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Clinical and radiological determinants of transient symptoms associated with infarction (TSI)

Molad J.[a], Ben-Assayag E.[a,b], Korczyn A.D.[b], Kliper E.[a], Bornstein N.M.[c], Hallevi H.[a,b], Auriel E.[d,*]

[a] Department of Neurology, Tel-Aviv Sourasky Medical Center, Tel-Aviv, Israel
[b] Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel
[c] Department of Neurology, Shaare-Zedek Medical Center, Jerusalem, Israel
[d] Department of Neurology, Carmel Medical Center, Haifa, Israel

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ABSTRACT

Background: The definition of transient ischemic attack was traditionally based on clinical features only. The wide use of magnetic resonance imaging (MRI) led to the definition of a new entity - transient symptoms associated with infarction (TSI). It is unclear why patients with similar radiological infarctions may have different clinical manifestation – ranging from complete symptoms resolution to major neurological sequelae.

We sought to determine which factors differentiate acute diffuse weighted imaging (DWI) lesion presentation - stroke versus TSI.

Methods: 282 Participants, recruited for the Tel-Aviv Brain Acute Stroke Cohort study (TABASCO), were enrolled consecutively. Participants underwent extensive cognitive evaluation, wide laboratory tests and brain MRI scans evaluated for cerebral small vessel disease (SVD) biomarkers, according to the STRIVE protocol. Demographic and clinical characteristics were also examined.

Results: A total of 239 patients had stroke and 43 patients had TSI. TSI patients had smaller average lesion volume (0.77 cm^3 versus 2.64 cm^3, $p = 0.002$). Lesion location did not differentiate TSI and stroke. Stroke patients had elevated inflammatory markers, unrelated to lesion size (CRP 4.2 mg/L versus 1.7 mg/L, $p = 0.011$). TSI patients had better global cognitive score and MoCA score at admission and 24 months following the index event ($p < 0.001$). TSI patients also had better Berg balance score ($p = 0.004$). No significant association was found with MRI SVD markers.

Conclusions: Lesion size, but not location, differentiates TSI and stroke, especially at a cutoff value of 10 cm^3. Elevated inflammatory response was linked to worse course independently of lesion volume. Cognitive and high function tests are associated to the clinical phenotype of ischemic lesion and may be a marker of brain reserve and compensatory abilities. SVD markers do not differ between TSI and stroke patients and probably do not fully capture the extent of brain vascular pathology and reserve.

1. Introduction

Transient ischemic attack (TIA) accounts for at least one third of all stroke cases, and is a significant prognostic factor for recurring vascular events [1]. The past definition of TIA was acute neurological symptoms lasting < 24 h, suspected to be of vascular origin [2,3]. In the last decade, with the increasing use of magnetic resonance imaging (MRI) and particularly diffuse weighted imaging (DWI) [4], many patients with the clinical diagnosis of TIA were found to have corresponding DWI hyperintense lesions [5]. In several studies, the rate of DWI hyperintense lesions among TIA patients was 21–68% [1,6], resulting in the requirement for no acute lesion on imaging to meet the new definition of TIA, and to the definition of a new group of patients - transient symptoms associated with infarction (TSI) [1,3].

It is still unknown why patients with similar DWI lesions experience different clinical courses. While some have persistent symptoms (ischemic stroke), in others symptoms resolve within 24 h (TSI) [4]. Previous studies, looking at clinical and radiological determinants showed inconsistent findings, including duration of symptoms, type of neurological deficit (motor deficit or aphasia) and lesion size [3,6].

We sought to determine which factors differentiate stroke from TSI. We evaluated the influence of epidemiological data, laboratory findings and clinical parameters including comprehensive cognitive assessments, balance and depression scores among patients with first ever

* Corresponding author at: Department of Neurology, Carmel Medical Center, 7 Michal St., Haifa 34362, Israel.
E-mail address: eitanur@clalit.org.il (E. Auriel).

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mild to moderate stroke. The interrelation of various radiological findings was also examined, including acute lesion characteristics as well as MRI markers of cerebral small vessel disease (SVD) [7].

2. Methods

2.1. Study population

282 Participants, recruited for the Tel-Aviv Brain Acute Stroke Cohort study (TABASCO) [8], were included in the present study. All participants, enrolled consecutively, were men or women aged over 50, admitted to Tel-Aviv Medical Center from April 2008 to January 2015, due to first ever TIA or mild to moderate acute ischemic stroke (NIH stroke scale [9] (NIHSS) < 17), who underwent brain MRI which demonstrated acute DWI lesions. We excluded patients with no acute DWI lesion or patients with one of the following: primary hemorrhagic stroke, history of prior ischemic stroke, severe disability, severe aphasia, known malignancy, stroke resulting from trauma or invasive procedure or pre-stroke history consistent with dementia. The TABASCO study was registered as ClinicalTrials.gov Identifier: NCT01926691. All participants signed informed consent forms, approved by the local ethics committee.

Medical records of all patients were reviewed for background and clinical details including cardiovascular risk factors, gender, age, socioeconomic status, medications (especially anti-aggregation, anticoagulation and statins) and more. Laboratory results (cholesterol, LDL, HDL, triglycerides, HbA1c, WBC, CRP) and carotid Doppler were also examined.

2.2. MRI acquisition and analysis

All participants underwent brain MRI using a 3 T GE scanner (GE Signa EXCITE, Milwaukee, WI, USA) within 7 days of stroke onset. Imaging parameters were previously described [8].

2.3. Ischemic infarct definition

All participants had acute DWI lesion consistent with ischemic stroke (DWI hyperintense, apparent diffusion coefficient (ADC) hypointense, and no correlating susceptibility weighted imaging (SWI) lesion). Lesion volume was assessed using the ABC/2 method [10]. Lesions were also divided by the involved hemisphere and the specific location: frontal, parietal, temporal, occipital, basal-ganglia, thalamus, brainstem and cerebellum. The involvement of the cortex was also examined, as any infarct that includes the cortex was defined as cortical infarct. Decisions were made by both a vascular neurologist and a neuroradiologist.

2.4. SVD markers

All MRI scans were fully evaluated for SVD radiological markers based on the STRIVE protocol [7] including: [1] White matter hyperintensities (WMH) were graded using Fazekas score [11,12] [2]. Chronic lacunar infarcts were defined as sharply demarcated hypointense lesions sized between 3 mm and 15 mm in diameter on T1-weighted images with corresponding hypointense lesions with hyperintense rim on T2 dark fluid [7] [3]. Cerebral microbleeds (CMB) were defined as round hypointense lesions on SWI with a diameter < 10 mm. CMBs were divided to lobar versus deep [7,13] [4]. Enlarged perivascular spaces (PVS) were defined as smooth margin, round, oval or linear-shaped lesions, sized up to 3 mm, with signal intensity equal to cerebrospinal fluid (CSF) on T1-weighted images. Enlarged perivascular spaces at the level of the basal ganglia as well as at the level of centrum semiovale in the most involved hemisphere were counted [7,14] [5]. Brain volume was estimated based on FreeSurfer V5.1 image analysis suite (http://surfer.nmr.mgh.harvard.edu/) [15,16]. Ventricular CSF volume was calculated and adjusted to intracranial volume to represent a measure of cerebral atrophy.

Our group Kappa score for SVD markers was 0.84 [17]. Specifically, Kappas for the presence of WMH, lacunes, CMB and PVS were 1.0, 0.7, 0.67, and 1.0 respectively.

2.5. Cognitive, depression and balance assessment

Participants underwent cognitive assessment using both Montreal cognitive assessment test (MoCA) [18] and NeuroTrax™ computerized cognitive testing [19]. Cognitive evaluation was performed within a week of the index event and 6 months, 12 months and 24 months later. NeuroTrax™ (NeuroTrax Corp., Bellaire, TX) is a computerized battery of neuropsychological tests that is used for reliable detection of cognitive state in cognitively healthy, mild cognitive impairment and mild dementia subjects [19]. It provides an overall measure of cognitive function (global cognitive score) as well as evaluation of specific cognitive domains (executive function, memory, visual spatial, verbal function and attention). Each domain score is normalized to fit a standardized scale (mean 100; standard deviation (SD) 15).

Depressive symptoms were assessed within 72 h of admission, and again 6, 12 and 24 months later, using the 15-item Geriatric Depression Scale (GDS) [20]. A Score ≥ 6 may indicate a depressive episode. The 15-item GDS has been shown to have acceptable internal consistency and reliability in older adults from a range of populations [21].

Gait and balance were assessed using the Berg Balance Scale [22]. This scale is a physical performance measure that includes 14 items designed to assess both static and dynamic balance.

2.6. Statistical analysis

Statistical analysis was done using SPSS statistics package version 22, using single and multi-variant modules. Continuous variables were analyzed for normality and displayed as mean ± SD. The cross tabs and descriptive procedures were used to produce frequencies of categorical variables. The different characteristics for TSI and stroke patients were compared by Student's *t*-test for normally distributed variables and by Mann-Whitney *U* test for non-normally distributed variables. As a secondary analysis designed to adjust for lesion volume and location effect, TSI patients were matched to stroke patients according to both their lesion volume and location (as mentioned above) in a matched-control model.

3. Results

A total of 575 patients were recruited to the TABASCO cohort. Among those, 282 patients had positive acute DWI lesion, thus included in the current study. 239 patients were diagnosed with stroke (acute DWI lesion and clinical symptoms lasting longer than 24 h) and 43 patients were diagnosed as TSI (acute DWI lesion and clinical symptoms lasting < 24 h [1,3]). As for MRI timing, no significant difference was found between groups ($p = 0.65$, Table1). Baseline patients' characteristics are shown in Table 1. No difference was seen between stroke and TSI patients in age or gender. In the matched-control model (see below), however, TSI patients were relatively younger ($p = .04$). Patients with TSI were taller relative to stroke patients (171 cm versus 167 cm, $p = .018$ after adjustment for lesion volume). TSI patients also showed higher income ($p = .004$), however significance was lost following adjustments. Education was not different between groups. NIHSS among stroke patients was obviously higher comparing to TSI patients (median 3 versus 0 respectively, $p < .001$). As for stroke etiology according to TOAST criteria, there was no significant difference between stroke and TSI.

Known cardiovascular risk factors including diabetes did not significantly differ between stroke and TSI. HbA1c levels on admission were lower in TSI patients compared to stroke patients ($p = .027$), but