

Monogenic cerebral small vessel diseases

Summary of Recommendations of the European Academy of Neurology – March 2020

Most common monogenic cerebral small vessel diseases (cSVD):

- *CADASIL (ischemic)*
- *CARASIL (ischemic)*
- *CARASAL (ischemic or hemorrhagic)*
- *PADMAL (ischemic)*
- *Fabry Disease (ischemic)*
- *MESLAS (ischemic)*
- *COL4 A1/2 (hemorrhagic)*
- *RVCL-S (ischemic)*

Red flags suggesting a case of cSVD:

- Positive family history
- Young age at onset
- Consanguinity
- Neuroimaging features
- Extracerebral systemic features
- Negative workup for other causes of cSVD

General principles for managing patients with cSVD:

- Genetic counseling for family planning, options for pre-natal diagnostics should be offered
- Genetic counseling of family members of the proband with geneticist should be offered
- Meticulous control of other vascular risk factors including healthy diet and exercise
- Patients should have a yearly evaluation of their vascular risk factors

CADASIL:

- ETIOLOGY:

- NOTCH3 mutation. NOTCH3 is a single-pass receptor protein that is important for vascular small muscle cell differentiation. Mutation in NOTCH3 leads to deletion or addition of cysteine residues in NOTCH3 protein (in one of the 34 EGFr domain)
- Earlier onset of stroke seen in patients with mutation leading to alteration in one of the EGFr domains 1-6 than 7-34 domains.

- DIAGNOSIS:

- **Clinical picture:** Migraine with aura, acute encephalopathy, lacunar strokes, cognitive decline and mood disorders.
- **Stroke onset** is usually between 40 and 60 years with progression to a mute bedridden state in 10 years.
- **Genetics:** Definitive diagnosis is done by genetic testing, in case of NOTCH3 variant of unknown significance (not affecting cysteine), CADASIL can be confirmed by skin biopsy examination with electron microscopy showing granular osmiophilic material (GOM) or NOTCH3 immunostaining
- **MRI:** anterior temporal white matter hyperintensities (WMHs) are present in 90% of cases, severe widespread WMHs with involvement of internal and external capsules in advanced cases.
- 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

- TREATMENT:

- Antiplatelets: No evidence to support use of antiplatelets in CADASIL patients primary or secondary stroke prevention, although it is commonly used
- Statins: no evidence to support their use
- Triptans: there is no evidence to contraindicate
- Acetazolamide: there is no evidence to support its use
- Anticoagulants: are not recommended for CADASIL treatment, however they are not contraindicated if there is another reason (atrial fibrillation).
- Oral contraception: no evidence to contraindicate
- Anesthetic procedures: maintain hemodynamic stability, cerebral autoregulation is impaired in CADASIL and low or high BP can result in stroke.
- Pregnancy & labor: pregnancy is not contraindicated, no need for prophylactic aspirin or heparin. Migraine can increase. Labor and puerperium are usually associated with transient neurological events, similar to migraine with aura.

CARASIL:

- ETIOLOGY:

- Autosomal recessive disorder, caused by biallelic mutation of HTRA1 gene (including homozygous missense or frameshift and compound heterozygous mutations).
- HTRA1 encodes a serine protease enzyme (cleaves other proteins in small pieces) both inside and outside cells. Serine protease also inhibits TGF-β (transforming growth factor beta) that is responsible for new blood vessel formation.
- CARASIL is mainly reported in Japanese and Chinese population
- HTRA1 gene heterozygous mutations can cause autosomal dominant cSVD, distinct from CARASIL

- DIAGNOSIS:

- **Clinical picture:** recurrent lacunar strokes, early vascular dementia, gait impairment, premature (during adolescence) head alopecia in 90% of patients and early lumbar disc herniation. Other symptoms include seizures, psychiatric disturbances, pseudobulbar palsy.
 - CARASIL should be suspected in patients with early onset premature scalp alopecia, severe spondylosis or unexplained early lacunar strokes/symmetric WMHs
 - CARASIL should always be considered in differential of early onset cSVD, CADASIL or CARASAL.
- **Onset:** first stroke onset at 30-40 years with rapid stepwise progression, most patients become bedridden in 10 years.
- **Genetics:** HTRA1 gene testing
- **Pathology:** no disease specific findings (no GOM as in CADASIL), but there is arteriosclerosis and loss of vascular smooth muscles with hyalinization.
- **MRI:** WMHs start on MRI at age of 20, may involve anterior temporal lobes.

- TREATMENT:

- Antiplatelets: No data to support its use

HTRA1 AUTOSOMAL DOMINANT DISEASE:

- ETIOLOGY:

- Heterozygous mutations in HTRA1 gene leads to decreased activity, inherited as AD.

- DIAGNOSIS:

- **Onset:** Later onset and less severe as compared to CARASIL. Stroke onset usually at 60 years.
- **Clinical picture:** lacunar strokes, cognitive impairment and encephalopathy. Less frequent alopecia and spondylosis.
- **Pathology:** Diffuse myelin pallor in white matter, sparing U fibers – resembling CADASIL.
- **Gene:** not all mutations are pathologic – activity of the enzyme sometimes need to be tested

CARASAL (Cathepsin-A-related arteriopathy with stroke and leukoencephalopathy):

- **ETIOLOGY:**
 - CTSA gene mutation, which encoded for cathepsin-A, a carboxypeptidase that stabilize a beta-galactosidase and neuroaminidase complex.
- **DIAGNOSIS:**
 - Very rare disease, only 19 cases were reported
 - **Clinical picture:** Ischemic or hemorrhagic strokes, cognitive impairment, dementia, migraine, and rarely dystonias. Dystonia is pathognomonic feature but rare. Some patients may not show symptoms despite the extensive WMHs.
 - **MRI:** leukoencephalopathy involving the brainstem, cerebellar peduncles, subcortical white matters sparing U fibers.
- **MANAGEMENT:**
 - No sufficient data to recommend specific treatments

COL4A1 – COL4A2:

- **ETIOLOGY:**
 - Missense or null mutation of collagen IV gene (COL4A1 or COL4A2) usually affecting glycine or stop codon, Type IV collagen makes the basement membrane of all blood vessels leading to widespread manifestations.
 - Autosomal dominant cSVD of hemorrhagic type
 - Some COL4A1 mutations can cause HANAC syndrome (hereditary angiopathy, nephropathy, aneurysms and cramps)
- **DIAGNOSIS:**
 - **Onset:** intracerebral hemorrhage can occur in fetus, kids, adults – usually related to trauma, physical activity or anticoagulation. Ischemic strokes usually start in 30s or 40s.
 - **Clinical picture:** widely variable from person to person
 - Kids: intracerebral hemorrhage, porencephaly, schizencephaly, intracranial aneurysms
 - Adults: hemorrhagic and ischemic strokes, renal insufficiency, renal and hepatic cysts, tortuosities of retinal arteries and focal retinal hemorrhage, early cataract.
 - **MRI:** ICHs, microbleeds, WMHs and lacunes – usually subcortical location.
 - It should be suspected in patients with:
 - Deep intracerebral hemorrhage of undetermined etiology.
 - WMHs of undetermined etiology
 - FHx of cerebral hemorrhage, porencephaly, retinal vessel tortuosities, hematuria, glomerular dysfunction, early cataracts, multiple intracranial aneurysms in a first or second degree relative
 - Workup includes:
 - MRI brain

- CTA of cranial and cervical vessels for aneurysms
 - TTE
 - Ocular and retinal vessels examination
 - CK levels
 - Pre-symptomatic testing of family members
- **MANAGEMENT:**
 - Antiplatelets and anticoagulants are not recommended
 - tPA is not recommended
 - Avoid sports with high risk of brain trauma
 - Caesarian sections should be considered in patients giving birth to a COL41/2 mutation

PADMAL:

- Etiology:
 - Another form of COL4A1/2 mutation that involve the 3' untranslated region, it affects the binding site of mRNA leading to upregulated expression.
 - Autosomal dominant disease
- Diagnosis:
 - Clinical picture: Adult early onset pontine infarcts and early death

RVCL-s (Retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations):

- **ETIOLOGY:**
 - TREX1 gene frameshift mutation that causes truncation of C terminus leading to mis-localization of the enzyme.
- **DIAGNOSIS:**
 - **Clinical picture:**
 - AD, very rare disease. Onset is usually in 4th or 5th decade, involves brain and retinal small vessel diseases.
 - Brain involvement manifest with cognitive impairment or focal deficits. Focal deficits may be associated with a large enhancing lesions mimicking a tumor or tumefactive inflammation on MRI.
 - Retinal exam shows progressive retinal vasculopathy
 - Extracerebral manifestations include kidney or liver failure, Raynaud's disease, GI bleeding or thyroid disease/
 - **MRI:** shows either punctate T2 hyperintensities, nodular enhancements or large enhancing lesions mimicking tumors or tumefactive inflammation. CT may also show calcifications in white matter in 50% of patients. TREX doesn't cause lacunar strokes though.
- **MANAGEMENT:**
 - No evidence of efficacy of antiplatelets
 - No evidence of efficacy of immunosuppressive therapy

FABRY DISEASE:

- **ETIOLOGY:**
 - GLA gene mutation results in α -galactosidase deficiency (lysosomal storage disease) that causes accumulation of sphingolipids.
 - X-linked trait, males develop the classic severe phenotype, heterozygous females can be symptomatic as well.
 - FD affects 1 in 40,000
- **DIAGNOSIS:**
 - Clinical picture:
 - **Classic form:** starts in childhood with burning pain in hands and feet triggered by stress, exercise, fatigue or illness, then decreased sweating, angiokeratomas in lower abdomen and upper thighs and GI symptoms.
 - **Non-classic (late) form:** Symptoms start later in adulthood and in some they present with specific organ complications without skin or neuropathic symptoms.
 - Peripheral nerves: peripheral neuropathy with remarkable burning pain, decrease sweating
 - Skin: angiokeratomas in lower abdomen and upper thighs (bath region)
 - Cornea: corneal verticillate
 - Brain: strokes start at age 20-50, usually ischemic but hemorrhagic and CVT can occur. Posterior circulation is predominantly affected. FD accounts for 1% of cryptogenic strokes.
 - Heart: cardiomyopathy and arrhythmias
 - Kidney: progressive kidney impairment
 - GI: abdominal cramps, constipation or diarrhea
 - **MRI:** WMHs seen in 50% of patients - pulvinar sign – basilar artery dolichoectasia can be seen
 - **Lab:**
 - In males by testing blood for α -galactosidase A and if low send genetic test.
 - In females: gene analysis is first step, as many females have normal enzyme levels in their blood.
- **MANAGEMENT:**
 - Two FDA approved therapies:
 - Enzyme replacement therapy, agalsidase beta (Fabrazyme)
 - Chaperone therapy: (Migalastat) which enhances activity of the residual enzyme (resolve misfolding of mutated enzyme, specific for some variants of FD)
 - Early diagnosis is important for effective treatment
 - Neuropsychological testing is recommended for all patients
 - tPA is not contraindicated
 - Antiplatelets: no evidence to use for primary prevention but should be used for secondary prevention

MELAS:

- **ETIOLOGY:**
 - Either mitochondrial gene mutation or POLG gene mutation (DNA Polymerase gamma, coded by autosomal genes then transferred to mitochondria for mitochondrial DNA replication)
- **DIAGNOSIS:**
 - **Clinical picture:**
 - Stroke like episodes (SLEs), a subacute syndrome manifesting with headache, nausea, vomiting, encephalopathy, focal neurological deficits and focal seizures.
 - Onset: typically before age of 40, but late onset presentation is recognized
 - Other features: ptosis, cardiomyopathy, muscle weakness, diabetes and lactic acidosis.
 - **MRI:** Affected area mainly affect cortex and juxtacortical white matter and doesn't confine to vascular territory. Some lesions resolve with time, but severe lesions may develop into cortical laminar necrosis and gliosis.
 - **Gene testing:** Urgent genetic testing should be considered in patients presenting with SLEs. M.3243A>G mutation should be tested (in urine where possible) and if negative POLG sequencing is required. If both are negative then muscle biopsy should be considered (as other mitochondrial mutations may be implicated)
 - Increased serum or CSF lactate or increased lactate by MRS indicates a mitochondrial pathology in SLEs.
 - Psychiatric manifestations are common
 - Arrhythmias are common, telemetry monitoring during SLEs, specially if antipsychotics are used
- **MANAGEMENT:**
 - **tPA** is not indicated for SLEs
 - **Antiplatelets:** not indicated for secondary prevention
 - **AED:** if seizure is suspected, should be treated aggressively with levetiracetam, lacosamide or benzos. Avoid valproic acid (specially in patients with PLOG mutation)
 - **L-arginine:** no evidence to support use
 - **Steroids:** Although no evidence to support use, it is not contraindicated

Disease	CADASIL	CARASIL	AD-HTRA	COL4A	PADMAL	CARASAL	RVCL-S	FD	MELAS
Gene	NOTCH3	HTRA1	HTRA1	COL4A 1,2	COL4A1	CTSA	TREX1	α-galactosidase	Mitochondrial DNA or POLG
	AD	AR	AD	AD	AD	AD	AD	X-linked	Maternal or AR (POLG)
Clinical:									
Ischemic stroke	X	X	X	X	X	X		X	
ICH	X (rare)			X		X		X	
STLEs									X
Cognitive impairment	X	X	X	X	X	X	X		X
Migraine	X		X			X			X
Seizures	X (rare)						X		X
Mood disorders	X	X	X			X		X	X
Alopecia		X	X						
Extracerebral		X		X		X	X	X	X
Imaging:									
Lacunar infarcts	X	X	X	X	X			X	
WMHs	X	X	X	X	X		X	X	
Micro-bleeds	X			X				X	
Anterior temporal WMHs	X	X	X						
Large enhancing WM lesions							X		
Cortical & Subcortical signals crossing vascular territories									X

