

Association of renal dysfunction with stroke subtypes in acute stroke patients

急性中風病人腎功能障礙與中風類型之關係

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Objectives: There are conflicting published data about the association of renal dysfunction with cerebrovascular diseases. Both diseases have shared risk factors such as hypertension, diabetes mellitus and smoking. In the present study, the relationship of renal dysfunction with stroke subtypes and stroke severity was investigated. **Materials and methods:** One hundred and sixty-two acute stroke patients without known history of renal disease and 148 control subjects were enrolled in the study. Serum urea, serum creatinine level and glomerular filtration rate (GFR) as estimated by the Modification of Diet in Renal Disease formula were used to evaluate renal dysfunction. Stroke patients were divided into two groups as haemorrhagic and ischemic stroke, the latter being further subdivided into small and large vessel disease subtypes according to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria. Stroke severity was assessed by the modified Rankin Scale. **Results:** Serum creatinine and urea levels were significantly higher and GFR was significantly lower in the stroke group than the controls ($p < 0.001$, $p < 0.001$, $p < 0.001$, respectively). Serum creatinine level was found significantly higher in haemorrhagic stroke than ischaemic stroke subtypes ($p < 0.001$). There was no difference between ischemic subtypes regarding the measured renal parameters. Stroke severity correlated with increased creatinine levels ($p < 0.001$, $\beta = 0.404$, 95% CI = 1.85-3.50). **Conclusion:** Acute stroke patients have impaired renal function. Renal dysfunction is particularly more prominent in haemorrhagic stroke and exists probably prior to the stroke. Whether renal dysfunction is an independent risk factor for stroke needs to be clarified by large population studies. (*Hong Kong j.emerg.med.* 2010;17:22-26)

目的：關於腎功能障礙與腦血管病之關係而所發表的資料互相抵觸。兩種疾病有共同的風險，例如高血壓、糖尿病及吸煙。這研究調查腎功能障礙與中風類型及嚴重性之關係。**資料及方法：**本研究招募了162名沒有腎病病歷的急性中風病人及148名人士作比對。使用血清尿素、血清肌酸酐水平及腎小球過濾率（以「腎病修訂飲食公式」估計）評估腎功能障礙。中風病人分為出血性及缺血性兩組，後

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者進一步根據多士 (TOAST) 標準再分為小血管病及大血管病類型。以「修訂蘭金尺度」評估中風的嚴重程度。**結果：**中風組的血清肌酸酐及尿素水平顯著較對照者高，而腎小球過濾率則顯著較低（分別為 $p < 0.001$, $p < 0.001$, $p < 0.001$ ）。發現出血性中風類型的血清肌酸酐水平顯著較缺血性中風類型為高（ $p < 0.001$ ）。於缺血性中風類型間所量度的腎參數沒有分別。中風嚴重程度與肌酸酐水平提升有關連（ $p < 0.001$, $\beta = 0.404$, 95% 置信區間 1.85-3.50）。**結論：**急性中風病人的腎功能減弱。腎功能障礙在出血性中風中特別顯著，很可能中風前已存在。腎功能障礙是否為中風的一個獨立風險因素，則需要大型人口的研究澄清。

Keywords: Creatinine, glomerular filtration rate, renal insufficiency, stroke

關鍵詞：肝酸酐、腎小球過濾率、腎衰竭、中風

Introduction

Acute stroke is one frequent cause of emergency admission. The Oxford Vascular Study group reported that the incidence of cerebrovascular diseases is 1.2 times that of coronary artery disease.¹ Stroke being the disease of the elderly population has a high morbidity and mortality rate. In prospective studies, advanced age, hypertension, diabetes mellitus, smoking and atrial fibrillation have been found as risk factors for stroke and the relevant mortality.² The first few hours after stroke are critical and important for effective management. In many studies, laboratory parameters such as blood glucose level, leukocyte count and erythrocyte sedimentation rate have been shown to have prognostic importance.³

In recent studies, renal dysfunction has been found to be a risk factor for cerebrovascular diseases,⁴⁻⁶ as well as a prognostic factor after stroke.^{2,3} It is increasingly apparent that individuals with chronic renal disease are more likely to die from cardio-cerebrovascular diseases.⁷ Conflicting results have been encountered regarding the association of renal dysfunction with stroke subtypes.^{5,6} Serum urea level, serum creatinine (SCr) level and glomerular filtration rate (GFR) are easily available parameters in the emergency service setting. In this study, we aimed to compare the difference in renal function between acute stroke patients and control subjects and to investigate the relationship among stroke subtypes.

Materials and methods

In the present study, 162 acute stroke patients and 148 control subjects without any stroke history were retrospectively evaluated. Subjects with a known history of chronic renal disorder or with a GFR < 15 ml/min/1.73 m² were excluded from the study. The control group consisted of subjects who were admitted to internal medicine. Data such as systolic and diastolic blood pressure, and stroke severity (estimated by means of the modified Rankin Scale) which were obtained in the first 24 hours of acute stroke were collected. After the identification of patients with intracerebral haemorrhages (n=31), the 131 patients with acute ischaemic stroke were further subdivided into two groups (large vessel disease [LVD] group [n=60] and small vessel disease [SVD] group [n=71]) by the investigators based on all available clinical and radiological information according to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification system criteria.⁸ The patients with LVD had clinical and brain imaging findings of either significant stenosis or occlusion of a major brain artery or branch cortical artery. Cerebral cortical impairment (aphasia, neglect, restricted motor involvement, etc) or brainstem or cerebellar dysfunction were present on physical examination. The SVD group had at least one of the traditional clinical lacunar syndromes (pure motor hemiparesis, pure sensory syndrome, sensorimotor syndrome, ataxic hemiparesis, and dysarthria-clumsy hand syndrome) and did not have evidence of cerebral cortical dysfunction.

The glomerular filtration rate was estimated by means of the Modification of Diet in Renal Disease (MDRD)-2 formula in which age, gender and serum creatinine level act as variants: $GFR (ml/min/1.73 m^2) = 186 \times (SCr)^{-1.154} \times (age \text{ in years})^{-0.203} \times (0.74 \text{ if female})$.⁹

All statistical analyses were performed by using SPSS 11.5 software for Windows. Data were expressed as mean \pm SD. The normality of the distribution of all variables was assessed by the Kolmogorov-Smirnov test. Student's t test and Pearson correlation analyses were used for normally-distributed variables. Mann-Whitney U test and Spearman rank correlation test were used for non-parametric variables. The data of the stroke subtypes were analysed by the ANOVA and Kruskal-Wallis tests. The logistic regression analysis test was used to determine factors affecting stroke severity.

P values <0.05 were considered statistically significant.

Results

The clinical and demographic characteristics of the age-matched patient and control groups are shown in Table 1.

Serum creatinine and urea levels were significantly higher and GFR was significantly lower in the stroke group than the controls ($p<0.001$), but the latter two parameters did not show any difference among ischaemic stroke subgroups with small and large vessel disease, and haemorrhagic stroke. Serum creatinine level was significantly higher in haemorrhagic stroke than ischaemic stroke ($p<0.001$), whereas similar levels were found in small and large vessel disease subgroups (Table 2).

Table 1. Clinical and demographic characteristics of the patient and control groups

	Stroke patient (n=162)	Control subject (n=148)	P
Gender (male/female)	89/73	93/55	NS
Age (year)	67.4 \pm 10.6	65.6 \pm 7.3	NS
Systolic blood pressure (mmHg)	152.7 \pm 33.2	142.6 \pm 22.7	<0.01
Diastolic blood pressure (mmHg)	87.7 \pm 16.3	86.9 \pm 10.6	NS
Serum urea (mg/dl)	42.0 \pm 19.1	31.1 \pm 10.6	<0.001
Serum creatinine (mg/dl)	1.02 \pm 0.28	0.86 \pm 0.19	<0.001
Glomerular filtration rate	71.8 \pm 19.0	88.7 \pm 22.8	<0.001

NS: not significant.

Table 2. Comparison of renal function parameters among stroke subtypes and controls

	SVD (n=71)	LVD (n=60)	Haemorrhagic stroke (n=31)	Control (n=148)
Serum urea	40.6 \pm 20.7	43.5 \pm 17.5	45.5 \pm 18.4	31.1 \pm 10.6*
Serum creatinine	0.99 \pm 0.27	0.96 \pm 0.18	1.2 \pm 0.37†	0.86 \pm 0.19*
Glomerular filtration rate	72.6 \pm 17.6	74.7 \pm 19.6	64.4 \pm 19.6	88.7 \pm 22.8*

* $p<0.001$; (difference between stroke groups and controls)

† $p<0.001$; (difference between haemorrhagic stroke and LVD and SVD subgroups)

LVD: Large vessel disease subtype of ischaemic stroke

SVD: Small vessel disease subtype of ischaemic stroke

The stepwise logistic regression analysis test was used to investigate the effect of serum creatinine on stroke severity with factors including age, GFR, status of diabetes mellitus, status of hypertension and serum urea level being controlled. Serum creatinine emerged as the only significant factor in determining stroke severity ($\beta=0.404$, $p<0.001$, 95% CI=1.85-3.50).

Discussion

Increased creatinine level, as a reflection of impaired renal function, is a good marker for some vascular diseases including stroke.^{10,11} Common risk factors and mechanisms such as hypertension, diabetes mellitus, hyperlipidemia, activation of the rennin-angiotensin system, and endothelial dysfunction are shared by both chronic kidney diseases and cerebrovascular diseases.⁷ It could be suggested that the pathologic process taking place in chronic renal disease might also involve the cerebral vascular bed. In the light of these data, we measured the serum creatinine level of acute stroke patients and found significantly higher levels compared to controls. No significant difference was found among the ischaemic stroke subtypes (small and large vessel diseases). In line with our results, Cohen et al¹² reported that serum creatinine levels were not distinctive among the subtypes of ischaemic stroke. However, haemorrhagic strokes were not included in Cohen's study. In our study, we found significant elevation of creatinine levels in the haemorrhagic stroke group; therefore we suggest that impaired renal function could be a risk factor for stroke, particularly for the haemorrhagic type.

Since 24 hour-urine collection is almost impossible in the emergency service setting, a reliable formula is needed to estimate the renal function. The Cockcroft-Gault formula is used to calculate creatinine clearance, but data about the weight of the patient is needed for the calculation. Because we were not able to obtain reliable weight data, MDRD-2 was used to estimate the GFR. In a study that compared the reliability of these two formula, MDRD was found to be more predictive for cardiovascular outcomes than the

Cockcroft-Gault formula.¹³ Our study revealed that the GFR significantly decreased in acute stroke patients as compared to the controls. No significant GFR difference was found between haemorrhagic and ischaemic stroke.

Ruilope et al¹³ and Weiner et al¹⁴ reported that decreased GFR was a risk factor for cardiovascular diseases and relevant mortality in the hypertensive population. No effect of decreased GFR could be determined on stroke incidence, which was regarded as one of the end-points in these studies. In contrast, Nakayama et al⁴ proposed that, after adjusting for classical risk factors such as age, hypertension, diabetes mellitus, smoking and history of cardiovascular disease, impaired renal function still acted as a risk factor for ischaemic and haemorrhagic stroke. They reported that creatinine clearance <40 ml/min increased stroke risk by 3.1 times, and 40-70 ml/min increased by 1.9 times. Kobayashi et al compared two hypertensive populations with and without chronic renal disease and demonstrated that asymptomatic cerebral lacunar infarcts occurred more frequently in patients with decreased GFR.⁵ The high prevalence of lacunar infarcts emerging as a result of lipohyalinosis and atherosclerosis of small vessels could be explained by insulin resistance, increased atherosclerotic process and hyperhomocysteinemia in patients with chronic renal disease.⁵ In a follow-up study of patients without any stroke history, decreased GFR was found to be a risk factor for haemorrhagic, but not for ischaemic stroke patients.⁶ Accordingly, a significant decrease in GFR was seen in haemorrhagic stroke patients than the controls in our study, but additionally we found a significant GFR decrease in ischaemic stroke patients. Two explanations are proposed for the association of low GFR and haemorrhagic stroke. Firstly, disease of thin vessels could be the common basis for both decreased GFR and intracerebral haemorrhage, the latter taking place as a result of the rupture of perforating cerebral arteries.¹⁵ The second possible explanation is that chronic renal disorders cause platelet dysfunction. Increased bleeding tendency even in the state of slightly decreased GFR might contribute to the development of intracerebral haemorrhage.

Several studies reported that the mortality at the 30th day after acute stroke was associated with elevated creatinine levels.^{2,3,7} Our study was limited by the absence of mortality data; therefore, we were not able to interpret the effect of renal dysfunction on mortality. However, in our study, the stroke severity of the patients was found to be related to increased creatinine levels. Stroke severity is one of the factors that influence early mortality rate.

Conclusion

We consider that acute stroke patients have impaired renal function, and the renal dysfunction is particularly more prominent in haemorrhagic stroke and probably exists prior to the stroke. Whether renal dysfunction is an independent risk factor for stroke needs to be clarified by large population studies.

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