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ORIGINAL ARTICLE

Serum Retinoic Acid as a Predictor of Cognitive Impairment after Acute Ischemic Stroke

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ABSTRACT

Background: Post-ischemic stroke cognitive impairment (PSCI) is one of the most prevalent complications of ischemic stroke affecting the brain with a negative impact on daily activity, quality of life of ischemic stroke survivors, their families, and society. These topics are gaining scholarly attention and may indicate new avenues for action in the prevention and treatment of PSCI so that they have a better quality of life. Previous studies about novel diagnostic biomarkers of PSCI are rare. We speculated that circulating retinoic acid (RA) level might be a prognostic biomarker relating to PSCI.

Aim: Early detection of cognitive impairment among patients with first-ever acute ischemic stroke.

Methods: This prospective cohort study has been carried out in Stroke and Intensive Care Units, Neurology Department,ZagazigUniversty Hospitals on patients who develop first-ever acute ischemic stroke within 7 days of stroke onset. Retinoic acid was measured in all cases.

Results: Retinoic acid was significantly higher among patients with PSCI compared to patients without. Only lower levels of retinoic acid and severe NIHSS were significantly associated factors with PSCI

.**Conclusion:**In a cohort of patients with ischemic stroke, lower blood RA levels were associated with an increased risk of 3-month PSCI.

Keywords:

Retinoic Acid PostIschemicStrokeCognitiveImpairement**;**Montreal Cognitive Assessment

INTRODUCTION

Stroke is considered one of the most prevalent cerebrovascular diseases, with 15 million individuals diagnosed with Stroke every year, making it a second reason for mortality and long-term disability worldwide [1].The majority of strokes are ischemic because there is a decreased blood flow, which is typically caused by arterial blockage [2].All stroke cases, even minor ones result in negative effects as regards everyday activities, executive functions, and mental processes that impact the quality of life, return to work, and activity performance [3].Cognition expresses the higher functions of the brain including: "orientation, memory, visuospatial function, language,executive function, focus, computation, and additional elements"Cognitive function impairment can affect stroke patients in one or more areas; executive dysfunction is primary symptom." of post-stroke cognitive impairment (PSCI) [4].

AlthoughIt is among the main issues following a stroke,PSCI is often diagnosed less than its occurrence, as it may be

neglected in the presence of motor or visual symptoms [5]. However, reports showed an increase in the occurrence of cognitive impairment in stroke cases by at least five to eight times more than non-stroke ones [6].PSCI affects negatively the recovery of motor function, daily activities, and contact with family and society in patients with stroke, with eventually financial burden [7].Accordinglycognitive function is utilized to forecast the functional prognosis for stroke patients[8].Neuropsychological evaluations was the base of assessment of PSCI , with limited accuracy and objectivity and affected by both education and age. Therefore, neuropsychological testing is insufficient to accurately diagnose and prognosticate PSCI [9].

Molecular biomarkers for stroke have drawn the interest of medical professionals worldwide in recent years due to their wide range of applications in diagnosing, assessing the extent and severity of clinical symptoms, predicting long-term prognosis, and choosing the best course of treatment [10].Recently, severalmeta-analytic studies have shown that serum, plasma, and cerebrospinal fluid biomarkers can determine the diagnosis, predict cognitive impairment in stroke patients, and help in treatment [11].Research is currently being conducted to assess certain blood-derived proteins for stroke, especially when considering brain damage and cognitive impairments, and to explore the potential of these proteins as PSCI biomarkers [12].

One of these biomarkers is Retinoic Acid (RA) which is a vitamin A metabolite. It has a role in protection of blood vessels, cell growth, differentiation, organogenesis, and mucosal immunity [13].The way inwhich BBB (blood-brain barrier) might be involved in explaining how circulating RA levels affect cognitive function, as BBB disruption has been linked to white matter destruction and the advancement of cognitive impairment. [14]. A recent clinical study reported that decreased levels of serum RA three months after ischemic stroke may be related to PSCI [15].

METHODS

This prospective cohort study has been carried out in Stroke and Intensive Care Units, Neurology Department,ZagazigUniversty Hospitals during the period from December 2022 to December 2023 on 92patients who developedfirst-ever acute ischemic stroke that occurred seven days after the onset of stroke. The patients gave their informed consent for the trial. The institutional ethical committee gave its approval to this.

Review Board (IRB number 9706), Faculty of Medicine, Zagazig University.The study was conducted according to the Helsinki Declaration.The study included individuals with first-everacute ischemic stroke that occurred seven days after the onset of stroke and were older than 18 and of both sexes. The study excluded participants with active or chronic central inflammatory disorders, significant medical illnesses, traumatic brain damage, tumors, hemorrhagic stroke, Parkinson's disease, severe neurological deficit coma, Alzheimer's disease, and psychiatric problems known to impair cognitive function.

All patients were subjected to detailed personal, and family history, full general examination, full neurological examination, CT and or MRI brain examination, ECG to detect ischemic heart disease and AF, regular laboratory testing, such as lipid profiles, blood glucose levels, liver and kidney function tests, and full blood counts, coagulation profile, serum electrolytes level and RA measurement, assessment of stroke severity and subtypes.Additionally noted were the subtype of stroke and the baseline neurological impairment. To assess neurological disability, the National Institutes of Health Stroke Scale (NIHSS) was utilized [16].The parameters used for the TOAST (Trial of Organization 10172 in Acute Stroke Treatment) stroke subtype classification [17].All patients were subjected to plain CT brain scans to exclude intracerebral hemorrhage and or MRI. Retinoic acid was measured in all cases.

Follow-up and Cognitive Function Evaluation

At the Montreal Cognitive Assessment (MoCA), every eligible patient was at the time of admission, one month later, and three months later. The following cognitive domains were assessed by the MoCA: language, abstraction, orientation, naming, memory, attention, and visuospatial/executive functioning. Patients were classified as PSCI if their overall MoCA score was less than 26[18].

STATISTICAL ANALYSIS

The data was collected, tabulated, and statistically analyzed using SPSS 24.0 for Windows (SPSS Inc., Chicago, IL, USA). Mann Whitney and Independent T-tests, Chi-square test, Fisher exact test, logistic regression analysis, and Receiver Operating Characteristic (ROC) curves were implemented.

RESULTS

Hypertension was more prevalent comorbid (63%) followed by dyslipidemia (37%) and smoking (32.6%) then DM (30.4%)(Table 1).The mean serum retinoic acid was 2.62 ± 1.05 ng/L and ranged between 1 – 6.6 ng/L at admission while after 3 months, the mean serum retinoic acid changed to 2.29 ± 1.04 ng/L and ranged between 0.8 – 5.4ng/L(Table 2).There is a significant difference regarding retinoic acid at admission and after 3 months between different NIHSS grades (Table 3).Retinoic acid at admission and after 3 months was significantly lower among patients with PSCI compared to patients without (Table 4).Regarding age and education, there is a substantial disparity between patients with PSCI and those without, Stroke etiology, NIHSS scores as well as Retinoic acid after 3 months of stroke onset (Table 5).There isa significant increase in PSCI in diabetic patients and patients with AF compared to patients without. Regarding other risk factors and comorbidities, there is no substantial distinction between patients with PSCI and those without (Table 6) Higher age, lower education, lower levels of retinoic acid, AF and severe NIHSS were significantly associated factors with PSCI(Table 7)..

Table 1: Demographic characteristics and comorbidities of the studied patients.

Variables	Patients (n=92)	
	Mean± SD Or number	Range Or percentage
Age (years)	63.57 ± 5.62	50 – 74
Gender		
Male	56	60.9%
Female	36	39.1%
Education		
<12 years	48	52.2%
>12 years	44	47.8%
BMI (kg/m2)	27.52 ± 2.74	23.8 – 34.2
Smoking	30	32.6%
Comorbidities		
SBP	146.93 ± 3.5	140 – 155
DBP	95.63 ± 3.87	89 – 100
Diabetes mellitus	28	30.4%
Hypertension	58	63%
Dyslipidemia	34	37%
Coronary heart disease	16	17.4%
Atrial fibrillation	24	26.1%

Table 2: Serum retinoic acid levels among the studied patients.

Variables	Patients (n=92)	
	Mean± SD	**Median (Range)**
Retinoic acid at admission (ng/mL)	2.62 ± 1.05	2.45 (1.0 – 6.6)
Retinoic acid after 3 months(ng/mL)	2.29 ± 1.04	2.1 (0.8 – 5.4)

Table 3: Serum retinoic acid levels distribution according to stroke severity by NIHSS among the studied patients

Variables	NIHSS score at admission			F	P
	Mild (n=29)	**Moderate** (n=54)	**Severe** (n=9)		
Retinoic acid at admission (ng/mL)				4.807	.01
Mean± SD	2.59 ± 0.256	2.49 ± 0.397	2.11±0.75		
Range	1.0 – 4.4	1.2 – 4.6	0.8 –3.7		
Variables	**NIHSS score after 3 months**			**F**	**P**
	Mild (n=45)	**Moderate** (n=35)	**Severe** (n=12)		
Retinoic acid after 3 months(ng/mL)				19.559	<.001
Mean± SD	2.86 ± 0.803	2.31± 1.15	1.03±0.13		
Range	0.9 – 4.4	0.8– 4.4	0.51 – 2.65		

This table shows that there is significant difference regarding retinoic acid at admission and after 3 months between different NIHSS grades.

Table 4: Retinoic acid levels distribution among the studied patients according to presence of PSCI.

Variables	PSCI (n=50)	No PSCI (n=42)	MW	P
Retinoic acid at admission (ng/mL)			832	.016
Mean± SD	2.03 ± 0.99	2.86 ± 1.04		
Range	1.0 – 4.6	1.0 – 4.4		
Retinoic acid after 3 months (ng/mL)			740	.015
Mean± SD	1.95 ± 0.687	2.58 ± 1.19		
Range	0.8 – 3.4	0.8 – 4.4		

Table 5: Demographic and clinical characteristics distribution among the studied patients according to the presence of PSCI after 3monthes of stroke onset

Variables		PSCI after 3 months (n=50)	No PSCI after 3 months (n=42)	t / χ^2	P
Age(years) Mean± SD		63.48 ± 5.89	60.67 ± 5.34	2.38	**.02**
Sex	Male	28 (56%)	28 (66.7%)	1.1	.296
	Female	22 (4%)	14 (33.3%)		
BMI (kg/m^2) Mean± SD		27.28 ± 2.55	27.81 ± 2.95	.923	.359

Education	<12 years	30 (60%)	18 (42.9%)	2.045	.153
	>12 years	20 (40%)	24 (57.1%)		
Radiological Laterality	Left	36 (72%)	20 (47.6%)	**4.719**	**.030**
	Right	14 (28%)	22 (52.4%)		
Infarct topography	Anterior circulation	40 (80%)	30 (71.4%)	0.511	.475
	Posterior circulation	10 (20%)	12 (28.6%)		
Stroke etiology	Cardio embolism	16 (20%)	2 (4.8%)	9.100	**0.003**
	Large artery	30 (72%)	24 (57.1%)	6.84	**0.009**
	Small Vessel	4 (8%)	16 (38.1%)	10.5	0.001
SBP (kg/m^2) Mean± SD		147.32 ± 3.02	142.48± 3.98	1.367	.264
DBP (mmHg) Mean± SD		95.72 ± 4.11	92.52 ± 3.62	.264	.821
NIHSS score Mean± SD		7.86 ± 3.69	6.1 ± 3.4	901	**.020**
Total cholesterol (mg/dl) Mean± SD		177.33 ± 31.7	174.2 ± 26.3	.518	.606
Triglycerides (mg/dl) Mean± SD		146.32 ± 30.1	156.57 ± 34.64	1.52	.132
LDL (mg/dl) Mean± SD		101.1 ± 11.93	102.43 ± 13.5	.509	.612
HDL (mg/dl) Mean± SD		48.4 ± 5.18	47.43 ± 6.03	.832	.408
Retinoic acid after 3 months (ng/mL)		1.95 ± 0.687	2.58 ± 1.19	**740**	**.015**

This table shows that there is a significant difference between patients with PSCI and patients without regarding age, education, Stroke etiology, NIHSS score as well as Retinoic acid after 3monthes 0f stroke onset.

Table 6: Risk factors and comorbidities distribution among the studied patients according to PSCI presence.

Variables	PSCI (n=50)	No PSCI (n=42)	χ^2	P
Smoking	17 (34%)	13 (31%)	.008	.930
Hypertension	32 (64%)	26 (61.9%)	.000	.992
DM	21 (42%)	7 (9.5%)	5.774	**.016**
Coronary heart disease	10 (26%)	6 (7.1%)	.197	.657
Atrial fibrillation	20 (40%)	4 (9.5%)	9.472	**.002**
Dyslipidemia	18 (36%)	16 (38.1%)	.043	.836

Table 7: Multivariate logistic regression analysis to determine the potential factors associated with post stroke cognitive impairment

	OR	S.E.	Sig.	95% Confidence Interval
Age	3.00	.012	**.012***	1.275 – 7.059
Male gender	.901	.537	.851	.303– 2.676
Education	0.743	.103	**0.004***	.607- .909

BMI	1.075	.096	.458	.888 – 1.302
HTN	.252	.819	.091	.051 – 1.246
DM	.583	.548	.326	.198 – 1.713
CHD	4.500	.780	.060	.941 – 21.52
AF	1.009	.135	**.041***	1.00 – 1.014
Dyslipidemia	1.555	.689	.529	.394 – 6.141
Smoking	2.605	.704	.178	.647 – 10.492
Severe NIHSS at admission	.514	.056	**.021***	.222 – 1.192
Retinoic acid at admission	.475	.275	**.008***	.274 - .823

DISCUSSION

The results of the current investigation indicated that the average age of the cases under investigation was 63.57 ± 5.62, Most of the studied cases were males (60.9%). This was comparable to a previous study by Shihmanter et al. [19]as they demonstrated that the majority of individuals were male and fell within the 46–55 age bracket (Table 1).After the age of 45, the incidence of stroke doubles with each decade, and over 70% of all strokes occur in individuals over the age of 65. The frequency of stroke increases with age [20]more prevalent in men and becoming more prevalent in women after the age of 85[21].

Regarding risk factors for ischemic stroke, we found that hypertension was a more prevalent risk factor (63%) followed by dyslipidemia (37%) and smoking (32.6%) then DM (30.4%) (table 2).Similarly, Bayona-Ortíz et al. [22]The primary risk factors were hypertension (75.6%), dyslipidemia (40%), and a previous stroke (38.5%).

Our study showed that mean serum retinoic acid at admission was 2.62±1.05 ng/ml and ranged between1.0 – 6.6 and after 3 months of ischemic stroke onset was 2.29 ± 1.04 ng/L and ranged between 0.8 – 5.4 ng/L.Xu et al. [23] showed that the median RA concentration was 2.9 ng/mL also,Hou et al. [15] found that the median serum RA level in patients with Poststroke Cognitive Impairment was 2.0 ng/mL (interquartile range, 1.1-3.2 ng/mL)

Our study showed that there is a significant decrease in retinoic acid levels in diabetic patients and also there is a decrease in retinoic acid in hypertensive, smokers, coronary heart disease, AF, and dyslipidemia without any significance.Our results are consistent with those of a few other research. According to Liu et al. [24], the concentration of serum RA determined by enzyme-linked immunosorbent assay (ELISA) was significantly lower in T2DM subjects than in normal glucose tolerance subjects.According to earlier research, those with type 1 diabetes appear to have low plasma levels of vitamin A, but individuals with type 2 diabetes had higher levels [25, 26]. Wang et al. [27]demonstrated a positive correlation between dyslipidemia and plasma retinol in both genders. These differences are probably due to the difference in study population, and sample size. Further studies with large sample sizes might be useful to clarify this association.

The present study showed that there is a significant decrease in retinoic acid with the increase in NIHSS (lower in severe than in moderate and lower in moderate than in mild) at admission and after 3 months.In accordance with our findings, Kadri et al.'s study [28] illustrated a strong correlation between the short-term clinical prognosis and serum levels of vitamin A and D during the acute phase of an ischemic stroke.Using the Spearman's correlation test, it was found that the acute phase vitamin A level and NIHSS on day 14 had a significant and strong correlation the higher the concentration of vitamins A and D, the lower the value of NIHSS.Additionally, even after controlling for a number of possible confounders,Xu et al. [23] discovered that lower baseline RA levels were independently linked to a higher chance of a bad outcome developed at three months and early neurological deterioration following ischemic stroke. Moreover, RA may enhance the ability to predict the likelihood of stroke outcomes when added to traditional risk variables. These findings indicated that serum

RA may serve as a valuable biomarker for the prediction of clinical outcomes in patients with acute ischemic stroke.

Wouters et al. [29]revealed that ninety days following a stroke, baseline NIHSS is a reliable indicator of functional outcome.Contrarily, Rist et al. [30] discovered that there was no correlation between elevated retinol-binding protein 4 (RBP4) levels and an increased risk of ischemic stroke.Our study showed that there is a significant increase in PSCI in patients with old age, low education, cardioembolic, large artery stroke, high NIHSS score and AF. Also, there is an increase in PSCI in patients with stroke onthe left side, higher blood pressure, higher cholesterol and triglycerides levels, and increased body mass index with no clinical significance.

Furthermore, a study discovered a substantial correlation between the onset of PSCI and advanced age, cardioembolic etiology, a higher initial NIHSS score, a larger stroke volume, and the presence of cortical or strategic lesions [31].Another study discovered no connection between PSCI and vascular risk factors such as diabetes, hyperlipidemia, ischemic heart disease, atrial fibrillation, TIA, and hypertension. They compared stroke survivors who had PSCI and those who did not, gathering data on possible risk factors through a questionnaire [32].On the other hand, Qu et al. [33] proposed that the primary factors influencing PSCI were stroke features and stroke complications, rather than demographic traits and cardiovascular risk factors.

Numerous investigations have evaluated the risk variables influencing PSCI. Many factors have been identified as independent risk factors for PSCI, including demographics (elder age, female gender, reduced education, low economic status), lifestyle and behavioral factors (alcohol use), cardiovascular disease risk factors (hypertension, hyperlipidemia, coronary heart disease, atrial fibrillation), stroke features (multiple lesions, recurrent stroke), and complications (urine incontinence, dyskinesia, pseudo bulbar palsy, depression, etc.) [34-37].Our study revealed that retinoic acid was significantly lower among patients with PSCI compared to patients without. also, lower levels of retinoic acid and severe NIHSS were significantly associated factors with PSCI (table 13). According to Hou et al. [15], lower In individuals with AIS, the serum level of RA was associated with 3-month poststroke cognitive impairment (PSCI), which is in agreement with our findings.

CONCLUSION

Higher incidences of 3-month PSCI were observed in patients with ischemic stroke when serum RA levels were lower.

CONFLICT OF INTEREST

The authors report no conflicts of interest. The authors are responsible for the content and writing of the paper.

FINANCIAL DISCLOSURE

None declared.

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