Monogenic cerebral small-vessel diseases: diagnosis and therapy. Consensus recommendations of the European Academy of Neurology

M. Mancuso[a] (iD), M. Arnold[b], A. Bersano[c], A. Burlina[d], H. Chabriat[e], S. Debette[f], C. Enzinger[g], A. Federico[h], A. Filla[i], J. Finsterer[j], D. Hunt[k], S. Lesnik Oberstein[l], E. Tournier-Lasserve[m] and H. S. Markus[n]

[a]*Department of Clinical and Experimental Medicine, Neurological Institute, University of Pisa, Pisa, Italy;* [b]*Department of Neurology, INSELSPITAL, University Hospital Bern, Bern, Switzerland;* [c]*Cerebrovascular Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan;* [d]*Neurological Unit, St. Bassiano Hospital, Bassano del Grappa, Italy;* [e]*Department of Neurology and CERVCO, DHU Neurovasc, INSERM U1141, University of Paris, Paris;* [f]*Department of Neurology, INSERM Centre Bordeaux Population Health (U1219), Bordeaux University Hospital, University of Bordeaux, Bordeaux, France;* [g]*Department of Neurology and Division of Neuroradiology, Vascular and Interventional Radiology, Department of Radiology, Medical University of Graz, Graz, Austria;* [h]*Department of Medicine, Surgery and Neurosciences, University of Siena, Siena;* [i]*Department of Neurosciences and Reproductive and Odontostomatological Sciences, Federico II University, Napoli, Italy;* [j]*Krankenanstalt Rudolfstiftung, Messerli Institute, Vienna, Austria;* [k]*MRC Human Genetics Unit, Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, UK;* [l]*Department of Clinical Genetics, Leiden University Medical Center, Leiden, The Netherlands;* [m]*Department of Genetics, Lariboisière Hospital and INSERM U1141, Paris-Diderot University, Paris, France; and* [n]*Stroke Research Group, Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK*

Keywords:
cathepsin-A-related arteriopathy with strokes and leukoencephalopathy (CARASAL), cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL), cerebral small-vessel disease, Fabry, mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS), monogenic cerebral small-vessel disease, pontine autosomal dominant microangiopathy and leukoencephalopathy (PADMAL), retinal

Background and purpose: Guidelines on monogenic cerebral small-vessel disease (cSVD) diagnosis and management are lacking. Endorsed by the Stroke and Neurogenetics Panels of the European Academy of Neurology, a group of experts has provided recommendations on selected monogenic cSVDs, i.e. cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL), autosomal dominant High Temperature Requirement A Serine Peptidase 1 (HTRA1), cathepsin-A-related arteriopathy with strokes and leukoencephalopathy (CARASAL), pontine autosomal dominant microangiopathy and leukoencephalopathy (PADMAL), Fabry disease, mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS) and type IV collagen (COL4)A1/2.

Methods: We followed the Delphi methodology to provide recommendations on several unanswered questions related to monogenic cSVD, including genetic testing, clinical and neuroradiological diagnosis, and management.

Results: We have proposed 'red-flag' features suggestive of a monogenic disease. General principles applying to the management of all cSVDs and specific recommendations for the individual forms of monogenic cSVD were agreed by consensus.

Conclusions: The results provide a framework for clinicians involved in the diagnosis and management of monogenic cSVD. Further multicentre observational and treatment studies are still needed to increase the level of evidence supporting our recommendations.

Correspondence: M. Mancuso, Department of Clinical and Experimental Medicine, Neurological Institute, Building 13, Santa Chiara Hospital, Via Roma 67, 56100 Pisa, Italy (tel.: +39 50 992560; fax: +39 50 992748; e-mail: michelangelo.mancuso@unipi.it).

EUROPEAN JOURNAL OF NEUROLOGY

Introduction

Although the most common hereditary cerebral small-vessel disease (cSVD), cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), was first described over two decades ago, in recent years additional monogenic cSVD genes have been identified. Apart from Fabry disease (FD), there are no available disease-modifying therapies. Therefore, cSVD treatment focuses on symptomatic management, using approaches for which there is often no clear evidence base. As a consequence, there are inconsistencies in treatment and preventive care regimens. Diagnosis can also provide challenges, particularly with the increasing use of next-generation sequencing techniques and the need to determine whether or not variants are disease causing.

This article reports the results generated by a European Academy of Neurology Delphi consensus panel on important clinical questions related to management of monogenic cSVD.

Materials and methods

The Delphi method provides a systematic approach for collecting opinions from experts (the 'Delphi panel') and has been widely applied to obtain consensus or recommendations on well-defined topics. Although described as 'panel', experts provide their opinions freely, individually and anonymously.

Phase I: pre-meeting

Endorsed by the Neurogenetics and Stroke Panels of the European Academy of Neurology, two facilitators (M.M. and H.S.M.) invited experts from established centres of excellence in cSVD within Europe. All experts are opinion leaders in the fields of neurogenetics, neuroimaging and cSVD. The experts decided to focus on the following selected monogenic cSVDs and working groups were created: CADASIL (led by S.L.O., with A.Be., A.Fe., H.C. and H.S.M.), cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL) (led by A.Be., with A.Fe., H.S.M. and E.T.-L.), cathepsin-A-related arteriopathy with strokes and leukoencephalopathy (CARASAL) (J.F.), pontine autosomal dominant microangiopathy and leukoencephalopathy (PADMAL) (led by H.C., with A.Be. and E.T.-L.), FD (led by A.Bu., with J.F. and M.A.), mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS) (led by M.M., with J.F.), type IV collagen (COL4)A1/2 (led by H.C., with A.Be. and E.T.-L.) and retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations (RVCL-S) (D.H.).

Each working group leader executed a comprehensive search strategy to November 2018 in the MEDLINE database. Only English language studies were included. Each leader screened citations, reviewed full-text papers for inclusion, appraised study quality and abstracted the data. Consensus was achieved for inclusion of papers by discussion within working groups (Fig. 1). Finally, each group provided a list of queries to be voted on, as well as the references used to address the specific disease (File S1), which was distributed to all experts.

The two facilitators created a survey (File S2) to gauge the level of consensus among experts; responses and votes were collected anonymously through the Google forms platform (https://docs.google.com/forms/u/0/) and analysed prior to the face-to-face meeting.

Citations identified through database searching

Identification & screening							
COL4A1\2 N: 205	CADASIL N: 1236	MELAS N: 2264	RVCL-S N: 35	FABRY N: 4171	CARASIL N: 78	CARASAL N: 7	PADMAL N: 7

Full-text articles reviewed for eligibility

Eligibility							
COL4A1\2 N: 150	CADASIL N: 106	MELAS N: 101	RVCL-S N: 9	FABRY N: 141	CARASIL N: 24	CARASAL N: 3	PADMAL N: 3

Original studies included in the Delphi process

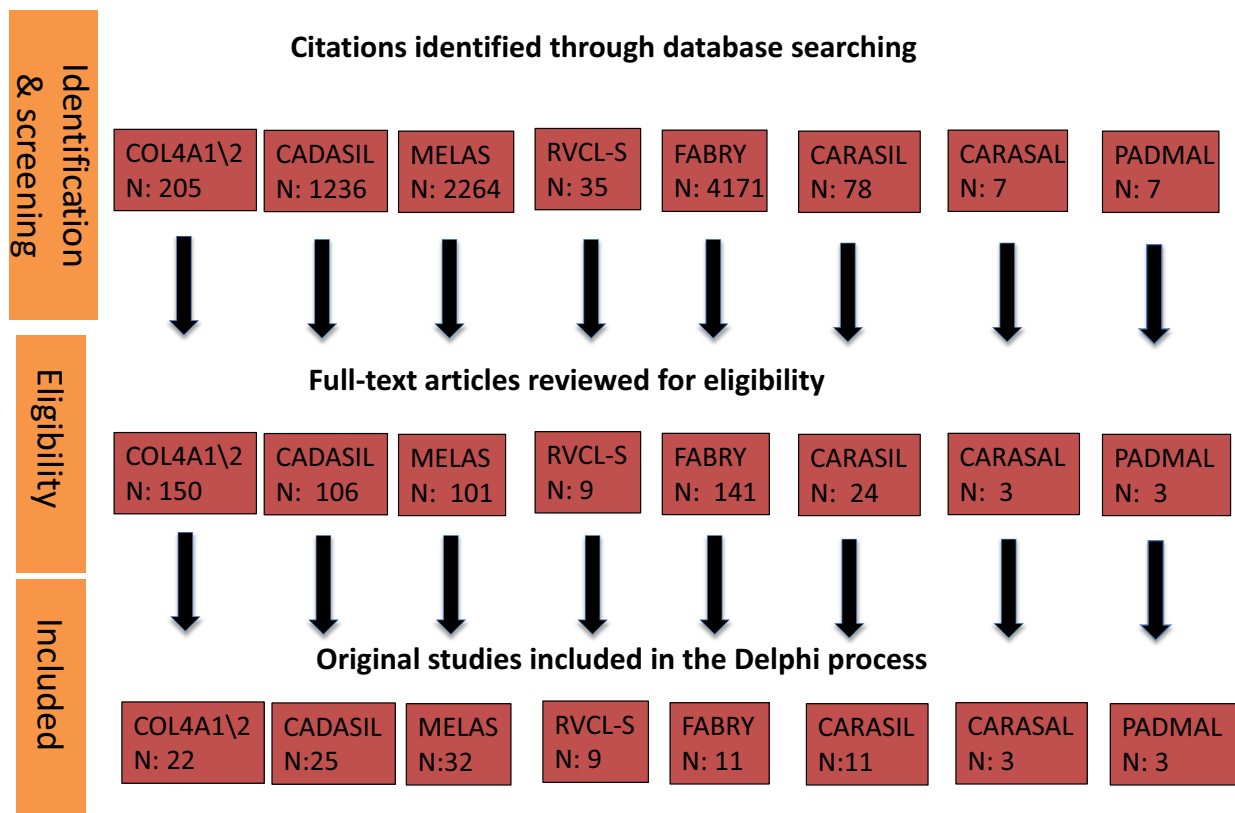| Included							
COL4A1\2 N: 22	CADASIL N:25	MELAS N:32	RVCL-S N: 9	FABRY N: 11	CARASIL N:11	CARASAL N: 3	PADMAL N: 3

Figure 1 Comprehensive search strategy in MEDLINE database used by the different working groups.

Participants voted using a five-point Likert scale [1] to indicate their level of agreement on each statement (1, absolutely disagree; 2, disagree; 3, no judgement; 4, more than agree; 5, absolutely agree). A 'strong consensus' was defined if >70% of scores were ≥4 and the mean score was ≥4. If only one of these two parameters was met, the consensus was considered a 'good consensus'. If both parameters were not met, the statement was considered to lack consensus agreement.

Phase II: Delphi panel

The 14 experts met in a face-to-face meeting in Vienna from 28 February to 1 March 2019. A delegate from the Lily Foundation participated in the meeting as patient advocate, without voting.

M.M. introduced the workshop aims. H.S.M. gave a brief overview on proposed red flags suggesting a diagnosis of monogenic cSVD. M.M. presented results from Phase I. Statements from Phase I without consensus were selected for discussion. The working group leaders presented individual diseases, discussing results of the first round of the survey and presenting the available data supporting the queries. After

discussion, when required, statements from the first round were modified or deleted and participants voted again on the revised statements. All participants were involved in all Delphi phases.

Statements were divided into three main areas: (i) identification of monogenic cSVD; (ii) clinical and features and diagnosis; and (iii) management.

Results

Table 1 presents the results of all statements.

Clues for diagnosis of monogenic cerebral small-vessel disease

Experts were asked to identify 'red-flag' features that suggested to them that a diagnosis of monogenic disease should be considered in a patient with cSVD. Strong consensus was reached on the following: family history, young age at onset, consanguinity, suggestive extracerebral/systemic features and clinical and neuroimaging characteristics of a specific monogenic disease. There was strong consensus that, even in patients with conventional vascular risk factors, a diagnosis of monogenic cSVD should not be excluded.

Table 1 Pre- and post-workshop weighted scores for all statements/recommendations

Query	Mean score	Percentage of people voting 4 or 5
General table: Thinking about the red flags of monogenic cSVD, which are the ones that a general neurologist should keep in mind to suspect a monogenic cSVD		
Family history	5	100
Young age at onset	4.92	100
Characteristic neuroimaging features	4.54	84.6
Consanguinity	4.92	100
Extracerebral/systemic features	4.54	100
Clinical phenotype characteristic of specific monogenic disease	4.61	92.8
Negative clinical workup for other causes of cSVD	4.15	69.2
Even in patients with traditional vascular risk factors we should consider monogenic stroke	4.54	84.6
Standard clinical care including general indications, contraindications, clinical monitoring and side effects for all drugs must always be kept in mind with or without genetic defect causing cSVD	4.46	84.6
General principles for all monogenic cSVDs		
Patients with monogenic cSVD should be followed up by specialized centres and/or an expert neurologist	4.77	100
Genetic counselling should include discussion of family planning, including the option of pre-natal diagnostics and pre-implantation genetic diagnosis	4.86	100
Family members of the proband should be offered at least one consultation with a clinical geneticist or equivalent for genetic counselling	4.84	100
At (genetic) diagnosis, patients with cSVD should be offered psychological support if needed	4.77	100
Because vascular risk factors have been shown to increase the severity of CADASIL and may well do the same for other rarer monogenic cause of cSVD, after genetic diagnosis the vascular risk factor profile of patients with monogenic cSVD should be carefully evaluated and lifestyle changes such as stopping smoking, healthy diet and physical exercise should be advised	4.84	100
Patients with cSVD should have a yearly evaluation of their vascular risk factor profile	4.92	100
At genetic diagnosis of cSVD, a cerebral MRI should be considered, irrespective of signs or symptoms	4.15	84.6
Follow-up cerebral MRI is not indicated unless new signs or symptoms appear	4.85	100
CADASIL		
CADASIL is caused by *NOTCH3* mutations leading to an uneven number of cysteine residues (usually 5 or 7) in one of the NOTCH3 protein's EGFr domains	4.85	100
NOTCH3 mutations leading to a cysteine alteration in one of the NOTCH3 EGFr domains 1–6 may predispose to an earlier onset of stroke than mutations located in one of the EGFr domains 7–34	4.46	92.8
CADASIL can only be definitively confirmed by genetic testing, revealing a NOTCH3 mutation altering the number of cysteines in one of the 34 EGFr domains of the NOTCH3 protein	4.92	100
CADASIL can be confirmed by skin biopsy, with electron microscopy showing GOM	4.38	92.8
CADASIL can be established by skin biopsy, but genetic testing should be the first diagnostic line investigation	4.61	92.8
In the case of a NOTCH3 variant of unknown significance, CADASIL can be confirmed using a skin biopsy for electron microscopy and/or NOTCH3 immunostaining	4.54	92.8
WMHs located in the anterior temporal lobes are present in 90% of cases but can be absent	4.38	92.8
The diagnosis of CADASIL should be considered in any patient with unexplained symmetrical periventricular WMHs and a positive family history of migraine with aura, stroke, mood disorders or dementia	4.92	100
CADASIL cannot be ruled out in the absence of a medical or family history of migraine with aura	4.38	84.6
CADASIL cannot be ruled out in the presence of common cerebrovascular risk factors and extensive WMHs	4.30	84.6
CADASIL can present with mild signs or symptoms, even in elderly individuals (>70 years) with a negative medical history of stroke and a negative family history	4.61	100
Most strokes in CADASIL are ischaemic, but intracerebral haemorrhage can rarely occur, especially in patients treated with anticoagulants	4.69	100
CADASIL should be considered in the differential diagnosis of multiple sclerosis	4.77	100
Patients with CADASIL should be monitored for subjective or objective cognitive impairment and when present should be offered neuropsychological assessment and support	4.77	100
Many clinicians prescribe an antiplatelet agent in a patient with CADASIL who has suffered a clinical ischaemic stroke, although there is no trial evidence supporting their use in CADASIL as opposed to stroke more generally	4.61	100
There is no evidence to support the use of antiplatelet agents in patients with CADASIL who have not suffered a clinical ischaemic stroke	4.85	100

(continued)

Table 1 *(Continued)*

Query	Mean score	Percentage of people voting 4 or 5
Patients with CADASIL should not receive thrombolysis for acute ischaemic stroke unless it is due to a large-artery occlusion secondary to a concurrent cause (this is very uncommon)	4.69	100
Statin therapy is not recommended for a patient with CADASIL who has normal cholesterol even after stroke, but is not contraindicated if there is another reason for its use	4.77	100
There is no evidence contraindicating the use of triptans in CADASIL	4.54	100
There is no evidence to recommend the use of acetazolamide; trials of its use are required	4.61	100
Patients with CADASIL can be treated with psychiatric drugs according to guidelines for other cerebrovascular disorders	4.61	100
Anticoagulants are not recommended for the prophylaxis of stroke in CADASIL due to the risk of intracerebral haemorrhage, but are not contraindicated if there is another indication for it (e.g. atrial fibrillation, pulmonary embolus)	4.77	100
There is no evidence to contraindicate the use of oral contraceptives in CADASIL	4.23	92.8
Anaesthetic procedures maintaining haemodynamic stability and avoiding hypotension are recommended for patients with CADASIL undergoing surgery	4.77	100
Pregnancy and labour are generally uncomplicated in CADASIL and do not warrant specific precautions or medical interventions	4.31	84.6
Pregnancy and labour are associated with an increased risk of transient neurological events especially during the puerperium, mostly consistent with migraine aura, of which the patient and obstetrician should be aware	4.69	92.8
CARASIL		
CARASIL is caused by biallelic mutations of *HTRA1* gene	5	100
Homozygous stop codon mutations, homozygous missense or frameshift and compound heterozygous mutations of HTRA1 gene have been identified as causative in CARASIL	5	100
HTRA1 gene heterozygous mutation can cause autosomal dominant cSVD, distinct from CARASIL	4.92	100
HTRA1 mutations behave as autosomal recessive mutations with heterozygous carriers clinically unaffected but also as autosomal dominant mutations, with heterozygous carriers being clinically affected	4.23	84.6
Skin biopsy examination does not show GOM typical of CADASIL	5	100
Premature diffuse scalp alopecia is seen in the majority of patients	4.85	100
The diagnosis CARASIL should be considered in any patient with early-onset premature scalp alopecia, severe spondylosis and unexplained early lacunar strokes and/or symmetrical WMHs	4.92	100
White matter changes in the anterior temporal lobe and external capsule may occur in CARASIL	4.77	92.8
HTRA1 heterozygous mutations may lead to a late-onset syndrome characterized by gait disturbances, mood depression, cognitive impairment, stroke, migraine as well as WMHs on MRI	4.77	100
CARASIL should be considered in the differential diagnosis of CADASIL, CARASAL and early-onset cSVD	4.7	92.8
No data to recommend antiplatelet therapy in CARASIL	4.92	100
HTRA1-autosomal dominant disease		
Heterozygous HTRA1 mutations cause an autosomal dominant cSVD	4.71	92.8
Clinical features may include lacunar strokes, cognitive impairment and encephalopathy	4.36	85.7
COL4A1-COL4A2		
An autosomal dominant cSVD of haemorrhagic type can result from missense or null mutations of COL4A1 or COL4A2	5	100
Missense mutations of *COL4A1* or *COL4A2* leading to replacement of a glycine of a GLY-X-Y motif in the triple helix and mutation leading to premature stop codon are pathogenic	4.78	100
A mutation of *COL4A1* or *CO4A2* should be sought in a patient with deep intracerebral haemorrhage of undetermined origin or WMHs of undetermined origin or porencephaly haemorrhage of undetermined origin when there is a family history of cerebral haemorrhage, porencephaly, retinal vessel tortuosities, haematuria, glomerular dysfunction, renal insufficiency, renal cysts, infantile hemiparesis, early cataracts, abnormalities of the anterior segment of eyes, multiple intracranial aneurysms, muscle cramps or hepatic cyst is present in at least one first- or second-degree relative	4.78	100
A non-invasive workup at different organ levels (including cerebral MRI, intracranial and cervical MR angiography, cardiac echography, detailed ocular and retinal vessel examination with visual acuity and ocular pressure measures, renal echography, muscular creatine kinase) is recommended in individuals with COL4A1 or COL4A2 mutation	4.93	100
Pre-symptomatic testing of family members is recommended because of potential benefit of preventive measures, including avoiding complications during childbirth	4.71	100
Antiplatelet and anticoagulant treatments are not recommended in COL4A1/2 cSVD	4.71	100

(continued)

Table 1 *(Continued)*

Query	Mean score	Percentage of people voting 4 or 5
Intravenous thrombolysis is not recommended in a patient with a diagnosis of COLA1/2 cSVD	4.71	100
Sporting activities with a high risk of head trauma or excessive or prolonged exercise should be avoided in a patient with COL4A1/2 cSVD	4.78	92.8
A Caesarean section should be considered in women giving birth where the fetus contains a *COL4A1/2* mutation	4.78	100
Mutations of COL4A1 at the binding site of MIR-29 gene can cause a distinct ischaemic cSVD with early onset in adults called PADMAL	4.86	92.8
CARASAL		
CARASAL manifests clinically not only in the central nervous system but also in other organs/tissues	4.46	84.6
Dystonia is a rare phenotypic feature of CARASAL	4.23	92.8
Extensive subcortical and brainstem hyperintensity is commonly observed in CARASAL	4.84	100
Clinical manifestations can be absent or mild despite extensive leukoencephalopathy	4.92	100
CTSA is the only gene mutated known to cause CARASAL	5	100
There are insufficient data to recommend any specific treatment in patients with CARASAL	4.92	100
Both ischaemic and haemorrhagic strokes occur in patients with CARASAL	4.61	100
RVCL-S		
Heterozygous C-terminal frameshift mutations in the TREX1 gene have been identified as causative in RVCL-S	5	100
Pathogenic frameshift mutations cause protein truncation in the C-terminus, which leads to subcellular mislocalization of the enzyme, but does not affect enzyme activity	4.38	100
Ophthalmological examination shows a distinctive and progressive retinal vasculopathy in almost all symptomatic patients	4.69	100
Brain involvement typically develops in the fourth to fifth decade	4.30	92.8
Neurological symptoms include focal deficits and progressive cognitive deficits	4.84	100
Focal brain disease can occur, in particular in association with mass-like lesions on brain MRI scanning	4.77	100
Brain MRI changes in RVCL-S typically involve punctate T2 hyperintensities that may also display nodular enhancement	4.46	92.8
Individuals with RVCL-S may develop larger T2 hyperintense white matter mass lesions with rim enhancement, mass effect and surrounding oedema	4.84	100
There is no evidence of efficacy of antiplatelet therapy in RVCL-S	4.77	100
There is no evidence of efficacy of immunosuppressive therapy in RVCL-S and clinical trials are needed	4.84	100
FD		
WMHs can be seen in patients with FD and progression of WMHs occurs in significant proportion of the patients with FD	5	100
Ischaemic stroke is the most common brain stroke subtype in patients with FD, but haemorrhage strokes have been reported	4.92	100
Early diagnosis is important for correct management of patients with FD	4.61	100
FD can explain <1% of the cryptogenic ischaemic strokes in young adults	4.92	100
Neuropsychological testing in FD is recommended	4.38	92.8
Systemic thrombolysis is not contraindicated in FD	4.69	100
Thrombectomy can be applied in case of proximal occlusion of cerebral arteries in patients with FD	4.54	92.8
There is no evidence to recommend antithrombotic treatment for primary prevention of stroke in FD	4.84	100
Patients with FD should receive antithrombotic therapy after the first cerebrovascular event	4.46	92.8
ERT is usually recommended to reduce complications of FD although there is no good evidence that such a treatment can prevent stroke recurrence	4.46	84.6
There is a causal relationship between FD and ischaemic stroke, but the underlying mechanisms are unclear	4.46	100
MELAS		
Diagnosis of an SLE requires the combination of clinical assessment, brain MRI and EEG	4.85	100
Fibrinolysis is not indicated to treat acute SLEs	4.85	100
Antiplatelet therapies are not indicated for secondary prevention of SLEs	4.61	100
If an SLE is suspected and focal seizures are evident, they should be managed with antiepileptic drugs	4.92	100
Seizures in SLEs should be treated with AEDs, with the exception of valproic acid, which is contraindicated, mainly in patients with POLG mutations	4.92	100
There is not enough evidence to recommend the use of intravenous venous L-arginine to treat acute SLEs	4.46	84.6
Acute psychiatric complications related to SLEs are common	4.61	100
Drugs like haloperidol, benzodiazepine, quetiapine, olanzapine may be safely used to treat psychiatric complications in MELAS	4.46	92.8

(continued)

Table 1 *(Continued)*

Query	Mean score	Percentage of people voting 4 or 5
Because of the frequent occurrence of arrhythmia in MELAS (especially if caused by m.3243A>G), ECG monitoring during an SLE, especially after the introduction of an antipsychotic drug with QT-prolonging side effect, should be considered	4.77	100
Urgent genetic testing for MELAS should be considered in patients presenting with suspected SLE	4.69	100
As for the genetic testing, urgent search for the M.3243A>G mutation (in urine where possible) and, if M.3243A>G mutation is negative, POLG sequencing are required	4.69	100
Muscle biopsy should be considered after excluding M.3243A>G and POLG mutations	4.38	92.8
Even though there is no scientific evidence of positive impact of steroids in SLEs, their use is not contraindicated	4.46	92.8
Increased lactate in blood and/or CSF or detected by proton magnetic resonance spectroscopy could provide additional evidence of mitochondrial aetiology of an SLE, although neither specific nor highly sensitive	4.30	84.6

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; COL4, type IV collagen; CSF, cerebrospinal fluid; cSVD, cerebral small-vessel disease; ECG, electrocardiogram; EEG, electroencephalogram; EGFr, epidermal growth factor-like repeat; ERT, enzymatic replacement therapy; FD, Fabry disease; GOM, granular osmiophilic material; HTRA1, High Temperature Requirement A Serine Peptidase 1; MELAS, mitochondrial encephalopathy, lactic acidosis and stroke-like episodes; MR, magnetic resonance; MRI, magnetic resonance imaging; PADMAL, pontine autosomal dominant microangiopathy and leukoencephalopathy; QT, QT interval (the time from the start of the Q wave to the end of the T wave at the electrocardiogram); RVCL-S, retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations; SLE, stroke-like episode; WMH, white matter hyperintensity.

Negative workup for other causes of cSVD reached good consensus.

A number of specific causes of cSVD were individually considered. These, with the associated key genetic, clinical and neuroimaging features are shown in Table 2.

Management recommended for all monogenic cerebral small-vessel diseases

General principles for all monogenic cSVDs, discussed and elaborated during the face-to-face meeting, are listed in Table 1.

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy

CADASIL, caused by *NOTCH3* gene variants [2], is the most prevalent monogenic cSVD, with a minimal estimated prevalence of 2–4:100 000 [3], although the true prevalence is likely to be much higher [4]. NOTCH3 is a single-pass receptor protein that plays an important role in vascular smooth muscle cell differentiation and maturation, and mutant NOTCH3 protein deposits are found in small arteries and capillaries throughout the body. However, despite this widespread vascular pathology, clinical manifestations are only related to the central nervous system, in the form of migraine with aura, acute encephalopathy, recurrent lacunar strokes, cognitive decline, gait and mood disorders [5,6]. Most strokes are ischaemic, but intracerebral haemorrhage can rarely occur, especially in patients treated with anticoagulants [6,7].

Stroke onset was classically described to be between the ages of 40 and 60 years, with a severe progression to a mute and bedridden state after 10–20 years. However, individuals with milder disease are increasingly reported [4]. NOTCH3 variants leading to a cysteine alteration in one of the NOTCH3 epidermal growth factor-like repeat (EGFr) domains 1–6 have been recently reported to predispose to an earlier onset of stroke than variants located in one of the EGFr domains 7–34 [4]. Classical vascular risk factors, such as smoking and hypertension, have been associated with earlier age of stroke onset [8].

The magnetic resonance imaging (MRI) features are central to diagnosis and features include symmetrical and progressive subcortical white matter hyperintensities (WMHs), lacunes, microbleeds and enlarged perivascular spaces (Fig. 2a) [9]. WMHs are widespread. Anterior temporal lobe WMHs are highly suggestive and often considered a radiological hallmark for CADASIL, but can be lacking in some cases and are also seen in CARASIL and High Temperature Requirement A Serine Peptidase 1 (HTRA1)-autosomal dominant disease.

Pathological hallmarks of the disease are small-vessel wall abnormalities, which typically include an increased and granular pattern of NOTCH3 staining using an antibody with an epitope in the extracellular domain and pathognomonic granular osmiophilic material (GOM)

Table 2 Clinical and neuroradiological features of the investigated monogenic diseases

Disease	CADASIL	CARASIL	AD-HTRA1	COL4A1/2	PADMAL	CARASAL	RVCL-S	FD	MELAS
Gene	NOTCH3	HTRA1	HTRA1	COL4A1/2	COL4A1	CTSA	TREX1	α-galactosidase A	Variety of mitochondrial DNA genes or POLG
OMIM	125310	600142	616779	614519	618564	256540	192315	301500	540000
Inheritance	AD	AR	AD	AD	AD	AD	AD	X-linked but females can also be affected	Maternally inherited or AR (POLG)
Clinical features									
Ischaemic strokes	X	X	X	X	X	X		X	
Intracerebral haemorrhage	X (rarely)			X	X	X		X	
SLEs									X
Cognitive impairment/dementia	X	X	X	X	X	X	X		X
Migraine	X		X			X			X
Encephalopathy	X		X						X
Seizures	X (rarely)						X		X
Mood disorders	X	X	X			X		X	X
Alopecia		X	X						
Lumbar spine problems		X	X						
Extracerebral features		X		X		X	X	X	X
Neuroimaging									
Lacunar infarcts	X	X	X	X	X		X	X	
WMHs	X	X	X	X	X		X	X	
Cerebral microbleeds (no specific location)	X		X	X				X	
Anterior temporal pole WMH	X	X	X						
Large contrast-enhanced white matter lesions							X		
Cortical and subcortical signal abnormalities often crossing vascular territories									X

AD, autosomal dominant; AR, autosomal recessive; 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; COL4, type IV collagen; FD, Fabry disease; HTRA1, High Temperature Requirement A Serine Peptidase 1; AD-HTRA1, High Temperature Requirement A Serine Peptidase 1; MELAS, mitochondrial encephalopathy, lactic acidosis and stroke-like episodes; OMIM, Online Mendelian Inheritance in Man; PADMAL, pontine autosomal dominant microangiopathy and leukoencephalopathy; RVCL-S, retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations; SLE, stroke-like episode; WMH, white matter hyperintensity.
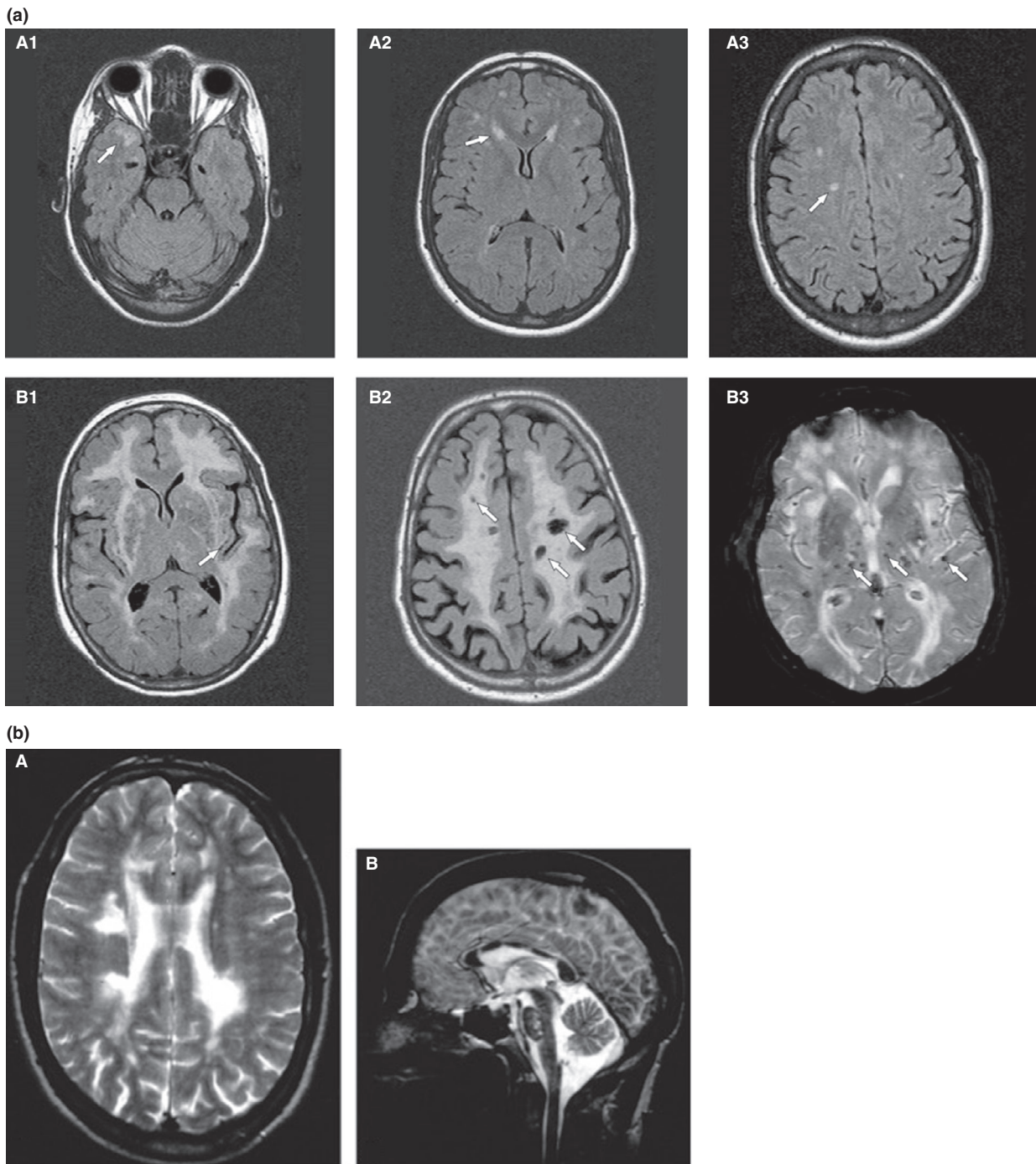
Figure 2(a) Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). Typical pattern of small-vessel disease-related abnormalities on magnetic resonance imaging in CADASIL. Two individuals with, respectively, an early (A) and a late (B) disease stage are shown. Both had a cysteine-altering NOTCH3 mutation and a positive family history for CADASIL. (A) Pre-symptomatic stage, individual in early twenties revealing discrete circumscript areas of white matter hyperintensities (WMHs) in the anterior temporal lobes (A1, arrow), periventricularv semi-oval centre (A3, arrow) (Fluid Attenuated Inversion Recovery (FLAIR) images). (B) Severe disease stage in an individual in his mid-fifties, revealing extensive areas of confluent and symmetrical WMHs (B1 and B2), including internal and external capsules (B1), enlarged perivascular spaces (B1, arrow) and lacunes (B2, arrows) on FLAIR images and microbleeds on susceptibility-weighted images (B3, arrows). (b) Corpus callosum involvement in CADASIL.

adjacent to mural cells using electron microscopy [10]. There is usually a family history, but this may not be apparent due to mild disease course or misdiagnosis in other family members or occasionally due to a *de-novo* variant.

CADASIL is confirmed by genetic testing, revealing a *NOTCH3* variant altering the number of cysteines in one of the 34 EGFr domains of the NOTCH3 protein encoded by exons 2–24, thereby disrupting normal disulphide bridge formation and resulting in a pro-aggregatory mutant NOTCH3 protein that sequesters extracellular matrix proteins.

There are few data on management of CADASIL and a paucity of randomized controlled trials. A multicentre trial of the cholinesterase inhibitor donepezil showed no improvement in the primary endpoint of the V-ADAS-cog score in CADASIL with cognitive impairment [11].

Consensus statement results

Genetic testing
- CADASIL diagnosis can be established by skin biopsy with electron microscopy showing GOM, but genetic testing should be the first diagnostic line of investigation.
- In the case of a *NOTCH3* variant of unknown significance, diagnosis can be investigated using a skin biopsy for electron microscopy and/or immunostaining to the NOTCH3 extracellular domain.

All or almost all variants leading to CADASIL result in a loss or gain of a cysteine in EGFr repeats. Some non-cysteine-changing variants have been reported but the consensus was that the vast majority of these variants are not pathogenic. In such cases, electron microscopy revealing GOM can be a useful diagnostic tool.

Clinical and neuroimaging diagnosis
- The diagnosis of CADASIL should be considered in any patient with unexplained symmetrical periventricular WMHs and a positive family history of migraine with aura, stroke, mood disorders or dementia.
- WMHs located in the anterior temporal lobes are often present, but can be absent.
- CADASIL cannot be ruled out in the absence of a medical or family history of migraine with aura.
- CADASIL can present with mild signs or symptoms, even in elderly individuals (>70 years) with a negative medical history of stroke and negative family history.
- Although most patients have a family history, if the clinical and imaging phenotype is consistent with CADASIL the diagnosis should be considered.
- CADASIL cannot be ruled out in the presence of common cerebrovascular risk factors and extensive WMHs.

CADASIL can occur in patients with and without cardiovascular risk factors, and indeed cardiovascular risk factors are associated with an earlier age of stroke onset[8].
- CADASIL should be considered in the differential diagnosis of multiple sclerosis.

CADASIL with established WMH has been diagnosed as multiple sclerosis. Corpus callosal involvement, typical of multiple sclerosis but rare in sporadic small-vessel disease, can occur in CADASIL[9] (Fig. 2b).

Management
- Patients with CADASIL should be monitored for cognitive impairment and, when present, neuropsychological assessment and support should be offered.
- There is no evidence to support the use of antiplatelet agents in patients with CADASIL who have not suffered clinical ischaemic stroke.
- Patients with CADASIL should not receive thrombolysis for acute small-vessel ischaemic stroke (which is almost always the case).
- Statin therapy is not recommended for a patient with CADASIL who has normal cholesterol, even after stroke, but is not contraindicated.
- There is no evidence contraindicating the use of triptans in patients with CADASIL with migraine.

Initial guidance was that triptans were contraindicated in patients with cerebrovascular disease such as CADASIL, but recent data suggest that they are safe in CADASIL and helped migraine episodes in about half of cases [12].
- There is no evidence to recommend acetazolamide; trials of its use are required.
- Patients with CADASIL can be treated with psychiatric drugs according to guidelines for other cerebrovascular disorders.
- Anticoagulants are not recommended for stroke prophylaxis in CADASIL due to the risk of intracerebral haemorrhage, but they are not contraindicated if there is another strong indication (e.g. atrial fibrillation, pulmonary embolus).
- There is no evidence to contraindicate the use of oral contraceptives.
- Anaesthetic procedures maintaining haemodynamic stability, and avoiding hypotension, are recommended for patients with CADASIL undergoing surgery.

In CADASIL, cerebral autoregulation is impaired and sudden and excessive blood pressure drops can result in white matter ischaemic damage.
- Pregnancy and labour are associated with an increased risk of transient neurological events, mostly consistent with migraine aura and especially
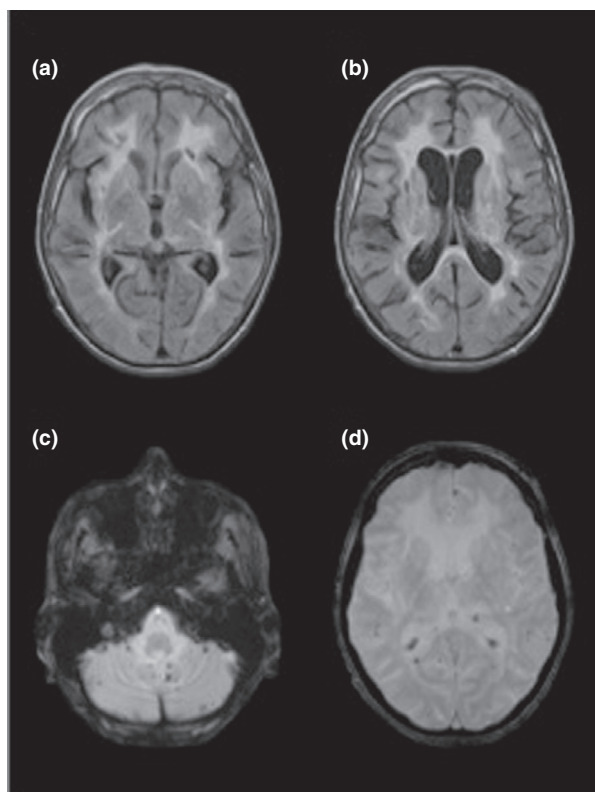
Figure 3 Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL). Diffuse vascular leukoencephalopathy, lacunar infarcts (a,b) and multiple microbleeds (c,d).

during the puerperium, of which the patient and obstetrician should be aware.

Pregnancy is not contraindicated in CADASIL, and no prophylaxis with heparin or aspirin is required. However, migraine can worsen especially around the puerperium when confusional migraine and encephalopathy can occur.

Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy

CARASIL is a rare autosomal recessive disorder caused by biallelic variants in the *HTRA1* gene on chromosome 10q26 [13,14], mainly reported in Japan but also in Chinese and Caucasian cases [15,16]. *HTRA1* encodes a homotrimeric serine protease that probably has a role in maintaining cerebral small-vessel integrity by regulating transforming growth factor beta signalling.

Recurrent lacunar stroke with onset from 20 to 44 years, early vascular dementia (usually by age 30–40 years), gait disturbance, depression, premature head alopecia in 90% of patients during adolescence and severe back pain with lumbar disc herniation are the main clinical features. Additional manifestations include seizures, psychiatric disturbances, pseudobulbar palsy and spondylosis deformans. The disease is rapidly progressive with stepwise deterioration of motor and cognitive function, and the average illness duration is 20–30 years, although most patients became bedridden within 10 years after onset [16]. T2-weighted cerebral MRI by age 20 years usually shows diffuse and symmetrical WMHs and lacunar infarcts (Fig. 3) [17]. WMHs sometimes involve the temporal lobes as in CADASIL.

In contrast to CADASIL, histological changes are not disease specific and are characterized by arteriolosclerosis and loss of vascular smooth muscle cells with subsequent hyalinization, intima fibrous thickening and internal elastic lamina disruption. GOM deposits have not been found.

No effective treatment of CARASIL is available.

Consensus statement results

Genetic testing
- Carriers of heterozygous *HTRA1* variants do not manifest with CARASIL but with a different form of heritable cSVD, i.e. HTRA1 autosomal dominant disease (described below).

Clinical and neuroimaging diagnosis
- CARASIL should be suspected in cases of recurrent unexplained lacunar strokes with severe WMHs, particularly when associated with premature alopecia, premature lumbago or spondylosis.
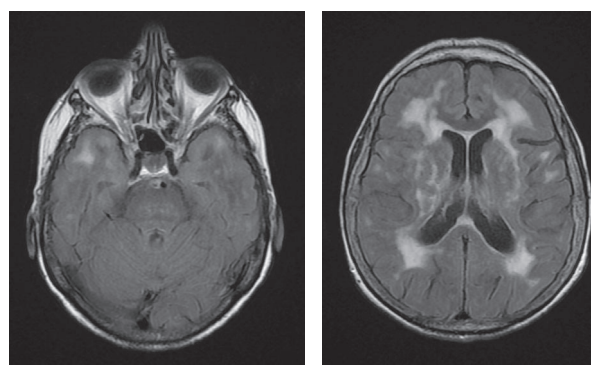
AD- HTRA1

Figure 4 (TRA1)-autosomaldominantdisease High Temperature Requirement A Serine Peptidase 1 (HAD-HTRA1). Fluid Attenuated Inversion Recovery (FLAIR) magnetic resonance imaging scan from a 68-year-old woman with a heterozygous HTRA1 mutation who presented with cognitive problems in her sixties and developed unsteadiness when walking. Showing extensive white matter changes including involvement of the corpus callosum.

Management

• There are not enough data to recommend antiplatelet therapy in CARASIL, even in the presence of cerebrovascular events.

HTRA1-autosomal dominant disease

In addition to biallelic *HTRA1* variants that cause CARASIL, heterozygous *HTRA1* variants have been shown to cause an autosomal dominant cSVD[18]. These dominant negative variants lead to decreased residual activity of the HTRA1 trimer through different mechanisms [19]. Clinical features differ from CARASIL by a later age of stroke onset (around 60 years) and less frequent alopecia and spondylosis deformans (Fig. 4). Cognitive impairment and encephalopathy also occur. Histological findings demonstrate diffuse and focally intensive myelin pallor in the white matter sparing U-fibres, resembling CARASIL [19].

Not all rare missense *HTRA1* variants are pathogenic. In order to establish pathogenicity of a *HTRA1* variant, the activity of the mutated enzyme and its ability to form trimers should be evaluated, as well as whether it segregates with disease within a family.

Collagen 4A1 and collagen 4A2 microangiopathy

Type IV collagen is a component of basement membranes and expressed ubiquitously in blood vessels and organs throughout the body. Missense or null variants in *COL4A1* and *COL4A2* cause an autosomal dominant cSVD of the haemorrhagic type that can be associated with extracerebral clinical manifestations [20]. These two genes encode the α1 and α2 chains of COL4 and share a common locus on chromosome 13 (13q34). Most pathogenic variants of *COL4A1*/2 lead to either substitution of a glycine with a different amino acid or haploinsufficiency.
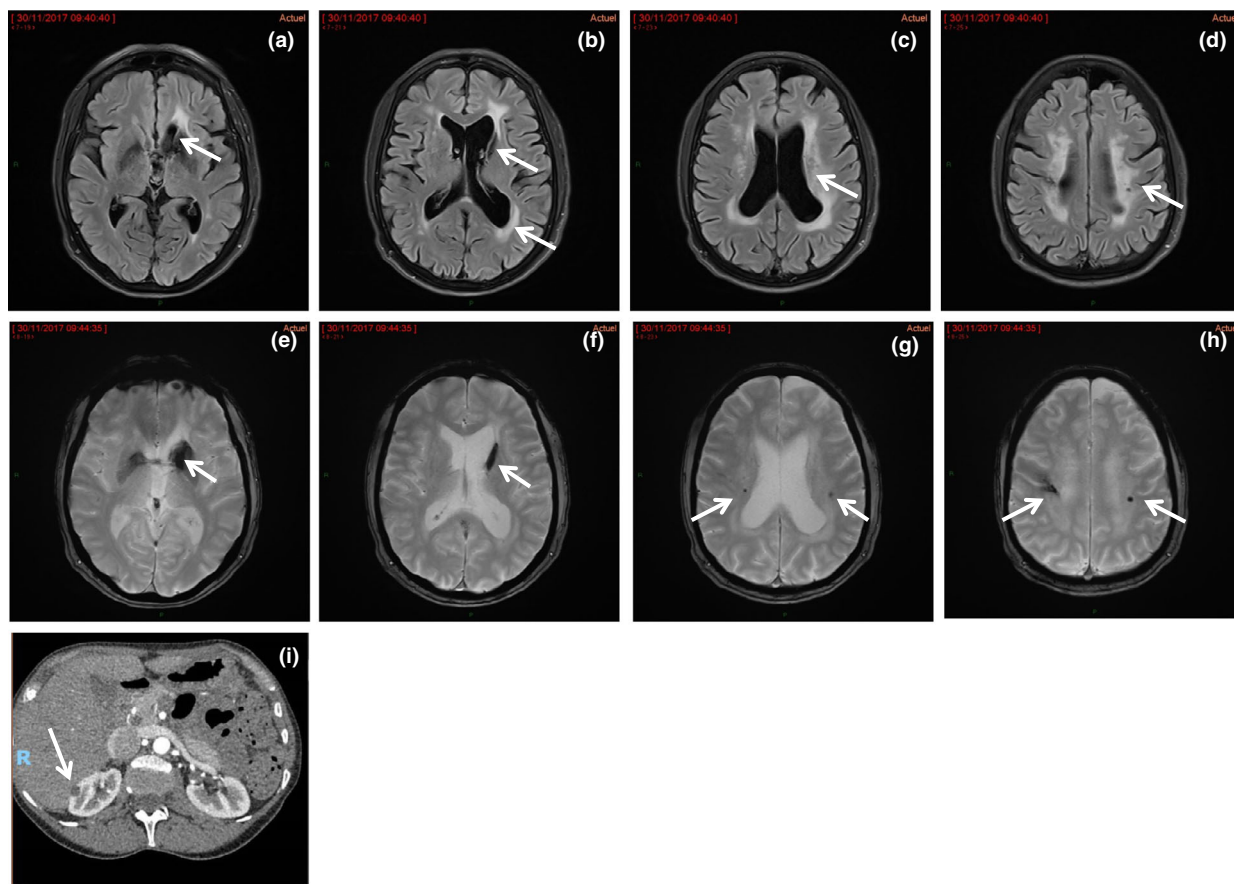

Figure 5 Type IV collagen (COL4)A1. White matter hyperintensities on Fluid Attenuated Inversion Recovery (FLAIR) images (a,b,c, d) and T2*-weighted images (e,f,g,h) in a 60-year-old woman with COL4A1 mutation who also presented a renal cyst and retinal vessel tortuosities. Note the moderate atrophy of the left hemisphere where a haemorrhagic lesion was observed in the caudate nucleus (arrows on images a and e), the presence of microbleeds in the deep white matter (g), small cavities (d) and an old haemorrhage at cortical level (h). The neurological examination was normal. A renal cyst was detected (i).

The clinical spectrum associated with pathogenic variants of monogenic *COL4A1/2* is highly variable [21,22]. Mean age at stroke onset is 30–40 years but intracerebral haemorrhage can occur in fetuses, children and adults, and has been associated with physical activity, trauma and anticoagulant therapy. Therefore, it is recommended that a carrier should avoid hard physical activity and anticoagulants. Due to risk of haemorrhage, a fetus carrying a pathogenic *COL4A1/2* variant should be delivered by Caesarean section. Haemorrhagic strokes are reported twice as often as ischaemic strokes. COL4A1/2 present in the paediatric and neonatal period with porencephaly or schizencephaly. Other manifestations include: intracerebral aneurysms, proteinuria, renal insufficiency, renal and hepatic cysts, tortuosities of retinal arteries, focal retinal haemorrhages, and early cataract or abnormal development of the anterior segment of the eye [23,24].

The clinical phenotype can vary widely between different affected family members.

Brain imaging may show intracerebral haemorrhages or cerebral microbleeds, WMHs and lacunes that are usually subcortical (Figs 5 and 6) [25].

Missense variants of *COL4A1* that disrupt the NC1 domain seem to be associated with antenatal cerebral haemorrhages and porencephaly, but not with kidney disease. Missense variants of *COL4A1* that encode the CB3 (IV) segment of the triple helical domain (exons 24 and 25) have been associated with hereditary angiopathy, nephropathy, aneurysms and cramps (HANAC) syndrome [24].

In contrast with *COL4A1/A2* microangiopathies associated with either glycine or stop codon variants, PADMAL is an autosomal dominant ischaemic cSVD caused by variants in the 3' untranslated region of *COL4A1*. These variants affect a binding site of a microRNA, miR29, and lead to upregulated expression of *COL4A1*. PADMAL clinical features are characterized by adult early-onset pons infarcts and early death [26]. No clinical manifestations have been reported so far in children.

Consensus statement results

Genetic testing
- Missense variants of *COL4A1* or *COL4A2* leading to replacement of a glycine of a gly-x-y motif in the triple helix and variant leading to premature stop codon are pathogenic.
- Variants of *COL4A1* at the binding site of mir-29 microRNA within COL4A1 3'UTR can cause a distinct ischaemic cSVD with early onset in adults called PADMAL.

Clinical and neuroimaging diagnosis
- A variant of *COL4A1* or *COL4A2* should be considered in a patient with deep intracerebral haemorrhage of undetermined origin OR WMHs of undetermined origin OR a cerebral haemorrhage, porencephaly, retinal vessel tortuosities, haematuria, glomerular dysfunction, renal insufficiency, renal cysts, infantile hemiparesis, early cataracts, abnormalities of the anterior segment of eyes, multiple intracranial aneurysms, muscle cramps or hepatic cyst is present in at least one first- or second-degree relative OR early-onset pontine infarcts.
- A multi-system non-invasive workup (including cerebral MRI, intracranial and cervical magnetic resonance angiography, cardiac echography, detailed ocular and retinal vessel examination with visual acuity and ocular pressure measures, liver and renal echography) is recommended in individuals with a *COL4A1/2* variant.
- Pre-symptomatic testing of family members is recommended, except in PADMAL, because of potential benefit of preventive measures, including avoiding complications during childbirth.

Management
- Antiplatelet and anticoagulant treatments are not recommended in *COL4A1/2* cSVD.
- Intravenous thrombolysis is not recommended in *COL4A1/2* cSVD.
- Sporting activities with a high risk of head trauma or excessive or prolonged exercise should be avoided.
- A Caesarean section should be considered in women giving birth where the foetus harbours a *COL4A1/2* mutation.

Cathepsin-A-related arteriopathy with strokes and leukoencephalopathy

CARASAL is an adult, ultra-rare, hereditary cSVD reported in only 19 patients [27–29], caused by a dominant variant in the *CTSA* gene, located on chromosome 20q13.12 [27], with the variant c.973C> T detected in 14/19 patients [27,28]. *CTSA* encodes the serine carboxypeptidase cathepsin-A, predominantly located in lysosomes where it stabilizes a multi-enzyme complex built up of beta-galactosidase and neuraminidase, and degrades endothelin-1 [27].

CARASAL manifests clinically as ischaemic or haemorrhagic stroke, cognitive impairment, dementia, headache, migraine, vertigo, movement disorders including, rarely, dystonia, gait disturbance or depression. Some patients present with extra-central nervous system manifestations, such as dysphagia,
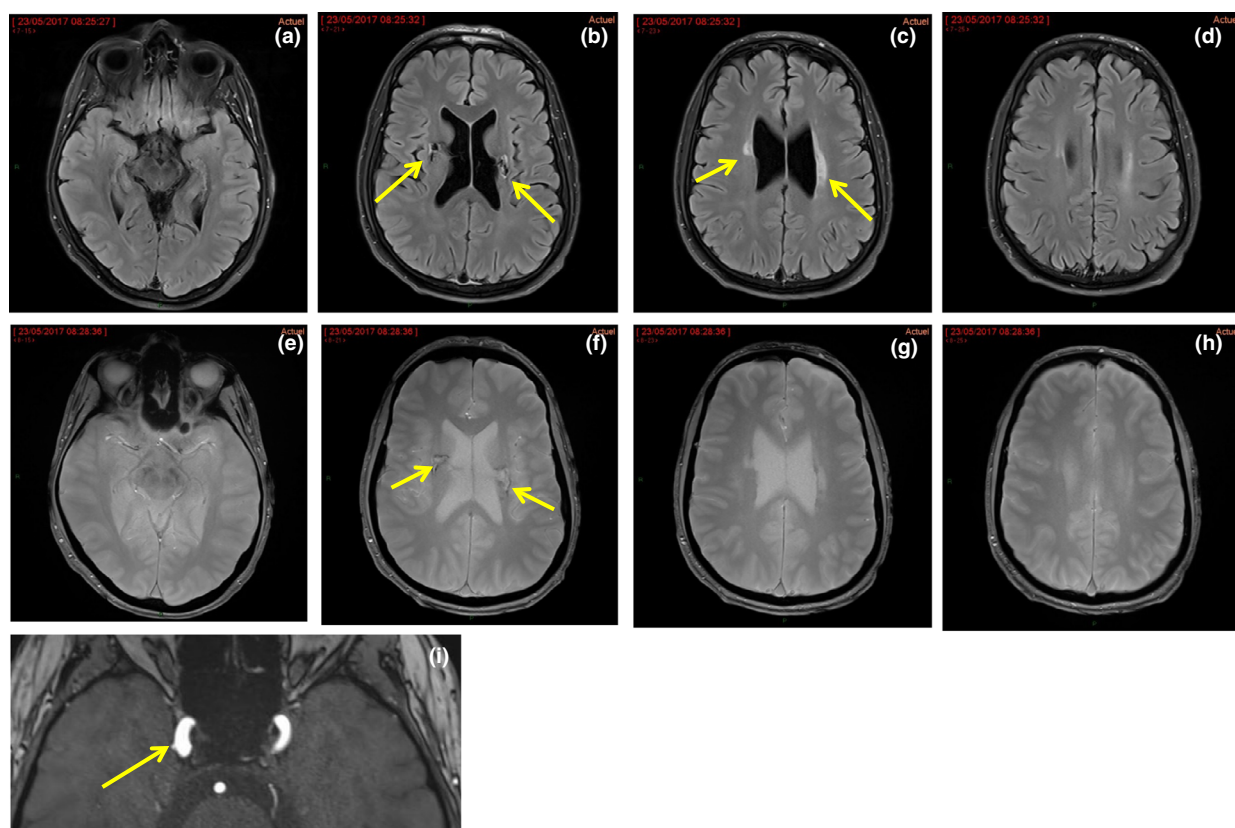
Figure 6 Type IV collagen (COL4)A1 angiopathy. Magnetic resonance imaging (MRI) Fluid Attenuated Inversion Recovery (FLAIR) (a, b,c,d) and T2* (e,f,g,h) lesions detected in a 37-year-old man with COL4A1 mutation who presented a right hemiplegia after an intracerebral haemorrhage at 33 years. He was readmitted after acute ischaemic lesions related to a stenosis of the distal part of the right internal carotid artery 4 years later. The patient had a small aneurysm (3 mm) of the right carotid artery (i). MRI shows both small cavities surrounded by hemosiderin deposits (b and f) in the deepest cerebral regions associated with a few white matter hyperintensities on FLAIR images in periventricular areas (c, d, f, g, h) not visible at brainstem level (a and e).

dry mouth, dry eyes, facial pain, muscle cramps, arterial hypertension or diabetes [27–29]. Cerebral imaging shows leukoencephalopathy involving the brainstem (pyramidal tracts, tegmental tracts, middle and superior cerebellar peduncles) and the subcortical white matter sparing the U-fibres [27]. Grey matter, including the thalamus, basal ganglia and dentate nuclei can be also affected [28]. Clinical manifestations can be absent or mild also in cases with extensive leukoencephalopathy.

There is no causal treatment available and no evidence that antithrombotic medication, anticoagulation or thrombolysis is indicated.
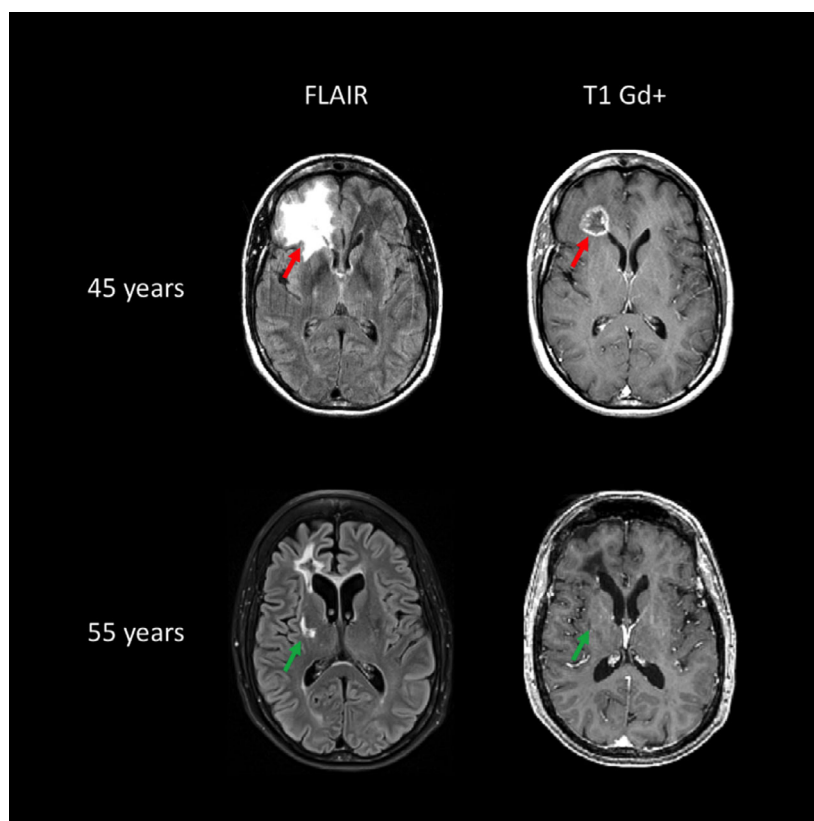
Consensus statement results

Management
■ There are insufficient data to recommend any specific treatment in CARASAL.

Retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations

RVCL-S is a genetic multi-organ small-vessel disease. The brain and retina are almost always affected, but microangiopathic disease can develop in other organs, most notably the kidneys and liver. The terms cerebroretinal vasculopathy, hereditary vascular retinopathy and hereditary endotheliopathy, retinopathy, nephropathy and stroke (HERNS) were initially used to describe affected families. However, the identification of a common genetic basis in 2007 suggested a single microvascular disorder, subsequently termed RVCL-S [30]. RVCL-S is an autosomal dominant disease caused by heterozygous C-terminal frameshift variants in the *TREX1* gene [30]. Although the biological functions of TREX1 are increasingly well described, the exact molecular mechanism whereby RVCL-S variants cause disease is unknown. TREX1 is a negative

Figure 7 Evolution of magnetic resonance imaging (MRI) changes in a patient with retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations. Pseudotumour adjacent to the right frontal horn (arrows on top images) with surrounding vasogenic oedema. The lesion demonstrates ring enhancement following gadolinium contrast. MRI scan a decade later demonstrates that the previous pseudotumour is inactive, without contrast enhancement or significant vasogenic oedema. Additional white matter hyperintensities have developed, without contrast enhancement (arrows on lower images). (With thanks to the team of Associate Professor Andria Ford and Professor John Atkinson, Washington University School of Medicine.) FLAIR, Fluid Attenuated Inversion Recovery.

regulator of innate immune pathways such as the type I interferon response, but prominent activation of this pathway is not typically observed in RVCL-S [31].

RVCL-S is a very rare disease and our understanding of clinical phenotype is largely based on details from an international study of 11 unrelated families with 78 variant carriers [32]. The clinical picture is usually dominated by microangiopathy of the retina and brain. Disease onset is typically in middle age [32]. Ophthalmological examination shows progressive retinal vasculopathy in almost all symptomatic patients. Clinical manifestations of the cerebral microangiopathy often develop in the fourth to fifth decade. Although the majority of patients develop cognitive impairment, brain disease can manifest as a large enhancing lesion, which can mimic tumours with pronounced mass effect or tumefactive inflammation [32]. Focal deficits can be associated with the development of contrast-enhancing lesions on MRI. These can become large and confluent, sometimes with perilesional oedema (Fig. 7). Calcifications in the white matter detected on computed tomography are common and were identified in 52% of mutation carriers [32]. Lacunar stroke is not a common manifestation and systematic screenings for *TREX1* in 1000 young-onset lacunar stroke patients detected no TREX1 pathogenic variants [33].

Microvascular disease affecting other organs is commonly seen and can be severe, mainly in kidney and liver, and can cause organ failure. Raynaud's disease, gastrointestinal bleeding, bone disease and thyroid disease are also seen.

Consensus statement results

Genetic testing
- Pathogenic frameshift variants in *TREX1* cause protein truncation in the C-terminus, which leads to subcellular mislocalization of the protein, but does not affect enzyme activity.

Management
- There is no established treatment of RVCL-S.
- There is no evidence of efficacy of antiplatelet therapy in RVCL-S.
- There is no evidence of efficacy of immunosuppressive therapy in RVCL-S and clinical trials are needed.

Fabry disease

Fabry disease is an inherited metabolic disease that results from a deficiency or absence of the enzyme α-galactosidase A due to a variant in the *GLA* gene. FD
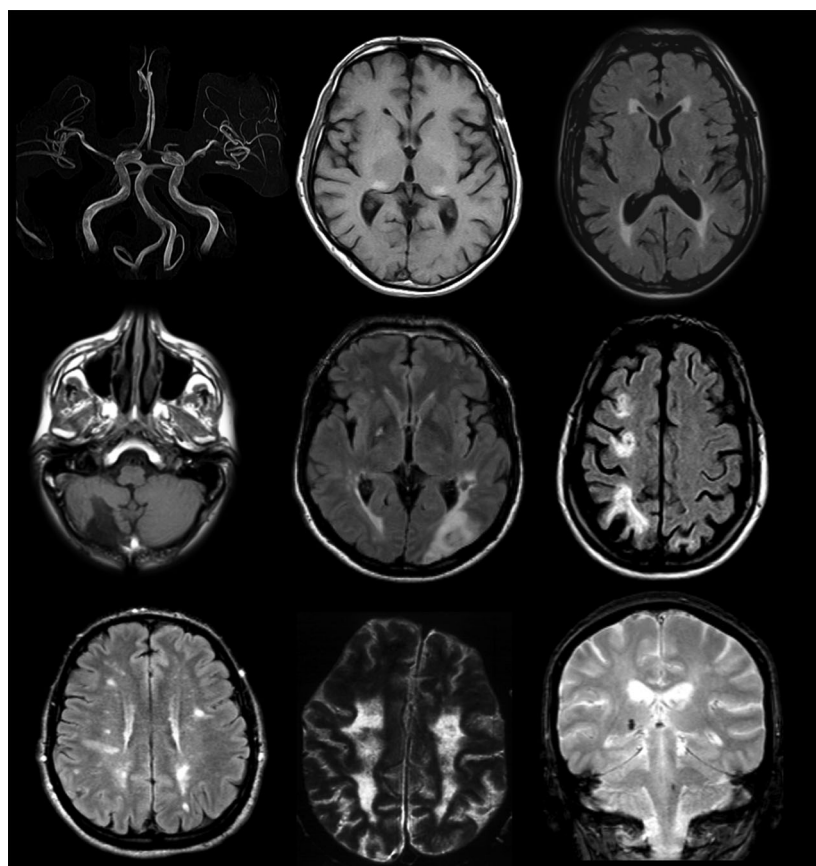
Figure 8 Brain magnetic resonance imaging findings in Fabry disease encompassing: (top row) dolichoectasia of the basilar artery, bilateral T1 hyperintensity of the pulvinar, lacunar strokes (left thalamus); (middle row) posterior circulation post-ischaemic encephalomalacia (right cerebellum), acute middle cerebral artery stroke (left hemisphere), watershed stroke (right hemisphere); and (bottom row) focal and confluent white matter changes, diffuse white matter changes and atrophy, T2*-hypointense microbleeds. Adapted from Burlina and Politei 2018. Reproduced with permission from Springer Nature. Authorization for this adaptation has been obtained from the publisher.

is inherited as an X-linked trait. Male patients can develop a classic severe phenotype of the disease (type 1), whereas heterozygous female patients present with phenotypes ranging from asymptomatic to severe involvement of vital organs. The classic forms exhibit early manifestations, whereas later-onset forms (type 2) can present clinical signs later in life. About 900 variants, most of them private, have been reported [34]. FD is a lysosomal storage disease, due to accumulation of the sphingolipid globotriaosylceramide (GL-3 or Gb3) and its deacetylated derivative lyso-globotriaosylceramide (lyso-GL-3 or lyso-Gb3).

Many different cell types are involved in FD, including vascular cells (endothelial cells and vascular smooth muscle cells), cardiomyocytes, renal cells, enteric neurons and nerve cells [34]. Therefore, heart, kidney, brain, peripheral nervous system and the gastrointestinal system are heavily involved in the disease [34,35].

There is a causal relationship between FD and ischaemic stroke, but the underlying mechanisms are still unclear. Ischaemic stroke is the most common subtype, but intracerebral haemorrhages and cerebral venous thrombosis have been reported [36]. The posterior circulation seems to be predominantly affected. The most common age of stroke onset is 20–50 years [36]. WMHs seen on T2-weighted MRI are a common finding in patients with FD, present in up to 46% (Fig. 8) [37], and progression of WMHs occurs in a significant proportion of them. Other
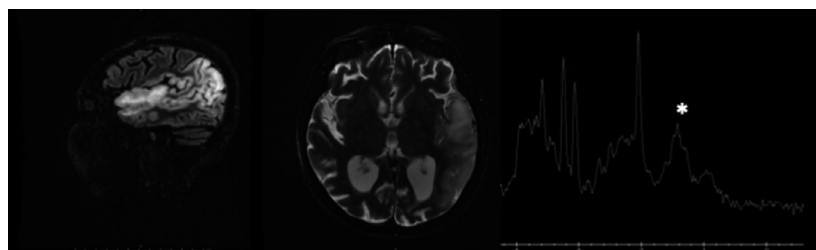

Figure 9 Mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS). Cranial magnetic resonance findings of stroke-like episodes in a young woman that do not respect the vascular territories of major cerebral arteries or border zones. Asterisk shows a lactate peak on proton spectroscopy.

neuroradiological features are basilar artery dolichoectasia and the pulvinar sign [36].

Fabry disease explains less than 1% of cryptogenic ischaemic strokes in young adults. An early study [38] suggested that FD might account for 4.9% of ischaemic stroke in young male patients but this has not been confirmed in replication studies [39,40].

Cognitive function has been less studied than other neurological complications in FD.

Besides symptomatic drugs, specific therapies are available. The latter include enzymatic replacement therapy (ERT) (agalsidase beta or alfa) and chaperone therapy for amenable variants. Recent recommendations regarding diagnosis, monitoring and treatment have been published [35].

Consensus statement results

Management
- Early diagnosis is important for the correct management of patients with FD.
- Systemic thrombolysis is not contraindicated in FD.
- Thrombectomy can be applied in case of proximal occlusion of cerebral arteries in patients with FD.
- There is no evidence to recommend antithrombotic treatment for primary prevention for stroke in FD.
- Primary stroke prevention in FD includes lifestyle modifications.
- Patients with FD should receive antithrombotic therapy after the first cerebrovascular event. Regarding stroke prevention, there are no data yet on whether antithrombotic drugs are effective in FD. Recent experts' recommendations include lifestyle modifications to control common risk factors and antithrombotic drugs for secondary prevention [35].
- ERT is usually recommended to reduce complications of FD although there is no good evidence that ERT can prevent stroke recurrence.

Stroke recurrence in patients with FD, with and without ERT, has been reported [34]. There was strong consensus that there was no clear evidence that ERT reduced stroke risk in FD. It was agreed that more data are required. Two recent systematic reviews reported a lower incidence of cerebrovascular events with agalsidase beta [41] and ERT [42], the latter suggesting an approximate halving of stroke risk. These are based on observational data and it was agreed that more data are required, ideally from randomized trials.

Mitochondrial encephalopathy, lactic acidosis and stroke-like episodes

MELAS is one of the most severe syndromes in mitochondrial disease. Although the majority of patients (80%) have the common MELAS pathogenic variant m.3243A>G in the mitochondrial DNA tRNA-leucine (MT-TL1) [43], the number of genotypes causing the MELAS phenotype continues to expand and may include nuclear genes, mainly *POLG* [44].

One of the clinical hallmarks of MELAS, the stroke-like episode (SLE), is characterized by headache, nausea and vomiting, encephalopathy, focal-onset seizures and focal neurological deficits. On conventional MRI, the affected areas do not correspond to vascular territories and involve the cortex and juxtacortical white matter (Fig. 9). Lesions may spread over days, weeks and even months or go to the contralateral side after the acute episode. Some lesions reverse completely with time; however, most severe lesions develop into cortical laminar necrosis, gliosis and atrophy.

Although SLEs were originally described in individuals <40 years of age, late-onset presentation is recognized. Although SLEs cannot be strictly classified as cSVD, they have to be considered in the differential diagnosis of cSVD and therefore MELAS was included in the consensus statement.

Additional common clinical and laboratory findings in MELAS are eyelid ptosis, cardio(myo)pathy, muscle weakness, diabetes and lactic acidosis.

Compared with strokes of vascular origin, there is higher incidence of bilateral clinical symptoms such as cortical blindness or auditory agnosia.

The underlying pathophysiological mechanism of SLEs remains unclear [45]. Limitations in the understanding of the disease mechanism are reflected in the controversies about the acute management of SLEs.

Consensus statement results

Genetic
- Urgent genetic testing for MELAS should be considered in patients presenting with suspected SLE. Search for the m.3243A>G variant (in urine where possible) and, if m.3243A>G variant is negative, *POLG* sequencing is required. Muscle biopsy should be considered after excluding m.3243A>G and *POLG* variants.

Clinical and neuroimaging diagnosis
- A mitochondrial SLE is a subacute, evolving brain syndrome driven by seizure activity in genetically determined mitochondrial disease, which can be present at any age with neurological symptoms typically associated with cortical/subcortical MRI changes and electroencephalogram abnormalities [45].
- The diagnosis of an SLE requires the combination of clinical assessment, cerebral MRI and electroencephalogram.

Management

- Fibrinolysis is not indicated to treat SLE.
- Antiplatelet therapies are not indicated for secondary prevention of SLEs.
- If an SLE is suspected and focal seizures are evident, they should be treated urgently with intravenous antiepileptic drugs, including levetiracetam, benzodiazepines or lacosamide.
- Valproic acid is contraindicated, mainly in patients with *POLG* variants.
- There is not enough evidence to support the use of intravenous L-arginine to treat SLEs.
- Even though there is no scientific evidence of positive impact of steroids in SLEs, their use is not contraindicated.
- Drugs like haloperidol, benzodiazepine, quetiapine, olanzapine may be safely used to treat psychiatric complications in MELAS.
- Because of the frequent occurrence of arrhythmia in MELAS (especially if caused by m.3243A>G), electrocardiogram monitoring during an SLE, especially after the introduction of an antipsychotic drug with QT (QT interval; the time from the start of the Q wave to the end of the T wave at the electrocardiogram)-prolonging side effect, should be considered.

Acknowledgements

Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

File S1. Full list of references used to address the specific disease.

File S2. Queries of the first online survey.

References

1. de Winter JCF, Dodou D. Five-point Likert items: t test versus Mann-Whitney-Wilcoxon. *Pract Assessment Res Eval* 2010; **15:** 1–10.
2. Joutel A, Corpechot C, Ducros A, *et al*. Notch3 mutations in CADASIL, a hereditary adult-onset condition causing stroke and dementia. *Nature* 1996; **383:** 707–710.
3. Narayan SK, Gorman G, Kalaria RN, Ford GA, Chinnery PF. The minimum prevalence of CADASIL in northeast England. *Neurology* 2012; **78:** 1025–1027.
4. Rutten JW, Van Eijsden BJ, Duering M, *et al*. The effect of NOTCH3 pathogenic variant position on CADASIL disease severity: NOTCH3 EGFr 1–6 pathogenic variant are associated with a more severe phenotype and lower survival compared with EGFr 7–34 pathogenic variant. *Genet Med* 2019; **21:** 676–682.
5. Chabriat H, Joutel A, Dichgans M, Tournier-Lasserve E, Bousser M-G. Cadasil. *Lancet Neurol* 2009; **8:** 643–653.
6. Di Donato I, Bianchi S, De Stefano N, *et al*. Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) as a model of small vessel disease: update on clinical, diagnostic, and management aspects. *BMC Med* 2017; **15:** 41.
7. Chabriat H, Joutel A, Dichgans M, Tournier-lasserve E, Bousser M. Review CADASIL. *Lancet Neurol* 2009; **8:** 643–653.
8. Adib-Samii P, Brice G, Martin RJ, Markus HS. Clinical spectrum of CADASIL and the effect of cardiovascular risk factors on phenotype: study in 200 consecutively recruited individuals. *Stroke* 2010; **41:** 630–634.
9. Ling Y, De Guio F, Jouvent E, *et al*. Clinical correlates of longitudinal MRI changes in CADASIL. *J Cereb Blood Flow Metab* 2019; **39:** 1299–1305.
10. Joutel A, Favrole P, Labauge P, *et al*. Skin biopsy immunostaining with a Notch3 monoclonal antibody for CADASIL diagnosis. *Lancet (London, England)* 2001; **358:** 2049–2051.
11. Dichgans M, Markus HS, Salloway S, *et al*. Donepezil in patients with subcortical vascular cognitive impairment: a randomised double-blind trial in CADASIL. *Lancet Neurol* 2008; **7:** 310–318.
12. Tan RYY, Markus HS. CADASIL: migraine, encephalopathy, stroke and their inter-relationships. *PLoS One* 2016; **11:** e0157613.
13. Hara K, Shiga A, Fukutake T, *et al*. Association of HTRA1 mutations and familial ischemic cerebral small-vessel disease. *N Engl J Med* 2009; **360:** 1729–1739.
14. Fukutake T. Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL): From discovery to gene identification. *J Stroke Cerebrovasc Dis* 2011; **20:** 85–93.
15. Nozaki H, Nishizawa M, Onodera O. Features of cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy. *Stroke* 2014; **45:** 3447–3453.
16. Bianchi S, Di Palma C, Gallus GN, *et al*. Two novel HTRA1 mutations in a European CARASIL patient. *Neurology* 2014; **82:** 898–900.
17. Nozaki H, Sekine Y, Fukutake T, *et al*. Characteristic features and progression of abnormalities on MRI for CARASIL. *Neurology* 2015; **85:** 459–463.

18. Verdura E, Hervé D, Scharrer E, et al. Heterozygous HTRA1 mutations are associated with autosomal dominant cerebral small vessel disease. *Brain* 2015; **138**(Pt 8): 2347–2358.

19. Nozaki H, Kato T, Nihonmatsu M, et al. Distinct molecular mechanisms of HTRA1 mutants in manifesting heterozygotes with CARASIL. *Neurology* 2016; **86**: 1964–1974.

20. Gould DB, Phalan FC, van Mil SE, et al. Role of COL4A1 in small-vessel disease and hemorrhagic stroke. *N Engl J Med* 2006; **354**: 1489–1496.

21. Zagaglia S, Selch C, Nisevic JR, et al. Neurologic phenotypes associated with COL4A1/2 mutations: Expanding the spectrum of disease. *Neurology* 2018; **91**: e2078–e2088.

22. Sato Y, Shibasaki J, Aida N, et al. Novel COL4A1 mutation in a fetus with early prenatal onset of schizencephaly. *Hum Genome Var* 2018; **5**: 4.

23. Gould DB, Marchant JK, Savinova OV, Smith RS, John SWM. Col4a1 mutation causes endoplasmic reticulum stress and genetically modifiable ocular dysgenesis. *Hum Mol Genet* 2007; **16**: 798–807.

24. Plaisier E, Gribouval O, Alamowitch S, et al. COL4A1 mutations and hereditary angiopathy, nephropathy, aneurysms, and muscle cramps. *N Engl J Med* 2007; **357**: 2687–2695.

25. Vahedi K, Alamowitch S. Clinical spectrum of type IV collagen (COL4A1) mutations: a novel genetic multisystem disease. *Curr Opin Neurol* 2011; **24**: 63–68.

26. Ding X-Q, Hagel C, Ringelstein EB, et al. MRI features of pontine autosomal dominant microangiopathy and leukoencephalopathy (PADMAL). *J Neuroimaging* 2010; **20**: 134–140.

27. Bugiani M, Kevelam SH, Bakels HS, et al. Cathepsin A-related arteriopathy with strokes and leukoencephalopathy (CARASAL). *Neurology* 2016; **87**: 1777–1786.

28. Lynch DS, Rodrigues Brandão de Paiva A, Zhang WJ, et al. Clinical and genetic characterization of leukoencephalopathies in adults. *Brain* 2017; **140**: 1204–1211.

29. Hervé D, Chabriat H, Rigal M, et al. A novel hereditary extensive vascular leukoencephalopathy mapping to chromosome 20q13. *Neurology* 2012; **79**: 2283–2287.

30. Richards A, van den Maagdenberg AMJM, Jen JC, et al. C-terminal truncations in human 3'-5' DNA exonuclease TREX1 cause autosomal dominant retinal vasculopathy with cerebral leukodystrophy. *Nat Genet* 2007; **39**: 1068–1070.

31. Hardy TA, Young S, Sy JS, et al. Tumefactive lesions in retinal vasculopathy with cerebral leucoencephalopathy and systemic manifestations (RVCL-S): a role for neuroinflammation? *J Neurol Neurosurg Psychiatry* 2017; **89**: 434–435.

32. Stam AH, Kothari PH, Shaikh A, et al. Retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations. *Brain* 2016; **139**: 2909–2922.

33. McGlasson S, Rannikmäe K, Bevan S, et al. Rare variants of the 3'-5' DNA exonuclease TREX1 in early onset small vessel stroke. *Wellcome Open Res* 2017; **2**: 106.

34. Burlina AP, Politei J. Fabry disease. In: Burlina AP, eds. *Neurometabolic Hereditary Diseases of Adults*. Cham: Springer International Publishing, 2018: 67–98.

35. Ortiz A, Germain DP, Desnick RJ, et al. Fabry disease revisited: Management and treatment recommendations for adult patients. *Mol Genet Metab* 2018; **123**: 416–427.

36. Kolodny E, Fellgiebel A, Hilz MJ, et al. Cerebrovascular involvement in Fabry disease: current status of knowledge. *Stroke* 2015; **46**: 302–313.

37. Körver S, Vergouwe M, Hollak CEM, van Schaik IN, Langeveld M. Development and clinical consequences of white matter lesions in Fabry disease: a systematic review. *Mol Genet Metab* 2018; **125**: 205–216.

38. Rolfs A, Böttcher T, Zschiesche M, et al. Prevalence of Fabry disease in patients with cryptogenic stroke: A prospective study. *Lancet* 2005; **366**: 1794–1796.

39. Doheny D, Srinivasan R, Pagant S, Chen B, Yasuda M, Desnick RJ. Fabry Disease: prevalence of affected males and heterozygotes with pathogenic GLA mutations identified by screening renal, cardiac and stroke clinics, 1995–2017. *J Med Genet* 2018; **55**: 261–268.

40. Kilarski LL, Rutten-Jacobs LCA, Bevan S, et al. Prevalence of CADASIL and Fabry disease in a cohort of MRI defined younger onset lacunar stroke. *PLoS One* 2015; **10**: e0136352.

41. El Dib R, Gomaa H, Ortiz A, Politei J, Kapoor A, Barreto F. Enzyme replacement therapy for Anderson-Fabry disease: A complementary overview of a Cochrane publication through a linear regression and a pooled analysis of proportions from cohort studies. *PLoS One* 2017; **12**: e0173358.

42. Sheng S, Wu L, Nalleballe K, et al. Fabry's disease and stroke: Effectiveness of enzyme replacement therapy (ERT) in stroke prevention, a review with meta-analysis. *J Clin Neurosci* 2019; **65**: 83–86.

43. Goto Y, Nonaka I, Horai S. A mutation in the tRNA (Leu)(UUR) gene associated with the MELAS subgroup of mitochondrial encephalomyopathies. *Nature* 1990; **348**: 651–653.

44. Deschauer M, Tennant S, Rokicka A, et al. MELAS associated with mutations in the POLG1 gene. *Neurology* 2007; **68**: 1741–1742.

45. Ng YS, Bindoff LA, Gorman GS, et al. Consensus-based statements for the management of mitochondrial stroke-like episodes. *Wellcome Open Res* 2019; **4**: 201.

46. Manara R, Burlina AP. Neuroimaging of inherited metabolic diseases of adulthood. In: Burlina AP, eds. *Neurometabolic Hereditary Diseases of Adults*. Cham: Springer International Publishing, 2018: 54.