Is the Evaluation and Treatment of Transient Ischemic Attack Performed According to Current Knowledge? A Nationwide Israeli Registry

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ABSTRACT: **Background:** Patients with transient ischemic attack (TIA) at a high risk of stroke can be identified and should be managed urgently.

Objectives: To investigate whether recognized recommendations are being implemented in Israel.

Methods: An Israeli nationwide registry (NASIS) on patients admitted with stroke and TIA was conducted in all acute care hospitals within 2 successive months during 2004, 2007 and 2010. A revised ABCD^2 score was applied retrospectively. Patients with TIA were divided into a low risk group (LRG, 0–3 points) and a high risk group (HRG, 4–6 points) and were compared to patients with minor ischemic strokes (MIS, NIHSS score ≤ 5 points).

Results: A total of 3336 patients were included (1023 with TIA: LRG 484, HRG 539, and MIS 2313). LRG patients were younger and had lower rates of most traditional risk factors as compared with HRG and MIS patients. Brain imaging was performed in almost all the patients. Ancillary tests (vascular and cardiac) were overall underused, yet were performed more in LRG (53.2% and 26.9% respectively) than in HRG patients (41.6%, 18.9%). Between periods there was no change in usage of ancillary tests for the LRG and a modest increase in both HRG and MIS patients. For performance of vascular investigations overall, the odds ratio was 1.69 (95% confidence interval 1.42–2.00) comparing 2010 with 2004, but 0.7 (95% CI 0.5–0.9) comparing HRG with LRG. Between periods an increase in statin usage was observed in all groups (OR 2.69, 95% CI 2.25–3.21) but was more marked in MIS patients (OR 3.06, 95% CI 2.47–3.8).

Conclusions: The approach to TIA risk stratification and management in Israeli hospitals does not follow standards set by current guidelines. Standardized protocols for TIA should be used to assure effective management.

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KEY WORDS: transient ischemic attack (TIA), minor ischemic stroke (MIS), national registry

Acute stroke is a medical emergency. With the introduction of acute thrombolytic therapy, it is essential that patients with relevant symptoms arrive as soon as possible to medical facilities for prompt diagnosis and treatment. Transient ischemic attacks, however, are short lived and were believed to carry a better prognosis, thus more time for their evaluation and initiation of treatment was allowed. Recently, however, with documented early stroke occurrence of up to 8% within a week [1] and up to 20% within 3 months after the event [2,3], TIA has become an urgent situation as well.

Several scales and methods have been developed to identify patients who carry the highest risks. The most popular is the ABCD^2 scale [3] which has five factors with seven points. Using this clinical scale Johnston et al. [3] found a very high early risk of recurrence (8.1% at 2 days) among patients with a score of 6 or 7 points [3]. Other important factors were also identified, including the underlying etiology, mainly the presence of large artery disease [4-6], and specific radiological findings [7-11]. Brain imaging (computed tomography or magnetic resonance imaging) in which previous or recent infarcts were demonstrated were found to be associated with high early risks. This led to the development of new composite scales. By adding the emergency room CT or MRI findings to the ABCD^2 score, the ability to identify those patients with the highest risks was augmented, as shown by the ABCD^{2}I and the ABCD^3-I scales [12,13]. The former includes brain findings (another 1 to 3 points), and the latter includes, in addition to the brain findings, a history of recent TIA and imaging for (significant) carotid stenosis with a total score of 13 points. The importance of intracranial stenosis was also demonstrated [11].

Options to reduce this high risk include prompt admission of patients to hospital for early investigation and treatment [14], and immediate administration of intensive medical treatment (antithrombotic, antihypertensive and statin), which

TIA = transient ischemic attack

reduced the early risk by 80% in a large study [15]. These facts have led to changes in the guidelines for TIA management which incorporate the above mentioned parameters [16,17], and it is expected that TIA patients at high risk will be treated as early as possible.

In Israel there are numerous hospitals distributed throughout the country, allowing for easy access to medical facilities. TIA patients are mostly referred and admitted to hospital for further evaluation and treatment. However, there is a lack of data regarding whether current guidelines are being applied in such patients. We therefore chose to compare, within the National Acute Stroke Israeli (NASIS) registry, TIA patients according to their stroke risk as measured by the ABCD^2 scale to assess whether (as suggested by the guidelines) those with the highest score receive a quicker and more comprehensive evaluation than those with lower scores and whether these are comparable (or even better) than for those arriving with minor ischemic strokes. Additional analysis comparing the different study periods (2004 to 2010) was also performed as we believe that changes occurred during these periods.

PATIENTS AND METHODS

The NASIS registry comprises all patients with acute stroke or TIA admitted to any of the 28 hospitals nationwide during February-March of 2004, March-April of 2007 and April-May of 2010. All periods used similar methods and data retrieval forms to collect demographic, clinical and radiological data and outcome measures, as previously described [18]. In the current study we included all patients with TIA and minor ischemic stroke. TIA patients were scored according to the ABCD^2 scale, which consists of the following parameters [3]:

- **A** for **a**ge: 1 point for age over 60 years
- **B** for **b**lood pressure: 1 point for BP over 140/90 mmHg
- **C** for **c**linical features: 2 points for limb paresis, 1 point for speech disturbance without weakness, none for sensory symptoms only
- **D** for **d**uration: 2 points for symptoms lasting more than 1 hour, 1 point when more than 10 minutes, none for less
- **D^2** for **d**iabetes: 1 point when present.

As this scale was applied retrospectively and in our registry we had data only for TIA lasting shorter or longer than 1 hour, we could only score 6 points (out of 7) in the ABCD^2 scale (modified, mABCD^2 scale): TIA over 1 hour received only 1 point and those lasting less than an hour received none. TIA patients were divided into two groups: The low risk group comprised patients with scores of 0–3 and the high risk group included those with scores of 4–6. This cutoff was chosen since it is the average of those suggested in previous publications and was used most recently [10,13]. MIS was defined as any stroke with admission NIHSS of 5 points or less [19].

NASIS = National Acute Stroke Israeli registry
BP = blood pressure

STATISTICAL ANALYSIS

Data were analyzed using SAS version 9.1. Percentages (categorical variables) were compared using the χ^2 test, means (normally distributed quantitative variables) using the *t*-test, and medians (non-normally distributed quantitative variables) using the Mann-Whitney U test. Odds ratios were adjusted for age and gender. ORs for vascular investigations and statins at discharge were calculated from logistic regression models. ORs for the time from arrival at the emergency department to performance of CT scan were calculated from an ordinal regression model. In order to meet the proportional odds assumption, ER-CT time entered the model after division into tertiles. $P > 0.05$ was considered not significant.

RESULTS

The NASIS registry comprised 6261 patients (2165 patients in 2004, 2101 in 2007 and 1995 in 2010). We excluded 2127 with admission NIHSS > 5 points, 484 patients with intracerebral hemorrhage, 103 with undetermined cause or those with cerebral venous thrombosis, and 211 patients with missing data. The remaining 3336 patients included 1023 patients with TIAs and 2313 patients with MIS. The TIA group was further divided according to their mABCD^2 score. There were 484 patients in the low risk TIA group (12 patients scored 0 points, 71 scored 1, 150 scored 2, 251 scored 3) and 539 patients in the high risk TIA group (286 patients scored 4, 192 scored 5, 61 scored 6).

Comparison of baseline characteristics of the study cohort between the three aforementioned groups is shown in Table 1. The most important differences were noted between the two TIA groups while there was much similarity between the high risk TIA group and the MIS group in most traditional risk factors (age, hypertension, coronary artery disease, dyslipidemia, obesity, peripheral artery disease) as well as prior stroke. Due to the ABCD^2 score constituents, some characteristics and risk factors were encountered somewhat more frequently in the high risk TIA patients (higher age, hypertension, diabetes). Of note is that prior TIAs were more common in both TIA groups as compared with the MIS group. As expected, major stroke symptoms were less common in the low risk TIA group.

Brain imaging [Table 2] was performed in about 90% of TIA patients and in 99% of MIS patients. Brain infarcts were recorded in a quarter of the low risk TIA patients and in 43% of the high risk TIA patients.

MIS = minor ischemic strokes
OR = odds ratio
ER-CT time = time from arrival at the emergency department to performance of CT scan
mABCD^2 = modified ABCD

Table 1. Patient characteristics

	Low risk TIA group (n=484)	High risk TIA group (n=539)	MIS group (n=2313)	*P* value
Age (yrs, mean ±SD)	60 ± 15	71 ± 12	68 ± 13	‹ 0.001
Females	227 (46.9)	275 (51)	956 (41.3)	‹ 0.001
Hypertension	247 (51.4)	427 (79.8)	1747 (75.9)	‹ 0.001
Prior stroke	63 (13.1)	131 (24.5)	573 (25)	‹ 0.001
Prior TIA	82 (17.1)	90 (17.2)	143 (6.3)	‹ 0.001
Past IHD & procedures	94 (19.7)	163 (30.7)	690 (30.2)	‹ 0.001
Congestive heart failure	34 (7.1)	61 (11.5)	246 (10.8)	0.04
Renal failure	29 (6)	77 (14.6)	258 (11.3)	‹ 0.001
Dyslipidemia	281 (58.4)	355 (66.4)	1482 (64.7)	0.02
Diabetes mellitus	74 (15.3)	258 (47.9)	947 (41.3)	‹ 0.001
Obesity	68 (14.6)	96 (19)	431 (19.9)	0.03
Current smokers	115 (24.1)	104 (19.8)	571 (25.1)	0.04
Peripheral artery disease	13 (2.7)	42 (8)	137 (6)	0.001
Dementia	15 (3.2)	52 (10.1)	392 (9.2)	‹ 0.001
Family history	24 (5.2)	18 (3.6)	51 (2.3)	0.003
Blood pressure (mmHg) (mean ± SD) Systolic Diastolic	 143.5 ± 25 81.2 ± 13	 160.2 ± 25 84.2 ± 15	 156.3 ± 27 84.3 ± 15	 ‹ 0.001 ‹ 0.001
Motor weakness	96 (19.8)	349 (64.7)	1414 (61.1)	‹ 0.001
Speech disturbance	111 (22.9)	293 (54.4)	797 (34.5)	‹ 0.001
Cholesterol (total, mg/dl) (mean ± SD)	194.9 ± 45	190.9 ± 45	193.5 ± 48	NS
WBC (mean ± SD)	8180 ± 2497	8237 ± 3883	8458 ± 3742	NS

Unless mentioned otherwise data are presented as n (%)
Low risk group mABCD^2 ≤ 3, high risk group mABCD^2 › 3
IHD = ischemic heart disease, WBC = white blood cells

Table 2. Brain imaging, investigations, etiology, medication, delay and hospital stay

	Low risk TIA group	High risk TIA group	MIS	*P* value
Imaging & investigations				
Brain imaging performance	438 (90.5)	480 (89.1)	2287 (98.9)	‹ 0.001
Any brain infarcts	107 (24.4)	206 (42.9)	1496 (65.4)	‹ 0.001
Vascular investigations	255 (53.2)	220 (41.6)	1106 (48)	‹ 0.001
Cardiac investigations	129 (26.9)	100 (18.9)	585 (25.4)	0.003
Median delay (min)				
ER to CT	167	145	148	‹ 0.001
Etiology				
Cardio-embolic	37 (7.6)	61 (11.3)	273 (11.8)	0.03
Large vessel disease	20 (4.1)	35 (6.5)	173 (7.5)	0.03
Small vessel disease	68 (14)	98 (18.2)	843 (36.4)	‹ 0.001
Other determined cause (including procedure related)	9 (1.8)	5 (1.0)	44 (1.9)	NS
Undetermined	307 (63.4)	307 (57)	990 (42.8)	‹ 0.001
Medications				
ASA at entry	168 (35.4)	274 (52.5)	1140 (50.3)	‹ 0.001
ASA at 48 hrs	366 (78.2)	382 (73.5)	1624 (72.7)	0.05
ASA at discharge	380 (79.5)	368 (69)	1566 (68.2)	‹ 0.001
Any antiplatelet agent				
At entry	183 (38.7)	304 (58.2)	1233 (54.6)	‹ 0.001
At 48 hrs	416 (88.5)	463 (87.9)	2000 (88.4)	NS
At discharge	440 (91.7)	478 (89.5)	2096 (91.2)	NS
Any antihypertensive agent				
At entry	221 (46.7)	400 (75.3)	1560 (68.5)	‹ 0.001
At discharge	271 (56.8)	434 (80.8)	1782 (77.7)	‹ 0.001
Statins				
At entry	166 (35.5)	257 (49)	983 (43.8)	‹ 0.001
At discharge	243 (50.9)	322 (60.4)	1413 (61.8)	‹ 0.001
Hospital duration (days, median)	3	4	4	‹ 0.001

Unless mentioned otherwise data are presented as n (%)
ER = emergency room, NS = not significant, ASA = acetyl salicylic acid

Investigations such as carotid duplex, transcranial Doppler or CT angiography or MR angiography (vascular investigations) as well as echocardiography (cardiac investigation) were unexpectedly performed more often in the low risk TIA group as compared with the high risk TIA group and quite similar to what was recorded in the MIS group. Yet the overall figures (in the acute setting) were low. These findings were achieved although the hospital duration time was, as expected, shorter in low risk TIA patients [Table 2].

Transportation to the hospital by ambulance or mobile intensive care units was less frequent in low risk TIA patients, yet similar in MIS patients and high risk TIA patients (30% vs. 39% and 42% respectively). Median delays in the performance of brain imaging were shorter in both the MIS and high risk TIA groups. About 60% of the TIA groups did not have a definite etiology upon discharge from the hospital and as a result all major etiologies were encountered more frequently in the MIS group.

Although antiplatelet agents were given to fewer patients in the low risk TIA group at entry, they were prescribed to about 90% of patients at hospital discharge with no significant difference between groups. The differences noted in acetyl salicylic acid utilization are due to higher usage of clopidogrel or the combination of ASA and dipyridamole in both the MIS and high risk TIA patients. Antihypertensive drug usage was slightly increased, mainly angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and calcium blockers (data not tabulated). Statin medication usage, although clearly increased compared to baseline, was prescribed to only about 60% of all patients at discharge.

During the different study periods there was no clear trend in antithrombotic drug utilization or in overall antihypertensive treatment [Table 3]. A clear difference, however, was recorded in the usage of statins, with more pronounced ARB trends and utilization in the MIS group. A shorter delay for ER to CT performance was recorded in all groups, yet more so in the high

ASA = acetyl salicylic acid
ARB = angiotensin receptor blockers

Table 3. Medications, delay and investigations by registry period

	Group		2004	2007	2010	*P* value
Any antiplatelet agent (%)	LRG TIA	At entry At discharge	32.9 91	48 91.6	33.3 92.6	0.005 NS
	HRG TIA	At entry At discharge	54.9 87.5	64.6 90.8	55.2 90.2	NS NS
	MIS	At entry At discharge	50.3 91.3	56.1 91.9	57.2 89.9	0.017 NS
Any antihypertensive agent (%)	LRG TIA	At entry At discharge	44.1 52.1	50.3 61.7	45.2 56	NS NS
	HRG TIA	At entry At discharge	76 81.9	79.8 83.9	69.4 76.4	NS NS
	MIS	At entry At discharge	67.2 75.3	71.2 80.2	67 77.4	NS NS
Statins (%)	LRG TIA	At entry At discharge	26.4 39.9	37 55.6	44.4 58.2	0.005 0.002
	HRG TIA	At entry At discharge	35.4 49.7	56.2 66.7	55.5 64.4	< 0.001 0.002
	MIS	At entry At discharge	31.4 46.2	46.9 65.6	52.3 72.5	< 0.001 < 0.001
Median delay (min) ER to CT	LRG TIA HRG TIA MIS		191 186 179	167 139.5 153.5	158 122 125	0.045 < 0.001 < 0.001
Investigations (%)						
Vascular	LRG TIA HRG TIA MIS		54.8 33.9 40.5	53.1 44.4 47.2	51.5 46.5 56	NS 0.036 < 0.001
Cardiac	LRG TIA HRG TIA MIS		28.9 16.4 19.9	26 22.5 25.4	25.7 17.8 30.6	NS NS < 0.001

LRG = low risk group, HRG = high risk group

Table 4. Adjusted odds ratios for vascular investigation, ER to CT time and statins at discharge

	OR 95% CI		
	2004	2007	2010
Vascular investigations			
All	1.00	1.19 (1.011.41)	1.69 (1.42-2.00)
LRG	1.00	0.87 (0.57-1.34)	0.85 (0.54-1.34)
HRG	1.00	1.41 (0.92-2.17)	1.72 (1.12-2.65)
MIS	1.00	1.23 (1.00-1.51)	1.94 (1.58-2.39)
Time from ER to CT*			
All	1.00	0.72 (0.61-0.86)	0.48 (0.4-0.57)
LRG	1.00	0.73 (0.46-1.15)	0.56 (0.35-0.92)
HRG	1.00	0.51 (0.33-0.79)	0.34 (0.22-0.53)
MIS	1.00	0.77 (0.63-0.95)	0.49 (0.4-0.61)
Statins at discharge			
All	1.00	2.09 (1.76-2.48)	2.69 (2.25-3.21)
LRG	1.00	1.88 (1.21-2.91)	2.19 (1.36-3.50)
HRG	1.00	1.92 (1.25-2.94)	1.81 (1.18-2.80)
MIS	1.00	2.18 (1.77-2.69)	3.06 (2.47-3.80)

ORs are adjusted to age and gender. ORs for vascular imaging and statins at discharge are calculated from logistic regression models. ORs for time from ER to CT (represented as tertiles) are calculated from an ordinal regression model.

*Data on time from ER to CT were missing in 17% of patients

risk TIA patients. Vascular and cardiac investigations were significantly increased during the different periods only in the MIS group [Table 3]. Interestingly, in the earlier periods these were performed more frequently in the low risk TIA patients.

Table 4 shows the adjusted odds ratios for different parameters. Compared to 2004, the performance of vascular investigations increased steadily for the whole group as well as for the MIS patients and high risk TIA patients. This change, however, was not observed in the low risk TIA group (OR 0.7, 95% confidence interval 0.5–0.9, when comparing the high with the low risk group; data not tabulated). Brain CT was performed more rapidly with the sequential years for the whole group including any TIA, and statins at discharge was prescribed more commonly during the years for all patients, with the highest increase observed in MIS patients.

DISCUSSION

Our study demonstrates that in Israel the performance of in-hospital TIA investigations is insufficient, with only about 50% of patients with TIAs completing any vascular investigation and less than a quarter undergoing cardiac investigations during their hospital stay. Unpredictably, this low usage was more pronounced in high risk compared to low risk patients despite longer hospitalization time (and higher risks). Improvement, however, was recorded in high risk TIA patients during the sequential years in accordance with the guidelines, but similar observations were not recorded in low risk TIA patients.

Statins were prescribed at discharge to only 60% of the patients. Significant improvement was recorded, as compared to 2004, for both of the TIA groups as well as the MIS group. Similarly, time to brain CT was significantly shorter in 2010 as compared to 2004.

The lower utilization rates resulted in lower rates of determining definite underlying etiologies, and possibly in withholding certain treatments (e.g., immediate carotid vascular intervention or initiation of anticoagulation therapy).

We assume that our observation of lower utilization of further investigations stems mainly from lack of resources and/or availability in the different centers and that these investigations were completed later by family physicians adhering to the recommendations written in the hospital discharge letters. Guidelines for urgent TIA management have been published [16] and, more recently, a suggested guideline for organized protocols for *all* TIA patients was published in the United States [17].

Our study, while demonstrating that the overall utilization of investigations and comprehensive treatments were not sufficient (as expected for patients hospitalized for TIAs), also shows that with the years the approach to these patients has improved as those with higher stroke risk were mostly treated quicker and more thoroughly. This was in accordance with

the above mentioned guidelines. A more comprehensive approach also includes, apart from speeding the in-hospital pace of investigations and treatment, efforts to increase the speed of response to the event by the patient him/herself and by the first medical care provider. The key is public awareness of TIA symptoms as well as general knowledge regarding the location of facilities with dedicated TIA services that provide early intervention and treatment

In conclusion, the approach to TIA risk stratification, investigation and treatment in Israeli hospitals does not follow standards set by current guidelines. Based on these findings we recommend that hospitals establish standardized protocols to assure rapid and effective evaluation and treatment for patients with TIA, with particular attention to patients at high risk of stroke. We believe that recognition of the urgency of TIAs by both patients and physicians, together with implementation of these guidelines and protocols, will lead to improved TIA services and eventually to a better outcome in these patients.

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Capsule

Genetic clues to meningioma

Meningiomas are the most common primary brain tumors in adults. Located within the layer of tissue covering the brain, these tumors are usually slow growing and benign but can cause serious neurological complications. About half of these tumors have mutations in the *neurofibromin* 2 gene (*NF2*). To identify other genes that contribute to meningioma pathogenesis, Clark et al. performed genome sequence analysis on 300 tumors. Meningiomas fell into two general classes: benign tumors located at the skull base – which tend to harbor mutations in the *TRAF7*, *KLF4*, *AKT1*, and *SMO* genes – and higher grade tumors located in the cerebral and cerebellar hemispheres harbor mutations in *NF2*.

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