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CASE REPORT **OLGU SUNUMU**

FATAL CEREBELLAR HEMORRHAGE IN A PATIENT WITH CARASIL

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ABSTRACT

Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL) is a monogenic, hereditary cerebral small vessel disease characterized by leukoencephalopathy and lacunar infarctions. The clinical manifestations are lacunar stroke, stepwise and / or progressive neurological deterioration, vascular dementia, spondylosis and premature alopecia. Intracerebral hemorrhage has been reported in only a few patients to date. We report a patient with CARASIL and fatal cerebellar hemorrhage and discuss the safety and efficacy of antiplatelets in patients with hereditary cerebral small vessel disease.
Keywords: Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy, CARASIL, hemorrhage, antiplatelet.

BİR CARASIL HASTASINDA FATAL SEREBELLAR HEMORAJİ

ÖZ

Subkortikal infarktlar ve lökoensefalopatiyle birlikte serebral otozomal resesif arteriopati (CARASIL), lökoensefalopati ve laküner infarktlarla karakterize monogenik herediter bir serebral küçük damar hastalığıdır. Klinik manifestasyonlar laküner inme, basamaklı ve / veya progresif nörolojik bozulma, vasküler demans, spondilozis ve prematür alopesidir. İntraserebral hemoraji bugüne dek birkaç hastada bildirilmiştir. Fatal serebellar hemorajisi olan bir CARASIL hastasını sunuyor ve herediter serebral küçük damar hastalığı olan kişilerde antiplateletlerin etkinlik ve güvenliğini tartışıyoruz.
Anahtar Sözcükler: Subkortikal infarktlar ve lökoensefalopatiyle birlikte serebral otozomal resesif arteriopati, CARASIL, hemoraji, antiplatelet.

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INTRODUCTION

Cerebral small vessel disease (CSVD) has enormous impact on brain health, causing not only lacunar infarctions but also white matter and cortical lesions, cerebral micro- and macro-hemorrhages (1). Although majority of patients with CSVD are sporadic, there are certain monogenic hereditary forms including CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy), CARASIL (cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy), collagen type IV mutations and others (2).

CARASIL is a rare monogenic CSVD caused by biallelic mutations in high-temperature requirement A serine peptidase 1 (HTRA1) gene located on 10q25 (3). The disease is characterized by early adult onset CSVD, alopecia and spondylosis (4,5).

To the best of our knowledge, intracerebral hemorrhage (ICH) has been reported in only a few patients with CARASIL to date (6). In this paper, we report a patient with CARASIL and ICH and discuss the safety of antiplatelet medications in patients with hereditary CSVD.

CASE REPORT

The first admission of the patient to our clinic was twelve years ago. At that time, the patient was twenty-nine-year-old and admitted to our clinic with the complaints of low back and neck pain, slowly progressive walking disturbance over two years and sudden onset weakness on the right side. She had undergone surgery for lumbar degenerative disease two years previously. The patient's medical history was otherwise unremarkable. Her parents were consanguineous, ie. first-cousins. She denied any relative with similar complaints. The patient had alopecia. Neurological examination revealed cognitive impairment, dysarthria, tetraparesis (Medical research Council grade was 3/5 on the right side and 4/5 on the left side), increased deep tendon reflexes, hemi-hypoalgesia on the right side and bilateral extensor plantar responses.

Brain magnetic resonance imaging (MRI) showed diffuse, symmetrical hyperintense signal changes in the subcortical and the periventricular white matter, external capsules, anterior temporal lobes and the pons on T2-weighted and fluid-attenuated inversion recovery (FLAIR) images (Figure 1A, B and C).

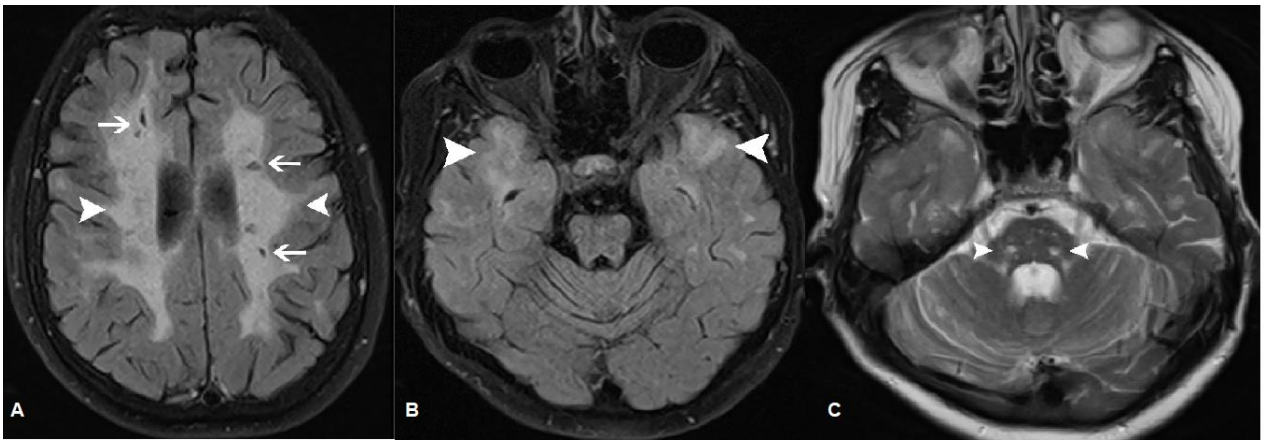

Figure 1A and B. Brain MRI. Axial FLAIR images show symmetrical confluent hyperintense signal changes in the periventricular and the subcortical white matter and the anterior temporal lobes (arrowheads). Note that the U-fibers are spared. **A.** Lacunar infarctions (arrows). **C.** Axial T2-weighted image shows lacunar infarctions in the brainstem (arrowheads).

The U fibers were spared (Figure 1A). There were lacunar infarctions in the subcortical white matter (Figure 1A). Diffusion-weighted imaging (DWI) revealed two discrete area of cytotoxic edema indicating acute lacunar infarctions in the right internal capsule and the left periventricular area (Figure 2A and B).

Cerebral microhemorrhages were not evident at this time. There were degenerative spondylosis and fixation materials in the lumbar vertebrae on MRI (Figure 3).

The patient's clinical manifestations including alopecia, spondylosis, acute-onset focal neurological deficits and slowly progressive

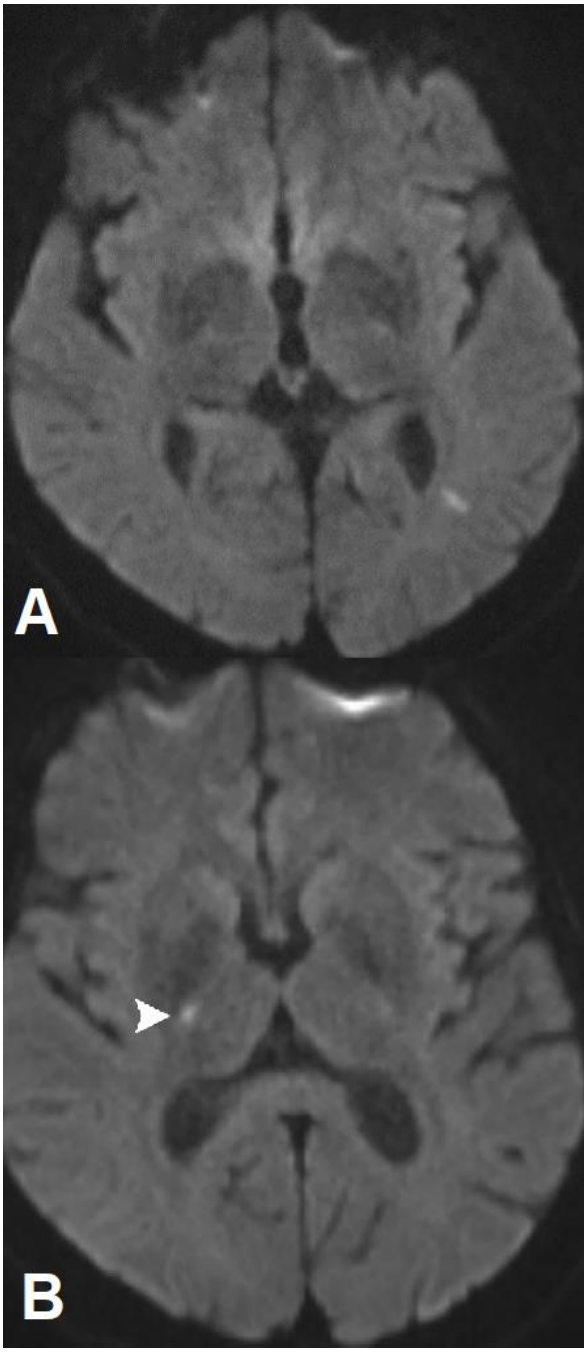

Figure 2A and B. Brain MRI. DWI images show diffusion restriction indicating lacunar infarctions in the left periventricular white matter and the right internal capsule (arrowheads).

neurological deterioration, and imaging findings indicating CSVD suggested the diagnosis of CARASIL, and a genetic test was performed, yielding a homozygous non-sense C to T transition at position 1108 (c.1108C>T) in exon 6 in the HTRA1 gene. Her parents as well as two brothers had heterozygous mutation. The patient has been reported previously (7). Because the patient had had lacunar stroke, she was given antiplatelet medication.

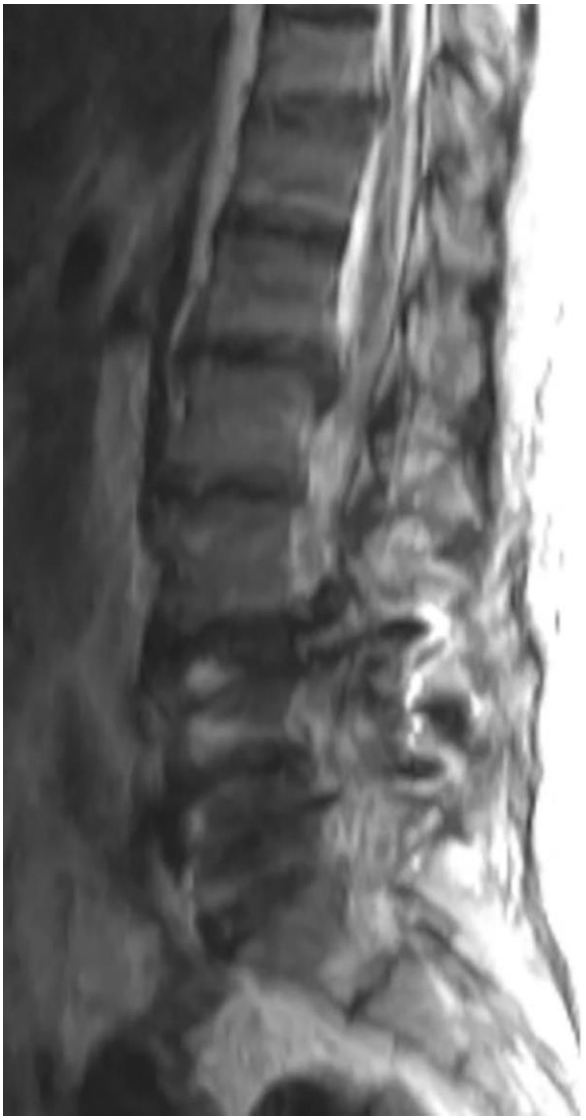

Figure 3. Spinal MRI. Sagittal T2-weighted image shows spondylosis and fixation materials.

In the following years, the patient's clinical condition worsened, and she developed severe cognitive disturbance, pseudobulbar palsy, spastic tetraparesis of the extremities, sphincter dysfunction, and she became bed ridden. Also, leukoencephalopathy and lacunar infarctions advanced (Figure 4A-D). Cerebral microhemorrhages became evident (Figure 5A and B).

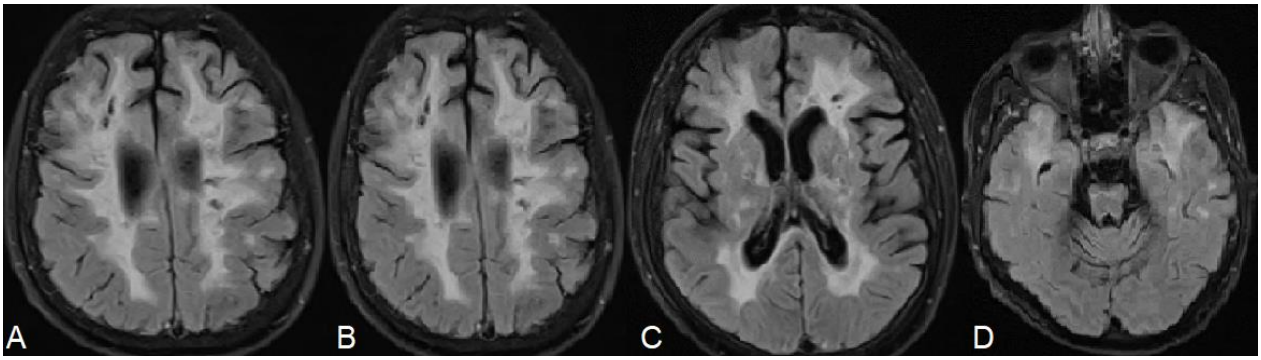

Figure 4A-D. Brain MRI. Axial FLAIR images show advanced leukoencephalopathy and lacunar infarctions in the periventricular and the subcortical white matter and in the anterior temporal lobes, and brainstem atrophy.

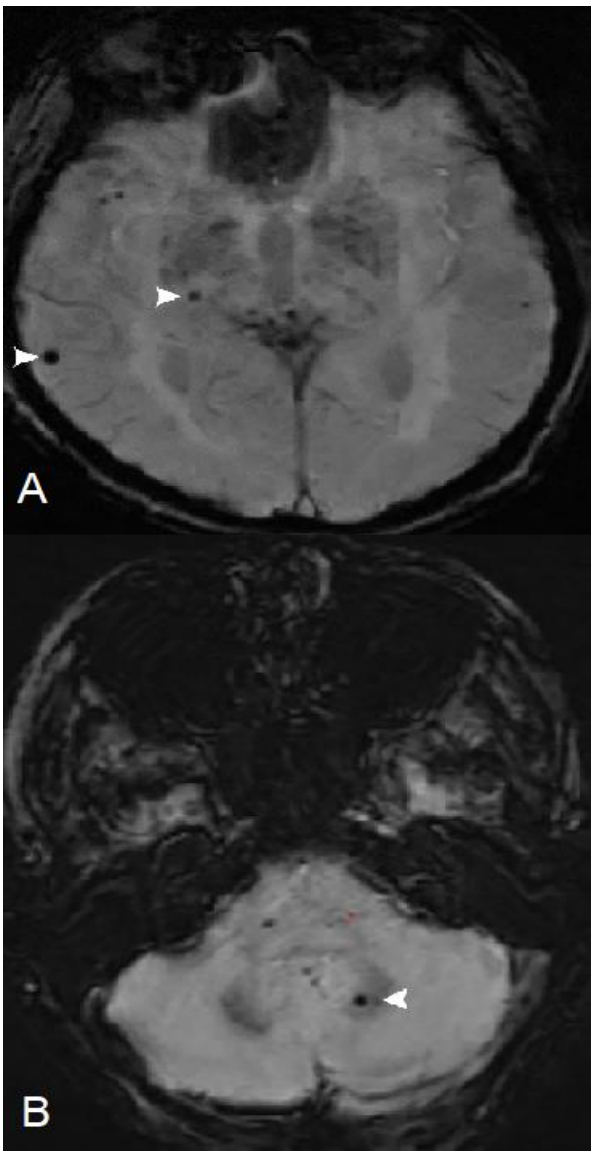

Figure 5A and B. Axial SWI images show cortical, deep and cerebellar microhemorrhages (arrowheads).

At age 41, the patient was admitted to the emergency department because of sudden onset of consciousness loss. Her Glasgow Coma Scale score was 4 (E1M2V1). Brain computed tomography revealed a large cerebellar hemorrhage (Figure 6). She was treated with mannitol, furosemide, barbiturates, hyperventilation and external ventricular drainage for hydrocephalus. The patient passed away 3 days later. Of note, signed consent was obtained from the patient for this case report.

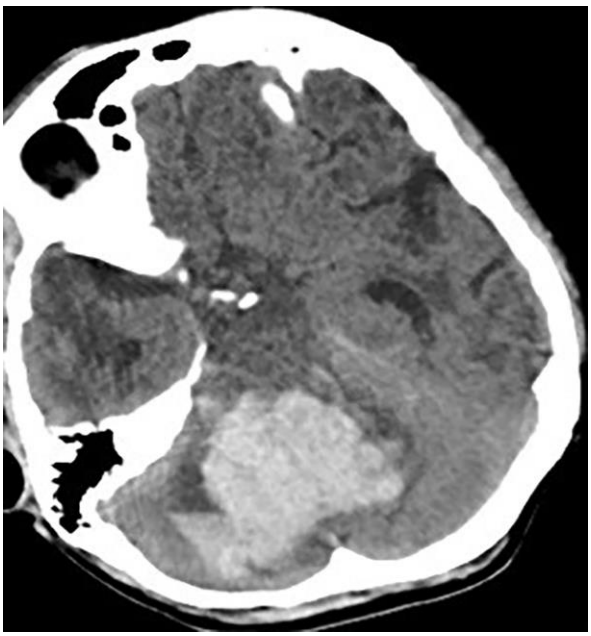

Figure 6. Brain CT showing large cerebellar hemorrhage.

DISCUSSION AND CONCLUSION

CARASIL is a hereditary form of CSVD; biallelic or compound heterozygous mutations of HTRA1 gene cause the disease (3).

The exact prevalence of CARASIL is unknown, most of the reported cases are from China and Japan (5,8).

The main clinical manifestations of the disease are lacunar stroke, stepwise and / or progressive deterioration of cerebral functions, dementia at the fourth or fifth decade, premature alopecia and spondylosis deformans, beginning in the early adulthood (4,5,8). The pathological findings are vascular smooth muscle cell loss and myointimal proliferation without granular osmophilic material or amyloid deposition in the penetrant arteries of the cerebral white matter and the basal ganglia (9,10).

The imaging findings of CARASIL are like those of CADASIL and include hyperintense signal changes in the periventricular white matter, anterior temporal lobes, external capsule and the thalamus on T2-weighted and FLAIR images and lacunar infarctions in the white matter and the basal ganglia (8,11,12). The white matter changes are more homogenous in CARASIL than those in CADASIL and U-fibers are spared (4,11,12). In the late stages, white matter changes, lacunar infarctions and brain atrophy progressively advance (11). Also, cerebral microhemorrhages have been reported in patients with CARASIL (13,14).

There is no cure for CARASIL. It has been suggested that increasing HTRA1 activity or decreasing transforming growth factor beta activity may be useful (4). The management consists of genetic counseling and supportive care (4). Antiplatelet use is controversial; the safety and the efficacy of antiplatelets in patients with hereditary CSVD have not been determined yet (15,16). However, patients with a history of prior stroke are usually given antiplatelets (16).

Although lacunar infarctions and progressive cerebral white matter changes are typical imaging features of CARASIL, ICH has not been included in the spectrum of the disease. A few patients with CARASIL and ICH have been reported to date (6). Because CARASIL is an extremely rare disease and ICH has been reported in only a few cases, it is not possible to determine if ICH is associated with cerebral microhemorrhages or antiplatelet use. ICH has been reported in patients with CADASIL with or without antiplatelet use and has been associated with cerebral microhemorrhages, higher burden of small vessel disease and high blood pressure levels (17,18).

The results of an observational study suggest that antiplatelet use is not associated with neither ischemic stroke nor ICH in patients with CADASIL (19).

In conclusion, premature alopecia, spondylosis in conjunction with stepwise and / or progressive neurological deterioration and the evidence of SCVD on brain MRI are suggestive of CARASIL. Cerebral microhemorrhages and ICH may be an internal component of hereditary CSVD. The use of antiplatelets is controversial.

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Ethics

Informed Consent: The authors declared that informed consent form was signed by the patient.

Copyright Transfer Form: Copyright Transfer Form was signed by the authors.

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