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ORIGINAL ARTICLE **ÖZGÜN ARAŞTIRMA**

ETIOPATHOGENESIS OF PONS INFARCTION DIFFERS ACCORDING TO THE LOCALISATION; A RETROSPECTIVE CLINICAL TRIAL

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ABSTRACT

INTRODUCTION: Of the ischemic strokes, 25 % involve the posterior circulation ischemic infarcts (POCI) and pontine infarctions account for about 7% of all ischemic strokes. Isolated pontine infarctions are usually classified into two types: paramedian pontine infarcts (PPIs) and small deep pontine infarcts (SDPIs). The main pathogenesis of each of the two types differ. Our study was designed to investigate the main causes of isolated pontine infarctions.
METHODS: A retrospective search of the patient database of our institution was performed for a total of 122 patients who were admitted to our neurology clinic between January 2010 and June 2018. Acute ischemic stroke patients, comprising 48 PPI patients and 74 SDPI patients, were enrolled. Routine etiological investigations were performed for each patient, and clinical data were collected.
RESULTS: Of the 122 enrolled patients, the most frequent etiological cause of isolated pontine infarction was small vessel disease. There were 48 with PPI and 74 with SDPI patients. Hypertension was the most frequent chronic risk factor with the ratio of 68 %. But there was no significant difference in the prevalence of hypertension, diabetes, dislipidemia, coronary artery disease between patients with PPI and SDPI. In PPI group echocardiography was normal in all patients. In SDPI group 11 patients had abnormal cardioembolic findings and it was significantly important. Also male predominancy was detected in SDPI group and in males cardioembolic echocardiography findings were more prevalent than females.
DISCUSSION AND CONCLUSION: Cardioembolism may be the major cause of SDPI while basillar artery (BA) atherosclerosis remains the cause of PPI in our study. This information may assist in therapeutic approaches of isolated pontine infarction subtypes.
Keywords: Pons, infarct, etiology, pathogenesis, localisation, risk factors.

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PONS ENFARKTLARINDA ETYOPATOGENEZ LOKALİZASYONA GÖRE DEĞİŞİR; RETROSPEKTİF BİR KLİNİK ÇALIŞMA

ÖZ

GİRİŞ ve AMAÇ: İskemik inmelerin % 25'i arka dolaşım enfarktları olup, tüm iskemik inmelerin % 7'sini pons enfarktları oluşturur. İzole pons enfarktları paramedian pons enfarktları (PPI) ve küçük derin yerleşimli pons enfarktları (SDPI) olmak üzere sınıflandırılmakta ve etyopatogenez farklılık göstermektedir.
YÖNTEM ve GEREÇLER: Çalışmamızda Ocak 2010- Haziran 2018 tarihleri arasında nöroloji kliniğimize başvurmuş 122 pons enfarktı tanılı (48 PPI, 74 SDPI) hasta retrospektif olarak incelenmiştir. Hastalar enfarkt lokalizasyonlarına göre iki gruba ayrılmış, rutin inmeye yönelik etyolojik incelemeleri ve mevcut klinik dataları not edilmiştir.
BULGULAR: 122 hastada en sık gözlenen etyolojik neden küçük damar hastalığı olmuştur. 48 hasta PPI, 74 hasta SDPI olarak sınıflandırılmıştır. % 68 ile hipertansiyon en sık saptanan kronik risk faktörü olmuştur. Ancak her iki grup arasında hipertansiyon, diabet, dislipidemi ve koroner arter hastalığı açısından anlamlı farklılık bulunmamıştır. PPI grubunda tüm hastalarda ekokardiyografi bulguları normaldir. SDPI grubunda 11 hastada ekokardiyografide kardiyoemboli açısından patolojik bulgu tespit edilmiş olup istatistiki olarak anlamlı bulunmuştur. Ayrıca SDPI grubunda erkek cinsiyeti hakimiyeti saptanmış ve erkeklerde patolojik ekokardiyografi bulgularının daha sık olduğu dikkati çekmiştir.
TARTIŞMA ve SONUÇ: Küçük derin yerleşimli pons enfarktlarında kardiyoembolizm etyolojiden sorumlu major neden olabilirken, basiller arter aterosklerozu PPI larda esas neden olarak kalmıştır. Bu bilgi izole pons enfarktlarında tedavi yaklaşımında yol gösterici olabilir.
Anahtar Kelimeler: Pons, enfarkt, etyoloji, patogenez, lokalizasyon, risk faktörleri.

INTRODUCTION

Strokes represent a major cause of morbidity and mortality worldwide. Ischemic strokes comprise 80%–90% of all strokes. Of the ischemic strokes, 25 % involve the posterior circulation ischemic infarcts (POCI) and 7% of all ischemic strokes are pontine infarctions (1,2).

In general, basillary artery (BA) branch disease is the most common cause of stroke in patients with isolated pontine infarctions, with a ratio of 40 % (3,4). However, isolated pontine infarctions are usually classified into two types: paramedian pontine infarcts (PPIs) and small deep pontine infarcts (SDPIs), according to the lesion shapes and locations (Figure I, II). In PPI, the infarct is located on the basal surface of the pons. In SDPI, the infarct does not reach to the surface of the pons (5,6). It has been known that the pathogenesis of isolated pontine infarction differ according to the localisation. Fisher and Caplan investigated that the pathogenesis of SDPI involved perforating small arterial disease caused by lipohyalinosis, whereas PPI was caused by atheromatous branch occlusion of the basilar branch (7,8,9).

This study was designed to investigate the main causes of isolated pontine infarctions based on the above mentioned issues, to determine the chronic risk factors of the infarctions and to asist to improve therapeutic approaches predicting the etiological parameters.

METHODS

This study was undertaken in our neurology clinic, between January 2010 and June 2018, with the participation of 122 eligible patients diagnosed as isolated pontine infarction. Demographic characteristics, laboratory and imaging study results, risk factors, NIHSS (National Institutes of Health Stroke Scale) and mRS (Modified Rankin Score) scores at presentation, and discharged were recorded.

Patients over 18 years of age with an isolated pontine infarc¬tion who had a diffusion-weighted magnetic resonance imaging (DW-MRI) study within 3 days after presentation, in addition to imaging of the vascular tree using carotid and vertebral artery doppler ultrasonography, contrast-enhanced and /or Time-of-Flight MR Angiography (MRA) or computerized tomographic angiography (CTA), 12- lead electrocardiography (ECG) and transthoracic echocardiography (TTE), and when required, transesophageal echocardiography (TEE) and Holter monitoring, were included .

Patient characteristics were recorded including age, gender, presence of coronary artery disease, hypertension (HT, use of antihypertensive medications, a systolic and diastolic blood pressure of ≥140 and ≥90 mmHg, respectively), diabetes (use of antidiabetic agents, a fasting blood glucose measurement of ≥ 126 mg/dL, or ≥200 mg/dL and HbA1c ≥6.5 at presentation), or

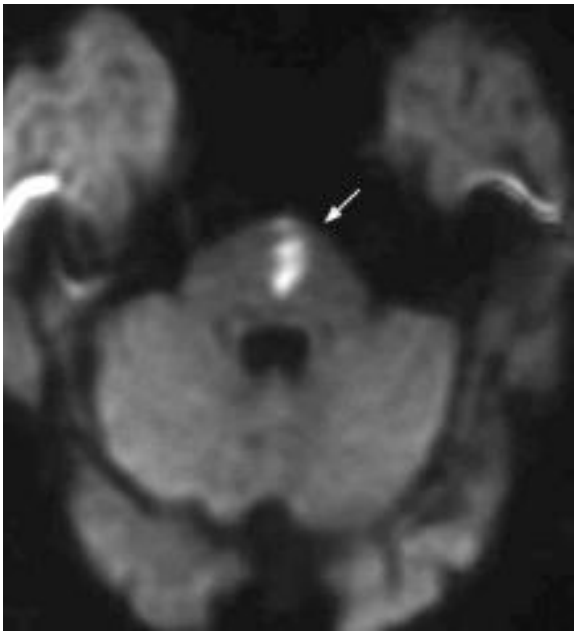

Figure I. Paramedian pontine infarction.

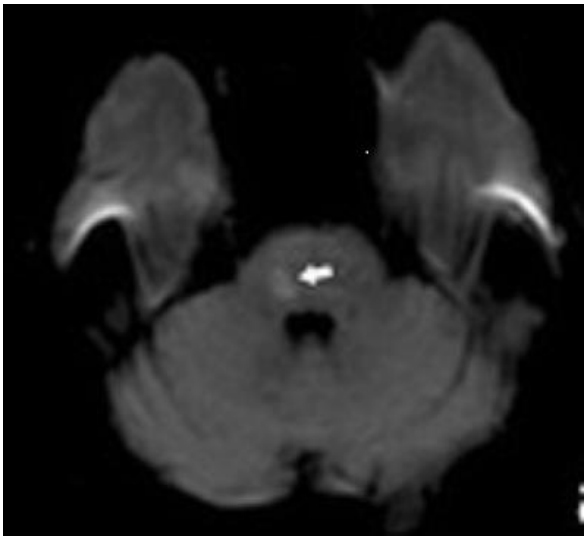

Figure II. Small deep pontine infarction.

hyperlipidemia (use of antihyperlipidemic agents, or an low density lipoprotein (LDL) ≥130 mg/dL at presentation).

Patients were defined as follows on the basis of trial of Org 10,172 in Acute Stroke Treatment (TOAST) classification system for the etiology of the stroke: large arterial atherothrombosis, cardioembolism, small vessel disease, ischemic stroke due to other rare causes, and strokes of unknown cause. Carotid and vertebral artery doppler ultrasonography, intracranial and extracranial CTA or MRA was performed in all patients in order to visualize the vessels. Patients with ≥ 50% narrowing in the vertebral and BA were considered as large arterial atherothrombosis after excluding cardioembolic etiologies.

A diagnosis of cardioembolic stroke was based on the presence of the following: atrial fibrillation (AF) in the ECG, paroxysmal AF in Holter monitoring, akinetic segments or thrombus formation in TTE/TEE, history of rheumatoid valvular disease or cardiac valvular prosthesis implantation, and patent foramen ovale as shown by TEE. Large arterial atherothrombosis was excluded by imaging of the vascular tree in these patients.

According to the DW-MRI, the type of isolated pontine infarction was classified as PPI or SDPI. In PPI, the infarct abuts the basal surface of the pons. In SDPI, the infarct does not reach the surface of the pons.

A diagnosis of small vessel disease was suspected in infarcts with a size of < 2 cm on DW-MRI and associated with clinical manifestations of lacuner syndromes.

NIHSS was used to assess the severity of stroke and was recorded at the time of admition to the emergency room. An NIHSS of <6 was considered as mild, and NIHSS of ≥6 was considered as severe stroke.

Dependency and functional improvements were assessed using mRS, where scores of 0, 1, and 2 were considered to indicate good prognosis, while scores of 3, 4, 5, and 6 were considered to signify poor prognosis.

This study was conducted in accordance with ethical principles and the study protocol was approved by the Ethics Committee of Bakırköy Prof. Dr. Mazhar Osman Training and Research Hospital (Number:150 Date: 06.03.2018). It was not considered necessary to get consent from the patients because the study was a retrospective data analysis.

Statistical Analysis: SPSS 16 for Windows statistical software pack was used for statistical analysis. All parameters were presented as mean ± SD. Data comparison was performed using the Fisher's exact chi-square test. The level of statistical significance was set at $P < 0.05$.

RESULTS

The data obtained from 122 patients with documented isolated pontine infarcts were examined. Of the overall population, 70 (58%) were males and 52 (42%) were females.

Chronic risk factors that could be associated with an underlying atherosclerotic process included HT in 83 (68%), diabetes in 62 (51%), hyperlipidemia in 45 (37%), coronary artery disease in 12 (10%) patients (Table I).

Small vessel disease, large arterial atherothrombosis, cardioembolism, and other rare causes of the stroke were determined in 51 (42%), 29 (24%), 17 (14%), and 7 (6%) of the patients, respectively. A total of 18 patients (15%) were classified as having a stroke of unknown cause despite a comprehensive assessment. (Table II). In the group with stroke due to other rare causes, there were 2 cases with vertebral artery (VA) dissection, 3 cases with vasculitis, and 2 patients with factor deficiency.

Seven patients (0.5%) were found to have AF in ECG, while 1 had paroxysmal atrial fibrillation in Holter monitoring, and 17 (14%) individuals were found to have a cardioembolic etiology in TTE/TEE.

In 84 of the patients (69%) the mRS score at presentation was ≥3, and it was ≤2 in the remaining 38 patients (31%). At discharge the number of patients with a mRS score of ≥3 and ≤2 was 64 (53%) and 49 (47%), respectively as shown in Table I.

NIHSS was used to assess the severity of stroke. The neurological examination score was ≤5 and ≥6 in 64 (52%) and 58 (48%) respectively, of the patients at presentation. And it was ≤5 and ≥6 in 79 (72%) and 34 (28%) respectively at discharge (Table I).

Of the 122 enrolled patients, there were 48 with PPI and 74 with SDPI. Among the PPI patients, 27 of them were lacunes, 11 of them were large vessel disease. Among the SDPI patients; 24 of them were lacunes, 18 of them were large vessel disease, 14 of them were cardioembolic, 12 of them were criptogenic. In SDPI group cardioembolic and criptogenic etiologies were significantly predominant (p=0.05). In PPI group echocardiography was normal in all patients. In SDPI group 11 patients had abnormal cardioembolic findings and it was significantly important (p=0.008). Also, male predominancy was detected in SDPI group (p=0.005) and in males cardioembolic echocardiography findings were more prevalent than females (p=0.002).

Table I. Characteristics, risk factors and dependence scores of the patients.

	All patients (n=122)	PPI (n=48)	SDIP (n=74)	P value
Age,	69,9±12,4	69,2±12,7	70,3±12,3	
Male sex	64	19	45	0.008
Hypertension	83	32	51	0.844
Diabetes	62	26	36	0.582
Hyperlipidemia	45	18	27	1.000
Coronary artery disease	12	2	10	0.123
Atrial fibrillation	8	3	5	1.00
NIHSS (severe) at attendance	82	35	47	0.675
NIHSS (severe) at discharge	57	23	34	1.00
mRs (independent) at attendance	64	28	36	0.841
mRs (dependent) at attendance	34	17	17	0.30

PPI: pontine paramedian infarcts, SDIP: small deep pontine infarcts, NIHSS: national institute of health stroke scale, mRs: modified rankin scale.

Table II. The etiologies of pontine infarctions.

	All patients (n=122)	PPI (n=48)	SDPI (n=74)	P value
Large vessel disease	29 (23 %)	11 (23 %)	18 (24 %)	> 0.05
Small vessel disease	51 (42 %)	27 (56 %)	24 (32 %)	> 0.05
Cardioembolic	17 (15 %)	3 (6 %)	14 (19%)	0.008
Rare causes	7 (5 %)	1 (2 %)	6 (8 %)	>0.05
Criptogenic	18 (15 %)	6 (12 %)	12 (16 %)	0.05

DISCUSSION AND CONCLUSION

Ischemic vertebrobasilar strokes comprise nearly 23% of all ischemic strokes of the brain, and brainstem infarcts are responsible for 11% of all ischemic strokes. Of the ischemic vertebrobasilar infarcts, 27 % occur in pons (10,11).

In a 2014 study by Lin et al, of the 199 patients with brainstem infarcts, 170 (85.4%) were found to have pons infarcts (12).

The majority of pathology leading to pontine infarction is BA atherothrombosis or perforator disease. Branch occlusion associated with BA stenosis is an important stroke mechanism of pontine base infarction. Even in patients without MRA, small plaques that obliterate the orifice of

perforating branches are seen occasionally if high resolution vessel wall MRI is used. Pontine infarcts limited to the tegmentum are mostly caused by small vessel disease and are seldom associated with BA stenosis. Embolism (from heart or proximal artery (e.g VA) is usually associated with infarcts in other parts of the brain, and is an uncommon cause of isolated pontine infarction. (13).

In our study, the most frequent etiological cause was small vessel disease, followed by large arterial atherothrombosis, cardioembolism, and undetermined causes while, other rare causes played a less significant etiological role. As like our study results, Lin et al found small vessel occlusion the most common cause of brainstem infarcts in his study involving 199 patients (38.7%), followed by large artery atherothrombosis, undetermined causes, and cardioembolism in 74 (37.2), 25 (12.6%), and 23 (11.6%) of the individuals respectively (12).

The main pathogenesis of each of the two types of isolated pontine infarction (PPI and SDPI) differs. So previous studies have investigated the main causes of PPI and SDPI, but their conclusions were conflicting. For several authors the main pathogenesis of each of the two types of isolated pontine infarction is suggested that the pathogenic mechanism of SDPI involves perforating small arterial disease caused by lipohyalinosis, whereas PPI was caused by atherosclerosis (7,8,9).

Marie and Fischer noted that SDPIs are frequently associated with abnormal thickening of the penetrating arteries, meaning lipohyalinosis. However with the development of neuroimaging technics, large vessel disease or cardiac thrombus have been identified as rare causes of SDPI (14,15).

In our study, small vessel disease was found to be the most underlying cause of isolated pontine infarction. But, cardioembolic and criptogenic strokes were the main pathogenetic mechanism underlying SDPI's and this result was statistically important. In our study pathologic echocardiography findings suggesting a cardioembolic etiology were more prevalent in the SDPI group, which supports that the main etiology of SDPI is probably cardioembolic. In our study group, in females no cardioembolic source were detected in echocardiography but19 % of males had cardioembolic findings and it was statistically significant. These results support that SDPI is mostly seen in males and the etiology is frequently cardioembolic.

MRA of 78% of PPI patients were atherosclerotic but this result was not statistically significant. But we consider that atherosclerotic etiology is more common in this group and PPI is mostly caused by BA atherosclerosis. In Klein et al.'s study, High-Resolution (HR) MRI detected BA atherosclerosis in 42 % of patients with pontine infarction despite to their normal BA MRA. Among patients with PPI, HR MRI detected a plaque in 61.5 % of patients, whereas only 35 % had BA lumen narrowing on MRA (6). If HR MRI could be used in the study, maybe the ratio of atherosclerosis would be higher and statistically significant.

The most common risk factors in previous series of small vessel pontine infarcts are hypertension, diabetes, and dislipidemia, respectively. There are no consistent differences between the risk factor profiles for PPI and SDPI in the current literature (16). Our study results were also similar with literature. Hypertension was the most frequent chronic risk factor with the ratio of 68 %. We found no significant difference in the prevalence of hypertension, diabetes, dislipidemia, coronary artery disease between patients with PPI and SDPI.

In Xia's study, neurological deficits in the PPI group were more severe than those in SDPI group. They explained this result by the difference of their sample sizes. PPI patients were more hospitalized than SDPI patients in the same period because of their more severe deficits (17). But, according to the NIHSS and mRs scores neurological deficits between PPI and SDPI group didnt differ in our study.

As a conclusion, our study suggests that the most frequent etiological cause of isolated pontine infarcts was small vessel disease. The main causes of PPI and SDPI also differed; cardioembolic and criptogenic strokes were the main pathogenetic mechanism underlying SDPI's and it was mostly seen in males.

Identification of infarct localization as well as known risk factors may assist in therapeutic approaches. So we believe our study results will be crucial for early therapy decisions and appropriate secondary prevention strategies especially for patients with unidentified etiopathogenesis.

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Ethics

Ethics Committee Approval: The study was approved by the Bakırköy Prof. Dr. Mazhar Osman Training and Research Hospital Ethical Committee (Number:150 Date: 06.03.2018).

Informed Consent: It was not considered necessary to get consent from the patients because the study was a retrospective data analysis.

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