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ORIGINAL ARTICLE **ÖZGÜN ARAŞTIRMA**

PROGNOSTIC SIGNIFICANCE OF ATRAUMATIC CONVEXAL SUBARACHNOID HEMORRHAGE IN PATIENTS WITH CEREBRAL AMYLOID ANGIOPATHY

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ABSTRACT

INTRODUCTION: Cerebral amyloid angiopathy (SAA) is a cerebrovascular pathology that develops due to the accumulation of amyloid beta-peptide (Aβ) in the media and adventisia layer of small and large cerebral arteries. Ischemic or hemorrhagic stroke, dementia and encephalopathy can be seen. In our study, we aimed to investigate the frequency of convexal subarachnoid hemorrhage and its effect on prognosis.
METHODS: Twenty-four patients diagnosed with cerebral amyloid angiopathy who were examined and treated in the neurology clinic between 2016 and 2017, and who received gradient ECO and SWI MR imaging were included in our study. Patients with a history of trauma and recent surgery were excluded from the study. Demographic features, vascular risk factors, antithrombotic or anticoagulant use, neuroimaging findings, application NIHSS and mRS values after 3 months were recorded.
RESULTS: 24 patients were included in the study. Eleven (45.8%) were women. The average age was 72.5 ± 8.79. 17% of our patients had convex subarachnoid hemorrhage and 21% had lobar hemorrhage. In 42%, both lobar hemorrhage and convex subarachnoid hemorrhage were observed. There was no significant difference between the groups in terms of prognosis and mortality.
DISCUSSION AND CONCLUSION: In our study, it was concluded that convexal subarachnoid hemorrhage did not have a significant effect on prognosis and was not related to hypertension, diabetes, smoking and anticoagulant use.
Keywords: Cerebral amyloid angiopathy, subarachnoid hemorrhage, prognosis.

ATRAVMATİK KONVEKSİYEL SUBARAKNOİD KANAMANIN SEREBRAL AMİLOİD ANJİYOPATİ HASTALARINDA PROGNOSTİK ÖNEMİ

ÖZ

GİRİŞ ve AMAÇ: Serebral amilod anjiopati (SAA), küçük ve büyük serebral arterlerin media ve adventisia tabakasında amiloid beta-peptid (Aβ) birikimine bağlı gelişen serebrovasküler bir patolojidir. İskemik veya hemorajik inme, demans ve ensefalopati görülebilir. Çalışmamızda konveksal subaraknoid kanama sıklığını ve prognoz üzerine etkisini araştırmayı amaçladık.
YÖNTEM ve GEREÇLER: 2016-2017 yılları arasında nöroloji kliniğinde yatarak tetkik ve tedavi edilen, gradient EKO ve SWI MR görüntüleme yapılan olası serebral amiloid anjiopati tanılı 24 hasta çalışmamıza dahil edildi. Travma öyküsü olan, yakın zamanda cerrahi geçiren hastalar, çalışmadan çıkarıldı. Tüm hastaların demografik özellikleri, vasküler risk faktörleri, antitrombotik veya antikoagülan kullanımı, nörogörüntüleme bulguları, başvuru NIHSS ve 3 ay sonraki mRS değerleri kaydedildi.
BULGULAR: Çalışmaya 24 hasta alındı. On bir (%45,8) kadındı. Yaş ortalaması 72,5±8,79 idi. Hastalarımızın %17'sinde konveksal subaraknoid kanama, %21'inde lober hemoraji mevcuttu. %42'sinde ise hem lober hemoraji hem de konveksal subaraknoid kanama izlendi. Gruplar arasında prognoz ve mortalite açısından anlamlı fark izlenmedi.

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TARTIŞMA ve SONUÇ: Çalışmamızda konveksal subaraknoid kanamanın prognoz üzerinde belirgin etkisinin olmadığı ve hipertansiyon, diabet, sigara kullanımı, antiagregan, antikoagülan kullanımı ile ilişkisinin olmadığı sonucuna varıldı.
Anahtar Sözcükler: Serebral amiloid anjiopati, subaraknoid kanama, prognoz.

INTRODUCTION

Intracranial hemorrhage is related to primary causes in 80-85% of patients and secondary causes in 15-20% of patients. Of the primary intracerebral haemorrhages cases, 50% are associated with hypertension, while 30% are associated with cerebral amyloid angiopathy (1). Cerebral amylod angiopathy (CAA) is a cerebrovascular pathology characterized by deposition of amyloid beta-peptide (Aβ) in the media and adventisia layers of small-sized and medium-sized cerebral arteries.(2). It is observed that deposition of Aβ occurs mostly in the cortical and corticosubcortical areas. The temporal and occipital lobe are the regions that are affected to the greatest extent (3). CAA can be manifested by clinical signs such as dementia, ischemic stroke and encephalopathy (4). CAA is also the most common cause of lobar hemorrhages caused by spontaneous and anticoagulant therapy in the elderly population. (5).

CAA can also cause cerebral microbleeds observed on gradient ECHO and susceptibility weighted imaging (SWI) and Magnetic Resonance Imaging (MRI) sequences. The high number of cerebral microbleeds provides information about the poor prognosis of the disease. Ischemic white matter changes may also be observed in CAA. Hemorrhagic and ischemic changes are thought to be responsible for the loss of cognitive function in patients.

Recent studies have shown that CAA neuroimaging markers are highly associated with the recurrence of intracerebral hemorrhage. (4).

According to the modified Boston criteria, the definition of possible CAA is used if there is a large number of micro-bleeds in the brain that cannot be explained by any other underlying condition over 55 years of age, and the definition of probable CAA is used in the presence of a single bleeding. (6).

Atraumatic localized convexal subarachnoid hemorrhage (cSAH) is an unusual form of subarachnoid hemorrhage in which the bleeding is localized in the convexity of the brain without spreading to the parenchyma or interhemispheric fissures. The rate of non-aneurysmal SAH is only 15%. The rate of cSAH in this is much lower, as expected. Venous thrombosis, systemic lupus erythematosus, pregnancy, reversible cerebral vasoconstriction syndrome (RCVS), coagulopathy, cocaine use and cerebral amyloid angiopathy can cause cSAH (7).

In this study, we aimed to systematically evaluate the frequency of cSAH and its effect on disease prognosis in patients diagnosed with possible CAA according to the modified Boston criteria.

METHODS

Study Group: The approval for our study was obtained from the Ethics Assessment Committee of Eskisehir Osmangazi University Faculty of Medicine (Date: 21.05.2020, Number: 80558721-050.99-E.49071) for retrospective analysis of medical records and neuroimaging which constituted a part of the patients' routine clinical care. Due to the retrospective design of the study, informed consent form was not obtained from the patients. The study was conducted in accordance with ethical standards of the Helsinki Declaration. Between August 2016 and August 2017, the medical records of patients, who were examined and treated inpatiently at Eskisehir Osmangazi University Faculty of Medicine, Neurology Clinic, were retrospectively screened, and all patients diagnosed with possible CAA according to the Boston criteria were included in the study. Hereditary cerebral amyloid angiopathy patients were excluded from the study. Patients with a history of trauma and recent surgery were excluded from the study. Demographic and clinical data such as age, gender, vascular risk factors, antithrombotic or anticoagulant use, presence of symptomatic cSAH or intracerebral hemorrhage, history of ischemic stroke, hematoma volume, NIHSS at admission and mRS values after 3 months were recorded. The patients were divided into two groups as with and without subarachnoid hemorrhage. The groups were compared.

Neuroimaging: Brain CT images of all patients at hospital admission were evaluated. Fluid-attenuated inversion recovery (FLAIR), diffusion-

weighted imaging (DWI) and gradient ECHO, T2-weighted MRI sequences (slice thickness 5 mm) were used for detection of previous-new bleedings or cortical vein thrombosis. MRI was performed on sixteen patients (80%) within 72 hours of the onset of symptoms. A single expert (CE) blinded to clinical data, evaluated the location and severity of cSAH, superficial siderosis, old intraparenchymal bleeding (5 mm) or micro bleeding (MB), and multiple bleeding or MBs were considered as possible CAA according to the modified Boston criteria. The presence and number of focal DWI MRI abnormalities, previous infarcts / lacunes (10 mm) and other morphological abnormalities were recorded. The hematoma volumes of the patients included in the study were calculated by the ABC / 2 method. (8). In particular, a representative section was chosen in the center of the hematoma. The maximum linear length (A), maximum width (B) and maximum depth (C) were measured in cm. The depth (C) was determined by multiplying the number of slices on which the hematoma could be visualized, and by the slice thickness listed on the CT scan. The final result was divided by 2 to get the volume in cm3 (8).

Statistical Analysis: The study data were evaluated with the statistical package for the social sciences for windows (SPSS) version 20. The student's t and chi square tests were used to compare parametric and nonparametric data. Measurement values were expressed as mean ± standard deviation. A p value of <0.05 was considered statistically significant.

RESULTS

The study was conducted on 24 patients who were diagnosed with possible CAA according to the modified Boston criteria, and eleven (45.8%) of the patients were female. The mean age was 72.5 ± 8.79 years. The demographic characteristics and medical history of the patients are shown in Table I. cSAH was observed in 15 patients.

The time from onset of clinical symptoms to CT ranged from 2 hours to 10 days (mean 29-56 hours), and was 96 hours in 22 patients (92%). Of the 24 patients, 20 underwent 1.5 Tesla brain MRI. The time from the onset of symptoms to door ranged from 6 hours to 16 days (mean 76-100 hours). Nine (40.9%) of the CAA patients also had lobar hemorrhage (p=0.41). Lobar hemorrhage was observed in 58.5% of all patients. Five patients with lobar hemorrhage had a history of antiplatelet use and four patients had a history of anticoagulant use. Six patients had bleeding with ventricular passage. Small vessel disease was observed in 92.9% of the patients with subarachnoid hemorrhage and in 8.6% of the patients with lobar hemorrhage. Seven patients who were on antiplatelet and three patients who were on anticoagulants had SAH.

Of the patients, 41.7% had a previous history of intracranial hemorrhage. Nine patients had a history of ischemic stroke. Fifteen (62.5%) patients had a history of hypertension, 7 had a history of diabetes mellitus, and 8 (34.8%) had a history of dyslipidemia. Coronary artery disease was present in 25% of the patients and 16.7% of the patients were smoker. Disease severity and clinical outcome characteristics according to hemorrhage localizations are shown in Table II.

Table I. Demographics and medical history of patients diagnosed with possible CAA based on Modified Boston Criteria

Variable- Clinical results	Number-(%)
Patient Characteristics	
Total Patient	24 (100)
Age	72,5±8,8 (60-93)
Woman	11 (46)
Medical History	
Hypertention	15 (63)
Diabetes Mellitus	7 (29)
Coronary Artery Disease	6 (25)
Small Vessel Disease	21 (91)
Dyslipidemia	8 (35)
Smoking	4 (17)
Atrial Fibrillation	5 (21)
Antiplatelet Usage	12 (50)
Anticoagulant Usage	5 (21)
Previous Ischemic Stroke	9 (38)
Previous Hemorrhagic Stroke	10 (42)

Table II. Disease severity, clinical result characteristics based on hemorrhagic localisation.

Variable- Clinical results	cSAH	Lobar Hemorr	cSAH+Lobar Hemorr
	N-(%)	N-(%)	N-(%)
Number *	4 (17)	5 (21)	10 (42)
Age	81±9	73±5	72±10
Woman	2 (50)	2(40)	5(50)
Ventricular Passage	2 (50)**	1(20)	3(21)
Hematoma Volume	34±27	51±44	30±37
NIHSS at Admission	10±8	15±9	7±6
mRS after 3 months	4±2	4±2	3±2
mRS after 9 months	4±3	2±2	2±2
Control Imaging duration***	16±4	15±8	18±10
Rebleeding at control	0	0	3(33)

*Percentage into total number (24) in the study. **Thalamic hematoma was observed in 3 of cSAH (4) patients without lobar hematoma, and 2 of them were found to ventricular passage. *** It was shown how many months later control imaging was performed.

DISCUSSION AND CONCLUSION

Previous studies have shown that the incidence of cSAH increases with cerebral amyloid angiopathy after the age of 60 years. (7). In our study, the median age was 73 years in the patients with SAH and 68 years in those without SAH. This result can be explained in two ways. The first one is the cumulative increase of amyloid-beta (Ab) peptide deposition in the walls of leptomeningeal arteries, arterioles and venules, and an increase in tendency to all bleedings including cSAH by a way of disruption in vascular structure, which are involved in the etiology of CAA (Figure I) (3). The second one is the fact that cSAH causes thunderclap headache with a higher rate in young people, but admission to hospital occurs with a higher rate in the population aged above 60 years, as it causes focal neurological symptoms as shown in previous studies (7,9).

In patients with cerebral amyloid angiopathy presenting with intracerebral hemorrhage, recurrent bleeding may occur at a rate of 9-16% annually (10). Ten of 24 patients in our study had a history of intracerebral hemorrhage. In our mean follow-up period of 15 ± 9.7 months, we detected recurrent hemorrhage in 3 patients. All of these were cSAH and the patients presented with a complaint of paresthesia. It was found that they showed an association of lobar hematoma and cSAH at previous presentations. Their symptoms were observed to be temporary. Although the cause of temporary symptom association with cSAH, which has been mentioned in many studies, has not been clearly revealed, it has been shown that blood accumulation in the subarachnoid space causes speading cortical depression until it is resorbed, but this is not supported by any electroencephalographic data (Figure II). This reminds the mechanism similar to migraine aura and is called aura-like symptom (7,11).

In our study, we did not find a significant relationship between previous ischemic stroke and cSAH or lobar hemorrhage. Although the relationship of cSAH with ischemic stroke has been previously demonstrated, the mechanisms underlying this relationship remain uncertain. (9).

When the patients with cSAH, lobar hemorrhage, and cSAH - lobar hemorrhage were evaluated in the form of groups, we did not find a significant difference between the rates of opening of hemorrhage into the ventricle, bleeding volume, mRS values after three months and nine months, and The National Institutes of Health Stroke Scale (NIHSS) scores. This showed that the clinical prognosis was not different from the others in CAA cases with cSAH, although it was previously determined that CAA was included in the etiology of cSAH.

As limitations, our study had a retrospective design. Our sample group consisted of a small number of patients.

According to the modified Boston criteria, neuropathological diagnosis is also required for the definitive diagnosis of CAA. However, the patients in our study did not undergo a brain biopsy. Possible CAA patients were included in the study. It will be more beneficial to conduct further studies in groups with a definite diagnosis according to the Boston criteria.

As conclusion, it is known that cerebral microbleeds are a significant marker and a poor prognostic factor in determining disease severity. In our study, cSAH did not have such a prognostic value and was not found to be etiologically associated with vascular risk factors such as hypertension, diabetes, coronary artery disease, dyslipidemia and smoking. However, new clinical trials should be conducted in order to elucidate the etiology with large-group, prospective, randomized studies.

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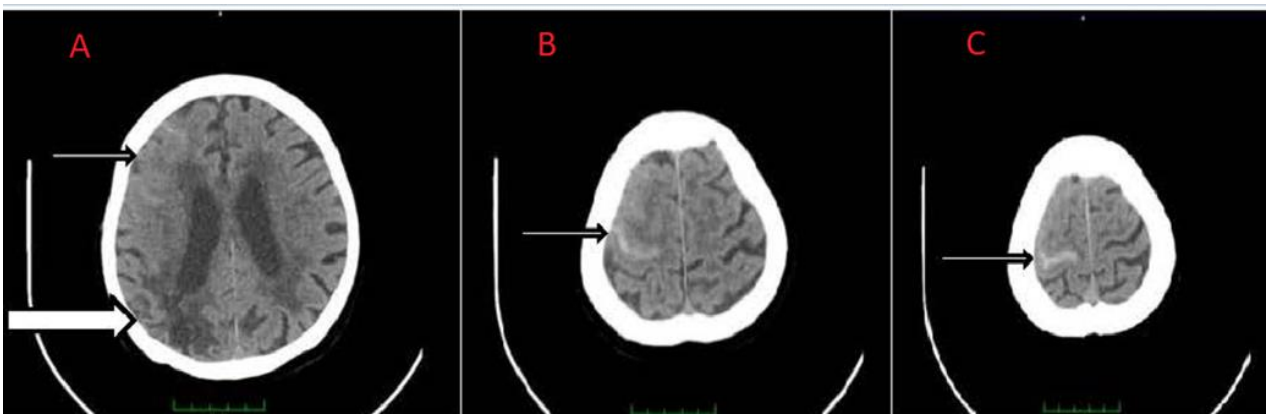

Figure I. A 89-year-old female patient admitted to the emergency room for focal motor seizure. A. Encephalomalasic area (thick arrow) due to hemorrhage on unenhanced brain CT, B and C convex subarachnoid hemorrhage (thin arrows).

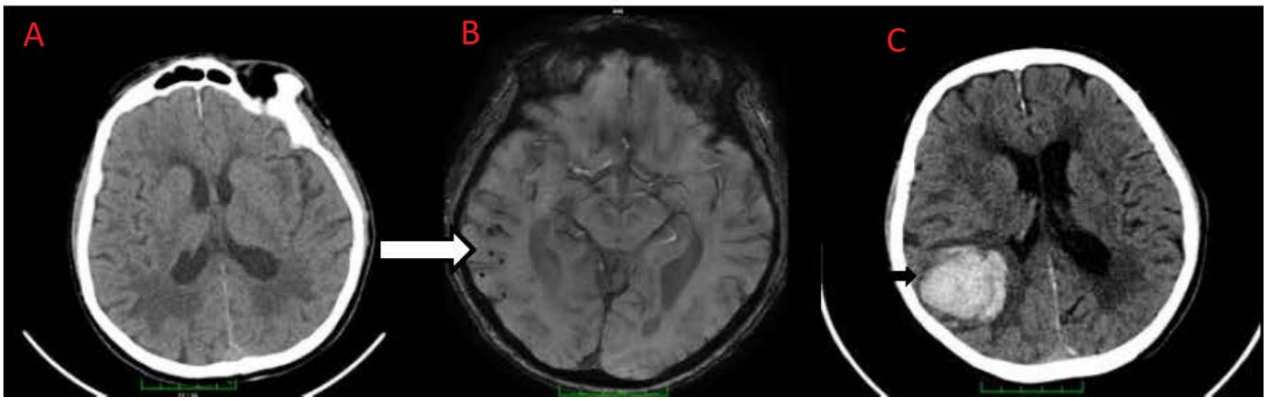

Figure II. A 72-year-old male patient who presented with headache and left hemihypoesthesia. A. Periventricular diffuse ischemic changes on brain CT, B. The MRI of the same patient obtained 5 months later because of left hemiplegia that developed while receiving warfarin for deep vein thrombosis. Microhemorrhages are visualized in the SWI sequence, C. Lobar hemorrhage on brain CT (thin arrow).

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Ethics

Ethics Committee Approval: The study was approved by the Eskisehir Osmangazi University Faculty of Medicine Noninterventional Clinical Studies Ethics Committee (Date: 21.05.2020, Number: 80558721-050.99-E.49071).

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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