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Shortened Activated Partial Thromboplastin Time could be an independent risk factor for acute ischemic stroke: a preliminary study

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Abstract

Alterations in hemostasis are linked to the development of ischemic stroke. Intrinsic coagulation pathway activity is typically assessed via Activated Partial Thromboplastin Time (APTT). This study investigates the association between shortened APTT duration and ischemic stroke development.

This retrospective case-control study included 85 patients with acute ischemic stroke who were admitted to the Ibb University-affiliated Hospitals, from Jun 2022 to Sept 2023 and 35 control subjects with no history of stroke. Shortened APTT was defined with a duration lower than 28.4 seconds. Multivariate analysis was conducted analyzing factors associated with acute ischemic stroke using Odds Ratio (OR) and 95% Confidence Interval (CI).

The mean age of control subjects and acute ischemic stroke cases was 40.69±8.28 years and 62.08±12.19 years, with female gender present in 10 (28.6%) and 41(48.2%) respectively. In the multivariate regression, advanced age (OR: 1.21; 95% CI: 1.13-1.30), APTT less than 28.4 seconds (OR: 7.61; 95% CI: 2.85-20.32), hypertension (OR: 28.74; 95% CI: 6.45-128.04), diabetes mellitus (OR: 10.96; 95% CI: 4.06-29.59), family history of cerebrovascular disease (OR: 13.37; 95% CI:1.73-103.27), current smoking status (OR: 2.48; 95% CI:1.09-5.64), higher cholesterol level (OR: 1.01; 95% CI:1.00-1.02), higher triglycerides level (OR: 1.05; 95% CI:1.03-1.08), and higher LDL level (OR: 1.07 95% CI:1.04-1.10) were predictive factors for acute ischemic stroke occurrence and were statistically significant (all $p<0.05$).

The study confirms advanced age, history of hypertension, cerebrovascular disease, diabetes mellitus, current smoking status, and higher Low-Density Lipoprotein (LDL), cholesterol, and triglycerides levels, as factors associated with increased risk of acute ischemic stroke occurrence. The possible predictive role of shortened APTT in patients with acute ischemic stroke seems to be interesting and warrants further studies in this direction.

Introduction

The brain tissue is exceptionally susceptible to ischemia. While different brain regions exhibit varying levels of resilience to ischemic insults, even brief episodes of ischemia have been linked to irreversible cellular necrosis.[1] Indeed, the pathogenesis of ischemic stroke primarily arises from disruptions in blood flow due to thromboembolic events, subsequently leading to oxidative stress, cytokine and free-radical-driven cytotoxicity, disruption of cellular barriers, and eventual gliosis and tissue death.[2] Shear stress, coupled with platelet activation, has been implicated in thrombus formation and propagation. However, several reports emphasize the significant role of coagulation alterations in arterial thrombosis.[3,4] This association is particularly observed among young patients, with notable heterogeneity in terms of gender and ethnicity.[5]

The excessive activation of the coagulation cascade (*i.e.*, hypercoagulability) can independently convert fibrinogen into fibrin and trigger platelet activation. Notably, elevated concentration of various coagulation factors including factor VIII, factor X, and factor XIII, along with von Willebrand factor, and fibrinogen was associated with increased ischemic stroke.[3,6] Furthermore, increased factor XI activity was linked to increased transit ischemic attacks.[7] Mouse studies have demonstrated a lower incidence of thrombosis with specific knockout deletions of intrinsic pathway factors IX and XII.[8] These findings were also reflected in human studies, revealing lower stroke rates among individuals with advanced factor XI deficiency.[9]

Prothrombin time and Activated Partial Thromboplastin Time (APTT) are the prevailing functional assays employed for assessing the coagulation pathways. These

tests correspond to the extrinsic and intrinsic pathways, respectively.[10] A prolonged APTT may indicate deficiencies in intrinsic (XII, XI, IX, and VIII) or common pathway factors (X, V, II, and I I).[11] Remarkably, a reduced APTT has shown clinical relevance, being linked to a heightened risk of thromboembolism.[12] However, limited studies have adjusted for various contributing factors. In this study, we endeavor to investigate the possible association of shortened APTT and its predictability in the context of acute ischemic stroke.

Materials and Methods

Study design and samples collection

This retrospective case-control study included 85 patients with acute ischemic stroke who were admitted to the Ibb University-affiliated Hospitals, from Jun 2022 to Sept 2023 and 35 control subjects with no history of stroke. Ideally, a control series would have been chosen from Edmonton citizens who had never had a stroke incident. It was not possible to generate this control series by randomly picking Edmonton citizens and inviting them to participate in the study. Costs were prohibitively high, and participation rates were expected to be low (~50-60%), making it difficult to ensure a representative study population. Instead, we chose to generate a control series of patients using hospitalization data. Controls were defined as patients who visited the Edmonton Emergency Departments (ED) during the study period. As stated in prior papers such as Johnson *et al*., the biggest issue with employing hospital controls emerges when they are not chosen independently.[13] However, we are confident that this is not the case

because there is no evidence that advanced age is associated with a higher incidence of CVA, which could be due to a shorter APTT, especially since all such cases would have been treated in hospitals rather than physician offices or walk-in clinics. The ethical approval was obtained from the Ethical Committee of Ibb University (IBBUNI.AC.YEM.2023.109). A case was defined as an adult patient (≥18 years old) presenting with acute ischemic stroke, as per the American Heart Association/American Stroke Association consensus, characterized as "an episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction".[14] The neurological dysfunction should persist for a minimum of 24 hours and should not be related to a non-vascular cause (*e.g.*, metabolic, space-occupying lesion, abscess), with the radiological exclusion of hemorrhagic causes using either Computed Tomography (CT) scan or Magnetic Resonance Imaging (MRI). The study excluded patients with advanced renal, hepatic impairment, malignancies, or recent infections. Control subjects were devoid of any past occurrences of stroke or coronary artery disease. The baseline review of the included cohorts involved assessing medical history for hypertension, diabetes mellitus, active smoking, or a recent history of smoking cessation (less than 15 years).[12] Furthermore, the diagnostic work-up included electrocardiography, complete blood count, prothrombin time, APTT, comprehensive metabolic panel, lipid profile, including triglycerides, High-Density Lipoprotein (HDL), and Low-Density Lipoprotein (LDL), and cholesterol, in addition to brain CT scan and/or MRI findings.

Sample size

The sample size was calculated using G Power version 3 software and selected by setting a 95% confidence interval, 80% power, and 5% alpha error and based on a previously reported relationship between shortened APTT and acute ischemic strokes score in the regression model (OR=1.86; 95% Confidence Interval, CI, 1.06-3.29, p=0.031) by Chun-Hsien Lin *et al.*[12] The sample size was determined to be 98 patients in the first stage. Taking into account 15% attrition, in the end, at least 115 samples were required in this study.

Analysis of biochemical parameters and assays for coagulation factor activity

The laboratory departments at Ibb University-affiliated Hospitals use Sysmex CA1500 Analyzer (Sysmex Corporation, Kobe, Japan) for the estimation of Activated Partial Thromboplastin duration, with the APPT reagents (FSL actin; Dade Behring, Newark, USA). The reference value of our labs is estimated by utilizing a confidence interval of 90% for a total of 30 healthy subjects, with a reference range of 23.3-39.3 seconds and a mean of normal value of 28.4 seconds. We, therefore, used a cutoff of less than 28.4 to define shortened APTT as mentioned in previous research.[12] The APTT results were expressed as a ratio of the test coagulation time to the reference coagulation time.

Data collection

Patient demographic characteristics include age, gender, history of Khat chewing, and current smoking status. Comorbidities include a history of diabetes mellitus,

hypertension, family history of CVD. The laboratory findings include APTT and shortened APTT, LDL, HDL, triglyceride, and cholesterol levels.

Study outcome

The primary outcome was to investigate the association between shortened APTT and acute ischemic stroke while the second outcome was to investigate the predictive factors of acute ischemic stroke occurrence.

Statistical analysis

For the presentation of numerical data, we utilized mean values accompanied by standard deviations, and for categorical data, we opted for expressing frequencies with corresponding percentages. The assessment of statistical differences in numeric data involved the application of an independent t-test, while categorical data underwent scrutiny using both the chi-square test and Fisher's exact test. The exploration of relationships between acute ischemic stroke and other influencing factors was conducted through logistic regression analysis, employing the maximum likelihood ratio approach. Odds Ratios (ORs) and their corresponding 95% Confidence Intervals (CIs) were calculated from the b coefficients and standard errors. Statistical significance was established at a P-value below 0.05. IBM SPSS version 22 software (IBM Corp., Armonk, New York) was used for statistical analyses.

After selecting the control series, we noticed that their age distribution differed from that of the case series. We ran further sensitivity analyses to see what influence, if any,

the age disparity had on our results. We accomplished this by randomly choosing a control series that was age-matched to the case (within 10 years) and using conditional logistic regression to assess the relationships between APTT and stroke.[13] Furthermore, the number of control groups were similar to previous reports such as Lin *et al.* (154 patients with acute ischemic strokes *vs* 71 control subjects with no history of stroke).[12]

Results

The mean age of control subjects and acute ischemic stroke cases was 40.69±8.28 years and 62.08±12.19 years, with female gender present in 10 (28.6%) and 41 (48.2%) respectively. Smoking was present in 34.3% and 56.5%, respectively. A family history of Cardiovascular Disease (CVD) was present in 24 (28.2%) of acute stroke cases while no cases in control subjects. Regarding comorbidities, hypertension was present in 2 (5.7%) of control subjects and 54 (63.5%) of acute ischemic stroke cases, while diabetes mellitus was present in 17.1% of control subjects and 69.4% of stroke cases, and khat chewing was present in 26 (74.3%) and 66 (77.6%) of cases. Laboratory tests showed APTT and total cholesterol levels in control subjects and acute ischemic stroke cases were 31.06±3.27 seconds and 29.32±6.07 seconds and was142.51±38.30 mg/dL and160.12±43.80 mg/dL, respectively. APTT≥28.4 seconds presented in 29 (82.9%) and 33(38.8%) in control subjects and acute ischemic stroke cases, respectively.

The clinical attributes of both acute ischemic stroke patients and controls are outlined in Table 1 providing a detailed account of continuous variables, and Table 2 presents an elaborate overview of categorical variables. In univariate analysis, continuous variables

associated with acute ischemic stroke were advanced age, higher cholesterol level, higher triglycerides level, lower HDL, and higher LDL level and were statistically significant (All p-values <0.05) (Table 1). Additionally, in univariate analysis, categorical variables associated with acute ischemic stroke were history of hypertension and diabetes mellitus, family history of CVD, current smoking status, and shortened APTT and were statistically significant (All p-values <0.05) (Table 2).

Predictive factors for acute ischemic stroke

In multivariate logistic regression analysis, advanced age (OR: 1.21; 95% CI: 1.13-1.30; p<0.001), shortened APTT of less than 28.4 seconds (OR: 7.61; 95% CI: 2.85-20.32; p<0.001), hypertension (OR: 28.74; 95% CI: 6.45-128.04; p<0.001), diabetes mellitus (OR: 10.96; 95% CI: 4.06-29.59; p<0.001), family history of CVD (OR: 13.37; 95% CI:1.73-103.27; p=0.013), current smoking status (OR: 2.48; 95% CI:1.09-5.64; p=0.029), higher cholesterol level (OR: 1.01; 95% CI:1.00-1.02; p=0.044), higher Triglycerides level (OR: 1.05; 95% CI:1.03-1.08 p<0.001), and higher LDL level (OR: 1.07; 95% CI:1.04-1.10; p<0.001) were a predictive factors for acute ischemic stroke and were statistically significant. While male gender (OR: 0.42; 95% CI: 0.18-1.00; p=0.051) and higher HDL level (OR: 0.77; 95% CI:0.70-0.85; p<0.001) were protective factors against acute ischemic stroke occurrence (Table 3).

Factors associated with shortened activated partial thromboplastin

In univariate analysis, female gender, diabetes mellitus, higher triglycerides level, higher LDL level, and lower HDL level were associated with shortened activated partial thromboplastin and were statistically significant (all p-values <0.05) (Table 4).

Discussion

This study establishes a noteworthy association, revealing a significant association between a shortened APTT as an independent predictor and risk factor for the occurrence of ischemic stroke. Furthermore, we identified advanced age, history of hypertension and diabetes mellitus, family history of CVD, current smoking status, higher cholesterol, triglycerides level, and LDL levels as a predictive variable for ischemic stroke occurrence.

Several evidence have attributed the role of the coagulation cascade, specifically secondary hemostasis, to thrombus stabilization, with increased activity linked to an elevated incidence of acute ischemic stroke.[3,6,14-18] Abnormalities in the intrinsic coagulation pathway are reflected by the APTT, representing the duration of fibrin activation via the intrinsic pathway. This activation is induced by exposure to negatively charged surfaces, including polyphosphate, and activates megakaryocytes' plasma membrane.[19] The prolongation of APTT is frequently used to evaluate bleeding diathesis, reflecting the deficiency of any intrinsic pathway coagulation factors. Additionally, it can indicate a common pathway disorder when associated with a concomitant prolongation of prothrombin time. Furthermore, APTT is often used as a therapeutic measure to assess heparin dosages.[20] While the clinical significance of

APTT prolongation is relatively well-described, little is known regarding the significance of shortened APTT. Prior reports correlated such a finding with the technical influence of used reagents.[21] Nevertheless, shortened APTT is associated with hypercoagulability. A study by McKenna *et al.* showed a 10 times increased risk of thromboembolic episodes.[22] Interestingly, Reddy *et al.* observed that almost one-quarter of patients with shortened APTT developed thrombosis, compared to less than 3% in the normal control group.[23] In another study by Madi *et al*., shortened APTT was associated with a relative risk of 2.8 of developing acute myocardial infarction.[24] Several hypotheses attribute shortened APTT to be an indicator of increased levels of activated coagulation factors or a reflection of chronic thrombotic consumptive coagulopathy or chronic inflammation.[25] Interestingly, among shortened APTT cohorts, ten Boekel *et al.* reported higher levels of C-reactive protein associated with increased inpatient mortality.[26] Similar to our findings, Madi *et al.* observed an increased risk of ischemic stroke with shortened APTT, suggesting a possible hemostatic inclination towards thrombosis.[24]

Lippi *et al.* observed higher levels of prothrombin fragments with shortened APTT.[20] Notably, higher thrombin levels were attributed to earlier onset ischemic stroke and linked to increased morbidity and mortality.[27] In this study, it was found that increased intrinsic pathway activity, as might be indicated by a shortened APTT, contributes to acute ischemic stroke. The proportion of shortened APTT was higher in patients with acute ischemic stroke compared to healthy individuals (OR: 7.61; 95% CI: 2.85-20.32).

We noted an increased occurrence of acute ischemic stroke associated with advanced age, consistent with previous studies suggesting that a significant proportion, up to two-thirds, of ischemic stroke instances manifest in individuals aged 65 and above.[5] These observations were linked to the elevated prevalence of comorbidities within this age demographic, such as hypertension and diabetes.[28] Remarkably, the relationship between hypertension and ischemic stroke was observed in several prospective and retrospective reports.[4,12] Similarly, diabetes mellitus was associated with an increased risk for ischemic stroke in our study, consistent with prior reports indicating increased thrombogenesis with hyperglycemia.[12,29,30] Furthermore, we identified the presence of a family history of CVD to be independently associated with ischemic stroke. While such a relationship appears to be complex, several reports underscored the significance of CVD history among first-degree relatives.[31,32] However, the pooling of these findings was inconclusive. For instance, a meta-analysis by Flossmann *et al.* suggested a possible genetic predisposition to ischemic stroke; however, significant heterogeneity hindered the establishment of a clear correlation.[33]

In our study, elevated triglyceride, LDL, and cholesterol levels were independently associated with an elevated risk for acute ischemic stroke. These findings aligned with several reports showing a higher incidence and prevalence of dyslipidemia with ischemic stroke.[34,35] Additionally, similar findings were shown to predict CVA occurrence following myocardial infarction.[36] Cigarette smoking was also an independent risk factor for acute ischemic stroke occurrence. The relationship between smoking and the risk of ischemic stroke has been in several published studies such as

Qian *et al.*[37], and Linden *et al.*[38] Khat chewing, in this study, did not stand as a significant predictor for ischemic stroke occurrence. Our findings differ from prior reports that showed a significant association between Khat chewing and ischemic stroke and mortality.[39] We attribute these differences to the possible variation heterogeneity of the study's setting and population.

Study limitations

The study is constrained by its retrospective design, by the difference in age, and by a relatively small sample size, especially within the control group, which may impede the adequate adjustment for various confounding factors. Additionally, the investigation did not assess the serum levels of several inflammatory markers, nor did it explore the potential presence of a co-existing hypercoagulable state among the study participants, that was not identified. Additionally, factors such as laboratory test changes after treatment and patients' survival were not investigated. This omission could lead to an incomplete understanding of the factors influencing treatment outcomes. A long-term, large multicenter study with longer follow-up should be conducted.

Conclusions

Our findings suggest that shortened APTT could be a significant and independent risk factor for ischemic stroke occurrence. For that, more attention and management strategies need to be paid to patients with acute ischemic stroke with shortened APTT. Our novel finding warrants further multicenter and prospective studies. Other

predictive factors for ischemic stroke occurrence in this study were advanced age, history of hypertension and diabetes mellitus, family history of CVD, current smoking status, higher cholesterol level, higher triglycerides level, and higher LDL level.

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Table 1. Comparison of continuous variables of clinical characteristics of stroke patients and controls.

Variable name	Total N=120 Mean ± SD	Groups		Mean difference (95% CI)	p-value
		No ischemic stroke 35 (29.2%) Mean ± SD	Ischemic stroke 85 (70.8%) Mean ± SD		
Age (year)	55.84±14.83	40.69±8.28	62.08±12.19	-21.39 (-25.85 to -16.93)	**<0.001**
APTT, seconds	29.83±5.45	31.06±3.27	29.32±6.07	1.74 (-0.41 to 3.89)	0.112
Total cholesterol mg/dL	154.98±42.87	142.51±38.30	160.12±43.80	-17.60 (-34.42 to -0.78)	**0.040**
Triglycerides, mg/dL	165.43±44.59	136.09±6.57	177.52±47.88	-41.43 (-57.56 to -25.30)	**<0.001**
HDL, mg/dL	44.98±14.74	62.29±6.41	37.86±10.73	24.42 (20.57 to 28.27)	**<0.001**
LDL, mg/dL	76.60±29.92	55.43±15.89	85.32±30.03	-29.88 (-38.25 to -21.52)	**<0.001**

APTT, Activated Partial Thromboplastin Time; CI, Confidence Interval; HDL, High-Density Lipoprotein; LDL, Low-Density Lipoprotein; SD, Standard Deviation

Bold indicates a statistically significant result ($p<0.05$)

Table 2. Comparison of categorical variables of clinical characteristics of stroke patients and controls.

Variable	Subgroup	Total N=120 N (%)	Groups		p-value
			No ischemic stroke 35 (29.2%) N (%)	Ischemic stroke 85 (70.8%) N (%)	
APTT, seconds	≥28.4	62 (51.7)	29(82.9)	33(38.8)	**<0.001**
	<28.4	58 (48.3)	6(17.1)	52(61.2)	
Hypertension	No	64 (53.3)	33(94.3)	31(36.5)	**<0.001**
	Yes	56 (46.7)	2(5.7)	54(63.5)	
Diabetes mellitus	No	55 (45.8)	29(82.9)	26(30.6)	**<0.001**
	Yes	65 (54.2)	6(17.1)	59(69.4)	
Gender	Female	51 (42.5)	10(28.6)	41(48.2)	**0.048**
	Male	69 (57.5)	25(71.4)	44(51.8)	
Family history of CVD	No	96 (80.0)	35(100)	61(71.8)	**<0.001**
	Yes	24 (20.0)	0(0.0)	24(28.2)	
Smoking	No	60 (50.0)	23(65.7)	37(43.5)	**0.027**
	Yes	60 (50.0)	12(34.3)	48(56.5)	
Khat chewing	No	28(23.3)	9(25.7)	19(22.4)	0.692
	Yes	92(76.7)	26(74.3)	66(77.6)	

APTT, Activated Partial Thromboplastin Time; CVD, Cerebrovascular Disease.

Bold indicates a statistically significant result ($p<0.05$)

Table 3. Factors associated with acute ischemic stroke in multivariate analysis.

Variable	Subgroup	B (SE)	OR (95% CI) *	p-value
APTT, seconds	≥28.4	Reference group		**< 0.001**
	<28.4	2.03 (0.50)	7.61 (2.85 – 20.32)	
Hypertension	No	Reference group		**< 0.001**
	Yes	3.35 (0.86)	28.74 (6.45 – 128.04)	
Diabetes mellitus	No	Reference group		**< 0.001**
	Yes	2.39 (0.50)	10.96(4.06 – 29.59)	
Gender	Female	Reference group		0.051
	Male	-0.84 (0.43)	0.42 (0.18 – 1.00)	
Family history of CVD	No	Reference group		**0.013**
	Yes	2.59 (1.04)	13.37(1.73 – 103.27)	
Smoking	No	Reference group		**0.029**
	Yes	0.91 (0.41)	2.48 (1.09 – 5.64)	
Khat chewing	No	Reference group		0.693
	Yes	0.18 (0.46)	1.20 (0.48 – 2.99)	
Age (years)	-	0.19(0.03)	1.21 (1.13 – 1.30)	**< 0.001**
APTT, seconds	-	-0.05 (0.03)	0.94 (0.87 – 1.01)	0.143
Total cholesterol mg/dL	-	0.01 (0.005)	1.01 (1.00 – 1.02)	**0.044**
Triglycerides, mg/dL	-	0.05 (0.01)	1.05 (1.03 – 1.08)	**< 0.001**
HDL, mg/dL	-	-0. 25 (0.05)	0.77 (0.70 – 0.85)	**< 0.001**
LDL, mg/dL	-	0.07 (0.01)	1.07 (1.04 – 1.10)	**< 0.001**

APTT, Activated Partial Thromboplastin Time; CI, Confidence Interval; CVD, Cerebrovascular Disease; HDL, High-Density Lipoprotein; LDL, Low-Density Lipoprotein; OR, Odds Ratio

*Crude odds ratio

Bold indicates a statistically significant result ($p<0.05$)

Table 4. Factors associated with shortened activated partial thromboplastin.

Variable	Subgroup	Total (N=120)	APTT>28.4 (N=62)	APTT≤28.4 (N=58)	p-value
Age (year)	Mean ±SD	55.8±14.8	53.9±16.3	57.9±12.8	0.133
Hypertension	No	64 (53.3)	38 (61.3)	26 (44.8)	0.105
	Yes	56 (46.7)	24 (38.7)	32 (55.2)	
Diabetes mellitus	No	55 (45.8)	35 (56.5)	20 (34.5)	**0.026**
	Yes	65 (54.2)	27 (43.5)	38 (65.5)	
Gender	Female	51 (42.5)	21 (33.9)	30 (51.7)	**0.048**
	Male	69 (57.5)	41 (66.1)	28 (48.3)	
Family history of CVD	No	96 (80.0)	50 (80.6)	46 (79.3)	1.000
	Yes	24 (20.0)	12 (19.4)	12 (20.7)	
Smoking	No	60 (50.0)	28 (45.2)	32 (55.2)	0.361
	Yes	60 (50.0)	34 (54.8)	26 (44.8)	
Khat chewing	No	28 (23.3)	10 (16.1)	18 (31.0)	0.087
	Yes	92 (76.7)	52 (83.9)	40 (69.0)	
Ischemic stroke	No	35.0 (29.2%)	29.0 (46.8%)	6.0 (10.3%)	**<0.001**
	Yes	85.0 (70.8%)	33.0 (53.2%)	52.0 (89.7%)	
Total cholesterol mg/dL	Mean ±SD	155.0±42.9	153.0±41.9	157.1±44.2	0.597
Triglycerides, mg/dL	Mean ±SD	165.4±44.6	153.9±35.8	177.8±49.8	**0.003**
HDL, mg/dL	Mean ±SD	45.0±14.7	50.3±14.7	39.3±12.5	**<0.001**
LDL, mg/dL	Mean ±SD	76.6±29.9	71.0±26.4	82.6±32.4	**0.032**

APTT, Activated Partial Thromboplastin Time; CVD, Cerebrovascular Disease; HDL, High-Density Lipoprotein; LDL, Low-Density Lipoprotein; SD, Standard Deviation

Bold indicates a statistically significant result ($p<0.05$)