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ORIGINAL ATRICLE

Cystatin C serum level and radiological findings in acute ischemic stroke

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ABSTRACT

Background: Cerebrovascular stroke is a costly disease. Cystatin C is an important biomarker for acute ischemic stroke due to the background of accumulating evidence indicating a link between vascular disease of the kidney and brain. We investigated the association of serum cystatin C levels with radiological findings of first ever acute ischemic stroke.**Methods:** We included in this prospective cohort study 58 adult patients with first ever acute cerebrovascular ischemic stroke of not more than 72 hours duration with normal kidney functions (26 males and 32 females with age ranged from 33 to 90 years). Serum cystatin C level was measured by enzyme-linked immune-sorbent assay (ELISA) . All patients were subjected to brain computed tomography (CT) scan to confirm the diagnosis of acute ischemic stroke and it was repeated after 48 hours. **Results:** We found statistically significant positive correlation between cystatin C serum level and early signs of middle cerebral artery (MCA) infarction and size of infarction. **Conclusion:** There is positive correlation between serum cystatin C level and size of infarction in acute ischemic stroke.

Keywords: Cystatin C, Stroke, Infarct size.

INTRODUCTION

Cystatin C is a 122-amino acid, 13-kDa protein that is a member of the family of cysteine proteinase inhibitors[1] .It is freely filtered by the glomerulus and is largely reabsorbed and metabolised in the proximal tubules[2].Cystatin C is a better estimate of renal function, particularly within the normal range of kidney function[3].The attractiveness of cystatin C as a biomarker for acute ischemic stroke is obvious, in the background of the assossiation between vascular disease of the kidney and brain. Vascular supply to kidney and brain have a lot of similarities. Both are exposed to high-volume blood flow throughout the cardiac cycle and are low resistance end-organs. It therefore seems logical that microvascular disease in the kidney and brain might be associated[4].

This study was undertaken to evaluate the association of serum cystatin C levels with first ever acute ischemic stroke, and to correlate it with the radiological findings in brain CT scan.

METHODS

We included in this prospective cohort study 58 adult patients with first ever acute cerebrovascular ischemic stroke with normal kidney functions.

Inclusion criteria:

Patients with first ever acute cerebrovascular ischemic stroke who were diagnosed according to the World Health Organization (WHO) criteria [5],confirmed by brain computed

tomography (CT) , Patients were asssessed in the first 72 hours of stroke , Age ≥ 18 years.

Exclusion criteria :

Those who suffered from hemorrhagic stroke (intracerebral hemorrhage or subarachnoid hemorrhage),any central nervous system (CNS) disease other than acute cerebral arterial infarction ,patients under thrombolytic therapy,patients with history of head injury ,patients with chronic kidney disease, patients with liver diseases.

Patients were subjected to the following:

Complete history taking, full general and neurological examination.

Laboratory investigations: Both routine and special laboratory investigations were done at Clinical pathology department, Zagazig university hospitals.

-Routine laboratory invesigations : complete blood count , liver and kidney function tests , erythrocyte sedminetation rate and lipid profile.

-Special laboratory investigations :measurement of cystatin C serum level in three ml of venous blood which were drawn from all ischemic stroke patients using standard venipuncture techniques, within 72 h of stroke onset. Blood samples were left to clot for 4 hours at room temperature, then centrifuged to obtain the serum which was stored frozen .The levels of cystatin C were measured by the use of double antibody sandwich enzyme-linked immune-sorbent assay technology.

Radiological investigations : Brain CT was done initially for detection of early signs of middle cerebral artery infarction and later on after 48 h for calculation of the infarction volume which was divided as small (less than 1.5 cm^3), moderate (1.5 cm^3 to 3 cm^3) and large (more than 3 cm^3)[5]

Follow up:

***** All patients were followed up for 1 week by National Institutes of Health Stroke Scale (NIHSS)

*** We classify patients into two groups:**

a) Group with early neurological deterioration (END): in which there is decrease in NIHSS by 2 points or more during the first 7 days following symptom onset including patients who died[6]

b) Group without early neurological deterioration (Non END)[6].

Written informed consent was obtained from all participants and the study was approved by the research ethical committee of Faculty of Medicine, Zagazig University. The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis:

The data were coded and entered using the statistical package SPSS. The data were summarized using mean and SD and median and IQ range 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 (MW) and Kruskal–Wallis (KW) tests were used for quantitative variables, which were not normally distributed. P values less than or equal to 0.05 were considered statistically significant.

RESULTS

We included in this prospective cohort study 58 adult patients with first ever acute cerebrovascular ischemic stroke of not more than 72 hours duration with normal kidney functions (26 males and 32 females with age ranged from 33 to 90 years).The mean age was 61.2± 14.5 **[Table 1]**.

Regarding vascular risk factors, 69% of our patients were hypersensitive, 56.9% were diabetic, 27.6% had cardiac risk factors, 17.2% were current smokers **[Figure 1]**

Table 2 shows that 17.2% of our ischemic stroke patients had early signs of middle cerebral artery (MCA) infarction. Ischemic stroke of anterior circulation had a high percentage, left sided brain lesion are more frequent than right sided lesion and regarding size of infarction, we found that medium sized infarctions are the most prevalent followed by small sized lesions.

We found statistically significant positive correlation between cystatin C serum level and

early signs of middle cerebral artery (MCA) infarction (p=0.03) and there was statistically significant positive correlation between cystatin C serum level and size of infarction (p<0.001) **[Table 3]**

There is highly statistically significant association between END and early signs of middle cerebral artery (MCA) infarction and size of lesion. END is associated with large size of infarction **[Table 4]**

Table 1. Age and sex distribution of studied patients

Variables	Studied patients (n=58)
Age (years): Mean ± SD Range	 61.2 ± 14.5 33.0 – 90.0
Sex: Males Females	 26 (44.8%) 32 (55.2%)

Table 2. Characteristics of brain imaging among stroke patients.

	Frequency	Percentage
Early signs of middle cerebral artery (MCA) infarction: Absent Present	 48 10	 40.8% 17.2%
Site of lesion: Anterior circulation Posterior circulation Multiple territory	 46 3 9	 79.3% 5.2% 15.5%
Side of lesion: Left Right	 22 36	 37.9% 62.1%
Size of lesion: Small Medium Large	 18 23 17	 31.0% 39.7% 29.3%

Table 3. Association between cystatin C serum level and brain imaging.

Size of lesion	Cystatin C ($x10^3$ ng/ml)			P
	Median	IQ-Range		
Early signs of middle cerebral artery (MCA) infarction:			MW	
Absent	8.2	5.5-16.3	300	0.03
Present	14.4	11.0-19.5		
Site of lesion:			KW	
Anterior circulation	4.2	3.5-9.0		
Posterior circulation	7.3	3.0-11.0	94	0.2
Multiple territory	5.5	4.5-13.0		
Side of lesion:			MW	
Left	7.3	4.5-13.5		
Right	5.9	3.0-15.2	260	0.1
size of lesion :			KW	
Small	4.2	3.4 – 9.4	204	<0.001
Medium	7.5	6.2 – 14.2		
Large	19.8	12.6 – 30.8		

Table 4. Association between END and brain imaging in the studied patients.

Size of lesion	END cases (n=13)		Non-END cases (n=45)		x^2	P
	No	%	No	%		
Early signs of middle cerebral artery (MCA) infarction:						
Absent	4	8.3	44	91.6	fisher	<0.001
Present	9	90	1	10		
Site of lesion:						
Anterior circulation	10	21.7	36	78.3	0.1	0.8
Posterior circulation						
Multiple territory	1	33.3	2	66.7	Fisher	0.5
	2	22.2	7	77.8	Fisher	0.9
Side of lesion:						
Left	7	31.8	15	68.2	1.8	0.1
Right	6	16.7	30	83.3		
Size of lesion:						
Small (n=18)	0	0.0	18	100		<0.001
Medium (n=23)	3	13.0	20	87.0	16.3	
Large (n=17)	10	58.8	7	41.2		

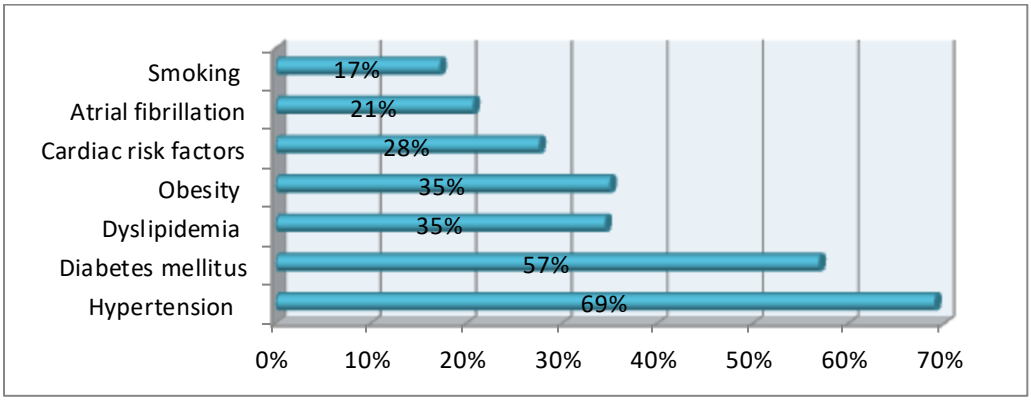

Figure 1. Risk factors in studied patients.

DISCUSSION

As one organ may tell us about the other, there is association between stroke and impaired renal functions as observed in previous various studies and this was based on evidence indicating a link between vascular disease of the brain and kidney[7].

Our study included 58 first ever acute cerebrovascular ischemic stroke patients. Their mean age was 61.2±14.5years with a range (33-90) which approximately near other studies [8-10] who stated that the mean age of their patients was (60 ±16.7, 63.35 ±11.18 and 61.5±10.5) respectively.

Regarding gender difference as a stroke risk, we found that the risk was higher among females than males and represents 55.2% and 44.8% of our stroke patients. Other studies[10-12] are in agreement with our results .

With regard to risk factors, 69% of our patients were hypersensitive, 56.9% were diabetic, 27.6% had cardiac risk factors, 17.2% were current smokers. These results were consistent with a previous study [13] who reported that 76.6% of their patients were hypertensive and 48.4% of them were diabetic.

Our study showed that 17.2% of our ischemic stroke patients had early signs of middle cerebral artery (MCA) infarction, while the percentage was 20.8% by another previous research[10].

In our study, ischemic stroke of anterior circulation had a higher percentage (79.3%) ,These results were consistent with previous studies[14-19].

However, A previous study [20] found that among patients with acute ischemic stroke (AIS), 48.1% patients suffered anterior circulation stroke; 23.8% patients suffered posterior circulation stroke and the remainder suffered multiple infarction including anterior and posterior circulation stroke.

Another study[21] found that among patients with AIS, 62% patients suffered anterior circulation stroke; 23% posterior circulation stroke and 15% multiple infarction including anterior and posterior circulation stroke.

In our study, left sided weakness (LSW) were more frequent than right sided weakness (RSW) .This is in agreement with a study [22] who reported 53.1 % of ischemic stroke patients was with LSW, 46.8 % with RSW and other study [17] in which 50% of cases presented with LSW, in comparison with 38% presented with RSW .

Regarding size of infarction, we found that medium sized infarctions were the most prevalent (39.7%) followed by small sized lesions (31.0%) . A previous research[9] also found that out of the studied ischemic stroke patients 36.6% had large size infarction , 40 % had medium size infarction and 23.3% had small size infarction ,while Other research [23] found that 44% of their patients had small size infarction , 27.9 % had medium size infarction and 27.6% had large size infarction . This variation between our study and their study may be caused by differences in the sample size

and the type of imaging as their patients were imaged with magnetic reasonance imaging [9].

As regards association between cystatin C serum level and brain imaging. We found statistically significant positive correlation between cystatin C serum level and early signs of middle cerebral artery (MCA) infarction and there was statistically significant positive correlation between cystatin C serum level and size of infarction .Cystatin C serum level is higher with larger size of infarction . This is in agreement with a study[24] who reported that patients with higher cystatin C serum level had larger size of infarction . Under ischemic stimuli, neuronal cells, including neurons and astrocytes, may release high levels of cystatin C[25].

Higher cystatin C level was consistently associated with a larger white matter lesion volume [26].

Elevated level of serum cystatin C is associated with the total burden of cerebral small vessel disease in patients with acute lacunar stroke independent of conventional risk factors[4]

In the present study , There was no statistically significant correlation between cystatin C serum level and site or side of the lesion. This is in agreement with a previous study [27] who found that serum cystatin C was not associated with the location of ischemic area .

Early neurological deterioration (END) after acute ischemic stroke is associated with several clinical, biochemical and radiological markers . This deterioration may be due to different processes, for example development of cerebral edema, progression of thrombus and hemorrhagic transformation ; it affects up to 25% of all acute stroke patients and raises the risk of death or disability two to three-fold [28].

Identifying those markers for END will lead to target curative interventions for prevention [

Regarding association between END and brain imaging.We found statistically significant positive correlation between END and early signs of middle cerebral artery (MCA) infarction and there was highly statistically significant association between END and size of lesion. END is associated with large size of infarction .This is in agreement with a previous study[21] However, There was no statistically significant correlation between END and site or side of the lesion.

CONCLUSION

In view of our results, we can conclude that there is statistically significant positive correlation between serum cystatin C level and early signs of middle cerebral artery (MCA) infarction and size of infarction.

We recommend that specialists should consider adding the use of cystatin C serum level to their routine admission testing in patients with acute ischemic stroke, since it is significantly correlated with size of infarction and for prediction of early neurological deterioration of acute ischemic stroke.

We recommend further studies with larger sample size and longer duration of follow up, with measurement of cystatin C during follow up period to assess the fluctuation and variability in its value with time in stroke patients.

Conflict of Interest: Nothing to declare.
Financial disclosure: Nothing to declare.

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