phase of stroke or later on. There is solid evidence that the progression of hyperglycemia from IGT to diabetes can be drastically reduced by lifestyle intervention, i.e., by diet and physical activity (17,36). It would be important to find out whether this could also be achieved in stroke survivors with IGT. Because the lifestyle intervention also reduces the levels of other risk factors of stroke, such as blood pressure, central obesity, and dyslipidemia, it may not only lead to lower rates of diabetes but also to an overall improvement of prognosis of stroke patients. Again, randomized controlled trials to test this hypothesis are needed.

In summary, the majority of acute stroke patients have disturbances of glucose metabolism, and in most cases these have been hitherto undiscovered. Many of these disturbances were only revealed by performing an OGTT and interpreting the 2-h post–glucose challenge values. Therefore, an OGTT screening in the post–acute phase has to be recommended in all stroke patients with no prior history of diabetes. Patients with pre-diabetic stages, i.e., IGT and impaired fasting glucose, are important targets for primary and secondary prevention strategies, including lifestyle modification, pharmacological anti-obesity treatment, and statin therapy. Long-term outcome after myocardial infarction has recently been shown to be worse in patients with newly detected abnormal glucose tolerance (26); therefore, further studies are warranted to assess the long-term prognosis of stroke patients with diabetes, IGT, or impaired fasting glucose and the effect of preventive measures.

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K.M., M.B., J.T., and K.K. conceived and designed the study. K.M., K.K., C.T., M.N., and A.D. obtained and analyzed the data. K.M. wrote the report, which was then revised by M.B. and J.T.

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