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Cognitive Impairment in Transient Ischemic Attack Patients: A Systematic Review

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Key Words

Transient ischemic attack · Cognitive impairment · Prevalence · Cognitive profile · Systematic review

Abstract

Background: Although by definition a transient ischemic attack (TIA) lasts less than 24 h, many patients experience cognitive complaints beyond focal symptom resolution. However, their prevalence, causes and profile are unclear. We therefore performed a systematic review on cognitive impairment after TIA. **Summary:** Medline and Embase were searched for relevant studies. Risk of bias was assessed, and data synthesis was performed according to the severity of cognitive impairment. Thirteen studies were included, with considerable heterogeneity concerning methods and timing of cognitive testing. Confounding, detection bias and attrition were the main causes of a high risk of bias in several studies. The prevalence of post-TIA mild cognitive impairment ranged from 29 to 68%. Severe cognitive impairment was found in 8–22% of patients. Studies using a cognitive screening instrument and those performed shortly after TIA or several years later, reported the highest frequencies of impairment. Patients evaluated with a screening tool were substantially older than those who underwent a full neuropsychological assessment (weighted mean age difference 10.9 years). Based on limited data, the post-TIA cognitive profile showed prominent executive function deficits. Insufficient

data refrained us from drawing conclusions on causality. The few studies that reported neuroimaging results found a minor correlation with cognitive impairment. **Key Messages:** Mild cognitive impairment is present in more than a third of the TIA patients and has a profile comparable with vascular cognitive impairment. Reported rates of post-TIA cognitive impairment are highly variable and higher frequencies are found with cognitive screening tools. Considerable heterogeneity and insufficient data limit further conclusions about potential causative factors.

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Introduction

The symptoms of a transient ischemic attack (TIA) by definition subside completely within 24 h [1–3]. Only one-third of the patients have signs of acute infarction on diffusion weighted imaging (DWI) [4]. Despite the transient nature of focal symptoms associated with TIA and the absence of visible brain lesions in most patients, many experience persistent cognitive problems afterward [5]. The prevalence of objective cognitive impairment after TIA is, however, unclear.

The post-TIA cognitive profile is unknown, since cognitive assessment is not part of the routine work-up [6]. Unrecognized cognitive dysfunction may affect the quality of life, highlighting the importance of reliable preva-

lence estimates of post-TIA cognitive impairment as well as knowledge about its profile and potential determinants [7, 8].

Symptom severity and infarct location are the main disease-related determinants of post-stroke cognitive impairment [9]. Whether these characteristics also apply to TIA is to date unknown. A persistent ischemic lesion after TIA might be the substrate for cognitive impairment, but the severity of TIA symptoms only weakly corresponds to the presence of vascular lesions on neuroimaging [4]. New cerebrovascular events that occur after a TIA might also have cognitive consequences, even though they often pass without recognized acute clinical symptoms [10, 11]. Vascular risk factors present in TIA patients increase the risk of progression of white matter hyperintensities, which are associated with cognitive decline as well [12, 13]. Moreover, anxiety, depressive symptoms and delirium shortly after TIA can affect cognitive function [14].

We performed a systematic review of the prevalence and profile of cognitive impairment in TIA patients. In addition, we aimed to assess potentially causative factors.

Methods

Reporting of this systematic review was done in accordance with the PRISMA guidelines (checklist provided in online suppl. methods; for all online suppl. material, see www.karger.com/doi/10.1159/000444282) [15].

Data Sources

Relevant studies were identified with a literature search of the electronic medical databases, Medline and Embase, last performed on May 20, 2015. Different medical subject headings and free search terms for 'cognition' and 'transient ischemic attack' were combined (search strategy provided in online suppl. methods). In addition, reference lists of all included articles were screened to identify potentially missed papers.

Study Selection and Eligibility Criteria

The search was limited to studies that had been performed in humans. Eligible articles were selected by a 2-step approach. First, one reviewer screened titles and abstracts of all retrieved records for the following characteristics: (1) original article published in English, (2) study concerning TIA patients defined by either the classical time-based definition or the newly proposed tissue-based definition [2, 6] and (3) presence of any information about cognitive function. From records fulfilling these criteria, full-text articles were obtained. These entered the next step of the selection process in which all papers were evaluated against the following inclusion criteria: (4) assessment of cognitive function by at least one test, (5) definition of cognitive impairment provided, (6) study concerning only TIA patients or results reported separately from other stroke patients and (7) time interval between TIA and assessment of cognitive function

reported. Two authors separately performed the second step of the selection process; in case of disagreement, a consensus meeting was held.

Risk of Bias Assessment

Risk of bias assessment was performed with the Research Triangle Institute (RTI) item bank, a tool to evaluate the quality of observational studies with a focus on bias and confounding [16, 17]. In a recent comparison study, the RTI item bank was found to provide a more complete quality assessment than the Newcastle-Ottawa Scale [18, 19]. In line with the developer's instructions, the tool was tailored to match the review topic and designs of the included studies. Eleven items that assessed the selection bias, detection bias, attrition bias, selective outcome reporting and confounding were selected (online suppl. methods).

Data Extraction and Synthesis

Reported frequencies of cognitive impairment were extracted, as were details on study design, inclusion and exclusion criteria, demographics, methods and timing of cognitive assessment, brain imaging results and vascular risk factors. When present, information on domain-specific cognitive performance was recorded.

Studies were grouped according to the severity of cognitive impairment reported, defined as mild or severe cognitive impairment [20]. Weighted mean age was calculated per study, with weighting according to study size. Qualitative synthesis of study results was performed with particular attention to the method and timing of cognitive testing, inclusion of TIA patients with a previous stroke, presence of vascular brain lesions, assessment of concurrent neuropsychiatric symptoms and judgment of cognitive function before the TIA. Due to a large between-study heterogeneity concerning methods and timing of cognitive testing, as well as inclusion criteria and patient characteristics, quantitative meta-analysis was deemed inappropriate.

Results

Literature Search and Study Selection

The literature search yielded 4,058 records, 13 articles of which were eligible for inclusion (fig. 1). Twelve studies (including 1,167 patients (mean age range 57–74 years)) reported the prevalence of mild cognitive impairment and 3 studies (including 330 patients (mean age range 60–74 years)) provided data on the prevalence of severe cognitive impairment (table 1). Online supplementary table S1 provides additional characteristics of the included studies on post-TIA cognitive impairment.

Study Characteristics and Risk of Bias Assessment

All but one study prospectively included consecutive eligible patients [21]. Two studies had a cross-sectional design [22, 23], 1 was a case-control study [24], and 9 were cohort studies [25–33]. One study restricted inclusion to patients with symptomatic ipsilateral internal carotid artery occlusion [25].

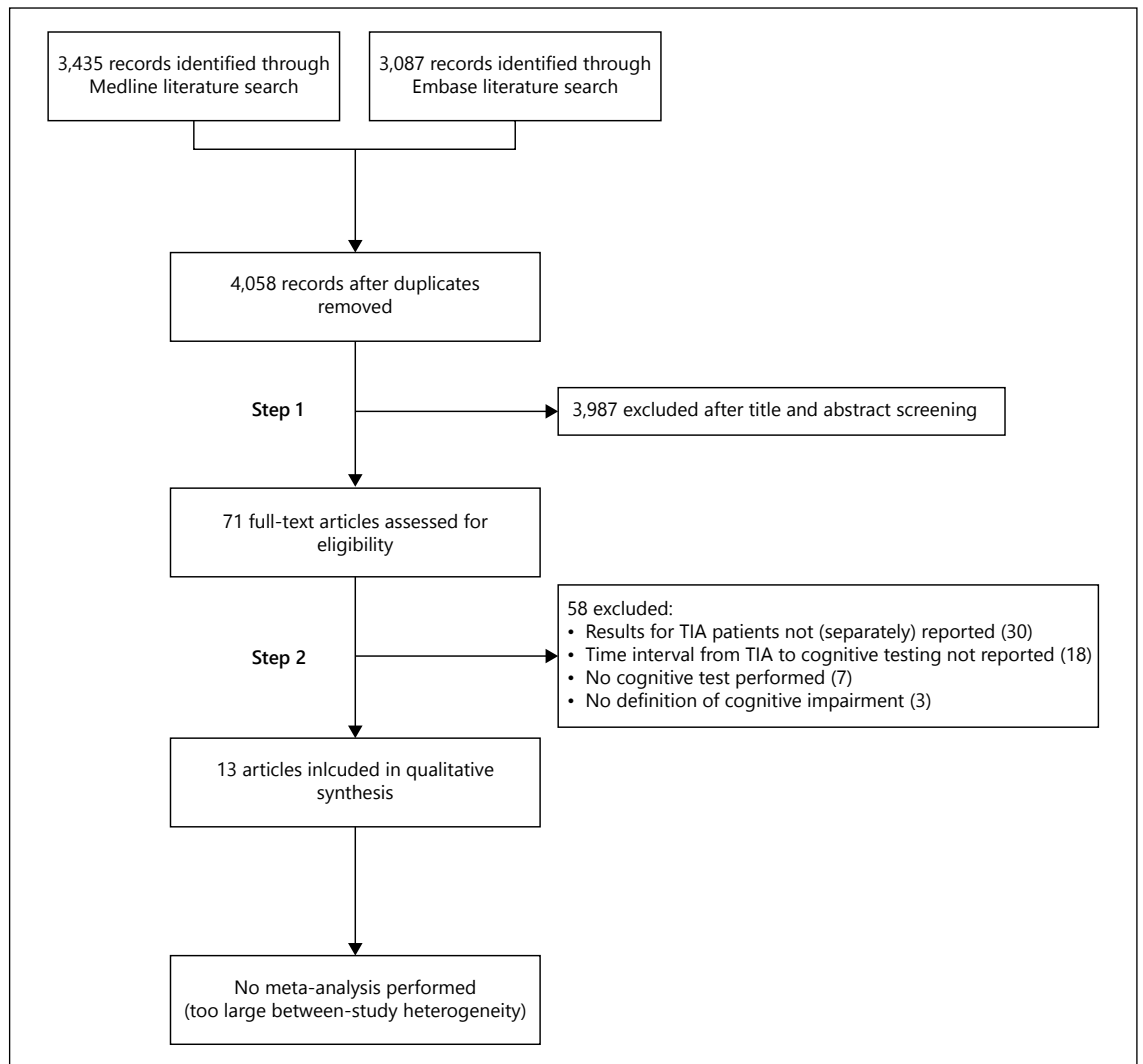


Fig. 1. Flowchart of the 2-step approach to the selection of eligible articles on post-TIA cognitive impairment.

Seven studies assessed cognitive function with a neuropsychological test battery (NPS) covering most cognitive domains [22, 23, 25–27, 29, 30] while the other studies used brief cognitive screening tools, including the Montreal Cognitive Assessment (MoCA), Mini Mental State Examination (MMSE) or modified Telephone Interview for Cognitive Status (TICS_m) [21, 24, 28, 31–33]. The time interval between TIA and cognitive testing varied from several days to 5 years. Different definitions of cognitive impairment were used. Studies using a cognitive screening instrument applied previously reported cutoff scores, while those performing a NPS used various cutoff criteria for a performance below age- and education-adjusted normative scores or a control group to define cognitive impairment (table 1).

Risk of bias assessment of individual studies showed an unclear or high risk of confounding, especially taking into account age, level of education, previous stroke and vascular risk factors. Although not invalidating the results of individual studies, it increased between-study heterogeneity and may as such be an important contributor to the large differences in observed rates of post-TIA cognitive impairment. To a lesser extent, there was a risk of detection bias and attrition (online suppl. fig. S1, table S2).

Prevalence of Cognitive Impairment after TIA

The reported rates of mild cognitive impairment after TIA were highly variable, ranging from 29 to 68% (table 1). Studies using MoCA or TICS_m generally reported higher frequencies than those applying a NPS, with the

Table 1. Summary of studies reporting the prevalence of cognitive impairment after TIA

Study	Year	Patients n	Patients age, low years education	Exclusion criteria		Cognitive testing mode of definition of testing impairment	Prevalence of cognitive impairment by time since TIA, %								
				prior stroke	prior dementia		1 week	2 weeks	1 month	4 months	6 months	1 year	5 years		
Hoffmann et al. [27]	2009	309	62*	-	-	Yes	NPS	-1.0 SD; ≥ 1 domain	36						
Sörös et al. [22]	2015	140	67	-	Yes	Yes	NPS	-1.5 SD; ≥ 1 test	57						
van Rooij et al. [23]	2014	107	57	<12 years: 26%	Yes	Yes	NPS	-1.65 SD; ≥ 1 domain	38						
Narasimhalu et al. [29]	2011	84	60*	-	No	-	NPS	-1.5 SD; ≥ 1 domain	30						
Bakker et al. [25]	2003	39	62	<12 years: 87%	No	-	NPS	-2.0 SD; overall	54						
Pendlebury et al. [30]	2013	42	70	<12 years: 67%	-	Yes	NPS	-1.5 SD; ≥ 1 test	29						
Dong et al. [26]	2012	36	60*	Mean 7.5 years*	No	Yes	NPS	-1.5 SD; ≥ 3 domains	22 [†]						
Guyomard et al. [24]	2011	68	74	-	Yes	Yes	MoCA	<26	57						
Blackburn et al. [21]	2013	13	67	-	No	-	MoCA	<26	46						
Kjörk et al. [28]	2015	44	69	-	No	Yes	MoCA	<26	41						
Pendlebury et al. [31]	2012	142	70	<12 years: 51%	Yes	Yes	MoCA	<26	52						
Volonghi et al. [33]	2013	142 182	73	Basic: 64%	Yes	-	TICSm MMSE	<25 <24	57						8 [†]
Pendlebury et al. [32]	2011	37 112	74*	<11 years: 71%*	-	Yes	MoCA MMSE	<26 <24	68 13 [†]						

* TIA and stroke patients combined.

[†] Severe cognitive impairment.

- Indicates no data available.

exception of one study that reported a prevalence of mild cognitive impairment of 54% using a NPS in patients with an ipsilateral internal carotid artery occlusion [25], and one study in which only executive function was tested and found to be impaired in 57% of TIA patients [22]. Patients evaluated with a screening tool were substantially older than those who underwent a full neuropsychological assessment (weighted mean age difference 10.9 years).

The highest frequencies of impairment were found shortly (within 2 weeks) and on the long-term (more than 1 year) after the qualifying TIA. Only 2 studies specifically stated that incident stroke between TIA and cognitive testing was an exclusion criterion [23, 33].

Severe cognitive impairment was present in 8–22% of patients (table 1). Studies on the prevalence of moderate to severe cognitive impairment included older patients than those on mild cognitive impairment (weighted mean age difference 6.1 years). Only one study used a test battery to determine severe cognitive impairment [26] and found a higher prevalence than 2 other studies that applied MMSE [32, 33].

Studies differed considerably in the proportion of patients with a low level of education, ranging from 26 to 87%. The definitions of a low level of education also differed and could have contributed to the between-study heterogeneity (table 1). Six studies did not provide any information about the educational level of TIA patients [21, 22, 24, 27–29].

Profile of Cognitive Function after TIA

Two studies performing a NPS provided information on the cognitive profile of TIA patients and found prominent impairment in the domains executive function, working memory, attention and information processing speed [23, 25]. One study performed a specific test battery focused on executive function [22]. The other studies either did not describe the cognitive profile or perform MMSE or MoCA. These instruments have not been formally validated for the assessment of specific cognitive domains in non-demented patients with cerebrovascular disease, although the non-amnesic cognitive impairment detected by these tools is consistent with the neuropsychological domains reported to be prominently affected in cerebrovascular patients [30, 31, 33–35].

Concomitant Cerebrovascular Disease and Structural Brain Changes

Only 5 studies reported the presence of vascular risk factors [23–25, 28, 33]. The prevalence of hypertension,

diabetes mellitus, hypercholesterolemia and smoking did not differ between these studies (online suppl. table S1). Two studies provided information on brain imaging after TIA. In one study, inclusion was restricted to patients with symptomatic ipsilateral internal carotid artery occlusion. Signs of prior infarction were found in 56–58% of patients, while white matter hyperintensities were present in 8–15% [25]. Patients with a previous stroke were not excluded in this study and concomitant cerebrovascular disease on brain imaging was unrelated to worse cognitive function. Another study excluded patients with previous stroke and performed either CT or MRI within 3 weeks after the qualifying event. The median age-related white matter changes score [36] was 1 and silent brain infarcts were present in 18% of TIA patients. The latter was related to worse executive functioning but could not explain the presence of overall cognitive impairment [23].

Concurrent Neuropsychiatric Symptoms

All but 2 studies reported that patients with pre-existing dementia were excluded [21, 25]. No studies specifically investigated the relationship between post-TIA cognitive impairment and psychiatric symptoms such as anxiety, depression or delirium. One study excluded patients with current depression [27], one adjusted for possible depression (defined as a Hospital Anxiety and Depression Scale, depression subscore ≥ 8 , present in 12%) [23], one study reported that 9% of patients were treated for depression at the time of cognitive testing [33] and one stated that no TIA patients had known pre-existing depression [24].

Discussion

Main Findings

This systematic review shows that post-TIA cognitive impairment is frequent, with mild cognitive impairment prevalent in 29–68% of patients and severe cognitive impairment in 8–22%. Since nearly all the included studies excluded prior dementia and the overall mean age is relatively low, the prevalence rate of cognitive impairment is likely higher in the total population with TIA and generalizability of our results is limited to the non-demented population [37]. Differences in reported rates of cognitive impairment after TIA are partly explained by differences in patient characteristics, methods and timing of cognitive testing. Higher frequencies of impairment are found with cognitive screening instruments, albeit in a substantially older population and within the first weeks after a TIA or

several years later. Based on limited data, deficits in executive function, attention and information processing speed appear to be most common. Between-study heterogeneity and lack of data impairs the possibilities to determine potential causative factors of post-TIA cognitive impairment.

Methodological Considerations

Considerable heterogeneity existed between studies on post-TIA cognitive impairment, limiting the possibilities to combine and meta-analyze results in a quantitative manner. First, classification of cognitive impairment was not uniform across studies. A variety of cognitive tests were used, ranging from short screening instruments to comprehensive neuropsychological test batteries. In addition, different cutoffs for impairment were applied. Studies using screening tools included patients who were, on an average, substantially older than those in studies applying a test battery. Furthermore, information about the level of education was often lacking. Since cutoffs for MoCA and MMSE are not age- and education-adjusted, this could at least partly explain the structurally reported higher frequencies of cognitive impairment in studies using these tools compared to those performing formal neuropsychological testing, which take age and education into account. Differences in test selection may not always be a methodological weakness, as long as the tests are validated and the assessment encompasses the same major cognitive domains (preferably those defined by the National Institute of Neurological Disorders and Stroke-Canadian Stroke Network vascular cognitive impairment harmonization standards working group, namely executive, visuospatial, language and memory functions) [38]. However, the use of different cutoffs for cognitive impairment may be a factor that reduces the combinability of study results [30]. That is, while some studies applied widely used and generally accepted cutoff criteria for cognitive impairment, such as 1.5, 1.65 or 2 SD below the age- and education-adjusted normative mean on ≥ 1 cognitive domain (corresponding with percentile scores of 5.9, 5.0 and 2.3, respectively), other studies defined cognitive impairment as a performance below 1 SD (a percentile of 15.8) or failure on only one test, which is typically considered too lenient, increasing the risk of false positive results [39].

Second, the small number of eligible studies and lack of data on vascular risk factors, brain imaging and concurrent neuropsychiatric symptoms limited the possibility of identifying possible causes and associated factors of cognitive dysfunction after TIA. As none of the included studies performed DWI and no study applied the newly

proposed tissue-based definition of TIA, we were not able to determine the influence of DWI-positivity on cognitive outcome and applied the classical time-based TIA definition throughout our study [2, 6]. Furthermore, since 4 studies originated from the same population-based cohort (Oxford Vascular Study) [40, 41], we cannot rule out the possibility that results partly overlap, although demographics differed between the individual study populations [30–33]. Next, using only papers written in English could be a bias. This is however not very likely since there is no reason why studies published in other languages should report systematically different results. Finally, the relatively young mean age of the cohorts in some studies limits the generalizability of these results to the overall TIA population, which is typically older.

Prevalence of Cognitive Impairment after TIA

Compared to the prevalence of cognitive impairment in the general population (7% in a Dutch population-based sample of 55–95 years of age community-dwelling persons) [42], post-TIA cognitive impairment is considerably more prevalent. It is, however, less prevalent than cognitive impairment after stroke, as reported by all but one study that performed a head-to-head comparison of cognitive function after TIA and stroke [21, 27, 29–31, 33]. This is to be expected given the presumably more widespread brain damage after stroke. Even when cognitive function after minor stroke (defined as National Institute of Health Stroke Scale ≤ 3) is compared to TIA, the prevalence of impairment after the latter is lower [31]. However, signs of acute infarction are present on DWI in up to 30% of TIA patients [4]. Whether these patients or those with longer symptom duration have worse cognitive performance afterward is unknown.

Large differences in delay were present between TIA and cognitive testing. Both studies carried out in the earliest (first weeks) and the late (after several years) phases found more patients to be cognitively impaired. Especially in the early phase, cognitive function can be influenced by stress, anxiety or delirium, leading to falsely high rates of persistent cognitive impairment. Transient cognitive impairment in the first month after TIA appears to be a common feature, and although its causes remain to be elucidated, patients with transient cognitive impairment had worse cognitive outcomes than those without [32]. As all other included studies focused exclusively on fixed rather than transient cognitive impairment, the concept of dynamic change in cognitive function is a topic that merits further research. When tested several years after a TIA, incident cerebrovascular events or progressive neu-

rodegenerative pathology may result in a larger proportion of patients being cognitively impaired. As most studies did not report whether incident strokes were an exclusion criterion, and since new cerebrovascular lesions often pass unnoticed [43], these potential causes of the higher rates of cognitive impairment in the late phase after TIA need further study.

Cognitive Profile after TIA

The cognitive profile of TIA patients appears to be consistent with that most often seen in vascular cognitive impairment, with prominent deficits in executive function, attention and information processing speed [44]. However, this conclusion is based on limited evidence. That is, sub-scores of MoCA and MMSE have not been validated and may also be insensitive to subtle decrements, as these tools have been developed to detect cognitive decline due to Alzheimer's disease [34] and vascular cognitive impairment is often characterized by a non-amnesic profile, driven by subcortical vascular damage disrupting subcortical–frontal connections [45]. Nevertheless, the cognitive profiles detected by MoCA and MMSE are generally in line with the results of studies using a NPS, which can be considered a form of validation [30, 31, 33].

Potential Causes and Underlying Mechanisms

Cognitive dysfunction after TIA can be explained in several ways, none of which can be confirmed on the basis of the currently reviewed literature. A TIA could, despite the transient nature of the focal symptoms, cause permanent brain damage, thereby disrupting networks involved in cognitive processes and leading to cognitive impairment [46]. This theory is however only partly supported by DWI studies, in which signs of recent infarction are found in about 30% of clinically defined TIA patients [4]. Furthermore, we recently showed that the clinical diagnosis of TIA may be inadequate, as more than 20% of patients not fulfilling the clinical criteria for TIA were found to have DWI lesions compatible with recent infarction [47]. This issue touches on the matter of the newly proposed, tissue-based definition of TIA, which discriminates between patients with and without signs of recent infarction on brain imaging and states that only the latter category truly meets the criteria for TIA. Patients with imaging signs of recent infarction are considered to have had brain infarction, regardless of symptom duration [6]. The relatively high prevalence of cognitive impairment after TIA suggests that some non-focal symptoms may not be as transient as the focal neurological symptoms and as such provides an additional argument for this re-

consideration of the diagnosis of TIA. Further studies are needed to identify whether there is a difference in cognitive outcome between patients with DWI-positive and DWI-negative TIA.

In addition, impaired cognitive function might have been present prior to TIA. Both TIA and cognitive impairment can result from the same underlying cerebrovascular disease process. Cerebral vascular damage including silent brain infarcts and white-matter hyperintensities of presumed vascular origin may lead to cognitive impairment and dementia [12, 13, 48]. Moreover, anxiety, depressive symptoms and delirium can occur after TIA and negatively influence cognitive function [49]. Although partly transient, these psychiatric disturbances may be a major cause of cognitive impairment when assessed shortly after TIA.

Conclusion

Cognitive impairment is remarkably prevalent in TIA patients. This contrasts with the lack of regular cognitive evaluation in TIA patients and urges attention to the possibility of persistent cognitive problems after seemingly completely subsided neurological symptoms. This systematic review shows a lack of available data on factors associated with cognitive impairment after TIA. Future studies preferably include brain imaging and evaluate both concomitant vascular risk factors and neuropsychiatric disturbances. In addition, to further determine the consequences of post-TIA cognitive impairment, assessment of subjective cognitive complaints both by patients and caregivers is important, in addition to comprehensive neuropsychological assessment using sensitive tests. Cognitive impairment is present in at least one-third of the TIA patients, which justifies scientific ventures to further identify this previously overlooked group at increased risk of cognitive decline.

Disclosure Statement

None of the authors reported any conflicts of interest.

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