Reviews/Mini-Reviews

CLINICAL and TRANSLATIONAL NEUROSCIENCE

Clinical & Translational Neuroscience
January-June 2020: 1–5

DOI: 10.1177/2514183X20914182
journals.sagepub.com/home/ctn
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CARASIL with coronary artery disease and distinct cerebral microhemorrhage: A case report and literature review

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Abstract

Cerebral Autosomal Recessive Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CARASIL, Maeda syndrome) is an extremely rare autosomal-recessive genetic disorder with a serious arteriopathy causing subcortical infarcts and leukoencephalopathy. In less than 20 cases, a genetic mutation was proven. Patients suffer from alopecia, disc herniations, and spondylosis. Between the age of 30 and 40, the patients typically develop severe cerebral infarcts. Clinical symptoms, genetic study, magnetic resonance imaging (MRI), and coronary angiography of a patient with proven CARASIL are presented. The patient showed the typical phenotype with cerebral small-vessel disease, cerebral infarcts, spondylosis, and abnormal hair loss. Additionally, distinct cerebral microhemorrhage and a severe coronary artery disease (CAD) were found, which have not been reported before for CARASIL. Mutation screening revealed the presence of a homozygous c.1022G > T substitution in the HTRA1 gene. Evidence from other publications supports a pathogenetic link between the HTRA1 mutation and CAD as a new feature of CARASIL. This is the first report about CARASIL with a concomitant severe CAD. Thus, in patients with CARASIL, other vessel diseases should also be considered.

Keywords

CARASIL, Maeda syndrome, small cerebral vessel disease, NSTEMI, HTRA1

Introduction

Cerebral Autosomal Recessive Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CARASIL) is a very rare genetic disorder. In contrast to the more common Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL), it follows an autosomal recessive inheritance. Most of the few cases are described in Japanese families.[1] Patients suffer from alopecia, sometimes even in childhood. At the age of 20–30, herniated disks, spondylosis, and gait disturbances are noticed. Between the age 30 and 40, patients develop severe cerebral infarcts causing debilitating symptoms.[2] Dementia-like complaints, like forgetfulness, loss of bladder control, and personality changes can occur in the beginning. In this phase, the cerebral small vessel disease is often rapidly progressing. Infarcts or bleedings can lead to serious neurological deficits and can cause death. However, an involvement of large vessels has not been reported. Here, we describe a female patient with CARASIL accompanied by a severe coronary artery disease (CAD).

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Case report

A 37-year-old woman from Sri Lanka was admitted to our hospital. Family history was unremarkable with regards to neurological disorders. However, there was consanguinity as her parents were cousins. When she was 11 years old, the patient suffered from patchy hair loss of unknown etiology. At the age of 28, a spastic-ataxic-gait was noticed. Three years later, she developed a bipolar personality disorder that was, however, not specifically treated. Over the following years, she suffered from progressive short-term memory disturbance and loss of concentration. The gait deteriorated until she became wheel-chair-bound at the beginning of 2019. Additional risk factors and co-diseases of CAD, for example, arterial hypertension, diabetes, or hypercholesterolemia, were not existent.

Human genetics

The first suspected diagnosis was a hereditary spastic paraplegia. Due to leukoencephalopathy, cavernomas and otherwise unclear clinical diagnosis, Exome-Sequencing (Nextera-Enrichment, Illumina NextSeq, detailed data available upon request) was performed. Analysis of a virtual panel including the genes CCM2, KRIT1, PDCD10, COL4A1, COL4A2, NOTCH3, and HTRA1 was performed The missense variant c.1022G > T in the HTRA1 (high temperature requirement protein A1) gene was found in homozygous state, resulting in the aminoacid change p.Gly341Val. Since it is not present in exome variation databases (ExAC or gnomAD) and also unknown in patients with CARASIL, it was initially classified as class 3 VUS (variant of unknown significance), according to the classification of the American College of Medical Genetics and Genomics (ACMG). Homozygosity of such a rare variant is also concordant to the known consanguinity of the patient's parents. This molecular finding suggested CARASIL as a possible diagnosis, which fits to the symptoms of leukoencephalopathy, dementia, spasticity, ataxia, and rapid disease progression. Furthermore, secondary CARASIL symptoms, such as alopecia and nystagmus, corroborate the diagnosis.

Acute worsening

While on the ward, the patient developed a progressive somnolence. The first suspected diagnosis was a stroke, influenced by known cerebral vessel disease. Computed tomography (CT) and magnetic resonance imaging (MRI) scan revealed no large acute cerebral infarction. She then worsened rapidly and developed ventricular fibrillation that could be successfully treated with defibrillation. While electrocardiogram did not show ST-elevations, troponin T was significantly elevated (1557 mg/dl, reference < 5.0 ng/l). Thus, the diagnosis of a non-ST-segment elevation myocardial infarction (NSTEMI) was made. Coronary angiography showed severe CAD with no possibility of acute intervention. The patient was transiently mechanically ventilated and referred to the intensive care unit where she slowly recovered under conservative treatment.

Neurological examination

On admission, the patient was disoriented with severe cognitive impairment (unable to correctly name the current date, place or personal information like age of her daughter) and occasionally behaved agitated or even aggressive. She showed a central facial paralysis on the left side and suffered from a non-fluent aphasia. The patient presented a moderate-to-severe spastic tetraparesis with increased tendon reflexes, bilateral positive Babinski, and Trömner reflexes and sustained clonus of the feet. Deep sensation was disturbed in both legs. Fecal and urinary incontinence were noticed.

Radiological findings

Initially, a CT scan showed diffuse hypodensities involving periventricular and deep white matter of both brain hemispheres with multiple lacunar infarcts. CT angiography did not show any vascular abnormalities. The patient underwent 3-Tesla MRI of the brain and whole spine. White matter hyperintensities were recognized on fluid-attenuated inversion recovery (FLAIR) and on conventional T2-weighted imaging. These T2 prolongations extended symmetrically and diffusely from the periventricular to the juxtacortical region and spared the U fibers. Furthermore, lacunar infarcts were detected in the thalamus, basal ganglia, and deep white matter (Figure 1(a) to (b)). Additional hyperintense signal alterations were observed in the basal ganglia and in the thalamus with involvement of the white matter of the internal and external capsule, brain stem, and cerebellum. Incomplete "arc-shaped" lesions, as described by Nozaki et al.,[3] were detected extending from the pons to the middle cerebellar peduncles (Figure 1(i) to (j)). Acute infarction of the right frontal white matter (Figure 1(c) to (d)) was found on diffusion-weighted images. Susceptibility-weighted imaging displayed a large amount of cerebral microbleeds (Figure 1(e) to (h)). Neither MR angiography reflected any intraluminal vascular pathology nor was contrast enhancement seen along the proximal cerebral arteries in 3-D T1-weighted black blood sequence. Spinal MRI showed multilevel disc degeneration and spondylosis deformans in cervical and lumbar spine (Figure 1(k) to (l)).

Cardiological findings

The coronary arteries were severely altered and calcified with severe stenosis of the proximal ramus interventricularis anterior (RIVA) (95%) and a chronic occlusion of the median RIVA and the right coronary artery (RCA)

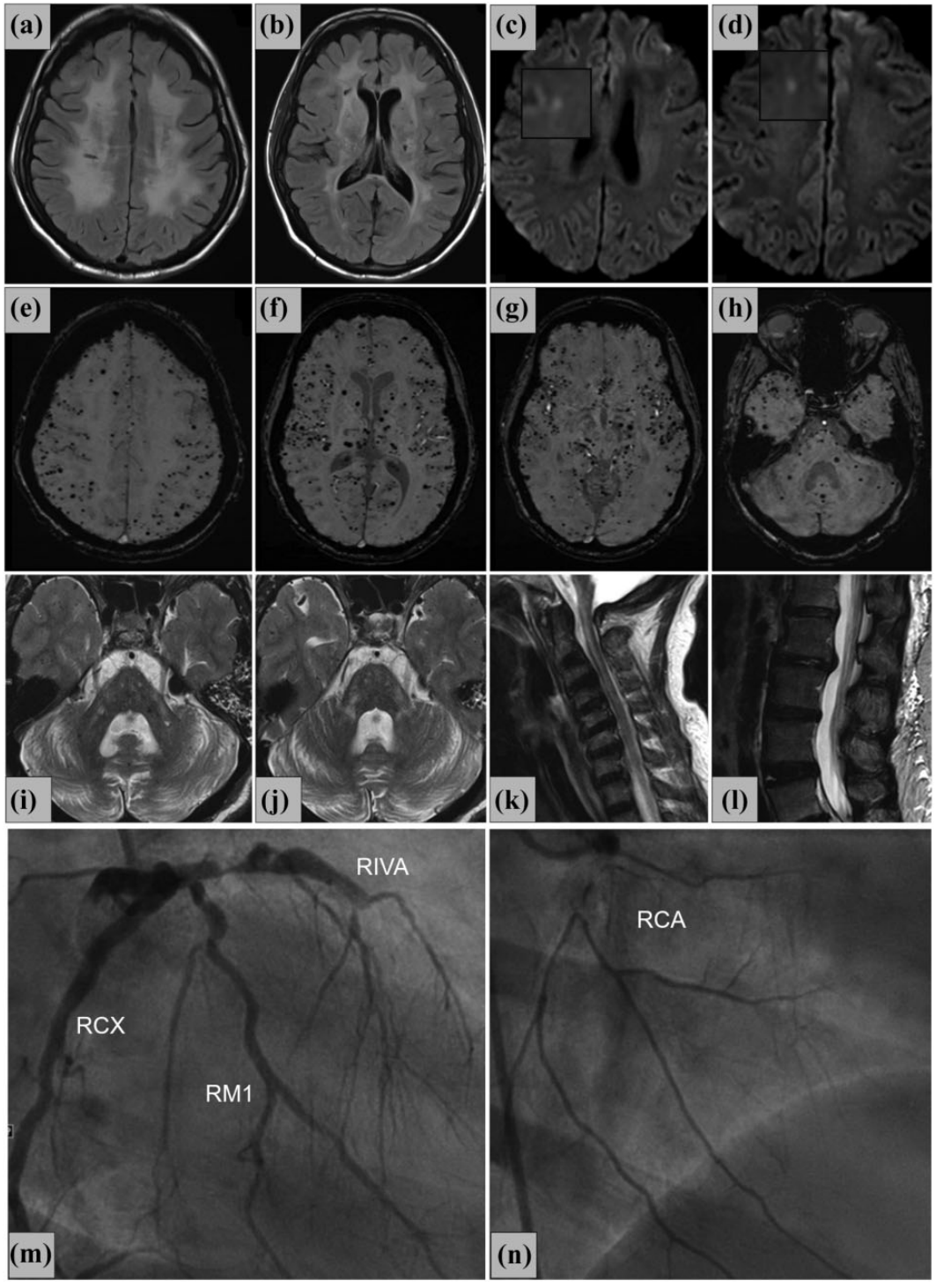

Figure 1. Findings in MRI and coronary angiography. Legend: (a) to (b) Axial view of fluid-attenuated inversion recovery (FLAIR) and conventional T2-weighted images; (c) to (d) axial view of diffusion-weighted images (DWI); (e) to (h) axial view of susceptibility-weighted imaging (SWI); (i) to (j) T2; (k) to (l) sagittal view of T2-weighted images, cervical and lumbar spine. (m) to (n) Coronary angiography: right anterior oblique (RAO)-projection. Findings: (a) to (b) White matter hyperintensity; (c) to (d) focusing/zooming on acute microinfarction of the right frontal white matter; (e) to (h) distinct cerebral microbleeds; (i) to (j) incomplete "Arc-Sign," arc-shaped lesions of the brainstem, pons, and cerebellum; (k) to (l) distinct degenerative changes, cervical spondylosis, and lumbar disc prolapse and bulgings. (m) to (n) Left-dominant coronary circulation. Stenosis of (m): ramus interventricularis anterior (RIVA) and (n) right coronary artery (RCA).

(Figure 1(m) to (n)). The distal RIVA was filled by collaterals. Therefore, a severe CAD was diagnosed. Laboratory work-up including HbA1c, cholesterols, and lipoprotein(a) showed normal values. Due to the ventricular fibrillation, an implantable cardioverter defibrillator was implanted.

Further treatment of the CAD was discussed interdisciplinary. A coronary artery bypass graft was judged to be too risky due to the necessary anticoagulation during the surgery with regards to the severe cerebral microbleeds. Interventional stenting of the coronary artery stenosis was also regarded to be very risky because of the severe arterial wall alterations and calcifications. Therefore, a medical treatment with acetylsalicylic acid (ASA) and clopidogrel was recommended first. After 3 months, a drug-eluting stent was successfully implanted into the proximal RIVA.

Discussion and conclusion

CARASIL was introduced by Maeda as a very rare disease in Japan. For a long time, it had been considered to be a local disease of families in Japan, China, and India. Recent reports showed the global occurrence.[4]

The patient presented here shows the typical clinical features of CARASIL described in the earlier presentations,[4] in particular alopecia, gait disturbance, and dementia. The latter two can be easily explained by the severe white matter changes seen on MRI caused by recurrent cerebral infarcts. Accordingly, spastic tetraparesis was found on neurological examination. The specific and initially unexpected finding in this patient was the severe coronary arteriopathy that led to life-threatening ventricular fibrillation.

Human genetics

Even if the causality of HTRA1 mutations regarding CARASIL has been described already,[1] only 19 mutations have been reported as pathogenic (Database HGMD® Professional 2019.2). Among these, the mutation c.1021G > A affecting the same aminoacid (p.Gly341Arg) as in our patient has been described before as disease-causing by Xie et al.[5] The phenotypic description of this patient is almost identical to that of our patient, supporting pathogenicity of the variant c.1022G > T in our case, as well. Therefore, the most probable ACMG classification today after detailed clinical characterization of our patient would be as class 4 (probably pathogenic).

Brain and spine

Leukoencephalopathy with lesions in deep brain structures, such as the basal ganglia, thalamus and internal capsule and lacunar subcortical infarcts, are classical signs of CARASIL[3] as well as CADASIL.[6] One of the most common radiological markers of CADASIL, a signal alteration in the anterior temporal lobes, was absent in this case. Cerebral microhemorrhages were rarely detected in patients with CADASIL and CARASIL. However, a large amount of cerebral microhemorrhages were found in this patient. The large cerebral vessels showed no pathologies in CT angiography. Typical degenerative changes beyond the age were observed in the spine as described by Roeben et al.[7]

CAD

Stroke and CAD share several pathophysiologic mechanisms. The genetic mechanisms and risk factors overlap partially.[8,9] While in typical manifestations of CARASIL only small vessels were described to be affected, our patient additionally suffered from large CAD. Thus, the central question remains whether CAD is pathogenetically related to the HTRA1 mutation or whether it occurred coincidentally in our patient. It was shown before that HTRA1 is an important regulator of Transforming Growth Factor Beta (TGF-β). A loss of function of HTRA1 leads to an attenuated signaling of TGF-β, which was claimed to be one of the major pathomechanisms in CARASIL.[10] Reduced TGF-β signaling on the other hand has been associated with atherosclerosis[11,12] and CAD.[13,14] In absence of any co-diseases and other risk factors, the occurrence of CAD in young patients is very improbable. Moreover, a study from Taiwan[15] showed a significant correlation of CAD with mutations in the HTRA1 gene. Hence, prophylactic examination for CAD should be considered in patients with CARASIL.

Acknowledgements

The authors would like to thank the patient and her family members for their cooperation.

Author contributions

S-M and J-K are the tutors of this project and conceived the manuscript. E-K was in charge of the neuroradiological analysis. I-A performed clinical and laboratory data collection. U-H provided and interpreted data from the genetics analysis. L-A wrote the human genetic part of the manuscript. G-H, M-B, C-R, and J-L provided a critical revision of the article and gave final approval of the version to be published.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The authors acknowledge support by the German Research Foundation and the Open Access Publication Funds of the Göttingen University.

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Supplemental material

Supplemental material for this article is available online.

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: 1729–1739.
2. Tikka S, Baumann M, Siitonen M, et al. CADASIL and CARASIL. *Brain Pathol* 2014; 24: 525–544.
3. Nozaki H, Sekine Y, Fukutake T, et al. Characteristic features and progression of abnormalities on MRI for CARASIL. *Neurology* 2015; 85: 459–463.
4. Menezes Cordeiro I, Nzwalo H, et al. Shifting the CARASIL paradigm: report of a non-Asian family and literature review. *Stroke* 2015; 46: 1110–1112.
5. Xie F and Zhang L. A Chinese CARASIL patient caused by novel compound heterozygous mutations in HTRA1. *J Stroke Cerebrovasc Dis* 2018; 27: 2840–2842.
6. Kalimo H, Viitanen M, Amberla K, et al. CADASIL: hereditary disease of arteries causing brain infarcts and dementia. *Neuropathol Appl Neurobiol* 1999; 25: 257–265.
7. Roeben B, Uhrig S, Bender B, et al. Teaching neuro images : when alopecia and disk herniations meet vascular leukoencephalopathy: CARASIL. *Neurology* 2016; 86: e166–e167.
8. Arima K, Yanagawa S, Ito N, et al. Cerebral arterial pathology of CADASIL and CARASIL (Maeda syndrome). *Neuropathology* 2003; 23: 327–334.
9. Baird AE. Genetics and genomics of stroke. *J Am Coll Cardiol* 2010; 56: 245–253.
10. Beaufort N, Scharrer E, Kremmer E, et al. Cerebral small vessel disease-related protease HTRA1 processes latent TGF-β binding protein 1 and facilitates TGF-β signaling. *Proc Natl Acad Sci USA* 2014; 111: 16496–16501.
11. Stefoni S, Cianciolo G, Donati G, et al. Low TGF-beta1 serum levels are a risk factor for atherosclerosis disease in ESRD patients. *Kidney Int* 2002; 61: 324–335.
12. Zeng L, Dang TA and Schunkert H. Genetics links between transforming growth factor β pathway and coronary disease. *Atherosclerosis* 2016; 253: 237–246.
13. Morris DR, Moxon JV, Biros E, et al. Meta-analysis of the association between transforming growth factor-beta polymorphisms and complications of coronary heart disease. *PLoS One* 2012; 7: e37878.
14. Pardali E. TGFβ signaling and cardiovascular diseases. *Int J Biol Sci* 2012; 8: 195–213.
15. Assimes TL, Lee I-T, Juang J-M, et al. Genetics of coronary artery disease in Taiwan: a cardiometabochip study by the Taichi consortium. *PloS One* 2016; 11: e0138014.