Worse Outcome in Patients with Acute Stroke and Atrial Fibrillation Following Thrombolysis*

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ABSTRACT: **Background:** Atrial fibrillation (AF) is the most common arrhythmia and a common cause of ischemic stroke. Stroke patients with AF have shown to have a poorer neurological outcome than stroke patients without AF.

Objectives: To determine the impact of pre-existing AF on residual degree of disability in patients treated with IV thrombolysis.

Methods: In this case-control study, data of 214 stroke patients (63 with AF, 151 without AF) were collected from the National Acute Stroke Israeli Registry, a nationwide quadrennial stroke database. Stroke severity and outcome were compared using the National Institute of Health Stroke Scale (NIHSS) at admission and the modified Rankin Scale (mRS) at admission and discharge. Demographics and stroke characteristics were also compared between the groups.

Results: Stroke severity, as determined by the NIHSS at admission, was higher in the AF group than the non-AF. In the group of patients who were treated with intravenous tissue plasminogen activator (tPA), more patients had favorable outcomes (mRS = 0–1 at discharge) in the non-AF group than in the AF group (P = 0.058, odds ratio = 2.217, confidence interval 0.973 to 5.05).

Conclusions: Our study suggests a worse outcome for thrombolized patients with AF compared to non-AF stroke patients. Therefore, AF itself is a poor prognostic factor for tPA sensitivity regarding the chance of revascularization and recovery after intravenous tPA.

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KEY WORDS: atrial fibrillation, thrombolysis, National Institute of Health Stroke Scale (NIHSS), tissue plasminogen activator (tPA)

Atrial fibrillation (AF) is the most common arrhythmia and a common cause of ischemic stroke [1], increasing stroke risk by fivefold and resulting in an independent increase in mortality [2]. Stroke patients with AF have been shown to have a poorer neurological outcome than stroke patients without AF [3-5].

To date, rapid and effective revascularization is the mainstay of acute ischemic stroke treatment. Tissue plasminogen activator (tPA) is the standard, and until recently the only treatment for acute stroke. It has been found to improve outcome in about 30% of all acute stroke patients. In the present study we sought to determine the impact of pre-existing AF on residual degree of disability in thrombolized patient.

PATIENTS AND METHODS

This retrospective case-control study enrolled post-tPA acute ischemic stroke patients from the National Acute Stroke Israeli Registry as described by Tanne and colleagues [6,7]. Data were based on the quadrennial 2 month period (February to March 2004, March to April 2007, April to May 2010, April to May 2013) of the National Acute Stroke Israeli Registry. The registry was approved by the ethical committees of all participating medical centers. Data were documented by each stroke unit in the participating centers. Patients were assessed both at admission and discharge. Data collected included demographic and clinical baseline characteristics as well as localization of the stroke. Stroke severity was determined by the National Institute of Health Stroke Scale (NIHSS) at admission, and the modified Rankin Scale (mRS) at both admission and discharge. Comparisons between patients with and without AF were conducted using the t-test, chi-square test and Kruskal-Walis test for the median. Logistic regression was used to explore the association of mRS and AF accounting for the covariates of age, gender and admission mRS. Statistical analysis was performed using SAS statistical software version 9.4 (SAS Institute, USA).

RESULTS

The study population comprised 214 patients aged 18 years and older who were hospitalized in 27 hospitals in Israel with acute ischemic stroke and received thrombolytic treatment. Of them, 63 had AF (age 72.6 ± 12.4 years, 40% men), the remaining 151 stroke patients had no documented AF (age 66.2 ± 11.7 years, 65% men).

Baseline characteristics, vascular risk factors and comorbid conditions are listed in Table 1. AF patients were significantly older than non-AF patients. Hypertension, heart failure and

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Table 1. Baseline characteristics

Clinical characteristics	No AF (n=151)	AF (n=63)	*P* value
Female (%)	53 (35)	38 (60)	‹ 0.001
Age, mean	66.2 ± 11.7	72.6 ± 12.4	‹ 0.001
Hypertension (%)	107 (72)	56 (89)	0.007
CHF (%)	15 (10)	18 (29)	‹ 0.001
Prior stroke (%)	24 (16)	9 (14)	0.752
Prior TIA (%)	8 (5)	3 (5)	1
Dyslipidemia (%)	108 (72)	38 (60)	0.08
Obesity (%)	40 (27)	18 (29)	0.81
Renal failure (%)	12 (8)	11 (17)	0.042
Aspirin treatment (%)	62 (42)	40 (66)	0.002
Coumadin treatment (%)	1 (1)	12 (19)	‹ 0.001
LDL-C, mean	111.5 ± 40.7	93.2 ± 32.6	0.016
Triglycerides, mean	140.3 ± 63.9	123.6 ± 54.7	0.197
Fasting glucose, mean	139.7 ± 64.7	113.7 ± 31.4	0.009
CRP, mean	7.4 ± 9.7	34.5 ± 53.9	‹ 0.001

AF = atrial fibrillation, CHF = congestive heart failure, TIA = transient ischemic attack, LDL = low density lipoprotein cholesterol, CRP = C-reactive protein

renal failure were more prevalent among the AF group. The frequency of prior stroke and/or transient ischemic attack (TIA) did not differ between the groups. Patients with AF had significantly higher C-reactive protein (CRP) values on admission (mean 34.5 ± 53.9 vs. 7.4 ± 9.7, $P < 0.001$). As expected, more patients with AF were previously treated with anti-aggregation or anticoagulation medications. Only one patient received anticoagulation treatment in the non-AF group vs. 12 (19%) in the AF group.

STROKE CHARACTERISTICS

Patients with AF more commonly presented with decreased consciousness (30% vs. 16%, $P < 0.05$). Presentation with visual disturbances was more common in AF than non-AF patients (29% vs. 17%, $P < 0.05$). Involvement of anterior circulation was more common in AF patients whereas posterior circulation strokes were more common in non-AF patients [Table 2].

NEUROLOGIC STATUS

Stroke severity, determined by NIHSS scores at admission, was higher in the AF than for the non-AF group. More patients had favorable outcomes (mRS 0–1 on discharge) in the non-AF group. This remained almost significant when adjusted for possible explanatory variables (gender, age, severe NIHSS defined as > 6) ($P = 0.058$, odds ratio = 2.217, confidence interval 0.973 to 5.05) [Table 3].

DISCUSSION

In the current study we found that among acute ischemic stroke patients receiving thrombolytic treatment in Israel, AF was

Table 2. Stroke characteristics

Clinical characteristics	Missing data (non-AF)	No AF (%)	Missing data (AF)	AF (%)	*P* value
On awakening	17	23 (17)	5	9 (16)	0.779
Consciousness	0	24 (16)	0	19 (30)	0.018
Speech/understanding	0	106 (70)	0	49 (78)	0.258
Motor/weakness	0	127 (84)	0	60 (95)	0.025
Sensory disturbances	0	51 (34)	0	26 (41)	0.298
Dizziness/unsteadiness	0	20 (13)	0	4 (6)	0.145
Visual disturbances	0	25 (17)	0	18 (29)	0.046
Confusion	0	7 (5)	0	6 (10)	0.21
Total anterior circulation	0	25 (17)	0	22 (35)	0.002
Partial anterior circulation	0	82 (54)	0	36 (57)	0.002
Posterior circulation	0	20 (13)	0	3 (5)	0.002
Lacunar	0	23 (15)	0	2 (3)	0.002
Large vessel atherosclerosis	80	16 (23)	31	4 (13)	0.233
Small vessel occlusive	80	9 (13)	31	1 (3)	0.167
Procedure related	80	1 (1)	31	1 (3)	0.527

AF = atrial fibrillation

Table 3. Logistic regression for mRS (0–1, vs. 2–6) model with age, gender and NIHSS variables

Variables	Coefficient (B)	SE	*P* value	OR	95%CI
(Intercept)	-0.688	1.041	0.509	0.503	0.0653–3.87
Atrial fibrillation	0.79616	0.4201	0.0581	2.217	0.973–5.05
AGE	0.00954	0.014	0.497	1.01	0.9822–1.04
Gender (male)	-0.29347	0.352	0.404	0.746	0.3741–1.49
NIHSS ≥ 6	1.24004	0.3854	0.0013	3.456	1.6236–7.36

mRS = modified Rankin Score; NIHSS = National Institute of Health Stroke Scale; OR = odds ratio; CI = confidence interval

associated with almost significant less favorable outcome in a multivariable regression.

Previous studies, not focusing exclusively on post tPA patients, have shown that cardio-embolic stroke is associated with a greater degree of neurological deficit and poorer outcome [8]. Of interest, a recent study indicated that AF in stroke patients is associated with greater volume of more severe hypoperfusion resulting in increased infarct growth and worse stroke outcomes. The latter was attributed to poorer collateral circulation quality [5]. Another possible cause is the sudden vessel occlusion by an emboli, as opposed to a more gradual process of chronic hypoperfusion in patients with atherosclerosis in large vessels or cerebral small vessel disease. Patients with AF are also older, have more co-morbidities and are more prone to bleeding than non-AF patients [1-3].

In thrombolized patients, AF has been suggested to be a cause of tPA resistance. Other factors preceding poor outcome include the location, size and composition of the occluding

thrombus [14,15]. A possible connection between thrombus composition, AF and tPA resistance was shown in recent histologic studies of the retrieved thrombi. These studies have shown that arterial platelet-rich clots are, in particular, more resistant to thrombolysis mediated by tPA [16]. This result is supported by the concept that cardio-embolic thrombi, being formed in regions of stasis or slow flow in the atrium, are mainly composed of entrapped erythrocytes, while thrombi occurring in atherosclerotic large arteries are mainly composed of fibrin and platelets. Confirmation of that assumption was recently shown by a study that evaluated the composition of clots retrieved by mechanical thrombectomy [17]. The lower fibrin proportion in cardio-embolic clots might provide a possible explanation to the tPA resistance concept as tPA targets fibrin activity within the clot.

The main strength of our study is the large sample size obtained from data collected in the NASIS survey, which is a national, prospective, multicenter study. Another strength is that all patients were evaluated by stroke specialists on admission and at discharge. The main disadvantages are the retrospective data collection obtained from a prospective study and not having mRS scores at 3 months but only at discharge. We also acknowledge not having data regarding bleeding rate and international normalized ratio values in patients receiving warfarin (n=13).

CONCLUSION

Our study suggests worse outcomes in thrombolized patients with AF compare with their non-AF counterparts. These findings, however should not discourage thrombolytic treatment, which has been shown to be beneficial and safe in both AF and non-AF acute ischemic stroke patients. However, it might encourage the use of an endovascular thrombectomy approach, especially in light of recent studies showing clear and persistent advantage for this approach in selected patients [18].

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Capsule

Fighting filoviruses with antibody therapy

Ravn and Marburg viruses cause hemorrhagic fever with high morbidity rates in humans. Mire and co-authors tested the ability of previously identified human monoclonal antibodies to protect guinea pigs from lethal infection. One candidate antibody was administered 5 days after otherwise lethal Marburg or Ravn infection in nonhuman primates and was able to reduce clinical symptoms and confer almost uniform protection. This antibody is a promising therapeutic that could be helpful in future filovirus outbreaks.

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