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Explicit Diagnostic Criteria for Transient Ischemic Attacks Used in the Emergency Department Are Highly Sensitive and Specific

Carl H. Göbel[a, b, c] Sarah C. Karstedt[a, b, c] Thomas F. Münte[a, b] Hartmut Göbel[c] Sebastian Wolfrum[d] Elena R. Lebedeva[e] Jes Olesen[f] Georg Royl[a, b]

[a]Department of Neurology, University of Lübeck, Lübeck, Germany; [b]Institute of Psychology II, University of Lübeck, Lübeck, Germany; [c]Kiel Migraine and Headache Centre, Kiel, Germany; [d]Interdisciplinary Emergency Department, University of Lübeck, Lübeck, Germany; [e]Department of Neurology, Ural State Medical University, Yekaterinburg, Russia; [f]Danish Headache Center, Department of Neurology, Glostrup Hospital, University of Copenhagen, Copenhagen, Denmark

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Transient ischemic attack · Explicit diagnostic criteria · Emergency department

Abstract
Background: Making a correct diagnosis of a transient ischemic attack (TIA) is prone to errors because numerous TIA mimics exist and there is a shortage of evidence-based diagnostic criteria for TIAs. In this study, we applied for the first time the recently proposed explicit diagnostic criteria for transient ischemic attacks (EDCT) to a group of patients presenting to the emergency department of a large German tertiary care hospital with a suspected TIA. The aim was to determine the sensitivity and specificity of the EDCT in its clinical application. ***Methods:*** A total of 128 patients consecutively presenting to the emergency department of the University Hospital of Lübeck, Germany, under the suspicion of a TIA were prospectively interviewed about their clinical symptoms at the time of presentation. The diagnosis resulting from applying the EDCT was compared to the diagnosis made independently by the senior physicians performing the usual diagnostic work-up ("gold standard"), allowing calculation of sensitivity and specificity of the EDCT. ***Results:*** EDCT achieved a sensitivity of 96% and a specificity of 88%. When adding the additional criterion F ("the symptoms may not be better explained by another medical or mental disorder"), specificity significantly increased to 98%. ***Conclusions:*** The data show that the EDCT in its modified version as proposed by us are a highly useful tool for clinicians. They display a high sensitivity and specificity to accurately diagnose TIAs in patients referred to the emergency department with a suspected TIA.

Background

A suspected transient ischemic attack (TIA) is a situation with particularly high uncertainty among emergency physicians [1, 2]. Inter-observer agreement has been shown to be low [3, 4] due to the fact that a TIA presents heterogeneously and is thus difficult to distinguish from a large variety of TIA mimics. Diagnosis is largely based on the clinical judgment of the treating physician without

Carl H. Göbel and Sarah C. Karstedt contributed equally to this work.

karger@karger.com
www.karger.com/ced

Carl H. Göbel
Department of Neurology, University of Lübeck
Ratzeburger Allee 160
DE–23538 Lübeck (Germany)
carlgobel@gmail.com

applying predefined explicit criteria. In a number of other disease areas, the introduction of explicit diagnostic criteria has improved diagnostic sensitivity and specificity, most notably in the area of headache diagnosis with the introduction of the International Classification of Headache Disorders (ICHD), currently in its third edition [5]. Lebedeva et al. [6] recently proposed explicit diagnostic criteria for transient ischemic attacks (EDCT) that were validated by Dolmans et al. [7] in a Dutch sample of 206 patients referred to a TIA clinic by their general practitioner (also see Table 3). Dolmans et al. [7] showed that the EDCT had a high sensitivity (98.4%) and specificity (61.3% or 73.8% in a slightly modified version). However, these results may not be generalizable to the setting of an emergency department, where only a minority of patients may be referred to by their GP, but a significant proportion also self-presents or arrives by ambulance after alerting the emergency services with likely impact on the clinical usefulness of the criteria (e.g., due to less filtering out of non-TIA patients). To our knowledge, the EDCT have never been tested in an emergency department before. In this setting, making a rapid and correct diagnosis is of particular importance which is why the EDCT might prove especially useful in the emergency department. The aim of our study was to (1) assess whether the EDCT criteria as published by Lebedeva et al. [6] achieve a high sensitivity and specificity when applied to the patient presenting to the emergency department of a large German tertiary care hospital (University Hospital Lübeck) and (2) whether any changes to the criteria would result in a higher sensitivity and/or specificity.

Methods

Study Population

The study population consisted of 128 patients who presented to the emergency department of the University Hospital of Lübeck, Germany, consecutively between August 2016 and January 2017 under the suspicion of a TIA. The suspected TIA diagnosis was formulated by the first point of medical contact, mostly the ambulance team transporting the patient to the hospital or, in the few cases where patients self-presented, by the triage nurse with special training in emergency medicine, including neurological emergencies. These patients were then approached by a member of the study team, in most cases still in the emergency department and at the very latest within 8 hours of presentation to the hospital, and consent for study participation was obtained. This was followed by a brief structured interview based on the EDCT (see Table 3). In cases where symptoms persisted at the time of the interview but the total symptom duration was still less than 24 h, criterion B ("Duration <24 h") could not be verified in the emergency department. If all the other criteria (A, C, D, and E) were fulfilled, a second interview was scheduled that took place more than 24 h after symptom onset to determine the symptom duration. Interviews were conducted by a junior doctor (CHG) or a senior medical student (SCK) with special interest in neurology.

Table 1. 2 × 2 table of EDCT

	Diagnosis of discharge	
	non-TIA patient	TIA patient
TIA test positive	6	75
TIA test negative	44	3

EDCT, explicit diagnostic criteria for transient ischemic attacks; TIA, transient ischemic attack.

All 128 patients were admitted to the hospital and received their standard care from physicians who were independent from the study team. After completion of the regular inpatient diagnostic workup (cranial DWI-MRI, extra- and intracranial duplex sonography, and at least 24 h of ECG monitoring), the treating senior physicians then formulated a final diagnosis at the time of discharge. These physicians were blinded to the results of the study interview and in fact mostly unaware of the study being carried out. No patient-related communication took place between the study team and the clinical team. The diagnosis of a TIA was in any case made according to the AHA/ASA definition, that is, patients with DWI positive lesions were classified as having had an ischemic infarction.

Statistical Analysis

We calculated the sensitivity and specificity of the EDCT [6] in our study population of suspected TIA patients. Sensitivity was defined as the number of true positives relative to all subjects that received the final diagnosis of a TIA. Specificity was defined as the number of true negatives relative to all subjects actually being negative for the specific analysis (true negatives plus false positives). Additionally, positive and negative likelihood ratios (as these variables allow conclusions independent of the prevalence of a disease) were calculated.

Results

Mean age of the 128 subjects (63 of which were female, 49.2%) was 68 years (standard deviation: 13.3 years). Most patients self-referred (n = 108, 84.4%) and arrived by ambulance (n = 58, 45.3%) or private transportation (n = 50, 39.1%), while a minority (n = 28, 21.9%) arrived by ambulance after being referred from their general practitioner.

The median symptom duration of all 128 patients was 47.5 min (interquartile range: 10–120 min). This group included patients with ischemic strokes with a symptom duration of over 24 h. The median symptom duration of

Table 2. Results of applying the EDCT to all 128 patients and the corresponding diagnoses of discharge

	Final diagnosis at time of discharge																	
	TIA	Ischemic infarction	Migraine with typical aura	Sixth nerve palsy	Syncope	Benign paroxysmal positional vertigo	Ménière's disease	Parkinson's disease	Transient global amnesia	Keratitis	Hypertensive encephalopathy	Cancer of unknown primary origin syndrome	Epilepsy	Somatoform disorder	Inflammatory CNS disease
TIA criteria fulfilled (n = 81)	**75**							1	1	1			1	1	1
TIA criteria not fulfilled (n = 47)	3	**30**	**4**	**1**	**1**	**1**	**1**				**1**	**1**	**2**	**2**	

Bold denotes true-positive and true-negative results, whereas regular font denotes false-positive and false-negative results. EDCT, explicit diagnostic criteria for transient ischemic attacks; TIA, transient ischemic attack.

all 78 patients that received the final diagnosis of a TIA was, therefore, shorter with 30 min (interquartile range: 5–112.5 min).

The most frequently experienced TIA symptoms were sensory (32.1%), motor (25.6%), and brainstem symptoms (24.4%), followed by aphasia and monocular visual deficits (14.1% each), binocular central deficits (10.3%), and least frequently dysarthria (6.4%). A detailed breakdown of symptom distribution is shown in online suppl. Table 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000512182).

Diagnosis of Discharge

The majority of all 128 patients referred with a suspected TIA actually received TIA as a final diagnosis by the treating physicians (n = 78, 60.9%). The second most common diagnosis was that of an ischemic stroke (n = 31, 24.2%) followed by migraine with aura (n = 4, 3.1%), epilepsy (n = 3, 2.3%), somatoform disorder (n = 2, 1.6%), and a number of less frequently made diagnoses detailed in Table 2.

Sensitivity and Specificity of EDCT

Applying the EDCT led to 75 true-positive, 44 true-negative, 6 false-positive, and 3 false-negative diagnoses, as shown in Table 1. This results in a sensitivity of 96% (95% confidence interval: 89–99%) and a specificity of 88% (95% confidence interval: 76–95%). The positive likelihood ratio was 8.0, and the negative likelihood ratio 0.04.

The 6 false-positive TIA diagnoses were keratitis, epileptic seizure, Parkinson's disease, inflammatory CNS disease, transient global amnesia, and somatoform disorder. In 2 of the 3 false-negative patients, symptoms were not reported as occurring suddenly (<1 min as per subcriterion C1). In another patient, the diagnosis of a Jacksonian seizure was made at time of discharge. The third of the false-negative patients reported sudden onset of vertigo without any other symptoms. He was eventually discharged with the diagnosis of a brainstem TIA. Due to the isolated symptom, criterion D of the EDCT was, however, not fulfilled.

The final diagnosis at time of discharge and the corresponding EDCT results are shown in Table 2. To reduce the number of false positive diagnoses and thereby increase specificity, the following criterion should, in our opinion, be added to EDCT: *F. The symptoms may not be better explained by another medical or mental disorder.*

Adding this extra criterion, the number of false positive diagnoses in the studied patient cohort would fall from n = 6 to n = 1. We determined this number (n = 1) based

Table 3. Original EDCT [1], the proposed changes to sub-criteria C1, C2, and C3 by Dolmans et al. [7] in bold [2] and the added criterion (criterion F) proposed by us

A	Sudden onset of fully reversible neurological or retinal symptoms (typically hemiparesis, hemihypesthesia, aphasia, neglect, amaurosis fugax, hemianopsia, or hemiataxia)
B	Duration <24 h
C	At least 2 of the following 1. At least 1 symptom is maximal in <1 min (no gradual spread) 2. 2 or more symptoms occur simultaneously 3. Symptoms in the form of deficits (no irritative symptoms such as photopsias, pins, and needles) 4. No headache accompanies or follows the neurological symptoms within 1 h
C	**At least 2 of the following** **1. All symptoms are maximal in <1 min (no gradual spread)** **2. All symptoms occur simultaneously** **3. All symptoms are deficits (no irritative symptoms such as photopsias, pins, and needles)** **4. No headache accompanies or follows the neurological symptoms within 1 h**
D	None of the following isolated symptoms (can occur together with more typical symptoms): shaking spells, diplopia, dizziness, vertigo, syncope, decreased level of consciousness, confusion, hyperventilation-associated paresthesia, unexplained falls, and amnesia
E	No evidence of acute infarction in the relevant area on neuroimaging
F	**The symptoms may not be better explained by another medical or mental disorder**

EDCT, explicit diagnostic criteria for transient ischemic attacks.

on whether or not the responsible junior doctor seeing the patient in the emergency department (i.e., independent from the study team) formulated "another medical or mental disorder" ($n = 5$) as the most likely diagnosis in the emergency department. This extra criterion would thus lead to an increase of the specificity from 88 to 98%.

Discussion

The present study is the first validation of the EDCT in an emergency department setting, where the criteria are applied at or just shortly after (<8 h) the time of patient presentation. This study design allows us to make conclusions about clinical usefulness of applying the EDCT criteria to patients that present to the emergency department under the clinical suspicion of a TIA.

We found that the EDCT criteria display an excellent sensitivity of 96% and a high specificity of 88% when applied at the time of first presentation. These numbers are similar to a Russian cohort of 120 inpatient TIA patients studied by Lebedeva et al. [6], where the EDCT sensitivity was found to be 99%. Retrospective analysis of EDCT specificity against a Danish (n = 1,390) and a Russian (n = 152) cohort of patients with migraine with aura diagnosed according to the International Classification of Headache Disorders 3 beta (ICHD-3 beta) [8] showed a somewhat higher specificity of 95 and 96%, respectively, than in our study. Thus, the EDCT criteria perform well in distinguishing between a TIA and a migraine with aura, but not quite so well when applied in an emergency department setting with an abundance of other TIA mimics. This is perhaps unsurprising given the fact that the EDCT criteria largely function as an antipode to the ICHD-3 criteria for migraine with aura [5].

The EDCT have very recently also been applied by Dolmans et al. [7] in a first clinical validation study to a Dutch cohort of 206 patients referred to a TIA clinic by their GP. Here, sensitivity was determined as 98.4% and the specificity was determined as 61.3%. Dolmans et al. [7] proposed a small modification to criterion C, which increased the specificity in their cohort from 61.3 to 73.8% with no negative effect on their measured sensitivity (see Table 3).

Our study design differs from Dolmans et al. [7] in the way that our cohort has a wider spectrum of referrals due to the study location of an emergency department as opposed to a TIA clinic. Patients were referred not just by their GP but mostly by themselves or by ambulance, making our sensitivity and specificity data more applicable to

other emergency departments with a similarly diverse patient referral background.

As presented in the results, we recommend adding a further criterion to the EDCT, which increased the EDCT specificity in our cohort from 88 to 98%. Table 3 shows the original EDCT criteria. The proposed changes to subcriteria C1–3 by Dolmans et al. [7] and the added criterion F proposed by us are shown in bold types.

While we did not test the modified EDCT criteria proposed by Dolmans et al. [7] on our cohort (and cannot perform a retrospective analysis on the existing data), we believe that the small changes to sub-criteria C1–3 would not negatively impact the sensitivity and specificity in our cohort. At the same time, we believe that adding criterion F would not have a negative effect on the sensitivity and specificity of other cohorts, such as the Dutch one. At best, it might increase specificity here even further; at worst, it should have a redundant effect on their cohort. Because both suggested changes had a significant effect on the specificity in the relevant cohorts, we propose to continue using a revised EDCT with both recommended changes combined.

When applying the EDCT in the emergency department setting, one particular situation creates difficulty. When criteria A, C, D, E (and F) are all fulfilled and the symptoms are still persisting but began less than 24 h ago, it is not possible to verify criterion B ("Duration <24 h"). In order to do so, one would have to wait for 24 h after symptoms began. This does not, however, in any way impact the clinical usefulness of the EDCT because when all other criteria are fulfilled, criterion B acts as a decision-making unit distinguishing the diagnosis of a TIA (duration <24 h) from the diagnosis of an ischemic infarction (duration ≥24 h), and in such a situation, the acute diagnostic and consecutive therapeutic pathway would be identical. Whether or not the cutoff should be set at 24 h or perhaps at a shorter duration has been a subject of scientific debate [9]. Indeed, up to 30% of TIA patients diagnosed clinically show diffusion-weighted imaging abnormalities when receiving an MRI as part of their diagnostic work-up [10, 11]. Nevertheless, even though the main clinical usefulness of the EDCT is to distinguish TIAs from diagnoses other than cerebral ischemia (including infarction), the criteria performed remarkably well in our cohort in distinguishing TIAs from the said cases with ischemic infarction only by using criterion B's duration parameter.

A potential limitation of our (as with any TIA) study may be the used diagnostic gold standard of TIA. Our gold standard was defined as the final diagnosis made by the responsible senior neurologist using all available diagnostic information at the time of discharge. Of course, even senior neurologists can misdiagnose TIAs. However, currently there is no consensus about a diagnostic gold standard of a TIA, and Fitzpatrick et al. [12] in a recent review of how TIAs are diagnosed noted that "expertise is currently the 'gold standard' for TIA diagnosis," and we believe expert judgment to be the best approximation of the true diagnosis at the moment.

Previous studies have displayed highly variable TIA mimic rates of between 6 and 73% [12]. Fitzpatrick et al. [12] determined a median TIA mimic rate of 36% across 27 studies, which is higher than the 14.8% found in our study population and one might question the generalizability of our data. There appears to be a trend with lower TIA mimic rates in emergency departments than in TIA clinics [12]. The aim of our study was to apply the EDCT specifically in an emergency department for the first time. Dolmans et al. [7] who applied the EDCT in an Utrecht TIA clinic found a TIA mimic rate of 39% [7]. As the EDCT resulted in similar sensitivity and specificity values both in this TIA clinic as well as in our emergency department, the EDCT seem to perform well irrespective of TIA mimic rate. Further studies in other emergency departments and TIA clinics are required to confirm this.

Another limitation of our study is that we could not retrospectively apply the modified EDCT criteria proposed by Dolmans et al. [7] to our cohort as their study was published after our data were collected. However, we feel the small changes would not have negatively impacted our sensitivity and specificity values. In any case, the newly proposed criteria should be continuously validated and, if possible, improved in other centers and populations in future studies.

Conclusions

TIAs are difficult to distinguish from TIA mimics, and diagnosis so far has not been based on explicit criteria. The new EDCT display an excellent sensitivity and specificity in the emergency department. Specificity can be further improved by adding criterion F to the EDCT: "The symptoms may not be better explained by another medical or mental disorder."

Statement of Ethics

The Medical Ethics Committee of the University of Lübeck approved the study prior to its start (reference number 16–312), and all participants provided written and informed consent.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Carl H. Göbel: design and conceptualization of the study, interpretation of the results, contributed to statistical analysis, and writing of the first draft of the manuscript. Sarah C. Karstedt: design and conceptualization of the study, interpretation of the results, contributed to statistical analysis, and writing of the first draft of the manuscript. Thomas F. Münte: contribution to interpretation and analysis. Hartmut Göbel: contribution to interpretation and analysis. Sebastian Wolfrum: contribution to interpretation and analysis. Elena R. Lebedeva: contribution to interpretation and analysis. Jes Olesen: design and conceptualization of the study and contribution to interpretation and analysis. Georg Royl: design and conceptualization of the study and contribution to interpretation and analysis.

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