orphanaesthesia

Anaesthesia recommendations for

# Cerebral arteriopathy, Autosomal Dominant, with subcortical infarcts and leukoencephalopathy; CADASIL

**Disease name:** CEREBRAL ARTERIOPATHY, AUTOSOMAL DOMINANT, WITH SUBCORTICAL INFARCTS AND LEUKOENCEPHALOPATHY; CADASIL (acronym of Cerebral Autosomal Dominant Arteriopaty with Subcortical Infarcts and Leukoencephalopathy)

**ICD 10:** F01.1 Vascular dementia; F01.2 Subcortical vascular dementia.

**Synonyms:** Hereditary multi-infarct dementia. CASIL

**Disease summary:** CADASIL is an inherited autosomal dominant progressive disorder that affects small arterial vessels. The disease is classified as a non-arteriosclerotic arteriopathy, and results in multiple cerebral subcortical infarcts with migraine, strokes, and white matter injuries with resultant dementia, cognitive impairment and other symptoms.
The prevalence is 1-9 / 100,000. CADASIL is the most frequent monogenic cerebral small vessel disease, and has received a lot of attention in recent years as a model for small vessel diseases, with an increased number of cases. This is approximately 100-fold higher than current estimates of the minimum prevalence of CADASIL, suggesting that CADASIL is much more prevalent than previously suspected.
It is the consequence in most cases of a mutation in the NOTCH3 gene located in the 19 chromosome (gene map locus 19p.13.2-p13.1).
NOTCH3 gene codify for the Notch3 protein, a membrane receptor that intervenes in cell differentiation (embryo), and that is involved in vascular vessel development (and specialization to a vascular cell to be arterial, venous or capillary). The alteration results in Notch3 protein with a default in a cystein residual, changing its conformational aspect and inhibiting its receptor function. In addition these proteins cannot be metabolized and accumulate in the membrane of the smooth muscle cells of the arterial wall. Although it is a generalized arteriopathy involving small and medium sized arteries, it affects preferably the central nervous system (however other vascular systems might be affected, mainly when the disease progresses and worsens).
The disease is most likely to appear in individuals of around 45 years of age or younger. The clinical findings consists of (see table 1 for a summary): migraine attacks, subcortical ischemic strokes, neuropsychiatric symptoms, and dementia with cognitive impairment. Severe deterioration follows in a mean of 25 years. Evidence of cerebral hypoperfusion appears early in the disease process, especially at night (that can worsen white matter lesions) , but the results of studies evaluating cerebrovascular autoregulation are contradictory. Moreover, there is an increased risk of sudden death of cardiac origin: it is associated with significant decrease in heart rate variability, which is consistent with anomalies in cardiac autonomic control; cardiac arrhythmias, QT variability index, and myocardial infarction are more frequent.

Life expectancy is reduced in CADASIL patients. An age at death in men of 64.6 years and in women of 70.7 years has been reported (411 subjects). Pneumonia in patients with disability was the major cause of death (38%), and a high number of sudden unexpected deaths were also observed, up to 26%.
The disease includes cases with a history of hypertension and foci of ischemic destruction in the deep white matter of the cerebral hemispheres. The cerebral cortex is usually preserved and this contrasts with the clinical picture which may closely resemble that of dementia in Alzheimer disease. In fact, the disease can mimic several neurological diseases both central and peripheral (table 2).
There are diagnostic criteria published by Davous et al, updated in Mizuta et al. A review can be found in Hack R, et al.
Apart from genetic test, the diagnostic imaging procedures includes MRI, functional MRI, 3D MRI and 7 tesla MRI.
No specific treatment has been developed. Patients have received symptomatic therapy: acetazolamide, sodium valproate (migraine), acetylcholine inhibitors (cognitive decline), antiplatelet drugs (primary and secondary stroke prevention). The latter one is under discussion due the possible increased haemorrhagic risk.

Medicine is in progress

Perhaps new knowledge

Every patient is unique

Perhaps the diagnosis is wrong

**Find more information on the disease, its centres of reference and patient organisations on Orphanet: www.orpha.net**

## Typical surgery

No special surgical procedures are related to the disease.

## Type of anaesthesia

An updated review of Pubmed, with the term CADASIL (Title and Abstract) AND 2013 to June 2019 (Date Publication) offered 421 references. Adding the term Anesthesia offered 5 articles.

Both general (balanced) and regional anaesthesia (spinal and combined spinal-epidural) have been used.

Very few cases have been published.

The main objective is to maintain cerebral perfusion pressure through systemic arterial pressure, and volume replacement. If needed, direct vasopressors are preferred, but the indirect ones have been used without problems (low dose).

Both hypo- and hypercapnia should be avoided because the limits of autoregulation of the diseased vessels are not known.

## Necessary additional pre-operative testing (beside standard care)

No preoperative diagnostic is needed regarding anaesthesia related problems.

Definitive diagnosis is the demonstration of the NOTCH3 gene mutation or the finding of GOM deposition in the biopsy of the skin or small peripheral nerve arteries.

## Particular preparation for airway management

Not needed.

## Particular preparation for transfusion or administration of blood products

Not needed (it depends on the surgical procedure).

## Particular preparation for anticoagulation

Patients are usually under antiplatelet drug therapy due to the risk of thrombosis. This should be taken into account regarding neuraxial techniques and intraoperative bleeding. Provided the procedure is not emergent, recommended delaying times should be followed.

Antiagregation should be restarted promptly.

## Particular precautions for positioning, transportation and mobilisation

No specific considerations.

Consider the degree of mental retardation.

## Interactions of chronic disease and anaesthesia medications

- Antiplatelet drug therapy (see before). Although no controlled trials has been published to date, bleeding time is probably increased and surgical haemorrhagic complications may be more common. This should be taken into account in elective surgery

- Anticholinesterasic drugs are increasingly being used for treatment of the cognitive problems in CADASIL patients, despite negative results in the only controlled trial reported to date. Bradycardia/asystole and bundle branch and atrioventricular block can occur more frequently in patients under treatment. On the other hand, withholding anticholinesterase drugs during hospitalization for surgery or medical reasons may result in delirium

- Antiepileptic drug(s) if epilepsy is present: ask neurologist whether blood level needs to be checked

- Antihypertensive drugs if systemic hypertension is present

- Acetazolamide is sometimes prescribed too; check plasma electrolytes

## Anaesthetic procedure

General (intravenous or balanced), and regional (central neuraxial, or peripheral and plexus nerve blocks) anaesthesia can be used.

In a published neurosurgical case (ventriculoperitoneal drainage to treat intracranial haemorrhage) after iv induction with propofol-fentanyl, balanced inhalational anaesthesia (enflurane) was used, with muscle relaxation (rocuronium) and local infiltration with 0.25% bupivacaine. MAP was maintained over 80 mmHg. Sugammadex was used for reversal of neuromuscular blockade. A progressive improvement in the symptoms was noted.

There is a published case of postoperative diagnosis of CADASIL in a 69 year-old man A 69-year-old man developed confusion, drowsiness, right hemiparesis, and slurred speech following orthopaedic surgeries. The symptoms improved quickly after treatment with fluid hydration and antiplatelet agent, and his consciousness and mentality totally recovered within 3 days. Two patient relative's (mother and one brother) suffered strokes and the patient genetic testing was positive for a mutation in the NOTCH3 gene.

## Particular or additional monitoring

As in patients with Moyamoya disease, monitoring cerebral regional oxygen saturation (e.g., NIRS®, Equanox®, etc.) is probably useful as it gives a rapid warning of cerebral hypoxemia (at least in the cortical region above which it is placed) in case of systemic hypotension, hypocapnia or anaemia. It should be placed, if possible, before induction of general anaesthesia in order to obtain the patient's baseline values.

As in children with cerebral palsy, monitoring of processed EEG (BIS®, Entropy®, etc.) is probably useless to evaluate depth of anaesthesia in dement patients. However, it is useful to know their baseline (awake) level in order to know which values to expect at awakening.

Invasive arterial blood pressure is recommended in the most invasive surgical procedures or if major blood loss is expected.

Because of patients' propensity to ECG abnormalities, arrhythmias or cardiac sudden death, close ECG monitoring is indicated.

## Possible complications

No special risk of ischaemic cardiovascular events.

Some patients also have systemic hypertension disease: its treatment should be adapted to avoid both hypotension following induction of anaesthesia and hypertensive crises.

## Post-operative care

See before (reintroduction of antiplatelet and antiepileptic drug therapy).

If opiate analgesia is administered caution about delayed respiratory depression and/or hypercapnia should be considered.

Usually no PCA devices can be used due to mental deterioration.

## Disease-related acute problems and effect on anaesthesia and recovery

Consider the basal clinical situation of the patient. Mental deterioration use to be progressive, not acute. Exceptions are undiagnosed cases showing delayed awareness or postoperative recovery, or agitation/confusion at recovery.

## Ambulatory anaesthesia

Can be interesting for superficial and not very painful procedures to avoid disorientation in dement patients but accompanying persons are needed. Deliver instructions to relatives or tutor.

## Obstetrical anaesthesia

A case of successful epidural anaesthesia for an emergent caesarean delivery has been published. In another undiagnosed pregnant patient suffering headache, slurred speech, cognitive dysfunction and restlessness at 35 weeks' gestation and diagnosed as hypertensive encephalopathy a caesarean section was indicated and performed under spinal anaesthesia and sedation. She was restless and with lethargy and hallucination episodes in the 1st postoperative day. The neurologist suspected CADASIL because of multiple lacunar infarct lesions on MRI and her family history. The diagnosis was confirmed by skin biopsy and a genetic test.

As the mean age of the disease presentation is between the 40's and 60's, and women use to became pregnant before the symptoms start (or symptoms are not severe in young patients), obstetric procedures might occur without incidences, but this is speculative.

Foetuses affected with CADASIL are not at an increased risk for intrauterine complications or complications during/after delivery.

In a retrospective study, women with CADASIL were at increased risk for neurologic events in pregnancy during and shortly after delivery. However, another retrospective study of 50 affected women and prospectively collected data of six women showed no association between CADASIL and risk for neurologic events or problems during pregnancy. Transient neurologic events are sometimes reported (mostly consistent with migraine aura).

**Table 1. Clinical CADASIL synopsis (from https://omim.org/entry/125310)**

**INHERITANCE**

Autosomal dominant

**HEAD and NECK**

*Eyes*
- Acute vision loss due to optic nerve infarction (rare)
- Nonarteritic anterior ischemic optic neuropathy (NAION)
- Abnormal electroretinogram (ERG)
- Abnormal visual evoked responses (VEP)

**CARDIOVASCULAR**

*Vascular*
- Vasculopathy of the small arteries penetrating the white matter
- Small and medium-sized leptomeningeal arteries show luminal narrowing or obliteration
- Long perforating arteries of the brain are affected
- Affected arteries have electron-dense granular material close to vascular smooth muscle cell membranes
- Affected arteries show loss of smooth muscle cells
- Varicose veins (reported in 1 family)

**GENITOURINARY**

*Bladder*
- Urinary incontinence

**SKIN, NAILS, and HAIR**

*Skin*
- Varicose veins (reported in 1 family)

*Electron Microscopy*
- Biopsy shows granular osmiophilic material of variable electron density adjacent to basal membrane of vascular smooth muscle cell

**NEUROLOGIC**

*Central Nervous System*
- Recurrent subcortical infarcts (strokes)
- Pseudobulbar palsy
- Subcortical dementia, progressive (6% of patients)
- Migraine (40% of patients)
- Seizures (2-10% of patients)
- Gait abnormalities
- Leukoencephalopathy
- Subcortical lacunar lesions seen early in disease
- Patients 20-30 years old have hyperintense lesions on T2-weighted MRI in the frontal and anterior temporal lobes
- Patients 30-40 years old have hyperintense lesions in periventricular areas, the external

capsule, basal ganglia, thalamus, and brainstem
- Lacunar infarcts develop after age 40 years
- Lesions in the internal capsule after age 40 years
- Microbleeds (most smaller than 5 mm) occur after age 40 years
- Patients older than 50 years have hyperintensities, lacunar infarcts, and microbleeds
- Vasculopathy of the small arteries penetrating the white matter
- Small and medium-sized leptomeningeal arteries show luminal narrowing or obliteration
- Long perforating arteries of the brain are affected
- Affected arteries have electron-dense granular material close to vascular smooth muscle cell membranes
- Affected arteries show loss of smooth muscle cells

*Behavioral Psychiatric Manifestations*
- Psychiatric disturbances (9% of patients)
- Mood disorders

**MISCELLANEOUS**
- Adult onset (third decade)
- Death usually in sixth decade
- Penetrance of disease is complete between 30 and 40 years of age
- Presents as early-onset strokes in 43% of patients

**MOLECULAR BASIS**
- Caused by mutations in the homolog of the Drosophila Notch 3 gene (NOTCH3, 600276.0001).

**Table 2. Typical and atypical clinical manifestations of CADASIL (modified from Di Donato et al).**

**Typical manifestations**
- Migraine, usually with aura, as the first symptom in the third decade of life
- Recurrent subcortical ischemic events (transient ischemic attack/stroke) in adulthood
- Mood disturbances, apathy and depression among other psychiatric symptoms
- Progressive cognitive decline, especially of executive functioning
- Seizures, in a smaller but well-defined portion of patients

**Atypical manifestations**
- Pathological gambling
- Recurrent status epilepticus
- Schizophreniform organic psychosis
- Encephalopathy
- Neuropathy (peripheral of cranial nerves; sensory cutaneous or autonomic denervation)
- Myopathy
- 'CADASIL coma'
- Early onset
- Late onset
- Bipolar disorder
- Inflammatory-like presentation
- Acute vestibular syndrome
- Spinal cord involvement
- Acute confusional migraine
- Sporadic hemiplegic migraine with normal imaging
- Post-partum psychiatric disturbances
- Parkinsonism
- Recurrent transient global amnesia
- Cerebral bleeding

**Additional information (hereditary related diseases, both clinical- and gene-related):**
From https://omim.org/entry/125310

Cerebral arteriopathy with subcortical infarcts and leukoencephalopathy - PS125310- 3 Entries

| Location | Phenotype | Inheritance | Phenotype mapping key | Phenotype MIM number | Gene/Locus | Gene/Locus MIM number |
|---|---|---|---|---|---|---|
| 10q26.13 | Cerebral arteriopathy, autosomal dominant, with subcortical infarcts and leukoencephalopathy, type 2 | AD | 3 | 616779 | HTRA1 | 602194 |
| 10q26.13 | CARASIL syndrome | AR | 3 | 600142 | HTRA1 | 602194 |
| 19p13.12 | Cerebral arteriopathy with subcortical infarcts and leukoencephalopathy 1 | AD | 3 | 125310 | NOTCH3 | 600276 |

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