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CASE REPORT

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A New CARASIL Family: Recurrent Lobar Hemorrhage as a Novel Characteristic of the Disease

Yeni Bir CARASIL Ailesi: Hastalığın Yeni Bir Özelliği Olarak Rekürren Lober Hemoraji

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ABSTRACT

Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL) is a rare monogenic cause of cerebral small vessel disease. Clinical manifestations include progressive motor and cognitive impairments, alopecia and spondylosis. The disease is caused by homozygous mutations in the gene coding for high-temperature requirement A serine peptidase 1 (HTRA1). Little is known about genotype–phenotype correlation in CARASIL. Here we report two consanguineous CARASIL patients having homozygous c.235C>T (p.Q79*) mutation of the HTRA1 gene. Despite having the same mutation, the patients had different clinical manifestations and neuroimaging findings; one of the patients presented with epileptic seizures and multiple recurrent lobar hemorrhages. Lobar hemorrhage has not been previously reported in CARASIL.

Keywords: Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy, CARASIL, HTRA1, hemorrhage.

ÖZ

Subkortikal infarktlar ve lökoensefalopatiyle birlikte serebral otozomal resesif arteriopati (CARASIL), serebral küçük damar hastalığının nadir bir monogenik nedenidir. Klinik manifestasyonlar progresif motor ve kognitif bozulma, alopesi ve spondilozu içerir. Hastalığa, high-temperature requirement A serine peptidase 1'i (HTRA1) kodlayan genin homozigot mutasyonu neden olur. CARASIL'de genotip-fenotip korelasyonuna ilişkin bilinenler sınırlıdır. Bu makalede HTRA1 geninde homozigot c.235C>T (p.Q79*) mutasyonu saptanan aynı aileye ait iki birey sunulmaktadır. Aynı mutasyona sahip olmalarına karşın iki hastanın farklı klinik özellikler ve nörogörüntüleme bulguları mevcuttu; hastalardan biri multipl rekürren lober hemorajiler ve epileptik nöbetlerle prezente olmuştu. Lober hemoraji CARASIL'de daha önce bildirilmemiştir.

Anahtar Kelimeler: Subkortikal infarktlar ve lökoensefalopatiyle birlikte serebral otozomal resesif arteriopati, CARASIL, HTRA1, hemoraji.

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CASE PRESENTATION

High-temperature requirement A serine peptidase 1 (HTRA1) disorder encompasses clinically diverse phenotypes including classical "cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy" (CARASIL) caused by homozygous mutations of the gene coding for HTRA1 and "HTRA1 cerebral small vessel disease" which is characterized by a milder disease course and caused by heterozygous mutations of the gene coding for HTRA1.[1,2] CARASIL is characterized by early adult-onset lacunar stroke, gait disorders, pseudo-bulbar palsy and cognitive and mood disturbances due to progressive leukoencephalopathy and subcortical infarcts. Alopecia and lumbago are common.[1,3] Typical neuroimaging findings are cerebral atrophy, hyperintense signal changes in the periventricular and the subcortical white matter, spared U fibers, multiple lacunar infarctions and microbleeds, and the "arc sign" (i.e. arc-shaped hyperintense lesions from the pons to the middle cerebellar peduncles).[4] Intracerebral hemorrhage (ICH) has been scarcely reported in CARASIL.[5-7]

We present two consanguineous CARASIL patients presenting with different clinical manifestations and imaging findings.

Case 1

The proband (40-year-old male) presented with progressive cognitive dysfunction, slurred and incoherent speech, epileptic seizures, gait disturbance, and urinary and bowel incontinence. The patient's symptoms began 12 years ago with mild gait difficulty, cognitive disturbance, hair loss and low back pain. Over the years, the symptoms gradually progressed. In addition, the patient had two episodes of intracerebral hemorrhage 8 and 9 years ago, causing a stepwise deterioration with superimposed acute hemiparesis and epileptic seizures. His medical history was otherwise unremarkable, and he did not report antithrombotic use. His parents were not consanguineous; however, they were born in the same village (Figure 1). The proband's older brother also had similar symptoms and prematurely died at age

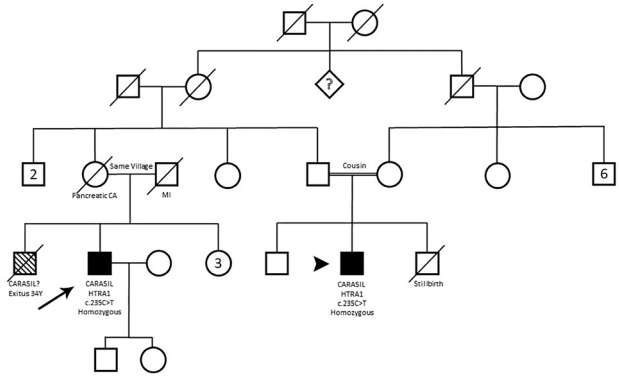

Figure 1. The pedigree chart of the family shows 5 generations with 2 members (Proband, arrow and Case 2, arrowhead) diagnosed as CARASIL.

MAIN POINTS

- This is the second CARASIL family with homozygous mutation of c.235C>T (p.Q79*).
- Diverse clinical and imaging findings of the patients having same mutation suggest that there may not be a clear phenotype-genotype correlation in CARASIL.
- Intracerebral hemorrhage has been scarcely reported in CARASIL. Recurrent lobar hemorrhage which has not been previously reported is a novel characteristic of the disease.

Neurological examination revealed severe dementia, spastic dysarthria and tetraparesis (upper extremities: 3/5, lower extremities: 2/5 on Medical Research Council, MRC) with extensor plantar responses and brisk deep tendon reflexes (DTRs). The patient had alopecia. Brain magnetic resonance images (MRI) showed cerebral and brainstem atrophy, diffuse hyperintense signal changes in the periventricular and the subcortical white matter extending to the temporal poles on T2-weighted (T2W) and fluid attenuated inversion recovery (FLAIR) images and lacunar infarctions (Figure 2).

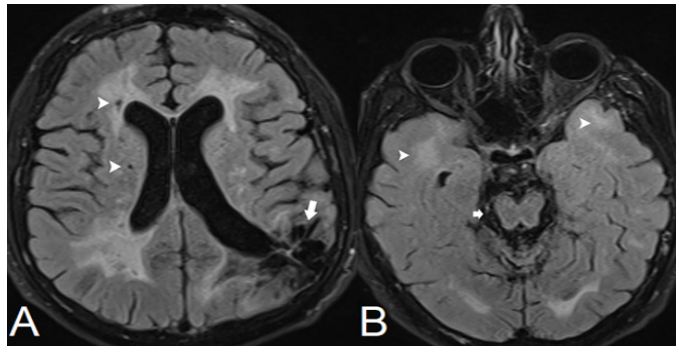

Figure 2. Brain MRI of Case 1. Axial FLAIR images. A. Symmetrical confluent hyperintense signal changes in the periventricular and the subcortical white matter and lacunar infarctions (arrowheads). Hypointense signal change indicating gliotic area due to previous lobar hemorrhage in the left parietal lobe (arrow). B. Hyperintense signal changes in the anterior temporal lobes (arrowheads) and brainstem atrophy (arrow).

Susceptibility-weighted images (SWI) revealed two discrete foci of hemorrhage in the right frontal and the left parietal lobes, and microbleeds in the brainstem surface (Figure 3). Cervical and lumbar spine MRI demonstrated spondylotic changes (Figure 4).

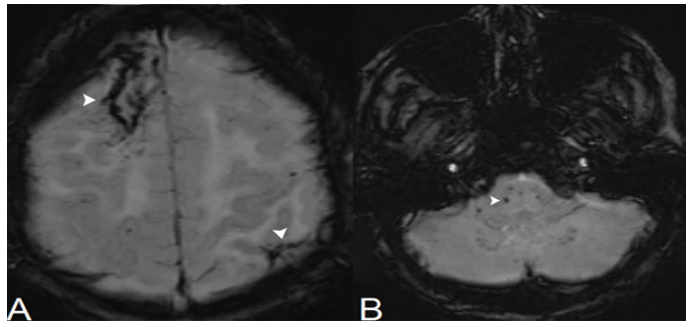

Figure 3. Brain MRI. Axial SWI images. A. Hypointense signal changes indicating hemorrhage in the right frontal and the left parietal lobes (arrowheads). B. Dot-like hypointense signal changes suggesting microbleeds in the brainstem surface (arrowheads).

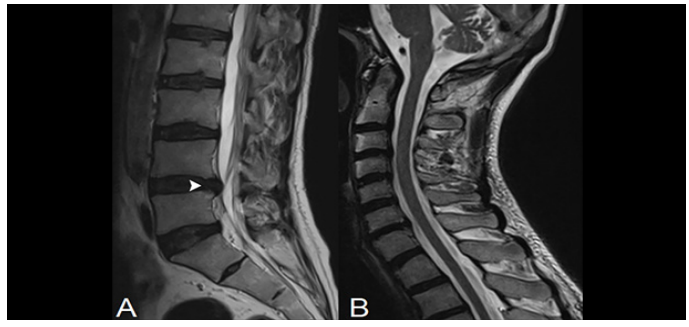

Figure 4. Sagittal T2W images of A. the lumbar and B. the cervical spine show degenerative spondylosis.

Case 2

A 64-year-old woman with a history of paroxysmal atrial fibrillation, hypertension, diabetes mellitus, chronic kidney disease, and an ischemic stroke 2.5 years ago presented with weakness in the left side of her body. She was examined at the stroke outpatient clinic. The neurological examination was normal. Current brain MR imaging of the patient showed multiple lacunar infarct areas prominent in the right hemisphere, and MR imaging during the ischemic stroke period showed millimetric diffusion restriction in the right cerebral hemisphere in the frontoparietotemporal, occipital, right centrum semioval, and right posterior external capsule (Figure 4). The follow-up CVUSG performed 2 years later found that the atherosclerotic changes that previously caused 30-35% stenosis at the right ICA entrance had progressed to cause more than 70% stenosis. Atherosclerotic changes causing a 90% stenosis at the narrowest part of the proximal part of the right ICA and a persistent variation of the trigeminal artery extending between the basilar artery and the apex of the right ICA were observed (Figure 5). An endovascular stent was placed in the right carotid artery and the patient was discharged with acetylsalicylic acid 100 mg 1x1 added to rivaroxoban 20 mg 1x1 treatment. Verbal and written informed consent was obtained from the patient to share data.

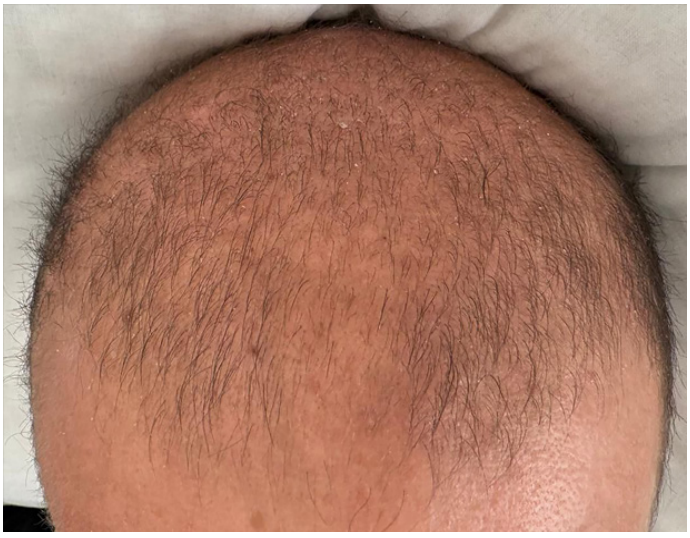

Figure 5. Case 2. Alopecia.

Neurological examination revaled cognitive dysfunction, pseudo-bulbar palsy, spastic tetraparesis (left extremities: 2/5, right extremities: 3/5 on MRC) with extensor plantar responses and brisk DTRs. Brain MRI showed pontine and cerebellar atrophy, diffuse hyperintense signal changes in the periventricular and the subcortical white matter extending to the temporal poles on T2W and FLAIR images with sparing of subcortical U fibers, lacunar infarctions in the subcortical white matter and the pons, arc-shaped hyperintense lesions from the pons to the middle cerebellar peduncles ("arc sign") and diffusion restriction in the pons suggesting acute infarction (Figure 6). There were no macro- or micro-hemorrhages on SWI images. Cervical and lumbar spine MRI revealed spondylotic changes (Figure 7).

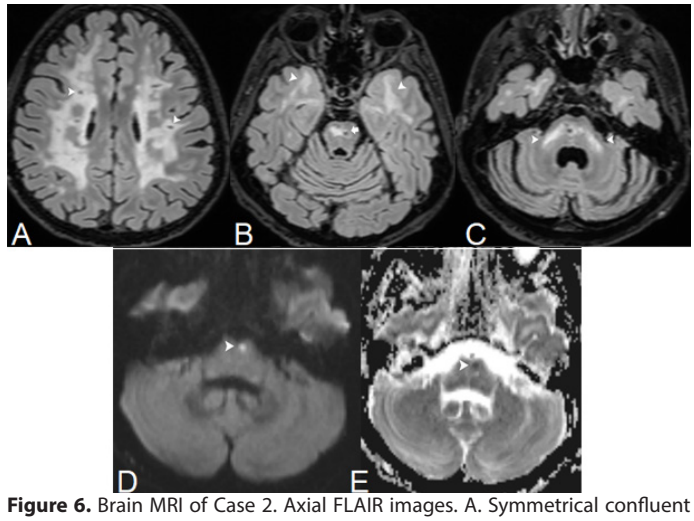

Figure 6. Brain MRI of Case 2. Axial FLAIR images. A. Symmetrical confluent hyperintense signal changes in the periventricular and the subcortical white matter and lacunar infarctions (arrowheads). Subcortical U fibers are spared. B. Hyperintense signal changes in the bilateral anterior temporal lobes (arrowheads) and the pons. There is a lacunar infarction in the pons (arrow). C. Arc-shaped hyperintense lesions from the pons to the middle cerebellar peduncles, the arc sign (arrowheads). Axial D. DWI and E. ADC images show restricted diffusion indicating lacunar infarction in the pons (arrowheads).

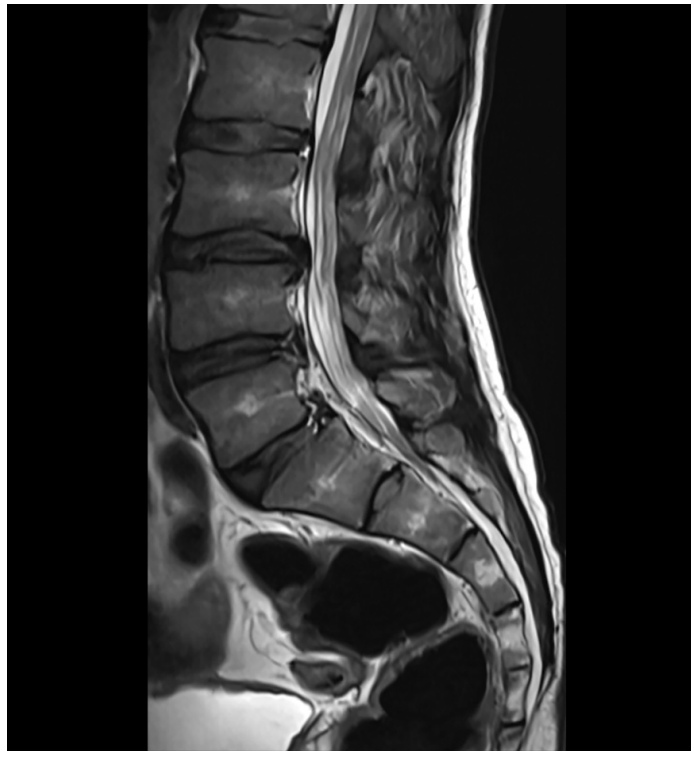

Figure 7. Sagittal T2W image of the lumbar spine shows degenerative spondylotic changes.

Genetic Analysis

Next Generation Sequencing was used for whole genome analyses and Sanger sequencing was performed using primers that matched the exon 1 of HTRA1 gene. Homozygous mutation in Exon 1 at c.235C>T (p.Q79*) was found in both patients.

DISCUSSION

CARASIL is a recessively inherited form of cerebral small vessel disease caused by mutations in the HTRA1 gene on chromosome 10q25.[1] HTRA1 mutation leads disinhibition of transforming growth factor β–family signaling causing arteriolosclerosis in cerebral small arteries, without granular osmophilic material or amyloid deposition.[1] CARASIL is characterized by early adult-onset lacunar infarctions, progressive and/or stepwise cognitive and motor dysfunction, prematüre alopecia and spondylosis.[1,3] CARASIL is a rare disease with most patients reported to date are from Japan.[2,3]

We report a CARASIL family carrying c.235C>T (p.Q79*) homozygous mutation. This mutation has been previously reported in a Turkish family.[8] The most distinctive finding of our report is that despite having the same mutation, clinical presentation and imaging findings substantially differed in our patients. Case 2 had typical imaging findings of CARASIL, whereas the proband (Case 1) also had recurrent lobar hemorrhages. Given the rarity of CARASIL, little is known about clinical heterogeneity. Available data indicate that there is no strong genotype-phenotype correlation.[1,9]

Case 1 had recurrent lobar hemorrhage resulting in hemiparesis and epileptic seizures. To the best of our knowledge, ICH has been reported in a few patients with CARASIL to date.[5-7] Previously reported patients with ICH including the patient we have reported, had infratentorial hemorrhage and were under antiplatelet treatment. However, Case 1 had recurrent lobar hemorrhage and was not under antithrombotic therapy. Our case is unique regarding the recurrence and location of ICH (lobar vs. infratentorial). Case 1 also had microbleeds on the brainstem. The unique appearance of superficial dot-like small hemorrhages on brainstem surface has been previously reported in one CARASIL patient and four patients with HTRA1 heterozygous variants.[10,11] Available findings suggest that ICH, particularly but not limited to posterior fossa, may be an underrecognized component of CARASIL.

CONCLUSION

In conclusion, we report the second CARASIL family with c.235C>T (p.Q79*) homozygous mutation. Clinical and imaging findings of the two members of the family suggest that there may not be a clear genotype-phenotype correlation in CARASIL. Recurrent lobar hemorrhage has not been previously reported in CARASIL.

Informed Consent: Written informed consent was obtained from patient who participated in this study.

Peer-review: Externally peer-reviewed.

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Declaration of Interests: The authors have no conflicts of interest to declare.

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REFERENCES

1. Hara K, Shiga A, Fukutake T, et al. Association of HTRA1 mutations and familial ischemic cerebral small-vessel disease. *N Engl J Med.* 2009;360(17):1729-1739. [CrossRef]
2. Yao T, Zhu J, Wu X, et al. Heterozygous HTRA1 Mutations Cause Cerebral Small Vessel Diseases: Genetic, Clinical, and Pathologic Findings From 3 Chinese Pedigrees. *Neurol Genet.* 2022;8(6):e200044. [CrossRef]
3. Yanagawa S, Ito N, Arima K, et al. Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy. *Neurology.* 2002;58(5):817-820. [CrossRef]
4. Nozaki H, Sekine Y, Fukutake T, et al. Characteristic features and progression of abnormalities on MRI for CARASIL. *Neurology.* 2015;85(5):459-463. [CrossRef]
5. Cordeiro IM, Nzwalo H, Sá F, et al. Shifting the CARASIL paradigm: report of a non-Asian family and literature review. *Stroke.* 2015;46(4):1110-1112. [CrossRef]
6. Kanat S, Kayım Yıldız Ö, Balaban H, et al. Fatal cerebellar hemorrhage in a patient with CARASIL. *Turk J Cerebrovasc Dis.* 2024;30(3):182-187. [CrossRef]
7. Fukutake T. Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL): from discovery to gene identification. *J Stroke Cerebrovasc Dis.* 2011;20(2):85-93. [CrossRef]
8. Rüstemoğlu BS, Samanci B, Tepgeç F, et al. Clinical and molecular genetic findings of cerebral arteriopathy with subcortical infarcts and leukoencephalopathy. *Turk J Neurol.* 2021;27:240-247. [CrossRef]
9. Nozaki H, Nishizawa M, Onodera O. Features of cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy. *Stroke.* 2014;45(11):3447-3453. [CrossRef]
10. Kobayashi Y, Kondo Y, Tazawa KI, et al. HTRA1-related cerebral small-vessel disease causes cerebral microbleeds on the brainstem surface. *J Neurol Sci.* 2024;466:123229. [CrossRef]
11. Shang T, Pinho M, Ray D, et al. Two unique mutations in HTRA1-related cerebral small vessel disease in North America and Africa and literature review. *J Stroke Cerebrovasc Dis.* 2021;30(11):106029. [CrossRef]