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ORIGINAL ARTICLE **ÖZGÜN ARAŞTIRMA**

ACUTE ISCHEMIC STROKE;

ETIOPATHOGENETIC CLASSIFICATION, NEURORADIOLOGICAL, CLINICAL, PROGNOSTIC CORRELATION

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ABSTRACT

INTRODUCTION: Acute ischemic stroke is a clinical picture, which can last more than 24 hours and result in death in 24 hours, and its main cause is cranial vascular disease. CCS is a programme which is organized by Harvard University. In this study, classification and possible ethiopathogenetical factors of acute ischemic stroke were indicated. And hemodynamic changes of the ischemic tissue were measured by DWI/PWI MRI mismatch methods. Our puposes were interpretingt the correlations between DWI/PWI MRI mismatch methods and ethiological factors an effect of this correlation on clinical findings and prognosis.
METHODS: Totally, 30 patients with acute ischemic stroke were involved in this study. Cranial MRI imaging DWI/PWI MRI mismatch methods and clinical measurements that determined by NIHSS and GOS were performed three times CCS forms were filled with whole clinical and laboratory findings. At perfusion MRI, rCBF, rCBV, and rTTP maps were created. During MRI, all patients NIHSS scores were measured. To standardize the status of patients after discharge, GOS was used.
RESULTS: In the result of this study, it is seen that the prognosis is related to deficient area seen the rCBV maps. NIHSS scores who seregional cerebral blood volume increased and by means deficient areas in the rCBV maps decreased. In these patients, much of them had a stroke due to the supra-aortic large arterial atherosclerosis. In the measurement of penumbra, rTTP maps were used. But with the rCBV maps, it was detected that more meaning fulresults could be gained. And this finding was compatible with the literature.
DISCUSSION AND CONCLUSION: Acute ischemic stroke is a disease in which we race with the time. And with the early diagnosis and treatment, the quality of patients life can be changed. According to obtained information, the timing of the treatment, deciding the treatment and also its dosage, Perfusion MRI methods can be used.
Keywords: Stroke, penumbfra, ischemia, etiopathogenesis, neuroradiology, prognosis.

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AKUT İSKEMİK İNME;

ETYOPATOGENETİK SINIFLANDIRMA, NÖRORADYOLOJİK, KLİNİK, PROGNOSTİK KORELASYON

ÖZ

GİRİŞ ve AMAÇ: Akut iskemik inme; ani başlangıçlı, sıklıkla fokal nörolojik defisite yol açan, travmatik olmayan nedenlerle ortaya çıkan beyin damar hastalığına bağlı olarak gelişen, 24 saatten uzun süren ya da 24 saat içinde ölümle sonuçlanabilen klinik tablodur. A Causutive Classification of Stroke (CCS) Harvard Üniversitesi tarafından düzenlenen ve internet bağlantısı ile herkesin ulaşım şansının olduğu, kullanımı kolay, standartize ve güvenilir bir program olarak tüm dünyada inme ile ilgilenen hekimler tarafından kabul görmektedir. Bu çalışmada iskemik inmelerin akut döneminde inme sınıflaması yapılarak olası etyopatogenetik faktörün ortaya konması ve bu dönemde inme alanındaki hemodinamik değişikliklerin DWI/PWI MRI mismatch alan ölçümleri ile değerlendirilerek etyoloji ile korelasyonu yanısıra bu durumun klinik bulgulara ve prognoza yansımasının değerlendirilmesi amaçlanmıştır.
YÖNTEM ve GEREÇLER: Çalışamaya toplam 30 akut iskemik inme hastası alınmıştır. Tüm hastalara ilk 24 saatte, 48. saatte ve taburculuk öncesi Kranial MRG, Difüzyon MRG ve Perfüzyon MRG tetkikleri yapıldı. Hastalara yapılan tetkikler sonrasında elde edilen sonuçlar eşliğinde CCS formları doldurulduldu. Tüm hastalarda inme subtipi analizi yapıldı. Hastaların perfüzyon MRG lerinde rCBv, rCBF ve rTTP haritaları oluşturuldu. MR çekimleri sırasında hastaların NIHSS skorları hesaplandı. İnme sonrası taburculuklarındaki mevcut durumun tespitini standardize etmek amacıyla GOS kullanıldı
BULGULAR: Çalışma sonucunda rCBV haritalarındaki defisit alanlarının hasta prognozu açısından anlamlı olduğu görüldü. rCBV artan böylelikle defisit alanı azalan hastaların NIHSS skorlarında gerileme izlendi. Bu hastaların çoğunlukla supra-aortikbüyük arter aterosklerozu nedenli inme geçirdiği saptandı. Penumbra hesaplamasında rTTP haritaları kullanıldı. Ancak rCBV haritaları ile prognostik olarak daha anlamlısonuçlar elde edilebileceği saptandı. Bu bulgumuz literatür ile uyumluydu.
TARTIŞMA ve SONUÇ: Akut iskemik inme zamanla yarıştığımız tedavi protokolü olan; erken tanı ve tedavinin hastanın yaşam kalitesini belirgin bir biçimde etkilediği bir hastalıktır. Trombolitik tedavi zamanı inme gelişimi baz alınarak yapılmaktadır. Elde edilen veriler eşliğinde bu zaman belirlemesinde, tedavi kararı verilmesinde ve doz belirlenmesinde perfüzyon MRG tetkikleri kullanılabilir. Bu amaçla daha çok çalışma yapılması gerekmektedir.

Anahtar Sözcükler: İnme, penumbra, iskemi, etyopatogenez, nöroradyoloji, prognoz.

INTRODUCTION

Acute ischemic stroke is a clinical picture with sudden onset, often causing focal neurological deficit, emerging due to non-traumatic causes, developing due to cerebrovascular disease, lasting longer than 24 hours or may result in death within 24 hours (1). As it is frequently seen in middle and advanced ages of life, especially the elderly population is also an important cause of morbidity and mortality. Stroke is the third cause of death and the first cause of disability in developed countries. It is estimated that 15 million people worldwide have an acute stroke each year. One third of these patients die due to secondary causes due to stroke, while the other third group continues their lives with permanent neurological deficits (2). The consequence of acute stroke is strictly time-oriented and is important for the patient who will benefit from early thrombolytic therapy. The most important step after anamnesis and neurological examination is to confirm the clinical prediagnosis and to make the differential diagnosis between hemorrhagic stroke and ischemic stroke. Although cranial CT is easy to perform and is available in almost every center, ischemic findings can be detected in approximately 50% of patients in acute ischemic stroke (3). With diffusion-weighted imaging, the ischemic brain area can be determined from the first minutes. The areas of cor (dead tissue), penumbra (recoverable tissue) and oligemia, which are 3 different areas of the ischemic process, can be determined by evaluating diffusion and perfusion-weighted examinations together. Detection of penumbra, which is around the unrecoverable tissue "Cor" defined as the center of ischemia, and which is the tissue that can be recovered by additional treatment to be applied after early diagnosis, causes significant reductions in mortality and morbidity (1,3,4). The application time of thrombolytic therapy can be extended with the detection of penumbra. Determination of stroke subgroup in acute ischemic stroke is important in terms of establishing treatment and follow-up protocols for possible etiological factor. For this purpose, many classification methods are used to determine stroke subgroup. Causative

Classification of Stroke (CCS) is accepted by physicians worldwide who are interested in stroke as an easy-to-use, standardized and reliable program organized by Harvard University where everyone has the opportunity to access with internet connection (5). Stroke subtype analysis is very important in the treatment approach, in determining the prognosis and in terms of ensuring that precautions against possible etiological factors are taken before a stroke occurs. The determination of the relationship between the recoverable tissue and reperfusion process with the stroke subgroup detected by diffusion/perfusion MR imaging enables the management of our treatment for recoverable tissue in the brain and, more importantly, the prevention of this process, which results in mortality/morbidity with the application of thrombolytic or interventional methods.

Although, during the formation of the research protocol, the literature was reviewed, many studies have been carried out and still being carried out regarding the determination of the subgroup of the stroke, the determination of the recoverable tissue with the "diffusion/perfusion mismatch" and the evaluation of the reperfusion process; it was seen that no other study was designed to evaluate the relationship of these two parameters with each other and their correlation with stroke subgroups. Therefore, our research is an original research project with its subject, scope and method.

In this study, it was aimed to determine the possible etiopathogenetic factor by performing stroke classification in the acute period of ischemic stroke, to evaluate the correlation of hemodynamic changes in the stroke area with DWI/PWI MRI mismatch area measurements, and to evaluate the reflection of this condition on clinical findings and prognosis.

METHODS

The study included all patients who were admitted to the Ege University emergency department in the first 24 hours with an acute ischemic stroke clinic, whose possibility of intracerebral hemorrhage was eliminated and hospitalized in the neurology service. Cases with bleeding detected on cranial CT, patients in a coma with Glasgow coma scale (GCS) below 8, patients with high urea / creatinine and with contraindicated/objectionable administration of contrast media, patients with orthopnea or dyspnea with breathing difficulties that cannot tolerate MRI, and cases with a prosthesis, pacemaker, metal valve, etc. implants in which MR imaging cannot be performed were excluded. In the study, the gender, age, blood pressure values, ischemic stroke risk factors (cardiac arrhythmia, coronary artery disease, hypertension, diabetes mellitus, dyslipidemia, coagulation disorder, peripheral vascular disease) of the patients who were hospitalized in our clinic with acute ischemic stroke clinic were determined.

Ischemic stroke type was determined for all patients by filling the CCS form. NIHSS scores were calculated at the first hospitalization and at the time of MRI applications.

To evaluate the systemic and metabolic status of patients with acute ischemic stroke in the study, the routinely used tests performed in the Clinical Biochemistry laboratory (Fasting blood sugar (FBS), Total Cholesterol, LDL-Cholesterol, HDL-Cholesterol, Triglyceride, Creatinine, AST, ALT, Total protein, T. bilirubin, Urea, Uric acid, D-dimer, Platelet) were used. In addition to these tests, carotid and vertebral artery doppler USG was performed by the Department of Radiology and Cardiac ECO tests were performed by the Department of Cardiology in patients with acute ischemic stroke, as routine.

In acute ischemic stroke cases, cranial MRI, Diffusion MRI and Perfusion MR imaging were also performed in the first 24 hours after stroke, on the 2nd day and before discharge.

Conventional and DSC examinations were performed using a 1.5 T MRI device (Magnetom Vision, Siemens, Erlangen, Germany) using a standard head wrap. In conventional MRI examinations, axial T1A and T2A and coronal FLAIR imaging were performed on the TSE and IR (TR/TE:3800/90-11520/60) and FLAIR (TR/TE:8000/110) sequences. In addition, diffusion-weighted images were obtained using the ecoplanar imaging sequence. In DSC imaging, images were obtained using EPI sequence, TR/TE/FA: 2000/63.86/90, section thickness: 5 mm, section number: 12, acquisition number: 50 parameters. Gadolinium was administered as bolus with an automatic injector at a rate of 0.1 mmol/kg and 3 ml/sec. Multishot EPI imaging was performed to observe changes in T2* relaxation

time. During postprocessing, DSC perfusion parameters and function maps were prepared and evaluated.

Glasgow Outcome Score was used to standardize the detection of the current condition in patients' discharge after the stroke.

The study was conducted in accordance with the Helsinki Declaration ethical standards and approved by the Ege University Faculty of Medicine Clinical Studies Ethics Committee (Number: 10-7/9, Date: 04.10.2010) and informed consent was obtained from all participants.

RESULTS

In our study, a total of 30 patients who were admitted to the emergency department or neurology outpatient clinic of the Ege University Faculty of Medicine and hospitalized in our clinic for the purpose of examination and treatment after the application and fell outside the exclusion criteria were included.

As statistical method in the study, mean, standard deviation, ratio and frequency values were used in the descriptive statistics of the data. Spearman's correlation analysis was used for correlation analysis. (SPSS 20.0 program was used in the analysis)

Of the patients included in the study, 12 were female and 18 were male. The mean age of the patients was detected to be 72.9±12.0 (Table I).

Table I. Gender and age characteristics of the patients.

		Min	Max	n	%
Gender	Male			18	60
	Female			12	40
Age		45	91	72.9±12.0	

The patients were questioned in terms of stroke risk factors. Of the patients, 21 had a history of hypertension. Hyperlipidemia was present in 9 patients, and 7 patients were being followed up with the diagnosis of cardiac arrhythmia. Of the patients, 12 had a diagnosis of diabetes mellitus. Of the patients, 12 were being followed up due to known coronary artery disease. Eight patients had a smoking history. It was determined that 7 of 30 patients had a transient ischemic attack or ischemic stroke previously. Other factors that posed a risk for ischemic stroke (coagulation disorder, peripheral vascular disease, family history of stroke, malignancy) were detected as positive in 4 of the patients (Table II).

Table II. Risk fators of the patients.

	n	%		n	%
Hypertension	21	70	CAD	12	40
Hyperlipidemia	9	30	Simoking	8	26.7
Cardiac arrhythmia	7	23.3	Other risk factors	4	13.3
DM	12	40	Stroke history	7	23.3

During the clinical follow-up of patients, carotid and vertebral artery doppler ultrasonography were performed in elective conditions in order to evaluate the main vascular structures of the patients. While no significant pathology was observed in 15 patients, 8 patients had significant stenosis in the ipsilateral internal carotid artery (ICA) (stenosis above 70%) and 3 patients had significant stenosis in the vertebral arteries. Doppler USG could not be performed in 3 of the patients since their clinical status was not appropriate and they were under monitorized follow-up in the intensive care conditions. In one patient, significant stenosis was detected in bilateral ICA (Table III).

Table III. Carotid-vertebral artery Doppler USG results of the patients.

		n	%
CVD USG	Normal	15	50
	İpsilateral ICA significant stenosis oclusion	3	26.7
	Significant stenosis oclusion in vertebral artery	3	10
	Bilateral ICA significant stenosis oclusion	1	3.3
	Doppler USG not done	3	10

At the first hospitalization of patients, in the first 24 hours after the onset of stroke, 12 patients were evaluated as serious stroke, 13 patients were evaluated as moderate and 5 patients as mild stroke. Similarly, during the second MRI shots of the patients, at the 48th hour after the onset of stroke, 10 patients were detected as severe stroke, 13 patients as moderate and 7 patients as mild stroke. During the third cranial MR imaging prior to discharge, no neurological deficits were detected in 1 patient (NIHSS 0), while 5 patients died (Table IV).

CCS program was used in order to perform etiological classification of stroke for each patient participating in the study. The patients were evaluated separately for both causal and phenotypic subtypes.

In the phenotypic classification of the patients, 36.7% were determined as supra-aortic major artery atherosclerosis, 20% as cardio-aortic embolism and 13.3% as lacunar infarct. Nine

patients were identified in the group that could not be phenotypically classified (Diagram I).

Table IV. NIHSS scores and MRI results of patients at the first hospitalization, 48th hour after stroke and before discharge.

		n	%
NIHSS first MRI	Mild stroke	5	16.7
	Moderate stroke	13	43.3
	Severe stroke	12	40
NIHSS second MRI	Mild stroke	7	23.3
	Moderate stroke	13	43.3
	Severe stroke	10	33.3
NIHSS third MRI	Normal	1	3.3
	Mild stroke	7	23.3
	Moderate stroke	13	43.3
	Severe stroke	4	13.3
	Death	5	16.7

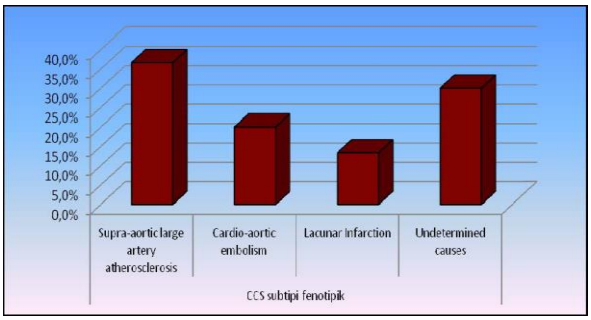


Diagram I. phenotypic classification of the patients.

In the causal classification of the patients, a large part as 36.7% were found to have supra aortic arterial atherosclerosis. In some of the patients, the causal classification was not completed due to the fact that the patient could not have advanced vascular imaging due to the exitus, and the patient was discharged before the cardiac examination was completed, and the examination entered the subtype of uncertain reasons.

GOS was used to standardize the detection of the current condition in patients' discharge after the stroke. While 9 of the patients were discharged with good improvement and minor deficit, one patient was discharged in a persistent vegetative state.

Diffusion MRI deficits of the patients were compared with the deficits in the rTTP, rCBV and rCBF maps (Table V).

Correlation analyses of GOS, NIHSS and CCS

Table V. Comparison of patients' diffusion MR deficits with deficits in the rTTP, rCBV and rCBF maps.

			n	%
TTP deficit from diffusion test	First MRI	Small	0	0
		Equal	14	46.7
		High	16	53.3
	Second MRI	Small	3	10
		Equal	15	50
		High	12	40
CBV deficit from diffusion deficit	First MRI	Small	12	40
		Equal	15	50
		High	3	10
	Second MRI	Small	12	40
		Equal	15	50
		High	3	10
CBF deficit from diffusion deficit	First MRI	Small	7	23.3
		Equal	18	60
		High	5	16.7
	Second MRI	Small	10	33.3
		Equal	16	53.3
		High	4	13.3

subtypes with the data obtained from the imaging of the patients were performed. There was no significant ($p>0.05$) correlation between the GOS score and TTP first MRI. There was a significant correlation between GOS score and TTP second MRI ($r=-0.595$ / $p=0.001$). There was a significant correlation between GOS score and CBV first MRI ($r=-0.595$ / $p=0.001$) and CBV second MRI ($r=-0.802$ / $p=0.000$). There was a significant correlation between GOS score and CBF first MRI ($r=-0.651$ / $p=0.001$) and CBF second MRI ($r=-0.701$ / $p=0.000$) (Table VI).

There was a significant correlation between NIHSS first MRI and CBV first MRI ($r=0.493$ / $p=0.012$), CBV second MRI ($r=0.609$ / $p=0.000$). There was a significant correlation between NIHSS first MRI and CBF first MRI ($r=0.622$ / $p=0.000$), CBF second MRI ($r=0.534$ / $p=0.002$) (Table VI).

There was a significant correlation between NIHSS second MRI and CBV first MRI ($r=0.534$ / $p=0.002$), CBV second MRI ($r=0.737$ / $p=0.000$). There was a significant correlation between NIHSS first MRI and CBF first MRI ($r=0.728$ / $p=0.000$), CBF second MRI ($r=0.711$ / $p=0.000$) (Table VI).

There was a significant correlation between NIHSS second MRI and CBV first MRI ($r=0.560$ / $p=0.001$), CBV second MRI ($r=0.756$ / $p=0.000$). There was a significant correlation between NIHSS first MRI and CBF first MRI ($r=0.680$ / $p=0.000$), CBF second MRI ($r=0.642$ / $p=0.002$) (Table VI).

Table VI. Correlation of GOS and NIHSS scores with MRI results.

		TTP first MRI	TTP second MRI	CBV first MRI	CBV second MRI	CBF first MRI	CBF second MRI
GOS score*	r	-0.258	-0.404	-0.595	-0.802	-0.651	0.710
	p	0.153	0.027	0.001	0.000	0.000	0.000
NIHSS first MRI*	r	0.113	0.112	0.452	0.609	0.522	0.534
	p	0.552	0.555	0.012	0.000	0.000	0.002
NIHSS second MR*	r	0.186	0.315	0.534	0.737	0.728	0.711
	p	0.324	0.090	0.002	0.000	0.000	0.000
Discharge NIHSS*	r	0.218	0.311	0.560	0.755	0.580	0.642
	p	0.246	0.094	0.001	0.000	0.000	0.000

*Spearman correlation

There was a significant correlation between GOS score and NIHSS first MRI (r=-0.757 / p=0.000), NIHSS second MRI (r=0.828 / p=0.000), discharge NIHSS (r=-0.917 / p=0.000) (Table VII).

Tablo VII. Correlation of GOC and NIHSS scores.

		NIHSS first MR	NIHSS second MR	Discharge NIHSS
GOS score*	r	-0.757	-0.828	-0.917
	p	0.000	0.000	0.000

*Spearman correlation

Imaging patterns of the patients included in our study are presented below (Figure I-IV).

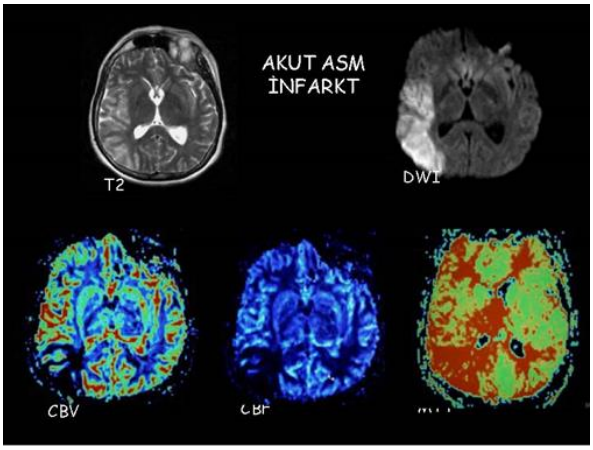


Figure I. The deficit areas rCBV ↓, rCBF ↓, rTTP ↑ in the DSK perfusion examination in the patient with a right ASM infarction on T2A and DWI.

DISCUSSION AND CONCLUSION

Stroke means sudden neurological deficit originating from vascular disorders. Cerebrovascular disease is the leading cause of deaths, hospitalizations and disabilities worldwide. Stroke is also one of the biggest health

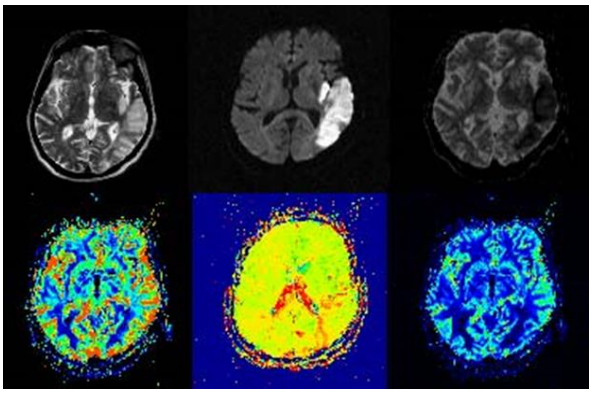


Figure II. There was no apparent deficit in all maps in the DSK perfusion examination in the patient who was found to be compatible with left temporoparietal acute infarction on T2A and DWI →.

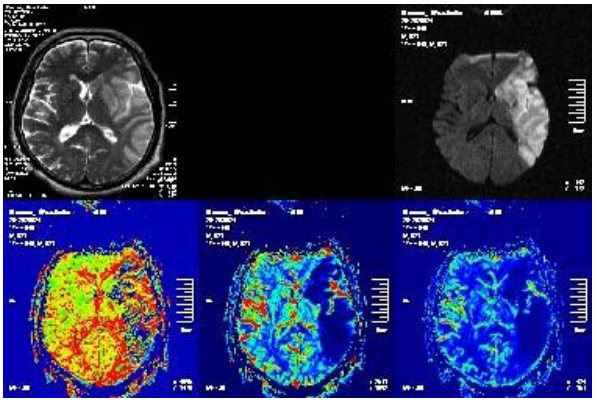
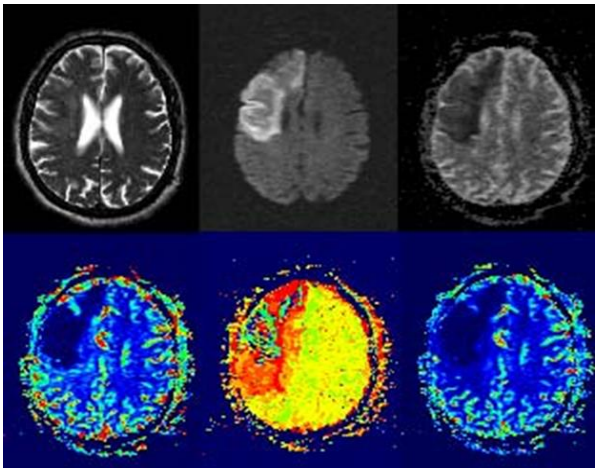


Figure III. Deficit areas in the DSC perfusion examination of the patient with a consistent appearance with left ASM infarction on T2A and DWI Equal, large, with rCBV, rCBF and rTTP fields; no penumbra.



Resim IV. On T2A and DWI, compatible appearance with right ASM and ASA infarction. On DSC perfusion imaging, there was a deficit bigger than those seen in rTTP mapping. (Penumbra) rCBV, rCBV deficits were equal to diffusion deficit.

problems leading to chronic care needs in the elderly population (1,2,3). Important risk factors for stroke are atherogenic factors such as hypertension, smoking, and hyperlipidemia.

One of the key criteria for the diagnosis of stroke is the compatibility of the area with abnormalities and the known vascular watershed area. If the area with altered attenuation and mass effect does not fit ASM, ASA or PSA watershed area, conditions such as venous obstruction or global ischemia should be suspected. In the case of global ischemia, bilateral edema and subsequent encephalomalacia areas can be seen in the areas named as 'watershed' zones between ASM and ASA or ASM and PSA watershed areas. Arterial occlusion forms a wedge-shaped configuration that extends to the brain surface, including gray matter (4).

In ischemic stroke, arterial occlusion is followed by cell death. While cell death has occurred in the center of the ischemic tissue, there is a high-risk area for irreversible damage around it. If proper and rapid treatment is not initiated, this area also results in cell death. Detection of infarcted and risky tissue in tissue after stroke plays an important role in clinical decision making, treatment plan and long-term results. The dysfunctional ischemic area at risk of infarction is called penumbra. Penumbra is an area that can be recovered by treatments such as opening the occluded vein urgently or giving an IV plasminogen activator. Therefore, the distinction between infarct area and penumbra is important (5).

Conventional MRI is an important modality in the diagnosis of brain ischemic lesions; however, it is insufficient in terms of distinction between infarct area and penumbra. For this reason, new searches have brought up diffusion MRI and dynamic contrast perfusion MR imaging. The diffusion restriction of cytotoxic edema may be shown with diffusion MRI within minutes after acute infarction; however, the distinction between infarct area and penumbra cannot be made clear. Cerebral hemodynamic status is demonstrated by dynamic contrasted perfusion. Diffusion perfusion mismatch shows critical hypoperfused area and requires rapid treatment as it can respond to treatment. In dynamic contrasted perfusion examination, contrast agent is given in bolus style. Detailed analysis can be made by forming time concentration curves, regional CBV maps and additionally hemodynamic maps containing CBF, MTT, TTP. In acute arterial infarcts, a significant decrease in perfusion in the infarct area and a more moderate decrease in the surrounding penumbra area are observed (6).

Early detection and grading of ischemia are the primary indications for perfusion MRI. In the images obtained after IV paramagnetic contrast agent is given, the signal decreases in normal perfused tissues, while the infarct area remains hyperintense. The combined use of perfusion and diffusion MRI techniques is recommended in determining many different areas, including irreversible parenchymal changes (the most severe), reversible ischemic and dysfunctional (penumbra), and oligemic but functional (lightest) in ischemia grading (7). In the Echo Planar Imaging perfusion technique, TTP is prolonged in that area as a result of acute obstruction of the feeding artery in the acute infarct area. If the collaterals are opened and the tissue begins feeding with collaterals, TTP prolongation continues again. Therefore, it is wrong to comment on tissue ischemia with TTP alone (8,9).

James et al. have dwelled on that if the lesion in perfusion was more than that of in diffusion in acute infarct cases, that is, if there was diffusion-perfusion mismatch, the tissue at risk (ie, penumbra) can be recovered by thrombolytic therapy by performing the calculation of the volume of the mismatch in a short time after the development of infarct. The methods used to measure the volume of mismatch are usually performed by visual inspection or manual calculation. The manual method is very time-consuming, not completely quantitative, and varies depending on the examiner. In this study, James et al. have calculated the mismatch from the DAG and MTT images and used the semiautomatic technique, which was shorter (less than 15 min) and quantitative method compared to manual technique. In this technique, after the user has placed point marks on the lesion boundaries, the software has combined these points and calculated the area (10).

Chen et al. in their study have examined delayed perfusion in the mouse infarction model. Thus, the relationship between spontaneous reperfusion and ischemic penumbra would be clarified. This study was obtained by examining T2A, DAG, perfusion-weighted imaging (PAG)

images with 1.5 T MR for 72 hours after phototrombotic occlusion of ASM on 8 mice and by performing micro-angiography, histopathological correlation of penumbra, and neurological deficit score. In some mice, rCBF increased approximately 6 hours after ASM occlusion, especially in the relevant cortex area. This model is an example of spontaneous reperfusion. In previous experimental studies, spontaneous reperfusion was observed between 3 to 8 hours, and in this study and clinical patient models, it was observed within 6 hours. The photochemically induced thrombus initially blocked the flow in the proximal ASM, and over time, the degree of occlusion also expanded to the distal ASM parts. Microthrombi rich in fibrin were observed in the superficial capillaries in the cortex and striatum. rCBF decreased over time and reached its lowest level at the 6th hour of ASM occlusion. Then, it was observed that the scattered thrombus began to dissolve with endogenous thrombolytic mechanisms (leptomeningeal collateral circulation, leukocyte infiltration) from the 6th hour of the ischemia and as a result, a significant increase in rCBF was detected. Penumbra decreases over time secondary to the increase of the infarct area with time. It is monitored between 1-12 hours of ischemia, in particular, the fact that the penumbra does not change between 6-12 hours has also been proven by clinical data. The existence of the penumbra or recoverable area for as long as 12 hours will improve the ischemic stroke treatment strategy. Thus, effective reperfusion is ensured, and penumbra is recovered, and the area of infarction is prevented. In this study, reperfusion has developed from the 6th hour of ischemia. The decrease of penumbra after 12 hours was attributed to prolonged ischemia, limited efficacy of reperfusion and damage formed after reperfusion. Another remarkable finding in the study is that delayed perfusion is due to cerebral collateral circulation. Cerebral collateral circulation, especially those between leptomeningeal vessels and secondary collateral vessels, play the main role in the hemodynamics of cerebral ischemia. Conventional angiography is the gold standard in the demonstration of collateral vessels, and noninvasive techniques remain inadequate in this regard due to their limited resolution. One of the most important findings in the study is that delayed perfusion findings correlate well with penumbra. The delayed perfusion finding is evidence of secondary collateral blood flow and indicates impaired hemodynamic stability. Collateral circulation has haemodynamic effects, such as maintaining the flow in the penumbra area and facilitating cleansing thrombi. However, in all cases, the presence of collateral flow is not necessary to prevent the infarct area from expanding.

In the study of Chen et al., detection of early developed leptomeningeal blood flow or observation of the delayed perfusion findings has been found to be associated with spontaneous reperfusion developing in ASM at 6 hours. Accordingly, rCBF has increased in the ischemic area. In addition, all these events have extended the presence of penumbra for up to 12 hours and have enabled thrombolytic therapy. In this way, wider ASM infarction has been prevented and the infarct area has been limited in the cortex and has not progressed to the striatum. However, in 4 mice, both the cortex and the striatum were affected, which was due to the longer delayed perfusion and delayed reperfusion time compared to the other group. This shows us that the early developed effective collateral blood flow and rapid reperfusion will prevent the expansion of the infarction that develops in the first 8 hours in the occluded ASM. In the light of all this information, the result obtained in the related study is that collateral blood flow, also known as delayed perfusion finding, and early reperfusion are two critical factors that prevent the penumbra area from protecting and enlarging the infarct area (11).

Our aim in our study was to investigate that it is possible to extend the duration of thrombolytic therapy, which is the only radical treatment that can be applied to ischemic stroke causing high mortality and morbidity, with MRI perfusion techniques. It was investigated that the prognosis could be predicted by associating the stroke subtype of the dynamic changes in the rCBV, rCBF and rTTP maps with patient history, with serial MRI controls performed on all patients.

In their study, Dalkara et al. have shown that ischemia in the mouse brain leads to continuous contraction in pericytes in the microvascular bed. In this study, it was seen that even if the occlusion of the middle cerebral artery was treated within the first 2 hours of ischemia (i.e. recanalization was achieved in MCA), pericytes have continued to

contract. Reducing oxidative stress decreases the pericyte contraction, thereby reducing erythrocyte involvement and ensuring microvascular integrity; so, the tissue survey increases. Conversely, peroxynitrite application causes pericyte contraction. They also have shown that in ischemia and reperfusion mediated microvascular dysfunction, the microvascular wall is the source of oxygen and nitrogen radicals. These findings show that even if recanalization is achieved in the occluded vessel, ischemia and reperfusion mediated damage affects the pericytes, preventing new flow formation in microcirculation and limiting substrate and medication access to the tissue under metabolic stress. Ischemia and reperfusion can prevent capillary flow by causing pericyte contraction, thereby tissue feeding and tissue medication adversely affected after occluded arterial recanalization. Oxygen and nitrogen radicals formed in the microvascular bed play a role in pericyte dysfunction as well as disruption of the blood brain barrier. Therefore, the use of agents that recure pericyte dysfunction and microvascular structure can increase the success of both thrombolytic and neuroprotective treatments (12).

In our study, 0.1mmol/kg contrast medium was given as a single dose and the findings were evaluated visually. Comparison of rCBV, rCBF, rTTP maps was performed individually with diffusion-weighted images. After comparing rTTP maps and diffusion maps, the presence of penumbra was investigated.

According to the studies compiled by Schaefer et al., perfusion images have been found to be less sensitive in detecting acute stroke than DAG images. (13) The sensitivity of rCBV, rCBF and MTT in stroke detection ranged from 74 to 84%. The causes of missed lesions in perfusion images are as follows: Small abnormal areas detected in DAG images are not detectable due to low resolution of perfusion images and early reperfused lesions cannot be monitored in perfusion. The specificity of perfusion ranges from 96-100%. In false positive results, an ischemic but alive hypoperfused area is observed, if any. Points to be taken into consideration in order to make an accurate assessment of perfusion images applied with DSC are patient movement, delay in contrast bolus, distribution of contrast bolus and errors caused by susceptibility artefacts due to air or metallic objects. It is necessary to pay attention to these traps while making the examination. In the majority of infarcts, the infarct volume in DAG increases 2-3 days after the postictal period. According to the research, the infarct area on the CBV and DAG maps has similar characteristics and this area is equal to the final infarct volume. In other words, DAG grows as much as the lesion area in the CBV. The correlation between CBF or TTP areas and the final infarct volume is lower. In small vessel infarcts (in perforator infarcts and distal embolic infarcts), the first obtained perfusion (CBV, CBF, MTT) and diffusion lesion volumes are generally the same, and the lesion volume either grows little or does not grow at all. Although the diffusion area is larger than the perfusion area or there is a restriction in diffusion, if no abnormality is detected in perfusion, this is an indication of early reperfusion and in these cases, an increase in lesion volume is not expected. In patients who have lesions in perfusion images, however, no lesions are detected in diffusion, it means there is a proximal occlusion or critical stenosis in the vessels, penumbra is perfused with collaterals. DAG abnormalities develop due to collateralization and reperfusion timing. They are candidates for reperfusion therapy. If the abnormal area in the perfusion is more than the diffusion, there is a proximal occlusion or critical stenosis in the vessels. Penumbra is partially perfused with collaterals. The DAG infarct area may expand to cover some or all of the lesion area in perfusion. This situation depends on collateralization and the reperfusion timing. Reperfusion therapy should be applied. If the perfusion and diffusion areas are equal, they usually represent lacunas or distal occlusion, however, there may also be occlusion in the proximal. Infarction has settled in the entire area and there is no risky area to be recovered (13).

In our study, we found that, although the area of ischemia in DAGs was detected, the scores of patients with rCBV deficit, which were smaller than the area of ischemia detected in diffusion, recovered in a short time, and that the ischemic stroke area regressed to the perfusion deficit in the controls. We predicted that early reperfusion could be evaluated with rCBv and that the patient could be discharged with minor deficits due to treatment approach changes during this process. We observed that penumbra detection with rTTP maps is not sufficient for predicting prognosis and the final infarct area.

In a study compiled by Shaefer et al., among the infarct patients with heavy hypoperfused tissue (> 6 seconds MTT), those who were given tPA via intravenous (IV) application were compared with those treated with the traditional method, and it was found that more tissue was recovered with IV tPA (13). In another study, despite the successful intra-arterial thrombolysis recanalization, some infarcts have been observed to grow towards the penumbra area (14). In cases where intra-arterial recanalization has been successfully performed in one study, the threshold value, Tmax, for determining irreversible infarction tissue was (time required to reach peak concentration) 6-8 sec or longer. In another study, intra-arterial thrombolysis has been performed in patients with infarct who have a hypoperfused area at first, and CBF has increased. These patients were compared with those in whom hypoperfusion was detected initially and then did not develop hyperperfusion, resulting in a higher incidence of infarction. In addition, the level of TTP delay correlates with the rate of recanalization in patients with acute stroke and IV tPA administration (15,16). In brain infarction, hemorrhagic transformation can be seen in the rate ranging from petechia to parenchymal hematoma due to bleeding into ischemic tissue. In the first 2 weeks of cerebral infarction, it is seen in 15-26%, while this rate increases up to 43% in the time up to first month. Predisposing factors underlying hemorrhagic transformation in brain infarcts are as follows: Etiology (hemorrhagic transformation is more common in embolic infarcts), reperfusion, good collateral circulation, hypertension, anticoagulant therapy, thrombolytic therapy, prolonged recanalization, low platelet count and high glucose level (16,17). The mechanism explaining the pathophysiology of hemorrhagic transformation is as follows. Severe ischemia causes impairment of cerebral microvascularity and blood-brain barrier. Reperfusion causes lesions ranging from damaged capillaries to blood extravasation, petechial hemorrhage to cerebral hematoma (16,17).

Schaefer et al. in their study have found that stroke patients (proximal stroke) with diffusion-perfusion mismatch had a worse prognosis than patients without a mismatch (distal or lacunar stroke). Diffusion-perfusion mismatch volume is related to clinical prognosis (13).

Sanak et al have examined the mismatch between the degree of neurological deficit in NIHSS and infarct volume in DAG, namely Clinical - Diffusion Incompatibility (CDI) in infarct cases. CDI is available if NIHSS> 8 and infarct volume DAG <25 ml. CDI was compared with diffusion-perfusion mismatch and significant similarity and high specificity were noted (16).

In our study, we also found that the perfusion findings correlated with NIHSS scores.

Sanak et al. have retrospectively analyzed 79 patients who were given IV thrombolytic in the first three hours after stroke, and better clinical results have been found in these patients who were detected to have CDI before thrombolysis (18).

In a study, it has been found that the growth of the infarct area after hyperacute ischemic stroke was associated with the degree of collateral circulation. In another study, it was emphasized that the degree of collateral circulation is an important factor in the follow-up of patients with significant collateral circulation and DPM findings in angiography. Since angiography is difficult to determine collateral circulation, in this study, researchers have used rCBV to evaluate the collateral circulation (19,20,21).

In hyperacute ischemic stroke, the detection of ischemic penumbra and the rapid initiation of thrombolytic therapy are important for prognosis. However, it is not reliable to make DPM finding only according to TTP or MTT maps. Adding the rCBV ratio to these findings shows the tissue at risk more realistic. In this study, spontaneous recanalization findings were compared in patients with and without expanding infarct area. Spontaneous recanalization was found to be the same in both groups and it was found that the presence of spontaneous recanalization was not significant in the expansion of the ischemic lesion (22).

In the article written by Beng, the contributions of MRI are mentioned in order to understand the individual pathophysiology in patients who develop stroke and to provide personalized treatment. Three MRI strategies have been discussed. The first was the blood brain barrier permeability in patients undergoing diffusion-perfusion mismatch, deoxygenation (oxygen use and oxygen level of the brain) and recanalization treatment in acute ischemic stroke. The second was the determination of the effects of the mechanism of stroke and the presence of

specific factors that cause stroke (patent foramen ovale, infective endocarditis, etc.), and finally the presence of hemodynamic indicators of carotid arteries for the prevention of recurrent stroke and the presence of the plaque with multimodal MRI (23).

Thrombolysis needs to be performed quickly because its usefulness decreases over time and the risk of bleeding increases. Timing so far has been made based on the onset of clinical symptoms. However, with the advances in neuroradiology, MRI-based timing will be useful in determining the prognosis of patients, in selecting patients who can benefit from recanalization treatment and in reducing treatment complications (23).

Diffusion-perfusion mismatch maps detected by MR imaging were found to be compatible with the PET which is accepted as gold standard (24).

The presence of mismatch can last up to 24 hours and the penumbra decreases over time. The presence of diffusion perfusion mismatch showed that recanalization treatment may be useful after 3 hours and in the study performed with phase 2 desmoteplase, thrombolysis was performed after 3 hours and worked (25,26).

In the study titled Diffusion - weighted Imaging Evaluation for Understanding Stroke Evolution (DEFUSE), patients with mismatch detected 3-6 hours after stroke onset have been given tPA treatment, and a decrease in recanalization and infarct growth have been determined (27).

According to the study of Beng et al., the risk of hemorrhagic transformation had increased in patients with permeability changes with MRI perfusion prior to treatment. If patients who have penumbra detected by MRI (i.e., the group of patients who can potentially benefit from recanalization) have impaired blood brain barrier, these patients will be damaged from treatment due to high risk of hemorrhagic transformation. It is possible to individualize stroke treatment with MRI findings and contribute to the prognosis of patients (28,29).

In our study, stroke subtypes were determined by CCS scale. We found that patients with increased rCBV and smaller rCBV deficits than the ischemic area detected in diffusion were frequently in the subtype of supra-aortic large artery atherosclerosis. Based on this, we found that brain tissue is better at providing autoregulation during the development of atherosclerosis, among these patients, the increase in rCBV after ischemia decreased the area of ischemia, and patients' GOS scores were significantly better.

In one study, lacunar infarcts (62%) have been more significant in patients with recurrent intracranial hemorrhage than other types of infarcts (21-30%). These results demonstrate that aggressive antithrombotic therapy and bleeding complications that may occur in cases with multiple micro-bleeding can be prevented with the use of GRE (30).

In the study of Kim et al., the hypothesis that the atherosclerosis-induced stroke (AIS) in the large intracranial arteries had different DPM and MRI Angiography –DAG mismatch profile compared to other stroke subtypes has been argued. The presence of good collateralization observed in AIS patients is associated with the development of occlusion over time. In cardioembolic stroke or cryptogenic embolic stroke, collateralization cannot occur due to the sudden development of the event. According to this mechanism, the complete blockage of the vessels before the stroke develops takes time, and this ensures adequate collateralization. (31)

As conclusion; ischemic stroke is a disease, that we compete against time, with high mortality and morbidity. In the acute period of ischemic stroke, the prolonged intervention period and the establishment of individual treatment strategies can create significant differences in terms of prognosis. The detection of recoverable tissue around the ischemic area, and the use of new agents to provide autoregulation may lead to the development of new treatment strategies to increase the flow in pericytes.

The use of perfusion MRI is a guide in the diagnosis and treatment of acute infarction. Penumbra is a dynamic tissue, and for its early detection, the most reliable perfusion map is still controversial and more studies should be carried out on this subject. According to the literature, the most reliable maps are rCBV and rCBF in terms of showing the final infarct area and providing prognostic predictions. Our findings are in this direction.

CCS is a method for determining the ischemic stroke subtype, which is fast and easy to access over the internet, has limited inter-rater variability, can provide consistency in data entry, and therefore has high inter-rater reliability in

stroke classification. In determining the prognostic characteristics of stroke patients, its use in studies related to stroke is important in terms of using a common language.

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Ethics

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