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Microalbuminuria

A potential prognostic marker for acute stroke

The term "microalbuminuria" (MA) denotes an increase in albumin excretion that remains below the lower limits of sensitivity for routine diagnostic methods [1]. MA was originally introduced to clinical practice as a marker for incipient diabetic nephropathy. In the past decade the role of MA has become apparent in acute diseases such as myocardial infarction and stroke [2].

MA is more prevalent in patients with increased risk of vascular events (e.g., diabetics and patients with hypertension) [3]. It predicts cardiovascular events and all-cause mortality in the general population and is a plausible risk factor for ischemic stroke [3]. Furthermore, MA occurs transiently in acute diseases with different etiologies and predicts greater short- and long-term mortality in stroke patients [4]. Although MA is clearly associated with clinical risk factors for stroke, there is little information regarding its possible role as an independent risk factor for stroke or as a predictor of stroke outcome.

Slowik et al. [5] were the first to report a significant correlation between MA and severity of stroke. Beamer et al. [6] described MA as an independent predictor of vascular end-point.

At present, however, the relevance of MA as a prognostic and risk factor for stroke in the acute phase is unclear. The aim of this study was to determine the prognostic value of MA in acute stroke patients.

Materials and methods

We included patients with ischemic stroke admitted to our stroke unit between June 2009 and July 2010. The inclusion criteria were acute stroke and admission to our unit, where 24-h collection of urine was possible. Exclusion criteria were intracerebral hemorrhage, head trauma, malignancy, urinary infection or other chronic infections, and unavailability of 24-h urine samples (due to hospital stay <24 h or logistic problems). During hospitalization, the patients' electrocardiogram, oxygen saturation, blood pressure, and respiration were monitored continuously. Body temperature, capillary glucose levels, and neurological status were evaluated several times per day. Swallowing function was monitored depending on the clinical status. All data were collected as part of the investigation of the quality of care.

The following information was recorded for each patient: (1) demographic factors (age and sex); (2) vascular risk factors (high blood pressure, diabetes mellitus, ischemic heart disease, atrial fibrillation, hypercholesterolemia, and previous cerebral ischemia); (3) chronic kidney disease; (4) HbA1c, baseline glucose, levels of C-reactive protein upon admission, and white blood cells upon admission; (5) blood pressure upon admission; (6) rtPA administration; (7) presence or absence of MA.

Urine was collected for 24 h after admission. Urinary albumin in the 24-h samples was assessed quantitatively by an immunonephelometric method (N-antiserum albumin, Dade Behring, Liederbach, Germany), and urine creatinine was measured quantitatively by an enzymatic colorimetric test. MA values <30 mg/day were considered normal, values between 30 and 299 mg/day were defined as indicating the presence of MA, and values ≥300 mg/day were considered to show macroalbuminuria.

Severity of stroke was assessed using the NIHSS score upon admission and discharge. The functional outcome upon discharge was measured on the modified Rankin scale (mRS). The mRS rater was not blinded to rtPA treatment and was not aware of the presence or absence of MA. A favorable outcome was defined as a mRS score of 0–2 and a poor outcome as a mRS score >2. Patients who died were assigned a modified Rankin score of 6.

Statistical analysis

Student's t-test was used to determine whether there were significant differences in normally distributed continuous variables between patients with and without albuminuria. Baseline variables were compared using Pearson's χ^2 and Mann–Whitney U tests as appropriate. In order to calculate odds ratios for the occurrence of poor outcome parameters, the population was grouped according to presence or absence of MA. NIHSS as an outcome parameter was measure at hospital discharge. Adjusted odds ratios were calculated using logistic regression models including age, gender, baseline NIHSS, CRP level, and pre mRS upon admission. The differences were considered statistically significant when $p<0.05$. All statistical analyses were performed using the SPSS software (Version 16.0).

Tab. 1 Baseline characteristics and univariate analysis for presence of microalbuminuria (*MA*) of included patients divided into those with and without MA, and univariate analysis for modified Rankin score (*mRS*) upon discharge in the studied population

Variable	With MA (n=57)	Without MA (n=81)	*p* for MA	*p* for mRS
Age	72.4±10.4	66.1±11.1	0.003*	0.055
Male sex	67%	77.8%	0.149	0.038*
Hypertension	98%	92.6%	0.315	0.704
Diabetes	54%	40.7%	0.004*	0.678
Prior stroke	9%	1.2%	0.067	0.055
Atrial fibrillation	32%	7.4%	0.0001*	0.143
Peripheral artery disease	30%	23.5%	0.278	0.152
HbA1C (%)	6.8±1.6	6.4±1.3	0.005*	0.663
CRP (mg/dl)	14.7±24.5	6.8±7.9	0.008*	0.0001*
Prior antiplatelet therapy	19%	14%	0.807	0.428
Glucose (mg/dl)	159.5±65.4	127.8±42.8	0.032*	0.180
$BP_{systolic}$ (mmHg)	168.7±23.3	161.5±24.6	0.046*	0.426
i.v. rtPA treatment	42%	32%	0.232	0.138
NIHSS admission	8 (5, 15)	4 (2, 6)	0.0001*	0.0001*
NIHSS discharge	5 (2, 12)	1 (0, 3)	0.0001*	0.055
Premorbid mRS score	0 (0, 2)	0 (0, 1)	0.019*	0.0001*
mRS score	3 (2, 4)	1 (0, 2)	0.0001*	

Categorical variables are expressed in percentage; continuous variables are expressed as mean values ±SD or as median values and interquartile (IQ) range.[a] χ^2 test was used for categorical variables and the Student t test for quantitative variables.[a]

CRP C-reactive protein, **BP** blood pressure, i.v. **rtPA** recombinant tissue-type plasminogen activator, **NIHSS** National Institute of Health Stroke Score. [a]Mann–Whitney U test, *value considered significant.

Tab. 2 Odds ratio (*OR*) for poor outcome (mRS>2) upon discharge

	mRS >2	
	p value	OR (CI 95%)
CRP (mg/dl)	0.79	1.032 (0.996–1.070)
Premorbid mRS	0.0001*	2.030 (1.369–3.011)
NIHSS admission	0.001*	1.116 (1.044–1.193)
Gender m/f	0.727	0.822 (0.274–2.469)
MA (presence of yes/no)	0.004*	5.07 (2.18–11.77)
Age (years)	0.67	0.954 (0.907–1.003)

*value considered significant. **mRS** modified Rankin score, **CRP** C-reactive protein.

Results

Over a period of 12 months, 525 stroke patients were admitted to our stroke unit for treatment of an acute cerebrovascular event. Of these, 138 patients fulfilled the inclusion criteria and were studied; their mean age was 67±11 years, and 73% were male. About 38% were treated with rtPA, with a mean interval from symptom onset to treatment of 160±90 min. The median NIHSS was 6 upon admission and 3 upon discharge. The median mRS score upon discharge was 2. MA was found in 43% of subjects (6% presented macroalbuminuria). Time interval to discharge differs between patients with and without MA (7.6 days vs. 6.6 days, p=0.024). The characteristics of patients studied for MA are shown in **Tab. 1**.

Univariate analysis showed that MA was associated with C-reactive protein (CRP) upon admission (p=0.008), HbA1c (p=0.005), diabetes mellitus (p=0.004), chronic kidney disease (p=0.05), glucose at baseline (p=0.032), systolic blood pressure upon admission (p=0.046), atrial fibrillation (p<0.0001), age (p=0.003), premorbid mRS (p=0.019), NIHSS upon admission (p<0.0001), NIHSS upon discharge (p<0.0001), and mRS upon discharge (p<0.0001), no association was found with white blood count (WBC) (p=0.831) Data are summarized in **Tab. 2**.

On multivariate analysis MA was a strong independent predictor of poor outcome (OR 5.07, 95%CI 2.18–11.77; p=0.004). Similarly, premorbid mRS score (OR 2.030, 95%CI 1.369–3.011; p=0.0001) and NIHSS upon admission (OR 1.116, 95%CI 1.044–1.193; p=0.001) were independent predictors of poor outcome as assessed by the mRS score upon discharge. Detailed data are shown in **Tab. 2**.

We also sought factors that might predict the presence of MA and found that glucose at baseline (OR 1.01, 95%CI 1.00–1.034; p=0.038), age (OR 1.00, 95% CI 1.00–1.17; p=0.05), and atrial fibrillation (OR 6.19, 95%CI 1.99–19.3; p=0.002) were independent predictors of MA. Separate analysis for macroalbuminuria was also performed. Patients with micro- or macroalbuminuria did not statistically differ with respect to risk factors, severity of stroke, and outcome.

Discussion

We are the first to report data regarding the association between MA and outcome in the acute phase of stroke. Our findings indicate that MA may be a predictor of poor outcome at discharge. Although the associations of MA with myocardial infarction, kidney disease, and metabolic syndrome are well described in the literature [7, 8, 9], there are limited data on the role and the prognostic value of MA in the acute phase of stroke. The association between MA and severity of neurological symptoms was first described by Slowik et al. [5]. They investigated the prevalence of MA and its relationship with neurological features in 60 non-diabetic patients with acute stroke compared to control groups. Stroke severity was not standardized. They described the prognostic value of MA with reference to mortality at 1-year follow-up. However, they reported no data on the association between MA and neurological severity or outcome in the acute phase. Toth et al. [10] did not confirm that immunoreactive (immunologically intact) albumin, which is typically measured as a marker MA serves as an independent risk factor for stroke severity. In this study of 98 patients, only a subtype of albumin (non-immunoreactive albumin) was an independent risk factor

for stroke severity. This study differs in some respects from our and most other published investigations: MA was assessed not with three independent measurements or with 24-h urine but by determination of the albumin/creatinine ratio in a single urine sample, and Toth et al. [10] do not give information about the outcome of stroke patients.

In agreement with other studies, we found that the severity of the neurological deficit (as measured by NIHSS score) and the CRP level were also independent predictors of poor outcome [11, 12]. We confirmed in our cohort the association of MA with the general cerebrovascular risk factors such as diabetes, atrial fibrillation, glucose level upon admission, age and chronic kidney disease reported in previous studies [13, 14]. Interestingly, we found a significant association between MA and CRP levels. It seems that MA is linked with the inflammatory response in the acute phase of stroke and is associated with higher CRP. This has also been described in cardiovascular patients: the presence of both MA and CRP predicted a higher risk of cardiovascular death, nonfatal myocardial infarction, or stroke [15]. The pathophysiological mechanism is still unclear. A plausible explanation for our findings is that MA is a marker of endothelial dysfunction [16] and plays an important role in the inflammatory response [7] in the acute phase of a vascular event.

Our study has several limitations. First, we cannot completely exclude recruitment bias. Our study did not have consecutive recruitment of patients, and the number of patients included is relatively small (albeit larger than in previous studies [5]). The data regarding the outcome may also be influenced by other factors. For example, atrial fibrillation was associated with MA in our study. Although atrial fibrillation had no influence on outcome in our study, it is a known risk factor for poor outcome. Furthermore, we did not systematically collect data on body temperature (which was measured as part of the clinical routine) or subacute infections; although urinary infection and chronic infection were exclusion criteria, other potential confounders could not be excluded. Nevertheless, serious infection or sep-

Abstract · Zusammenfassung

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Microalbuminuria. A potential prognostic marker for acute stroke

Abstract

Introduction. Stroke is potentially preventable through risk factor reduction. Over the past decade, the role of microalbuminuria (MA) as a risk factor for chronic diseases has become apparent. The aim of this study was to determine the prognostic value of MA in acute stroke patients.

Materials and methods. Patients with acute ischemic stroke admitted to our stroke unit were included in this study. Clinical history and vascular risk factors were recorded. Severity of stroke and outcome were assessed by NIHSS and modified Rankin scale (mRS) upon admission and discharge. Urinary albumin excretion was measured in 24-h urine samples. Multivariate analysis was performed to investigate predictors of poor outcome.

Results. MA was found in 43% of 138 patients and was associated with elevated levels of C-reactive protein (CRP), glucose at baseline, and HbA1c; higher rates of diabetes mellitus and atrial fibrillation; higher systolic blood pressure; greater age; and higher premorbid mRS, NIHSS upon admission/discharge, and mRS upon discharge. In a multivariate analysis, MA (OR 5.07, 95%CI 2.18–11.77; p=0.004), premorbid mRS (OR 2.030, 95%CI 1.369–3.011; p=0.0001), and NIHSS upon admission (OR 1.116, 95%CI 1.044–1.193; p=0.001) were independent predictors of poor outcome upon discharge.

Conclusion. MA was frequently found in acute ischemic stroke patients. It was associated with severe neurological deficit upon admission and severe functional impairment upon discharge. MA in the acute phase was shown to be an independent predictor of poor outcome. The association between MA and CRP levels points to potential linkage of MA to the inflammatory response in acute stroke.

Keywords

Microalbuminuria · Risk factors · Acute stroke · Stroke unit · Outcome

Mikroalbuminurie. Ein potenzieller prognostischer Marker für den akuten Schlaganfall

Zusammenfassung

Einleitung. Durch eine Reduktion von Risikofaktoren sind Schlaganfälle prinzipiell vermeidbar. In den letzten Jahren hat eine Mikroalbuminurie (MA) eine zunehmende Bedeutung als Risikofaktor für chronische Erkrankungen erlangt. Ziel dieser Untersuchung ist, die Bedeutung einer Mikroalbuminurie als prognostischen Marker bei Patienten mit akuten ischämischen Schlaganfällen zu untersuchen.

Material und Methoden. Einhundertachtunddreißig auf unsere Stroke-Unit aufgenommene Patienten mit ischämischen Schlaganfällen wurden prospektiv in die Studie eingeschlossen. Vorerkrankungen und vaskuläre Risikofaktoren wurden erhoben. Schlaganfallschwere und Outcome wurden mittels der National Institute of Health Stroke Scale (NIHSS) und mittels der modifizierten Rankin-Skala (mRS) bei Aufnahme und Entlassung bestimmt. Die Albuminausscheidung wurde in einem 24-Stunden-Sammelurin bestimmt. Es erfolgten multivariante Analysen zur Untersuchung von Prädiktoren für ein schlechtes Outcome.

Ergebnisse. Bei 43% der 138 Schlaganfallpatienten wurden eine MA festgestellt. MA war mit erhöhten Werten für das C-reaktive Protein (CRP), Blutglukose bei Aufnahme, HbA1c, Diabetes mellitus, Vorhofflimmern, arterieller Hypertonie, höherem Lebensalter, höheren prämorbiden mRS, höheren NIHSS bei Aufnahme und Entlassung und höheren mRS bei Entlassung assoziiert. In einer multivarianten Analyse waren MA (OR 5,07, 95%KI 2,18–11,77, p=0,004), prämorbider mRS (OR 2,030, 95%KI 1,369–3,011, p=0,0001) und NIHSS bei Aufnahme (OR 1,116, 95%KI 1,044–1,193, p=0,001) unabhängige Prädiktoren für ein schlechtes Outcome bei Entlassung.

Diskussion. Eine MA wurde in unserer Studie häufig bei Patienten mit einem ischämischen Schlaganfall festgestellt und war mit einem höheren NIHSS bei Aufnahme und einem schlechteren funktionellen Outcome bei Entlassung assoziiert. Eine MA ist unserer Studie zufolge ein unabhängiger starker Prädiktor für ein schlechtes Outcome in der Akutphase des Schlaganfalls. Weiterhin deutet eine Assoziation zwischen einer MA und erhöhten CRP-Werten auf eine potenzielle Verflechtung zwischen einer MA und der Immunantwort in der Schlaganfallakutphase hin. Auch aufgrund der potenziellen Therapierbarkeit sollte dieser Marker bei Schlaganfallpatienten weiter untersucht werden.

Schlüsselwörter

Mikroalbuminurie · Risikofaktoren · Akuter Schlaganfall · Stroke-Unit · Outcome

sis during the hospital stay was reported for patients in this study. Another limitation of our study is that we did not use a predefined endpoint for outcome (e.g., 7 days). We used hospital discharge as an endpoint.

Despite these potential limitations, however, we believe that our data underline the importance of MA as a marker not only in patients with kidney or metabolic disease but also in those with acute stroke. Physicians should keep in mind the likelihood that MA and stroke have closely similar underlying pathophysiologic processes (e.g., generalized endothelial dysfunction) and that MA could serve as a useful, easily measured, and inexpensive marker of risk and outcome in future stroke studies. Furthermore, it should be investigated whether a reduction of MA lead to a reduction in stroke risk.

Conclusion

MA was found in approximately half of the patients studied with acute ischemic stroke. Stroke patients with MA seem to have poorer outcome at discharge from hospital. We found a significant association between MA and CRP levels, which points to a linkage of MA to the inflammatory response in acute stroke. Although the results of our study need to be confirmed in a larger cohort, we believe further studies should investigate whether MA is only a biomarker of severity of stroke and a predictor for poor outcome or a potential modifiable risk factor for stroke.

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Conflicts of interest. On behalf of all authors, the corresponding author states that there are no conflicts of interest.

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