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ADAMTS13 Deficiency with Left Atrial Dilatation can Predict Left Atrial Thrombosis in Patients with Atrial Fibrillation

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Abstract

Atrial fibrillation (AF) represents the most common sustained cardiac arrhythmia. The thrombo-embolic complication is a frequent and serious event with high morbidity and mortality in patients with atrial fibrillation. This study aimed to assess plasma levels of ADAMTS13 as a risk factor for left atrial thrombosis in patients with atrial fibrillation and correlate it with spontaneous echocardiographic parameters. This study was conducted on 60 atrial fibrillation patients. The patients were diagnosed clinically and confirmed by ECG and transthoracic M-mode, two-dimensional echocardiography, and Doppler. They were classified according to transesophageal echocardiography into 31 AF without spontaneous echocardiography contrast (SEC) and 29 AF with SEC. Plasma ADAMTS13 was measured in addition to measurement von Willebrand Factor (vWF) antigen and activity. The results showed a significant decrease in the ADAMTS13 level in AF cases when compared to control subjects. In addition to significantly lowered ADAMTS levels were observed in AF patients with SEC when compared to AF patients without SEC and a significant negative correlation between ADAMTS13 level and left atrial diameter in AF cases. ADAMTS13 deficiency is a potential risk factor of left atrial thrombosis in patients with atrial fibrillation (AF). ADAMTS13 could be implemented in laboratory workup of AF patients with left atrial dilatation for predicting left atrial thrombosis.

Keywords: ADAMTS13 • Atrial Fibrillation • SEC • Echocardiography • Left Atrial Dilatation

Introduction

Atrial fibrillation (AF) represents the most common sustained cardiac arrhythmia [1]. It is recognized to be an independent predictor of morbidity and even mortality in cardiac diseases with a high risk of thrombo-embolic stroke [2]. Its risk factors include advancing age, diabetes mellitus, hypertension, congestive heart failure, cardiac valve disease, and myocardial infarction [3]. Stroke is a common and serious event in the setting of AF, it was nearly twice as likely to be fatal [4]. Even, Survivors of stroke as complicated from AF had longer hospital stays with increased disability and more likely to be recurrent strokes [5].

Cardio-embolic stroke pathogenesis begins with the left atrial appendage thrombus formation [6]. This highly frequent complication of AF results from left atrium mechanical function deterioration which is reflected by reduction in left atrial appendage emptying velocity, development of spontaneous echocardiographic contrast (SEC), and progression of left atrial distension [7]. Atrial fibrillation-related thrombus formation includes all the determinants of the Virchow triad; stasis, endothelial damage, and coagulation factors abnormalities which are centrally involved in AF-related thrombus formation [8].

Von Willebrand Factor (vWF), a large multimeric glycoprotein, has a critical function in primary hemostasis. It facilitates platelet adhesion and aggregation by interacting with the glycoprotein Ib receptor on platelets and it is also a carrier protein of factor VIII, thereby protecting it from proteolytic degradation [9]. The thrombogenic potential of vWF is directly proportional to vWF activity (vWF: Act) which is determined by both plasma concentration and multimer size [10].

ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) is a zinc-containing metalloprotease enzyme that cleaves vWF. It is secreted into the blood and degrades large vWF multimers, decreasing their activity [11]. Previous literature observed lower levels of ADAMTS13 in thrombotic thrombocytopenic purpura [12], which is characterized by intravascular platelet aggregation and microvascular thrombi that lead to life-threatening cerebral ischemia and arterial thrombosis [13]. Moreover, ADAMTS13 reduces atherosclerosis in hypercholesteremic apolipoprotein E (ApoE-/-) deficient mice via a vWF-dependent mechanism [14].

Extensive studies have focused on the role of vWF in the pathogenesis of arterial thrombosis on the occurrence of the first event and on recurrence [15]. In this study, we assessed plasma levels of ADAMTS13 as a risk factor for left atrial thrombosis in patients with atrial fibrillation and also correlated it with spontaneous echocardiographic parameters and plasma vWF antigen (vWF: Ag) and vWF: act.

Patients and Methods

This study was conducted on 60 atrial fibrillation patients, selected from 165 patients recruited to the cardiology department at Specialized Medical Hospital, Mansoura University. Our patients were diagnosed clinically by an expert cardiologist and confirmed by ECG and transthoracic M-mode, two-dimensional echocardiography and Doppler (Vivid 3 pro and Vivid S5; GE Healthcare, Horton, Norway) using 3.5 MHz multi-frequency transducer. The patients were 25 males, 35 females, their ages ranged from 42 to 81 years. The cohort study classified them according to transesophageal echocardiography into 31 AF without spontaneous echocardiography contrast (SEC) and 29 AF with SEC. SEC was defined as a pattern of dynamic "smoke-like" slowly swirling, intracavitary echo-densities imaged with gain setting adjusting to eliminate background noise. Patients with acute cardiovascular or cerebrovascular events, collagen diseases, active malignancy, disseminated

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intravascular coagulation, and chronic renal or hepatic disease were excluded from this study. In addition to 20 normal sinus rhythm healthy subjects matched with age and sex as a reference control. All patients gave informed consent to their participation in this study and the local ethics committee (IRB) gave their approval to study MFM-IRB/18.06049. Data were collected prospectively and entered into paper-based case record forms. Follow up information for one year was obtained either by outpatient visits.

Patients sampling

Venous blood sample (1.8 ml) was collected from all controls and patients by clean venipuncture using plastic disposable syringes then delivered into 5 ml sterile vacutainer containing 200 µl sodium citrate solutions with avoiding of venous stasis and pressure on a tourniquet. Samples were centrifuged and the obtained plasma was frozen at -20°C to preserve them until testing, repeated freeze-thaw cycles are avoided. Plasma ADAMTS13 was measured using human vWF Cleaving Protease (vWFCP/ADAMTS13) ELISA kit, procured from Sun Red Biological Technology Company, Shanghai, China.

Automated measurement of vWF: Ag and vWF: act

Measurement vWF: Ag and vWF act was done using Siemens lypholized reagent, detection was done on a fully automated BCS coagulation analyzer system (Roche, USA). Briefly, the lyophilized reagent was reconstituted by 1 ml purified distilled water, shake well and gently by both hands to ensure complete solubility. The reagent was applied at a cold room of analyzer then 100 µl of plasma was mixed into a cleaned cuvette with 100 µl of reagent. According to the standard curve, measurements were detected.

Statistical Analysis

Data were analysed on a personal computer running SPSS® for Windows (Statistical Package for Social Scientists) Release 17. A two-tailed p-value of ≤ 0.05 was considered statistically significant. For descriptive statistics of qualitative variables, the frequency distribution procedure was run with the calculation of the number of cases and percentages. For descriptive statistics of quantitative variables, the mean and standard deviation or the median and range were used to describe central tendency and dispersion as appropriate. The normality of the sample distribution of each continuous variable was tested with the Kolmogorov–Smirnov test. Association between categorical variables was tested by the chi-square test. Fisher's exact test was used if the assumptions of the chi-square were violated. The independent-sample t-test was used to compare the means between the two groups. For nonparametric analysis, the Mann–Whitney U test or Kruskal–Wallis test was used. Correlations between variables were determined by Pearson's correlation coefficient.

Results

Our patient group included 60 AF cases; 25 males and 35 females, their mean age was 57.6 year (± 8.6). Besides, the control group included 20 healthy subjects comprising 10 males and 10 females with a mean age of 54.55 year (± 6.8). Thirty-five patients were using Aspirin 81 mg three times daily, fifteen patients on oral warfarin therapy, and ten patients only on Plavix therapy.

There was no significant difference between patients and control groups as regard age and sex. Forty-one patients suffered from hypertension (68.3%), 22 patients of DM (36.7%), and 38 patients of angina (63.3%).

As regarding comparison of transthoracic echocardiography parameters in all studied groups, it revealed that there was a significant increase in left ventricular end-systolic diameter (LVESD), left ventricular end-diastolic diameter (LVEDD), right ventricular diameter (RVD), and a highly significant increase in left atrial diameter (LAD) in AF cases when compared to control subjects, while there was no significant increase in interventricular septum and posterior wall thickness in AF cases when compared with control subjects. Also, there was a non-significant decrease in ejection fraction and fractional shortening in AF cases when compared to control subjects as shown in Table 1.

No significant difference in vWF: Ag and vWF: act between AF patients and normal sinus as shown in Table 2. However, the results showed a significant decrease in ADAMTS13 level in AF cases when compared to control subjects as illustrated in Table 2 and Figure 1.

Our cohort study was classified according to echo contrast into 29 with SEC and 31 without SEC, significant lowered ADAMTS13 levels were observed in AF patients with SEC when compared to AF patients without SEC as shown in Table 3 and Figure 2.

Table 1. Comparison of transthoracic echocardiography parameters in all studied groups.

Variables	Control group n=20			AF patients n=60			p-value
	Median	Range		Median	Range		
LVESD (cm)	3.8	3	4	4.3	4	5	0.023
LVEDD (cm)	4.9	4	6	5.5	5	7	0.026
RVD (cm)	2.9	3	3	3.2	3	3	0.04
LAD (cm)	3.6	3	4	4.7	4	6	<0.001
EF (%)	68	58	80	59	46	66	0.231
FS (%)	45.5	37	50	38.5	30	45	0.342
IVS (cm)	0.8	1	1	0.9	1	1	0.462
PWT (cm)	0.8	1	1	0.9	1	1	0.536

Note: AF: Atrial Fibrillation; cm: Centimeter; EF: Ejection Fraction; FS: Fractional Shortening; IVS: Interventricular Septum; LAD: Left Atrial Diameter; LVEDD: Left Ventricular End Diastolic Diameter; LVESD: Left Ventricular End Systolic Diameter; N: Number; PWT: Posterior Wall Thickness; RVD: Right Ventricular Diameter

Table 2. Comparison of ADAMTS13 level, vWF: Ag and vWF: Act in all studied groups.

Variables	Control group		AF patients		p-value
	Median	Range	Median	Range	
ADAMTS13 (ng/mL)	5.53	2.5-8.4	3.1	2.0 -5.19	<0.001
vWF: Ag (IU/dL)	145	115-175	160	132-198	0.086
vWF: Act (IU/dL)	165	120-210	175	120-230	0.092

Note: p-value significance <0.05.

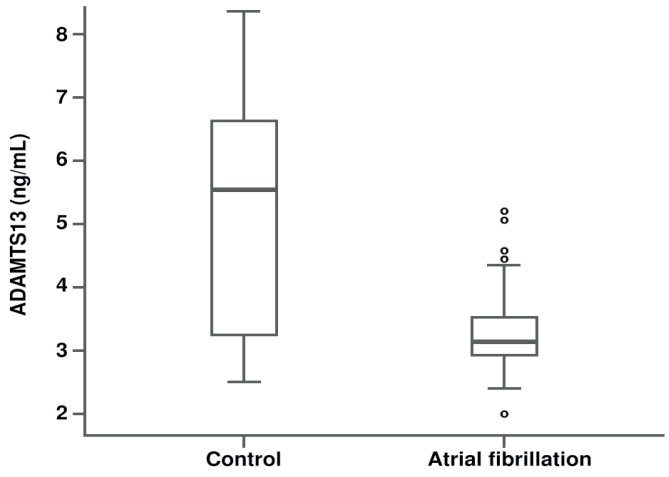

Figure 1. ADAMTS13 level in all studied groups.

Table 3. Comparison of ADAMTS13 level in AF patients according to SEC.

Variables	Without SEC n=31		With SEC n=29		p-value
	Median	Range	Median	Range	
ADAMTS 13 (ng/mL)	3.5	3.13 – 5.19	3.1	2.0 – 3.18	< 0.001
vWF: Ag (IU/dL)	150	133 – 175	160	138 – 198	0.085
vWF: Act (IU/dL)	128	124 – 210	175	150 – 230	0.02

Note: p-value significance <0.05.

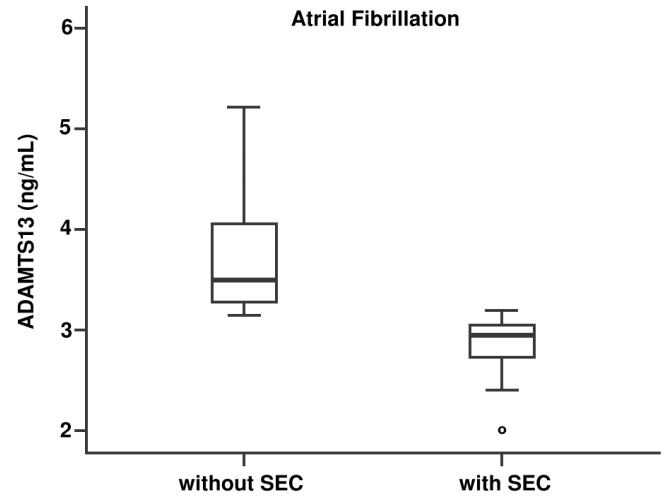

Figure 2. ADAMTS13 level in cases with AF according to spontaneous echo contrast.

Discussion

The Thrombo-embolic complication is a frequent and serious event with high morbidity and mortality in atrial fibrillation which results from a reduction in left atrial appendage emptying velocity, development of spontaneous echocardiographic contrast (SEC), and progression of left atrial distension [7]. ADAMTS13 is a circulating plasma enzyme responsible for cleavage of the platelet-adhesive ultra-large forms of Von Willebrand factor (vWF) into smaller molecules which is an important regulatory mechanism in hemostasis, as these smaller vWF molecules have reduced platelet-aggregating capacity [16].

Our results showed a significant decrease in the ADAMTS13 level in AF cases when compared to the control subject. The detailed mechanism by which plasma ADAMTS13 levels are reduced in AF patients is uncertain. However, Fukuchi in 2001 reported that atrial distension injures local endothelium and stimulates the endothelial release of ultra-large vWF multimer [17].

Furthermore, it has been demonstrated that under normal laminar blood flow conditions, ultra-large vWF is rapidly degraded by ADAMTS13. However, in static conditions like AF, vWF proteolysis by ADAMTS13 is retarded 1000-fold so that, within the fibrillating left atrial appendage, inadequate ADAMTS13 cleavage results in elevated local concentrations of ultra-large vWF multimers, thus favoring thrombus formation [18]. Moreover, it has been reported that ADAMTS13 activity was suppressed by elevated levels of interleukin-6 in AF [19].

Analysis of transthoracic echocardiography parameters in this study, revealed that there was a significant increase in LVESD, LVEDD, RVD, and a highly significant increase in LAD in AF cases when compared to control subjects. Stratification of AF cases according to spontaneous echo contrast (SEC) revealed that SEC has been demonstrated in 29 cases (48.3%) compared to 31 cases (51.7) without SEC. AF cases with SEC showed significantly lower ADAMTS13 when compared to those without SEC. There was a significant negative correlation between the ADAMTS13 level and LAD in AF cases. Our results are in agreement with Uemura et al. [20] (Figure 3 and Table 4).

Furthermore, no significant difference in vWF: Ag in AF patients, while vWF: act is increased significantly in AF patients presented with SEC than those presented without SEC, this finding was in agreement with Feys et al. [21]. However our results didn't match with Ammash in 2011 who used the transesophageal echocardiography to assess the presence and intensity of SEC and left atrial appendage thrombosis as an indicator of left atrial blood stasis. His results revealed that SEC varied directly with plasma vWF: Ag level and vWF: act but not with ADAMTS13 activity [22].

We prospectively followed up AF patients for 12 months for the occurrence of the major thrombotic events. Interestingly, two AF patients (3.33%) experienced a new episode of symptomatic cerebral infarction during the follow-up period. The plasma ADAMTS13 in those patients tended to be lower than that of AF patients without major thrombotic events. This observation matched with the finding of Waldemar et al., [23]. Decreased ADAMTS13 level might play an important role in the development and progression of vascular disease with related complications and cardiovascular mortality in patients with AF, so it represents an additional help to risk stratification in AF patients.

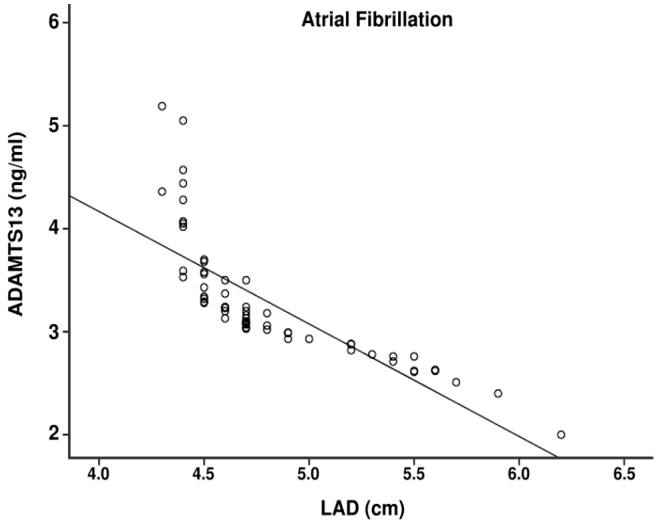

Figure 3. Correlation of ADAMTS13 level with LAD in AF group.

Table 4. Correlations of ADAMTS13 level with LAD.

Variables	Control group n=20		AF patients n=60	
	r	p-value	r	p-value
LAD (cm)	– 0.281	0.23	– 0.965	<0.001

Note: LAD: Left Atrial Diameter; r: correlation coefficient. p-value significance <0.05.

Conclusion

ADAMTS13 deficiency is a potential risk factor of left atrial thrombosis in patients with atrial fibrillation (AF). ADAMTS13 could be implemented in laboratory workup of patients with AF for predicting complications like left atrial thrombosis. It could be used as a preventive and therapeutic target for atrial thrombosis in AF patients. A large study is needed to support this finding.

Conflict of Interest

The authors declare that they have no competing interests.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

Ethical Approval

The study was conducted according to the institutional ethical standards.

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