

orphananesthesia

Anaesthesia recommendations for patients suffering
from
CADASIL

Disease name: Cerebral arteriopathy, autosomal dominant, with subcortical infarcts and leukoencephalopathy; CADASIL (acronym of Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy)

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

"Include cases with a history of hypertension and foci of ischaemic 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."

See annex 1 for related diseases.

Synonyms: Dementia, hereditary multi-infarct type, Casil

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.

Medicine in progress

 Perhaps new knowledge

Every patient is unique

Perhaps the diagnostic is wrong

Disease summary

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 codifies 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 consist of: 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 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.

Typical surgery

No special surgical procedures are related to the disease.

Type of anaesthesia

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

Very few cases have been published (four to our knowledge).

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 diagnostic procedures (preoperative)

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 (see annex 2).

Particular preparation for airway management

Not needed.

Particular preparation for transfusion or administration of blood products

Not needed (depending on the surgery).

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.

Antiaggregation should be restarted promptly.

Particular precautions for positioning, transport or mobilisation

Not reported.

Probable interaction between anaesthetic agents and patient's long term medication

- Antiplatelet drug therapy (see before). Although no controlled trials have 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 arrive more frequently in patients under treatment. On the other hand, withholding anticholinesterasic drugs during hospitalisation 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.

Anaesthesiologic procedure

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

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 hypoxaemia (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 these 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.

Postoperative care

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

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

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

Information about emergency-like situations / Differential diagnostics

caused by the illness to give a tool to distinguish between a side effect of the anaesthetic procedure and a manifestation of the diseases, e.g.:

Consider the basal clinical situation of the patient. Mental deterioration used to be progressive, not acute.

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

No information available. As familial presentation is the rule, obstetric procedures are expected to course uneventfully. Although there are younger patients, the mean age of presentation is the 40-50th decade, and women were usually pregnant before symptoms start or are not severe.

Direct references

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Additional information (hereditary related diseases, both clinical- and gene-related):

Annex 1

The main CADASIL diseases are in **bold letters**.

1. **#125310 - CEREBRAL ARTERIOPATHY, AUTOSOMAL DOMINANT, WITH SUBCORTICAL INFARCTS AND LEUKOENCEPHALOPATHY; CADASIL**
2. Cytogenetic locations: 19p13.2-p13.1
3. OMIM: 125310
4. **Select item 600276**
5. 2.*600276 - NOTCH, DROSOPHILA, HOMOLOG OF, 3; NOTCH3
6. Cytogenetic locations: 19p13.2-p13.1
7. OMIM: 600276
8. Select item 141500
9. #141500 - MIGRAINE, FAMILIAL HEMIPLEGIC, 1; FHM1
10. MIGRAINE, FAMILIAL HEMIPLEGIC 1, WITH PROGRESSIVE CEREBELLAR ATAXIA, INCLUDED
11. Cytogenetic locations: 19p13
12. OMIM: 141500
13. Select item 602576
14. *602576 - LUNATIC FRINGE; LFNG
15. Cytogenetic locations: 7p22
16. OMIM: 602576
17. Select item 601367
18. #601367 - STROKE, ISCHEMIC
19. Cytogenetic locations: 1q23, 14q22-q23, 13q12, 11p11-q12, 7q36
20. OMIM: 601367
21. Select item 160900
22. #160900 - MYOTONIC DYSTROPHY 1; DM1
23. Cytogenetic locations: 19q13.2-q13.3
24. OMIM: 160900
25. Select item 605770
26. *605770 - ILVB-LIKE; ILVBL
27. Cytogenetic locations: 19p13.1
28. OMIM: 605770
29. Select item 615293
30. #615293 - MYOFIBROMATOSIS, INFANTILE, 2; IMF2
31. OMIM: 615293
32. Select item 607595
33. #607595 - BRAIN SMALL VESSEL DISEASE WITH HEMORRHAGE
34. BRAIN SMALL VESSEL DISEASE WITH AXENFELD-RIEGER ANOMALY, INCLUDED
35. Cytogenetic locations: 13q34
36. OMIM: 607595
37. Select item 602768
38. *602768 - DELTA-LIKE 3; DLL3
39. Cytogenetic locations: 19q13
40. OMIM: 602768
41. Select item 601920
42. +601920 - JAGGED 1; JAG1
43. DEAFNESS, CONGENITAL HEART DEFECTS, AND POSTERIOR EMBRYOTOXON, INCLUDED
44. Cytogenetic locations: 20p12
45. OMIM: 601920
46. Select item 600142
47. #600142 - CEREBRAL AUTOSOMAL RECESSIVE ARTERIOPATHY WITH SUBCORTICAL INFARCTS AND LEUKOENCEPHALOPATHY; CARASIL
48. OMIM: 600142
49. **Select item 221820**
50. #221820 - LEUKOENCEPHALOPATHY, DIFFUSE HEREDITARY, WITH SPHEROIDS; HDLS

51. Cytogenetic locations: 17q21-q22
52. OMIM: 221820

Annex 2

1. Laboratories and test used for the diagnostic of the disease (data from OMIM, see OMIM page for specific considerations and limitations)
2. CADASIL Methods: Sequence analysis of select exons, C Sequence analysis of the entire coding region
3. Analytical Validity: This test detects 99% of described mutations in the analysed genes
4. Lab: Molecular Diagnostic Laboratory London Health Sciences Centre
5. Directors: Peter Ainsworth, PhD, MBChB, Lab Director
6. CADASIL Methods: Sequence analysis of the entire coding region
7. Analytical Validity: 97% or greater
8. Lab: Gene Analysis Service
9. Directors: Alfred Looman, PhD, Lab Director
10. CADASIL Methods: Sequence analysis of the entire coding region
11. Analytical Validity: PCR-based sequencing detects 99% of the reported mutations in the gene. The sensitivity of DNA sequencing is over 99% for the detection of nucleotide base changes, small deletions and insertions in the regions analyzed
12. Lab: Bioscientia GmbH Center for Human Genetics
13. Directors: Carsten Bergmann, MD, PD, Lab Director
14. Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy Methods: Sequence analysis of select exons
15. Analytical Validity: Sensitivity of DNA sequencing is over 95%
16. Target Population: Patients with a progressive disorder of the small arterial vessels of the brain manifest by migraine, strokes, and white matter lesions
17. Lab: Sheffield Diagnostic Genetics Service Sheffield Children's NHS Foundation Trust
18. Directors: Ann Dalton, PhD, FRCPath, Lab Director
19. CADASIL Methods: Deletion/duplication analysis, C Sequence analysis of the entire coding region
20. Analytical Validity: Sequencing method will detect 99% of sequence variants. External quality assessment (EMQN, DGKL-RFB) in DNA sequencing (technical performance and medical interpretation) is annually performed with good results (details available upon request)
21. Lab: Institute of Inherited Metabolic Disorders General University Hospital in Prague
22. Directors: Viktor Kozich, PhD, MD, Lab Director
23. CADASIL Methods: Deletion/duplication analysis, C Sequence analysis of the entire coding region
24. Analytical Validity: The sensitivity of MLPA approaches is about 100% for deletion or duplication detection, but errors can be made when a polymorphism is present in the probe binding site, thus resulting in a false allele dropout as described by the manufacturer. The sensitivity for genomic sequencing also approaches about 100% for mutation detection, but errors can be made because of polymorphisms causing allele dropout
25. Lab: bio.logis Center for Human Genetics
26. Directors: Daniela Steinberger, PhD, MD, Lab Director
27. Methods: Sequence analysis of select exons
28. Analytical Validity: This test detects 99% of described mutations in the analysed genes
29. Lab: BURC Genetics Diagnostic Center
30. Directors: Ozdal Etilik, MD, Lab Director
31. Methods: Sequence analysis of select exons
32. Analytical Validity: Analytical sensitivity and specificity are 99 percent.
33. Lab: CGC Genetics
34. Directors: Paula Rendeiro, Scientific Director
35. Test for CADASIL Methods: E Sequence analysis of select exons
36. Analytical Validity: Analytical Sensitivity 99,9% for the detection of nucleotide base changes
37. Lab: Secugen SL
38. Directors: Raúl Sanz, PhD, MSc, Lab Director
39. CADASIL Methods: Sequence analysis of the entire coding region

40. Analytical Validity: PCR-based sequencing detects 99% of the reported mutations in this gene. The sensitivity of DNA sequencing is over 99% for the detection of nucleotide base changes, small deletions and insertions in the regions analyzed
41. Lab: Center for Human Genetics Cliniques Universitaires Saint Luc
42. Directors: Miikka Vakkula, PhD, MD, Lab Director
43. Comprehensive Sequence Analysis for Epilepsy and Seizure Disorders
44. Methods: Sequence analysis of the entire coding region
45. Analytical Validity: The assay covers ~98% of the target region at 10x or greater with an average sequencing depth of 400x.
46. Target Population: Patients with suspected epilepsy or other seizure related illness should consider this assay. This test covers both syndromic and non-syndromic forms of epileptic disorders in categories including glycosylation disorders, infantile epilepsy, progressive myoclonic, neurodegenerative related, metabolic disease related, and idiopathic generalized epileptic conditions
47. Lab: Courtagen Diagnostics Laboratory Courtagen Life Sciences
48. Directors: Katherine Sheldon, PhD, Lab Director
49. Methods: Deletion/duplication analysis, E Sequence analysis of select exons
50. Analytical Validity: Single direction sequence analysis using Mutation Survey or software - sensitivity 99% and specificity 99% (in-house data).
51. Lab: Department of Molecular Genetics Royal Devon and Exeter Hospital
52. Directors: Sian Ellard, PhD, BSc, Lab Director
53. CADASIL syndrome: NOTCH3 gene sequence analysis
54. Methods: Sequence analysis of the entire coding region
55. Analytical Validity: 99% sensitivity
56. Lab: GENETAQ Molecular Genetics Centre and Diagnosis of Rare Diseases
57. Directors: Juan Lopez, PhD, Scientific Director
58. CADASIL syndrome: NOTCH3 gene sequence analysis (exons 2, 5, 6, 11)
59. Methods: Sequence analysis of the entire coding region
60. Analytical Validity: 99% sensitivity
61. Lab: GENETAQ Molecular Genetics Centre and Diagnosis of Rare Diseases
62. Directors: Juan Lopez, PhD, Scientific Director
63. CADASIL syndrome: NOTCH3 gene sequence analysis (exons 3-4)
64. Methods: Sequence analysis of the entire coding region
65. Analytical Validity: 99% sensitivity
66. Lab: GENETAQ Molecular Genetics Centre and Diagnosis of Rare Diseases
67. Directors: Juan Lopez, PhD, Scientific Director
68. Methods: Sequence analysis of the entire coding region
69. Analytical Validity: Sequencing system Roche GS Junior 454: Q20 read length of 400 bases (99% accuracy at 400 bases and higher for preceding bases)(Roche). Error rates usually originate in homopolymeric stretches. If such problems are encountered or if pathogenic sequence variants are found, we validate the NGS data with Sanger sequencing
70. Lab: Praxis fuer Humangenetik Wien
71. Directors: Martin Gencik, Lab Director.