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Pentraxin 3 and Cognitive Decline in Chronic Kidney Disease

Ghada khalifa, Tamer Abd El Tawab, Maged A. Gomaa, Mai Abdel samie, Doaa M Abdou, Dalia Khalifa *

1Assistant professor of Nephrology, Theodor Bilharz Research institute, Egypt. ghadakhalifa05@gmail.com

2Lecturer of Nephrology, Theodor Bilharz Research institute, Egypt. drtamer243@yahoo.com

3Assistant professor of Psychiatry, Kasr Al Ainy Hospitals, Faculty of medicine, Cairo University, Cairo, Egypt. maged.gomaa@staff.cu.edu.eg

4Lecturer or of Psychiatry, Kasr Al Ainy Hospitals, Faculty of medicine, Cairo University, Cairo, Egypt. poeticdr@yahoo.com

5Assistant professor of clinical and chemical pathology, Kasr Al Ainy Hospitals, Faculty of medicine, Cairo University, Cairo, Egypt. doaa.mohamed@kasralainy.edu.eg

Corresponding Author: Dalia Khalifa

Lecturer of psychiatry, Faculty of Medicine, Cairo University, Cairo, Egypt. Tel. :01002676349, Email: dalia.khalifa@kasralainy.edu.eg

Orcid ID: https://orcid.org/0000-0001-9174-2197

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Abstract

Background: Pentraxin 3 (PTX3) is a novel biomarker of vascular inflammation The importance of vascular inflammation, in the pathophysiology of CKD has been demonstrated; however, the role of vascular inflammation and its role in cognitive impairment in those patients is less understood. This study aimed to evaluate relationship between levels of serum Pentraxin 3 and cognitive changes in patients with chronic kidney disease (CKD).

Methods: This study is a cross-sectional study. 75 patients who presented with chronic kidney disease and on renal dialysis were evaluated clinically for neurocognitive impairment. They were divided into two groups; the first group showed normal cognitive functions and second group presented with deterioration of cognitive functions. Montreal cognitive assessment (MOCA) was done for the two groups. Plasma pentraxin 3 levels were measured using a specific enzyme-linked immunosorbent assay.

Results: Group 2 showed significantly lower mean scores than group 1 on executive function, fluency, abstraction, memory, visuospatial, naming and attention subscores and also on the total mean score. However, there were no significant statistical difference regarding the mean serum level of PTX3 in both groups (p=0.103). The correlation between the level of PTX3 and the MOCA mean scores in group 2 showed no significant statistical difference (r= -0.016, p = 0.931)

Conclusions: There is no significant relation between levels of PTX3 and decline in different cognitive functions in patients with chronic kidney disease. This suggests the poor evidence of using vascular biomarkers for identifying patients at risk of cognitive decline.

Keywords: Pentraxin3, cognition, chronic kidney disease, vascular biomarkers.

Introduction

Chronic kidney disease (CKD) is a major health burden. According to the 2019 Global Burden of Disease, 697.29 million patients presented with CKD allover the world leading to about 1.427 million deaths. It is a rapidly growing health problem in which the global prevalence and incidence of CKD reached up to 9.37% and 0.05%, respectively(1, 2). It is related to different complications including anemia, bone disorders, increased cardiovascular morbidity and mortality in addition to cognitive impairment (3).

Cognitive impairment in patients with chronic kidney disease may include different cognitive domains such as learning, memory, attention and speed of processing. Its prevalence usually depends on the stage of CKD ((4). At end stage renal disease that requires hemodialysis, 85% of patients may develop memory loss, impairment in executive functions, or language deficits (5). However, the incidence of impairment of cognitive functions in pre-dialysis patients is 25% and may reach up to 62% in some studies (6,7), compared to f 11–26% in matched general population (6,8).

In (REGARDS) (Reasons for Geographic and Racial Differences in Stroke) Study, it was shown that there was 11% increase in the prevalence of cognitive impairment associated with each 10 mL/min/1.73 m^2 decline in e GFR <60 mL/min/ 1.73 m^2 (9). It also showed that patients on hemodialysis are three times more likely to suffer from cognitive deterioration than age-matched non-dialysis patients (10).

So, the development of cognitive impairment in patients with CKD is associated with the lower glomerular filtration rate in addition to the presence of albuminuria. Also, Cerebrovascular disease is a predominant underlying pathology more than the impaired clearance of uremic metabolites. Other factors like depression, sleep abnormalities, anemia, and polypharmacy may play a role in further deterioration of cognitive functions. It has also

been found that there may be inflammatory cross-talk between the brain and the kidney that may contribute to the increased incidence of cerebrovascular and neuropsychiatric disorders in patients with CKD (11)

The pentraxin family is a superfamily of proteins with common domain known as the pentraxin domain at C-terminal. This family consists of two subgroups; short pentraxins group (C-reactive protein and serum amyloid P component) and long pentraxins (neuronal pentraxin 1, neuronal pentraxin 2, neuronal pentraxin receptor in addition to pentraxin 3 and pentraxin 4. (12). Many studies revealed the functions of different pentraxin family members which are associated with human innate immunity (13).

Several acute phase proteins, such as C-reactive protein (CRP) and PTX3 are elevated among patients presenting with chronic renal failure (CRF). PTX3 protein represents an additional and stable marker of inflammation. PTX3 levels are markedly increased in hemodialysis (HD) patients. The procedure of hemodialysis itself contributes to elevated PTX3 levels and this is supported by the relative increase in PTX3 in whole blood after dialysis. Moreover, the association between PTX3 and cardiovascular morbidity reflects possible connection of PTX3 with atherosclerosis and cardiovascular morbidity in HD patients (14).

Also, pentraxin 3 (PTX3), as a marker of vascular inflammation, may play a role in neuroinflammation and endothelial dysfunction and influence cognitive decline in patients with chronic renal failure (15). However, the current studies are still contradictory and inconclusive. This reflects the need to investigate possible influences of inflammation and innate immunity in the Central Nervous System. In this study, the aim of work was to assess the relation between Pentraxin3 (PTX3) level and degree of cognitive impairment as a whole and each cognitive function in patients with CKD (16).

Methodology

This is a case control study in which 75 patients presenting with chronic renal failure and on renal dialysis were included. The patients were homogenous in age and sex and were recruited from the nephrology department in Theodor Bilharz institute in Egypt. Patients with diagnosis of malignancy, acute infection or sepsis were excluded from the study. Five patients dropped out due to the severe deterioration of their medical condition. The 70 patients were subjected to clinical assessment to assess cognitive functions after which they were divided into two groups. The first group included 39 patients who showed normal cognitive functions and didn't present with symptoms suggestive of cognitive deterioration. The second group included 31 patients who presented with memory impairment and attention deficit.

Blood samples were collected from both groups to measure Pentraxin 3 (PTX3) serum level. Informed oral and written consents were provided and the aim of the study was explained to them and the procedures of sampling and the psycho- metric tests that were applied. Serum PTX3 was measured using a commercially available enzyme-linked immunosorbent assay (ELISA) technique, according to the manufacturer's instructions. (Human PTX3 ELISA Kit, Cosmo bio USA, Catalog Number. CSB-E12926h. www.cusabio.com).This assay follows the quantitative sandwich enzyme immunoassay technique. PTX3 antibody has been pre-coated onto microplates. Standards and samples are pipetted into the wells and any PTX3 present is bound by the immobilized antibody. After removing any unbound substances, a biotin-conjugated antibody specific for PTX3 was added to the wells. After washing, avidin conjugated Horseradish Peroxidase (HRP) was also added to the wells. Washing was done to remove any unbound avidin-enzyme reagent then a substrate solution was added to the wells and color developed in proportion to the amount of PTX3 bound in the initial step. The color development was stopped and the intensity of the color was measured.

Montreal cognitive assessment (MOCA) tests was done for both groups for accurate assessment of cognitive functions. MOCA is one of the most important and widely used screening tools. It is a brief questionnaire that includes 30 questions and takes from 10- 15 minutes to apply. It is used in the assessment of different cognitive functions such as orientation, memory ,visuo-spatial abilities, executive function in addition to language, and attention. The score lies between 0–30. scores which are 26 indicate the presence of cognitive deficit related to Mild cognitive impairment and other major neurocognitive disorders. An additional point can be the number of years of education are considered in which education more than 12 years can have an additional point. This is done through different neuropsychological tasks such as draw a clock test, follow-the- sequence test and copy the 3D cube which are used to assess visuo-spatial abilities and executive functions (5 points). Memory is assessed by delayed recalling of 5 items (5 points). Assessment of orientation and abstraction are also included (6 points and 2 points respectively). Serial subtraction, letters list, digits forward and backwards are used to assess attention (6 points). Language is tested by Fluency task (1 point), repetition of complex sentences (2 points) and identifying names of animals (3 points) [17]. Arabic version validation was done in which a cut-off value of 21/22 showed 92.5% sensitivity and 98.2% specificity in detection of mild cognitive impairment. A lower cut- off value of 16/17 showed sensitivity of 90.7% and specificity of 97.4% for major neurocognitive disorders [18].

Ethical consideration

This study has been approved by the ethical committee of Theodor Bilharz institute , Higher Education Academy With approval number FWA 00010609. The research has involved human participants and has been done in accordance with Declaration of Helsiniki.

Statistical analysis:

Data were coded and entered using the statistical package for the Social Sciences (SPSS) version 28 (IBM Corp., Armonk, NY, USA). Data was summarized using mean, standard deviation, median, minimum and maximum in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were done using the non-parametric Mann-Whitney test (**19)**. For comparing categorical data, Chi square ($\chi 2$) test was performed. Exact test was used instead when the expected frequency is less than 5 **(20)**. Correlations between quantitative variables were done using Spearman correlation coefficient **(21)**. P-values less than 0.05 were considered as statistically significant.

RESULTS

As shown in table 1, both groups were well matched as regards gender and educational level. However, the mean age in group 2 (with cognitive impairment) was substantially greater than in group 1 (p=0.04) (table 2) which may have contributed to the presence of cognitive deficits in the former group. Concerning the clinical profile of the patients, the duration of dialysis (years) in both groups was comparable (p=0.263) (table 2). Assessment of the degree of cognitive impairment in group 2 using the MOCA cut off scores revealed that 36.7% had mild cognitive impairment, 13.3%, moderate impairment while only 1.7% showed severe cognitive impairment.

Upon comparing both groups, regarding the MOCA mean scores, group 2 showed significantly lower mean scores than group 1 on executive function, fluency, abstraction, memory, visuospatial, naming and attention subscores and also on the total mean score revealing an overall substantially lower cognitive performance in group 2 (table 2). Only the orientation and calculation mean subscores were not considerably different in both groups (table 2). However, there were no significant statistical difference regarding the mean serum level of PTX3 in both groups (p=0.103) (table 2).

The correlation between the level of PTX3 and the MOCA mean scores in group 2, revealed a significant positive correlation between the level of PTX3 and the fluency and calculation subscores of MOCA. However the executive function, visuospatial and attention subscores and MOCA total score were negatively but insignificantly correlated to PTX3 level (table 3). Additionally, none of the MOCA test mean scores nor the level of PTX3 were significantly correlated to the duration of dialysis in years.

Table 1: **Comparison between both groups as regards gender and educational level**

		Group 1 (Normal cognitive function)		Group 2(Impaired cognitive function)1		P value
		Count	%	Count	%	
Education	No	3	10.3%	10	32.3%	0.059
	Low	8	27.6%	11	35.5%	
	Medium	9	31.0%	3	9.7%	
	High	9	31.0%	7	22.6%	
Gender	Female	10	34.5%	13	41.9%	0.553
	Male	19	65.5%	18	58.1%	

Table 2: Comparison between group1 and group2 regarding age, MOCA scores, level of PTX3 and duration of dialysis

	GROUP 1 (Normal cognitive function)					GROUP 2 (Impaired cognitive function)					P value
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	
Age	49.41	13.72	50.00	24.00	74.00	56.29	13.01	60.00	25.00	77.00	0.041
PTX3 (0.3-7µg/L)	9.48	11.23	2.60	0.10	40.00	4.39	7.59	0.80	0.10	33.00	0.109
Executive functions	0.66	0.48	1.00	0.00	1.00	0.19	0.40	0.00	0.00	1.00	< 0.001
Fluency	1.72	0.45	2.00	1.00	2.00	1.23	0.56	1.00	0.00	2.00	0.001
Orientation	5.93	0.26	6.00	5.00	6.00	5.58	1.03	6.00	1.00	6.00	0.080
Calculation	2.48	0.74	3.00	0.00	3.00	2.42	0.67	2.00	0.00	3.00	0.540
Abstraction	2.52	0.63	3.00	1.00	3.00	1.97	0.95	2.00	0.00	3.00	0.017
Memory	4.17	0.93	4.00	2.00	5.00	3.23	1.43	3.00	1.00	5.00	0.009
visuo spatial	2.48	0.57	3.00	1.00	3.00	1.42	0.99	2.00	0.00	3.00	< 0.001
Naming	4.00	0.00	4.00	4.00	4.00	3.19	1.38	4.00	0.00	4.00	< 0.001
Attention	2.90	0.41	3.00	1.00	3.00	1.48	1.39	2.00	0.00	3.00	< 0.001
Total score	26.90	1.61	27.00	25.00	30.00	20.32	3.82	22.00	9.00	24.00	< 0.001

Duration of dialysis (years)	5.24	2.98	5.00	2.00	15.00	5.23	1.84	5.00	1.00	10.00	0.263

Table 3: Correlation between PTX3 level and the MoCA test scores in group 2

	Group 2(impaired cognitive function)		
	PTX3 (0.3-7µg/L)		
MoCA scores	**Correlation Coefficient**	**P value**	**N**
Executive functions	-0.078-	0.677	31
Fluency	0.441	0.013	31
orientation	0.048	0.798	31
calculation	0.443	0.012	31
abstraction	0.131	0.484	31
memory	0.136	0.467	31
visuo spatial	-0.136-	0.464	31
Naming	0.032	0.866	31
attention	-0.224-	0.225	31
Total score	-0.016-	0.931	31

Discussion

Pentraxin-3 (PTX3) is a member of the pentraxin family of proteins that has been studied in inflammatory diseases. Its role as a biomarker of vascular inflammation in cognitive decline is still controversial. This study investigated the relation between plasma PTX3 and cognitive decline in patients with CKD. There was no significant relation between levels of PTX3 and decline in different cognitive functions using MOCA test.

In a systematic review regarding the Relationship between Cognition and the levels of PTX-3, and Mannose Binding Lectin (MBL), it was shown that high levels of PTX-3 could be predictors of cognitive impairment while high levels of MBL could have a protective effect on cognition. However, they also concluded that studies are still contradictory and inconclusive, but highlighted the possible genetic influences of innate immunity in the Central Nervous System (**16)**.

On the other hand, another study was done to find the relation between different inflammatory biomarkers as interleukin-2, -6, and -10 (general systemic inflammation); pentraxin 3 (PTX3) and serum amyloid P (SAP) (vascular inflammation);plasminogen activator inhibitor-1, adiponectin, and resistin (metabolic function); receptor for advanced glycation end product (oxidative stress); and endothelin-1 (endothelial function) in 1315 individuals aged 75 and older with no neurological or neurodegenerative disorder . They were examined every 6 months for 7 years using modified Mini-Mental State Examination, the study did not find strong evidence of the utility of the biomarkers evaluated for identifying individuals at risk of cognitive decline. (22).

Moreover,the relationship between PTX3 levels in patients with neurodegenerative disorders was investigated . It showed that by measuring PTX3 levels using specific enzyme-linked immunosorbent assay, Plasma pentraxin 3 levels were significantly higher in the Parkinson disease (PD) patients than in the patients with mild cognitive impairment and Alzheimer's disease and in the control subjects. The study concluded that Plasma pentraxin 3 levels could be a new biochemical marker for PD, and they may be associated with the severity of motor dysfunction rather than cognitive impairment **(**23**)**

The role of Inflammation in aging brain is present. Different types of Dementia are associated with chronic inflammatory process due the release of proinflammatory factors form microglia resulted from the activation of brain immune cell following tissue damage. This resulted in the production of the neurotoxic reactive oxygen species which cause damage of brain cells in hippocampal and other limbic structures that become apparent in decline in different cognitive functions. Inspite of these facts, many researchers spotted the negative relation between different biological inflammatory markers and cognitive performance using MMSE and Wechsler Adult Intelligence Scale-Revised [WAIS-R] subtests), language (abbreviated Boston Naming Test) (24**).**

Also, Ptx3 has shown to have different functions in different stages of kidney diseases. In acute kidney injury, PTX3 protects kidney cells during ischemia. It increases cell viability, reduces [Ca2+] in ischemic cells, reduces reactive oxygen and free radicals, retains mitochondrial membrane potential (MMP) in ischemic cells and reduces apoptosis in ischemic cells **(**25). however, in CDK, plasma PTX3 were found to be significantly high and related to decreased glomerular filtration rate (GFR). Moreover, PTX3 detected in human saliva shows limited correlation with biomarkers associated with systemic inflammation (26).

Conclusion

There is no significant relation between levels of PTX3 and decline in different cognitive functions in patients with chronic kidney disease. This suggests the poor evidence of using vascular biomarkers for identifying patients at risk of cognitive decline. However, larger sample size is needed for further verification of the role of different biological inflammatory markers in cognitive impairment aiming to find new methods of management of decline of cognitive functions.

List of abbreviations:

CKD: chronic kidney disease

PTX3: Pentraxin 3

ESRD: End stage renal disease.

GFR: Glomerular filtration rate**.**

MOCA: Montreal cognitive assessment

WAIS-R: Wechsler Adult Intelligence Scale-Revised

PD: Parkinson disease

MMP: mitochondrial membrane potential

MBI: Mannose Binding Lectin

HRP: conjugated Horseradish Peroxidase

Compliance with Ethical Standards:

Statement of Ethics: Written Informed consent was obtained from all participants. The study protocol was revised and approved by Ethical committee and Institutional Research Board at Theodor Bilharz research institute, Approval number FWA 000 10609

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Author Contributions: G.k: Aim and objective formulation, patient recruitment, data collection, writing manuscript. T.A: Data analysis, patient recruitment, writing and editing manuscript. M.A: Survey formulation, data analysis, writing manuscript. D.K: Survey formulation, data analysis, writing manuscript. M.G: Aim and objective formulation, data collection, writing manuscript, D.A: laboratory measurement of ptx3.

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