

Hyperuricemia And Carotid Atherosclerosis Or Stenosis In Egyptian Stroke Patients

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Abstract

Aim Of Study: To Access The Hemodynamic Changes Of Carotid Circulation, Either Atherosclerosis Or Stenosis, And Its Correlation With Uric Acid Level As A Marker Of Atherosclerosis.

Methods: This Is A Cross Sectional Observational Study Was Done On 130 Stroke Egyptian Patients Who Attended Al Zahraa University Hospital From Period January 2019 To December 2020. Demographic, Clinical Data And Extracranial And Transcranial Carotid Ultrasound Findings Are Analyzed And Correlated With The Level Of Uric Acid.

Results: There Were 81.5% Of Our Subjects Suffered From Carotid Atherosclerosis. 48 (37.1%) Of Them Developed Plaque 48.7% Of These Plaques Causing Extracranial Significant Stenosis More Than 50%. Of All The Stroke Patients 92 Of Them Has A Good Transtemporal Window And Can Be Investigated Well By Transcranial Duplex. We Found That 37.5 (28.5 %) Subjects Developed Significant Intracranial Anterior Circulation Stenosis More Than 50% In Different Segments Of Detected Arteries. The Highest Percentage Was Found In Aca. The Relationship Between Ua Level And Nihss Was Inversely Correlated (P-Value=0.002) (R=- 0.26). Pearson Correlation Analysis Showing That Statistical Correlation Between The High Level Of Ua And Ica Stenosis In Our Studied Patients(P-Value=0.01) (R =-0.372), And Statistical Correlations Between Hyperuricemia And Aca (P-Value=0.009, 0.03) (R=0.276, 0.231) Stenosis And Transcranial Ica Stenosis (P-Value = 0.001) (R = 0.349).

Conclusion: Hemodynamic Significant Of Atherosclerosis In Extracranial And Transcranial Ica And Its Cerebral Branches Among Egyptian Stroke Patients And Significant Correlation Between Serum Ua Level And Intracranial Stenosis.

Key Words: Atherosclerosis, Stenosis, Uric Acid, Stroke.

INTRODUCTION:

Cerebrovascular Stroke (Cvs) Has Become The Second Leading Cause Of Mortality (Cohen Et Al., 2017). 61% Of Ischemic Stroke Are Of The Anterior Circulation Type (Heldner Et Al., 2016)

Cerebral Autoregulation Maintains Stable Cerebral Blood Even With Variations Of Arterial Pressure(Yang & Liu, 2017). Failure Of Autoregulation Mechanisms To Keep Adequate Cerebral Blood Flow To Meet The Requirement Of The Brain. When The Metabolic Demands

Of The Brain Increase Collaterals Cannot Compensate And Ischemia Occurred (**Derdeyn Et Al., 2002**).

Atherosclerosis Is A Disease Of The Intima And Later The Media Bifurcation Of The Blood Vessels. (**Tegos Et Al., 2001**). The Molecular-Level Explanation Of Stroke Is Characterized By Loss Of Neurons, Astroglia, Oligodendrocytes, And Disruption Of The Synaptic Pathway. (**Rodrigo Et Al., 2013**) Resulting In More Calcium Influx To The Cell (**Xu Et Al., 2020**) ,Synaptic Imbalance (**Lai Et Al., 2014**).

Hyperuricemia Is Abnormal Elevation Of Serum Urate More Than 7mg/Dl In Men And 6 Mg/Dl In Women(**Rahmat, Et Al. 2019**). It`S Linked To The Severity Of Some Diseases Like Hypertension, Cardiovascular Disease That Are Affect Health Burden (**Lu Et Al., 2020**)In Egypt, The Prevalence Of Hyperuricemia In The Studied Hypertensive Patients Was 55.4%. (**Afifi Et Al., 2013**).

The Role Of Hyperuricemia In Atherosclerosis Is Controversial. Some Contribute To Increasing The Adverse Outcome And Mortality While Others Thought That It Has A Protective Role Against Poor Outcomes (**Mapoure Et Al., 2019**). **Ua** Was The Independent Predictor Of **Icas**, Rather Than For **Eca**. It May Be Due To The Component Of Atherosclerotic Plaques Was Not The Same Between Intracranial And Extracranial Arteries From Autopsies Of Ischemic Stroke Patients (**Li, 2019**).

Carotid Duplex Is One Of The Noninvasive Investigations That Provide Information About The Carotid Tree And The Plaque (**Bornstein Et Al., 1988**) And The Intracranial Hemodynamics Through Transcranial Color-Coded Duplex Sonography (**Tccs**) (**Barrientos-Guerra Et Al., 2020**)

We Aimed To Demonstrate The Distribution Pattern Of Atherosclerosis With/Without Stenosis Of Extra Cranial And Intra Cranial Arteries (Of Carotid System) And Its Correlation With Uric Acid In Egyptian Hospitalized Patients With Ischemic Stroke.

SUBJECTS AND METHODS

Type, Place and Period of the Study

This Is An Observational Cross-Sectional Study Done At The Neurology Department At Al Zahra University Hospital, Al- Azhar University. It Was Carried Out During The Period From January 2019 To December 2020 (With Off Time From May 2020 To August 2020 Due To Covid19 Pandemic).

Study Population

It Is Conducted On 130 Patients Aged ≥ 40 Years Old, Diagnosed With Acute Ischemic Stroke According To The Who Definition And Confirmed By Computer Tomography (**Ct**)Scan.

Exclusion Criteria

Patients With Ischemic Stroke With Lacunar Infarctions, Cardio Embolic Stroke, Artery Stenosis Were Excluded From The Study. In Addition, Patients With Vessel Occlusion Caused By Non-

Atherosclerotic Factors Such As Dissection, Arteritis, Moyamoya Disease, And Muscle Fiber Dysplasia Or Patients With Cerebral Hemorrhage Were Also Excluded.

Ethical Consideration

The Study Protocol Was Approved By The Ethical Review Committee Of The Faculty Of Medicine For Girls, Cairo, Al-Azhar University, Egypt. Participants Of The Study Were Voluntary; And Informed Written Consent Was Taken From Each Participant Before Enrolment Into The Study. Data Were Unnamed And Coded To Guarantee Privacy Of The Participants.

Methods

All Patients Were Be Subjected To The Following 1) Cardiovascular Risk Factors Assessment Including Age, Sex, Smoking, Hypertension, Diabetes Mellitus (**Dm**) And Obesity. Hypertension Was Defined As Blood Pressure $>140/90$ Mm Hg For >2 Repeated Readings Or If A Subject Was On Antihypertensive Medications; Diabetes Mellitus Known By Repeated Fasting Plasma Glucose >126 Mg/Dl Or A Patient On Antidiabetic Measures; Dyslipidemia As Fasting Serum Total Cholesterol Of >200 Mg/Dl Or Triglyceride Concentration Of >150 Mg/Dl Or If The Subject Was On Lipid-Lowering Drugs Or Gave A History Of Established Diagnosis Of Dyslipidemia. 3)The National Institutes Of Health Stroke Scale (**Nihss**).

In Addition, We Performed Serum Uric Acid (**Ua**) Complete Blood Picture (**Cbc**), Prothrombin Time (**Pt**), Prothrombin Concentration (**Pc**), International Normalization Ratio (**Inr**) Were Done To Exclude Patients With Coagulation Disorder. Also, Liver And Kidney Function Tests Were Accessed To Exclude Other Secondary Causes Of Hyperuricemia.

Radiological Investigation Including:

A) Imaging Studies: Brain Computed Axial Tomography (**Ct**) (Aquilion Prime 160), It Was Done For All Patients On Admission To Exclude Hemorrhagic Stroke.

B) Sonological Investigation Including:

All Patients Underwent A Complete Cervical and Intracranial Ultrasound Assessment with A High-Resolution Color-Coded Duplex Sonography Scanner (Samsung Hs60) Using A High-Frequency (5- To 10-Mhz) Linear Probe For The Cervical Arteries And A Low-Frequency (2- To 5-Mhz) Phased-Array Probe For The Intracranial Arteries.

Statistical Analysis

The Studied Data Were Analyzed By Statistical Program For Social Science (Spss) Version 24. Parametric Variables Were Presented As Mean \pm Standard Deviation (Sd). Pearson's Correlation Coefficient (R) Was Used To Assess The Relationship Between The Two Parametric Variables In The Same Group.

RESULTS:

Table (1) This Table Shows The Description Of Demographic Data In All Studied Patients. As Regard Age, The Mean Age Of All Studied Patients Was 60.2 ± 10.1 Years. As Regard Sex, There Were 110 Males (84.6%) And 20 Females (15.4%) In All Studied Patients.

Table (1) Showing the Demographic Data.

Demographic Data			Studied Patients (N = 130)	
Demographic Data	Age (Years)	Mean ±Sd	60.2 ± 10.1	
		Min - Max	40 – 87	
	Sex	Male	110	84.6%
		Female	20	15.4%

Table (2) Shows The Description Of Risk Factors In All Studied Patients. There Were 92(70.8%) Hypertensive Patients **Htn**, 64(49.2%) Ischemic Heart Disease **Ihd**, 79 (60.8%) Diabetic Patients **Dm**, 86 (66.2%) Patients with Hypercholesterolemia **Chol**, 104 (80%) Patients with Hypertriglyceridemia **Tg** & 84 (64.6%) Patients with Hyperuricemia **Ua** in All Studied Patients.

Table (2) Showing Risk Factors

Risk Factors	No.	%
Htn	92	70.8%
Ihd	64	49.2%
Dm	79	60.8%
Chol	86	66.2%
Tg	104	80%
Ua	84	64.6%

Table (3) Shows The Extracranial Carotid Findings. Of The Included Subjects 106 Of Them Developed Atherosclerosis. About 48.25 (37.15) Of Them Had Plaques Of Different Characters In Which 24.75 (49.8%) Of Them Develop Stenosis Less Than 50% And 23.25 (44.25).

Table (3) Showing The Extracranial Characteristics Of Stroke Patients

		Imt		Plaque		Stenosis	
		Normal	Increase d	Absent	Present	< 50%	> 50%
Rt. Eca	N	27	103	83	47	23	23
	%	20.8%	79.2%	63.8%	36.2%	50%	50%
Rt. Ica	N	---	---	83	47	20	27
	%	---	---	63.8%	36.2%	42.6%	57.4%
Lt. Cca	N	21	109	84	46	23	23
	%	16.2%	83.8%	64.6%	35.4%	50%	50%
Lt. Ica	N	---	---	77	53	33	20
	%	---	--	59.2%	40.8%	62.3%	37.7%

Rt: Right, Lt: Left, Cca: Common Carotid Artery, Ica: Internal Carotid Artery

Figure (1) Shows **Tccd** Findings Were Detected Allover Stenosis Less Than 50% In 64.625 (71.08%) And Stenosis More Than 50% In 26.25 (28.9).

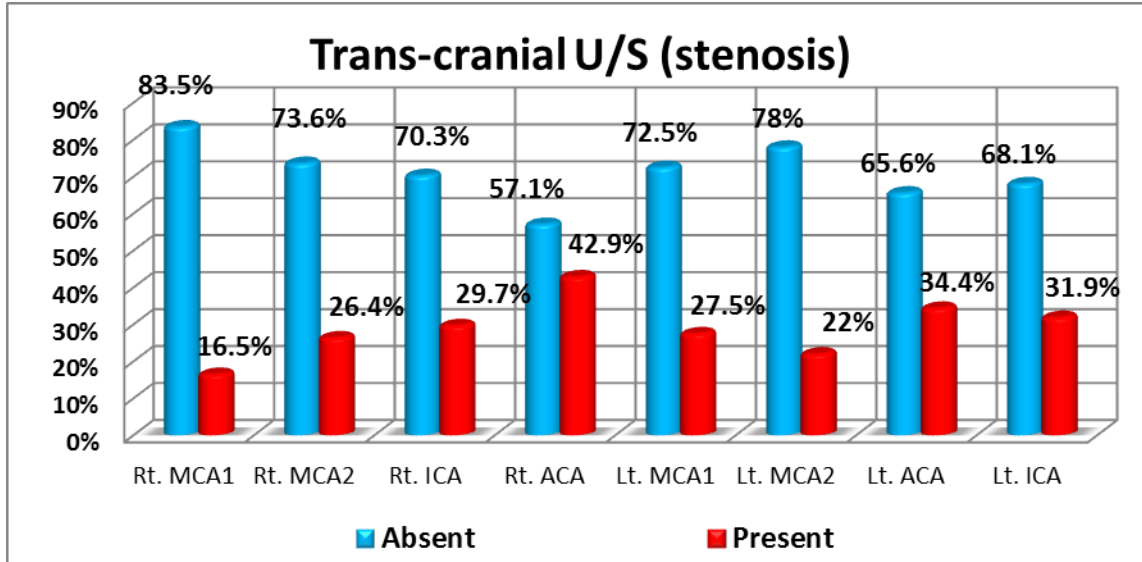
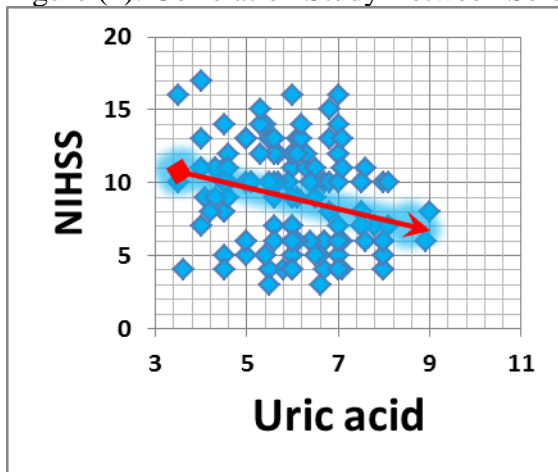


Figure (1) The Transcranial Characteristics Of Stroke Patients.

Mca Middle Cerebral Artery, **Aca** Anterior Cerebral Artery, **Ica** Internal Carotid Artery.

Figure (2) Shows Statistically Significant (**P-Value = 0.002**) Negative Correlation (**R = - 0.26**) Between Serum **Ua** & **Nihss** Score In All Studied Patients.

Figure (2): Correlation Study Between Serum Ua



(R): Person Correlation Coefficient.

S: P-Value < 0.05 Is Considered Significant

Table (6) Represents The Correlation Between Serum **Ua** And Extra-Cranial As There Is Statistically Significant (P-Value = 0.01) Negative Correlation (R = - 0.372) Between Serum **Ua** & **Rt. Ica** Stenosis In All Studied Patients.

Table (7) Shows Statistically Significant Serum **Ua** & **Rt. Aca** Stenosis (P-Value = 0.009) And Between Serum **Ua** & **Rt. And Lt. Ica** Stenosis (P-Value = 0.001, 0.03 Respectively)

Table (6) Correlation Between Serum Ua And Nihss And Nihss In All Studied Groups. Studied Patients.

Extra-Cranial	Studied Patients (N = 130)		
	R	P-Value	
Ua Vs Rt. Cca Stenosis	- 0.098	0.507	Ns
Ua Vs Rt. Ica Stenosis	- 0.372	0.01	S
Ua Vs Lt. Cca Stenosis	- 0.109	0.475	Ns
Ua Vs Lt. Ica Stenosis	- 0.101	0.476	Ns
Ua Vs Rt. Cca Imt	0.048	0.591	Ns
Ua Vs Lt. Cca Imt	0.008	0.926	Ns

(R): Person Correlation Coefficient. S: P-Value < 0.05 Is Considered Significant
Ns: P-Value > 0.05 Is Considered Non-Significant.

Table (7): Correlation Study Between Serum Ua And Trans-Cranial In All Studied Groups.

Trans-Cranial	Studied Patients (N = 130)			Trans-Cranial	Studied Patients (N = 130)		
	R	P-Value			R	P-Value	
Ua Vs Rt Mca1 Stenosis	0.037	0.732	Ns	Ua Vs Lt Mca1 Stenosis	- 0.015	0.886	Ns
Ua Vs Rt Mca2 Stenosis	0.031	0.771	Ns	Ua Vs Lt Mca2 Stenosis	0.078	0.468	Ns
Ua Vs Rt. Ica Stenosis	0.349	0.001	S	Ua Vs Lt. Aca Stenosis	0.231	0.03	S
Ua Vs Rt. Aca Stenosis	0.276	0.009	S	Ua Vs Lt. Ica Stenosis	0.172	0.112	Ns

(R): Person Correlation Coefficient. S: P-Value < 0.05 Is Considered Significant. Ns: P-Value > 0.05 Is Considered Non-Significant.

DISCUSSION:

Stroke Is Considered The Second Cause Of Death And One Of The Major Health Problems In The Egyptian Population (**Abd-Allah Et Al., 2018**). Atherosclerosis Is A Disease Of The Intima And Later The Media Bifurcation Of The Blood Vessels. It Is Considered One Of The Main Etiological Causes Of Ischemic Stroke (**Meschia Et Al., 2014**).

The Overall Prevalence Of Hyperuricemia In Us Adults Was 21.4%, (**Zhu Et Al., 2011**). In Egypt, The Prevalence Of Hyperuricemia In The Studied Hypertensive Patients Was 55.4% (**Afifi Et Al., 2013**). The Prevalence Of Intracranial Stenosis In The Egyptian Population Is Low As It's Account For 11% In An Egyptian Epidemiological Study (**Abd-Allah Et Al., 2014**).

We Conduct An Observational Cross Sectional Study On Stroke Patients Who Attended Al Zahraa University Hospital Through The Emergency Department Or The Outpatient Clinic From 1 January 2019 To 1 December 2020, With 4 Months Rolled Out From The Study Due To Covid 19 Pandemic,. We Aimed To Access The Hemodynamic Changes Of Carotid Circulation, Either Atherosclerosis Or Stenosis, And Its Correlation With Uric Acid Level As A Marker Of Atherosclerosis.

As Regards Risk Factors Of Stroke, Our Study Showed That Anterior Circulation Stroke Is Present Mainly In Elderly Patients At Age Of 60.2 ± 10.1 About 84.6% Of Them Were Males In Which The Stroke Is 5.5 Times Common In Males Than Females. These Results Matched With An Epidemiological Study That Reported Most Stroke Patients Developed The Disease Insult After The Age Of Sixty (**Haq Et Al., 2017**).

The Most Prevalent Risk Factors Found In Our Study Were Hypertension And Hypertriglyceride By 70% And 80% Respectively. This Is Explained By Increasing The Flow Velocity Process By Hypertension Causing Tearing Of The Intima Wall, Atherosclerosis, And Plaque Formation. The Second Prevalent Factors In Our Study Were **Dm**, Hypercholesteremia And, Hyperuricemia. It Was Account For 60.8%, 66.2%, And 64.6% Respectively. These Results Match With Haq Et Al`S Results (**Haq Et Al., 2017**).

Carotid **Imt** Is Considered A Sensitive Marker For Cerebrovascular Vascular Diseases **Cvd**. Increasing **Imt** In A Progressive Process Forming Plaques That`S May Lead To Stenosis (**Haq Et Al., 2017**). Our Study Showed That Out Of 130 Included Stroke Patients, There Were 81.5% Of Them Suffered From Carotid Atherosclerosis In The Form Of Pathological Increased **Imt**. These Results Correlated With An Epidemiological Study That Concluded That; **Imt** Is Important For The Prevalence And Incidence Of Stroke (**Arévalo-Lorido Et Al., 2019**).

Plaque Is Defined As Increasing The **Imt** By More Than 0.2 Cm(**Park Et Al., 2002**). There Are 48 (37.1%) Of Our Subjects Who Developed Plaque. This Percent Was Less Than That Of Hag Et Al`S Study That Showed About 60% Of The Patients Developed Plaque (**Haq Et Al., 2017**). It May Be Due To The Smaller Sample Size Than Our Study.

According To **Nacet** Criteria Of Stenosis, We Found In Our Study That 48.7% Of These Plaques Causing Extracranial Significant Stenosis More Than 50%.

These Results Were Higher Than That Conducted In Abd Allah Et Al`S Study On Egyptian Patients In 2010 Which Included 4733 Subjects, 758 Of Them With Stroke Or Tias Showed That Significant Prevalence Of Carotid Atherosclerosis Is 2.5% Only (**Abd Allah Et Al., 2010**) And Also Much Higher Than The Reported Data From European And American Populations. In An American Cohort Study Conducted In Framingham, Included 1119 Stroke Subjects Showed 16% Of Them Developed Significant Carotid Stenosis (**Goldstein Et Al., 2001**). The Higher Percentage In Our Subjects May Be Due To The Relatively Smaller Sample Size, And It Included The Stroke Patients Only.

The Sensitivity Of The Transcranial Duplex In The Detection Of Intracranial Stenosis Is Very High (**Baumgartner Et Al., 1999**). Of All The Stroke Patients, 92 Of Them Have A Good Transtemporal Window And Can Be Investigated Well By Transcranial Duplex. We Found That 37.5 (28.5 %) Subjects Developed Significant Intracranial Anterior Circulation Stenosis More Than 50% In Different Segments Of Detected Arteries. The Highest Percentage Was Found In The **Aca**.

In Abd Allah Et Al`S Study About The Prevalence Of Transcranial Arterial Diseases (**Tcas**) In Coronary Artery Disease Patients In The First 48 Hours From Onset Is About 27%. This Result

Was Near Or Equal To Our Study It May Be Due To The Difference In Time Of Onset Of The Disease And Most Of Our Subjects Suffered From More Than One Risk Factor (**Abd-Allah Et Al., 2014**). Also, Hispanics And Italians Who Have Nearer Percent As They Share The Same Environmental And Geographical Factors (**Viaro Et Al., 2012**).

Biomarker Of Stroke Is Important For Early Detection And Prognosis Of Stroke However There Is No Known Specific Brain Biomarker. One Of The Oxidative Biomarkers Is Uric Acid. Its Normal Level Acts As An Antioxidant, But At A Higher Level, It Reverses The Pro-Oxidant Effect (**Ng Et Al., 2017**).

Surprisingly, The Relationship Between **Ua** Level And **Nihss** Was Inversely Correlated. This Paradoxical Relationship May Be A Chance Finding Or May Attribute To Single Measurement Of **Ua**, Or Finally Due To Our Small Sample Volume. These Results Match With Lord's Study There Was An Inverse Association Between **Ua** And **Nihss** System Which Explained This Result By The Vascular Protective Effect Of Uric Acid (**Arévalo-Lorido Et Al., 2019**).

There Was Statistical Correlation Between The High Level Of **Ua** And **Ica** Stenosis In Our Studied Patients. In Lorodo'S Study That Was Done In 245 Stoke Patients Who Classified Patients Into Three Groups; Neither Plaque Nor Stenosis, Early Non-Stenotic Plaque, And Advanced Plaques Showing That The Highest Degree Of Stenosis Had The Highest Level Of **Ua** (**Arévalo-Lorido Et Al., 2019**).

Our Study Showed A Statistical Correlation Between Hyperuricemia And **Aca** Stenosis And Transcranial **Ica** Stenosis. Li Et Al'S Study Was Done In Elderly Asian People Conducted Through 2 Years Period And Classify The Patients Into Four Groups To (1) Intracranial Stenosis Atherosclerosis (**Icas**) Group, (2) Combined Intracranial And Extracranial Atherosclerosis Stenosis (**Coas**) Group, (3) Extracranial Carotid Stenosis Atherosclerosis (**Ecas**) Group, And (4) Non-Cerebral Stenosis Atherosclerosis (**Ncas**) Group. This Is Showed The Statistical Significance Of Hyperuricemia And **Icas** And Its Level Positively Correlated With The Severity Of The Intracranial Lesions (**Li, 2019**).

There Are Many Cellular And Molecular Explanations. In The Cellular Aspect, There Are Many Mechanisms Between Uric Acid And Atherosclerosis As **Ua** Promotes Platelet Adhesion To Endothelial Cells, Increasing Platelet Size, Stimulates Endothelial Cell Proliferation, Stimulates The Macrophages Causing More Platelet Aggregation (**Arévalo-Lorido Et Al., 2019**).

The Molecular Mechanism Is **Ua** Causing Lipid Peroxidation Causing Multibed Oxidized Radicals And Atherosclerosis, Excess **Ua** Level Precipitate In The Vessel Wall And Causes Larger Plaque Formation ,Activate Other Inflammatory Cytokines As Interleukin (Il)-1b, Tumor Necrosis Factor-A, And Il-6, And Activate Renin-Angiotensin Aldosterone System And Promote Oxidant'S Effect On Endothelial Cells And Decrease The Level Of Nitric Oxide **No** (**Arévalo-Lorido Et Al., 2019**).

The Ultrasound Technique Is Truly Noninvasive Nor Radiation Exposure Hazards. Even That Ultrasonographic Is An Operator-Dependent. However, If It Performed By Well-Trained,

Experienced Technologists. It Provides An Accurate And Relatively Inexpensive Assessment Of The Carotid System (**Powers Et Al., 2019**).

Our Study Limitations Were Small Sample Size Due To Months Off From Covid 19 Pandemic And Little Flow To The Hospital After The First Wave Of The Pandemic.

In Future Research We Recommend Increasing Sample Size, Correlate The Site Of The Plaque With The Site Of Ischemic Stroke, The Relations Between Transcranial And Extracranial Stenosis And Assess If There Is A Relationship Between The Level Of Hyperuricemia And Volume Of Ischemic Infarction Or With A Sub-Acute Ischemic Insult That's Not Present Well In **Mri** Brain Helping To Prevent The Neurological Defect.

We Concluded That Hyperuricemia And Can Be Used As A Predictor Marker For Significant Intracranial And Extracranial Carotid Stenosis.

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