Articles

Ischemic stroke in the vertebrobasilar system

Risk factors, etiology, and localization

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ABSTRACT

Objectives: To investigate and determine the clinical findings, lesions, risk factors, and variety of etiology in Turkish patients suffering from vertebrobasilar ischemia.

Methods: The clinical, radiological, and prognostic features of patients with ischemic stroke in the vertebrobasilar system (VBS) are not homogeneous. The mechanism, localization, and severity of the vascular lesions and the presence of coexisting vascular risk factors influence the prognosis. The study included 134 patients with ischemic strokes in the VBS that were evaluated according to age, gender, clinical findings, risk factors, lesion localization, echocardiography, Doppler sonography, and cervical magnetic resonance angiography at Haydarpaşa Numune Education and Research Hospital, Istanbul, Turkey between 1998-2002.

Results: Hypertension, heart disease, smoking, diabetes mellitus, and hyperlipidemia were the most commonly observed risk factors. While infratentorial involvement was seen at a higher ratio (75.4%), acute multi-infarcts appearing simultaneously were mostly localized in the thalamus and the brain stem (18.7%). Large and small vessel disease incidences have been found in 32.8% and 20.1% of the patients. Cardioembolism with an incidence rate of 41.8% was the most frequent etiological cause in VBS ischemia. No significant meaning has been developed with age and gender as compared to the relationship between localization and etiological subgroups.

Conclusion: The most common risk factors were hypertension and cardiac diseases, and the most common localization of the infarcts was the infratentorial region. The cerebellum was seen as the most coexisting localization with all multiple infarcts. Cardioembolism accounted for the largest etiological group in all localizations and in multiple infarcts.

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Atherosclerotic stenosis of the major intracranial arteries is an important cause of ischemic stroke. Specific neurological deficits may occur due to the localization of infarct induced by ischemia in the carotid or vertebrobasilar circulation. When compared with the carotid system, the vertebrobasilar system (VBS) displays different progress and it undergoes countless variations during fetal development. Congenital variations in the configuration and the size of the cranial arteries may predispose to ischemic stroke.[1] The mechanism and clinical features of patients with vertebrobasilar ischemia are not homogeneous.[2] While most of the patients suffer from severe disability or may die, some of the patients may experience only transient or minor disabilities. The prognosis may vary according to multiple factors. The nature, localization, and severity of the vascular lesions, the presence of coexisting vascular lesions,

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and the congenital constitution of the individual vascular bed are the contributing factors that influence the prognosis.[3] In previous studies, the incidence of vertebral artery (VA), basilar artery (BA) or posterior cerebral arterial stenosis was reported between 2.5-5.5%.[4] In this study, we aimed to investigate and determine the clinical findings, the lesions, the risk factors, and the variety of etiology in Turkish patients suffering from ischemic stroke in the VBS.

Methods. This hospital-based study included 134 patients with ischemic stroke in the VBS who were hospitalized in the Neurology Clinic and followed-up in the stroke outpatient clinic of Haydarpaşa Numune Education and Research Hospital, Istanbul, Turkey, between 1998-2002. Permission was obtained from the local ethical committee of the hospital. All patients were assessed with a standard protocol of investigation; patient history, physical and neurological examinations, routine biochemical and hematological tests, complete blood cell count and urinalysis, B-mode Doppler sonography of the carotid and vertebral arteries, ECG, cranial CT or cranial MRI, or cervical MRA. In selected cases, transthoracic or transesophageal echocardiography was also performed. Vertebrobasilar insufficiency was accepted when the total blood volume of right and left vertebral arteries was under 200 ml/min in B mode Doppler sonography. Cranial MRI and cervical MRA were performed with a Siemens Magnetom 1.5-T imager, and readings were carried out by a neuroradiologist blind to the findings on the neurological evaluations: T1-weighted (repetition time [TR], 450-600 ms; echo time [TE], 12-20 ms), T2-weighted (TR, 2000-5500 ms; TE, 80-120 ms), proton density–weighted (TR, 2000-5500 ms; TE, 10-40 ms), diffusion-weighted (DWI) (B=1000 s/mm^2). The criteria for the diagnosis of acute multiple infarction on DWI included the following: 1. Focal bright high signal intensities; 2. A location or configuration not thought to represent the normal anisotropy of diffusion; and 3. A location or configuration not thought to represent a magnetic susceptibility artefact (namely, typically seen near the interfaces between the brain and air-filled paranasal sinuses).[5] The MRI examinations and MRA (3-dimensional time-of-flight technique sensitive to arterial flow) were performed within the first week of stroke. As it was classified by the "TASK FORCE" of the World Health Organization (WHO), the risk factors were evaluated according to hypertension (systolic blood pressure ≥150 mm Hg and diastolic blood pressure ≥90 mm Hg), diabetes mellitus (DM) (patients with fasting blood sugar ≥120 mg/dl), cardiac diseases, the medical history of transient ischemic attacks, hyperlipidemia (borderline for normal values were total cholesterol ≥200 mg/dl, HDL-C ≤35 mg/dl, LDL-C ≥130 mg/dl, and triglyceride 150 ≥mg/dl). The other factors that were examined included cigarette smoking, alcohol consumption elevated hematocrit, oral contraceptive use, peripheral artery disease, snoring, and family history. The etiological sub-groups were classified according to the TOAST (Trial of Org 10172 in Acute Stroke Treatment) system. The initial examinations of the patients were performed during the hospitalization, and the additional examinations were completed in the stroke outpatient clinics during the follow-up period and were then included within the relevant etiological groups. According to this classification, the patients were divided into 5 subgroups: large vessel disease, cardioembolism, small vessel disease (lacunar), other causes (including hematological diseases), and undetermined causes.[6] According to the results obtained from the cranial CT or MRI examinations, the infarct localization was grouped as supratentorial, infratentorial, and supratentorial plus infratentorial together. All of the data obtained were evaluated according to age, gender, clinical findings, risk factors, lesion localization, echocardiography, B-mode Doppler sonography, and cervical MRA.

Results. There were 51 female (38.1%), and 83 male patients (61.9%) included in the study. The median age was determined as 62.2 and the age group ranged between 28-87. The determined vascular risk factors included arterial hypertension in 84 patients (62.7%), DM in 35 patients (26.1%), hyperlipidemia in 34 patients (25.4%), cigarette smoking in 28 patients (20.9%), elevated hematocrit in 14 patients (10.4%), snoring in 11 patients (8.2%), family history of stroke in 9 patients (6.7%), alcohol consumption in 8 patients (6%), transient ischemic attacks in 6 patients (4.5%), peripheral artery disease in 2 patients (1.5%), and oral contraceptive use in 2 patients (1.5%). Furthermore, 60 patients were diagnosed with cardiac problems (44.8%): atrial fibrillation in 19 patients (31.7%), valvular heart disease in 15 patients (25%), ischemic heart disease in 10 patients (16.7%), heart failure in 9 patients (15%), and myocardial infarction in 7 patients (11.7%). The most common clinical symptoms and findings observed were cerebellar deficits in 65 patients (48.5%), hemiparesis in 63 patients (47%), and sensory deficits in 27 patients (20.1%). Impairment of consciousness was observed in 31 patients, of whom 10 were in a state of coma (7.5%). Of the patients hospitalized in coma, 7 patients were diagnosed with pontine infarct, and 3 patients were diagnosed with thalamic infarct. The prognosis was

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poor for 8 of the patients who were in coma, and for 3 patients who were in the state of somnolence, who eventually died. The most common eye movement disorders were visual field deficits in 17 patients, horizontal gaze paresis in 14 patients, anisocoria in 11 patients, and ptosis in 10 patients (3 as bilateral). The other ocular motor disorders included vertical gaze paresis in 5 patients, internuclear ophthalmoplegia (INO) in 5 patients, skew deviation in 2 patients, and the Fisher's one and a half syndrome in one patient. All of the patients had cranial imaging (CT in 46, MRI in 54, both in 34). The most common localization of the infarcts was infratentorial involvement. The distribution of the infarct localization included supratentorial involvement in 14 patients (10.4%), infratentorial involvement in 101 patients (75.4%), and combined supratentorial and infratentorial involvement in 19 patients (14.2%). Regarding the infarcts localized in the supratentorial involvement, 9 patients had infarcts in the unilateral occipital cortex, 4 patients had infarcts in the regions of bilateral occipital cortex, and one patient had an infarct in the thalamus. In respect to the infarcts localized in the infratentorial involvement, 47 patients had infarcts in the cerebellum; 37 patients in the brainstem; 7 patients had infarcts in the cerebellum and medulla oblongata; 6 patients had infarcts in the cerebellum and pons; the remaining 4 patients had infarcts in the regions of cerebellum, medulla oblongata and pons. For the infarcts localized in combined supratentorial and infratentorial involvement, 9 patients had infarcts in the thalamus and brain stem, 4 patients had infarcts in the thalamus and cerebellum, 5 patients had infarcts in the occipital cortex and cerebellum, and one patient had infarcts in the regions of occipital cortex, thalamus and cerebellum. When these localizations were investigated, it was seen that 43 patients (32%) had multiple infarcts, and diffusion MRI revealed simultaneously occurring acute infarcts in 25 (18.7%) patients. Acute infarcts were determined in the regions of thalamus and brain stem in 9 patients, the cerebellum and brain stem in 7 patients, the cerebellum and occipital cortex in 4 patients, the thalamus and cerebellum in 3 patients, bilateral occipital cortex in one patient, and the occipital cortex, thalamus and cerebellum in one patient. The most common localization of multiple infarcts was combined supratentorial and infratentorial involvement, and simultaneously occurring acute infarcts were most commonly seen in the thalamus and brain stem. The cerebellum was the most commonly affected region with single or multiple infarcts.

All the patients were examined by ECG. The diagnoses included atrial fibrillation in 19 patients, ischemic heart disease in 10 patients, right bundle blockage in 3 patients, left bundle blockage in 2 patients, and myocardial infarction in 7 patients. One hundred and thirteen patients had echocardiography, 101 patients had B-mode Doppler sonography of the carotid and vertebral arteries and 41 patients were investigated with cervical MRA. All the findings related to these procedures are shown in **Tables 1-3**. The most common stroke mechanism determined was cardioembolism with an incidence rate of 41.8% (56 patients). Large vessel disease was found in 44 patients (32.8%), and small vessel diseases in 27 patients (20.1%). Hematological problems were encountered in 4 patients (2.9%); elevated anticardiolipin antibodies in one, protein C and S deficiency in 2, and the presence of antinuclear antibody in one patient. Two patients died before the final etiological assessment, and the etiology in one patient could not be determined. Among patients with supratentorial infarct, cardioembolism was defined in 6 (42.9%), large vessel disease in 4 (28.6%), small vessel disease in 3 (21.4%), and hematological causes in one patient (7.1%). For the patients with infratentorial infarct, 39 (38.6%) had cardioembolism, 35 (34.7%) had large vessel disease, 21 (20.8%) had small vessel disease, and 3 (2.9%) had hematological causes. The etiology was undetermined in one patient (0.9%), and 2 (1.8%) patients died during the early period of stroke before the etiological investigation was completed. Among patients with both supratentorial and infratentorial infarcts, cardioembolism was determined in 11 patients (57.9%), large vessel disease in 5 patients (26.3%), and small vessel disease in 3 (15.8%) patients. Considering all localizations, the most common etiologic cause was cardioembolism. No significant meaning was developed according to age and gender between the localization and etiological subgroups.

Discussion. Various clinical findings occur in a different manner depending on the region of circulation of the artery subject to stenosis. The prognosis in VBS ischemic stroke is dependent on factors such as the primary site of the infarct, the stroke mechanism, the formation of thrombosis, the presence of collateral circulation, and the hemodynamic and hematological factors.[7] Embolism of cardiac origin is one of the common causes (19-41%) observed among ischemic stroke mechanisms in VBS.[2,8,9] The most frequent sites effected by emboli include the distal segments of the BA, superior cerebellar artery, posterior cerebral artery, intracranial parts of the VA, and posterior inferior cerebellar artery.[2] Cardioembolism is mostly induced

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Table 1 - Echocardiographic findings in the study group.

Echocardiography	Patient no.
Valvular heart disease	15
Mitral valve incompetence	5
Mitral stenosis	3
Mitral stenosis + tricuspid valve incompetence	2
Aortic stenosis	2
Aortic valve incompetence	2
Mitral stenosis + pulmonary hypertension	1
Left ventricular hypertrophy	14
Left ventricular diastolic dysfunction	11
Left ventricular systolic dysfunction	4
Undetermined	54
Total	**113**

Table 2 - Cervical magnetic resonance angiography findings in the study group.

Magnetic resonance angiography	Patient no.
Left vertebral artery occlusion	8
Left vertebral artery stenosis	7
Left vertebral artery hypoplasia	3
Right vertebral artery occlusion	4
Right vertebral artery stenosis	6
Right vertebral artery hypoplasia	5
Basilar artery stenosis	4
Basilar artery dolichoectasia	3
Basilar artery aneurysm	1
Total	**41**

Table 3 - Carotid-vertebral artery Doppler sonography findings in the study group.

Doppler sonography	Patient	
	n	(%)
Vertebrobasilar insufficiency	29	(28.7)
Right ICA stenosis	14	(13.9)
Left ICA stenosis	12	(11.9)
Bilateral ICA stenosis	11	(10.9)
Left VA stenosis	8	(7.9)
Right VA stenosis	7	(6.9)
Left CCA stenosis	4	(4)
Right VA hypoplasia	3	(3)
Left VA hypoplasia	2	(2)
Undetermined	11	(10.9)
Total	**101**	

ICA - internal carotid artery, VA - vertebral artery, CCA - common carotid artery

by atrial fibrillation, ischemic heart disease, atrial-septal aneurysm, left ventricular dysfunction, valvular heart diseases, and rheumatic heart diseases.[10,11] In our study, the etiological mechanism of cardioembolism, with an incidence rate of 41.8%, was the highest compared to other etiologies, and the most frequent causes of cardioembolism were determined to be atrial fibrillation (33.9%), valvular heart diseases (19.6%), and heart failure (16.1%).

In many studies, atherosclerotic large vessel disease was found as the most common etiology in VBS ischemia.[12-14] Occlusive large vessel disease mainly develops depending on the contributing factor of stenosis or occlusion in the VA, basilar artery, and posterior cerebral artery regions. Atherosclerosis is mainly characterized by plaque formation, bleeding, ulceration, and thrombosis in the arteries. It has been determined that the atherosclerotic lesions in VBS were much less ulcerative, and that the incidence of stroke associated with large vessel disease (43%) in the VBS was lower when compared to lesions in the carotid system.[3,15] However, small vessel diseases (lacunar) are the other common etiologies found in investigations, and the incidence rate of ischemic strokes induced by small vessel disease in VBS has been specified as 18%.[3] In our country, Kumral et al[16,17] observed a higher ratio of large vessel disease than cardioembolism and small vessel disease in their studies in Turkish patients with ischemic stroke in VBS. But in our study, when compared with these previous studies, the ratio of large vessel disease was 32.8%, and the ratio of small artery disease was 20.1%, which are lower than the ratio of cardioembolism (41.8%).

The configuration of the arteries and their variations in size was also considered as predisposition for VBS ischemic strokes. Some abnormalities, such as persistence of the trigeminal artery, can occasionally be associated with stroke in the vertebrobasilar territory.[18,19] It has been reported that BA hypoplasia is frequently seen with VA hypoplasia, and these can predispose to VBS ischemia.[1] Basilar artery dolichoectasia is a well-defined abnormality that is rarely encountered, and may be an independent risk factor for stroke. It has been considered that the developmental defect in the arterial wall is associated with the ectasis, and that this disorder is induced by arterial hypertension, and sometimes the atheromatous state contributes to the damage in the elastic components of the arteries.[14,19] Conversely, some traumatic or non-traumatic dissections may occur in the vertebrobasilar arterial system.[20] Dissection of the VA is an unusual pathology especially if there is not a direct trauma to the neck, and causes only 0.4-2.5%

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of all strokes. It has been increasingly identified as a cause of ischemic stroke in young patients with an incidence from 5-20%.[21-23] In a study with 41 Turkish patients with mesencephalic and associated infarcts, spontaneous VA dissection was determined in 2 young adults.[16] Although angiography is the most commonly used imaging modality for the diagnosis of the dissection, MRA and Doppler can also be used noninvasively for the diagnosis.[24,25] No VA dissection was observed in our study group, even though a detailed investigation had been performed. This could be due to 11 patients being under 45 years old in our study group.

The other causes of vertebrobasilar ischemic stroke include traumatic occlusion of the VA, fibromuscular dysplasia, atlantoaxial dislocation, traumas, temporal arteritis, migraine, and decreased levels of vitamin B12 and folate.[20,26,27] None were encountered in our study. Risk factors such as age, gender, race, family history, and genetic factors have been considered as non modifiable factors, while factors such as arterial hypertension, DM, heart diseases, transient ischemic attack, hyperlipidemia, cigarette smoking, and alcohol consumption have been considered as modifiable risk factors. The potential risk factors have been reported as insufficient physical activity, snoring, hemostatic factors, obesity, migraine, hyperuricemia, oral contraceptive use, hypothyroidism, and narcotics and drug abuse.[11,28,29] Considering the distribution of risk factors in our study group, we found that hypertension (62.9%), heart disease (41.8%), DM (26.1%), hyperlipidemia (25.4%), and cigarette smoking (20.9%) were determined as the most commonly observed risk factors.

Multiple infarcts can be observed in different localizations in cases of VBS strokes. Acute multiple ischemic lesions can be observed shortly after the onset of ischemic damage by diffusion MRI.[5] The ratio of multiple infarct development in the VBS system has been determined as 11%, and most of these cases have been observed in the regions of the thalamus, brain stem, parieto-occipital lobe and the cerebellum.[30] It has been reported that infarcts of the thalamus, with the other regions, are more frequently observed, and that simultaneous brainstem and posterior cerebral artery territory infarcts sparing the cerebellum are uncommon.[30,31] In our study, we observed multiple infarcts in 32.1% of the patients, and DWI revealed simultaneously occurring acute multiple infarcts, especially localized at the thalamus and brainstem in 18.7% of our cases, a higher ratio compared with the previous report.[30] In the multiple infarct etiology, cardioembolism is more commonly diagnosed,[5,32,33] and we also found cardioembolism with a ratio of 69.7% as the most common etiologic cause in patients with multiple infarcts.

In conclusion, we evaluated age, gender, etiology, risk factors, and infarct localizations in VBS ischemic strokes. We observed the most common risk factors were hypertension and cardiac diseases, and that the most common localization of the infarcts was the infratentorial region, mostly confined to the cerebellum. Multiple infarcts have been observed with supratentorial and infratentorial involvement together, and simultaneously occurring acute infarcts have been most commonly localized in the thalamus and brain stem. The cerebellum was seen as the most coexisting localization with all multiple infarcts. Cardioembolism accounted for the largest etiological group in all localizations and in multiple infarcts.

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