Received Date : 21-Sep-2015

Revised Date : 24-Jan-2016

Accepted Date : 01-Mar-2016

Article type : Original Papers

Frequency and predictors of acute ischemic Lesions on Brain MRI in young Patients with a clinical Diagnosis of TIA

Christian Tanislav^{a§}, MD; Ulrike Grittner^{b,c§}, PhD; Franz Fazekas^d, MD; Vincent Thijs^f, MD; Turgut Tatlisumak^{g,h}, MD, PhD; Roman Huberⁱ, Bettina von Sarnowski^k, MD; Jukka Putaala^g, MD; Reinhold Schmidt^d, MD; Peter Kropp^l, PhD; Bo Norrving^m, MD; Peter Martus^b, MD; Anne Kathrin Gieseⁿ, MD; Arndt Rolfsⁿ, MD; Christian Enzinger, MD^{d,e§}

§Authors contributed equally

^a*Justus Liebig University, Giessen, Germany*

^b*Department for Biostatistics and Clinical Epidemiology, Charité-Universitätsmedizin Berlin, Germany*

^c*Center for Stroke Research, Charité-Universitätsmedizin Berlin, Germany*

^d*Department of Neurology, Medical University of Graz, Graz, Austria*

^e*Division of Neuroradiology, Department of Radiology, Medical University of Graz, Graz, Austria*

^f*Clinical and Experimental Neurology, Leuven, Belgium*

^g*Institute of Neuroscience and Physiology and Department of Neurology, University of Gothenburg, and Department of Neurology, Helsinki University Central Hospital, Helsinki, Finland. ^hInstitute of Neuroscience and Physiology, Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden and Department of Neurology, Sahlgrenska University Hospital, Gothenburg, Sweden*

ⁱ*Department of Neurology, Friedrichshafen, Germany*

^k*Department of Neurology, University of Greifswald, Greifswald, Germany*

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as doi: [10.1111/ene.13012](https://doi.org/10.1111/ene.13012)

This article is protected by copyright. All rights reserved

^l*Institute of Medical Psychology and Medical Sociology, University of Rostock, Rostock, Germany*

^m*Department of Clinical Neuroscience, Lund University Hospital, Lund, Sweden*

ⁿ*Albrecht-Kossel-Institute for Neuroregeneration, University of Rostock, Rostock, Germany.*

Corresponding Author:

Christian Tanislav, M.D.

Department of Neurology, Justus Liebig University, Giessen, Germany

Klinikstrasse 33, 35392 Giessen, Germany

Tel.: +49/64198545372; Fax: +49/6419945418

E-mail: christian.tanislav@neuro.med.uni-giessen.de

Running title: Acute lesions in young TIA

Keywords: Acute Cerebral Infarction; MRI; TIA; young stroke

Disclosure: all authors report no conflict of interest related to the submitted manuscript

Abstract

Background: Acute lesions in patients with transient ischemic attack (TIA) are important, as they are associated with increased risk for recurrence. We therefore investigated characteristics associated with acute lesions in young TIA patients.

Methods: The sifap1 study prospectively recruited a multinational European cohort (n=5023) of patients aged 18-55 years with acute cerebrovascular event. The detection of acute ischemic lesions was based on diffusion weighted imaging (DWI). We assessed the frequency of DWI lesions in 829 TIA patients who met the criteria of symptom duration <24 hours and analyzed their association with demographic, clinical and imaging variables.

Results: The median age was 46 years (IQR 40-51years), 45% of the patients were female. In 121 patients (15%) ≥ 1 acute DWI lesion was detected. In 92 patients, DWI lesions were found in the anterior circulation, mostly located in cortical-subcortical areas (n=63). Factors associated with DWI lesions in multiple regression analysis were: left hemispheric presenting symptoms (OR 1.92, CI: 1.27– 2.91), dysarthria (OR 2.17, CI: 1.38 – 3.43) and old brain infarctions on MRI (territories of the middle and posterior cerebral artery: OR: 2.43, CI: 1.42 – 4.15; OR: 2.41, CI: 1.02 – 5.69, respectively).

Conclusions: In young patients with a clinical TIA 15% demonstrated acute DWI lesions on brain MRI, with an event pattern highly suggestive of an embolic origin. Except for the

association with previous infarctions there was no clear clinical predictor for acute ischemic lesions, which indicates the need to obtain MRI in young individuals with TIA.

Clinical Trial Registration-URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT00414583.

Introduction

A transient ischemic attack (TIA) is defined as an episode with neurological deficits caused by temporary brain ischemia lasting less than 24 hours [1,2]. Although it might seem harmless, a TIA is prognostically relevant, as it indicates an increased risk for subsequent cerebrovascular events [3]. This risk might increase dramatically in those TIA patients with acute ischemic lesions, as observed on diffusion-weighted imaging (DWI) on brain MRI [4,5]. Recent studies on young stroke patients provided detailed information on age and gender distribution, risk factors, etiologic factors, and imaging findings [6,7]. They emphasized the limitation in translating knowledge from general stroke populations to the specific subgroup of younger stroke patients [8]. Therefore, we investigated the frequency of and clinical parameters associated with the detection of DWI-lesions in young TIA patients included in the “Stroke in Young Fabry Patients” study (sifap1), a large multicentre European study on young stroke [9]. To the best of our knowledge, no prior large-scale study has attempted to assess the features of TIA in young patients.

Methods

Design of the study and patients

The multinational sifap1 study (47 centers in 15 European countries) prospectively recruited (between April 2007 and January 2010) 5023 patients aged 18 to 55 years with a cerebrovascular event (CVE) to establish the prevalence of Fabry disease. Details of this study have been published previously [6,7,9]. The study was approved by the ethics committees at the leading centre and at each study site. Each patient or his legal representative gave written informed consent to the participation. A secondary aim of the sifap1 study was to better characterize patterns of stroke in young patients by collecting a broad range of clinical, laboratory, and radiological data using mandatory strict and standardized methods. For inclusion in the sifap study, an MRI scan with specified quality requirements was mandatory. MRI sequences followed optimised stroke imaging protocols at participating centres but were not standardized. The present secondary analysis aimed to investigate the frequency of acute

lesions detected by DWI in the subgroup of patients with TIA and to identify characteristics associated with such lesions. TIA patients with complete MRI dataset with sufficient image quality for the interpretation and a time interval between MRI and the acute CVE ≤ 10 days (to separate acute infarcts from chronic lesions adequately by DWI) were considered for the analysis [10].

Baseline Characteristics

A TIA was defined clinically by stroke experienced neurologists at the individual sites as a CVE with symptoms suggestive of cerebral ischemia lasting < 24 hours. Demographics (age, sex, and ethnicity) were included in the mandatory core data set. Ischemic stroke subtypes were classified according to the published criteria in the Trial of Org 10172 in Acute Stroke Treatment (TOAST) [11]. The following vascular risk factors were considered: diabetes, arterial hypertension, dyslipidaemia, tobacco use and cardiovascular disease. Cardiovascular disease was considered when one of the following conditions was fulfilled: ischemic coronary artery disease, myocardial infarctions, peripheral artery occlusive disease, congestive heart failure, and valvular heart disease [6,7,9]. The following parameters documented in the case report form were included in the analysis: presenting symptoms, ultrasound data from brain supplying arteries (including stenoses and occlusions), previous CVE, prior TIA, atrial fibrillation, snoring and obstructive sleep apnoea [6,7,9].

Anthropometric measurements were used to calculate the body mass index. Details of further lifestyle risk factors were based on patients' self-report and standardized questionnaires including: physical inactivity, short night sleep (duration ≤ 6 at night time per 24 hours), and regular alcohol consumption. Results of the laboratory blood tests were obtained from medical records [6,7,9]. For the present analysis values recorded for haematocrit (volume percentage of red blood cells in blood), C reactive protein, and the calculated estimated glomerular filtration rate (eGFR) were considered.

Cerebral magnetic resonance imaging (MRI)

Cerebral MRI was required for all study participants. Standardized MRI sequences were necessary per protocol (at least T2-weighted and/or fluid-attenuated inversion recovery images and diffusion-weighted imaging sequences) [12]. All images were analysed offline centrally by experienced readers blinded to clinical and demographic data (C.E., F.F., R.S.). For ischemic infarcts they noted infarct type and number, infarct location, size, and vascular territories involved using the templates established by Tatu et al [13]. DWI sequences served

to identify areas of acute ischemia [12,13]. Old infarcts were defined as areas of T2 hyperintensity with associated focal atrophy and / or containing fluid-filled spaces [12]. White matter hyperintensities (WMHs) were defined as lesions with high signal intensity on T2-weighted images in the absence of evidence for complete tissue destruction and were rated according to the Fazekas scale [12]. Deep WMHs were classified as 0=absent, 1=punctuate, 2=early confluent, and 3=confluent; periventricular white matter hyperintensities (PWMH) were categorized as: 0=absent; 1=pencil-thin lining; 2=halo of ≥ 5 mm thickness; 3=irregular WMH extending into deep white matter [12].

Statistical analyses

First, we conducted descriptive analyses. Bivariate analysis was completed to test associations of several characteristics with the presence of DWI lesions in patients with TIA. A multiple logistics regression analysis was conducted to test which characteristics were independently associated with DWI lesions in TIA patients after adjustment for other covariates. A stepwise backward procedure was applied. Only covariates with a p-value <0.1 in bivariate analyses were selected for the multiple regression models. All p-values were adjusted for center heterogeneity using random effects models. A two-sided significance level of $\alpha=0.05$ was considered. No adjustment for multiple testing was applied. All statistical analyses were conducted using IBM® SPSS® Statistics 22 (©SPSS, Inc., IBM Company, 2013, Chicago-IL) and Stata 13 IC (StataCorp. 2013. *Stata Statistical Software: Release 13*. College Station, TX: StataCorp LP.).

Results

Among the 5023 patients included in the sifap1 study, 1071 patients had a symptom duration <24 hours, consistent with the definition of a TIA. According to Fazekas et al. 142 patients were excluded due to a MRI taken later than 10 days after the acute event and further 82 patients had a MRI of insufficient quality for interpretation [12]. 829 patients who had MRI data satisfying the requirements for the analysis were included in the final analysis. 121 patients (15%) demonstrated an acute DWI lesion (Figure 1, Table 1). There was no difference in age between patients with DWI lesions versus those without DWI lesions (DWI+ median: 47 years versus DWI- median: 46 years; $p=0.569$). Dichotomizing between the youngest age group and the reminder of the cohort did also not yield significant differences in the frequency of DWI lesions [18-35 years: 15/109 (13.8%) versus >35 years:

106/720 (14.7%); $p=0.315$]. The median time interval between the CVE and brain MRI was 2 days (IQR 1-4 days), (DWI positive: 2 days (IQR 1-4 days) versus DWI negative: 1 day (IQR 1-4 days); $p=0.378$). In the majority of the patients the acute lesions were found in the anterior circulation ($n=92$, 77%), and they occurred predominantly in the cortico-subcortical areas (63/92, 68%). Seventy one patients had a lesion ≤ 1 cm, 48 presented lesions >1 cm. In 57 patients (47.1%) more than one lesion was identified; among these patients ten (17.5%) had two or more lesions in different territories (Table 1). In 53 patients (43.8%) a right sided lesion was evident, in 60 patients (49.7%) lesions left sided were detected, 14 patients (11.6%) had a brainstem or cerebellar lesion and 7 patients showed bilateral lesions. 73% of the patients with an acute left sided lesion had a left hemispheric clinical presentation; and 43% of these patients presented with a right-sided paresis. In 27 patients DWI lesions and the clinical manifestation were ipsilateral; six of those had lesions bilaterally. Almost all patients with cerebellar lesions had vertigo as a presenting symptom (6/7) (Table 2).

Comparing TIA patients with acute DWI lesions to those without any acute lesions, acute lesions were associated with left hemispheric presenting symptoms, dysarthria as presenting symptom, stroke aetiology, and old infarctions as demonstrated by MRI (table 3a and 3b). Patients with acute DWI lesions more often had a cardioembolic aetiology or large artery atherosclerosis causing the current event (cardioembolism: 19.5% vs. 10.1%, $p=0.005$; large-artery sclerosis: 14.4% versus 8.1%, $p=0.005$). In a subgroup of patients ($n=446$), ultrasound data on brain supplying arteries had been documented within this sipap cohort. Regarding the frequency of vessel stenosis, there were no differences between patients with a DWI lesion versus those without a DWI lesion (Table 3a). Old infarctions in the brain MRI were identified in 143 patients (17.2%). A previous cerebrovascular event (including TIA and brain infarction) was more often evident in patients with old infarctions in the brain MRI (78/140, 55.7% versus 139/680, 20.4%; $P<0.001$); in 62/140 (44.3%) patients with old infarctions on brain MRI no previous CVE was documented.

Using a multiple logistic regression analysis, the following parameters were identified as independent predictors for an acute lesion: left hemispheric presenting symptoms (OR 1.92, CI: 1.27– 2.91), dysarthria as presenting symptom (OR 2.17, CI: 1.38 3.43) and old infarctions as demonstrated by MRI (territories of the middle and posterior cerebral artery: OR: 2.43, CI: 1.42 – 4.15; OR: 2.41, CI: 1.02 – 5.69, respectively) (Table 4).

Discussion

Our study demonstrated a regular DWI scan is the common finding in young TIA patients. In 15% of young stroke patients with symptoms suggestive of a CVE lasting <24 hours, hence clinically classified as TIA, an acute lesion in the DWI was identified. Apart from left hemispheric presenting symptoms there was a weak association between clinical presentation and the lesion location. Characteristics associated with acute DWI lesions were: left hemispheric presenting symptoms, dysarthria, and old infarctions on the brain MRI.

Because of the lack of research in this specific area, no previous investigations of exclusively young stroke patients are available for direct comparison. When discussing our findings we therefore need to refer to data derived from studies addressing general stroke populations. The lower yield of DWI lesions in this particular population compared to elderly TIA patient populations is an interesting finding. Conceptually, several potential explanations could be raised (e.g. that DWI lesions already had disappeared, that not enough cytotoxic oedema had formed because of short duration of ischemia, that part of clinically diagnosed TIA's were not caused by an ischemic event or that the quality of the DWI sequences was suboptimal) which will be discussed subsequently.

According to the literature there is a large variety in the prevalence of DWI lesions in acute TIA patients [14]. A potential cause of this observation may be the procedural TIA definition. Some authors claim a clinical TIA with acute lesions may be classified as stroke, thereby modifying proportions by placing TIAs into stroke subgroups [14,15]. Previous research has shown that acute lesions in TIAs could be expected in 30-40% of the cases, yet the prevalence in our specific group of young TIAs is low [14]. This result could be attributed to the fact we investigated specifically a group of young TIA patients which is not comparable to studies specified in the literature [14]. On the other hand, this result could reflect accurate findings. In our study the bias in adjudication clinical TIAs with acute lesions to strokes can be considered low because in the case report form in the sifap1 study we simply asked for the duration of the clinical manifestation. To what extent TIAs without DWI lesions represent TIA mimics rather than a result of a cerebrovascular event remains unclear. When interpreting our results this general problem, which inevitably occurs when investigating patients with TIA, needs to be taken into account [16].

A further bias influencing the detection of acute lesions in the DWI might be the time delay between the current event to the MRI examination [17]. However this aspect should not have influenced our results to a greater extent, as no relevant differences with regard to the time delay were observed between DWI positive versus DWI negative patients. In line with this observation Brazzelli et al. found in a meta-analysis no impact of increasing time delay from

event to the MRI regarding the proportion of DWI positive patients. Instead, the most important factor influencing the rates of DWI positive patients was the sample size [14]. Large populations ($n \geq 200$) had fewer rates of DWI positive patients [14]. This is in accordance with our results as with 829 subjects our study is the largest investigation on this issue.

The parameter of left hemispheric presenting symptoms was associated with acute lesions; a left hemispheric lesion presented with a left hemispheric symptom in 73% of the cases. However, in accordance with a previous investigation by van Rooij et al. [18], in a considerable proportion of our patients the clinical presentation did not match the lesion location. This result suggests that acute lesions in TIA patients might rather indicate a general embolic arterial ischemic activity accompanying the acute cerebrovascular event. This conclusion is also supported by the fact that the occurrence of DWI lesions in our patients was associated with embolic stroke aetiologies including stroke subtypes of cardioembolism and large artery atherosclerosis. Both aetiologies are known to cause embolic infarction pattern in the acute DWI, with some of the lesions without clinical correlates [19,20]. In addition, in half of our patients (47.1%) more than one DWI lesion (partially in different vascular territories) was evident, the majority of them were small (1cm) and located in the cortical or subcortical regions, which is also suggestive of embolic pattern [19-21]. In accordance with this hypothesis, other authors suspected DWI lesions in TIA patients might be cerebrovascular “footprints” of a cardiac disorder causing embolic events [22].

Old infarctions in brain MRI were noted more often in TIA patients with acute DWI lesions. While the evidence regarding the prognostic relevance of acute lesions in TIA patients is still controversial, this observation indicates the duplicity of a pathomechanism, which already had caused former ischemic brain injury [4,5]. This provides indirect evidence for a prognostic value of imaging-proven brain infarctions in predicting future cerebrovascular events. While Anticoli and colleagues recently failed to identify such a prognostic relevance for acute lesions in TIA patients, Ay and co-workers found a higher predictive value of subsequent strokes for acute DWI lesion in TIA patients in comparison to a simply narrative test such as the ABCD² score [4,5]. An ABCD² score ≥ 4 showed a 4.65 fold increased risk for a subsequent stroke, in contrast a DWI lesion alone determined an 11.1 fold increase [4]. ABCD² scores < 4 represents a risk for a recurrent stroke of less than 1%, at this stage an additional DWI lesion increases this value to 4.9%. This needs to be taken into account, as ABCD² scores < 4 with acute DWI lesions apply to a considerable proportion (9%) of TIAs. Therefore, considering the ABCD² score alone would lead to an underestimation of the

recurrence risk in these patients [4]. Nevertheless the ABDC² score was addressed in numerous publications, boosting its reputation [3,5,23,24]. As clinical TIAs might result in an acute ischemic brain injury, potentially not correlated to the clinical presentation and most likely of embolic origin, the MRI should be prioritized in the acute delivery of care. The concept of establishing a diagnosis of a TIA solely based on clinical aspects has been challenged by cases with a clinical diagnosis of TIA and acute DWI lesions on MRI. Therefore, given the implications for prognosis, a tissue-based definition of TIAs has been suggested e.g. by Giles and co-authors [25]. Future studies might therefore wish to follow this approach.

Since some studies identified the symptom duration of a TIA relevant for the long term prognosis as well as an important determinant for DWI lesions in TIAs, this missing information in our study represents a limitation [4,5,26]. Furthermore, although the sifap study documented a comprehensive data set, information on substance abuse is not available. This aspect needs to be taken into account regarding the identification of etiologic factors, since especially among young individuals substance abuse may be more strongly implicated in the stroke pathogenesis [27]. Along the same lines, the use of transcranial doppler ultrasound for detection of microembolic signals would have usefully augmented the diagnostic-workup. However, this approach was not followed routinely within the sifap study. Similarly, the documentation of ultrasound studies of the brain supplying arteries was not undertaken constantly. However, in a smaller subset of patients, we did not find a correlation between the presence of a vessel stenosis and DWI lesions, except for a trend for a higher frequency of ICA occlusions in the DWI positive group. However, in the interpretation of these findings, the small number of events in these subgroups has to be considered. With regard to the diagnosis of acute ischemic brain lesions on MRI, the three imaging raters also used ADC maps to confirm DWI positive lesions via focal ADC restriction (and thus to distinguish lesions from “shine-through” effects or vasogenic oedema), but no quantitative measurements were done as sequences had not been standardized within sifap.

In summary, in a small proportion (15%) of young TIA patients a DWI lesion was found. Most of the lesions were located in the cortical or subcortical region and were not associated with the clinical presentation, suggesting an embolic origin for the actual cerebrovascular event. TIAs with acute DWI lesions were associated with old infarctions on brain MRI, indicating a recurrent stroke mechanism. As acute ischemic lesions with TIA are of significant value in predicting future events and cannot be predicted on clinical grounds, early brain MRI examination is warranted in these patients.

Acknowledgments

The authors would like to thank all centres and all patients having contributed to the study.

Disclosures of conflict of interest

The authors declare no financial or other conflict of interest related to the submitted manuscript.

Sources of funding

The sifap1 study (Stroke in Young Fabry Patients, www.sifap.eu, NCT00414583) has been supported by an unrestricted scientific grant from Shire Human Genetic Therapies to the University of Rostock.

References

1. Special report from the National Institute of Neurological Disorders and Stroke. Classification of cerebrovascular diseases III. *Stroke* 1990; **21**: 637-676.
2. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. *Cerebrovasc Dis* 2008; **25**: 457-507.
3. Johnston SC, Rothwell PM, Nguyen-Huynh MN *et al*. Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. *Lancet* 2007; **369**: 283-292.
4. Ay H, Arsava EM, Johnston SC *et al*. Clinical- and imaging-based prediction of stroke risk after transient ischemic attack: the CIP model. *Stroke* 2009; **40**: 181-186.
5. Anticoli S, Pezzella FR, Pozzessere C *et al*. Transient Ischemic Attack Fast-track and Long-Term Stroke Risk: Role of Diffusion-Weighted Magnetic Resonance Imaging. *J Stroke Cerebrovasc Dis* 2015; **24**: 2110-2116.
6. Thijs V, Grittner U, Dichgans M *et al*. Family History in Young Patients With Stroke. *Stroke* 2015; **46**: 1975-1978.
7. Tanislav C, Kropp P, Grittner U *et al*. Clinically relevant depressive symptoms in young stroke patients - results of the sifap1 study. *Neuroepidemiology* 2015; **44**: 30-38.

8. Tanislav C, Grittner U, Misselwitz B *et al.* Lessons from everyday stroke care for clinical research and vice versa: comparison of a comprehensive and a research population of young stroke patients. *BMC Neurol* 2014; **14**:45.
9. Rolfs A, Fazekas F, Grittner U *et al.* Acute cerebrovascular disease in the young: the Stroke in Young Fabry Patients study. *Stroke* 2013; **44**: 340-349.
10. Eastwood JD, Engelter ST, MacFall JF. Quantitative assessment of the time course of infarct signal intensity on diffusion-weighted images. *AJNR Am J Neuroradiol* 2003; **24**: 680-687.
11. Adams HP, Jr., Bendixen BH, Kappelle LJ *et al.* Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke* 1993; **24**: 35-41.
12. Fazekas F, Enzinger C, Schmidt R *et al.* MRI in acute cerebral ischemia of the young: the Stroke in Young Fabry Patients (sifap1) Study. *Neurology* 2013; **81**: 1914-1921.
13. Tatu L, Moulin T, Bogousslavsky J, Duvernoy H: Arterial territories of the human brain: cerebral hemispheres. *Neurology* 1998; **50**: 1699-1708.
14. Brazzelli M, Chappell FM, Miranda H *et al.* Diffusion-weighted imaging and diagnosis of transient ischemic attack. *Ann Neurol* 2014; **75**: 67-76.
15. Furie KL, Kasner SE, Adams RJ *et al.* Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: a guideline for healthcare professionals from the american heart association/american stroke association. *Stroke* 2011; **42**: 227-276.
16. Dutta D, Bowen E, Foy C. Four-year follow-up of transient ischemic attacks, strokes, and mimics: a retrospective transient ischemic attack clinic cohort study. *Stroke* 2015; **46**: 1227-1232.
17. Lecouvet FE, Duprez TP, Raymackers JM, Peeters A, Cosnard G. Resolution of early diffusion-weighted and FLAIR MRI abnormalities in a patient with TIA. *Neurology* 1999; **52**: 1085-1087.
18. van Rooij FG, Vermeer SE, Goraj BM *et al.*: Diffusion-weighted imaging in transient neurological attacks. *Ann Neurol* 2015; **78**: 1005-1010.

19. Depuydt S, Sarov M, Vandendries C *et al.* Significance of acute multiple infarcts in multiple cerebral circulations on initial diffusion weighted imaging in stroke patients. *J Neurol Sci* 2014; **337**: 151-155.
20. Man BL, Fu YP, Chan YY *et al.* Lesion patterns and stroke mechanisms in concurrent atherosclerosis of intracranial and extracranial vessels. *Stroke* 2009; **40**: 3211-3215.
21. Kastrup A, Schulz JB, Mader I, Dichgans J, Kuker W. Diffusion-weighted MRI in patients with symptomatic internal carotid artery disease. *J Neurol* 2002; **249**: 1168-1174.
22. Ay H, Oliveira-Filho J, Buonanno FS *et al.* 'Footprints' of transient ischemic attacks: a diffusion-weighted MRI study. *Cerebrovasc Dis* 2002; **14**: 177-186.
23. Merwick A, Albers GW, Amarenco P *et al.* Addition of brain and carotid imaging to the ABCD(2) score to identify patients at early risk of stroke after transient ischaemic attack: a multicentre observational study. *Lancet Neurol* 2010; **9**: 1060-1069.
24. Rothwell PM, Giles MF, Flossmann E *et al.* A simple score (ABCD) to identify individuals at high early risk of stroke after transient ischaemic attack. *Lancet* 2005; **366**: 29-36.
25. Giles MF, Albers GW, Amarenco P *et al.* Early stroke risk and ABCD2 score performance in tissue- vs time-defined TIA: a multicenter study. *Neurology* 2011; **77**: 1222-1228.
26. Rovira A, Rovira-Gols A, Pedraza S, Grive E, Molina C *et al.* Diffusion-weighted MR imaging in the acute phase of transient ischemic attacks. *AJNR Am J Neuroradiol* 2002; **23**: 77-83.
27. Siniscalchi A, Bonci A, Mercuri NB *et al.* Cocaine dependence and stroke: pathogenesis and management. *Curr Neurovasc Res* 2015; **12**: 163-172.

Figure 1. Patients' selection **Table 1.** Distribution of acute lesions in young TIA patients (n=121) stratified by lesion size (lesion ≤ 1 cm versus lesion > 1 cm)

	No. of patients with	No. of patients with	No. of patients with	<i>P</i> ^a

	at least one lesion n=121 ^b	at least one lesion ≤1cm n=71	at least one lesion >1cm n=48	
>1 acute DWI lesion	57 (47.1%)	30 (42.3%)	27 (56.3%)	0.179
In two different territories ^c	10 (8.3%)	6 (8.5%)	4 (8.3%)	0.958
Anterior circulation	92 (76.0%)	57(80.3%)	35(72.9%)	0.347
>1 acute DWI lesion	49 (40.5%)	29 (40.8%)	20 (41.7%)	0.931
Anterior cerebral artery	5 (4.1%)	3 (4.2%)	2 (4.2%)	0.877
Middle cerebral artery	90 (74.3%)	57 (80.3)	33 (68.8%)	0.141
Cortico-subcortical	63	33	30	
White Matter	34	21	13	
Basal ganglia	15	7	8	
Thalamus	2	2	0	
Posterior circulation	29 (24.0%)	15 (21.1%)	14 (29.2)	0.318
>1 acute DWI lesion	9 (7.4%)	1 (1.4%)	8 (16.7%)	0.015
Posterior cerebral artery	15 (12.4%)	9 (12.7%)	6 (12.5%)	0.977
Cortico-subcortical	6	1	5	
White Matter	3	2	1	
Thalamus	1	0	1	
Vertebrobasilar	15 (12.4%)	6 (8.5%)	9 (18.8%)	0.119
Brainstem	7	5	2	
Cerebellum	7	1	6	

^aP value based on logistic regression adjusted for centre heterogeneity; ^bin two patients no information on lesion side was available; ^cdistributed bilaterally and across the territories of the anterior cerebral artery, middle cerebral artery, posterior cerebral artery, brain stem and cerebellum.

Table 2. Presenting symptoms in young TIA patients with acute DWI lesions (n=121)

	Distribution of acute lesions on DWI						
	Lesion right	Lesion left	Bilateral lesions	Lesions in the anterior circulation	Posterior cerebral artery	Brainstem	Cerebellum
	n=53	n=60	n=7	n=92	n=15	n=7	n=7
Presenting symptoms according to the anatomical localisation							
Left hemispheric (n=59)	11 (20.8%)	44 (73.3%)	3 (42.9%)	47 (51.1%)	9 (60.0%)	1 (14.3%)	1 (14.3%)
Right hemispheric (n=38)	25 (47.2%)	10 (16.7%)	3 (42.9%)	31 (33.7%)	6 (40.0%)	--	2 (28.6%)
Brainstem (n=11)	6 (11.3%)	4 (6.7%)	1 (14.3%)	3 (3.3%)	2 (13.3%)	3 (42.9%)	3 (42.9%)
Uncertain	11 (20.8%)	2 (3.3%)	--	11 (12.0%)	--	--	--
Symptoms at the time of CVE ^a							
Paresis (n=57)	20 (37.7%)	34 (56.7%)	2 (28.6%)	48 (52.1%)	6 (40.0%)	1 (14.3%)	3 (42.9%)
Left (n=26)	17 (32.1%)	8 (13.3%)	1 (14.3%)	21 (22.8%)	2 (13.3%)	1 (14.3%)	3 (42.9%)
Right (n=30)	2 (3.8%)	26 (43.3%)	1 (14.3%)	26 (28.3%)	4 (26.7%)	--	--
Both sided (n=1)	1 (1.9%)	--	--	1 (1.1%)	--	--	--
Somatosensory deficit (n=44)	32 (60.3%)	29 (48.3%)	4 (57.1%)	52 (56.5%)	8 (53.3%)	5 (71.4%)	3 (42.9%)

Left (n=34)	24 (45.3%)	8 (13.3%)	2 (28.6%)	26 (28.3%)	4 (26.7%)	2 (28.6%)	3 (42.9%)
Right (n=31)	7 (13.2%)	21 (35.0%)	2 (28.6%)	26 (28.3%)	4 (26.7%)	2 (28.6%)	--
Both sided (n=1)	1 (1.9%)	--	--	--	--	1 (14.3%)	--
Aphasia (n=21)	4 (7.5%)	17 (28.3%)	--	18 (19.6%)	3 (20.0%)	--	--
Dysarthria (n=38)	17 (32.1%)	19 (31.7%)	2 (28.6%)	27 (29.3%)	6 (40.0%)	2 (28.6%)	4 (57.1%)
Hemianopia (n=13)	6 (11.3%)	7 (11.7%)	--	8 (8.7%)	2 (13.3%)	1 (14.3%)	
Ataxia (n=13)	4 (7.5%)	8 (13.3%)	2 (14.3%)	7 (7.6%)	4 (26.7%)	--	3 (42.9%)
Vertigo (n=33)	14 (26.4%)	15 (25.0%)	4 (57.1%)	22 (23.9%)	1 (6.7%)	4 (57.1%)	6 (85.7%)
Diplopia (n=11)	4 (7.5%)	4 (6.7%)	3 (42.9%)	5 (5.4%)	4 (26.7%)	1 (14.3%)	1 (14.3%)
Headache (n=30)	13 (24.5%)	15 (25.0%)	2(28.6%)	24 (26.1%)	1 (6.7%)	--	3 (42.9%)

^aCVE refers to cerebrovascular event

Table 3a. Acute lesions in young TIA patients.

	n	Total cohort (n=829)	DWI positive (n=121)	DWI negative (n=708)	P
Age (years) median (interquartile range, IQR)	82 9	46 (40-51)	47 (41-52)	46 (40-51)	0.56 9
46-55 years		437 (52.7%)	66 (54.5%)	371 (52.4%)	0.72 3
36-45 years		283 (34.1%)	40 (33.1%)	243 (34.3%)	
18-35 years		109 (13.1%)	15 (12.4%)	94 (13.3%)	
Sex	82 9				
Female		372 (44.9%)	48 (39.7%)	324 (45.8%)	0.23 6
Time CVE to MRI (days); median (IQR)	82 9	2 (1-4)	2 (1-4)	1 (1-4)	0.37 8
Presenting Symptoms					
Left hemispheric	82 9	302 (36.4%)	59 (48.8%)	243 (34.3%)	0.00 4
Right hemispheric	82 9	284 (34.3%)	38 (31.4%)	246 (34.7%)	0.58 8
Paresis	81 1	340 (41.9%)	57 (47.9%)	283 (40.9%)	0.12 5
Somatosensory deficit	78 6	486 (61.8%)	66 (60.0%)	420 (62.1%)	0.73 8
Aphasia	78 3	118 (15.1%)	21 (19.3%)	97 (14.4%)	0.32 9
Dysarthria	82 2	165 (20.1%)	38 (31.4%)	127 (18.1%)	0.00 1
Ataxia	81 8	93 (11.4%)	13 (10.8%)	80 (11.5%)	0.80 7
Hemianopia	82 8	83 (10%)	13 (10.8%)	70 (9.9%)	0.74 3
Diplopia	82	77 (9.3%)	11 (9.2%)	66 (9.3%)	0.85

	7				4
Vertigo	82 5	250 (30.3%)	33 (27.3%)	217 (30.8%)	0.55 8
Headache	82 7	216 (26.1%)	30 (25.0%)	186 (26.3%)	0.82 3
Vascular risk factors					
Hypertension	82 7	320 (38.7%)	55 (45.5%)	265 (37.5%)	0.09 1
Diabetes mellitus	82 6	65 (7.9%)	13 (10.9%)	52 (7.4%)	0.15 5
Hyperlipidemia	80 0	271 (33.9%)	40 (34.2%)	231 (33.8%)	0.93 7
Tobacco smoking ^a	82 1	392 (47.7%)	67 (55.8%)	325 (46.4%)	0.05 5
Previous CVE	82 9	196 (23.6%)	32 (26.4%)	164 (23.2%)	0.40 8
Prior TIA	81 0	124 (15.3%)	17 (14.4%)	107 (15.5%)	0.69 0
Cardiovascular disease ^b	81 0	64 (7.9%)	7 (5.9%)	57 (8.2%)	0.40 6
Atrial fibrillation	82 1	12 (1.5%)	2 (1.7%)	10 (1.4%)	0.45 2
Anthropometric and behavior risk factors					
BMI median (IQR)	82 6	26.0 (23.2-29.4)	25.5 (23.3-28.5)	26.0 (23.2-29.4)	0.89 3
Physical inactivity ^c	81 3	340 (41.8%)	49 (40.8%)	291 (42.0%)	0.76 1
Snoring	79 6	470 (59.0%)	61 (51.7%)	409 (60.3%)	0.17 6
Obstructive sleep apnea	80 7	36 (4.5%)	5 (4.1%)	31 (4.5%)	0.93 8
Sleep ≤ 6 h at night time	82 8	155 (18.7%)	25 (20.7%)	130 (18.4%)	0.60 1

Regular alcohol consumption ^d	82 1	444 (54.1%)	65 (54.2%)	379 (54.1%)	0.86 8
Laboratory values					
Hematocrit (%); median (IQR)	63 2	42 (40-44)	42 (39-45)	42 (40-44)	0.50 1
CRP (mg/l); median (IQR)	49 7	2.0 (0.8-5.0)	2.0 (1.0-4.6)	2.0 (0.7-5.0)	0.32 8
Medication prior to TIA					
Antiplatelet agents	82 9	640 (77.2%)	91 (75.2%)	549 (77.5%)	0.74 9
Anticoagulants	82 9	31 (3.7%)	7 (5.8%)	24 (3.4%)	0.22 0
Antihypertensive drugs	82 9	254 (30.6%)	42 (34.7%)	212 (29.9%)	0.25 7
Statins	82 9	350 (42.2%)	58 (47.9%)	292 (41.2%)	0.17 5
TOAST	82 0				
Large-artery atherosclerosis		74 (9.0%)	17 (14.4%)	57 (8.1%)	0.00 5
Cardioembolism		94 (11.5%)	23 (19.5%)	71 (10.1%)	
Small-artery occlusion		106 (12.9%)	14 (11.9%)	92 (13.1%)	
Other determined etiology		104 (12.7%)	11 (9.3%)	93 (13.2%)	
Undetermined aetiology		442 (53.9%)	53 (44.9%)	389 (55.4%)	
Ultrasound findings					
ACI ^f stenosis $\geq 50\%$	46 6	17 (3.6%)	3 (3.1%)	15 (3.7%)	0.70 9
ACI ^f occlusion	46 6	17 (3.6%)	5 (7.8%)	12 (3.0%)	0.05 6
MCA ^g stenosis $\geq 50\%$	34 6	17 (4.9%)	2 (4.7%)	15 (5.0%)	0.93 2
MCA ^g occlusion	34 6	1 (0.3%)	1 (2.3%)	-	-
Vertebral artery stenosis $\geq 50\%$	33	4 (1.3%)	1 (2.6%)	3 (1.1%)	0.45

	7				3
Vertebral artery occlusion	33 7	4 (1.3%)	1 (2.6%)	3 (1.1%)	0.45 3
Stenosis of the basilar artery	33 7	3 (0.9%)	1 (2.4%)	2 (0.7%)	0.27 1

^acurrent smoking or quit within last 5 years; ^bcardiovascular disease considers one of the following conditions: ischemic coronary artery disease, myocardial infarction, peripheral artery occlusive disease, congestive heart failure, and valvular disease; ^cphysical inactivity consists in <1 mile per day walking; ^dconsumption of at least one drink/week; ^fACI refers to internal carotis artery; ^gMCA refers to middle cerebral artery.

Table 3b. Imaging findings in young TIA patients.

	n	Total cohort n=829	DWI positive n=121	DWI negative n=708	P
Old infarction					
≥1 old infarct	829	143 (17.2%)	36 (29.8%)	107 (15.1%)	<0.001
Left hemispheric	829	60 (7.2%)	19 (15.7%)	41 (5.8%)	<0.001
Right hemispheric	829	46 (5.5%)	8 (6.6%)	38 (5.4%)	0.559
Vascular territory					
Anterior cerebral artery	829	6 (0.7%)	1 (0.8%)	5 (0.7%)	0.951
Middle cerebral artery	829	95 (11.5%)	28 (23.1%)	67 (9.5%)	<0.001
Posterior cerebral artery	829	32 (3.9%)	10 (8.3%)	22 (3.1%)	0.009
vertebrobasilar	829	46 (5.5%)	10 (8.3%)	36 (5.1%)	0.134
Infarct type					
territorial	829	82 (9.9%)	22 (18.2%)	60 (8.5%)	0.001
watershed	829	9 (1.1%)	--	9 (1.3%)	0.974
Lacunar	829	72 (8.7%)	18 (14.9%)	54 (7.6%)	0.011
White Matter Hyperintensities					
Deep WMH ^a	812				

0		529 (65.1%)	59 (50.9%)	470 (67.5%)	0.003
1		225 (27.7%)	45 (38.8%)	180 (25.9%)	
2 or 3		58 (7.1%)	12 (10.3%)	46 (6.6%)	
Periventricular WMH ^a	812				
0		660 (81.3%)	83 (71.6%)	577 (82.9%)	0.014
1		123 (15.1%)	26 (22.4%)	97 (13.9%)	
2 or 3		29 (3.6%)	7 (6.0%)	22 (3.2%)	
WMH ^a at all	812	317 (39.0%)	61 (52.6%)	256 (36.8%)	0.004
No non acute lesions					
No old infarcts	829	686 (82.8%)	85 (70.2%)	601 (84.9%)	<0.001
No WMH ^a	812	495 (61.0%)	56 (47.4%)	439 (63.2%)	0.004
No WMH ^a and no old infarctions	829	455 (54.9%)	50 (41.3%)	405 (57.2%)	0.004

^aWMH refers to white matter hyperintensities.

Table 4. Multiple logistic regression OR (95%CI) for acute lesions in TIA. All factors with bivariate $p < 0.1$ were tested. Only variables with significant coefficients remained in the final model, a random-intercept model (n=786 patients / 45 centers).

	Model 1 (n=786 patients / 45 centers)		Model 2 (n=786 patients / 45 centers)	
	OR (95%CI)	p	OR (95%CI)	p
Fixed effects				
Presenting symptoms left hemispheric	1.83 (1.19-2.83)	0.006	1.98 (1.29-3.03)	0.002
Dysarthria	2.01 (1.24-3.26)	0.005	2.13 (1.33-3.40)	0.002
TOAST			--	
Large-artery atherosclerosis (ref.)	1			
Cardioembolism	1.47 (0.63-3.41)	0.370		
Small artery occlusion (lacune)	0.59 (0.24-1.44)	0.250		

Other determined etiology	0.57 (0.23-1.45)	0.241		
Undetermined etiology	0.61 (0.30-1.26)	0.186		
Tobacco smoking ^a	1.16 (0.75-1.80)	0.501	--	
Hypertension	1.06 (0.66-1.70)	0.808	--	
Old infarction left hemispheric	2.04 (0.90-4.64)	0.088	--	
White matter lesions at all	1.43 (0.90-2.27)	0.126	--	
Old territorial lesion	1.04 (0.46-2.35)	0.929	--	
Old lacunar lesion	0.59 (0.22-1.60)	0.297	--	
Old A. cerebri media infarct	2.24 (0.95-5.27)	0.064	2.41 (1.42-4.15)	0.002
Old A. cerebri posterior infarct	2.34 (0.88-6.20)	0.088	2.50 (1.06-5.90)	0.037
Random effects			Beta (SE)	
Between center variation	0.37 (0.18)	0.089	0.41 (0.16)	0.034

^acurrent smoking or quit within last 5 years

References

1. Special report from the National Institute of Neurological Disorders and Stroke. Classification of cerebrovascular diseases III. *Stroke* 1990; **21**: 637-676.
2. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. *Cerebrovasc Dis* 2008; **25**: 457-507.
3. Johnston SC, Rothwell PM, Nguyen-Huynh MN *et al*. Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. *Lancet* 2007; **369**: 283-292.
4. Ay H, Arsava EM, Johnston SC *et al*. Clinical- and imaging-based prediction of stroke risk after transient ischemic attack: the CIP model. *Stroke* 2009; **40**: 181-186.
5. Anticoli S, Pezzella FR, Pozzessere C *et al*. Transient Ischemic Attack Fast-track and Long-Term Stroke Risk: Role of Diffusion-Weighted Magnetic Resonance Imaging. *J Stroke Cerebrovasc Dis* 2015; **24**: 2110-2116.
6. Thijs V, Grittner U, Dichgans M *et al*. Family History in Young Patients With Stroke. *Stroke* 2015; **46**: 1975-1978.
7. Tanislav C, Kropp P, Grittner U *et al*. Clinically relevant depressive symptoms in young stroke patients - results of the sifap1 study. *Neuroepidemiology* 2015; **44**: 30-38.

8. Tanislav C, Grittner U, Misselwitz B *et al.* Lessons from everyday stroke care for clinical research and vice versa: comparison of a comprehensive and a research population of young stroke patients. *BMC Neurol* 2014; **14**:45.
9. Rolfs A, Fazekas F, Grittner U *et al.* Acute cerebrovascular disease in the young: the Stroke in Young Fabry Patients study. *Stroke* 2013; **44**: 340-349.
10. Eastwood JD, Engelter ST, MacFall JF. Quantitative assessment of the time course of infarct signal intensity on diffusion-weighted images. *AJNR Am J Neuroradiol* 2003; **24**: 680-687.
11. Adams HP, Jr., Bendixen BH, Kappelle LJ *et al.* Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke* 1993; **24**: 35-41.
12. Fazekas F, Enzinger C, Schmidt R *et al.* MRI in acute cerebral ischemia of the young: the Stroke in Young Fabry Patients (sifap1) Study. *Neurology* 2013; **81**: 1914-1921.
13. Tatu L, Moulin T, Bogousslavsky J, Duvernoy H: Arterial territories of the human brain: cerebral hemispheres. *Neurology* 1998; **50**: 1699-1708.
14. Brazzelli M, Chappell FM, Miranda H *et al.* Diffusion-weighted imaging and diagnosis of transient ischemic attack. *Ann Neurol* 2014; **75**: 67-76.
15. Furie KL, Kasner SE, Adams RJ *et al.* Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: a guideline for healthcare professionals from the american heart association/american stroke association. *Stroke* 2011; **42**: 227-276.
16. Dutta D, Bowen E, Foy C. Four-year follow-up of transient ischemic attacks, strokes, and mimics: a retrospective transient ischemic attack clinic cohort study. *Stroke* 2015; **46**: 1227-1232.
17. Lecouvet FE, Duprez TP, Raymackers JM, Peeters A, Cosnard G. Resolution of early diffusion-weighted and FLAIR MRI abnormalities in a patient with TIA. *Neurology* 1999; **52**: 1085-1087.
18. van Rooij FG, Vermeer SE, Goraj BM *et al.*: Diffusion-weighted imaging in transient neurological attacks. *Ann Neurol* 2015; **78**: 1005-1010.

19. Depuydt S, Sarov M, Vandendries C *et al.* Significance of acute multiple infarcts in multiple cerebral circulations on initial diffusion weighted imaging in stroke patients. *J Neurol Sci* 2014; **337**: 151-155.
20. Man BL, Fu YP, Chan YY *et al.* Lesion patterns and stroke mechanisms in concurrent atherosclerosis of intracranial and extracranial vessels. *Stroke* 2009; **40**: 3211-3215.
21. Kastrup A, Schulz JB, Mader I, Dichgans J, Kuker W. Diffusion-weighted MRI in patients with symptomatic internal carotid artery disease. *J Neurol* 2002; **249**: 1168-1174.
22. Ay H, Oliveira-Filho J, Buonanno FS *et al.* 'Footprints' of transient ischemic attacks: a diffusion-weighted MRI study. *Cerebrovasc Dis* 2002; **14**: 177-186.
23. Merwick A, Albers GW, Amarenco P *et al.* Addition of brain and carotid imaging to the ABCD(2) score to identify patients at early risk of stroke after transient ischaemic attack: a multicentre observational study. *Lancet Neurol* 2010; **9**: 1060-1069.
24. Rothwell PM, Giles MF, Flossmann E *et al.* A simple score (ABCD) to identify individuals at high early risk of stroke after transient ischaemic attack. *Lancet* 2005; **366**: 29-36.
25. Giles MF, Albers GW, Amarenco P *et al.* Early stroke risk and ABCD2 score performance in tissue- vs time-defined TIA: a multicenter study. *Neurology* 2011; **77**: 1222-1228.
26. Rovira A, Rovira-Gols A, Pedraza S, Grive E, Molina C *et al.* Diffusion-weighted MR imaging in the acute phase of transient ischemic attacks. *AJNR Am J Neuroradiol* 2002; **23**: 77-83.
27. Siniscalchi A, Bonci A, Mercuri NB *et al.* Cocaine dependence and stroke: pathogenesis and management. *Curr Neurovasc Res* 2015; **12**: 163-172.

ene_13012_f1.tif

Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:

Tanislav, C;Grittner, U;Fazekas, F;Thijs, V;Tatlisumak, T;Huber, R;von Sarnowski, B;Putala, J;Schmidt, R;Kropp, P;Norrving, B;Martus, P;Gramsch, C;Giese, AK;Rolfs, A;Enzinger, C

Title:

Frequency and predictors of acute ischaemic lesions on brain magnetic resonance imaging in young patients with a clinical diagnosis of transient ischaemic attack

Date:

2016-07-01

Citation:

Tanislav, C., Grittner, U., Fazekas, F., Thijs, V., Tatlisumak, T., Huber, R., von Sarnowski, B., Putala, J., Schmidt, R., Kropp, P., Norrving, B., Martus, P., Gramsch, C., Giese, A. K., Rolfs, A. & Enzinger, C. (2016). Frequency and predictors of acute ischaemic lesions on brain magnetic resonance imaging in young patients with a clinical diagnosis of transient ischaemic attack. EUROPEAN JOURNAL OF NEUROLOGY, 23 (7), pp.1174-1182. <https://doi.org/10.1111/ene.13012>.

Persistent Link:

<http://hdl.handle.net/11343/291202>