Features of Cerebral Autosomal Recessive Arteriopathy With Subcortical Infarcts and Leukoencephalopathy

Hiroaki Nozaki, MD, PhD; Masatoyo Nishizawa, MD, PhD; Osamu Onodera, MD, PhD

The cerebral small vessel system plays a fundamental role in maintaining higher brain function. Although lacunar stroke has been recognized as a disease in which small vessels are mainly affected, advances in neuroradiological examination extend our knowledge of small vessel disease to white matter lesions, microbleeds, and cortical microinfarction. Accumulating evidence indicates that the risk factors and the therapeutic strategies are different for large vessel disease and small vessel disease. Moreover, the recent discoveries on monogenic disorders, which mainly affect small vessels, clearly indicate that the human cerebral small vessels have distinct molecular characteristics of cerebral large vessels. However, little is known about the molecular pathogenesis of small vessel disease and how it is different from that of large vessel disease. The investigation of hereditary small vessel disease is necessary to clarify the molecular pathogenesis of cerebral small vessel disease (CSVD).

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy is the most common dominant inherited CSVD, whereas cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL) is a rare form of inherited CSVD. Fukutake has proposed the clinical triad for CARASIL, leukoencephalopathy, alopecia, and lumbago and has summarized the clinical findings of CARASIL in these patients. The identification of the causative gene for CARASIL allows a new understanding of the molecular pathogenesis of CSVD. Although CARASIL has been considered to be restricted to Japan, we now know that CARASIL exists in other populations. In this review, we update the clinical findings of CARASIL confirmed by genetic analysis and molecular pathogenesis of CARASIL.

What Is CARASIL?

In 1976, Maeda et al reported familial unusual encephalopathy of theBinswanger’s type without hypertension in siblings whose parents were consanguineous. They showed early adult-onset dementia, pseudobulbar palsy, and pyramidal and extrapyramidal symptoms. Postmortem studies revealed diffuse and focal demyelination with sparing of U-fibers, multiple small foci of perivascular softening in the cerebral white matter and the basal ganglia, and severe arteriosclerotic changes in the meningeal small arteries and long arteries in the cerebral white matter. The other characteristic features were severe lumbago and alopecia during the teenage years. In 1995, Fukutake and Hirayama studied the reported cases, including their own cases of juvenile-onset Binswanger-type encephalopathy accompanied by alopecia and lumbago in an autosomal recessive form and proposed new disease criteria for CARASIL.

In 2009, Hara et al identified that the mutation in the high-temperature requirement serine peptidase A1 (HTRA1) gene codes a protease in patients with CARASIL. To date, 10 mutations in the HTRA1 gene have been identified in 12 families (Figure 1A; Table). Most patients with CARASIL have been reported in Japan; however, in families with CARASIL, we cannot find any founder haplotype that explains this regional accumulation. Moreover, 2 Chinese families, 2 white families, and 1 Turkish family have been identified as having CARASIL. As described later in this review, clinical heterogeneity has been recognized in CARASIL. These findings indicate that CARASIL is not unique to the Japanese population and might be underdiagnosed.

Clinical Features of CARASIL

We have obtained and summarized clinical features of patients with genetically proven CARASIL from the literature or medical records (Table). Patients with CARASIL present with early adult-onset dementia, gait disturbance, alopecia, and low back pain. Motor and mental abnormalities develop at the age of ≈30 years (dementia: mean age of onset, 35.1 years [range, 24–50 years]; gait disturbance: mean age of onset, 30.7 years [range, 23–39 years]). Then, a diffuse symmetrical white matter lesion is noticed on neuroradiological
examination, suggesting CARASIL. The patients do not have hypertension or diabetes mellitus, which are the major risk factors for sporadic CSVD. Diffuse thinning of hair without hairline recession beginning during the teenage years or when patients are in their 20s has been recognized in 9 of 12 families (mean age, 16.7 years; range, 0–27 years). Pubic hair loss and body hair loss have not been reported. Acute mid- to lower-back pain has been noticed at a mean age of 24.9 years (range, 14–39 years). Mood changes (apathy and irritability), pseudobulbar palsy, hyper-reflexia, Babinski sign, and urinary incontinence are frequently observed. Motor and cognitive functions slowly decline, and 7 of 13 patients needed wheelchairs by 30 to 40 years of age. An acute ischemic stroke event has been reported in 23.1%, and no hemorrhagic stroke events have been reported. Five of 13 patients (38.5%) have experienced horizontal nystagmus. Two of 13 patients (15.4%) have experienced advanced-stage seizures. Obvious migraines have not been reported in these patients, and there has been no skin color change in the extremities. Retina and kidney involvement have not been reported; however, in other small vessel diseases, involvement of retinal vessels or involvement of renal dysfunction has been reported.

Neuroradiological Findings in CARASIL

We have directly reviewed brain MRI results from 7 patients with CARASIL (Table). White matter hyperintensity on T2-weighted or fluid-attenuation inversion recovery images is symmetrically distributed and located periventricular to subcortical white matter (Figure 1B). Abnormalities are observed in the white matter of the anterior temporal lobe, cerebellum, brain stem, and external capsule. Although these findings resemble those of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, it is not clear whether the white matter changes in the anterior temporal poles and external capsule, which are characteristic early signs in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, are also observed in early stages of CARASIL. The magnetic resonance spectroscopy finding of a patient with dementia and pyramidal signs has shown a normal N-acetyl aspartate peak in the white matter lesion, indicating the absence of neuroaxonal degeneration. In contrast, the choline peak was elevated, which is a finding consistent with ischemia-induced demyelination. Lacunar infarctions are detected in the thalamus, basal ganglia, and deep white matter. At the progressive stage, diffuse brain atrophy and both lobar and nonlobar microbleeds in cerebral cortex, thalamus, and cerebellum are observed. U-fibers are relatively preserved even during the late stage. Brain magnetic resonance angiography and conventional angiography do not show any pathological changes. Single-photon emission computed tomography shows hypoperfusion in the frontal lobe. On spinal MRI, spondylosis deformans and disk degeneration are observed in cervical and lumbar spine at the age of ≈30 years. Interestingly, these findings have not been identified during their early stages. Therefore, it is still unknown why lumbago symptoms occur during the teenage years.

Cerebral Small Vessel Pathology in CARASIL

The autopsy findings of CARASIL have been reported in 3 instances: in a patient with p.Arg302end, a mutation in the HTRA1 gene; in a sibling with p.Ala252Thr; and in the original patient. In the cerebral small arteries, smooth muscle cells were extensively lost, even in arteries without
### Table. Summary of Clinical Features in Patients With Cerebral Autosomal Recessive Arteriopathy With Subcortical Infarcts and Leukoencephalopathy and HTRA1 Mutations

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Information from the patients whose clinical features are available. + indicates present; and −, not available.
sclerotic changes. Sclerotic changes were mild and infrequent; most of the arteries were enlarged rather than exhibiting luminal stenosis. Tunica media of the cerebral small arteries exhibited hyalinosis and were immunopositive for fibrinogen. These pathological findings resemble those observed in nonhereditary ischemic CSVD. In the patients with nonhereditary ischemic CSVD, marked degeneration of vascular smooth muscle cells with collapse and dilatation in the cerebral small arteries, the so-called earthen pipe phenomenon, were observed. These changes might disturb autoregulatory mechanisms for cerebral blood flow, resulting in ischemic changes in the deep white matter.

The internal elastic membrane, which is composed of elastin, is split into multiple layers and fragmented. Some intima is thickened with fibrosis and involves myointimal cells, which were sparsely stained by α-smooth muscle actin antibody. Arterial adventitia was thin and decreased immunoreactivity for type I, type III, and type VI collagens. These changes were relatively limited in cerebral small arteries and were not detected in intracranial large arteries and extracranial arteries. Lysosome-like bodies were found in the cytoplasm of smooth muscle cells in small arteries. No obvious deposit or inclusion, including granular osmiophilic material or amyloid, was observed. Diffuse myelin pallor in the cerebral white matter with sparing U-fibers and multiple small foci of perivascular softening in the cerebral white matter, basal ganglia, and brain stem were observed.

**Loss of HTRA1 Protease Function Causes CARASIL**

The HTRA1 gene consists of 9 exons producing HTRA1, a serine protease belonging to the HTRA protein family whose members have dual activities as chaperones and serine proteases (Figure 1A). HTRA1 has an N-terminal insulin-like growth factor–binding protein domain, a Kazal-type serine protease inhibitor domain, a trypsin-like serine protease domain, and a C-terminal PDZ domain. HTRA1 proteases exist as trimers, thus allowing communication between adjacent subunits to regulate protease. The activation cascade is initiated by the ligand-dependent interaction of neighboring HTRA1s in a trimer, thereby inducing the proper adjustment of the activation domain His220, Asp250, and Ser328 in the trypsin-like serine protease domain.

To date, 10 mutations in the HTRA1 gene have been identified in 13 patients from 12 families (Figure 1A). They include 7 missense mutations, 2 nonsense mutations, and 1 deletion mutation. The premature termination codons, which are caused by the nonsense or deletion mutations, fulfill the criteria of the nonsense-mediated mRNA decay, indicating the marked reduction of the amounts of mRNA from these alleles. All of the missense mutations were located in or around the protease domain of HTRA1, suggesting the reduction in the protease activity. The disease-associated mutant HTRA1s (p.Ala252Thr, p.Arg274Gln, and p.Val297Met) decrease their protease activity. These findings indicate that CARASIL is caused by the loss of HTRA1 or its protease activity. Among the mutations with HTRA1, the residual HTRA1 activity of p.Arg302end, which completely loses its protease domain, should be the lowest. Therefore, we can speculate that patients with p.Arg302end show the most severe phenotype with CARASIL; however, the onset and the clinical severities are similar for the patients with p.Arg302end and other patients (Table).

**Dysregulation of Transforming Growth Factor-β Signaling Underlies Molecular Pathogenesis in CARASIL**

Studies have shown that HTRA protein decreases transforming growth factor-β (TGF-β) family signaling. TGF-β is a cytokine that promotes cell differentiation and fibrous proliferation in response to tissue damage and has an important role in vascular integrity. Loss of HTRA1 activity leads to an increase in TGF-β signaling. CARASIL-associated mutant HTRA1s fail to decrease TGF-β family signaling. Moreover, the extra domain A of fibronectin and versican, which are induced by increased TGF-β signaling, accumulate in the hypertrophic intima of cerebral small arteries. In addition, hyaluronan, an extracellular matrix protein that is induced by TGF-β1 signaling, also accumulates in small cerebral arterial walls. In endothelial cells of small cerebral arteries, the expression of phosphorylated Smad2, which is induced by TGF-β1 signaling, increased. Finally, TGF-β1 and latency-associated peptide, which forms a complex with TGF-β1, increase in the cerebral small arteries of patients with CARASIL. No expression of extra domain A of fibronectin was detected in arterial walls of coronal tissue, renal arteries, or the aorta from a patient with CARASIL. These findings indicate that the increased TGF-β signaling plays a pivotal role in the pathogenesis of CSVD in CARASIL. Acceleration of TGF-β signaling might cause the degeneration of vascular smooth muscle cells because TGF-β signaling has an important role in the differentiation of vascular smooth muscle cells. In extracranial nervous system symptoms of CARASIL, upregulation of TGF-β family signaling might cause alopecia or spondylosis deformans.

**How the HTRA1 Inhibits TGF-β Signaling**

TGF-β signaling is temporally and spatially regulated by balance among maturation, sequestration, and presentation (Figure 2). TGF-β is synthesized as a homodimeric proprotein (proTGF-β) and is subsequently cleaved into an N-terminal latency-associated peptide and a C-terminal mature TGF-β by a proprotein convertase, such as furin, in the trans-Golgi network. latency-associated peptide forms a noncovalent complex with a dimer of mature TGF-β. This complex binds to a latent TGF-β-binding protein, and the bound complex is then secreted and anchored to the extracellular matrix, resulting in the sequestration of the mature TGF-β in the extracellular space. The sequestered mature TGF-β is activated by serine protease, matrix metalloproteinase, or acidic microenvironments in the extracellular space. The extracellular matrix, which stores TGF-β in a complex with latency-associated peptide and latent TGF-β-binding protein, also regulates the bioavailability of TGF-β. The activation of mature TGF-β is the rate-limiting step for TGF-β signaling.
Tighter regulation of bioavailability of TGF-β in intracellular and extracellular spaces is important for regulating its signaling.

For the downregulation mechanism of TGF-β signaling by HTRA1, we have proposed that HTRA1 cleaves the prodomain of proTGF-β1 in the endoplasmic reticulum before furin processes proTGF-β1 in the trans-Golgi network.35 The aberrant cleaved products of proTGF-β1 are degraded by the endoplasmic reticulum–associated degradation system, leading to a reduced amount of mature TGF-β1. In contrast, it has been reported that HTRA1 cleaves mature TGF-β1 or TGF-β1 receptors in extracellular space.31,36,37 However, all results in regard to the downregulation of TGF-β1 signaling by HTRA1 were obtained by the overexpression conditions; thus, the downregulation mechanism under physiological conditions is still unclear.

Why Vascular Pathology Is Predominant in Cerebral Small Vessels

The selectivity of cerebral small vessels in CARASIL is not explained by the expression of HTRA1. Although the specificity of the antibodies has not been evaluated fully, HTRA1 is ubiquitously expressed in various human tissues.38 Therefore, we have to consider a unique role of HTRA1 or TGF-β1 in maintaining the integrity of cerebral small vessels. TGF-β1 is secreted from astrocytes, microglia, smooth muscle cells, and endothelial cells in neurovascular units and plays an important role in maintaining their function and survival.39 HTRA1 is expressed in endothelial cells and astrocytes in cerebral small vessels.40 HTRA1 cleaves proTGF-β1 and downregulates TGF-β1 synthesis in these cells.30 The intracellular cleavage of proTGF-β1 is a unique mechanism for regulating the amount of TGF-β1 family protein, indicating that this mechanism has some specific role for circumstance-dependent regulation of TGF-β signaling in cerebral small vessels.

The other factors that regulate TGF-β signaling are an activation system and receptors for TGF-β. Fibrinogen-bound latent TGF-β interacts with astrocytes, leading to active TGF-β formation.39 In CARASIL patients, fibrinogen deposited in tunica media of cerebral small arteries might accelerate the TGF-β signaling in cerebral small vessels. TGF-β1 binds type I and type II receptors on the plasma membrane, and each type involves several different receptors. On ligand-induced heteromeric complex formation, the type I receptor is phosphorylated by the type II receptor. TGF-β signaling is temporally and spatially regulated by the diversity of these receptors and coreceptors in each cell type.41 Different expressions of the receptors in each type of cell in cerebral small arteries might be associated with the vascular pathology of CARASIL. The profiles of the receptors and coreceptors in the cerebral small arteries should be elucidated.

Clinical Heterogeneity of CARASIL

Although leukoencephalopathy, lumbago, and alopecia are the clinical triad of CARASIL, we have realized that some patients with mutations in the HTRA1 gene do not show signs of alopecia (Table). The frequency of alopecia in families with genetically proven CARASIL is 72.7%. Moreover, when low back pain begins, sometimes there is no apparent neuroradiological finding in the lumbar spine.

We have to be cautious because most of the reported cases of CARASIL are suspected because of the existence of early-onset leukoencephalopathy. However, there is a possibility that residual protease activity could affect the severity of the disease. Thus, we imagine that some patients show later-onset...
and milder phenotypes. In elderly individuals, it is more difficult to suspect the mutation in \textit{HTRA1} gene because these individuals frequently lose hair and have spondyloïtic deformities. Therefore, investigation of \textit{HTRA1} gene is of interest in these populations.

Does heterozygosity for \textit{HTRA1} mutation cause development of CSVD? Heterozygote individuals with p.Arg302end did not exhibit early adult-onset dementia or gait disturbance. Their HTRA1 activity is speculated as being half that of normal individuals, suggesting that 50% activity of HTRA1 is enough to prevent the progression of CARASIL. There have been no reports of patients with early-onset leukoencephalopathy, alopecia, and lumbago with heterozygote mutations in \textit{HTRA1} gene. In 7 of 10 families with \textit{HTRA1} mutations indicated in the neurological information of the parents, there is a history of cerebral infarction in ≥2 of the parents. Four individuals with p.Pro285Leu, p.Gly295Arg, p.Glu42fs, or p.Ala321Thr heterozygotes exhibited white matter lesions.\textsuperscript{16–18} However, CSVD is frequently observed in the elderly. Therefore, further evaluation of individuals with \textit{HTRA1} mutations is needed to elucidate this issue.

\section*{Therapeutic Strategy for CARASIL}

Increasing the activity of HTRA1 or decreasing the TGF-\(\beta\) activity is a therapeutic strategy for CARASIL. For patients with p.Arg370end mutation, the drugs that read through the premature termination codon might be effective in increasing the active HTRA1.\textsuperscript{30} The product of p.Arg370end retains normal protease activity, and it has been revealed that the C-terminal PDZ domain is dispensable in HTRA1.\textsuperscript{3} Thus, the inhibitor of nonsense-mediated mRNA decay should increase the amounts of active HTRA1.\textsuperscript{30,42} The denatured citrate synthase, which increases activity of HTRA1 by promoting HTRA1 multimerization, could also be useful.\textsuperscript{29}

Inhibition of accelerated TGF-\(\beta\) signaling is another therapeutic strategy for CARASIL, and it is also used to prevent the progression of aortic aneurysm in Marfan syndrome. Marfan syndrome is caused by the mutation in \textit{fibrillin-1} gene, resulting in the increase in TGF-\(\beta\) signaling.\textsuperscript{32} Interestingly, in the aortic artery, degeneration of smooth muscle cells and fragmentation of elastic membrane are observed. These histological findings partially resemble those of CARASIL. In Marfan syndrome, angiotensin II type 1 receptor antagonist, which inhibits TGF-\(\beta\) signaling, prevents the dilatation of aorta in mice models and in human patients.\textsuperscript{33,44} Moreover, several lines of drugs for blocking TGF-\(\beta\) signaling in other diseases might be therapeutic candidates for CARASIL.\textsuperscript{35}

\section*{Perspectives}

The cerebral small vessel is not a single structure and has marked diversity, not only in size but also in histology, function, and regulation of the nervous system.\textsuperscript{1} Moreover, the pericyte and astrocyte are also diverse, depending on the locus in the brain. These marked diversities of the small arteries have been given little attention, making it difficult to understand the molecular mechanism and pathogenesis of these structures. Although most of the pathological studies have focused on the arteries having internal elastic membrane and smooth muscle cells, the most important and unique structure in small vessels is the capillary, which loses the internal elastic membrane and smooth muscle cells. Instead of these structures, the capillary is surrounded by the pericyte and astrocyte. The investigation of whether the dysfunction of capillary, pericyte, or astrocyte contributes to the hyperintensity on MRI and the mental or motor deterioration in humans might be of interest. To address this issue, the elucidation of the molecular mechanisms for CARASIL will provide new insights on significance of cerebral small arteries in humans and will allow new opportunities for therapeutic strategies, not only for CARASIL but also for nonhereditary CSVD.

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\section*{Disclosures}

None.

\section*{References}

Features of Cerebral Autosomal Recessive Arteriopathy With Subcortical Infarcts and Leukoencephalopathy
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