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Diagnostic Yield of Diffusion-Weighted Brain Magnetic Resonance Imaging in Patients with Transient Global Amnesia: A Systematic Review and Meta-Analysis

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Objective: To investigate the diagnostic yield of diffusion-weighted imaging (DWI) in patients with transient global amnesia (TGA) and identify significant parameters affecting diagnostic yield.

Materials and Methods: A systematic literature search of the MEDLINE and EMBASE databases was conducted to identify studies that assessed the diagnostic yield of DWI in patients with TGA. The pooled diagnostic yield of DWI in patients with TGA was calculated using the DerSimonian-Laird random-effects model. Subgroup analyses were also performed of slice thickness, magnetic field strength, and interval between symptom onset and DWI.

Results: Twenty-two original articles (1732 patients) were included. The pooled incidence of right, left, and bilateral hippocampal lesions was 37% (95% confidence interval [CI], 30–44%), 42% (95% CI, 39–46%), and 25% (95% CI, 20–30%) of all lesions, respectively. The pooled diagnostic yield of DWI in patients with TGA was 39% (95% CI, 27–52%). The Higgins I^2 statistic showed significant heterogeneity (I^2 = 95%). DWI with a slice thickness ≤ 3 mm showed a higher diagnostic yield than DWI with a slice thickness > 3 mm (pooled diagnostic yield: 63% [95% CI, 53–72%] vs. 26% [95% CI, 16–40%], p < 0.01). DWI performed at an interval between 24 and 96 hours after symptom onset showed a higher diagnostic yield (68% [95% CI, 57–78%], p < 0.01) than DWI performed within 24 hours (16% [95% CI, 7–34%]) or later than 96 hours (15% [95% CI, 8–26%]). There was no difference in the diagnostic yield between DWI performed using 3T vs. 1.5T (pooled diagnostic yield, 31% [95% CI, 25–38%] vs. 24% [95% CI, 14–37%], p = 0.31).

Conclusion: The pooled diagnostic yield of DWI in TGA patients was 39%. DWI obtained with a slice thickness ≤ 3 mm or an interval between symptom onset and DWI of > 24 to 96 hours could increase the diagnostic yield.

Keywords: *Transient global amnesia; Magnetic resonance imaging; Diffusion-weighted imaging; Systematic review and meta-analysis; Diagnostic yield*

INTRODUCTION

Transient global amnesia (TGA) presents as sudden-onset anterograde or retrograde amnesia that usually resolves within 24 hours without neurological deficits. The following diagnostic criteria for TGA, proposed by Caplan and validated by Hodges and Warlow in 1990 [1], are currently used: anterograde amnesia witnessed by an observer, no clouding of consciousness or loss of personal identity, cognitive impairment limited to amnesia, no focal neurological deficit or epilepsy, no recent history of head injury or seizures, and resolution of symptoms within 24 hours.

Although the etiology of TGA is unclear, transient dysfunction of the medial temporal lobes is considered one of the main pathophysiological mechanisms [2]. Previous studies have consistently reported small punctate hyperintense lesions in the hippocampus on diffusion-weighted imaging (DWI) as the only structural abnormality

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in patients with TGA, which could reflect transient hippocampal dysfunction [3-5]. Therefore, in the clinical setting, brain magnetic resonance imaging (MRI) including DWI can support the diagnosis of TGA by excluding alternative diagnoses and revealing typical TGA lesions in the hippocampus [2].

The reported diagnostic yields of DWI in patients with TGA vary widely among cohorts and MRI settings [6-9]. Although many studies have suggested optimal parameters and ideal timing of DWI to increase the detection of typical lesions of TGA, an established standard imaging protocol is lacking. Moreover, precipitating factors, including emotional or psychological stress, can trigger TGA [3,10,11], but more studies are required to clarify the association between DWI lesions and precipitating factors. To the best of our knowledge, the diagnostic yield of DWI in patients with TGA has not been systematically evaluated. Therefore, this systematic review and meta-analysis aimed to investigate the diagnostic yield of DWI in patients with TGA and identify significant parameters affecting its diagnostic yield.

MATERIALS AND METHODS

This meta-analysis was performed in accordance with the preferred reporting items for systematic reviews and meta-analysis guidelines [12]. No overlapping systematic review covered the topic in the Cochrane Library. Institutional Review Board approval and written informed consent were not required owing to the nature of our study.

Literature Search

A systematic literature search of the MEDLINE, EMBASE, and Cochrane databases was conducted to identify studies assessing the diagnostic yield of DWI in patients with TGA. The first search was performed on July 25, 2020. The following search query was used: (transient global amnesia) AND (magnetic resonance imaging) OR (MR imaging) OR (MRI) OR (diffusion) OR (DWI). The search was confined to articles published in English.

Inclusion Criteria

Articles satisfying the following requirements according to the Population, Intervention, Comparison, and Outcomes criteria were included: 1) inclusion of patients clinically diagnosed with TGA; 2) inclusion of patients who underwent brain MRI including a DWI sequence; and 3) reporting of sufficient results to obtain the diagnostic yield of DWI in patients with TGA [12].

Exclusion Criteria

Articles that met any of the following criteria were excluded: 1) inclusion of a small number of patients ($n < 5$); 2) reviews, case reports, case series, editorials, letters, consensus statements, guidelines, and conference abstracts; and 3) inclusion of overlapping cohorts.

The eligible articles were independently selected by 2 reviewers (an in-training radiologist with 4 years of experience in diagnostic radiology, and a radiologist with 7 years of experience performing meta-analyses and 9 years of experience in diagnostic radiology). Disagreements between the 2 reviewers were resolved by consensus.

Data Extraction and Quality Assessment

We extracted the following data from the chosen articles using a standardized form: 1) study characteristics: first author, publication year, institution, patient recruitment duration, prospective vs. retrospective study design, and consecutive vs. non-consecutive enrollment; 2) patient characteristics: number of patients with TGA who underwent brain MRI including DWI sequence, mean age with age range, sex, symptom duration, number of patients with precipitating events, number of patients with recurrence, and clinical diagnostic criteria; 3) technical characteristics of brain MRI: vendor, scanner, magnetic field strength, median interval, mean interval, or interval between symptom onset and MRI when the highest detection rates were observed, slice thickness, interslice gap, b value, and DWI plane; 4) lesion characteristics: laterality (right, left, or both), location in the hippocampus (head, body, or tail), size, and total number in each cohort; 5) interpretation of brain MRI: number of readers and their experience; and 6) diagnostic yield of DWI (number of patients with DWI-positive findings in each TGA cohort).

The methodological quality of the selected articles was evaluated using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool [13]. The data extraction and quality assessment were independently conducted by 2 reviewers.

Data Synthesis and Analysis

Diagnostic yield was the primary endpoint for assessing the diagnostic utility of DWI. Since we performed a "per-patient" analysis, the diagnostic yield (positivity) was defined as the ratio of the number of patients with TGA

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with small hippocampal hyperintense lesions suggestive of TGA to the total number of patients with TGA.

The pooled diagnostic yields and 95% confidence intervals (CIs) were obtained using the DerSimonian-Laird random-effects model, and a forest plot was created. The heterogeneity of the pooled data was assessed using Cochran's Q test and Higgins inconsistency index (I^2) test [14,15]. An I^2 value > 50% indicated heterogeneity. Publication bias was assessed using Egger's test and a funnel plot [16]. The pooled diagnostic yields were also compared by slice thickness, main magnetic field strength, interval between symptom onset and DWI, and b values of DWI by subgroup analyses based on the random-effects model. All statistical analyses were performed by one investigator using R version 3.6.3 with the "meta" package (The R Foundation for Statistical Computing).

RESULTS

Literature Search

A total of 156 articles were identified through a systematic search of the MEDLINE and EMBASE databases. After the removal of 8 duplicates, the titles and abstracts of the remaining 131 articles identified 28 potentially eligible articles. The full-text review further excluded 6 more articles: 3 that did not include DWI, 1 that was not written in English, 1 that included fewer than 5 patients, and 1 that included incomplete information. Finally, 22 eligible articles (1732 patients) were included in this meta-analysis [2,6-8,17-34]. Figure 1 shows the detailed study selection process.

Characteristics of the Included Studies

The study and patient characteristics are shown in Table 1. Among the 22 studies, 5 were prospective [6,7,18,22,34], 12 were retrospective [2,8,17,19-21,23,24,28,30-32], and 5 were not classified [25-27,29,33]. Consecutive patient enrollment was performed in 7 studies [2,7,8,20,27,29,30], whereas the patient enrollment method was not clearly described in 15 studies [6,17-19,21-26,28,31-34]. The range of included patients was 5–390, and the mean patient age was 58.6–68.7 years. Female predominance was noted

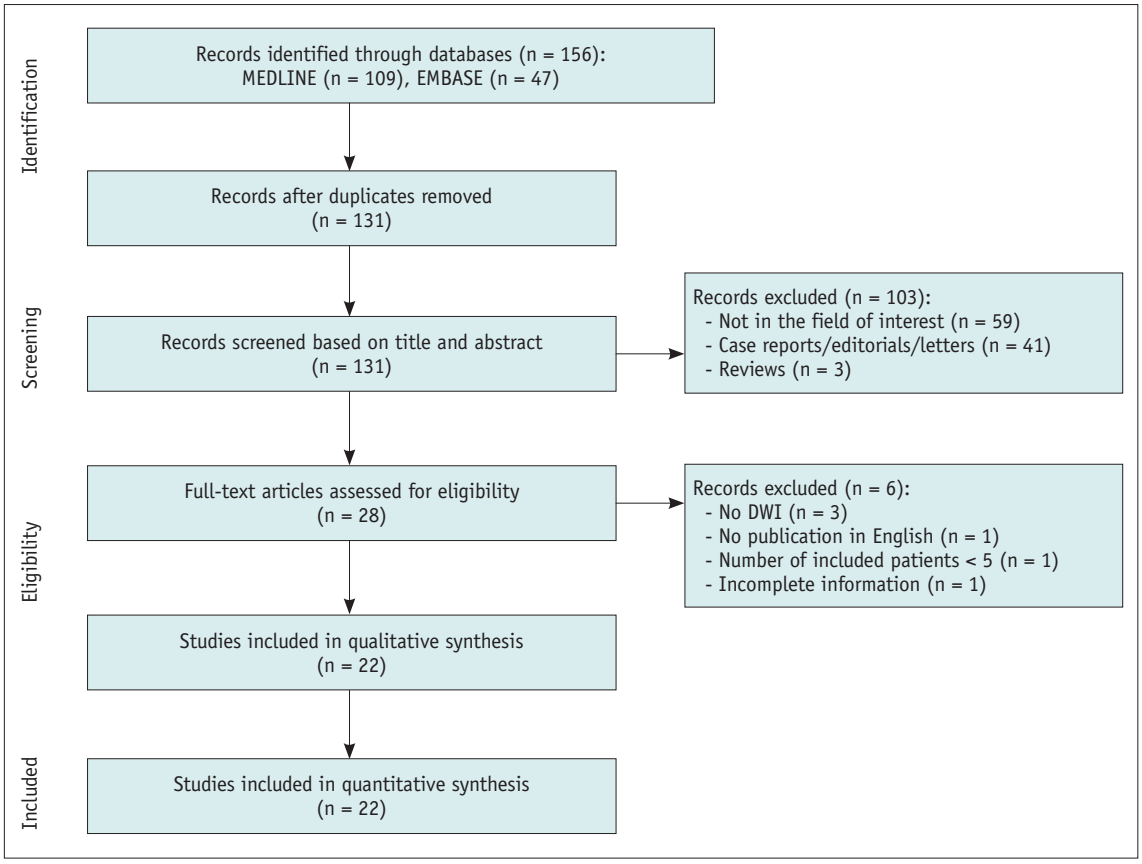

Fig. 1. Preferred reporting items for systematic reviews and meta-analyses flow diagram showing the study selection process for the meta-analysis. DWI = diffusion-weighted imaging

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Table 1. Study and Patient Characteristics

Study	Institution	Duration of Patient Recruitment	Patient Characteristics								Study Characteristics	
			No. of Patient (n)	Mean Age (Years)	Age Range (Years)	Male: Female	Symptom Duration (Hours)	Precipitating Events (n)	Recurrence (n)	Clinical Diagnosis	Study Design	Consecutive Enrollment
Higashida et al. [32]	Osaka University Hospital, the National Cerebral and Cardiovascular Center, the National Hospital Organization Osaka National Hospital, Kobe City Medical Center General Hospital, Japan	2006.04–2018.03	261	65.3 ± 8.6	NA	102:159	NA	128	22	Hodges and Warlow (older than 20)	Retrospective, multicenter	NA
Shimizu et al. [33]	Tokyo Medical and Dental University, Japan	NA	10	66.5 ± 6.1	NA	4:6	NA	NA	NA	NA	NA, single center	NA
Szabo et al. [2]	University Medical Centre Mannheim, Medical Faculty Mannheim, Heidelberg University, Germany	1999.07–2018.08	390	66.1 ± 7.8	37–86	154:236	3.2 ± 3.64	238	13	Hodges and Warlow (emergency department)	Retrospective, single center	Yes
Tynas and Panegyres [34]	Joondalup Health Campus, Australia	2004–2016	93	59.5 ± 10.3	17–78	49:44	4.5 (IQR: 2–6.5)	85	15	Hodges and Warlow (emergency department)	Prospective, single center	NA
Jain et al. [30]	Calvary Public Hospital, Australia	2013.10–2016.10	12	65.7	61–74	5:7	NA	NA	NA	Hodges and Warlow	Retrospective, single center	Yes
Lanzone et al. [31]	University Campus Bio-Medico of Rome, Italy	2010–2018	64	62.8 ± 9.4	NA	27:37	4	32	14	NA (emergency department)	Retrospective, single center	NA
Güngör Tunçer et al. [28]	Istanbul Bilim University Faculty of Medicine, Turkey	2006.01–2011.01	13	65 ± 11	51–78	5:8	8 (range: 1–24)	6	NA	NA (emergency department)	Retrospective, single center	NA
Park et al. [29]	Haeundae Paik Hospital, South Korea	2020.03–2013.12	54	NA	NA	NA	NA	NA	NA	Hodges and Warlow	NA, single center	Yes
Döhring et al. [26]	University Hospital Schleswig-Holstein, Kiel, Germany	2003–2010	108	NA	NA	NA	NA	NA	NA	Hodges and Warlow (emergency department)	NA, single center	NA
Kim et al. [27]	Seoul National University Bundang Hospital, South Korea	2003.06–2011.06	145	60.6	39–80	45:100	6.1 (range: 0.25–17)	120	NA	Hodges and Warlow	NA, single center	Yes
Scheel et al. [24]	Major university hospital in Berlin, Germany	2000.01–2011.07	198	64.7 ± 8.5	NA	75:123	NA	NA	NA	NA	Retrospective, single center	NA
Uttner et al. [25]	University of Ulm, Germany	2005–2006	17	68.7	55–82	6:11	NA	NA	NA	Caplan	NA, single center	NA
Ahn et al. [8]	Asan Medical Center, South Korea	2003.01–2010.05	200	60.1 ± 9.3	NA	84:116	5 (IQR: 3–9)	104	3	Hodges and Warlow (emergency department)	Retrospective, single center	Yes
Auyeung et al. [23]	Pamela Youde Nethersole Eastern Hospital, Hong Kong	2005.11–2009.11	27	58.6 ± 7.7	NA	9:18	6.8 ± 4.8	14	5	Caplan, Hodges and Warlow	Retrospective, single center	NA
Ueno et al. [22]	Suiseikai Kajikawa Hospital, Japan	NA	7	63	57–83	2:5	11.6 (range: 4–21)	NA	0	Caplan, Hodges and Warlow	Prospective, single center	NA
Lee et al. [21]	Yonsei University College of Medicine, South Korea	NA	41	60.7 ± 9.6	26–81	10:31	6.1 ± 3.7 (range: 1–13)	NA	2	NA	Retrospective, single center	NA
Alberici et al. [19]	C. Mondino Institute of Neurology Foundation, Italy	2004.05–2008.05	21	66 ± 7	52–84	9:12	NA	NA	NA	Caplan, Hodges and Warlow	Retrospective, single center	NA
Enzinger et al. [20]	Medical University Graz, Austria	2002.01–2006.12	86	65.9 ± 10.9	25.6–84.8	33:53	NA	NA	NA	Hodges and Warlow	Retrospective, single center	Yes
Winbeck et al. [18]	Technical University of Munich, Germany	2000.06–2003.06	28	61.5	57.5–65.5	13:15	6.1 (range: 4.3–8.0)	27	NA	Caplan, Hodges and Warlow	Prospective, single center	NA
Sedlaczek et al. [7]	University Medical Centre Mannheim, Medical Faculty Mannheim, Heidelberg University, Germany	NA	31	64 ± 7	44–83	15:16	4.6 (range: 0.5–12)	12	NA	Caplan	Prospective, single center	Yes
Huber et al. [17]	University of Ulm, Germany	1998.01–2001.01	10	63 ± 9	41–71	5:5	NA	0	2	Caplan	Retrospective, single center	NA
Strupp et al. [6]	Klinikum Grosshadern, University of Munich	1994–1996	10	59.2	53–71	7:3	12.8 (range: 3–24)	7	0	Hodges and Warlow	Prospective, single center	NA

IQR = interquartile range, NA = not available

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in most cohorts (range, 30–71%). The mean duration of TGA symptoms was 3.2–12.8 hours. The percentage of patients with any precipitating event was 0–96% (27/28), while 0–22% (14/64) of the patients had recurrent TGA. All studies included patients who visited the clinic with acute or subacute memory impairment and were clinically diagnosed with TGA. The diagnostic criteria proposed by Hodges and Warlow [1] were used in 17 studies [2,6-8,17-20,22,23,25-27,29,30,32,34]. Clinical diagnostic criteria were not clearly noted in 5 studies [21,24,28,31,33].

The technical characteristics of the brain MRI are summarized in Supplementary Table 1. A total of 11 studies used 1.5T [6-8,17-20,22,23,25,31], 3 used 3T [26,29,33], 5 used 1.5T or 3T [2,21,27,30,32], 1 used 1T, 1.5T, or 3T [24], and 2 did not describe the magnetic field strength [28,34]. The overall interval between symptom onset and MRI was 1–576 hours, and the median study interval was 6–96 hours. A total of 12 studies mentioned their median interval [6,8,17,18,20,22,25,27,29,30,33,34], 2 mentioned their mean interval [21,28], 5 mentioned only their time range [2,7,19,22,26], and 3 did not mention their median, mean, or range of time for all included patients [24,31,32]. However, 1 of the 3 studies had several time interval subgroups and showed the detection rates for each [32]. Therefore, the other 6 studies were used for subgroup analysis of time intervals [6,7,22,25,26,33].

The slice thickness used in DWI varied among the studies, ranging from 2 to 8 mm. Among the 22 studies, 6 used 5 mm [7,8,17,20,22,29], 2 used 2 mm [2,33], 2 used 3 mm [25,26], 1 used 4 mm [19], and 1 used 6 mm [6]. DWI scans with different slice thicknesses were performed in 5 studies [18,21,24,27,32], 4 of which were included in the subgroup analysis [18,21,24,32]. One study performed 89 DWI scans with a slice thickness of 2–3 mm and 262 DWI scans with a slice thickness of 5–8 mm, which were grouped into "≤ 3 mm" and "> 3 mm" groups, respectively [32]. In another study, 47 patients underwent DWI with a slice thickness of 3 mm and 151 patients underwent DWI with a slice thickness of 5–6 mm, and the latter patients were categorized into a "> 3 mm" group [24]. The other 2 studies used 4 mm or 5 mm [21], or 4 mm or 6 mm [18], and the patients were grouped into "> 3 mm" group. However, 1 study was not included in the subgroup analysis because the detection rates for each slice thickness (3 mm vs. 5 mm) could not be obtained separately [27]. In 5 studies, the slice thickness used was not specified [23,28,30,31,34] The interslice gap was 1.5 mm in 1 study [22], 1 mm in 2 studies [20,30], 0 mm in 1 study [7], and unavailable in the remaining studies [2,6,8,17-19,21,23-29,31-34]. The b value of DWI was 2000 in 1 study [29], 1000 in 7 studies [8,17,18,20-22,25), 1000 or 2000 in 5 studies [2,7,30,32,33], 1000, 2000, or 3000 in 1 study [27], and unavailable in 8 studies [6,19,23,24,26,28,31,34]. Although most studies did not mention the reader's level of experience, it was 10 years in 1 study [33].

Quality Assessment

The quality of the included studies was evaluated using the QUADAS-2. With regard to the patient selection domain, most of the studies had an unclear risk of bias except 3 with a low risk of bias [2,27,29] and 1 study with a high risk of bias [33] because there were no detailed exclusion criteria or information about whether consecutive enrollment was performed. Regarding the index test domain, more than half of the studies had a high risk of bias [2,8,17,19-21,23,24,28,30-32] since they used a retrospective design in which the MRI examinations were reviewed and interpreted after the clinical diagnosis of TGA had been made. All studies showed an unclear risk of bias in the reference standard domain because it was uncertain whether the clinical diagnosis of TGA was made without the use of DWI results. With respect to concern for applicability in the reference standard domain, unclear concerns were noted in 4 studies [24,28,31,33] because they did not mention how the clinical diagnosis was made. Supplementary Figure 1 shows detailed information about the quality assessment.

Characteristics of Lesions Detected on DWI

The radiologic definition of DWI-positive lesions in each study and the characteristics of each DWI lesion are shown in Supplementary Table 2. While no study directly mentioned lesion multiplicity, it could be inferred by comparing the total number of lesions with the number of patients who had positive results. As a result, 7 studies showed lesion multiplicity [2,20,23,25,30,32,34], 3 studies did not [7,8,17], and 12 studies had no information thereof [6,18,19,21,22,24,26-29,31,33]. In 16 studies that described lesion laterality [2,6-8,19,21-24,27-30,32-34], the pooled incidence of right, left, and bilateral hippocampal lesions was 37% (95% CI, 29–44%), 42% (95% CI, 39–46%), and 25% (95% CI, 20–30%) of all lesions. Only 1 study specified lesion location within the hippocampus as follows: 11 (12.6%) patients had lesions in the hippocampal head, 56 (64.4%) had them

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in the hippocampal body, and 20 (23.0%) had them in the hippocampal tail in 1 study [32]. The overall lesion size was 1–15.1 mm, while the mean lesion size was 2.8–10.2 mm. Corresponding T2 abnormalities were found in 3 studies [7,19,26], while another 3 studies did not detect any corresponding T2 lesions [6,20,22] and 16 studies did not focus on the presence of T2 abnormalities [2,8,17,18,21,23-25,27-34].

Diagnostic Yield of DWI

The diagnostic yield of DWI was 0–92%. The pooled diagnostic yield of DWI in patients with TGA according to the random-effects model was 39% (95% CI, 27–52%) (Fig. 2). The Q test and Higgins I^2 statistic showed significant heterogeneity ($p < 0.001$ and $I^2 = 95\%$). A funnel plot assessing publication bias is shown in Supplementary Figure 2. Linear regression analysis of the funnel plot's asymmetry indicated that there was no significant asymmetry ($p = 0.43$).

Subgroup Analysis

Figure 3, Supplementary Figures 3 and 4 show the diagnostic yields of DWI in the subgroup analyses according to the slice thickness, magnetic field strength, and interval between symptom onset and DWI, respectively. A slice thickness ≤ 3 mm was used in 6 studies [2,24-26,32,33], while a slice thickness > 3 mm was used in 12 studies (Supplementary Table 3) [6-8,17-22,24,29,32]. DWI with a slice thickness ≤ 3 mm showed a higher diagnostic yield than DWI with a slice thickness > 3 mm (pooled diagnostic yield, 63% [95% CI, 53–72%] vs. 26% [95% CI, 16–40%], $p < 0.01$). There was no significant difference in the diagnostic yield between 3T and 1.5T imaging (pooled diagnostic yield, 31% [95% CI, 25–38%] vs. 24% [95% CI, 14–37%], $p = 0.31$). Regarding the interval, 6 studies included a ≤ 24 hours subgroup [6,7,22,25,32,33], 7 studies had a > 24 to 96 hours subgroup [6,7,22,25,26,32,33], and 4 studies had a > 96 hours subgroup (Supplementary Table 4) [6,22,32,33]. As a result, DWI performed at an interval between 24 and 96 hours after symptom onset showed

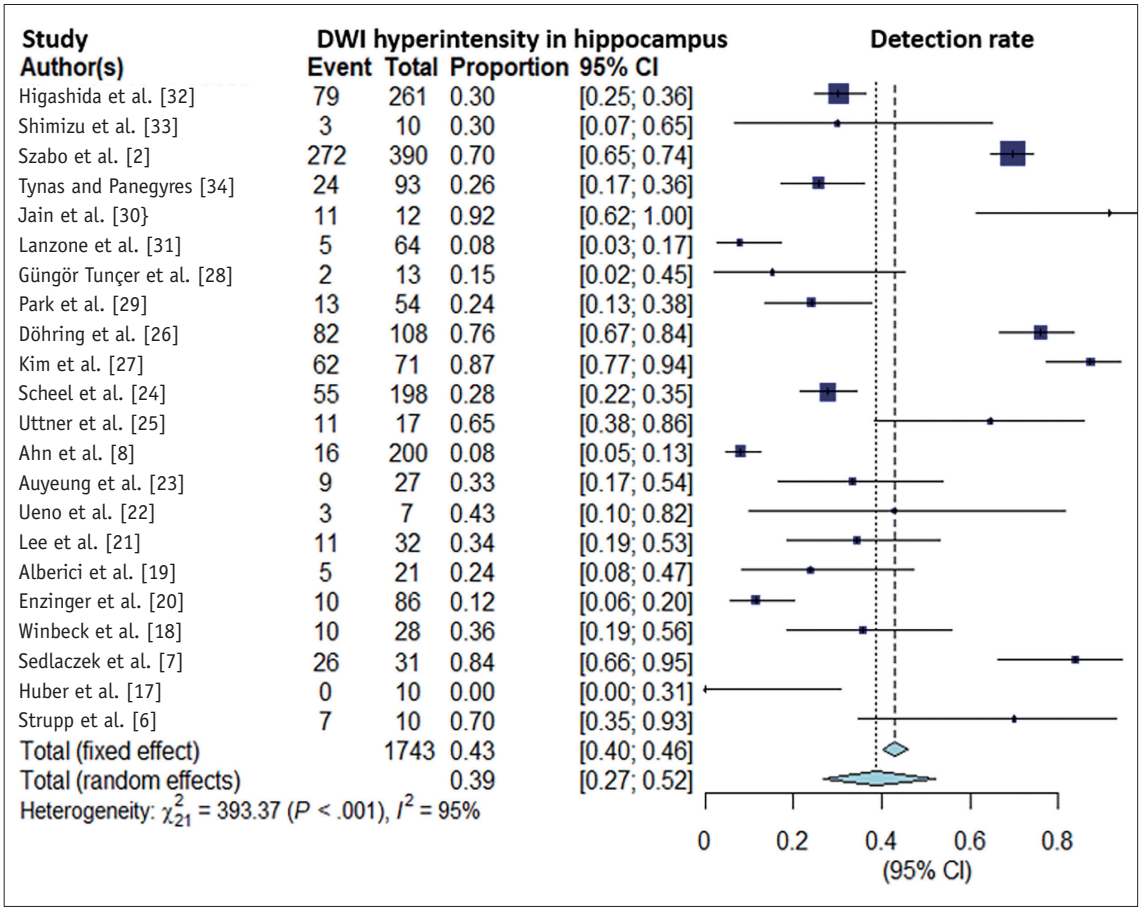

Fig. 2. Forest plot of the diagnostic yield of DWI in clinically diagnosed transient global amnesia. CI = confidence interval, DWI = diffusion-weighted imaging

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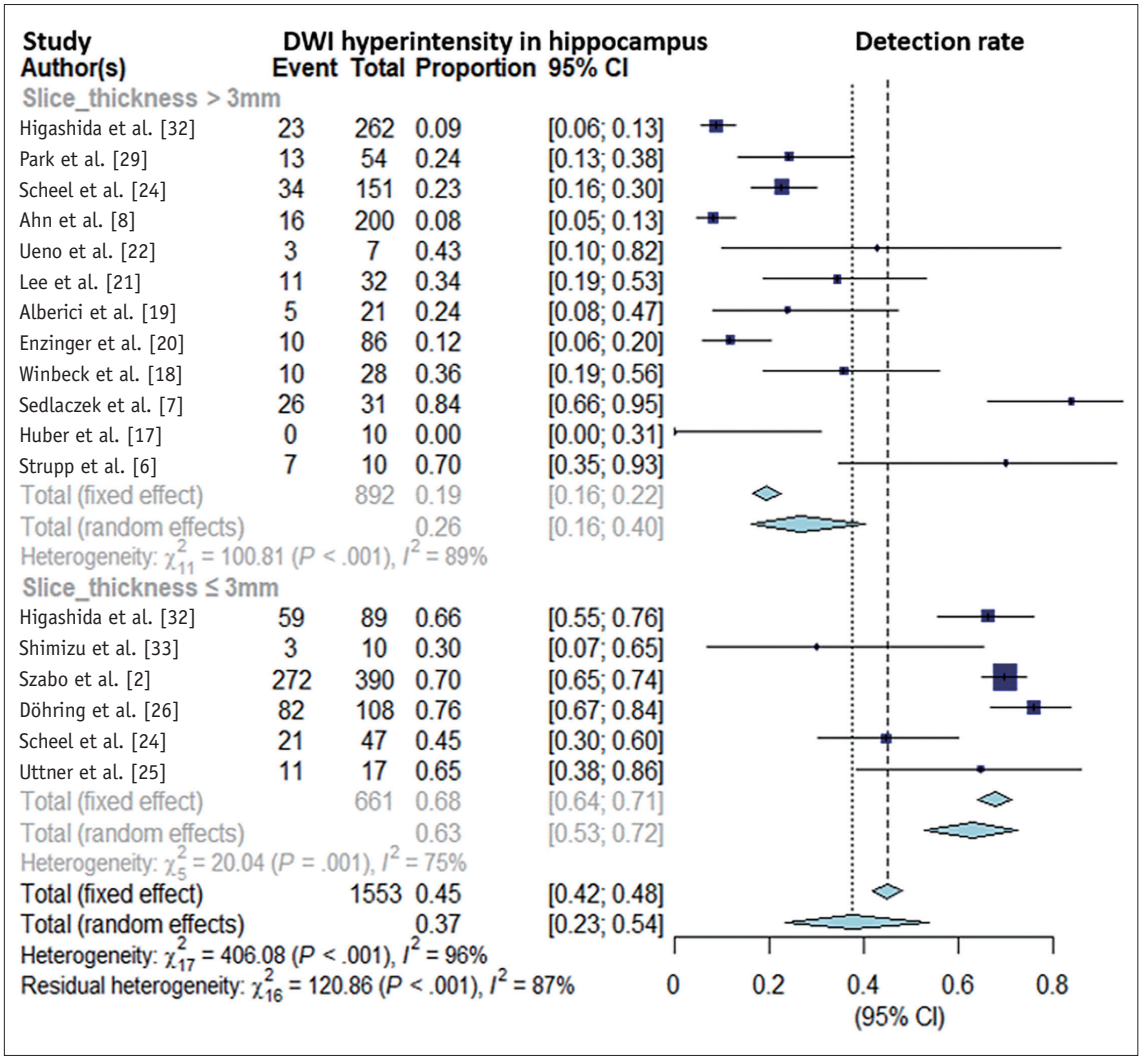

Fig. 3. Forest plot of the diagnostic yield of DWI in clinically diagnosed transient global amnesia grouped by slice thickness. CI = confidence interval, DWI = diffusion-weighted imaging

a higher diagnostic yield (68% [95% CI, 57–78%], p < 0.01) than DWI performed within 24 hours (16% [95% CI, 7–34%]) or later than 96 hours (15% [95% CI, 8–26%]). No subgroup analysis for b value was available since a b value ≥ 2000 subgroup was included by few articles. For b = 1000, the pooled diagnostic yield of DWI according to the random-effects model was 23% (95% CI, 9–48%).

DISCUSSION

In this study, we evaluated the diagnostic yield of DWI in patients with TGA. The pooled diagnostic yield of DWI was 39% (95% CI, 27–52%). Moreover, DWI with a slice thickness ≤ 3 mm showed a higher diagnostic yield than DWI with a slice thickness > 3 mm (pooled diagnostic yield, 63% [95% CI, 53–72%] vs. 26% [95% CI, 16–40%], p < 0.01). In addition, DWI with an interval of > 24 to 96 hours showed a higher diagnostic yield (68% [95% CI, 57–78%], p < 0.01) than DWI with an intervals ≤ 24 hours (16% [95% CI, 7–34%]) or 96 hours (15% [95% CI, 8–26%]). There was no statistically significant difference in the diagnostic yield between 3T and 1.5T imaging (p = 0.31). These results support the use of DWI in patients with TGA to provide imaging evidence supporting the clinical diagnosis. Furthermore, DWI obtained with a slice thickness ≤ 3 mm or an interval of > 24 to 96 hours, is recommended to increase the diagnostic yield.

The diagnosis of TGA currently depends on the clinical diagnostic criteria of Hodges and Warlow [1], and other causes of amnesia including posterior cerebral artery territorial infarction, post-traumatic brain injury, encephalitis, or epilepsy should be excluded [4]. Brain

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MRI, including DWI, can support the diagnosis of TGA by excluding alternative diagnoses and revealing typical TGA lesions in the hippocampus [2]. Furthermore, it can assist with the diagnosis of TGA, especially in unwitnessed cases that do not meet the diagnostic criteria, and supports the theory that an ischemic vascular process is an etiology of TGA [28]. Although multiple studies using brain MRI with DWI have revealed that DWI lesions in the hippocampus are frequently observed, varied diagnostic yields of DWI have been reported depending on clinical and MRI settings [6-9]. In our meta-analysis, the pooled diagnostic yield of DWI in TGA was 39% (95% CI, 27–52%), 63% with a slice thickness ≤ 3 mm and up to 68% with an interval of > 24 to 96 hours, which supports the use of DWI in patients with TGA.

Multiple subgroup analyses were performed to detect significant heterogeneity. Slice thickness is of the most significant parameters affecting the detectability of DWI. In particular, there was a significant difference between slice thicknesses of ≤ 3 and > 3 mm (pooled diagnostic yield, 63% [95% CI, 53–72%] vs. 26% [95% CI, 16–40%], $p < 0.01$). Considering that the typical TGA lesion is very small (1–3 mm), it is not surprising that DWI with a thin slice thickness could detect more lesions than DWI with a thick slice thickness. Moreover, the diagnostic yield of DWI with a thin slice thickness was 63%, which implies that we might miss many TGA lesions in daily practice using a thick slice thickness with inter-image gaps. Problems with the prolonged acquisition time in thin-slice imaging could be resolved by using simultaneous multi-slice techniques. Another significant parameter was the interval between symptom onset and the DWI scan. Two previous studies demonstrated that DWI at 3 days post-onset showed the highest lesion detectability for TGA [9,35] and that DWI performed within 24 or after 84 hours had a lower ability to detect lesion changes [7,32]. From these results, we assumed that there would be an optimal time interval, not too early or late. Therefore, we performed a subgroup analysis of 3 different time intervals (≤ 24 hours, > 24 to 96 hours, and > 96 hours) and found that DWI with a time delay of > 24 to 96 hours showed the highest detection rates (pooled diagnostic yield, 68% [95% CI, 57–78%] vs. 16% [95% CI, 7–34%] vs. 15% [95% CI, 8–26%], $p < 0.01$). On the other hand, 3T DWI did not demonstrated increased detectability compared to 1.5T DWI (pooled diagnostic yield, 31% [95% CI, 25–38%] vs. 24% [95% CI, 14–37%], $p = 0.31$). This result is inconsistent with the results of previous studies demonstrating that high-field-strength MRI has a higher diagnostic yield for TGA or other vascular ischemia than low-field-strength MRI, probably owing to higher signal-to-noise and contrast-to-noise ratios [21,36]. In our opinion, 1.5T DWI might have equivalent detectability to that of 3T if it is performed with a thin slice thickness, which explains why the higher field strength did not increase the detectability of DWI in this study.

Previous studies investigated the impact of the b value of DWI on diagnostic yield and recommended the use of DWI with a higher b value to improve diagnostic yield [7,27,37]. However, a subgroup analysis of b value could not be performed in this meta-analysis because only a few studies described performing DWI scans performed with a high b value ≥ 2000. Further studies are warranted to evaluate the effects of b values.

By definition, TGA symptoms resolve within 24 hours without any neurological sequelae. Therefore, previous studies of the prognosis of patients with TGA have focused on the presence of recurrent events or cognitive performance, and no significant difference in prognosis was noted between patients with TGA with and without hippocampal lesions on DWI [34]. Our meta-analysis did not demonstrate any relationship between recurrent events or cognitive performance and DWI lesions because of the small number of appropriate studies included in the analysis.

Among the 22 included studies, only 3 demonstrated corresponding T2 abnormalities in the hippocampus among acute or subacute TGA patients [7,19,26]. Therefore, it is uncertain whether the finding of accompanying T2 lesions added value in the diagnosis of acute or subacute TGA. Moreover, the corresponding hyperintense T2 lesions were no longer detected in a follow-up study performed 2 months later [3,19]. This complete reversibility of hippocampal hyperintensity without structural sequelae does not conform to the time course of a classic ischemic lesion [3,38]. Consequently, adding T2-weighted imaging to DWI does not have merit as a diagnostic or follow-up study in patients with TGA, as DWI remains the only imaging tool that can verify the TGA diagnosis [2].

Our meta-analysis has several limitations. First, more than half of the included studies had a retrospective design, which may have caused biased patient selection. Second, our pooled analysis showed significant heterogeneity, influencing the general applicability of the summary estimates. Hence, multiple subgroup analyses were performed. Slice thickness, but not main magnetic field strength, is an important factor affecting heterogeneity.

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Other technical factors, including b value, might have affected the heterogeneity, but this could not be evaluated in our study. Third, owing to recent advances in imaging technologies to improve the diagnostic yield of DWI, some recent studies were conducted using MRI with a higher b value, thinner slice, and more appropriate timing than previous studies. However, the 2 studies performed in the late 1990s or early 2000s showed relatively high diagnostic yields of 70–83.9%, suggesting that these factors did not considerably affect the study results. Fourth, among the 22 studies, 8 did not have information on apparent diffusion coefficient values or diffusion restriction, which prevented discrimination between the T2 shine-through effect and true diffusion restriction [2,6,26,27,29,31,32,34]. Therefore, we performed a subgroup analysis of the presence or absence of apparent diffusion coefficient information or diffusion restriction and found that the diagnostic yields were not significantly different between the 2 groups (pooled diagnostic yield, 48% [95% CI, 28–68%] vs. 33% [95% CI, 21–48%], $p = 0.25$). Fifth, previous studies already demonstrated that DWI with a thinner slice thickness and a certain time interval showed higher detection rates [2,7,9,24,27,32]. However, the optimal time interval has varied among studies. Our study showed that DWI performed at > 24 to 96 hours after the start of symptoms increased the lesion detectability by up to 68%. Moreover, this meta-analysis of 22 studies involving 1732 patients tried to increase the evidence level of the clinical value of DWI for making the diagnosis of TGA.

In conclusion, the pooled diagnostic yield of DWI in patients with TGA was 39%. DWI obtained with a slice thickness ≤ 3 mm or an interval between symptom onset and DWI of > 24 to 96 hours could increase the diagnostic yield.

Supplement

The Supplement is available with this article at https://doi.org/10.3348/kjr.2020.1462.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Su Jin Lim, Chong Hyun Suh, Sang Joon Kim. Data curation: Su Jin Lim, Chong Hyun Suh, Sang Yeong Kim. Formal analysis: Su Jin Lim, Chong Hyun Suh. Investigation: Su Jin Lim, Chong Hyun Suh, Sang Yeong Kim. Methodology: Su Jin Lim, Chong Hyun Suh. Project administration: Chong Hyun Suh, Sang Joon Kim. Resources: Chong Hyun Suh. Software: Chong Hyun Suh. Supervision: Chong Hyun Suh, Sang Joon Kim. Validation: Chong Hyun Suh. Visualization: Su Jin Lim, Chong Hyun Suh. Writing—original draft: Su Jin Lim, Chong Hyun Suh. Writing—review & editing: all authors.

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