REVIEW

Genetic Causes of Cerebral Small Vessel Diseases

A Practical Guide for Neurologists

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Abstract

Cerebral small vessel disease (CSVD) includes various entities affecting the brain and, often, systemic small arteries, arterioles, venules, and capillaries. The underlying causes of CSVD are different, and some of them are genetic. Monogenic CSVDs are responsible for 1%–5% of all strokes and for several other disturbances. Despite many genes being involved, the phenotypes of monogenic CSVD partly overlap. Given that the genetic testing for different diseases can be challenging and time-consuming, the practicing neurologist should be adequately informed of the genetic background of CSVD and should be able to select patients to undergo genetic assessment and the genes to be analyzed. The purpose of this review was to summarize clinical, neurologic and non-neurologic, and neuroimaging features of monogenic CSVD and to provide a flowchart to be used in clinical practice to guide neurologists in this field. The proposed flowchart and the relative tables can be applied to 3 different settings, depending on the presentation: (1) ischemic stroke and/or transient ischemic attack, (2) cerebral hemorrhage, and (3) other neurologic, non-neurologic, and/or neuroimaging features of monogenic CSVD, in the absence of stroke syndromes because of infarction or hemorrhage.

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Glossary

CAA = cerebral amyloid angiopathy; **CADASIL** = cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; **CARASAL** = cathepsin-A–related arteriopathy with strokes and leukoencephalopathy; **CSVD** = cerebral small vessel disease; **DADA2** = deficiency of ADA2; **HANAC** = hereditary angiopathy with nephropathy, aneurysms, and muscle cramps; **HCHWA** = Hereditary Cerebral Hemorrhage with Amyloidosis; **ICH** = Intracerebral Hemorrhages; **IS** = Ischemic Stroke; **NGS** = Next-Generation Sequencing; **PADMAL** = pontine autosomal dominant microangiopathy and leukoencephalopathy; **RVCL-S** = retinal vasculopathy with cerebral leukodystrophy and systemic manifestations; **VUS** = variants of unknown significance; **WES** = whole-exome sequencing; **WMH** = white matter hyperintensities.

The category cerebral small vessel disease (CSVD) embodies a variety of entities affecting brain small arteries, arterioles, venules, and capillaries with different underlying etiologies. In patients with CSVD, the pathologic alterations are often also systemic. Brain alterations predominantly involve the subcortical areas and consist of various combinations of white matter lesions, lacunes of presumed vascular origin, recent small subcortical infarcts, large hemorrhages, and microbleeds.[1] White matter lesions occurring in patients with CSVD appear as bilateral, symmetrical hyperintensities on T2-weighted and fluid-attenuated inversion recovery MRI sequences (thus the definition of "white matter hyperintensities" [WMHs]) and are located in the hemispheric white matter.[1] They can be classified as focal, beginning confluent and diffuse confluent, and occur in the basal ganglia, corona radiata, centrum semiovale, and deep brainstem.[2] Lacunes of presumed vascular origin, instead, appear as hypointense signals on T1-weighted images and are often associated with WMHs and sited in the basal nuclei, internal capsule, thalamus, and pons.[1]

The etiologic classification of CSVD encompasses arteriolosclerosis, cerebral amyloid angiopathy (CAA), inflammatory and immunologically mediated CSVD, inherited or genetic disorders, and other CSVD, such as postradiation angiopathy and nonamyloid microvessel degeneration in Alzheimer disease.[1]

In recent years, an increasing number of genes have been associated with CSVD (Table 1). Patients affected by genetic CSVD share common clinical and neuroimaging features with the sporadic ones so that monogenic CSVDs are considered a great opportunity to investigate the pathogenesis of the latter.[3] Patients affected by different genetic CSVD often show overlapping phenotypes, thus suggesting the possibility of some common pathophysiologic pathways,[4] but also making the diagnosis challenging. The resulting diagnostic difficulties make it mandatory for the practicing neurologists to be adequately informed on the genetic background of CSVD and on the genotype-phenotype correlation. Furthermore, neurologists should be able to select patients for genetic testing and the specific genes to be analyzed.

The role of genetic testing in the clinical setting will become crucial in case of available effective therapeutic approaches (i.e., the enzyme replacement therapy with recombinant agalsidase alfa and beta for patients with Fabry disease due to deficiency of alpha-galactosidase A).[5] Even in the absence of therapeutic options, genetic testing and appropriate counseling can help provide patients and families knowledge about disease course that will help in planning for the future.

In the research setting, genetic testing is the starting point to explore the pathogenesis of diseases and to investigate the impact of molecular therapies. For instance, antisense oligonucleotides producing exon skipping represent a promising therapeutic strategy for cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) (*NOTCH3*, autosomal dominant).[6,7] The identification of carriers of specific sequence variations could guide the selection of participants for clinical trials aimed at testing target therapies involving the associated molecular pathways.

Recently, the development of next-generation sequencing (NGS) techniques, which include gene panels, whole-exome sequencing (WES), and whole-genome sequencing, has expanded our knowledge on genetic disorders, including monogenic CSVD. The major challenge generated by NGS, however, is the huge amount of data with some possible uncertainties such as the emergence of variants of unknown significance, whose interpretation requires familiarity with the genetic background and clinical expression of the suspected diseases.

Starting from the complexity of monogenic CSVD, this review arises from the need for practical advice to guide neurologists in the world of genetic testing. To this aim, we have developed a flowchart to be used in clinical practice (Figure). To follow this step-by-step diagram, the reader should use the tables provided, which report the clinical, both neurologic and nonneurologic (Tables 2 and 3), and neuroimaging features (Table 4) found in patients with genetic CSVD. These features are also described in the consecutive paragraphs of this article and schematically presented in eTables 1, 2, and 3 (links.lww.com/WNL/C547). The flowchart provided derives from an extensive review of medical literature, whose search strategy is reported in eMethods; the complete list of references are presented in eReferences. This algorithm can be used in 3 different settings: (1) patients with an ischemic stroke and/or transient ischemic attack (TIA) (blue path), (2) patients with cerebral hemorrhage (red path), and (3) patients

Table 1 Genes Associated With Monogenic CSVD

Gene (abbreviation)	Gene (complete name)	Disease	Inheritance pattern	Sequence variants' specific features	Other possible phenotypes	Clinical practice
NOTCH3	Notch receptor 3	CADASIL	Autosomal dominant			Sequencing of exons 2–24, where all CADASIL mutations have been reported In case of VUS, perform skin biopsy to reveal GOM at electron microscopy and/or NOTCH3 extracellular domain at immunostaining (at least 5 arteries)
HTRA1	High-Temperature Requirement A Serine Peptidase 1	CARASIL HTRA1-AD	Autosomal recessive Autosomal dominant			
COL4A1	Collagen type IV alpha 1 chain	*COL4A1*-associated CSVD	Autosomal dominant	Frequently introducing a premature stop codon or affecting a glycine of a GLY-X-Y (X and Y any possible amino acid) motif in the triple helix Phenotype penetrance strongly associated with the location of the mutation (i.e., amino-terminal and retinal arteriolar tortuosity; carboxy-terminal and cataract, glaucoma, anterior segment dysgenesis and microphthalmia)		
		PADMAL	Autosomal dominant	Located in the 3′ UTR affecting the binding site of the microRNA mir29		
		HANAC	Autosomal dominant	Affecting glycine in exons 24 and 25		
COL4A2	Collagen type IV alpha 2 chain	*COL4A2*-associated CSVD	Autosomal dominant			
TREX1	Three Prime Repair Exonuclease 1	RVCL-S	Autosomal dominant	Frequently frameshift mutations involving the C-terminal of the *TREX1*-encoded exonuclease	Aicardi-Goutieres syndrome, systemic lupus erythematosus, familial chilblain lupus, Cree encephalitis, cryofibrinogenemia	
CECR1	Cat Eye Syndrome Chromosome Region 1	DADA2	Autosomal recessive	Loss-of-function (reduced ADA2 activity in plasma and protein levels in cell lysates)		
CTSA	Cathepsin A	CARASAL	Autosomal dominant	One single sequence variation (p.R325C)	Homozygous *CTSA* variants are responsible for galactosialidosis (lysosomal storage disorder; β-galactosidase (GLB1) and neuraminidase 1 deficiency)	
GLA	Galactosidase Alpha	Fabry disease	X-linked			Diagnosis in male patients (classic severe phenotype): α-Gal A activity in peripheral leukocytes (or plasma, when leukocytes are not available) or, alternatively, *GLA* sequencing Diagnosis in female patients (variable phenotype, including asymptomatic carriers): *GLA* sequencing (because α-Gal A activity in peripheral leukocytes can be normal and plasma levels are treacherous)

Continued

Table 1 Genes Associated With Monogenic CSVD *(continued)*

Gene (abbreviation)	Gene (complete name)	Disease	Inheritance pattern	Sequence variants' specific features	Other possible phenotypes	Clinical practice
ABCC6	ATP-Binding Cassette Subfamily C Member 6	Pseudoxanthoma elasticum	Autosomal recessive			Revised diagnostic criteria (Plomp et al., 2010): gene testing is required when a definite diagnosis is not reached by the association of clinical signs (yellowish papules and/or plaques on the lateral side of the neck and/or flexural areas of the body" and "peau d'orange of the retina") and skin biopsy or fundoscopy findings
APP	Amyloid Beta Precursor Protein	HCHWA	Autosomal dominant	Codon 693: Dutch type (p.E693Q) Codon 693: Italian type (p.E693K) Codon 694: Iowa type (p.D694N) Codon 692: Flemish type (p.A692G)		
CST3	Cystatin C	HCHWA	Autosomal dominant	Icelandic type (p.L68Q)		
ITMB2/BRI	Integral membrane protein 2B	Familial British Dementia	Autosomal dominant			

Abbreviations: AD = autosomal dominant; CADASIL = cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CARASAL = cathepsin-A–related arteriopathy with strokes and leukoencephalopathy; CARASIL = cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy; CSVD = cerebral small vessel disease; DADA2 = deficiency of ADA2; GLY = glycine; GOM = granular osmiophilic material; HANAC = hereditary angiopathy with nephropathy, aneurysms, and muscle cramps; HCHWA = Hereditary Cerebral Hemorrhage with Amyloidosis; PADMAL = pontine autosomal dominant microangiopathy and leukoencephalopathy; RVCL-S = retinal vasculopathy with cerebral leukodystrophy and systemic manifestations; UTR = untranslated region; VUS = variant of unknown significance.

with other neurologic, non-neurologic, and/or neuroimaging features of monogenic CSVD, in the absence of stroke syndromes because of infarction or hemorrhage (green path).

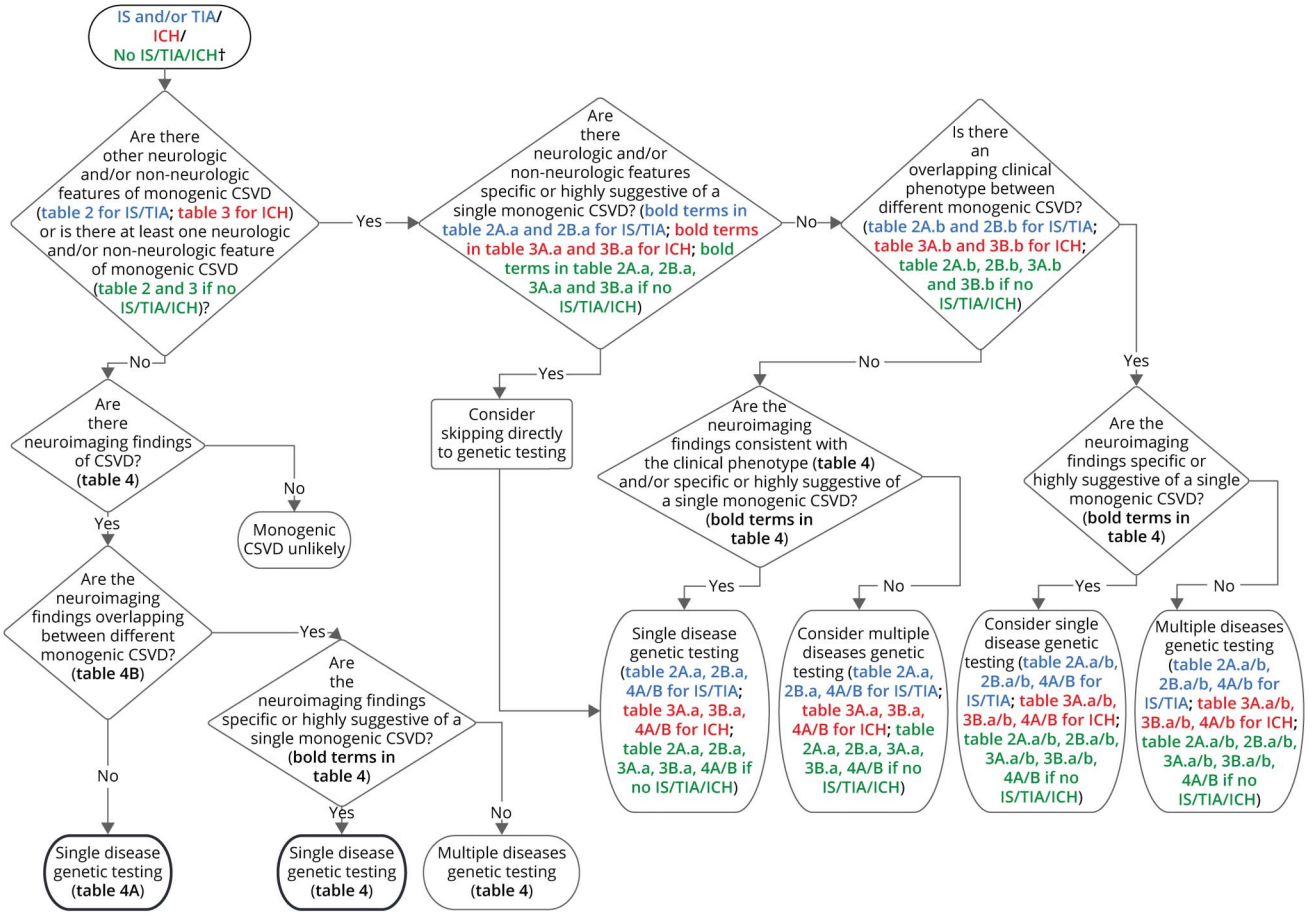
Clinical-Neuroimaging Features of Monogenic CSVD

Stroke Syndromes Due to Infarction or Hemorrhage

The natural history of most patients with CSVD is characterized by the occurrence of one or more stroke syndromes due to either infarction or hemorrhage (Figure, blue and red paths). Indeed, an ischemic stroke or a hemorrhage is often the clinical feature that leads to the suspicion of a genetic CSVD. The reader should follow the blue path of the flowchart in case of stroke syndrome due to infarction and the red path when hemorrhages occur (Figure). The presence of one of the 2 types of stroke syndrome usually differentiates the form of CSVD, with some exceptions. For example, although most strokes occurring in patients affected by CADASIL and cathepsin-A–related arteriopathy with strokes and leukoencephalopathy (CARASAL) (*CTSA*, autosomal dominant) are ischemic (and, specifically, small subcortical) (blue path, Figure), cerebral hemorrhages are described, especially in case of anticoagulant therapy (red path, Figure).[8,9] Cerebral hemorrhages are exclusively deep in patients with CARASAL, while they might be also lobar in those affected by CADASIL.[10-12] Stroke syndromes due to hemorrhages or infarctions are more suspected for a genetic form of CSVD if they are recurrent and occur at young age (Table 5).[8]

In this scenario, some specific features of ischemic strokes and hemorrhages could help distinguish the different genetic etiologies of CSVD. For instance, in patients with CARASAL, ischemic strokes and TIAs frequently appear later in life compared with CADASIL (average age at onset, seventh decade vs fifth decade) (blue path, Figure).[8] Similarly, recurrent small subcortical infarcts appear later during disease progression in carriers of heterozygous *HTRA1* variations (*HTRA1*, autosomal dominant) compared with patients affected by cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL) (*HTRA1*, autosomal recessive) (average age at onset, seventh decade vs third-fourth decades) (blue path, Figure).[13] In addition to subcortical and periventricular white matter, basal ganglia, corpus callosum, and cerebellar peduncles, recurrent subcortical infarcts located in the pons are characteristic of patients with pontine autosomal dominant microangiopathy and leukoencephalopathy (PADMAL) (*COL4A1*, autosomal dominant) (blue path, Figure).[14] Small subcortical infarcts prevail over deep intracerebral hemorrhages also in patients with retinal vasculopathy with cerebral leukodystrophy and systemic manifestations (RVCL-S) (*TREX1*, autosomal dominant) (blue path, Figure).[15] The coexistence of small and large arteries involvement represents a distinctive hallmark of patients with Fabry disease (*GLA*, X-linked), pseudoxanthoma elasticum (*ABCC6*, autosomal recessive), and hereditary

Figure Diagnosis Flowchart of Monogenic Cerebral Small Vessel Diseases (CSVDs) Presenting With Ischemic Stroke (IS) and/or TIA With Intracerebral Hemorrhage (ICH) or in Absence of Stroke Syndromes Due to Infarction or Hemorrhage



†Patients With No IS/TIA/ICH Who are Assessed for Monogenic CSVD Might be (1) Those With a Family History of Suspected or Confirmed Disease, (2) Those Presenting With Neurologic And/or Non Neurologic Clinical Features other Than Cerebrovascular Manifestations, and (3) Those With "Incidental" Discovery of Imaging Findings. Abbreviations: CSVD = cerebral small vessel disease; ICH = intracerebral hemorrhage; IS = Ischemic Stroke; TIA = transient ischemic attack. Presenting with IS and/or TIA: follow the blue path and use Tables 2 and 4; ICH: follow the red path and use Tables 3 and 4; no stroke syndromes due to infarction or hemorrhage: follow the green path and use Tables 2–4.

angiopathy with nephropathy, aneurysms, and muscle cramps (HANAC) (*COL4A1*, autosomal dominant) (blue and red paths, Figure). In these subjects, indeed, large vessel strokes result from cardiac embolism or large arteries disease (i.e., atherosclerosis, dolichoectasia, or aneurysms of intracranial vessel or extracranial vessel dissection), while small vessel disease typically produces small subcortical infarcts or results in neuroimaging markers of CSVD, such as WMHs, which are described in the Neuroimaging section.[16] In patients with Fabry disease, most strokes are ischemic. However, deep intracerebral (i.e., thalamus and basal ganglia), and subarachnoid hemorrhages, cerebral venous thrombosis can also occur (blue and red paths, Figure).[16] Cerebrovascular complications (small subcortical infarcts more than deep intracerebral and subarachnoid hemorrhages, aneurysms, carotid rete mirabile, and cerebral venous thrombosis) usually appear years after the onset of dermatologic and ocular manifestations in patients with pseudoxanthoma elasticum (blue and red paths, Figure).[17] In addition to strokes caused by small subcortical infarcts (i.e., deep brain nuclei and brainstem), which are the most frequent cerebrovascular events in subjects affected by deficiency of ADA2 (DADA2) (*CECR1*, autosomal recessive), deep intracerebral hemorrhages (i.e., basal ganglia, thalamus, and brainstem), hemorrhagic transformation of ischemic infarcts, and Sneddon syndrome are sometimes reported (blue and red paths, Figure).[18]

Cerebral hemorrhages beginning in the fourth or fifth decades of life represent the main neurologic aspect of patients with *COL4A1*-associated and *COL4A2*-associated CSVD (*COL4A1* and *COL4A2*, autosomal dominant) and can be spontaneous or secondary to trauma, anticoagulant therapy, or physical activity (red path, Figure).[19] They are mainly subcortical, sited in the white matter, deep gray nuclei, or brainstem.[19] More rarely, lobar, intraventricular, or subarachnoid post-traumatic hemorrhages have been reported.[19] However, small subcortical infarcts are described (Figure).[19] A lower risk of intracerebral hemorrhages (mainly post-traumatic) and the presence of intracranial

aneurysms help distinguish patients with HANAC from those with *COL4A1*-associated and *COL4A2*-associated CSVD (red path, Figure).[20] Similar to *COL4A1*-associated and *COL4A2*-associated CSVD, patients affected by HANAC develop small subcortical infarcts (i.e., in the brainstem) (blue path, Figure). Recurrent intracerebral lobar hemorrhages starting from middle age (usually younger than 55 years), often associated with subarachnoid bleeding, can be a warning sign of Dutch, Italian, Iowa, Flemish, and Piedmont subtypes of Hereditary Cerebral Hemorrhage with Amyloidosis (HCHWA) (*APP* and *CST3*, autosomal dominant) (i.e., the genetic counterpart of sporadic CAA) (red path, Figure).[21] In the Icelandic type, instead, cerebral hemorrhagic events occur between age 20 and 30 years, remarkably earlier than the other subgroups.[22] Recurrent intracerebral lobar hemorrhages are also found in patients with CAA and Alzheimer disease because of *APP* duplication and triplication (autosomal dominant) and in those with the hereditary transthyretin leptomeningeal CAA (*TTR*, autosomal dominant).[23-25] To a lesser extent, small subcortical infarcts are described in the Dutch and Piedmont subtypes of HCHWA (blue path, Figure).[26] Conversely, deep and small intracerebral hemorrhages are rarer in patients with Familial British Dementia (*ITMB2*/*BRI*, autosomal dominant) (red path, Figure).[27]

Other Neurologic Features

Patients affected by monogenic CSVD may show various neurologic features, many of which are common to different forms, while others are more specific for a single disease (Tables 2A.a, A.b and 3A.a, A.b). An additional problem is the fact that the expression of these neurologic characteristics is variable during the course of the disease and across patients.

A variable combination of neurologic features in addition to ischemic strokes and TIAs, including cognitive impairment, migraine with typical and/or atypical aura, and mood disturbances, is found in patients with CADASIL, the most common form of genetic CSVD (Tables 2A.b and 3A.b).[8] Migraine attacks, reported in up to 45% of patients, are an early characteristic of CADASIL.[28] Other possible neurologic features are seizures, gait disturbances, pseudobulbar palsy, urinary urgency, parkinsonism, hypoacusis, and episodes of acute encephalopathy (Tables 2A and 3A). However, the presence of MRI alterations consistent with CADASIL should support the diagnostic hypothesis even if neurologic features are limited to ischemic strokes, migraine with aura, or psychiatric symptoms.[29] When facing the patient with suspected CADASIL, we suggest that the clinician use the CADASIL Scale as a screening tool to select patients for *NOTCH3* gene analysis.[29] The scale includes the following items: migraine, migraine with aura, TIA/stroke, TIA/stroke onset younger than 50 years, psychiatric disturbances, cognitive decline/dementia, leukoencephalopathy, leukoencephalopathy extended to temporal pole, leukoencephalopathy extended to external capsule, subcortical infarcts, family history in at least 1 generation, and family history in at least 2 generations.[29] The total score ranges from 0 to 25; a total score ≥15 is suggestive of CADASIL.[29] In 2019, Koizumi et al. developed the CADASIL Scale-J, adjusted for the Japanese population, which includes subcortical infarcts, family history, leukoencephalopathy at temporal pole, age at onset 50 years or younger, stroke/TIA, and absence of diabetes.[30]

Except for the lower rate of migraine attacks, the neurologic phenotype of patients with CARASIL resembles that of CADASIL (i.e., recurrent ischemic strokes, progressive dementia, and gait disturbances) (Table 2A).[31] Further neurologic features are mainly seizures and pseudobulbar palsy and to a lesser extent psychiatric symptoms, horizontal nystagmus, and urinary urgency.

When rapidly progressive cognitive and motor impairment accompanies recurrent pontine ischemic strokes by age 35–45 years in the absence of cerebral hemorrhages and extracerebral symptoms, PADMAL should be considered (Table 2A.b).[32]

In CARASAL, in addition to ischemic strokes and TIAs, cognitive impairment and mood disturbances are described (Tables 2A and 3A).[9] Other neurologic symptoms which might help distinguish it from other entities, especially CADASIL, include transient movement disorders, vertigo, postural instability, cranial nerve involvement, muscle cramps, and rapid eye movement sleep rapid behavior disorder (RBD).[9] Furthermore, headache, altered gait, reduced concentration, and disinhibition are frequently found at early disease stages, unlike the cerebral infarctions.[10]

Focal neurologic deficits (i.e., hemiparesis, facial weakness, aphasia, and hemianopsia), cognitive impairment, psychiatric symptoms, seizures, and headache are found in patients affected by RVCL-S (Table 2A.b).[15]

Limb pain starting from hands and feet and progressing proximally, called "Fabry crisis," is one of the earliest and most disabling neurologic manifestations of patients with Fabry disease (Tables 2A and 3A). Pain crises, which are triggered by environmental factors and are difficult to be managed, are not accompanied by physical alterations and can persist throughout life, although the number of crises usually decreases with age.[33] Both pain and acroparesthesia result from small fiber neuropathy.[33] Autonomic neuropathy produces sweating alterations that mainly appear as hypohidrosis and, to a lesser extent, hyperhidrosis.[33] Other neurologic symptoms include cognitive impairment, psychiatric symptoms, progressive/sudden hearing loss, and tinnitus.[33]

The involvement of the peripheral nervous system (i.e., myositis and neuropathy), ataxia, seizures, and cranial nerve deficits (i.e., vertigo, hypoacusis, optic nerve atrophy, and oculomotor disturbances) can be found in DADA2 patients (Tables 2A and 3A).

Migraine, seizures, and progressive dementia might accompany early onset intracerebral hemorrhages in patients affected by *COL4A1*-associated and *COL4A2*-associated CSVD (Tables 2A and 3A).[19] Notably, when first manifestations

Table 2 Other Neurologic and Non-neurologic Features Found in Patients With Monogenic Cerebral Small Vessel Disease (CSVD) and Presenting With Ischemic Stroke (IS) and/or TIA or in the Absence of Stroke Syndromes Due to Infarction or Hemorrhage

	Other neurologic features	Disease		Non-neurologic features	Disease
A.a	Acute encephalopathy	CADASIL	**B.a**	**Alopecia**	**CARASIL** ***HTRA1*** **heterozygotes**
	Parkinsonism	CADASIL		**Spondylosis deformans**	**CARASIL** ***HTRA1*** **heterozygotes**
	Nystagmus	CARASIL		Low back pain/disk herniation	CARASIL *HTRA1* heterozygotes
	Transient movement disorders	CARASAL		Diabetes	CARASAL
	RBD	CARASAL		Macular skin rash and punctate skin lesions	RVCL-S
	Facial pain	CARASAL		Thyroid disease	RVCL-S
	Hyperacusis	CARASAL		**Vasculitis (polyarteritis nodosa, Sneddon syndrome)**	**DADA2**
	Ataxia	DADA2		**Pure red cell aplasia and/or other cytopenia, immune deficiency mainly affecting B cells, hypogammaglobulinemia, and hypercoagulability**	**DADA2**
	Optic neuritis and optic nerve atrophy	DADA2		**Livedo racemosa**	**DADA2**
	Oculomotor deficit	DADA2		Arthritis	DADA2
	Myositis	DADA2		Renovascular arterial aneurysms	DADA2
	Acroparesthesias	Fabry disease		**Cornea verticillata** and other ocular abnormalities (whorl keratopathy, conjunctival lymphangiectasia)	**Fabry disease**
	Hypohidrosis, anhidrosis, and/or hyperhidrosis	Fabry disease		**Angiokeratoma**	**Fabry disease**
	Infantile hemiparesis/ tetraparesis	*COL4A1/2*-related CSVD[a]		Azoospermia	Fabry disease
	Developmental delay	*COL4A1/2*-related CSVD[a]		Pulmonary symptoms	Fabry disease
	Muscular dystrophy	*COL4A1/2*-related CSVD[a]		Facial dysmorphology	Fabry disease
	Myoglobinuria	*COL4A1/2*-related CSVD[a]		Parapelvic cysts	Fabry disease
A.b	Dementia	CADASIL CARASIL *HTRA1* heterozygotes RVCL-S CARASAL PADMAL Fabry disease *COL4A1/2*-related CSVD[a] HCHWA (Dutch, Piedmont, Icelandic)[a]		**Retinal peau d'orange, retinal angioid streaks, comitial lesions**	**Pseudoxanthoma elasticum**
	Migraine	CADASIL CARASIL *HTRA1* heterozygotes RVCL-S CARASAL *COL4A1/2*-related CSVD[a] HANAC[a] HCHWA Dutch type[a]		**Skin papules**	**Pseudoxanthoma elasticum**

Continued

Table 2 Other Neurologic and Non-neurologic Features Found in Patients With Monogenic Cerebral Small Vessel Disease (CSVD) and Presenting With Ischemic Stroke (IS) and/or TIA or in the Absence of Stroke Syndromes Due to Infarction or Hemorrhage *(continued)*

Other neurologic features	Disease		Non-neurologic features	Disease
Psychiatric symptoms	CADASIL CARASIL *HTRA1* heterozygotes RVCL-S CARASAL PADMAL Fabry disease		Angina pectoris	Pseudoxanthoma elasticum
Seizures	CADASIL CARASIL RVCL-S DADA2 *COL4A1/2*-related CSVD[a] HANAC[a]		**Axenfeld-Rieger and other ocular abnormalities** (microphthalmia and microcornea, anterior segment dysgenesis, glaucoma, optic nerve and iris hypoplasia, strabismus, posterior embryotoxon, high myopia, aphakia)	***COL4A1/2*-related CSVD[a]**
Hypoacusis	CADASIL CARASAL DADA2 Fabry disease		Glomerulopathy	*COL4A1/2*-related CSVD[a]
Vertigo	CARASAL DADA2 Fabry disease	**B.b**	Retinal vasculopathy and hemorrhages	RVCL-S Fabry disease Pseudoxanthoma elasticum HANAC[a] *COL4A1/2*-related CSVD[a]
Tinnitus	CARASAL Fabry disease		Visual impairment and/or visual field defect	RVCL-S DADA2 Fabry disease Pseudoxanthoma elasticum HANAC[a] *COL4A1/2*-related CSVD[a]
Gait disturbances	CADASIL CARASIL *HTRA1* heterozygotes CARASAL		Sicca syndrome	CARASAL Fabry disease
Urinary urgency	CADASIL CARASIL		Cataract	Fabry disease *COL4A1/2*-related CSVD[a]
Pseudobulbar palsy	CADASIL CARASIL		Proteinuria and renal failure	RVCL-S Fabry disease HANAC[a]
Neuropathy	Fabry disease DADA2		Hematuria	*COL4A1/2*-related CSVD[a] HANAC[a]
Muscle cramps and elevated serum creatine kinase level	CARASAL *COL4A1/2*-related CSVD[a] HANAC[a]		Renal cysts	*COL4A1/2*-related CSVD[a] HANAC[a]
			Raynaud phenomenon	RVCL-S *COL4A1/2*-related CSVD[a] HANAC[a]
			Cardiomyopathy	RVCL-S Fabry disease (left ventricular hypertrophy, myocardial fibrosis) Pseudoxanthoma elasticum (restrictive)
			Mitral valve prolapse	Pseudoxanthoma elasticum *COL4A1/2*-related CSVD[a]
			Cardiac rhythm disorders	Fabry disease (short PR interval, sinus bradycardia, conduction abnormalities, atrial fibrillation, sudden death) *COL4A1/2*-related CSVD[a] (supraventricular arrhythmias) HANAC[a] (supraventricular arrhythmias)

Continued

Table 2 Other Neurologic and Non-neurologic Features Found in Patients With Monogenic Cerebral Small Vessel Disease (CSVD) and Presenting With Ischemic Stroke (IS) and/or TIA or in the Absence of Stroke Syndromes Due to Infarction or Hemorrhage *(continued)*

Other neurologic features	Disease	Non-neurologic features	Disease
		Anemia	DADA2 RVCL-S *COL4A1/2*-related CSVD[a] (hemolytic)
		Spontaneous hemorrhages into extracerebral organs	RVCL-S (gastrointestinal bleeding) Pseudoxanthoma elasticum (gastrointestinal bleeding) *COL4A1/2*-related CSVD[a]
		Gastrointestinal symptoms	DADA2 Fabry disease
		Hepatic disease	RVCL-S (liver failure) DADA2 (hepatosplenomegaly) *COL4A1/2*-related CSVD[a] (cysts) HANAC[a] (cysts)
		Bone disease	RVCL-S Fabry disease (osteopenia, osteoporosis)
		Therapy-resistant hypertension	CARASAL RVCL-S Fabry disease Pseudoxanthoma elasticum

Abbreviations: CADASIL = cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CARASAL = cathepsin-A–related arteriopathy with strokes and leukoencephalopathy; CSVD = Cerebral small vessel disease; DADA2 = deficiency of ADA2; HANAC = hereditary angiopathy with nephropathy, aneurysms, and muscle cramps; HCHWA = Hereditary Cerebral Hemorrhage with Amyloidosis; ICH = Intracerebral Hemorrhages; IS = Ischemic Stroke; PADMAL = pontine autosomal dominant microangiopathy and leukoencephalopathy; RBD = rapid behavior disorder; RVCL-S = retinal vasculopathy with cerebral leukodystrophy and systemic manifestations; TIA = transient ischemic attack.
(A.a-A.b) Other neurologic features found in patients with monogenic CSVD and presenting with IS and/or TIA. The same neurologic features might be found in patients with monogenic CSVD in the absence of stroke syndromes due to infarction or hemorrhage. Box A.a includes neurologic features not overlapping between monogenic CSVD, while box A.b reflects those overlapping. (B.a-B.b) Non-neurologic features found in patients with monogenic CSVD and presenting with IS and/or TIA. The same non-neurologic features might be found in patients with monogenic CSVD in absence of stroke syndromes due to infarction or hemorrhage. Box B.a includes non-neurologic features not overlapping between monogenic CSVD, while box B.b reflects those overlapping. Neurologic and non-neurologic features which are specific or highly suggestive of a single CSVD are in bold.
[a] Monogenic CSVD which are usually associated with ICH but might also produce IS.

appear in the neonatal period or in childhood because of the presence of porencephaly, they are represented by hemiparesis and other focal neurologic deficits, psychomotor delay, and congenital hydrocephalus.[34]

In addition to recurrent intracerebral hemorrhages, progressive dementia is a cardinal feature of subjects affected by Dutch, Italian, Flemish, Iowa, and Piedmont subtypes of the HCHWA, by the CAA and Alzheimer disease because of *APP* duplication and/or triplication and by the hereditary transthyretin leptomeningeal CAA (Tables 2A and 3A).[21,23-25] Recurrent headaches, poststroke epilepsy, and psychiatric disturbances are frequently reported (Tables 2A and 3A).[21,23-25] Only in 1 Flemish pedigree, the frequency of cerebral hemorrhages was far lower than cognitive decline.[35] In addition, patients with the hereditary transthyretin leptomeningeal CAA show ataxia, spasticity, hydrocephalus, myelopathy, hearing loss, and both axonal sensorimotor neuropathy and radiculopathy (Table 3A).[25] The progressive triad of dementia, cerebellar ataxia, and spastic tetraparesis, with onset at around the fifth decade of life and death after an average of 10 years, is typically associated with Familial British Dementia, produced by *BRI2* mutations (Table 3A).[27] Additional features are represented by psychiatric symptoms, brainstem signs, seizures, headache, and stroke-like episodes (Table 3A).[27]

Non-neurologic Features

Extracerebral features are frequent in patients with CSVD (Tables 2B.a, B.b and 3B.a, B.b).[36] An exception is represented by subjects with CADASIL, who rarely develop symptoms other than the neurologic ones.[8]

The presence of sicca syndrome and therapy-resistant hypertension should orient the practicing clinician to search for CARASAL (Tables 2B and 3B).[10]

When leukoencephalopathy appears at around age 30 years and is accompanied by premature and diffuse alopecia, lumbago, and spondylosis before the fifth decade, especially in Japanese patients, CARASIL should be considered and *HTRA1* genetic testing performed (Table 2B).[31] However, phenotype is sometimes incomplete, thus making differential diagnosis challenging.[31] Extracerebral features are rarer in carriers of heterozygous *HTRA1* sequence variations compared with CARASIL.[32]

Angiokeratomas, which appear as reddish-purple skin lesions concentrated in the genitalia or umbilical regions, are an early

sign of Fabry disease and can guide diagnosis (Tables 2B and 3B).[33] The presence of cornea verticillata represents another distinctive hallmark of these patients: starting from the center of the cornea, corneal opacities grow radially without affecting visual acuity (Tables 2B and 3B).[33] Further relevant ocular manifestations consist of retinal vessels tortuosity and opacities of the posterior lens (Tables 2B and 3B).[33] Renal impairment appears as hyperfiltration, microalbuminuria, proteinuria, and isosthenuria during the teenage years and progressively proceeds to renal failure, unless enzyme replacement therapy is performed (Tables 2B and 3B).[33] Gastrointestinal symptoms frequently occur in childhood (Tables 2B and 3B).[33] Heart involvement is often described, with severe diastolic and systolic dysfunction due to left ventricular hypertrophy; ECG aberrations (mainly supraventricular arrhythmia and nonsustained ventricular tachycardia); valve dysfunction, frequently affecting the left heart and producing mild-to-moderate insufficiency with no significant hemodynamic consequences (Tables 2B and 3B).[33] Azoospermia, osteopenia, osteoporosis, pulmonary symptoms, facial dysmorphism, and parapelvic cysts are described in a reduced number of cases (Tables 2B and 3B).[33]

Skin lesions ("cobblestone", "Moroccan leather", and "plucked chicken skin") are usually the first appearance of pseudoxanthoma elasticum (Tables 2B.a and 3B.a).[37] The small yellowish xanthoma-like papules are symmetrically distributed on the lateral side of the neck and, more rarely, in other flexural areas, in the periumbilical region, and in the oral or anogenital mucosa and can fuse into plaques.[37] Pigmented spots of the fundus oculi known as "peau d'orange" of the retina, located in the temporal part of the fovea, and brownish-gray irregular lines called "angioid streaks", which are Bruch membrane fractures irradiating from the optic disc, are typical ocular signs (Tables 2B.a and 3B.a).[37] Both "yellowish papules and/or plaques on the lateral side of the neck and/or flexural areas of the body" and "peau d'orange of the retina" represent major diagnostic criteria of the revised diagnostic criteria for pseudoxanthoma elasticum proposed in 2010 by Plomp et al.[38] With disease progression, patients develop the pathognomonic chorioretinal atrophies called "comitial lesions" (Tables 2B.a and 3B.a).[37] The development of neovascular membranes from the choroid can lead to subretinal and retinal hemorrhages (Tables 2B.b and 3B.b).[37] Both choroidal neovascularization and macular atrophy are responsible for the possible progressive visual loss.[37] Pseudoxanthoma elasticum can produce gastrointestinal bleeding and cardiovascular complications, including intermittent claudication, angina pectoris, mitral valve prolapse, myocardial infarction, and sudden cardiac death (Tables 2B and 3B).[37]

Polyarteritis nodosa and hematologic features dominate the systemic picture of patients with DADA2 (Tables 2B and 3B).[39] Immunodeficiency (consisting of reduced differentiation and increased death of B cells and hypogammaglobulinemia), cytopenia (predominantly pure red cell aplasia), periodic fever, and livedo racemosa have been often described (Tables 2B.a and 3B.a).[39] In addition, patients can present with rheumatologic (i.e., arthritis), kidney (i.e., renovascular aneurysms), liver (i.e., hepatosplenomegaly), and gastrointestinal involvement (Tables 2B and 3B).[39]

The suspicion of *COL4A1*-associated and *COL4A2*-associated CSVD is supported by the combination of ocular and renal involvement. Notably, both cerebral and extracerebral *COL4A2*-associated phenotype is milder than the *COL4A1* one.[40] Ocular manifestations include cataract (frequently bilateral and congenital), retinal vascular tortuosity, microphthalmia and microcornea, anterior segment dysgenesis, glaucoma, optic nerve and iris hypoplasia, strabismus, posterior embryotoxon, aphakia, and high myopia (Tables 2B and 3B).[19] Some of them are part of the ocular abnormalities found in subjects with the Axenfeld-Rieger syndrome.[41] Kidney cysts and hematuria are developed by most patients (Tables 2B and 3B).[19] *COL4A1*-associated CSVD is rarely associated with hemolytic anemia, Raynaud phenomenon, cardiac arrhythmias, spontaneous hemorrhages in extracerebral organs, and hepatic cysts (Tables 2B and 3B).[19] Recognizing *COL4A1* phenotype is crucial nowadays because potential therapeutic approaches (i.e., phenyl butyric acid) are under investigation.[42]

The combination of ocular and kidney involvement appears also in RVCL-S. In this case, retinopathy is secondary to occlusive endotheliopathy and often leads to visual loss and/or visual field defects (Table 2B).[15] The ocular evaluation will demonstrate telangiectasias, microaneurysms, perifoveal obliterations, and neovascularization, but not intraocular inflammation, intraretinal hemorrhages, and leakage, which can help in differential diagnosis (Table 2B).[15] It can be accompanied by nonspecific signs and symptoms, as renal failure and proteinuria, rarely progressing to end-stage renal disease, liver failure, mild Raynaud phenomenon, gastrointestinal bleeding and anemia, bone disease, skin alterations (i.e., macular rash and punctate lesions), and subclinical hypothyroidism (Table 2B).[15]

Some non-neurologic features help diagnose the hereditary transthyretin leptomeningeal CAA, including cardiomegaly and ocular abnormalities, such as vitreous opacities, glaucoma, dry eye, and ocular amyloid angiopathy (Table 3B).[25]

Neuroimaging Features

Neuroimaging is a fundamental tool in the identification and differential diagnosis of monogenic forms of CSVD (Table 4). Despite being rarely diagnostic by itself, it is often very useful.

As previously mentioned, WMHs represent the neuroimaging hallmark of almost all CSVDs.[1] The detection of a specific pattern of distribution of WMHs, together with the presence of additional neuroimaging features, constitutes the keystone of differential diagnosis in the field of monogenic CSVD. WMHs usually show no enhancement, unless otherwise described. Lacunes of presumed vascular origin are frequently associated with WMHs and should be differentiated from dilated perivascular spaces, an additional sign of CSVD.[1] Indeed, these enlargements of the Virchow-Robin spaces (i.e., those surrounding

Table 3 Other Neurologic and Non-neurologic Features Found in Patients With Monogenic Cerebral Small Vessel Disease (CSVD) and Presenting With Intracerebral Hemorrhages (ICH) or in the Absence of Stroke Syndromes Due to Infarction or Hemorrhage

	Other neurologic features	Disease		Non-neurologic features	Disease
A.a	Developmental delay	*COL4A1/2*-related CSVD	**B.a**	**Axenfeld-Rieger and other ocular abnormalities** (microphthalmia and microcornea, anterior segment dysgenesis, optic nerve and iris hypoplasia, strabismus, posterior embryotoxon, high myopia, aphakia)	***COL4A1/2*-related CSVD**
	Muscular dystrophy	*COL4A1/2*-related CSVD		Glomerulopathy	*COL4A1/2*-related CSVD
	Myoglobinuria	*COL4A1/2*-related CSVD		**Vasculitis (polyarteritis nodosa, Sneddon syndrome)**	**DADA2**
	Optic neuritis and optic nerve atrophy	DADA2		**Pure red cell aplasia and/or other cytopenia, immune deficiency mainly affecting B cells, hypogammaglobulinemia**, and hypercoagulability	**DADA2**
	Oculomotor deficit	DADA2		**Livedo racemosa**	**DADA2**
	Myositis	DADA2		Arthritis	DADA2
	Acroparesthesias	Fabry disease		Renovascular arterial aneurysms	DADA2
	Hypohidrosis, anhidrosis and/or hyperhidrosis	Fabry disease		**Cornea verticillata** and other ocular abnormalities (whorl keratopathy, conjunctival lymphangiectasia)	**Fabry disease**
	Myelopathy	*TTR* CAA		**Angiokeratoma**	**Fabry disease**
	Hydrocephalus	*TTR* CAA		Azoospermia	Fabry disease
	Acute encephalopathy	CADASIL[a]		Pulmonary symptoms	Fabry disease
	Parkinsonism	CADASIL[a]		Facial dysmorphology	Fabry disease
	Transient movement disorders	CARASAL[a]		Parapelvic cysts	Fabry disease
	RBD	CARASAL[a]		**Retinal peau d'orange, retinal angioid streaks, comitial lesions**	**Pseudoxanthoma elasticum**
	Facial pain	CARASAL[a]		**Skin papules**	**Pseudoxanthoma elasticum**
	Hyperacusis	CARASAL[a]		Angina pectoris	Pseudoxanthoma elasticum
A.b	Dementia	*COL4A1/2*-related CSVD Fabry disease HCHWA (Dutch, Italian, Flemish, Iowa, Piedmont, Icelandic, *APP* duplication/triplication) FBD *TTR* CAA CADASIL[a] *HTRA1* heterozygotes[a] CARASAL[a] RVCL-S[a]		**Alopecia**	***HTRA1* heterozygotes**[a]
	Migraine	*COL4A1/2*-related CSVD HANAC HCHWA (Dutch, Italian, Iowa, *APP* triplication) Familial British Dementia CADASIL[a] *HTRA1* heterozygotes[a] CARASAL[a] RVCL-S[a]		**Spondylosis deformans**	***HTRA1* heterozygotes**[a]

Continued

Table 3 Other Neurologic and Non-neurologic Features Found in Patients With Monogenic Cerebral Small Vessel Disease (CSVD) and Presenting With Intracerebral Hemorrhages (ICH) or in the Absence of Stroke Syndromes Due to Infarction or Hemorrhage *(continued)*

Other neurologic features	Disease	Non-neurologic features	Disease
Psychiatric symptoms	Fabry disease HCHWA (Iowa) Familial British Dementia *TTR* CAA CADASIL[a] *HTRA1* heterozygotes[a] CARASAL[a] RVCL-S[a]	Low back pain/disc herniation	*HTRA1* heterozygotes[a]
Seizures	*COL4A1/2*-related CSVD HANAC DADA2 HCHWA (Italian, Flemish, Iowa, *APP* duplication/triplication) Familial British Dementia *TTR* CAA CADASIL[a]	**Diabetes**	**CARASAL[a]**
Hypoacusis	DADA2 Fabry disease *TTR* CAA CADASIL[a] CARASAL[a]	Macular skin rash and punctate skin lesions	RVCL-S[a]
Vertigo	DADA2 Fabry disease CARASAL[a]	Thyroid disease	RVCL-S[a]
Tinnitus	Fabry disease CARASAL[a]	**B.b** Retinal vasculopathy and hemorrhages	*COL4A1/2*-related CSVD HANAC *TTR* CAA Fabry disease Pseudoxanthoma elasticum RVCL-S[a]
Gait disturbances	CADASIL[a] *HTRA1* heterozygotes[a] CARASAL[a]	Visual impairment and/or visual field defect	*COL4A1/2*-related CSVD HANAC DADA2 Fabry disease Pseudoxanthoma elasticum RVCL-S[a]
Urinary urgency	CADASIL[a]	Sicca syndrome	*TTR* CAA Fabry disease CARASAL[a]
Pseudobulbar palsy	Familial British Dementia CADASIL[a]	Cataract	*COL4A1/2*-related CSVD *TTR* CAA Fabry disease
Neuropathy	Fabry disease DADA2 *TTR* CAA (sensorimotor polyneuropathy, radiculopathy, dysautonomia)	Glaucoma	*COL4A1/2*-related CSVD *TTR* CAA
Hemiparesis/ tetraparesis	*COL4A1/2*-related CSVD (infantile) Familial British Dementia (adult-onset)	Proteinuria and renal failure	HANAC Fabry disease RVCL-S[a]
Ataxia	DADA2 Familial British Dementia *TTR* CAA	Hematuria	*COL4A1/2*-related CSVD HANAC
Muscle cramps and elevated serum creatine kinase level	*COL4A1/2*-related CSVD HANAC CARASAL[a]	Renal cysts	*COL4A1/2*-related CSVD HANAC
		Raynaud's phenomenon	*COL4A1/2*-related CSVD HANAC RVCL-S[a]

Continued

Table 3 Other Neurologic and Non-neurologic Features Found in Patients With Monogenic Cerebral Small Vessel Disease (CSVD) and Presenting With Intracerebral Hemorrhages (ICH) or in the Absence of Stroke Syndromes Due to Infarction or Hemorrhage *(continued)*

Other neurologic features	Disease	Non-neurologic features	Disease
		Cardiomyopathy	*TTR* CAA (cardiomegaly) Fabry disease (left ventricular hypertrophy, myocardial fibrosis) Pseudoxanthoma elasticum (restrictive) RVCL-S[a]
		Mitral valve prolapse	*COL4A1/2*-related CSVD Pseudoxanthoma elasticum
		Cardiac rhythm disorders	*COL4A1/2*-related CSVD (supraventricular arrhythmias) HANAC (supraventricular arrhythmias) Fabry disease (short PR interval, sinus bradycardia, conduction abnormalities, atrial fibrillation, sudden death)
		Anemia	*COL4A1/2*-related CSVD (hemolytic) DADA2 RVCL-S[a]
		Spontaneous hemorrhages into extracerebral organs	*COL4A1/2*-related CSVD Pseudoxanthoma elasticum (gastrointestinal bleeding)
		Gastrointestinal symptoms	DADA2 Fabry disease
		Hepatic disease	*COL4A1/2*-related CSVD (cysts) HANAC (cysts) DADA2 (hepatosplenomegaly)
		Bone disease	Fabry disease (osteopenia, osteoporosis) RVCL-S[a]
		Therapy-resistant hypertension	Fabry disease Pseudoxanthoma elasticum CARASAL[a]

Abbreviations: CAA = cerebral amyloid angiopathy; CADASIL = cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CARASAL = cathepsin-A–related arteriopathy with strokes and leukoencephalopathy; CSVD = cerebral small vessel disease; DADA2 = deficiency of ADA2; HANAC = hereditary angiopathy with nephropathy, aneurysms, and muscle cramps; HCHWA = Hereditary Cerebral Hemorrhage with Amyloidosis; ICH = intracerebral hemorrhages; IS = Ischemic Stroke; PADMAL = pontine autosomal dominant microangiopathy and leukoencephalopathy; RBD = rapid behavior disorder; RVCL-S = retinal vasculopathy with cerebral leukodystrophy and systemic manifestations.
(A.a-A.b) Other neurologic features found in patients with monogenic CSVD and presenting with ICH. The same non-neurologic features might be found in patients with monogenic CSVD in absence of stroke syndromes due to infarction or hemorrhage. Box A.a includes neurologic features not overlapping between monogenic CSVD, while box A.b reflects those overlapping. (B.a-B.b) Non-neurologic features found in patients with monogenic CSVD and presenting with ICH. The same non-neurologic features might be found in patients with monogenic CSVD in absence of stroke syndromes due to infarction or hemorrhage. Box B.a includes non-neurologic features not overlapping between monogenic CSVD, while box B.b reflects those overlapping. Neurologic and non-neurologic features which are specific or highly suggestive of a single CSVD are in bold.
[a] Monogenic CSVD which are usually associated with IS but might also produce ICH.

the vessels which penetrate in the brain parenchyma) are found in different locations (i.e., anterior commissure and vertex), have reduced dimensions, and are isointense compared with the cerebrospinal fluid on proton density images.[1] The presence of lacunes of presumed vascular origin and microbleeds is not diagnostic of any monogenic CSVD but strongly suggests a vascular origin of the leukoencephalopathy and therefore might be useful in differentiating leukodystrophies from CSVD.

WMHs in external capsules, anterior temporal poles, and superior frontal gyrus are typical of CADASIL in its advanced phases, while punctiform alterations in periventricular areas and in the centrum semiovale can be detected in the early phases of disease.[8] Basal ganglia, thalamus, brainstem, and corpus callosum are frequently involved.[8] In patients affected by CADASIL, lacunes of presumed vascular origin are found in basal ganglia and are developed later during disease progression.[8] No specific features differentiate them from those found in the sporadic forms of CSVD.

WMHs are diffuse and symmetrical in patients with CARASIL and *HTRA1* heterozygotes, with sporadic involvement of the anterior part of the temporal lobes and of the external capsules.[13,43] In *HTRA1* heterozygotes, however, the burden of WMHs is reduced compared with CARASIL.[43] In the advanced stages of disease, the "arc sign" (i.e., a T2-hyperintensity going from the pons to the middle cerebral peduncles) might be seen.[43] The distribution of lacunes of presumed vascular origin in

Table 4 Neuroimaging Features Found in Patients With Monogenic Cerebral Small Vessel Diseases (CSVDs)

	Neuroimaging features	Disease
A	**Symmetrical periventricular and subcortical WMHs from centrum semiovale to external capsule, anterior temporal lobe, and superior frontal gyrus**	**CADASIL**
	"Arc sign"	**CARASIL**
	Brainstem atrophy	PADMAL
	Gray matter alterations (thalamus, basal ganglia, red nuclei, dentate nucleus)	CARASAL
	Mass-like lesions (rim enhancement, mass effect, surrounding edema)	**RVCL-S**
	"Pulvinar sign"	**Fabry disease**
	Dolichoectasia of intracranial vessels (especially vertebrobasilar)	Fabry disease
	Carotid rete mirabile	**Pseudoxanthoma elasticum**
	Periventricular WMHs with possible predominantly posterior pattern	*COL4A1*-related CSVD
	Porencephaly, schizencephaly, hydranencephaly	***COL4A1/2*-related CSVD**
	Cortical malformations	*COL4A1/2*-related CSVD
	Cerebellar atrophy	*COL4A1/2*-related CSVD
	Cerebral siderosis	**HCHWA (Dutch, Italian)**
	External carotid artery dysplasia	**HCHWA (Iowa)**
	Enhancement of cerebral and spinal meninges	*TTR* CAA
B	Symmetrical periventricular and subcortical WMH	CARASIL (sometimes in external capsule, temporal pole, cerebellum, brainstem) *HTRA1* heterozygotes (often in internal and external capsules, rare involvement of temporal lobes) PADMAL (especially in the centrum semiovale, mild in anterior temporal lobes, external and internal capsules) CARASAL (brainstem, pyramidal tracts, tegmental tracts, middle and superior cerebellar peduncles, fronto-parietal; temporal lobes' sparing) Fabry disease Pseudoxanthoma elasticum HANAC (frontal and parietal predominantly in posterior regions, sparing of temporal lobes and arcuate fibers) HCHWA (Dutch, Italian, Flemish, Iowa, Icelandic, *APP* duplication/triplication) Familial British Dementia (around frontal and occipital horns of the lateral ventricles) RVCL-S (eventually with nodular enhancement)
	Lacunes of presumed vascular origin	CADASIL CARASIL *HTRA1* heterozygotes PADMAL CARASAL DADA2 Fabry disease Pseudoxanthoma elasticum *COL4A1/2*-related CSVD HANAC HCHWA (Dutch, Piedmont) Familial British Dementia
	Recent small subcortical infarcts	CADASIL CARASIL *HTRA1* heterozygotes PADMAL (pons, subcortical hemispheres) CARASAL DADA2 Fabry disease Pseudoxanthoma elasticum *COL4A1/2*-related CSVD HANAC HCHWA (Dutch, Piedmont) Familial British Dementia

Continued

Table 4 Neuroimaging Features Found in Patients With Monogenic Cerebral Small Vessel Diseases (CSVDs) *(continued)*

Neuroimaging features	Disease
Microbleeds	CADASIL CARASIL *HTRA1* heterozygotes PADMAL (rare) CARASAL Fabry disease Pseudoxanthoma elasticum *COL4A1/2*-related CSVD HANAC HCHWA (Dutch, Iowa, Piedmont, *APP* triplication)
Dilated perivascular spaces	CADASIL CARASIL *HTRA1* heterozygotes Fabry disease *COL4A1/2*-related CSVD HANAC HCHWA (Dutch)
Brain atrophy	CADASIL CARASIL HCHWA (Flemish, *APP* duplication/triplication) Familial British Dementia (corpus callosum)
Deep cerebral hemorrhages	*COL4A1/2*-related CSVD Fabry disease Pseudoxanthoma elasticum DADA2 Familial British Dementia HANAC CADASIL *HTRA1* heterozygotes
Cerebral lobar hemorrhages	HCHWA (Dutch, Italian, Flemish, Iowa, Piedmont, Icelandic, *APP* duplication/triplication) *TTR* CAA *COL4A1/2*-related CSVD
Subarachnoid hemorrhages	Fabry disease Pseudoxanthoma elasticum HCHWA (Dutch, Italian, Flemish, Iowa, Piedmont, Icelandic, *APP* duplication/triplication) *TTR* CAA *COL4A1/2*-related CSVD
Cerebral venous thrombosis	Fabry disease Pseudoxanthoma elasticum
Intracranial cerebral aneurysms	DADA2 Pseudoxanthoma elasticum HANAC (carotid siphon) *COL4A1*-related CSVD
Cerebral calcifications	RVCL-S *COL4A1/2*-related CSVD HCHWA (Iowa) (occipital)
Ventricular dilation	Familial British Dementia *TTR* CAA
Involvement of corpus callosum	CADASIL *COL4A1*-related CSVD

Abbreviations: CAA = cerebral amyloid angiopathy; CADASIL = cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CARASAL = cathepsin-A–related arteriopathy with strokes and leukoencephalopathy; CSVD = cerebral small vessel disease; DADA2 = deficiency of ADA2; HANAC = hereditary angiopathy with nephropathy, aneurysms, and muscle cramps; HCHWA = Hereditary Cerebral Hemorrhage with Amyloidosis; PADMAL = pontine autosomal dominant microangiopathy and leukoencephalopathy; RVCL-S = retinal vasculopathy with cerebral leukodystrophy and systemic manifestations.
Box A includes neuroimaging features not overlapping between monogenic CSVD, while box B reflects those overlapping.
Neuroimaging features which are specific or highly suggestive of a single CSVD are in bold.

CARASIL and *HTRA1* heterozygous patients is similar to CADASIL.[13] In CADASIL, CARASIL, and *HTRA1* heterozygous patients, dilated perivascular spaces are detected in the white matter of the temporal lobes and in the basal ganglia, where they can produce a "status cribrosum."[44] Additional features of CADASIL, CARASIL, and *HTRA1* heterozygous patients

include microbleeds, found on gradient echo sequences, and rapidly progressive brain atrophy, which is advanced for age.[8,13,43]

Temporal lobes are spared by WMHs in patients with CARASAL, while signal changes can be detected in the periventricular and deep frontoparietal white matter, basal ganglia, thalamus, internal and external capsules, and brainstem.[9]

WMHs can be superficial, subcortical, and periventricular in subjects with PADMAL syndrome.[45] During the first disease stages, they predominate in the centrum semiovale[45]; later, during disease progression, they can be detected in anterior temporal lobes, external, and internal capsules.[45] Lacunes of presumed vascular origin are located in the pons in PADMAL syndrome and in subcortical and/or periventricular hemispheres.[14,45] The typical distribution of brain atrophy in patients with PADMAL involves the brainstem, while microbleeds are rare.[14,45]

Lacunes of presumed vascular origin in deep brain nuclei, brainstem, and thalamus in the absence of WMHs and, rarely, cerebral aneurysms are detected in patients with DADA2.[39]

When both small and large vessels are involved, Fabry disease and pseudoxanthoma elasticum should be taken into consideration. Therefore, neuroimaging findings are not limited to WMHs, lacunes of presumed vascular origin, and microbleeds (i.e., small vessel disease). In a significant number of cases, patients with Fabry disease show an increased risk of vertebrobasilar dolichoectasia because of altered vascular remodeling (i.e., large vessel disease).[33] The "pulvinar sign," a bilateral hyperintensity on T1-weighted images which likely corresponds to posterior thalamus calcifications and is usually found in patients with hypertrophic cardiomyopathy and severe renal dysfunction, is highly suggestive of Fabry disease.[46] The correlation between pseudoxanthoma elasticum and intracranial aneurysms is doubtful.[47]

In patients with *COL4A1*-associated CSVD, symmetrical periventricular white matter lesions are mainly located in the posterior cerebral regions and, rarely, in the pons.[19,48] Lacunes of presumed vascular origin and dilated perivascular spaces are usually found in basal ganglia and deep regions.[48] Microbleeds, which appear in more than 50% of *COL4A1/COL4A2*-related patients with CSVD, are detected in deep hemispheric white matter, basal ganglia, brainstem, and cerebellum.[19,48] Unlike patients with *COL4A2* mutations, a variable degree of brain atrophy is described in those affected by *COL4A1*-related CSVD, with rare involvement of corpus callosum.[48,49] In subjects with the HANAC syndrome, WMHs can be periventricular, subcortical, and/or subtentorial, involving the centrum semiovale, internal and external capsules, frontal and parietal lobes, and, rarely, the pons, but sparing the posterior cerebral regions.[50] A specific additional MRI element of *COL4A1*-related CSVD and HANAC syndrome is represented by intracranial aneurysms, which are often asymptomatic, multiple in up to 50% of patients and mainly involve intracranial carotid (as in HANAC) and middle cerebral and basilar arteries.[19,50] Another neuroimaging clue to *COL4A1/COL4A2* microangiopathy diagnosis, especially in the neonatal and infantile but also antenatal period, is represented by porencephaly (i.e., a cyst with communication with the lateral ventricle, usually secondary to parenchymal hemorrhage).[34,51] In exceptional cases, extensive bilateral porencephaly resembling hydranencephaly and periventricular leukomalacia has been reported.[51] In a subset of patients, brain calcifications, schizencephaly, and cerebellar atrophy have been found.[49]

Patients with all the subtypes of HCHWA develop a neuroimaging picture which resembles that of the sporadic forms of CAA. Besides periventricular and/or subcortical WMHs, hemorrhages in different stages of evolution are commonly found.[21,52,53] Microbleeds are mainly detected at the gray-white matter junction and, rarely, in the cerebellum, while basal ganglia, thalamus, and brainstem are usually spared.[52] The number of microbleeds increases with disease progression.[52] Dilated perivascular spaces in the centrum semiovale are frequent both in hereditary and sporadic patients.[54] In the Iowa type, occipital calcifications and external carotid artery dysplasia have been reported.[53] In contrast with HCHWA, the most relevant neuroimaging finding in patients with Familial British Dementia is represented by ventricular dilation, accompanied by periventricular WMHs, predominantly located in the frontal and occipital white matter.[27] In addition to ventricular dilation and intracerebral and/or subarachnoid hemorrhages, patients with the hereditary transthyretin leptomeningeal CAA show enhancement of cerebral and spinal meninges at brain and spinal MRI.[25] Periventricular and subcortical WMHs are also found in patients with RVCL-S.[55] These white matter lesions can show either no enhancement or nodular enhancement, sometimes associated with diffusion restriction.[55] A distinctive feature of RVCL-S, usually appearing during advanced disease stages, is represented by mass lesions of size up to 6 cm with rim enhancement, mass effect, and surrounding edema.[55]

Tips About Genetic Approach

Since the development of NGS techniques, our capability of identifying disease-causing mutations has improved. In the field of CSVD, a recent work, in which authors revised their *NOTCH3* mutation testing data from 1997 to 2017 collected with either Sanger sequencing, NGS panels and WES, has shown that the use of a specific NGS panel can increase the diagnostic rate of CADASIL by 5% compared with the traditional sequencing techniques.[56] However, the access to NGS procedures within the clinical context can be challenging. Therefore, the possibility of sequencing strong candidate genes, although time, resources, and cost expensive, might remain the first choice in different settings. In these cases, NGS panels or diagnostic WES can be used in the absence of

Table 5 Features That Support a Genetic Etiology of the Condition

Supportive features
Recurrence of stroke syndromes due to hemorrhage or infarction
Age at onset younger than 50 y
Absence of common etiologies for ischemic stroke or cerebral hemorrhage
Presence of family history
Presence of CSVD neuroimaging features
Symmetrical periventricular and subcortical WMH
Lacunes of presumed vascular origin
Recent small subcortical infarcts
Dilated perivascular spaces
Microbleeds
Brain atrophy
Deep/lobar cerebral hemorrhages

Abbreviations: CSVD = cerebral small vessel disease; WMH = white matter hyperintensity.

candidate genes or as a secondary approach. Sanger sequencing should be performed to confirm the identified variants, and dosage assay techniques are required to complete the analysis. Depending on the country, the clinician can refer to the diagnostic section of genetics laboratories of hospitals and/or to private laboratories for both traditional and innovative sequencing techniques.

When dealing with patients with CSVD, the suspicion of a monogenic disorder can arise from different elements (as summarized in Table 5) in addition to the clinical and neuroimaging features discussed above. First, the recurrence of stroke syndromes due to hemorrhages or infarctions and the presence of other family members sharing typical neurologic or systemic symptoms are considered highly suspicious. A practical example of the usefulness of family history in the monogenic CSVD diagnostic process is represented by the CADASIL Scale developed by Pescini et al. in 2012, which includes "family history in at least 1 or 2 generations," as defined by the presence of at least one of the typical disturbances (headache, TIA/stroke, cognitive decline, and psychiatric disturbances) in 1 or 2 generations, respectively.[29] Nevertheless, the absence of affected family members does not represent a good reason to stop searching, considered the possibility of a de novo occurrence of pathogenic variants.[57] Furthermore, Razvi et al. documented that the family history of a conspicuous number of patients with CADASIL is inadequately investigated at initial presentation (i.e., by focusing only on premature stroke), thus leading to misdiagnosis.[58] Second, young age at onset of ischemic strokes and/or cerebral hemorrhages (i.e., younger than 50 years) represents a red flag, if other possible causes have been excluded. Although this is true for some etiologies, especially in case of autosomal recessive disorders (i.e., CARASIL), a late age at disease onset cannot exclude the presence of monogenic CSVD. Third, a complete workup for ischemic stroke and/or cerebral hemorrhage (i.e., MRI, 24-hour ECG monitoring, transthoracic and/or transesophageal echocardiography, and head and neck computed tomography angiography) should be performed to exclude common causes of stroke. Although vascular risk factors, most of all hypertension, are associated with sporadic CSVD, their presence cannot exclude a monogenic etiology, especially in case of suggestive features. Furthermore, if untreated, they can exacerbate the risk of ischemic stroke and/or cerebral hemorrhage in monogenic CSVD.[59]

As proven by a previous multicenter experience, prescreening of patients with clinical algorithms increases the detection rate of monogenic disorders, at least for those with higher prevalence among the general population (i.e., CADASIL, Fabry disease, and HCHWA).[60] Overall, we provided detailed descriptions of genetic, neurologic, systemic, and neuroimaging features of all the known CSVD monogenic forms. Furthermore, as phenotypes of different disorders often overlap and the clinical presentation of a single monogenic CSVD can vary among separate families, we created a flowchart that could be followed by the practicing clinician when dealing with stroke syndromes due to infarction or hemorrhage or other neurologic, non-neurologic, and/or neuroimaging features of CSVD to unravel their genetic causes.

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Appendix Authors

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Arianna Manini, MD	Stroke and Dementia Lab, Department of Biomedical and Clinical Sciences, University of Milan; IRCCS Istituto Auxologico Italiano, Department of Neurology and Laboratory of Neuroscience, University of Milan, Italy	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design
Leonardo Pantoni, MD, PhD	Stroke and Dementia Lab, Department of Biomedical and Clinical Sciences, University of Milan, Italy	Drafting/revision of the manuscript for content, including medical writing for content

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