Review

Cerebral Autosomal Recessive Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CARASIL): From Discovery to Gene Identification

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Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL) is a single-gene disorder directly affecting the cerebral small blood vessels, that is caused by mutations in the *HTRA1* gene encoding HtrA serine peptidase/protease 1 (HTRA1). CARASIL is the second known genetic form of ischemic, nonhypertensive, cerebral small-vessel disease with an identified gene, along with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). The exact prevalence of CARASIL is currently unknown, and to date approximately 50 patients have been reported, most of them from Japan and two from China. Genetically, no founder haplotype has been identified, and thus the disease is expected to be found more widely. The main clinical manifestations of CARASIL are ischemic stroke or stepwise deterioration in brain functions, progressive dementia, premature baldness, and attacks of severe low back pain or spondylosis deformans/disk herniation. The most characteristic findings on brain magnetic resonance imaging are diffuse white matter changes and multiple lacunar infarctions in the basal ganglia and thalamus. Histopathologically, CARASIL is characterized by intense arteriosclerosis, mainly in the small penetrating arteries, without granular osmiophilic materials or amyloid deposition. CARASIL is a prototype single-gene disorder of cerebral small vessels secondary to and distinct from CADASIL. CARASIL-associated mutant *HTRA1* exhibited decreased protease activity and failed to repress transforming growth factor-β family signaling, indicating that the increased signaling causes arteriopathy in CARASIL. Therefore, *HTRA1* represents another new gene to be considered in future studies of cerebral small-vessel diseases, as well as alopecia and degenerative vertebral/disk diseases. **Key Words:** Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy—ischemic stroke—alopecia—spondylosis deformans—small-vessel disease—*HTRA1*.

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Cerebral small-vessel diseases (SVDs) are a major disease burden in Japan as well as in most developed countries. SVDs usually manifest with lacunar infarction, intracerebral hemorrhage, and vascular dementia. Although hypertension, dyslipidemia, and diabetes mellitus are known to be important risk factors for SVDs, many hereditary or idiopathic SVDs also have been identified.[1-3] Among these, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy

(CADASIL) was the first to be genetically identified and is the most common single-gene disorder of the cerebral small arteries. CADASIL is caused by mutations in the *Notch3* gene.[4] The condition was first described more than 30 years ago in Europe, although the acronym "CADASIL" did not emerge until the early 1990s, when the responsible gene mutations were identified. During the same period, several young adult patients (with or without familial occurrence) whose symptoms resembled those of CADASIL in nonhypertensive arteriopathy were reported in the Japanese literature. In 1995, I and a colleague first reviewed 17 Japanese patients with a young adult–onset arteriosclerotic leukoencephalopathy accompanied by peculiar extraneural symptoms, including alopecia and lumbago/spondylosis deformans, noting that the disorder was possibly transmitted in an autosomal recessive mode.[5] The term "cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL)" was proposed by Bowler and Hachinski,[6] based on the disorder's recessive inheritance and resemblance to CADASIL.

The main clinical manifestations of CARASIL are recurrent stroke or stepwise deterioration of motor ability, cognitive deficit, and the aforementioned systemic symptoms. Although CARASIL is very rare, recently two siblings were reported from China, the first reports from outside of Japan.[7] Because no founder haplotype has yet been identified, this disorder is expected to be found more widely.[8]

This review summarizes the historical background, epidemiology, characteristic clinical findings, neuroimaging, pathology, genetics, and treatment of CARASIL. Although to date only a few genetically proven cases have been reported, approximately 50 patients have been diagnosed based on the clinical and pathological/neuroradiologic criteria proposed by our group.[9-11] This review is based mainly on those latter clinical cases.

History

What was possibly the first recorded encounter with a patient with CARASIL (at that time genetically unproven) was reported by Nemoto[12] in 1960, when a 30-year-old male was admitted to Tohoku University's Department of Neuropsychiatry. The patient died 18 months later following frequent seizures after cerebral angiography, and an autopsy was performed. Nemoto[12] described the clinical and pathological features of that patient and of two similar brothers of another family at his leading professor's retirement festschrift in 1966. In 1965, Maeda et al[13] presented a preliminary description of the autopsy findings in one of those brothers at a clinicopathological conference, at which the first case was also discussed.

Subsequently, in 1976, Maeda and coworkers, including Nemoto, reported the complete clinical and pathological findings of the two brothers, born of consanguineous parents, using the term "familial unusual encephalopathy of Binswanger's type without hypertension."[14,15] These 3 patients presented with organic dementia, pyramidal and extrapyramidal symptoms, and pseudobulbar palsy, accompanied by severe lumbago and premature baldness.[13-15] The condition started in the third decade, with steady progression leading to death within 9 years. 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 of 100- to 400-μ caliber in the cerebral white matter. Vessel changes included fibrous intimal proliferation, severe hyalinosis, and splitting of the intima and/or internal elastic membrane.[13-15]

In the period between 1965 and 1976, two other groups reported clinical and autopsy findings of similar but sporadic cases of young male patients. Tanaka et al[16] described a case presenting with personality change at age 36, low back pain, and lack of hypertension and baldness. Kondo et al[17] described a case presenting at age 29 with right leg weakness and lumbago due to lumbar disc hernia, baldness, and lack of hypertension.

In 1985, my group reported a family of 3 brothers with strikingly similar clinical features and cerebral diffuse white matter disease on computed tomography (CT) scan, and proposed a new systemic syndrome that we termed "familial juvenile encephalopathy (Binswanger type) with alopecia and lumbago."[18] Subsequently, based on our clinical and pathological/neuroradiologic criteria,[9-11] approximately 50 similar patients have been reported, almost exclusively from Japan.[19] In 2009, Hara et al[20] applied linkage analysis and fine mapping in 5 consanguineous families with CARASIL and identified homozygous mutations in the *HTRA1* gene on chromosome 10q25.

Epidemiology

The exact prevalence of CARASIL is unknown; to date, approximately 50 patients have been reported, all but two from Japan.[19] Recently, two siblings of a Chinese family have been described.[7] Genetically, no founder haplotype has yet been identified, and thus CARASIL is expected to be found more widely.[8] The age of onset of encephalopathy ranges from 20 to 45 years (mean, 32 years), earlier than in CADASIL (mean, 45 years) and Binswanger's disease (BD) (50-60 years). Alopecia also develops earlier, in the second decade, and attacks of severe low back pain occur in the time frame as the onset of encephalopathy.[5,9-11,19] The average duration of illness was up to 10 years in early reports, but survival for as long as 20-30 years has been reported recently, although almost all of these patients became bed-ridden within 10 years of onset.[5,10,19,20] Males are predominantly affected (a male:female ratio of 3:1 in clinically definite cases and of

1.3:1 in all cases, including probable cases).[11] Consanguinity is present in approximately 50% of affected families.[19]

Clinical Features

Ischemic stroke or stepwise deterioration of brain functions, progressive dementia, premature baldness/alopecia, and attacks of severe low back pain or spondylosis deformans/disk herniation are the cardinal clinical features of CARASIL.[5,9-11,18,19]

Ischemic Stroke or Stepwise Deterioration

The most common manifestation of CARASIL is a typical lacunar stroke, mainly in the basal ganglia or brainstem. This occurs in approximately 50% of patients; about half of the remaining patients experience a stepwise deterioration in brain function. Some patients have a long plateau period, as reported in BD.[21] Neurologic signs and symptoms include pseudobulbar palsy; pyramidal and extrapyramidal signs, such as hyperreflexia and (rigido-) spasticity; brainstem signs, such as vestibular symptoms, ophthalomoplegia, and facial palsy; and gait disturbances due to leg weakness and/or ataxia. Some patients develop convulsions.[12,22-24] A patient of ours developed cerebral hemorrhage in an advanced stage.[19]

Cognitive Deficits

Cognitive deficit is the second most frequent symptom in CARASIL, seen in almost all patients who develop dementia by age 30-40 years. Patients first develop forgetfulness and gradually exhibit calculation disturbances, disorientation to time, personality changes, emotional incontinence, and severe memory dysfunction, finally manifesting abulia (lack of spontaneity) and apallic syndrome (akinetic mutism). Neither cerebral focal signs (eg, aphasia, apraxia) nor abnormal behavior (eg, stereotypy, day–night sleep inversion) are seen. Personality changes, including irritability and emotional lability, are sometimes apparent even at onset or in early stages of the disorder, but depression usually does not develop. The characteristics of cognitive deficits in CARASIL are distinct from those of cortical dementias (eg, Alzheimer's disease) and subcortical dementias (eg, progressive supranuclear palsy, Huntington's disease), and thus can be categorized as white matter dementia.[25]

Premature Baldness/Alopecia

Alopecia is the most common initial symptom, present in approximately 90% of patients with CARASIL, and frequently occurring as early as adolescence. A sibling with white matter disease without alopecia has been reported.[26] Hair loss is confined to the head; there is no obvious body hair loss. The baldness is diffuse and not confined to the frontal or parietal regions (Fig 1). Miscellaneous dermatologic symptoms seen in some patients include keratosis and ulcers, xeroderma, pigmentary nevus, and dry skin with sclerema.[5]

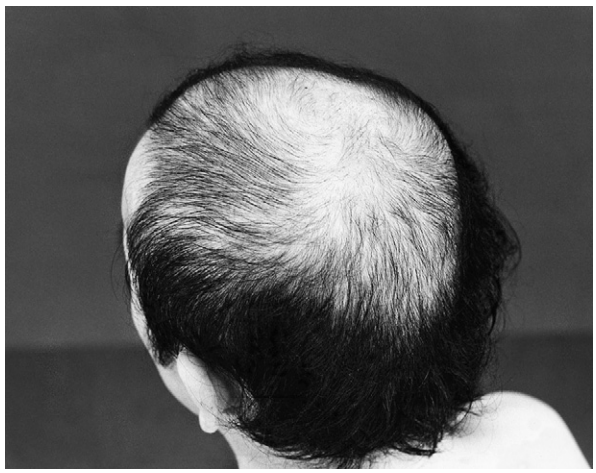

Figure 1. *Diffuse baldness in a 33-year-old man with CARASIL.*

Acute Lumbago/Spondylosis Deformans

Acute middle to lower back pain (lumbago) occurs in approximately 80% of patients with CARASIL, with onset at age 20-40 years. Magnetic resonance imaging (MRI) and X-ray show spondylosis deformans and/or disk degeneration in the cervical and/or thoracolumbar spine. Myelography in some of the patients described in early reports found that an obstruction was often located between the lower thoracic and upper lumbar portions, which is higher than the most common sites of lumbar disk herniation.[5] The orthopedic postoperative diagnoses in two of our patients were arachnoid adhesion and neurinoma (suspected).[18] Other skeletal disorders seen in some patients include kyphosis, ossification of intraspinal canal ligaments, sclerosis of the nuchal ligaments, and arthralgia and/or osteoarthritis in the elbows and/or knees.[5,26]

Additional Manifestations

One patient with CARASIL also had nasopharyngeal squamous cell carcinoma, detected 4 years after the onset of encephalopathy.[22] Another patient had associated optic neuritis and retinal vascular changes.[27] Two patients developed mild arteriosclerosis in the eyes in advanced disease stages.[19,26]

No patient with CARASIL has been found to have chronic persistent arterial hypertension. Routine laboratory examinations are usually noncontributory. Serum very-long-chain fatty acids, serum and urine amino acids, and leukocyte lysosomal enzymes were all normal in examined patients.[5]

Brain Imaging

CT scans showed diffuse homogeneous white matter changes in all examined patients and small foci with softening in approximately 50% of patients, even in early stages of

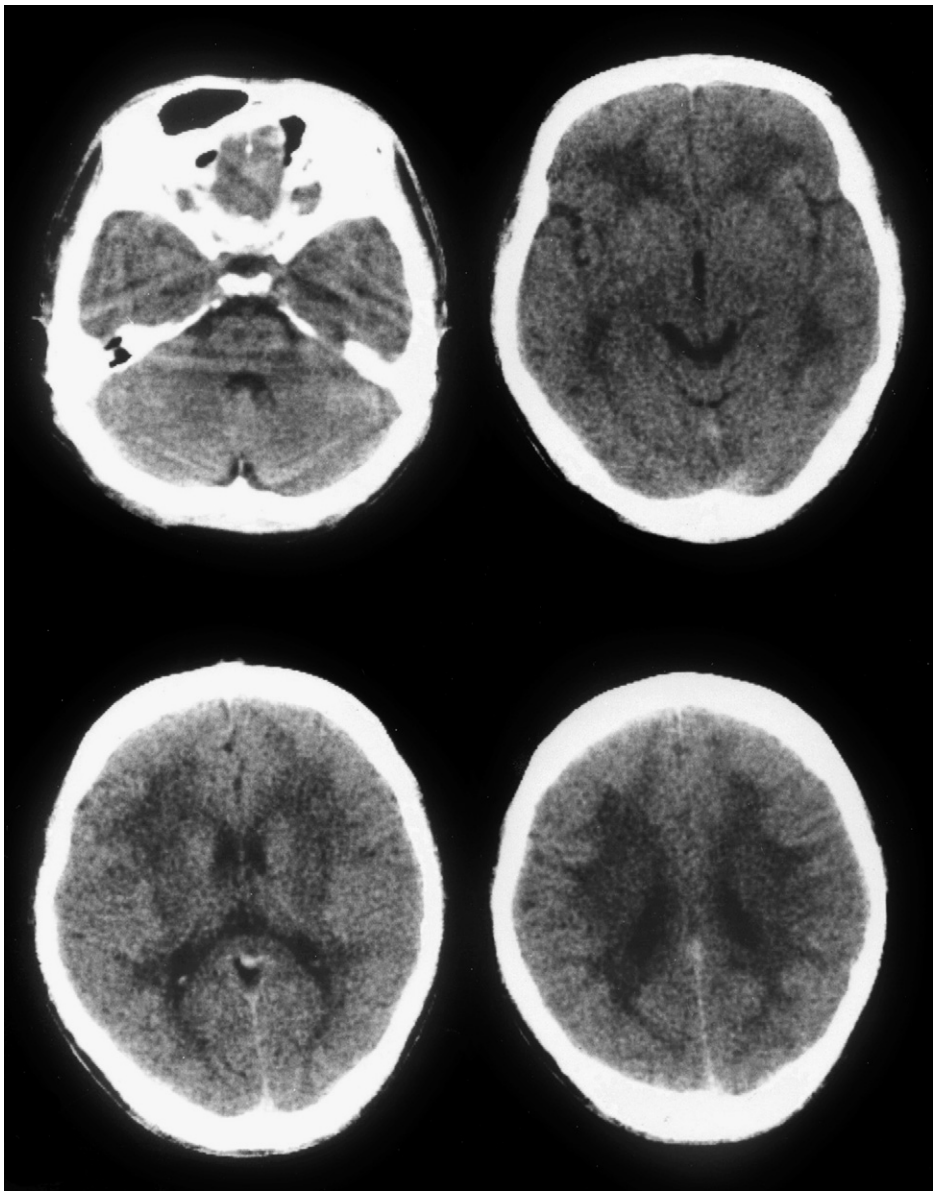

Figure 2. *CT scan of the 26-year-old brother of the patient shown in Figure 1 who demonstrated only mild hyperreflexia of the extremities but no dementia, revealing extensive low-density areas in the cerebral white matter and two small low-density areas in the pontine base.*

CARASIL. Dilatation of the lateral ventricles and cerebral sulci was noted with varying levels of severity.[5] Approximately 25% of patients had small areas of low attenuation in the pontine base, suggesting Wallerian degeneration of the cortico-descending tracts, but not lacunes (Fig 2).[5]

The most characteristic brain MRI findings in patients with CARASIL are white matter high–signal intensity (HSI) lesions and multiple lacunar infarctions in the basal ganglia and thalamus.[5,19] T2-weighted MRI images revealed HSI lesions in the white matter in almost all patients, more often in the periventricular and deep white matter than in the superficial white matter (U-fibers). HSI lesions start to appear in the subcortical white matter diffusely and symmetrically by age 20 years in the absence of deep infarcts, suggesting that the white matter changes precede the onset of neurologic symptoms. These lesions subsequently extend into the basal ganglia, thalami, brainstem, and cerebellum. Involvement of the anterior temporal lobes and external capsules, which are characteristic early signs in CADASIL,[28,29] is seen in some patients (Fig 3).[5,26,29,30] Although the progression of MRI changes is not well documented in CARASIL, MRI/CT white matter changes appear to develop homogeneously from the early stage in CARASIL,[30] whereas those in CADASIL seem at first to be punctiform or nodular and only later produce confluent lesions.[30]

Cerebral angiography showed no significant abnormalities in approximately 50% of the examined patients, but the remainder had abnormal findings compatible with arteriosclerosis.[5] Single photon emission computed tomography showed reduced cerebral blood flow in various parts of the cerebrum, including the unilateral frontal lobe, bilateral frontal cortex, and diffuse subcortical region, and in the entire brain in some patients.[5]

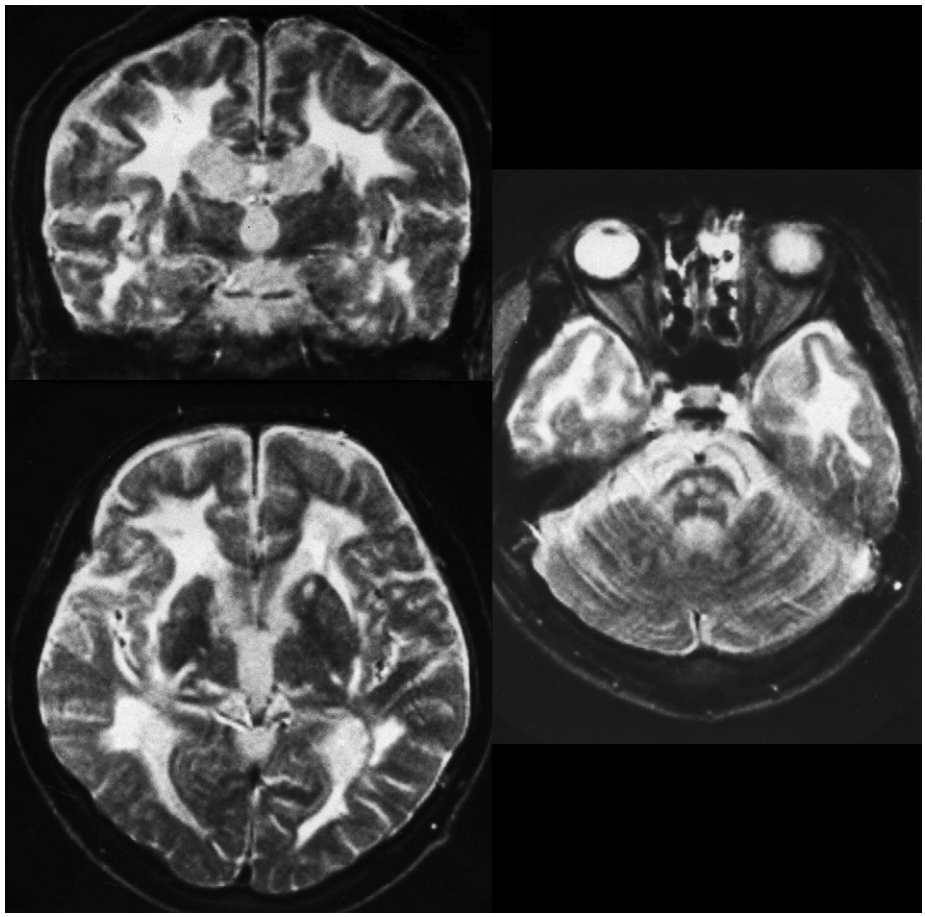

Figure 3. *T2-weighted MRI of the patient shown in Figure 1 revealing diffuse confluent HSI areas in the cerebral white matter extending to the anterior temporal lobe and internal and external capsules, as well as small lesions in the basal ganglia and brainstem.*

Pathology

Histopathologically, CARASIL is characterized by intense arteriosclerosis mainly in the small penetrating arteries, without granular osmiophilic materials or amyloid deposition.[12-17,22,26,28,31,32] Arteriosclerotic changes are most intense in the cerebral white matter and basal ganglia. Fibrous intimal proliferation, hyaline degeneration of the media, loss of vascular smooth muscle cells, thickening and splitting of the internal elastic lamina, and concentric narrowing of the lumen are characteristic features.[32] Abnormal segmental dilatation of the small arteries is seen in some patients.[32] In periodic acid-Schiff preparations, small arteries are occasionally stained homogeneously as a result of exudative changes, but never with the granular appearance characteristic of the granular osmiophilic materials in CADASIL.[32] The small arterial changes are intense in the cerebral medullary and leptomeningeal arteries, leading to multifocal, confluent, or diffuse ischemic changes in the cerebrum.[32] The pathology in other organs is less severe, and skin biopsy is not useful for diagnosis.[5,32]

Genetics and Molecular Pathogenesis

HTRA1 is the only gene known to be associated with CARASIL.[20] No other phenotypes with mutations in the *HTRA1* gene are known. A single-nucleotide polymorphism at the promoter region of *HTRA1* for which homozygosity for the AA genotype increases the risk of wet (neovascular) age-related macular degeneration has been identified as age-related macular degeneration 7.[33]

Genome-wide linkage analysis of the disease has revealed a link to the 2.4-Mb region on chromosome 10q (10q25.3-q26.2) that contains the *HTRA1* gene[20] in 5 families with CARASIL.[18,21,23,24,31,34] HTRA1 is a serine peptidase/protease that represses signaling by transforming growth factor (TGF)-β family members; its protease domain exists in exons 3-6. Of the 4 causative mutations in *HTRA1* identified to date, 2 are nonsense mutations and 2 are missense mutations in exons 3 and 4.[20] The two missense mutations and one of the nonsense mutations results in protein products that have comparatively low levels of protease activity and do not repress signaling by the TGF-β family.[20] The other nonsense mutation results in the loss of HTRA1 protein by nonsense-mediated decay of messenger RNA.[20] As a result, the amount of TGF-β1 is increased in the media of cerebral small arteries of CARASIL patients.[20] In addition, increased expression of extra domain A fibronectin and versican, which is induced by TGF-β signaling, was found in the intima of cerebral small arteries of a patient with CARASIL.[26]

Table 1. *Single-gene disorders causing cerebral vasculopathy and leukoaraiosis in adulthood*

Disease	Inheritance	Gene	Unique clinical features
CADASIL[46]	AD	*NOTCH3*	Migraine, depression, MRI hyperintensities involving the temporal poles; skin biopsy can be evaluated for NOTCH3 protein expression and granular osmophilic material by electron microscopy
Retinal vasculopathy with cerebral leukodystrophy (RVCL), also known as hereditary endotheliopathy with retinopathy, nephropathy, and stroke (HERNS) and hereditary cerebroretinal vasculopathy (HCRV)[47,48]	AD	*TREX1*	Retinal artery abnormalities (macular capillary dropout, tortuous telangiectasia) with progressive visual loss, Raynauds phenomenon, migraine, contrast-enhancing lesion mimicking tumor, proteinuria and hematuria
Hereditary angiopathy with nephropathy, aneurysms, and muscle cramps (HANAC)[49]	AD	*COL4A1*	Renal abnormalities (hematuria, cystic kidney), intracranial aneurysm, muscle cramps, retinal arteriolar tortuosity (retinal hemorrhages)
Fabrys disease[50]	AD	*GLA*	Periodic severe pain in the extremities, angiokeratoma; renal insufficiency, hypohidrosis, left ventricular hypertrophy, corneal opacity
Familial cerebral amyloid angiopathy[51]	AD	*APP*	Lobar hemorrhage, mutiple microbleeds
Familial British dementia[52]	AD	*ITM2B*	Ataxia, rigidospasticity
Familial Danish dementia[53]	AD	*ITM2B*	Ataxia, intention tremor, psychosis, cataracts, hearing loss

Abbreviation: AD, autosomal dominant.
Modified from.[8]

Signaling by members of the TGF-β family is closely associated with vascular angiogenesis and remodeling and plays multiple roles in vascular endothelial and smooth muscle cells.[35,36] Reduced TGF-β signaling due to mutations in TGF-β receptors leads to hereditary hemorrhagic telangiectasia, whereas activation of TGF-β signaling contributes to Marfan's syndrome and associated disorders.[36] The spectrum of diseases associated with the dysregulation of TGF-β signaling may be extended to include hereditary ischemic cerebral SVDs.[20]

Dysregulation of the inhibition of signaling by members of the TGF-β family also has been linked to alopecia and spondylosis, the other cardinal clinical features of CARASIL.[20] Transgenic mice overexpressing bone morphogenetic protein (BMP)-4, BMP-2, and TGF-β exhibit hair loss or retarded development of hair follicles.[37,38] Members of the BMP family are well-known regulators of bone formation, repair, and regeneration.[39] Furthermore, overexpression of HTRA1 decreases BMP-2–induced mineralization, whereas decreased expression of HTRA1 accelerates mineralization.[40] Recently some authors have reported an association between polymorphism in the *HTRA1* gene and disk degeneration or spondylosis deformans.[41]

The hypothesis that increased signaling by the TGF-β family contributes to the pathogenesis of CARASIL has been proposed, although why disinhibition of signaling by TGF-β family members caused by mutant *HTRA1* results in narrowly restricted clinical phenotypes remains unclear.[20]

Differential Diagnosis

The differential diagnosis of CARASIL includes sporadic SVDs, including BD, primary angiitis of the nervous system, and chronic progressive multiple sclerosis. The clinical characteristics and MRI abnormalities in these conditions may resemble those of CARASIL. The presence of diffuse white matter lesions on MRI extending to the temporal poles or external capsules; the presence of extraneural symptoms, such as acute low back pain and premature baldness; the absence of known vascular risk factors; and the absence of optic nerve and spinal cord involvement are critical in this regard. However, some young hypotensive patients with BD[42] and elderly normotensive patients with BD with and without familial occurrence have been reported.[43,44]

Other inherited disorders in the differential diagnosis include hereditary SVDs, including CADASIL (Table 1).[1-3,8,45-52] These disorders can be distinguished from CARASIL by clinical signs and symptoms, MRI findings, mode of inheritance, and laboratory results. Although CARASIL shares many features with CADASIL, there are differences, including the earlier onset of encephalopathy in CARASIL (mean, 32 years vs 45 years), different inheritance modes, the absence of migraine and severe depression in CARASIL, the

absence of the peculiar extraneural symptoms in CADASIL, and possibly different progression patterns of MRI white matter changes.

Several types of leukodystrophy associated with dermatologic or skeletal disorders in young adulthood must be differentiated from CARASIL. These include membraneous lipodystrophy (or Nasu-Hakola disease)[53] and adrenoleukodystrphy/adrenomyeloneuropathy,[54,55] both of which are readily differentiated by clinical and laboratory hallmarks. Although two progeric syndromes, Hutchinson-Gilford syndrome[56] and Werner syndrome,[57] share premature arteriosclerosis and early baldness with CARASIL, the presence of cardiac complications, cataracts, diffuse skin sclerosis, and systemic hair loss, along with the pathological predominance of atheromatous changes with manifest extension to the whole body, are distinguishing features of these syndromes.

Treatment

At present there is no effective treatment for patients with CARASIL. Primary treatments include genetic counseling, supportive care, and medications for treating dementia and secondary prevention of ischemic stroke. The effects of antiplatelet agents and anticoagulants are unclear in these patients, however.

Conclusion

CARASIL is a systemic genetic disease of the cerebral small vessels, spine, and hair follicles. Four causative mutations in the *HTRA1* gene have been identified to date. Disinhibition of signaling by TGF-β family members caused by mutant *HTRA1* is believed to contribute to the pathogenesis of CARASIL. This condition has never been reported outside Asia, although it is the second most common hereditary cerebral SVD in Japan. Genetically, no founder haplotype has yet been identified, and thus CARASIL is expected to be found more widely. The phenotypic presentation of the neurologic and neuroimaging features of CARASIL is similar to that of BD and CADASIL but distinct from in terms of the underlying vasculopathy, mode of inheritance, and extraneural symptoms. Like CADASIL, CARASIL is a prototype single-gene disorder directly affecting cerebral vessels that has evolved into a unique model for studying the mechanisms and therapeutic strategies not only for cerebral SVDs, but also for alopecia and spondylosis deformans/disk degeneration.

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