Is low cystatin C in acute stroke a blessing or a curse? a pilot study on Egyptian patients

Elham M. Sobhy[a], Yasser M. Abdelhamid[a], Enas Hamdy[b], Mona M. Adam[c]

Departments of [a]Internal Medicine, [b]Clinical and Chemical Pathology, Kasr Al Ainy Hospitals, Faculty of Medicine, Cairo University, Cairo, [c]Department of Internal Medicine, Al-Agouza Police Hospital, Cairo, Egypt

Correspondence to Yasser M. Abdelhamid, MD, Mokatam- Alhadaba Alwosta- Alhai Alsabe (7th Area) 11571
Tel: 01001450049;
e-mail: dyabdelhamid@kasralainy.edu.eg

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Introduction
Cerebrovascular stroke is a costly disease. Elevated cystatin C levels were independently associated with both ischemic and hemorrhagic stroke. In contrast, cystatin C has been found to play protective roles in the nervous system.
Aim
The aim of the present study was to find out the relationship between serum cystatin C level and the outcome of acute cerebrovascular stroke in middle aged and elderly Egyptian patients.
Patients and methods
This study was conducted on 49 patients with recent stroke and normal kidney functions and 30 healthy matched controls. All patients were followed up for 1 week. Cystatin C was determined for both patients and controls.
Results
Cystatin C level tended to be lower in patients than in controls, both below and above the age of 60. Females tended to have higher levels of cystatin C. There was a gradual decrease in the cystatin C level according to the outcome, being least in the deteriorated group. However, the differences were insignificant.
Conclusion
The results suggest that low cystatin C level — in a patient with normal kidney function – may predict worse prognosis. Accordingly, creatinine estimation is mandatory in assessing the kidney function in these patients and cystatin cannot replace it, as it may represent another risk factor.

Keywords:
cerebrovascular, cystatin, stroke

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Introduction

Cerebrovascular stroke is a costly disease from human, family, and social perspectives [1].

The prognosis after acute ischemic stroke varies greatly, depending on the stroke severity and on the patient's premorbid condition, age, and complications after stroke [2]. There is no single blood marker for the prediction of prognosis in ischemic stroke. The combination of multiple blood markers may enhance the predictability of long-term outcome following an ischemic stroke [3].

Cystatin C is a serum measure of renal function that appears to be independent of age, sex, and lean muscle [4]. Elevated cystatin C levels were independently associated with both ischemic and hemorrhagic stroke, and cystatin C was a strong predictor for the risk of cardiovascular events and death [5]. A close relationship was found between cystatin C levels and cerebral small vessel disease, independently of conventional risk factor in community-based elderly patients [6].

In contrast, cystatin C has been implicated in the response of the nervous system to neuronal degeneration. Recent in-vitro and in-vivo data have demonstrated that cystatin C plays protective roles in the nervous system through pathways that are dependent on the inhibition of cysteine proteases, such as cathepsin B, by the induction of autophagy, induction of proliferation, and the inhibition of amyloid-β aggregation [7].

The aim of this work was to find out the relationship between serum cystatin C level and the outcome of acute cerebrovascular stroke in middle aged and elderly Egyptian patients.

Patients and methods

This study was conducted on 49 Egyptian patients presented with recent onset cerebrovascular stroke and 30 healthy age-matched and sex-matched matched controls.

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All patients were recruited from the Internal Medicine Department, Kasr Al-Ainy Hospitals at Cairo University [25/49 (51%)], and from Al-Agouza Police Hospital [24/49 (48.97%)]. The study was conducted from September 2011 to May 2012.

Inclusion criteria were recent cerebrovascular accidents (within 2 days of diagnosis) proved by history, examination, and radiological investigation; and normal serum creatinine level.

Exclusion criteria were acute embolic stroke (fibrillating patients), abnormal serum creatinine level, current corticosteroid therapy, and patients with more than 2 days of diagnosis, known to have malignancy, with liver disease, and those who suffered from a stroke because of cerebral venous thrombosis.

All patients were followed up for 1 week during their hospital stay concerning their conscious level using the Glasgow Coma Scale.

Patients were subjected to the following:

(1) Complete history taking.
(2) Complete physical examination with special stress on neurological deficit and the level of consciousness using the Glasgow Coma Scale in following up of the patients.
(3) Routine laboratory investigation, which included measurement of blood glucose, serum urea and creatinine, and lipid profile. Liver enzymes were measured to exclude liver diseases.
(4) Measurement of cystatin C by using the enzyme-linked immunosorbent assay test.
(5) Radiological investigation, which included a computed tomography scan or MRI brain to diagnose the condition.
(6) ECG and echocardiography to exclude embolic stroke.
(7) All patients were followed up for 1 week to assess the improvement or deterioration of their conscious levels.

Estimation of serum cystatin C

Serum cystatin C was measured by using an enzyme-linked immunosorbent assay using a kit supplied by BioVendor.

Statistical analyses

The data were coded and entered using the statistical package SPSS (version 15; SPSS Inc., Chicago, Illinois, USA). The data were summarized using mean and SD for quantitative data, and number and percentage for qualitative data.

Student's *t*-test was used to assess statistical differences between the two groups of quantitative data. Nonparametric Mann–Whitney and Kruskal–Wallis tests were used for quantitative variables, which were not normally distributed. As for qualitative data, statistical differences and potential relations were assessed using the χ^2-test. Pearson's correlation was used to study the relation between quantitative data.

P values less than or equal to 0.05 were considered statistically significant.

Results

This study was conducted on 79 participants divided into two groups:

(1) Group A (the study group), which comprised 49 patients with recent onset of cerebrovascular stroke with an age range of 46–75 years.
(2) Group B (the control group), which comprised 30 normal individuals who were age and sex matched with the patients.

Table 1 shows the demographic data of the patients and Table 2 shows comparison between patients and controls (Fig. 1).

According to the age group, patients and controls were divided into two groups: less than 60 years and more or equal to 60 years.

Cystatin C tended to be higher with increased age but was found to be lower in patients than in controls in

Table 1 Demographic data of patients

Variables	Value (mean ± SD)
Age(years)	60.92 ± 8.24
Sex (female/male)	23/26
Hypertension [*N* (%)]	31/49 (63.26)
Diabetes [*N* (%)]	22/49 (44.89)
Type of insult [*N* (%)]	
Infarction	35/49 (71.42)
Hemorrhage	14/49 (28.57)
Urea (mg/dl)	31.52 ± 13.79
Creatinine (mg/dl)	0.90 ± 0.23
Cholesterol (mg/dl)	213.80 ± 57.11
Triglycerides (mg/dl)	185.21 ± 122.52
ALT (μg/l)	23.71 ± 11.95
AST (μg/l)	30.03 ± 12.59
Cystatin C (ng/ml)	2450.76 ± 1150.62
Outcome	
Improved	14/49 (28.57)
No change	29/49 (59.18)
Deteriorated	6/49 (12.24)

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

both age groups (P = 0.273 and 0.835, respectively) (Fig. 2).

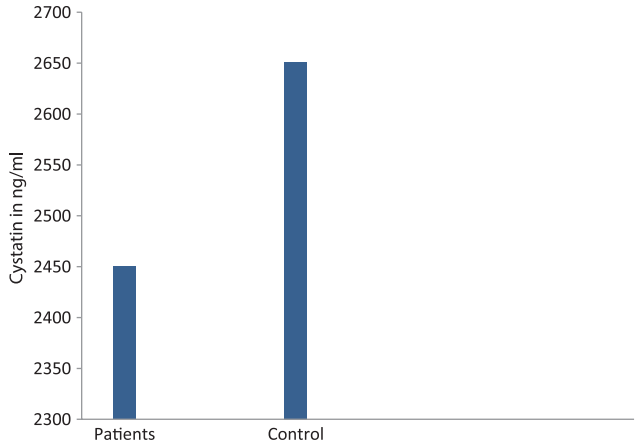
Regarding sex, women tended to have higher levels of cystatin C compared with men in both groups (P = 0.429 and 0.089, respectively).

Levels of cystatin C were lower in patients than in controls (Fig. 3).

Table 2 Comparison between patients and controls

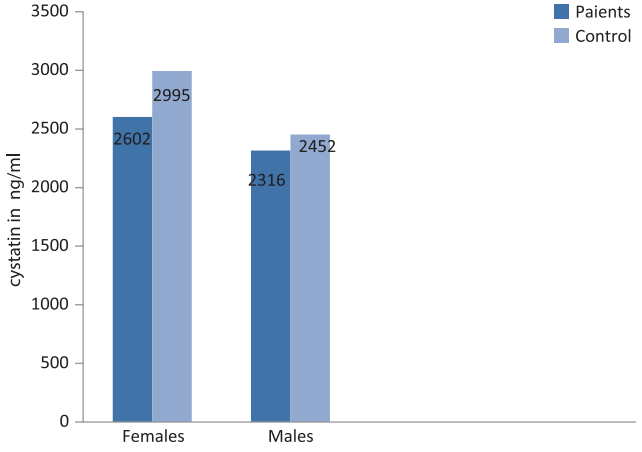
Variables	Cases (n = 49)	Control (n = 30)	P value
Age (years)	60.92 ± 8.24	58.50 ± 7.08	0.186
Sex (female/male) [n (%)]	23/26 (46.9)	11/19 (36.7)	0.371
Urea (mg/dl)	31.52 ± 13.79	24.91 ± 10.06	0.025
Creatinine (mg/dl)	0.90 ± 0.23	0.90 ± 0.30	0.799
Cystatin (ng/ml)	2450 ± 1150.62	2651.72 ± 1097.56	0.312

Figure 1



Cystatin C level in patients and controls.

Figure 3



Cystatin C in male and female patients and controls.

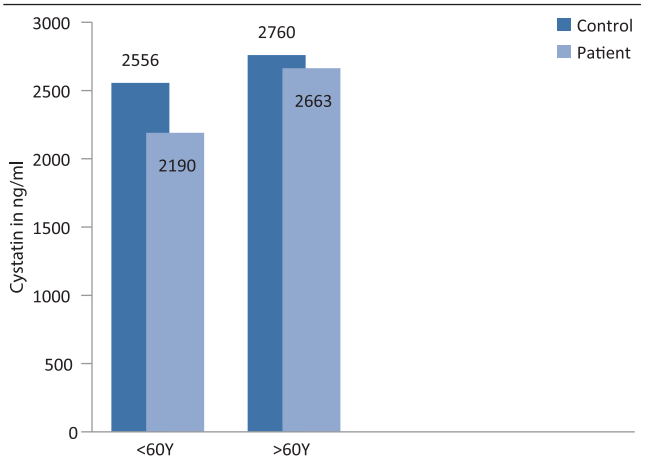
As regards its relation to the patients' outcome, there was a gradual decrease in the cystatin C levels according to the outcome, being least in the deteriorated group. However, the difference did not amount to the level of significance (Fig. 4).

The cystatin C level was insignificantly higher in patients who had suffered an ischemic stroke than in those who had suffered a hemorrhage (2595.09 ± 1241.48 and 2089.93 ± 813.06; P = 0.224).

In group A patients, a positive significant correlation was found between cystatin C and creatinine, whereas there was no significant correlation between cystatin C, age, triglycerides, fasting blood sugar, urea, and liver function.

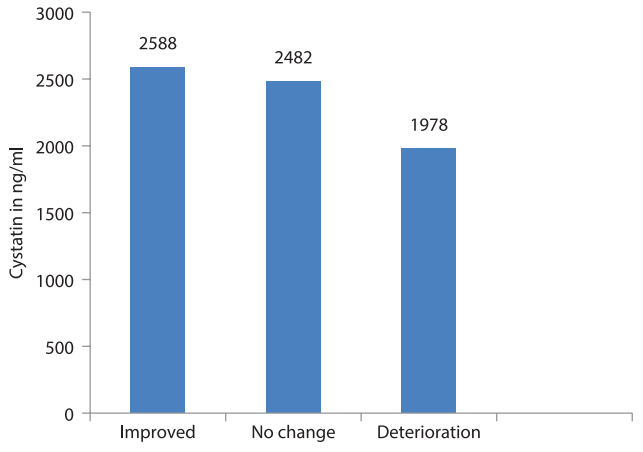
No significant difference was found in cystatin C in patients with diabetes or hypertension.

Figure 2



Cystatin C in patients and control aged less than 60 and more than 60 years.

Figure 4



Cystatin in patients according to the outcome.

In the control group, no significant correlation was detected between age, blood urea and serum creatinine, and cystatin C.

Discussion

Cerebrovascular stroke is a major worldwide health problem. Stroke is the second cause of death in the world population after ischemic heart disease.

The finding of a predictive and/or prognostic marker may be helpful in preventing the disease and/or dealing with expected consequences.

The role of cystatin C in the brain has been reported to be mysterious and enigmatic.

In contrast, a significant protective role has been proposed through different mechanisms including the inhibition of cysteine proteases, regulation of cell proliferation, autophagy, and antiamyloidogenesis [7].

In this sense, low cystatin C levels may be an ominous predictive sign and grave prognostic sign.

In contrast, cystatin C is a serum measure of kidney function that approximates direct measures of glomerular filtration rate and is more precise compared with creatinine.

A significant amount of data support a relation between kidney diseases and stroke incidence. Over the past decade, substantial evidence has been accumulated on the increased stroke incidence and mortality associated with chronic kidney disease before the need for dialysis [8]. Thus, low cystatin C level may be a blessing and a good sign as it points out surely to normal kidney functions and thus less risk for stroke.

We found that serum level of cystatin C tended to be lower in patients than in controls. It also tended to be lower in patients who deteriorated than those who followed a stable course or those who improved. No association could be detected between cystatin C level and ischemic or hemorrhagic stroke. This is in favor of the idea that cystatin C plays a protective role.

This is in contrast to the finding of a study by Ni *et al*. [5], who stated that elevated cystatin C levels were independently associated with both ischemic and hemorrhagic stroke, and that cystatin C was a strong predictor for the risk of cardiovascular events and death. However, they did not exclude patients with abnormal renal functions (creatinine was 1.12 ± 0.49 mg/dl). This may represent merely the increased risk imposed by renal impairment on the incidence of stroke.

Our findings were also not in agreement with a study by Xiao *et al.* [9], who found that cystatin C was significantly higher in patients with ischemic stroke than in controls. However, the creatinine level was significantly higher in patients with ischemic stroke than in control, signifying renal affection. In patients with cerebral hemorrhage, mean creatinine level and SD was outside the normal range (86.100 ± 81.771 μmol/l). Xiao *et al.* [9] in their study also found cystatin C to be positively correlated with age, which was not in agreement with our results. Our results agree with theirs in that cystatin is correlated with creatinine and urea and not correlated with hypertension, diabetes, or the cholesterol level.

The possible neuroprotective role of cystatin C agrees with previous studies conducted on neurodegenerative diseases. In their study, Kaur and Levy [10] found low concentrations of cystatin C levels in cerebrospinal fluid and plasma of Alzheimer's disease patients, and they also stated that in-vitro results showed that cystatin C protected neuronal cells from a variety of insults that may cause cell death. They also suggested that reduced levels of cystatin C manifested in Alzheimer's disease contributed to increased neuronal vulnerability and impaired neuronal ability to prevent neurodegeneration. Moreover, an analysis of cystatin C levels in plasma revealed a significant tendency of conversion from mild cognitive impairment to dementia in patients with cystatin C levels lower than 1067 ng/ml.

Our results also showed that cystatin C levels tended to be higher in females than in males, both in controls and patients, and increased with age. This was in disagreement with the findings of a study by Groesbeck *et al.* [11], who found that the mean serum cystatin C level was higher in males than in females and decreased with age. This may be due to different age groups studied, as the study was conducted on the age group 12–19 years. The disagreement may also be attributed to different ethnicity. However, our results were in agreement with a study by Al Wakeel *et al.* [12], who found that mean serum cystatin C in females was significantly higher than in males and increased with age. This can be attributed to similar ethnicity and the age group studied.

There was no correlation between cystatin C level and diabetes and no difference could be detected between diabetic and nondiabetic individuals. This was in agreement with a study by Maahs *et al.* [13], who found that serum cystatin C levels were similar in adolescents (age: 12–19 years) with and without type 1 diabetes. Their findings also agreed with those of a study by Tayeh *et al*. [14], who found no difference

or correlation between cystatin C levels in diabetic and nondiabetic patients with ischemic heart disease.

There was a statistically significant difference in blood urea between patients and controls, as dehydration may cause an alteration in the level of consciousness of the stroke patient, and may result in irregularity in oral intake.

In conclusion, although our study group was small and the numbers failed to show significance, these results may be a forward step in the way to reconsider the role of cystatin C in acute stroke.

This is the first study, to our knowledge, percussing the area of protective role of cystatin C in acute stroke. The results suggest that low cystatin C in a patient with normal kidney function may predict worse prognosis than in those with higher levels. According to this theory, creatinine estimation is mandatory in assessing the kidney function in these patients and cystatin C cannot replace it as it may represent another risk factor.

Further studies using larger number of patients are essential to verify this finding and to identify a 'cutoff' level for serum cystatin C to be protective.

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Nil.

Conflicts of interest
There are no conflicts of interest.

References

1 Strong K, Mathers C, Bonita R. Preventing stroke: saving lives around the world. Lancet Neurol 2007; **6**:182–187.

2 Adams HP, Davis PH, Leira EC, Chang KC, Bendixen BH, Clarke WR, *et al.* Baseline NIH Stroke Scale score strongly predicts outcome after stroke: a report of the Trial of 10172 in Acute Stroke Treatment (TOAST). Neurology 1999; **53**:126–131.

3 Park SY, Kim J, Kim OJ, Kim JK, Song J, Shin DA, Oh SH. Predictive value of circulating interleukin-6 and heart-type fatty acid binding protein for three months clinical outcome in acute cerebral infarction: multiple blood markers profiling study. Crit Care 2013; **17**:R45.

4 Shlipak MG, Sarnak MJ, Katz R, Fried LF, Seliger SL, Newman AB, *et al.* Cystatin C and the risk of death and cardiovascular events among elderly persons. N Engl J Med 2005; **352**:2049–2060.

5 Ni L, Lü J, Hou LB, Yan JT, Fan Q, Hui R, *et al.* Cystatin C, associated with hemorrhagic and ischemic stroke, is a strong predictor of the risk of cardiovascular events and death in Chinese. Stroke 2007; **38**:3287–3288.

6 Wada M, Nagasawa H, Kawanami T, Kurita K, Daimon M, Kubota I, *et al.* Cystatin C as an index of cerebral small vessel disease: results of a cross-sectional study in community-based Japanese elderly. Eur J Neurol 2010; **17**:383–390.

7 Gauthier S, Kaur G, Mi W, Tizon B, Levy E. Protective mechanisms by cystatin C in neurodegenerative diseases. Front Biosci 2011; **3**:541–554.

8 Townsend RR. Stroke in chronic kidney disease: prevention and management. Clin J Am Soc Nephrol 2008; **3**(Suppl 1):S11–S16.

9 Xiao D, Liu H, Zhang H, Luo Y. Impact of cystatin C levels on infarct size and hemorrhage volume in acute cerebral stroke. J Neurol 2012; **259**:2053–2059.

10 Kaur G, Levy E. Cystatin C in Alzheimer's disease. Front Mol Neurosci 2012; **5**:79.

11 Groesbeck D, Köttgen A, Parekh R, Selvin E, Schwartz GJ, Coresh J, Furth S. Age, gender, and race effects on cystatin C levels in US adolescents. Clin J Am Soc Nephrol 2008; **3**:1777–1785.

12 Al Wakeel JS, Memon NA, Chaudhary A, Mitwalli AH, Tarif N, Isnani A, Hammad D. Normal reference levels of serum cystatin C in Saudi adults. Saudi J Kidney Dis Transpl 2008; **19**:361–370.

13 Maahs DM, Prentice N, McFann K, Snell-Bergeon JK, Jalal D, Bishop FK, *et al.* Age and sex influence cystatin C in adolescents with and without type 1 diabetes. Diabetes Care 2011; **34**:2360–2362.

14 Tayeh O, Rizk A, Mowafy A, Salah S, Gabr K. Cystatin-C as a predictor for major adverse cardiac events in patients with acute coronary syndrome. Egypt Heart J 2012; **64**:87–95.