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ORIGINAL ARTICLE

Clinical Progress and Prognosis in TIA: Experiences of a Specialised Neurology Hospital

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ABSTRACT

Objective: The current development of acute stroke units led to an increase in morbidity of stroke patients while causing a decrease in overall mortality. Therefore, the cost of stroke care and treatment took a serious toll on national economies worldwide. Primary prevention of stroke should remain the main objective of primary healthcare. Following a transient ischemic attack (TIA), the patients have a 10-20% risk of developing an ischemic stroke. Our main objective in the present work was to summarize risk factors, imaging modalities, etiologic factors, and treatment modalities in TIA patients and to determine the rate of recurrence of TIA and ischemic stroke incidence in 1 year follow up in an academic medical center specialized in neurology.

Method: 119 patients with TIA who received inpatient management in a 3-year period were included in this study. Patients were grouped by age, gender, distribution and duration of symptoms; recurrence, risk factors, and history of antiplatelet/anticoagulant use. A routine stroke protocol was followed for all patients. The patients were stratified by OCSP and TOAST criteria. The patients were re-evaluated at 3rd, 6th, and 12th months after discharge, and new stroke/TIA occurrence rate, risk factors and the presence of ischemic lesions on neuroimaging were recorded.

Results: Of the patients who were included in this study, 52.9% was male, 42.1% was female. 87 of the patients (73.1%) had anterior circulation and 32 of the patients (26.9%) had posterior circulation pathologies. Recurrence of symptoms was observed in 60 patients (50.4%) after the first event. Diabetes, hyperlipidemia and hypertension were discovered to be the closest risk factors to be proven statistically significant. Posterior circulation TIA, and cardioembolic TIA ratios were more frequent when compared to the literature. During the one year follow up 8.4% of the patients reported experiencing new ischemic stroke or TIA, and only 2 patients died.

Conclusion: Tight risk factor control and adherence to treatment protocols selected based on etiology are critical to decreasing ischemic stroke incidence following TIA.

Keywords: TIA, recurrent TIA, TIA etiology, branch hospital, specialized neurology hospital.

INTRODUCTION

Transient ischemic attack (TIA) is defined as a clinical syndrome which is characterized by acute onset of focal cerebral or monocular dysfunction symptoms that last shorter than 24 hours and are caused by interruption of cerebral blood flow. Most attacks last 2-15 minutes. TIAs are predominantly recurrent. TIA is an important risk factor for subsequent ischemic strokes. Of all the ischemic stroke patients, 10% reported experiencing a previous TIA. The first month after a TIA has the greatest risk of developing an ischemic stroke. The risk increases to 15-20% in 12 months [1-6]. Especially when it is considered that frequent TIAs carry a higher risk of stroke, it becomes imperative to provide the patients with appropriate investigations and treatment options [2,6-10]. Our objective with this study was to evaluate approach to TIA management as it heralds stroke, in a hospital specializing in neurology and the results of our clinical follow-up.

METHOD

119 TIA patients who were admitted to our unit in three-year period were included in the study. Patient history including medical history, family history, history of smoking, alcohol use, and prior medications were recorded; and focused physical exams were performed. The patients were grouped by their age, gender, risk factors, prior use of antiplatelet and anticoagulant medications, as well as the localization, duration and recurrence of symptoms.

Routine stroke protocol, including routine biochemistry, complete blood count, coagulation profile, urinalysis, and 12 lead ECG, was performed on all the patients. On admission, computed tomography (CT) of the head was obtained and imaging was repeated after 48 to 72 hours via CT or magnetic resonance imaging (MRI). Transthoracic echocardiography along with doppler of the carotid and vertebral arteries were performed to determine the etiology, and when indicated transesophageal echocardiography, MRI Angiography of the brain and digital subtraction angiography (DSA) were performed as well. The patients were categorized based on Oxfordshire Community Stroke Project (OCSP) and Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification systems and treatment protocols. The patients were re-evaluated at three, six, and 12 months after discharge. The ratio of patients who experienced another ischemic attack or infarct, risk factors, and the presence of lesions on neuroimaging were evaluated. Scoring systems such as $ABCD^2$ were not studied in this study due to data being unavailable to complete such calculation and the recent controversy about their clinical validity.

SPSS 17.0 was used for data analysis. Logistic regression, chi squared test and Fisher's exact test of probability was used for comparison. The data was normally distributed, and two sample t test was used to compare the mean values of variables between two groups. Kaplan Meier estimator and Logrank tests were applied to compare the results of the observation period and estimate the survival function related to a risk factor. $p < 0.05$ was determined statistically significant.

RESULTS

Of all the 119 patients who were included in this study, 52.9% were male and 42.1% were female, with a mean age of 64.1. We were able to follow up with 117 of the 119 participants. Two patients (1.7%) died during the follow up period, one of which (0.85%) was caused by a vascular pathology.

When grouped based on the localization of symptoms, 87 patients (73.1%) had findings associated with the anterior circulation, whereas 32 patients (26.9%) experienced posterior circulation related events. 72 (60.5%) of the patients' complaints lasted less than an hour, and 47 patients (39.5%) had episodes lasting longer than an hour. Transient ischemic attacks recurred in 60 patients (50.4%) within the first 24 hours of the primary event.

The patients were stratified based on risk groups (Figure 1). 48.7% of the patients had history of hypertension, 40.3% had coronary artery disease or atrial fibrillation, 32% smoked or consumed alcohol regularly, 21% of the patients had hyperlipidemia, and 19.3% had concomitant diabetes. Twenty-seven of the patients (22.7%) had previous history of cerebrovascular disease. Thirty patients (25.2%) were regularly using antiplatelets at the time of the transient ischemic attack.

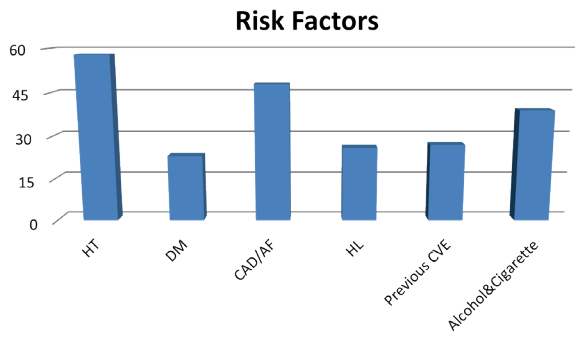

Figure 1. Percentages of different risk factors in the sample population.

The clinical findings upon admission were evaluated using OCSP classification by a neurologist, and 11.8% had total anterior circulation syndrome (TACS), 55.5% partial anterior circulation syndrome (PACS), 25.2% posterior circulation syndrome, and 7.6% lacunar syndrome (Figure 2).

Fifty-three patients (44.5%) fell under the category of stroke of undetermined etiology. Thirty-four patients (11.8%) were classified as large-artery atherosclerosis, 13 patients (10.9%) had small vessel occlusion, and two or more causes were identified in 5 patients (4.2%) (Figure 3).

Diffusion MRI was obtained from 59 patients (49.6%), and only 29 (24.4%) had acute lesions. All the patients who had lesions on the MRI were treated as transient ischemic attack patients.

Upon discharge 9 patients (7.6%) were started on dual antiplatelet therapy (a combination of acetylsalicylic acid 300mg/day and dipyridamole 225mg/day or acetylsalicylic acid 100mg/day and

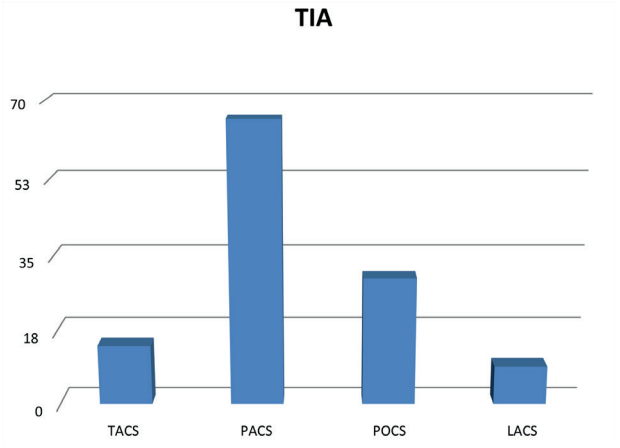

Figure 2. Percentages of OCSP classifications of the patients. TACS: total anterior circulation stroke, PACS: partial anterior circulation stroke, POCS: posterior circulation stroke, LACS: lacunar stroke.

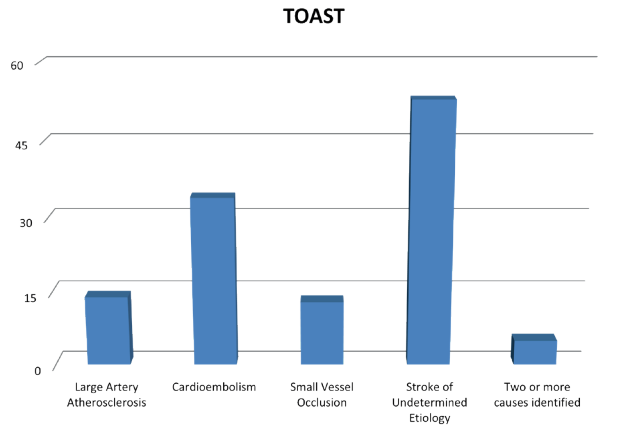

Figure 3. Distribution of etiological factors according to TOAST classification.

clopidogrel 75mg/day), 30 patients (25.2%) were placed on either acetylsalicylic acid 300mg/day or clopidogrel 75mg/day, and 80 (67.2%) were started on oral anticoagulant therapy as secondary prophylaxis (Figure 4). Different treatment strategies classified by TOAST criteria are displayed in Table 1.

On one year follow up, 11 patients (9.2%) were on dual antiplatelets, 43 (36.1%) used only one antiplatelet, and 65 patients (54.7%) were on anticoagulants (Figure 4). Treatment modalities at one year follow up are presented in Table 2.

During the one year clinical follow up 10 patients (8.4%) experienced further ischemic stroke or transient ischemic attacks, and only 2 patients (1.7%) died.

There were not statistically significant relationships between the localization of symptoms and occurrence of new onset TIA/stroke (p=0.464); nor between recurrent TIA and new onset TIA/stroke (p=0.164, 0.382) on year follow up.

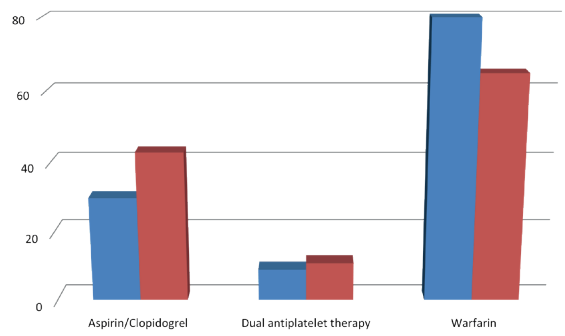

Figure 4. Comparison of distributions of different treatment modalities upon discharge (blue) and upon 1 year follow up (red).

Table 1. Treatments upon discharge

TOAST	OAC	Antiplatelet therapy	Dual antiplatelet therapy	n (%)
Stroke of undetermined etiology	43 (81.1%)	10 (18.9%)	0	53 (44.5%)
Cardioembolism	34 (100%)	0	0	34 (28.6%)
Large vessel atherosclerosis	0	5 (35.7%)	9 (64.3%)	14 (11.8%)
Small vessel occlusion	0	13 (100%)	0	13 (10.9%)
Stroke of other determined etiology	3 (60%)	2 (40%)	0	5 (4.2%)
TOTAL	80	30	9	119

Table 2. Treatments upon 1 year after discharge

TOAST	OAC	Antiplatelet therapy	Dual antiplatelet therapy	n (%)
Stroke of undetermined etiology	30 (56.6%)	23 (%43.4)	0	53 (44.5%)
Cardioembolism	34 (100%)	0	0	34(28.6%)
Large vessel atherosclerosis	0	6 (42.8%)	7 (57.2%)	13 (11.8%)
Small vessel occlusion	0	13 (100%)	0	13 (10.9%)
Stroke of other determined etiology	1 (20%)	1 (20%)	3 (60%)	5 (4.2%)
TOTAL	65	43	10	118

Logistic regression model of the relationship between risk factors (age, hypertension, hyperlipidemia, diabetes, history of previous stroke, cardiac pathologies and atrial fibrillation, alcohol, cigarettes) and new onset TIA/stroke yielded no statistically significance. The Kaplan - Meier survival analysis and Logrank tests to compare the rates of recurrence and risk factors revealed no statistically significance (P=0.082). Diabetes, hypertension, and hyperlipidemia were found to be the most likely risk factors for TIA/ischemic stroke, although not statistically significant (p=0.168, 0.181, 0.212).

On the follow up, the number of risk factors and recurrence of TIA/ischemic stroke rates revealed no statistically significant relationship as well (p=0.61). The association between the cardioembolic etiology and new occurrence of TIA/stroke were compared using chi square and Fisher probability exact tests. It revealed no statistically significance (p=0.730, p=0.360). New onset of TIA/ ischemic stroke on follow-up and large vessel stenosis as an etiology were compared using chi square and Fisher probability exact tests and revealed no statistically significance (p=0.163).

New onset of TIA/stroke on follow up and OCSP and TOAST classifications were compared using chi square and Fisher probability exact tests and no statistically significant relationship was revealed (p=0.221, 0.761).

The patients' past usage of antiplatelets and duration of symptoms were compared using chi square and Fisher probability exact tests and no statistically significant relationship was determined (p=0.557).

DISCUSSION

Twenty percent of the patients with ischemic stroke have history of TIA days or hours prior to the event. Since the 80% of ischemic strokes that follow a TIA is preventable; early diagnosis, recognition of risk factors and management strategies play a pivotal role [6,8,11-14].

In our research, the mean age of TIA is found to be 64.09. This value is similar to the median age that is reported on the literature which is 63 - 72 [2,15-19]. Gender distribution of our research (57.9% male) matches to the data in the literature which shows 60-65% male dominance in TIA cases [15,18,20].

When the localization of the symptoms was compared, 73.1% of the patients presented with anterior circulation symptoms and 26.9% of them had features of posterior circulation insult. The results of other studies showed that patients with posterior circulation symptoms compose 10-15% of the total patients. In our study the ratio of posterior circulation TIAs is higher than that is reported in

the literature [16]. It is contemplated that less than 10% of TIA patients are evaluated by a neurologist during the time period that they are symptomatic. It is reported that the rate of discordance between the efficient utilization of the information obtained from the patient, and the description of TIA is 42-86%. Since this study is conducted in a medical center specialized in neurology, all the patients are evaluated by neurologists upon arrival. Therefore, we conclude that the "undetermined" group, which is present in other studies, reside in the posterior circulation group in our study [2,11,16,19].

In terms of the duration of the symptoms; 60.5% of the patients (72 patients) had symptoms lasting less than an hour, whereas 39.5% of them (47 patients) had symptoms for more than an hour. In the literature, it is reported that 60% of the patients have symptoms less than an hour, 71% of the patients' symptoms last more than 2 hours, and 14% of the patients have symptoms that last more than 6 hours [2,6].

In terms of risk factors, hypertension and coronary artery disease/atrial fibrillation were more frequent than previous reports and history of ischemic stroke was encountered in fewer patients. Hyperlipidemia and diabetes had similar frequencies [9,10]. The rate of antiplatelet use prior to admission was 25.2%, and this was consistent with the ratio of previous history of stroke/TIA (22.7%).

The distribution of OCSP classification was consistent with the current literature [13]. When stratified according to the TOAST, stroke of undetermined etiology was leading with 44.5% of the patients, followed by cardioebolism with 28.6% of total patients [21-23]. When the duration of in-hospital stay is considered, lack of extensive cardiac follow up may be the underlying reason for the accumulation of patients in the stroke of undetermined etiology group.

AHA/ASA guidelines recommend "neuroimaging evaluation within 24 hours of symptom onset" with diffusion weighted imaging (DWI) MRI because it is more sensitive than CT with TIA patients in detecting minor infarcts. If MRI is unavailable cranial CT and cranio-cervical CT-Angiography is recommended. The studies that reported using MRI showed that 21 - 67% of TIA patients had infarcts on imaging [15,16]. Of the patients that MRI was obtained, 49% had acute ischemic lesions. Calvet et al. reported the prevalence of ischemic lesions on DWI in TIA patients as 40% in 339 patients. The same study showed that the patients with lesions on DWI usually have longer lasting TIA episodes, present with symptoms of anterior circulation, and the frequency of large-artery atherosclerosis and cardioembolism rate was found to be higher [24]. There was no statistically significant difference in our patients with lesions on DWI in terms of localization and duration of symptoms, large-artery atherosclerosis, and cardioembolism.

When we analyzed the treatment modalities after TIA, we discovered that 67.2% of TIA patients were prescribed oral anticoagulants. However, the cardioembolism incidence in our study was calculated to be 28.6%. Upon one year follow up, the oral anticoagulant therapy ratio decreased to 54.7%. Considering 44.5% of the patients fell under the stroke of undetermined etiology group, 28.6% of patients had cardioembolism, and 4.2% had two or more causes identified; we deducted that these patients were high risk in terms of TIA/ ischemic stroke recurrence, therefore we placed them on anticoagulant therapy [1,3,16,25,26].

The risk of ischemic stroke after a TIA is 4-5% for the first two days and 11% for the first week. It is estimated that 10% of the patients that experience a TIA or minor ischemic stroke will suffer from an ischemic stroke in the following 90 days [2-6,9,15,16,25,26]. Rothwell et al. reported the 3-month recurrence rate as 17%. The same study claims that the half of the ischemic stroke cases consequent to a TIA are seen within the first 24 hours [2,8,27]. In our study at 3rd month 2.5%, at 6th month 4.2%, and at 12th month 8.4% of the patients experienced a new episode of TIA/ ischemic stroke. Only 2 of the patients (1.7%) died of vascular causes. The mortality of TIA in the first 3 months is reported to be 1.9% by Bahit et al., and 2.6% by Johnston et al. [8, 14]. The mortality rate of in our study is lower compared to the literature.

The lack of statistical significance of the difference between the duration and recurrence of symptoms; and recurrence of TIA/ischemic stroke may be due to the limited number of patients included in our study. Larger scale, multi-centered studies are needed to determine the mortality rates of recurrent TIAs and understand their contribution to following ischemic strokes.

There wasn't a statistically significant difference between the risk factors and recurrence of TIA/ischemic stroke; however, diabetes, hyperlipidemia, and hypertension were the risk factors closest to being statistically significant which is consistent with the current literature. The number of risk factors an individual has wasn't statistically significant either.

One of the important results of our study is that there wasn't a statistically significant relationship between the presence of an ischemic lesion on DWI and recurrence of TIA/ischemic stroke. The presence of acute ischemic lesions on DWI in TIA patients is a widely disputed subject. American Academy of Neurology (AAN) is working to standardize the approach to the patients with TIA. The new proposed description of TIA is a brief (lasting under an hour) cerebral or retinal ischemic attack without any sign of acute infarction. All the other neurological findings excluded by this description, whether the symptoms are transient or permanent, are described as "ischemic stroke" if they are related to cerebral infarction. This tissue-based description provides a safe transition to objectivity in terms of TIA interpretation. The disadvantage of this description is that it solely depends on the sensitivity and availability of neuroimaging. As stated in AHA/ASA guidelines, the term "acute neurovascular syndrome" can be used in cases that neuroimaging isn't readily available or is inadequate to show the infarction area. When the new tissue-based description of TIA is used as a reference, TIA may be perceived as a low-risk situation [6,16,25,26,28]. According to a pooled analysis of a study of 12 centers and 4574 TIA patients, the risk of an ischemic stroke in TIA patients within the first 7-day without signs of infarction is 0.4%. Whereas TIAs with positive neuroimaging findings represent a very unstable syndrome and this risk is increased twenty-fold [25,29,30].

Even though our study is based on similar criteria, we didn't utilize ABCD2 scoring system. Recent reports showed that the scoring systems that are supported by imaging findings are more successful in predicting recurrence of TIA in TIA/minor ischemic stroke patients than the ones that are solely based on clinical findings [14,25,26,31]. In a meta-analysis composed of 29 studies and more than 130,000 patients, ABCD2 score was found to be unreliable in determining the risk of recurrent ischemic stroke and determining the patients with large-artery atherosclerosis which is an important prognostic factor in early stroke recurrence [6,26,31-36].

CONCLUSION

Being a medical center, which specializes in neurology provided the patients with the advantage of evaluation by a neurologist upon first admission. We believe that the high rate of anticoagulant use in the stroke of undetermined etiology group is because the follow-ups were conducted by the same specialized team. Follow up by ischemic stroke clinics, such as acute ischemic stroke centers, decreases the recurrence rates by the aggressive control of risk factors.

Limitations of our study are the limited number of patients and brain MRIs, lack of extensive cardiac investigations due to the short duration of the in-patient follow up of TIA patients; and owing to these two factors, the high probability of misclassification by TOAST system.

Author contribution

Study conception and design: IKA; data collection: IKA; analysis and interpretation of results: IKA and IS; draft manuscript preparation: IKA and IS. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the SBU Prof. Dr. Mahzar Osman Mental Health and Neurology Research and Training Hospital Ethics Committee (Protocol no. 2017/4/6.11.2017).

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Conflict of interest

The authors declare that there is no conflict of interest.

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