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Original Article / Özgün Araştırma

Diffusion-Weighted-Imaging Negative Stroke Syndromes

Difüzyon Ağırlıklı Görüntüleme Negatif İnme Sendromları

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Abstract

Objective: Normal diffusion-weighted imaging (DWI) during the acute symptomatic phase of an ischemic stroke is a rare, but a well-known phenomenon. The exact rate and the clinical correlates of this phenomenon are not satisfactorily elucidated.

Materials and Methods: Consecutive patients who were hospitalized with the diagnosis of acute ischemic stroke in the last 10 years and who had DWI (with a bmax of 1000 s/mm^2) in the first 12 hours were included. A systematic review of published DWI-negative stroke cases and case series was performed. Alternate diagnoses including transient ischemic attack or stroke mimics such as seizure, migraine, functional disorders, and post-stroke recrudescence were excluded.

Results: The diagnosis of DWI-negative stroke syndrome was made in 20 (1.3%) of 1.506 patients hospitalized in Hacettepe Hospitals. A literature search disclosed another 535 (6.6%) DWI-negative strokes out of 8.101 cases. A total of 115, identified in case reports and cohort (n=19) articles, were combined with our cases to delineate further characteristics of DWI-negative clinical stroke syndromes. DWI-negative syndromes (n=135) were "brainstem mini-strokes" (31.1%), "cortical small embolic infarcts" (5.2%), "pure penumbral stroke" (normal DWI with magnetic resonance perfusion deficit) (34.8%); "aborted stroke" (early and fully recanalized stroke, only diagnosable in patients with documented acute vessel occlusion) (5.2%); and "miscellaneous" (23.7%). Corresponding clinical stroke syndromes include partial hemispheric deficits (36.1%), focal cortical syndromes (4.3%), caudal brainstem syndromes (9.3%), acute isolated vertigo (9.3%), vertigo-plus syndromes (10.1%), ocular syndromes (7.4%), movement disorders (1.9%), typical lacunar syndromes (11.1%), and atypical lacunar syndromes such as ataxia ± dysatrhria (9.3%).

Conclusion: In clinical practice of acute ischemic stroke, early DWI imaging can be negative in various clinical syndromes. Imaging repetition is necessary for the diagnosis and management plan of these patients.

Keywords: Diffusion-weighted imaging, neurologic examination, neurologist, medical history taking, stroke, imitator

Öz

Amaç: İskemik inmenin akut fazında normal diffüzyon ağırlıklı görüntüleme (DAG) izlenmesi nadir, ama iyi bilinen bir fenomendir. Bu durumun kesin oranı ve karşılık gelen klinik korelasyonları yeterli derecede incelenmemiştir.

Gereç ve Yöntem: Son 10 yıl içerisinde akut iskemik inme tanısı ile hastaneye yatırılan ve ilk 12 saat içerisinde DAG çekilen peşi sıra hastalar çalışmaya alındı. Ek olarak, literatürde yayınlanan DAG negatif inme olgu sunumu ve serileri sistematik olarak derlendi. Geçici iskemik atak ve epileptik nöbet, migren, fonksiyonel bozukluklar, inme rekrüdesansı gibi inme taklitçileri dışlandı.

Bulgular: Hacettepe Hastaneleri'nde yatan 1,506 hastanın 20'sinde (%1,3) DAG negatif inme sendromu tanısı kondu. Literatür taramasında 8,101 olgudan 535 (%6,6) DAG negatif inme olgusu daha saptandı. Olgu sunumları ve kohort makalelerinde tanımlanan toplam 115 olgu DAG negatif klinik inme sendromlarının özelliklerini tanımlamak için bizim olgularımızla birleştirildi. DAG negatif sendromlar (n=135) "beyin sapı mini-inmeler" (%31,1), "kortikal küçük embolik enfarktlar" (%5,2), "saf penumbral inme" (manyetik rezonans perfüzyon defekti olduğu halde normal DAG; %34,8), "durdurulmuş "(aborted)" "inme" (erken/tamamen rekanalize inme, sadece akut damar tıkanıklığının tıkanıp açıldığı gösterilen olgularda teşhis edilebilir; (%5,2) ve "çeşitli" (%23,7). Karşılık gelen klinik inme sendromları "kısmi hemisferik defisitler" (%36,1), "fokal kortikal sendromlar" (%4,3), "kaudal beyin sapı sendromları" (%9,3), "akut izole vertigo" (%9,3), "vertigo-plus sendromlar" (%10,1), oküler sendromlar (%7,4), hareket bozuklukları (%1,9) ile tipik laküner sendromlar (%11,1) ve ataksi ± dizatri gibi atipik laküner sendromlar (%9,3) şeklindedir.

Sonuç: Akut iskemik inme klinik pratiğinde "DAG negatif inme sendromu" nadir değildir. Ancak, çok sayıda klinik tablo ve nöroanatomik lokalizasyonla birlikte olabildiği için spesifik olmaktan uzaktır. Klinik bulgular temelinde kontrol görüntüleme alınması ve difüzyon negatifliğinin mekanizmasının aydınlatılması makuldur.

Anahtar Kelimeler: Diffüzyon ağırlıklı görüntüleme, nörolojik muayene, nörolog, anamnez, inme, taklitçi

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Introduction

Diffusion-weighted imaging (DWI) is a critical neuroimaging modality in the management of acute ischemic stroke. DWI has been reported to have a perfect (in the range of 95%) sensitivity and almost 100% specificity (1). Despite this high accuracy, the reported false negativity rate is not negligible. Failure to diagnose acute stroke due to DWI-negativity may pose a serious risk of recurrence due to delayed/missed treatment plan (2,3). Herein, we aimed to delineate the frequency and demographic, clinical and neuroimaging features of DWI-negative acute ischemic stroke.

Materials and Methods

Patients

First Part

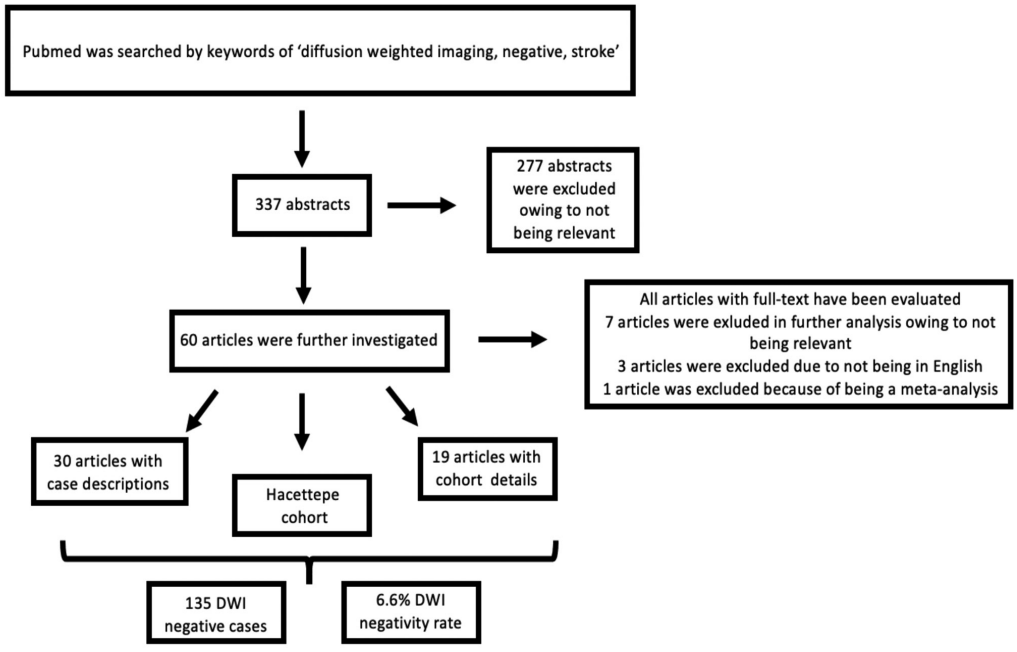
In the first part of the study, the last ten years of the Hacettepe University Stroke Unit database was retrospectively searched for patients admitted to the emergency department with signs and symptoms suggestive of acute ischemic stroke. Patients with transient ischemic attack (TIA), and those with subsequent alternate diagnoses such as seizure, migraine attack, functional disorder or post-stroke recrudescence were excluded. The analyses were then restricted to the remaining patients who were finally diagnosed as having an ischemic stroke in whom an initial DWI study was performed within 12 hours after symptom onset. Patients with no evidence of an acute ischemic lesion in the initial study despite the persistence of signs and symptoms beyond 24 hours, and having a DWI lesion compatible with neurologic signs at a follow-up study comprised the "DWI-negative ischemic stroke" group. "t1 time" was defined as the interval between the onset of symptoms to the first DWI study. "t2 time" was defined as the duration between symptom onset and the second DWI. Sex, age, stroke risk factors, National Institute of Health Stroke Scale (NIHSS), clinical presentation, DWI features in the second neuroimaging study and t1/t2 durations were recorded.

Approval was obtained from Hacettepe University Non-Interventional Clinical Research Ethics Committee for this study (decision number: 2020/16-25, date: 06/10/2020).

Second Part

In the second part of the study, we searched PubMed® with the keywords of "diffusion-weighted imaging," "negative," and "stroke," which yielded a total of 337 abstracts. From those, 60 abstracts were found to be relevant to our study in the initial screening. At the second stage, where the full-texts of these abstracts were evaluated, seven articles were not considered relevant to our research, three were not in the English language, and one article was a meta-analysis. Thus, the remaining 49 articles were evaluated for further analyses (Supplementary Figure 1).

To identify the exact rate of DWI-negative stroke, we extracted 19 of these articles where both the number of DWI-negative strokes and the total number of patients with stroke in the cohort were given. We also investigated the articles from this perspective because we aimed to describe the demographic and clinical features of patients who were DWI-negative. In 30 articles (21 of which were case reports or case series), the patients were described with their demographic, clinical, and magnetic resonance imaging (MRI) characteristics. From these articles, information about sex, age, stroke risk factors (described in most of the articles), NIHSS, clinical presentations, lesion location on second DWI-MRI, and t1/t2 durations were extracted. Although either t1 or t2 times have not been stated in some studies, all patients included in the current study underwent a second (confirmatory) MRI. Finally, this information was combined with the data of our center.



Supplementary Figure 1. The flowchart of the study

DWI: Diffusion-weighted imaging

Statistical Analysis

All values are represented as mean ± standard deviation, 95% confidence intervals (95%), percentages, medians with inter-quartile ranges as appropriate. The SPSS 23 IBM® software provided by Hacettepe University Medical Faculty was used for calculations.

Results

First Part

A total of 1.506 patients with ischemic stroke were evaluated in Hacettepe University during the study period, of which 20 (1.3%) were diagnosed as DWI-negative (on imaging obtained with a b_{max} of 1000 s/mm^2, which is the routine application in our institute) ischemic stroke. Ten (50%) female. The mean age was 65±16 years. The median NIHSS was 4 (0-12) on admission. There was a history of chronic hypertension in 80% of these patients, the prevalence of dyslipidemia was 40%, diabetes mellitus was 35%, atrial fibrillation was 25%, and prior stroke was 15%. The median t1 time was 5 (range, 3-9) hours, whereas the median t2 time was found as 34 (range, 24-73) hours.

Second Part

The combination of our series with the other 19 compatible cohorts from relevant literature yielded a DWI negativity rate of 6.6% in patients with ischemic stroke (535 DWI-negative-strokes among a total of 8.101 ischemic stroke patients). We were able to identify individual patient characteristics of 115 patients reported in the literature and combined them with our data. Among these 135 patients, 54 (40%) were female. The mean age was 66±15 years and the median NIHSS was found as 4 (range, 0-10) on admission. Additional disease information, which could not be obtained in all patients, is summarized in Table 1. Sixteen (84%) out of 19 cohorts and most of the other reports included used a DWI sequence obtained with a b_{max} of 1000 s/mm^2. In the remaining cohorts, no information related to the issue was provided. The median t1 time, obtained in just 96 (71%) patients, was 5 (range, 3-17) hours, whereas the median t2 time obtained in 89 (66%) patients was 29 (range, 20-84) hours.

DWI negative syndromes (n=135) were classified as "brainstem mini-strokes" (31.1%, Figure 1); "pure penumbral stroke," which defines a DWI-negative imaging finding in the setting of certain perfusion deficit (34.8%, Figure 2); "cortical small infarcts" (5.2%, Figure 3); "aborted stroke," which defines early complete recanalization of initially documented acute cerebral artery occlusion (5.2%, Figure 4); and "miscellaneous" (23.7%). The miscellaneous group consisted of 10 patients who presented solely with cerebellar infarcts, five with centrum semiovale - capsular infarcts, and 17 with DWI lesions scattered through a variety of subcortical white matter. Detailed information on each classified condition can be found in Table 1.

The corresponding clinical stroke syndromes were determined in 80% (n=108) of patients with DWI-negative stroke. The majority (n=39, 36.1%) of patients with DWI-negative stroke had hemispheric neurologic deficits such as anopia, dysphasia or hemiparesis (plegia). Further, six (4.3%) had "focal cortical syndromes", which involved isolated hand/crural paresis in three, elements of Gerstmann's syndrome in two, and abulia in one patient. "Acute isolated vertigo" was diagnosed in 10 patients (9.2%, Figure 5), all of whom had an acute small cerebellar infarct. "Vertigo-plus," described as vertigo with ataxia, nystagmus or dysmetria, was seen in 11 (10.1%) patients. "Caudal brainstem syndromes," which included solely lateral medullar syndrome, were diagnosed in 9.3% (n=10). A variety of "ocular syndromes" consisting of internuclear ophthalmoplegia in five, up-gaze palsy, diplopia with tinnitus, nystagmus with skew deviation in one each was diagnosed in eight (7.4%) patients. "Movement disorders" presenting as hemiballismus was seen in two (1.9%) patients. The remaining 22 (20.3%) lesions were classified as "others," in which 12 patients had classic lacunar syndromes including six with ataxic hemiparesis, four with pure motor hemiparesis, and two with pure sensorial stroke. The remaining 10 patients presented with ataxia and/or dysarthria secondary to involvement of various posterior system arterial territories.

Table 1. Features of DWI negative cases in the entire cohort

	Age* (years)	Sex (female)	HT	DM	HL	AF	Prior stroke	CAD	t1** (hours)	t2** (hours)
Brainstem (n=42, 31.1%)	65±14	26%	59%	28%	17%	17%	10%	7%	5 (2-13)	42 (24-99)
Small cortical (n=7, 5.2%)	67±13	57%	71%	57%	29%	43%	14%	29%	5 (4-9)	96 (26-116)
Pure-penumbral (n=47, 34.8%)	68±15	43%	71%	41%	12%	45%	6%	17%	6 (3-120)	24 (19-96)
Aborted (n=7, 5.2%)	62±22	71%	0%	0%	0%	0%	25%	25%	3 (2-4)	45 (27-60)
Miscallenous* (n=32, 23.7%)	68±13	47%	47%	28%	16%	6%	9%	22%	5 (4-8)	25 (17-34)
Total (n=135, 100%)	67±14	40%	55%	32%	16%	21%	11%	17%	5 (3-17) 71%	29 (20-84) 66%

*mean + SD, *see text, **median (IQR). HT: Hypertension, DM: Diabetes mellitus, HL: Hyperlipidemia, AF: Atrial fibrillation, CAD: Coronary artery disease, SD: Standard deviation, IQR: Inter-quartile ranges

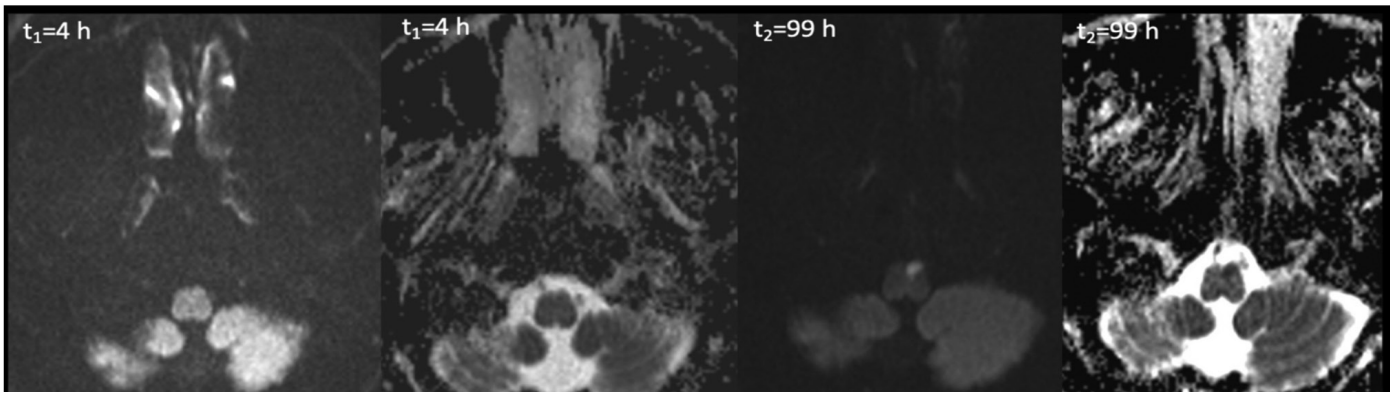


Figure 1. Brainstem mini-stroke: A 61-year-old man with hypertension and dyslipidemia was admitted with acute onset right-sided hemihypoesthesia, dysphagia and mild ataxia (admission NIHSS: 12; 24th-hour NIHSS: 10). While the lesion is not detected in the DWI and apparent diffusion coefficient (ADC) mapping performed at the fourth hour following the onset of the symptom, a DWI bright-ADC dark acute medullary infarction in the left medullary pyramid is clearly discerned in the control imaging taken at the ninety-ninth hour

NIHSS: National Institute of Health Stroke Scale, DWI: Diffusion-weighted imaging

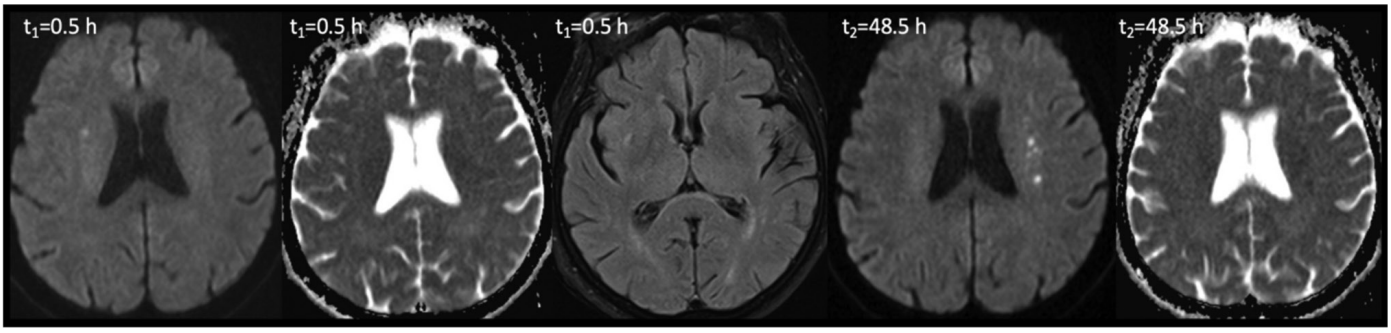


Figure 2. Pure penumbral stroke. A 76-year-old woman with known prior history of hypertension and coronary artery disease was consulted while she was being followed at the cardiovascular and chest surgery department after a coronary artery by-pass graft surgery. Transcortical sensorial aphasia and a left-sided central facial paresis were found on examination (admission NIHSS: 7; 24th-hour NIHSS: 6). Diffusion restriction is not seen in DWI, which is completed a half-hour after the onset of the symptom. However, distal left MCA segment occlusion is detected on CT angiography. The vessel signs in FLAIR sequences are indirect markers of perfusion deficit are visible. In the second imaging taken 48 hours after the first one, the culprit lesion can be clearly detected as DWI bright and ADC dark ischemic lesion. There was no change in the patient's neurologic deficit during the interval

NIHSS: National Institute of Health Stroke Scale, DWI: Diffusion-weighted imaging, CT: Computed tomography, MCA: Middle cerebral artery, ADC: Apparent diffusion coefficient, FLAIR: Fluid-attenuated inversion recovery

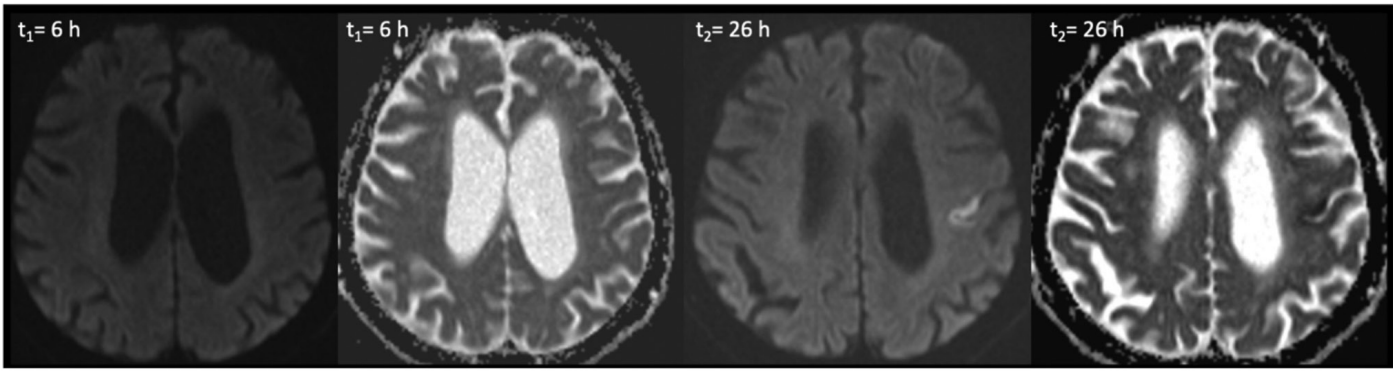


Figure 3. Isolated cortical syndrome: A 81 year-old-female with hypertension and atrial fibrillation was admitted with acute onset central facial paresis and dysarthria. (Admission NIHSS: 4; 24th hour NIHSS: 4) While DWI performed at the sixth hour after the onset of the symptom did not document the lesion, DWI performed twenty hours later showed a small-sized cortical infarction in the posterior frontal lobe. The lesion involves the facial area of the homongulus in accordance with the clinic deficit

NIHSS: National Institute of Health Stroke Scale, DWI: Diffusion-weighted imaging

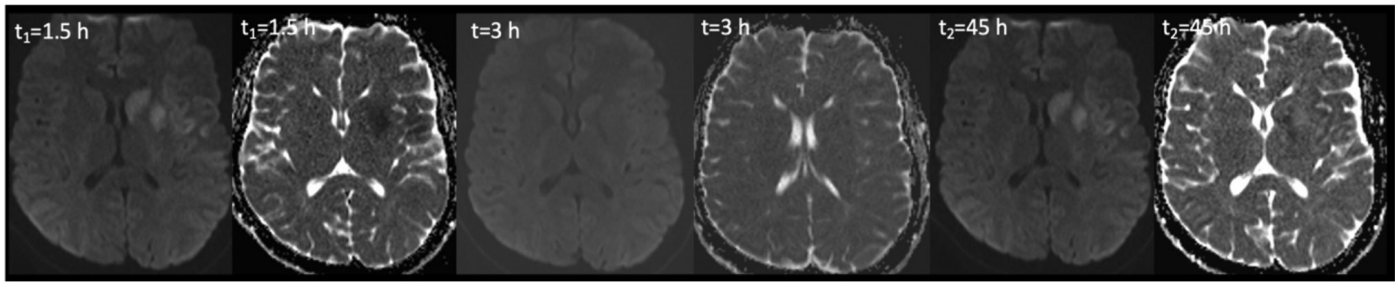


Figure 4. Aborted stroke: A previously healthy 32-year-old woman was admitted with acute onset right-sided hemiplegia and aphasia (admission NIHSS: 10; 24th-hour NIHSS: 3). Left-sided basal ganglia and insular infarction were observed in the DWI performed at the ninety minute after the onset of the event, lesions disappeared at the third-hour DWI, and the lesion reappeared at the end of the second day

NIHSS: National Institute of Health Stroke Scale, DWI: Diffusion-weighted imaging

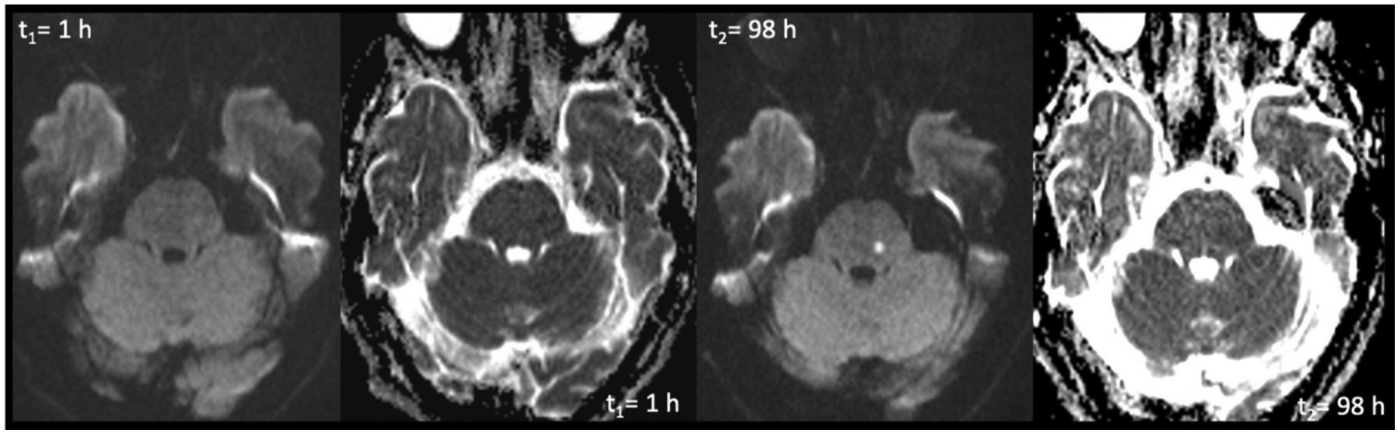


Figure 5. Vertigo: A 73-year-old woman with hypertension was admitted with acute onset vertigo and mild ataxia. (admission NIHSS: 4; 24th-hour NIHSS: 4). The left mid pons small infarction, which cannot be visible in DWI obtained at the end of the first hour of the symptom occurrence, is clearly observable at the ninety-eighth hour DWI

NIHSS: National Institute of Health Stroke Scale, DWI: Diffusion-weighted imaging

Discussion

DWI negativity is a problematic issue while managing ischemic stroke in the acute setting. Hitherto, to the best of our knowledge, no study has investigated DWI-negative stroke prevalence along with the individual features of patients by their demographic, clinical, and neuroimaging characteristics. The frequency of DWI-negative stroke is highly variable in the literature, ranging from 2.2% to 32.9% (2,3). In our study, when our single-center observations were combined with prior reports in the literature, DWI-negative stroke frequency was found as 6.6% of patients among patients with ischemic stroke. That is compatible with a previous meta-analysis (4) in which this rate was stated as 6.8%. However, the 1% rate in our cohort is obviously below this level. This low rate may originate from various reasons including, but not limited to, different hospital logistics such as the distance of MR units to the emergency room, MR techniques used such as b-values and population characteristics such as stroke clinic-imaging phenotype.

It is a matter of debate why some acute ischemic stroke lesions remain unnoticeable in DWI. Recently, it was shown that nearly 11% of patients with transient cerebrovascular dysfunction might depict an infarction on follow-up scans obtained beyond 24 hours, which evoked the importance of the timing of DWI to detect an acute ischemic lesion (5). It was stated that the sensitivity of 1.5 T DWI-MRI was 99.1% within the first 6 hours (1). However, the median imaging time was 10 hours in our study, which was much later than the period in this report. This gives the impression that the sensitivity of hyperacute DWI may not be as perfect as it is stated and perhaps needs to be revisited. On the other hand, the increasing signal intensity on DWI over the ensuing hours and days (reaching a maximum of 40 to 72 hours after the insult) increases the signal-to-noise ratio of DWI and thereby improves the detectability of lesions (6). This is in line with our results because the average t2 time was 70 hours.

In addition to the timing of DWI, another important variable in terms of the sensitivity is the technical aspects of the imaging. It is shown that acute ischemic stroke lesions could be more easily detected by 3T MRI DWI sequences in comparison to 1.5T MRI, especially when lesions are small and localized in the brainstem (7). However, there is not a comparison regarding the use of magnetic power of MRI in patients with DWI-negative stroke. In addition to the magnet power of MRI, the slice thickness is also crucial, especially in infratentorial ischemic strokes. As a reflection of partial volume averaging, the sensitivity to detect an infratentorial infarction was found as 81.1% in 5 mm-thick studies, improving

to 94.6% in 3-mm thick studies; the corresponding specificity was found as 100% and 97.7%, respectively (8). On the other hand, the false-negative rate of DWI for an infratentorial infarct was found as 5.6% for 5-mm thick sequences and 1.6% for 3-mm thick sequences (8). The initially negative ischemic stroke lesions were usually small (average 4.8 mm in diameter) and tended to settle in the brainstem in the same study (8). An alternative opinion to explain the DWI negativity in the brainstem, apart from timing and technical features, is the diminution of the intra-vascular space, producing intracellular dehydration and delayed edema formation (9). Other opinions include the insufficient signal-to-noise ratio and magnetic susceptibility artifacts at the brainstem (10). The region-specific response to ischemia may be another mechanism because some brain regions are known to be more susceptible to ischemia than others (11). DWI can be falsely negative in strokes exclusively limited to the intensely axon-dense regions such as the posterior limb of the capsula interna.

In a recent study, 27% of patients with an acute transient vestibular syndrome were found to have a stroke in which nearly half had a cerebellar infarction on DWI and the rest had cerebellar hypoperfusion on perfusion-weighted imaging (12). In certain circumstances, cerebral blood flow reductions cause hypoperfusion, which is enough to produce symptoms but not severe enough to produce a diffusion positivity, thereby, hypoperfusion without restricted diffusion may be seen (13,14). In a recent study, 44% of patients with ischemic stroke who had a perfusion deficit on the initial MRI scan showed at least a new DWI lesion in the following week (15,16). Accordingly, MR imaging and region-specific features are responsible for DWI negativity and perfusion deficits, which are not severe enough to produce a DWI lesion, might be suggested as another mechanism.

The other mechanism of DWI-negative ischemic stroke can be attributed to recanalization, which makes the DWI image appear normal (17,18). Spontaneous recanalization could be seen in up to 25% of cases with ischemic stroke (19,20); however, when it occurs very early it might lead to "aborted stroke". The accompanying pseudo-normalization of the DWI signal might obscure the appearance in initial imaging, which might become conspicuous during follow-up. The spontaneous recanalization phenomenon is related to both clinical improved outcomes and electrophysiologic recovery (15,21). This scenario is equivalent to TIA when it occurs spontaneously, not as a result of recanalization treatments such as thrombectomy.

Study Limitations

In addition to strong features such as being a systematic review/pictorial assay with the largest number of patients ever performed, our article also has some limitations. In addition, the use of only the English language for literature search, the limited number of keywords selected, and no request for additional information from the authors are considered minor limitations. Furthermore, as an inevitable nature of systematic reviews, publication bias could not be ruled out due to significant heterogeneity in population characteristics, imaging timing, and parameters including MRI field strength. Finally, because no comparison with patients DWI-positive stroke was made, the specificity of the syndromes described could not be clarified.

Conclusion

In this analysis, in which we combined our own experience with a literature review, we documented that diffusion-negativity was more frequent than it was thought in acute stroke, it occurred with many different mechanisms and the corresponding clinical syndrome was not specific. Stroke cannot be excluded in many clinical scenarios because "early" diffusion imaging is negative. However, the term "early" is not a simple time interval, but a process that varies individually for a given patient. There is no doubt that further, preferably prospective, studies are needed in this regard. In the current situation, our study carries importance by reporting clear rates for DWI negativity in acute ischemic stroke, revealing this separately for presumed mechanisms, compiling the largest number of patients, describing at least some of the syndromes in sufficient detail.

Ethics

Ethics Committee Approval: Approval was obtained from Hacettepe University Non-Interventional Clinical Research Ethics Committee for this study (decision number: 2020/16-25, date: 06/10/2020)

Informed Consent: Due to the retrospective nature of the study no informed consent was obtained from patients. Only ethics committee board approval was gathered.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.Y.P., E.M.A., R.G., K.K.O., M.A.T., Concept: M.Y.P., E.M.A., R.G., K.K.O., M.A.T., Design: M.Y.P., E.M.A., M.A.T., Data Collection or Processing: M.Y.P., M.A.T., Analysis or Interpretation: M.Y.P., E.M.A., R.G., K.K.O., M.A.T., Literature Search: M.Y.P., M.A.T., Writing: M.Y.P., E.M.A., R.G., K.K.O., M.A.T.

Conflict of Interest: No conflict of interest was declared by the authors.

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