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REVIEW

Migraine in transient global amnesia: a meta-analysis of observational studies

Ioannis Liampas[1] · Athanasios S. Siouras[2] · Vasileios Siokas[1] · Zisis Tsouris[1] · Dimitrios Rikos[1] · Alexandros Brotis[3] · Athina-Maria Aloizou[1] · Metaxia Dastamani[1] · Efthimios Dardiotis[1]

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Abstract

Background Purpose Although many studies have investigated the relationship between transient global amnesia (TGA) and migraine, to date, no meta-analysis has confirmed the existence and size of their association.

Methodology Literature search involved MEDLINE, EMBASE, CENTRAL and PsycINFO. Observational controlled studies including TGA patients (Caplan, Hodges and Warlow) were retrieved. Quality evaluation was based on the Newcastle-Ottawa scale. The prevalence of migraine was compared in TGA patients vs. healthy controls (HC), as well as in TGA against TIA individuals. Data from case-control, cross-sectional and cohort studies were pooled separately.

Results Literature search yielded 1178 articles, 12 of which were included in the present meta-analysis. Results from case-control (ten), cohort (one) and cross-sectional (one) studies were compatible with an association between TGA and migraine. The nationwide inpatient cross-sectional study was of lesser value due to its inpatient orientation. The high-quality, population-based, retrospective cohort (158,301 participants per group) determined a higher relative-risk (RR) of TGA for migraine vs. non-migraine individuals [RR = 2.48, 95%confidence-interval (95% CI) = (1.32, 4.87)]. Sensitivity testing based on stricter diagnostic criteria strengthened the estimated association [RR = 3.84, 95% CI = (1.57, 9.38)]. Additionally, pooled data from eight case–control studies (700 TGA, 746 HC) yielded similar results [Odds-Ratio, OR = 2.51, 95% CI = (1.85, 3.41)], with the association mainly driven by the three high-quality studies, rather than the five articles of moderate quality. Finally, pooled findings from four case–control studies of moderate-quality revealed a higher prevalence of migraine among TGA compared to TIA patients [OR = 1.82, 95% CI = (1.22, 2.73)].

Conclusions A significant association between TGA and migraine was established. The underlying connecting mechanism remains undetermined, yet.

Keywords Migraine · Aura · Transient ischemic attack · Transient global amnesia

Introduction

Transient global amnesia (TGA) constitutes an enigmatic amnestic syndrome characterized by temporary memory dysfunction of abrupt onset and total resolution within 24 h from emergence [1, 2]. Anterograde memory is more severely affected, while retrograde memory presents a variable level of dysfunction [1, 2]. The clinical diagnosis of TGA is based on the criteria of Hodges and Warlow as follows [3, 4]: (1) attacks must be witnessed and information must be available from a capable observer who has to be present for most of the attacks; (2) there must be a clear-cut anterograde amnesia during the attack; (3) clouding of consciousness and loss of personal identity must be absent, and the cognitive impairment must be limited to

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✉ Ioannis Liampas
liampasioannes@gmail.com; iliampas@uth.gr

[1] Department of Neurology, School of Medicine, University Hospital of Larissa, University of Thessaly, Larissa, Greece

[2] Department of Computer Science and Biomedical Informatics, School of Science, University of Thessaly, Lamia, Greece

[3] Department of Neurosurgery, School of Medicine, University Hospital of Larissa, University of Thessaly, Larissa, Greece

amnesia (i.e., no aphasia, apraxia, etc.) (4) there should be no accompanying focal neurological symptom during the attack and no significant neurological sign afterward; (5) epileptic features must be absent; (6) attack must resolve within 24 h; and (7) patients with a recent head injury or active epilepsy (i.e., patients who have continued to receive medication or have had one seizure in the past 2 years) are excluded.

Although clinical and neuroimaging evidence is suggestive of an underlying hippocampal (and most notably cornu ammonis -CA1- located) dysfunction [5–7], the aetiology of TGA has yet to be determined. Soon after the introduction of the term TGA by Fisher and Adams, the hypothesis of an underlying epileptic mechanism was formulated [8, 9]. However, the performance of electroencephalographic studies on TGA individuals [10], as well as the low recurrence rate of the disease [11], led to the progressively declining popularity of this theory. Epileptic amnesia is now considered part of the differential diagnosis of TGA rather than a possible underlying mechanism [12].

The acute onset of the disease reasonably generated postulations about a vascular mechanism leading to focal ischemia [13]. In this context, the long-term risk of vascular events in TGA patients has been extensively assessed and compared to both healthy controls (HC) [14, 15] and individuals with transient ischemic attacks (TIA) [4, 16–18]. Results were indicative of a long-term vascular risk similar to HC and lower than patients with TIA. Apart from the good vascular-related prognosis of the syndrome, follow-up neuroimaging in TGA patients was compatible with a reversible nature of magnetic resonance imaging (MRI) lesions [6], limiting the possibility of an arterial-ischemic underlying mechanism. Additionally, a venous vascular mechanism involving internal jugular vein incompetence and congestion, ultimately leading to transient hippocampal ischemia, has been hypothesized. The existing evidence for the aforementioned theory [19–21] is complementarily supported by the multiple recordings of TGA cases triggered by Valsalva manoeuvre-related events [22]. However, the focal, hippocampal manifestations and imaging findings of TGA are difficult to associate with the global cerebral venous congestion.

Finally, the last among the most prevailing theories implicates migraine and the neurophysiologic substrate of aura, which is Cortical Spreading Depression (CSD) [7, 12]. CSD consists of a spreading neuronal depolarization followed by a suppression of the neuronal activity, with respect to the clinically (aura-wise) relevant cerebral areas. Based on experimental data, it has been hypothesized that CSD extending through the hippocampus may be accountable for the transient hippocampal dysfunction during TGA [23]. The possible relationship between migraine and TGA has been investigated by several authors, but to date the only published meta-analysis (2006) revealed no association between the two entities [24].

On the grounds of the above-mentioned hypotheses and the vague pathophysiological background of TGA we decided to evaluate the existing clinical evidence supporting the possible underlying pathophysiological mechanisms of TGA. In this paper, we focused on one of the previously described hypotheses, the migraine-related theory. Observational (case–control, cross-sectional and cohort) controlled studies assessing the prevalence of a migraine history among TGA individuals and HC were retrieved for this purpose. In view of the association between migraine and TIA (as well as other cerebrovascular events) [25], it was additionally decided to retrieve observational controlled studies that investigate the prevalence of a migraine history in TGA vs. TIA patients (the main differential diagnosis of TGA). To the best of our knowledge, the present article is the first meta-analysis to systematically evaluate the association between migraine and TGA since the study of Quinette et al. 2006 [24].

Materials and methods

The present systematic review and meta-analysis adheres to the MOOSE reporting guidelines [26]. Each step of the review process was performed by two authors (unblinded to study information), independently (I.L., A.S.). Discrepancies were resolved by a third author (E. D.).

Search method

The search strategy is presented in the online resource. The structured search involved the following databases: MEDLINE (through PubMed), EMBASE (through Elsevier), CENTRAL (Cochrane Central Register of Controlled Trials, the Cochrane Library) and PsycINFO. An additional manual search involved the references included in the retrieved articles, as well as all articles that cited the papers retrieved by the structured literature search (through Google Scholar). Conference abstracts and abstracts in English from articles with full texts not published in English would be evaluated in case relevant information was provided. Titles and abstracts were manually screened for eligibility. Full texts were retrieved in case of inability to establish the eligibility of an article.

Eligibility criteria

Inclusion criteria were as follows:

- Studies published between 1985 and Aug 7, 2020, that is following the introduction of Caplan's diagnostic cri-

teria [27], validated by Hodges and Warlow in 1990 [3]. Thereon, the clinical recognition of TGA was based on these criteria. Hence studies published before that period (1985) were not considered for inclusion.
- Observational controlled studies (case–control, cross-sectional, cohort).
- For case control and cross-sectional studies: inclusion of at least two groups of participants (outcome-wise). TGA patients constituted the first group and either HC (without a history of TGA) and/or individuals with TIA consisted the control group. Migraine was evaluated as part of the exposures. Any other CNS (Central Nervous System) disease-specific control group, e.g., patients with stroke, epilepsy, encephalitis and so on, was not considered as an appropriate control group.
- For cohort studies: inclusion of at least two groups of participants (exposure-wise), subjects with migraine and HC (without a migraine history). TGA was assessed as part of the investigated outcomes.

Exclusion Criteria were as follows:

- Studies implementing non-validated diagnostic criteria
- Uncontrolled studies. Case–control and cross-sectional studies involving control groups other than HC and TIA were excluded. Cohort studies not assessing migraine vs. healthy individuals were excluded
- Controlled studies not assessing the parameters of interest
- Studies (all types) with equal or less than 10 participants per group
- Studies other than observational, including Reviews, Meta-analyses, Case reports, Editorials-Commentaries-viewpoints, and so on
- Study protocols
- Book chapters-reviews
- Studies not published in English. In case a study abstract was available in English it was evaluated for inclusion (as part of the grey literature)

Data extraction—quality assessment

The following data were extracted according to data extraction forms: first author, year of publication, study design and data collection process, country of origin and settings, set of diagnostic criteria and definitions for TGA, TIA and migraine, number of participants, age and sex distribution, as well as obtained results.

Case–control and cohort studies were assessed according to the Newcastle–Ottawa Scale (NOS) [28], while cross sectional studies were evaluated based on a modified version of the NOS, adapted to the context of our study (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp and online resource). NOS evaluates nine methodological items and their reporting (participant selection, comparability of groups and ascertainment of exposure/outcome), with values ≥ 7 compatible with a good study quality, between 2 and 7 with a moderate study quality and ≤ 2 with a poor study quality. Modified NOS evaluates eight methodological items and their reporting (adapted from the initial NOS), with values ≥ 6 consistent with a good study quality, between 2 and 6 with a moderate study quality and ≤ 2 with a poor study quality.

Statistical analysis

Statistical analyses were conducted using RevMan 5.4 statistical software [29]. A two-tailed p-value < 0.05 was used for the determination of statistical significance. Effect-sizes and their precision [95% confidence intervals (95% CIs)] were estimated using as weights the inverse variance of individual effects. Case–control (Odds-Ratio, OR), cross-sectional (OR) and cohort studies (Risk Ratio, RR, cumulative incidences would not be meta-analysed) investigating the association between migraine and TGA were separately analysed. Statistical heterogeneity was estimated by the calculation of the Q and I^2 statistics (homogeneity accepted if both $P_Q > 0.1$ and $I^2 < 30\%$). In the absence of statistical heterogeneity, fixed effects (FE) model was utilized, otherwise, random effects (RE) model was implemented. ORs and 95%CIs were illustrated with forest plots. In case of ten or more studies (rule of thumb) being combined, funnel plots were created for the determination of potential publication bias.

Two separate analyses were planned, TGA vs. HC and TGA vs. TIA. Subgroup analyses according to the type of migraine (with or without aura) were prespecified. Methodological flaws were statistically addressed with the stratification of the results according to the methodological quality of the retrieved studies based on the NOS (high, moderate, low), so that the quality of studies accountable for the existence and size of the association would be revealed.

Results

The structured literature search provided 1178 studies (MEDLINE; 901, EMBASE; 243, CENTRAL; 25 and PsycINFO; 9), while the manual search retrieved seven additional articles. After the manual screening of titles and abstracts, 97 full texts were evaluated for inclusion and, finally, 12 papers were involved in the present systematic review and meta-analysis [4, 14, 17, 18, 30–38]. Among the retrieved studies one was a retrospective cross-sectional study based on an inpatient database [30], one was designed as a retrospective cohort study based on a National Health Insurance database [32] and 10 were case–control studies

with retrospective, prospective or mixed data collection. Among conference abstracts and abstracts in English from articles not published in English, none presented adequate reporting to be included in the present systematic review and meta-analysis (as part of the grey literature). The literature search is depicted in Fig. 1. Excluded studies with corresponding reasons are presented in the online resource. Table 1 summarizes the characteristics of the retrieved articles, while Table 2 summarizes the quality evaluation based on the NOS. For the comparison of TGA vs. HC, among the included papers, five recorded a moderate quality [4, 31, 33, 35, 36], whereas the rest registered a good methodological quality [14, 18, 30, 32, 34, 37]. For the comparison of TGA vs. TIA, all of the retrieved papers ($n=4$) were appraised as of moderate quality [4, 17, 18, 34].

TGA vs. HC

Yi et al. performed the only cross-sectional study using data from the Nationwide Inpatient Sample (NIS), which represents 20% of the U.S. community hospitals [30]. A fraction of the participants in the control group (inpatient database) corresponded to patients with other CNS diseases. Moreover, the data collection process was based on record linkage (it was not reported if diagnoses established by non-specialists, that is non-neurologists, were considered acceptable, claims data are generally susceptible to coding deviations) and each patient discharge was considered as the unit of analysis (it was assumed that each discharge appeared once per patient, probable overlap was not addressed). Furthermore, the demographic characteristics of the two groups presented significant differences both in terms of sex and age (Table 1**,** the majority of the controls belonged to a younger age group in which TGA is extremely rare, future appearance of the disease cannot be ruled out). Despite the aforementioned very serious limitations, in view of the unprecedented numerical power of the study we decided to present obtained results. It was determined that individuals with TGA headache presented with six-fold greater odds [OR = 5.98, 95% CI = (5.42, 6.60)] of migraine headache compared with non-TGA patients (socio-demographic factors along with comorbidities were adjusted in the context of the statistical analysis). Nevertheless, the prevalence of migraine in both groups (0.76% in the non-TGA group and 4.94% in the TGA group) is much lower than the established prevalence in the general population [38] indicating a substantial underestimation in both groups (probably due to the focus on inpatient evaluations). Therefore, although the overall study quality was good (Table 2), the innate inpatient orientation of the NIS database substantially limited its value in the investigation of the association between migraine and TGA.

Lin et al. conducted the only cohort study (of high quality) using data from Taiwan's National Health Insurance program which covers approximately 98% of Taiwan's residents [32]. The data collection process was based on record linkage. Migraine diagnosis was ascertained if coded

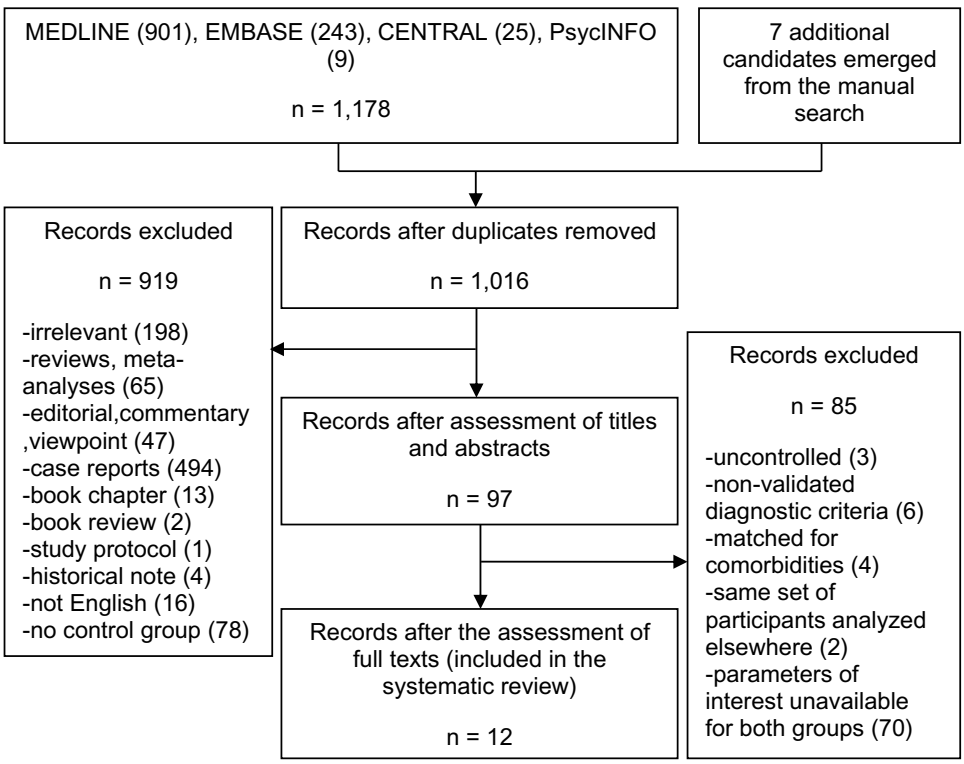

Fig. 1 Flow chart of the literature search

Table 1 Characteristics of the included studies

First author (year)	Design	Settings	Diagnostic criteria-definitions			Participants	Total *N*	Sex (male/female)	Age (years)
			TGA	TIA	Migraine				
Yi (2018)	Cross-sectional, retrospective data collection	U.S.A., Nationwide inpatient database (20% of U.S. community hospitals)	ICD-9	NA	ICD-9	TGA	9723	48.01/51.99%	64.93 ± 0.18
						HC	58,191, 569	41.22/58.78%	47.74 ± 0.25
Arena (2017)	Case–control (1 case/1 HC matched for age and sex), retrospective data collection	U.S.A., medical records from a collaboration of medical facilities	Caplan, Hodges and Warlow	NA	NP	TGA	221	110/111	65.6 ± 12.2
						HC	221	110/111	63.3 ± 16.5
Jovanovic (2017)	Case–control (2 cases/1 HC matched for age and sex), prospective data collection	Serbia, one university neurology clinic	Hodges and Warlow	NA	NP	TGA	100	33/67	61.6 ± 9.4
						HC	50	20/30	60.6 ± 10.8
Baracchini (2014)	Case–control (1 case/1 HC matched for age and sex)	Italy, two (one university, one regional) neurology departments	Hodges and Warlow	NA	NP	TGA	75	31/44	60.3 ± 8.0
						HC	75	31/44	60.3 ± 8.0
Lin (2014)	Cohort (1 case/1 HC matched for age ± 5 years, sex and vascular comorbidities), retrospective data collection	Taiwan, National Health Insurance database	ICD-9	NA	ICD-9	Migraine	158, 301	27.5/72.5%	40.3 ± 14
						HC	158, 301	27.5/72.5%	40.2 ± 14.5
Pantoni (2005)	Case–control (no matching), prospective data collection	Italy, one university neurology department	Hodges and Warlow	(1)	NP	TGA	51	24/27	62.7 ± 6.7
						TIA	51	41/10	63.8 ± 6.7
Akkawi (2003)	Case–control (subjects were matched for age), prospective data collection	Italy, one civil neurology department	Hodges and Warlow	(2)	NP	TGA	48	21/27	63.6 ± 5.1
						TIA	42	22/20	61.9 ± 4.7
						HC	48	26/22	62.4 ± 6.3
Sander (2000)	Case–control (1 case/1 HC matched for age and sex)	Germany, one university neurology department	Caplan, Hodges and Warlow	NA	NP	TGA	21	8/13	65 (61–68)
						HC	21	8/13	65 (61–68)
Schmidtke (1998)	Case–control (1 case/2 HC matched for age ± 2 years and sex), retrospective-prospective data collection	Germany, one university neurology department	Caplan	NA	IHS 1st edition	TGA	57	25/32	60.6
						HC	114	Matched for age ± 2 years and sex	
Zorzon (1995)	Case–control (1 case/1 TIA/2 HC matched for age ± 2 years and sex), prospective data collection	Italy, one university neurology department (cases, TIA), two general practices (HC)	Caplan	NP	IHS 1st edition	TGA	64	28/36	61.6 ± 7.5
						TIA	64	Matched for age ± 2 years and sex	
						HC	108	47/61	61.8 ± 7.6

Table 1 (continued)

First author (year)	Design	Settings	Diagnostic criteria-definitions			Participants	Total *N*	Sex (male/female)	Age (years)
			TGA	TIA	Migraine				
Melo (1992)	Case–control (1 case/2 HC matched for age ± 5 years and sex), prospective data collection	Portugal, one university neurology department (cases), one general practice (HC)	Caplan	NA	IHS 1st edition	TGA		51 26/25	59.8 ± 10.5
						HC		102 Matched for age ± 5 years and sex	
Hodges (1990)	Case–control (1 case/2 TIA/1 HC matched for age ± 2 years and sex), retrospective-prospective data collection	UK, one university neurology department (cases), one general hospital (TIA), two general practices (controls)	Hodges and Warlow	(3)	NP	TGA		114 69/45	62.3 ± 8.5
						TIA		212 122/90	62.4 ± 8.8
						HC		109 70/39	65.4 ± 8.5

N number, *TGA* transient global amnesia, *HC* healthy controls, *TIA* transient ischemic attack, *NP* not provided, *NA* not applicable, *ICD-9* International classification of diseases—ninth revision, *IHS* International headache society

TIA was defined (1) according to the classification of the National Institute of Neurological Disorders and Stroke Ad Hoc Committee (1975) (2) as brief reversible episodes of focal, ischaemic neurological disturbance and duration less than 24 h (3) as an acute loss of focal cerebral or ocular function, with symptoms lasting less than 24 h and which after adequate investigation was thought to be due to embolic or thrombotic vascular disease (Warlow and Morris, 1982)

Table 2 Quality assessment according to the Newcastle–Ottawa scale (NOS)

Study (year)	Selection	Comparability	Outcome	NOS score
Yi 2018[a]	**	**	**	6/7
Arena 2017[b]	***	**	**	7/8
Jovanovic 2017[c]	**	**	*	5/9
Baracchini 2014[d]	*	**		3/9
Lin 2014[e]	****	**	*	7/9
Pantoni 2005[f]	***	**	**	5/8
Akkawi 2003[g]	****	**	*	7/9, 5/8
Sander 2000[h]	**	**		4/9
Schmidtke 1998[i]	**	**		4/9
Zorzon 1995[j]	****	**	*	7/9, 5/8
Melo 1992[k]	****	**	*	7/9
Hodges 1990[l]	****	**		6/9, 4/8

The number of * corresponds to the number of items assessed positively in each category. The studies of Hodges et al., Zorzon et al. and Akkawi et al. were assessed in the context of both comparisons (TGA vs. HC and TGA vs. TIA). Therefore, two NOS values were attributed to each of these studies (one for each comparison, in view of the different methodological features). The values for the comparison of TGA vs. HC are presented on the left side of the column, while for TGA vs. TIA on the right side of the column. Selection of community controls was not applicable for the TGA vs. TIA comparison (assessed according to an 8-item NOS). Patients with history of vascular disease (e.g., stroke) were not excluded from the studies ($n=4$) involving TIA participants; therefore, a one * penalty was set for the selection process. The rest of the methodological or reporting flaws of each study are listed below

[a]Response rate was not applicable (medical records), the unit of analysis was each hospital discharge rather than each individual patient; therefore, misclassification of the participants could not be ruled out with certainty

[b]The control group comprised of patients from both outpatient and inpatient settings, response rate was not applicable (medical records)

[c]The control group comprised of inpatients with diseases of the peripheral nervous system, potential representativeness of cases was not described, exposure was ascertained by an interview not-blinded to the case–control status, response rate was not described at all

[d]The origin of the control group was not reported, potential representativeness of cases was not described, potential inclusion of controls with a history of TGA could not be ruled out (data collection process – retrospective or prospective – was not described, method for confirmation and exclusion of individuals with TGA history was not reported), the method for exposure ascertainment was not reported, response rate was not reported

[e]The length of follow up was very short (mean years ± standard deviation; migraine: 3.00 ± 1.51, HC 3.09 ± 1.52) especially when considering the mean age of the participants (migraine: 40.3 years, HC: 40.2 years), loss to follow-up was not described at all

[f]Response rate was not reported

[g]Exposure was ascertained by an interview not-blinded to the case–control status, response rate was not reported

[h]Potential representativeness of cases was not described, potential inclusion of controls with a history of TGA could not be ruled out (data collection process – retrospective or prospective – was not described, method for confirmation and exclusion of individuals with TGA history was not reported), ascertainment of exposure was not described at all, response rate was not reported

Table 2 (continued)

[i]The control group comprised of patients who were seen for peripheral nerve or spinal disc problems, potential misclassification of the participants could not be ruled out (method for confirmation and exclusion of individuals with a TGA history was not reported in the context of the retrospective data collection process), exposure was ascertained by reviewing medical records or by an interview not-blinded to the case–control status, response rate was only partially described for the TGA group

[j]Exposure was ascertained by an interview not-blinded to the case–control status, response rate was reported solely for the control group

[k]Exposure was ascertained by an interview not-blinded to the case–control status, response rate was not reported

[l]Exposure was ascertained either by reviewing medical records (a fraction of the cases, TIA controls) or by an interview not-blinded to the case–control status (a fraction of the cases, healthy controls), response rate was only reported for the healthy control group

by a neurologist during the study period (treatment-seeking individuals were included in the migraine group, parallel misclassification of non-treatment seeking individuals with migraine in the control group was possible). Antecedent TGA, cerebrovascular disease or epilepsy diagnoses led to the exclusion of candidates from both groups. Two different approaches were implemented for the diagnosis of TGA. A primary approach included all TGA cases coded by neurologists, as well as non-specialists, and a sensitivity approach involved only cases diagnosed by neurologists and having undergone neuroimaging within 1 month from coding (coding deviations were less probable with the latter approach). Despite the relatively young mean age of the participants and the short follow-up period, the migraine cohort presented a significantly higher TGA risk than the (age, sex, vascular comorbidity and Charlson score matched) HC cohort [primary analysis: RR = 2.48, 95% CI = (1.32, 4.87), sensitivity analysis: RR = 3.84, 95% CI = (1.57, 9.38)]. Notably the above-mentioned effect was driven by the subgroup of 40–60-year-old female individuals. Similarly, adjusted cumulative rates of TGA were determined higher in the migraine cohort (relevant figures were not provided), with no apparent difference in the TGA incidence between aura and non-aura individuals.

The majority of the retrieved articles followed a case–control design. For the comparison of TGA cases with HC, the results from eight articles were pooled (700 TGA patients and 746 HC). Retrospective, prospective and mixed data collection strategies were implemented (Table 1). Claims data were not used in any of the studies; therefore, an accurate diagnosis is more probable even in the context of retrospective studies (direct evaluation of medical records). Only the paper of Akkawi et al. (high-quality) did not match cases with controls for sex (age-matching was performed, the rest of the studies reported both age and sex matching) during the study design (statistical analysis was adjusted) [33]. Pooled results were indicative of a significantly higher migraine history in the TGA group [OR = 2.51, 95% CI = (1.85, 3.41), $P_Q = 0.33$, $I^2 = 13\%$] (Fig. 2). A stronger association between migraine and TGA was determined by the high-quality case control studies [OR = 3.48, 95% CI = (2.13, 5.71), $P_Q = 0.32$, $I^2 = 11\%$] [14, 18, 34] in comparison with the

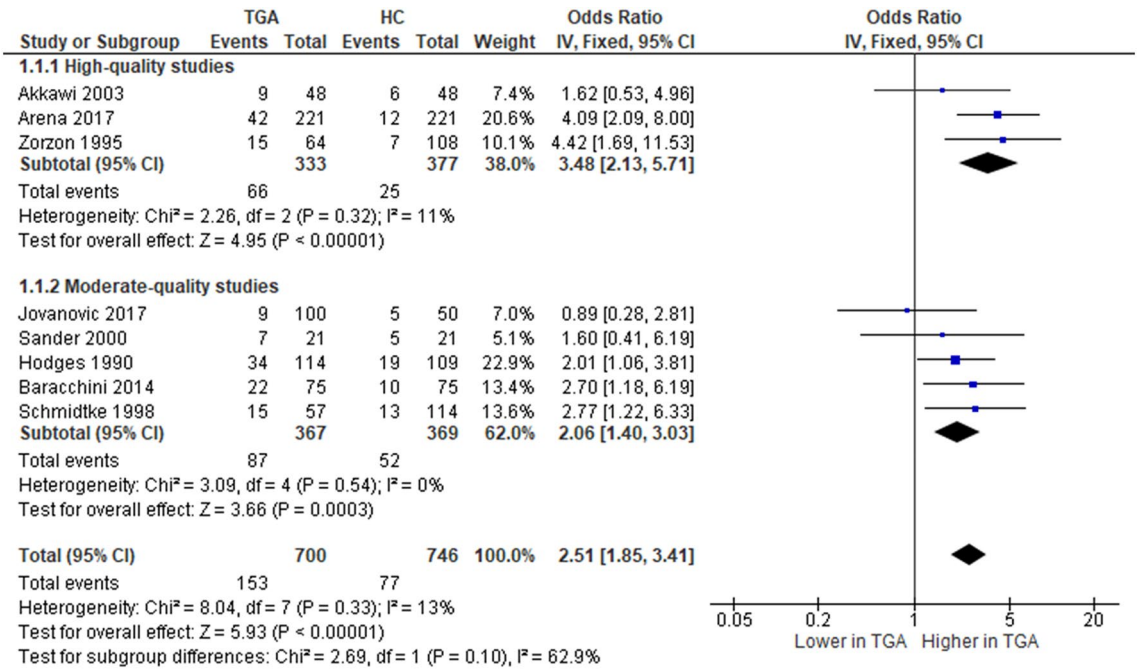

Fig. 2 Prevalence of migraine in patients with transient global amnesia (TGA) vs. healthy controls (HC)

moderate-quality articles [OR = 2.06, 95%CI = (1.40, 3.03), $P_Q = 0.54$, $I^2 = 0\%$] [4, 31, 33, 35, 36]. The study of Melo et al. (high quality) provided results indicative of a more common history of migraine in TGA patients compared to HC [OR = 8.67, 95% CI = (2.66, 44.6)], but absolute values were not provided for both groups, impeding its inclusion in the meta-analysis. Finally, the association of migraine according to the presence of aura or not was examined only in the classic case–control study of Hodges et al. [4], with obtained results suggestive of an increased prevalence of a migraine history among TGA individuals (Fig. 3).

TGA vs. TIA

Among the retrieved papers, only four case–control studies of moderate quality evaluated the prevalence of a positive migraine history between TGA and TIA individuals [4, 17, 33, 36]. The article of Melo et al. [37] contained a TIA group, but relevant figures (Effect size with 95% CI) were provided only for the TGA and HC groups. Vascular comorbidities were generally more common (significantly in the case of two studies [4, 17]) in the TIA groups. Despite the long-established relationship between migraine (especially with aura) and vascular comorbidities (TIA included) [25, 39, 40], pooled results were compatible with a higher prevalence of migraine in TGA individuals compared to TIA patients [$P_Q = 0.71$, $I^2 = 0\%$, OR = 1.82, 95% CI = (1.22, 2.73)] (Fig. 4). The studies of Zorzon et al. and Hodges et al. recruited matched cases and controls for the parameters of age and sex [4, 36] (the other two studies addressed demographical differences during statistical analyses). Finally, the association of migraine according to the presence of aura or not was examined only in two case–control studies [4, 17], with obtained evidence suggestive of no difference in the prevalence of migraine history between the TGA and TIA groups (Fig. 3).

Discussion

The purpose of the present systematic review and meta-analysis was to evaluate the clinical association between migraine and TGA. Results from case–control (ten), cohort (one) and cross-sectional (one) studies were in accordance with an existing relationship between the two entities. The previous findings of the only other published meta-analysis

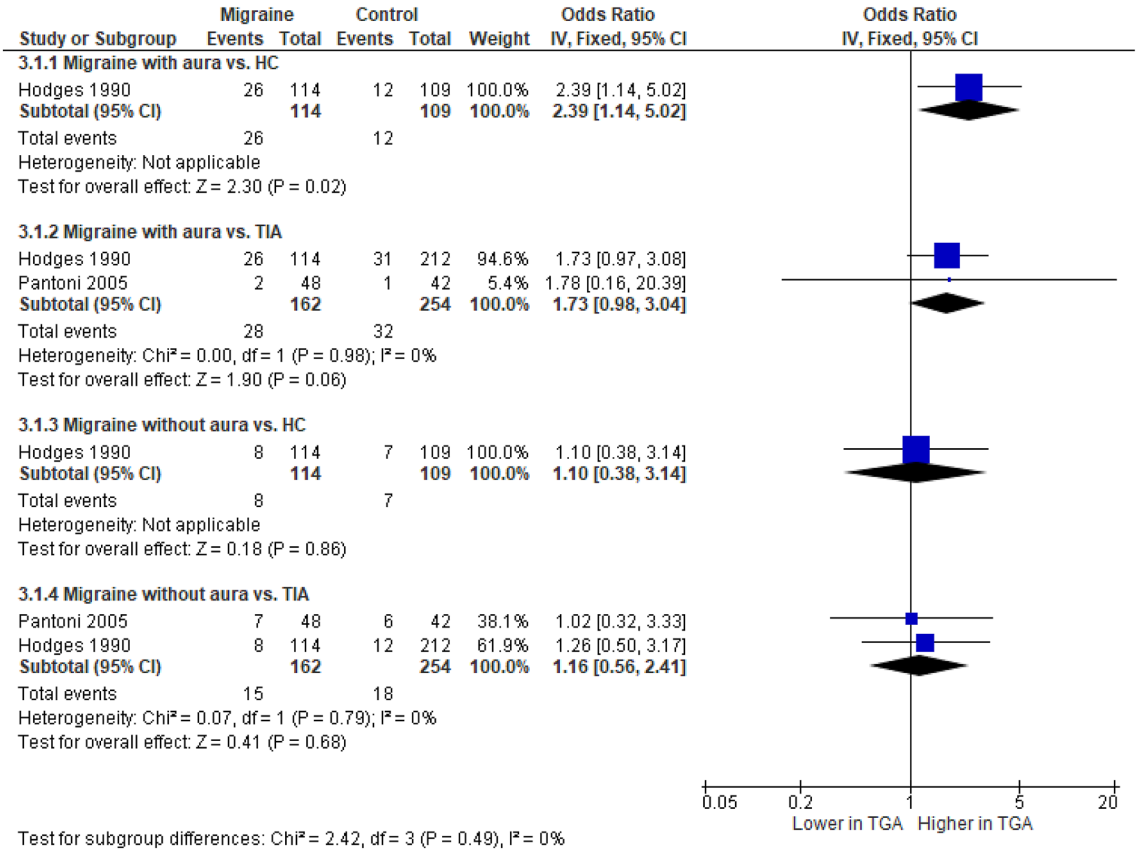

Fig. 3 Prevalence of migraine in patients with transient global amnesia (TGA) vs. either healthy controls (HC) or patients with transient ischemic attacks (TIA), according to the presence or not of aura

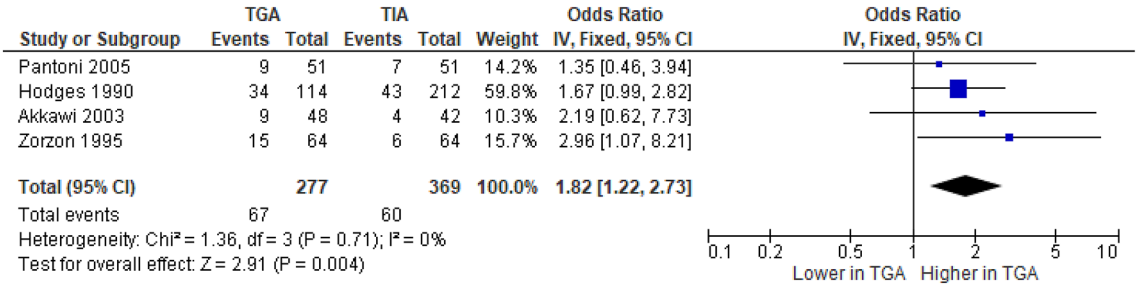

Fig. 4 Prevalence of migraine in patients with transient global amnesia (TGA) vs. patients with transient ischemic attacks (TIA)

(2006), involving only five of the twelve retrieved articles failed to reach similar conclusions [24]. In the present meta-analysis, migraine was determined more common among TGA patients in comparison with HC (2 to 3.5-fold, according to both case–control and cohort studies with higher figures generated in the context of higher-quality studies), as well as TIA individuals (less than two-fold, based on case–control studies), a group of patients that have already been associated with a personal history of migraine (therefore, an attenuated association was anticipated) [25]. High-quality evidence originated principally from case–control and cohort studies, whereas the single cross-sectional study was appraised as of limited value due to its inpatient orientation. Unfortunately, the association between TGA and the presence of aura was poorly studied; therefore, a safe conclusion cannot be reached.

Migraine has been, additionally, investigated as a potential risk factor contributing to the recurrence of TGA. Four recent articles focused on the examination of the parameters conferring a risk for recurrence. The study of Morris et al., a retrospective cohort based on the medical records of the Mayo Clinic (Rochester, Minnesota), reviewed a total of 1044 cases among which 143 suffered from recurrent TGA [11]. Recurrent episodes were significantly associated with both a personal and a family history of migraine headache. Similarly, the retrospective cohort of Alessandro et al. (203 TGA individuals, 16 with recurrent episodes) obtained results suggestive of a significantly increased tendency for recurrence in migraine patients compared to individuals free of migraine [41], whereas the prospective cohort of Tynas et al. (93 cases, 15 with recurrent disease), as well as the retrospective cohort of Oliveira et al. (70 patients with TGA, 19 with recurrent disease) did not provide evidence indicative of an association between migraine and recurrence (although absolute numbers for migraine were higher in the recurrent TGA groups) [42, 43]. Despite the non-significant results of the latter studies it is apparent that a history of migraine may assume a role in the recurrence of the disease, which is of probably affinity to our results suggesting an association between migraine and TGA in general (unique as well as recurrent).

The retrospective cohort of Lin et al. provided complementary evidence for the relationship between migraine and TGA, by examining the effect of a positive migraine history on the age of TGA onset [31]. Among individuals developing TGA after the age of 40, those with a migraine history presented a significantly younger age of onset (mean age 56.6 years) against those without a history of the disease (mean age 61.4 years). In addition to that, the association between migraine and TGA was mainly driven by the group of 40–60-year-old female individuals. Morris et al. supported these results with similar findings (mean age of onset for migraine patients 61.1 years vs. 65.4 years for non-migraine controls) [11]. Finally, a previous hierarchical clustering analysis of TGA cases classified the characteristics of a younger age of TGA onset (< 56 years) and a history of migraine together, proposing that migraine may represent a risk factor for TGA in younger individuals [24]. Taking all the aforementioned evidence into consideration, it is probable that migraine is not only associated with an overall elevated risk of TGA (and probably of the recurrent form of the disease as well), but also with an earlier age of TGA onset. Given this background, the latent effect of migraine might be accountable for the association between a younger age of onset with recurrent episodes of TGA (mean age of onset for recurrent TGA 58.8 years vs. mean age for unique TGA 65.2 years [11]), a theory which is based on the relationship of migraine with both of the aforementioned parameters. Overall, it could be argued that in a hypothetical continuum of clinical severity, a positive history of migraine appears to be associated with a more severe form of TGA (younger onset, recurrent disease).

As mentioned earlier, migraine-related theories regarding the underlying pathophysiological mechanisms of TGA are among the most prevalent ones. CSD extending through the hippocampus has been proposed as the missing link that unifies the two entities [44]. CSD has been associated with the presence of aura [45, 46] (despite a relatively few exceptions for migraine without aura [47, 48]). Therefore, the limited evidence with respect to the association of TGA with the presence of aura comes in contradiction with this theory. Intriguingly, our findings demonstrated that migraine

is even more common among TGA individuals compared to TIA patients. TIAs [25], as well as vascular events in general, have been associated with a history of migraine, an association which is stronger in the presence of aura [39, 40]. Additionally, individuals with aura demonstrate a more prominent prothrombotic predisposition compared to those without aura [49, 50]. Given the above-mentioned knowledge, as well as the benign vascular sequelae after a TGA episode, the association of TGA with migraine might lie in aura-irrelevant parameters. In addition to the above, hippocampal CSD is triggered at a higher threshold compared to other cortical areas suggesting that concomitant aura manifestations ought to be present during a TGA episode [7]. However, although migraine episodes have been recorded as possible triggers of TGA [51], TGA episodes are not consistently accompanied by aura or headache manifestations, while a positive history of migraine appears to contribute a risk towards TGA regardless of the status of the disease: active or inactive migraine [7].

At this point, it is prudent to point-out the complex neurohormonal-metabolic background of migraine [52–54] and subsequently the multiple possible pathophysiological pathways that may be implicated and shared in both entities. Inferentially, migraine and TGA may be linked by multiple underlying mechanisms other than CSD. Of note, there is accumulating evidence indicative of an association between migraine and cerebral energy, as well as oxidative mismatch [52]. Interventions that ameliorate the mitochondrial function and present anti-oxidative properties appear to exert a prophylactic effect against migraine [49, 54]. Considering the selective sensitivity of the CA-1 region of the hippocampus to oxidative and metabolic stress, migraine could create a local energy and oxidative disequilibrium that facilitates the emergence of TGA [55–57]. The alternative scenario that the relationship between migraine and TGA is no more than an indirect association between the two entities may, also, be the case. For example, a relatively more recent TGA theory suggests that psychological disorders could lead to the induction of brain metabolism disturbances, which in turn may lead to transient amnesia [58]. The psychological burden of migraine individuals is well recognized [59]. Herein the shared affinity of both diseases with psychological disorders, may provide the missing link between the two entities. Finally, a positive family history of migraine has been associated with recurrences, a finding that might imply the existence of a genetic predisposition towards TGA [11].

Intriguingly, TGA presents many similarities with a migrainous syndrome defined as late onset migraine accompaniments (LOMAs). Epidemiological evidence suggests that TGA does not affect individuals younger than 50 years [60]. On the other hand, migraine attacks tend to decrease in frequency and severity among patients older than 50 years; headaches are generally milder with less important functional consequences [61]. However, typical aura without headache and even without a prior history of migraine can occur at any age and are relatively more common among patients over the age of 50 (mainly with visual manifestations that last for several minutes) [62, 63]. These symptoms, termed as LOMAs, mimic the presentation of transient ischemic phenomena and seizures, but their prognosis is considered benign [61]. Consequently, LOMAs and TGA present several similarities, regarding their demographics, as well as their transient-reversible nature and benign prognosis. Nonetheless, the stereotypic recurrences, along with the focal neurological (or retinal) deficits accompanying the former offer a clear distinction between the two entities.

The present study has several limitations. First of all, the presence of aura was poorly studied by the retrieved articles and, therefore, concluding evidence for an existing association was not obtained. Secondly, TGA was diagnosed according to the long-established clinical criteria of Caplan and Hodges and Warlow. Published evidence suggests that a clinical diagnosis may not always be accurate (ischemic amnesia could mimic this condition [64, 65]) and, occasionally, might be compromised even after neuroimaging investigations [66]. Therefore, the presence of ascertainment bias cannot be ruled out, especially in the context of retrospective data collection that additionally includes a risk for information bias (TGA diagnosis based on medical records). On the grounds of the recognized increased prevalence of migraine in stroke patients, the misclassification of individuals with stroke in the TGA group may be accountable for the higher frequency of migraine compared to HC [39, 40]. However, sensitivity analysis based on stricter diagnostic criteria (involving neuroimaging), performed in the retrospective cohort of Lin et al., strengthened the estimated association between TGA and migraine [32]. Finally, the majority of the retrieved case–control studies were performed in tertiary neurological department settings (except for Arena et al.) and, therefore, are prone to referral and Berkson's (hospitalization) biases, with cases presenting more important comorbidities being involved in these studies. Nevertheless, the population-based retrospective cohort of Lin et al. determined a similar size of association with the pooled results of the retrieved case–control studies [32].

In conclusion, existing evidence is suggestive of a potential association between TGA and migraine. Additional high-quality studies are warranted for the acquisition of more robust conclusions with respect to the relative importance of aura in this association. To delve into the relationship between TGA and migraine, it would be of value if future research applied clustering approaches that will give prominence to the parameters closely related with migraine in TGA individuals. In this way the latent underlying component of migraine headache and TGA may be, ultimately, revealed. Future studies should always conform

to the reporting guidelines to ensure the capitalization of the obtained results [67, 68].

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Compliance with ethical standards

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