Introduction

CADASIL testing is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan’s procedure code list for management requirements.

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What is CADASIL

Definition

CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy) is an adult-onset form of cerebrovascular disease. There are no generally accepted clinical diagnostic criteria for CADASIL and symptoms vary among affected individuals.

Signs and symptoms

Typical signs and symptoms include:¹ ² ³

• Transient ischemic attacks and ischemic stroke, occurs at a mean age of 47 years (age range 20-70 years), in most cases without conventional vascular risk factors
• cognitive disturbance, primarily affecting executive function, may start as early as age 35 years
• psychiatric or behavioral abnormalities
• migraine with aura, occurs with a mean age of onset of 30 years (age range 6-48 years), and

Less common symptoms include:
• recurrent seizures with onset in middle age, usually secondary to stroke
• acute encephalopathy, with a mean age of onset of 42 years

Life expectancy for men with CADASIL is reduced by approximately five years and for women by 1 to 2 years. 4

**Diagnosis**

Brain Magnetic Resonance Imaging (MRI) findings include T2-signal-abnormalities in the white matter of the temporal pole and T2-signal-abnormalities in the external capsule and corpus callosum. 1,2

CADASIL is suspected in an individual with the clinical signs and MRI findings. A positive family history for stroke or dementia is also indicative of disease in symptomatic individuals. However, a negative family history should not exclude the diagnosis, as de novo mutations may occur, and affected family members are frequently misdiagnosed. 1,5

Sequencing of all NOTCH3 exons encoding EGF–like domains fails to identify a mutation in up to 4% of individuals with CADASIL. Therefore, skin biopsy with histopathologic evaluation for characteristic granular osmiophilic material (GOM) deposits is appropriate for patients with a high index of clinical suspicion for CADASIL and negative genetic testing. 2,4

For a firm diagnosis of CADASIL, at least one of the following is required:

• Documentation of a typical NOTCH3 mutation by genetic analysis. 1,2,5
• Documentation of characteristic GOM deposits within small blood vessels by skin biopsy. 1,2,5

**Prevalence**

CADASIL is a rare disease. The exact prevalence is unknown. CADASIL is probably still underdiagnosed. The minimum prevalence is estimated to be between 2-5 per 100,000 based on multiple small and national registries. 1,4 A founder effect has been reported for Finnish individuals and patients in the Marche region of Italy. 1

CADASIL is the most prevalent inherited cause of cerebral small-vessel disease. 6

**Cause**

CADASIL is an autosomal dominant disease caused by mutations in the NOTCH3 gene. Each offspring of an individual with CADASIL has a 50% chance of inheriting the disease-causing mutation.

To date, NOTCH3 is the only gene in which mutations are known to cause CADASIL. 1 NOTCH3 has 33 exons. All CADASIL pathogenic variants occur in exons 2–24, which encode the 34 epidermal growth factor repeats (EGFR). 1,7 The majority of pathogenic variants occur in exons 2-6. 2 NOTCH3 encodes a transmembrane receptor that is
primarily expressed in vascular smooth-muscle cells, preferentially in small arteries.\(^1\)

"In CADASIL, the extracellular domain of the Notch3 receptor accumulates within blood vessels. Accumulation takes place at the cytoplasmic membrane of VSMCs and pericytes in close vicinity to the granular osmiophilic deposits (GOM) that characterize the disease. NOTCH3 recruits other proteins into the extracellular deposits, among them vitronectin and tissue inhibitor of metalloproteinase-3 (TIMP3), which may be relevant for disease pathogenesis."\(^2\) There is a hypothesis that structural abnormalities in the vascular smooth-muscle protein NOTCH3 trigger arterial degeneration, vascular protein accumulation, and cerebrovascular failure.\(^6\)

No clear genotype-phenotype correlations exist for individuals with CADASIL.\(^5,8\) Some studies describe phenotype-genotype correlations. There can be significant intrafamilial variability with the age of onset, disease severity, and disease progression. The genotype cannot be used to predict the phenotype.\(^1,6\)

**Management and treatment**

A correct diagnosis of CADASIL is important because the clinical course of disease is different from individuals with other types of cerebral small-vessel disease and proven therapies for stroke have not been validated in individuals with CADASIL.\(^5\) However, no specific disease-modifying treatments for CADASIL exist. Management and treatment of individuals is generally symptomatic and supportive.\(^1,2,3,5\)

**Test information**

**Introduction**

Testing for CADASIL may include a skin biopsy, sequence analysis, deletion/duplication analysis, or known familial mutation analysis.

**Skin biopsy**

"The pathologic hallmark of CADASIL is electron-dense granules in the media of arterioles, and increased NOTCH3 staining of the arterial wall, which can be evaluated in a skin biopsy."\(^1\) Specificity of skin biopsy findings is high as the characteristic deposits have not been documented in any other disorder. Sensitivity has been reported to range from 45%-100%. Sensitivity and specificity can be maximized to >90% by immunostaining for NOTCH3 protein.\(^5\) When interpreted by an experienced (neuro) pathologist, combined analysis by electron microscopy and immunohistochemistry usually allows for a conclusive CADASIL diagnosis.
Sequence analysis

NOTCH3 mutation detection may reach >95% in individuals with strong clinical suspicion of CADASIL. To date, all mutations in NOTCH3 causing CADASIL have been in exons 2-24, including intron-exon boundaries. In the United States, laboratories offering CADASIL testing appear to perform sequencing of, at minimum, exons 2-24 at the time of this review.

Deletion/duplication analysis

Deletion/duplication analysis will find gene rearrangements that are too large to be detected by sequencing. Large deletions and duplications in the NOTCH3 gene have not been reported.

"Molecular testing approaches can include sequence analysis of exons 2-24 and intron-exon boundaries of NOTCH3 followed by deletion/duplication analysis if no pathogenic variant is found."

Known familial mutation analysis

Once a mutation in an affected individual has been identified, targeted testing of at risk individuals in the family is possible.

Guidelines and evidence

Introduction

This section includes relevant guidelines and evidence pertaining to CADASIL testing. No evidence-based U.S. testing guidelines have been identified.

Pescini et al (2012)

Pescini et al (2012) published a scale to help guide clinicians in selecting patients for NOTCH3 genetic analysis due to a high probability of a CADASIL genetic diagnosis. This scale assigns weighted scores to common features of CADASIL. The authors state that their scale is “accurate with optimal sensitivity and specificity values (96.7% and 74.2%, respectively); however, our results need to be confirmed and further validated.”

Choi et al (2010)

A two-center cohort study found that blood pressure and hemoglobin A1c levels were associated with cerebral mini bleeds in CADASIL patients. Therefore, controlling blood pressure and glucose levels may improve the clinical course of the disease. It is also reasonable to control for high cholesterol and high blood pressure given the high rate of ischemic stroke seen in CADASIL.
Tikka et al (2009)

Evidence from one 2009 retrospective cohort study suggests that an adequate skin biopsy for analysis of granular osmophilic material is a cost effective way to determine a diagnosis of CADASIL in symptomatic individuals.\textsuperscript{10}

The authors suggest that biopsy results can be used to guide the decision for who should have genetic testing, particularly in individuals with no known familial mutation or from ethnic populations with no evidence of founder mutations.\textsuperscript{10}

Clinical utility

Patients with CADASIL should avoid anticoagulants, angiography, and smoking to avoid disease-related complications, so clinical utility is represented.\textsuperscript{1,5} Because of the risk for cerebral hemorrhage, use of antiplatelets rather than anticoagulants is considered for prevention of ischemic attacks. Evidence against the use of intravenous tissue plasminogen activator (IV tPA) has been suggested due to the possibility of hemorrhage; however, this is not conclusive.\textsuperscript{11} Statins are used for treatment of hypercholesterolemia and antihypertensive drugs are used for hypertension and hypertension treatment may have an additional benefit.\textsuperscript{2}

Criteria

Introduction

Requests for CADASIL testing are reviewed using these criteria.

Known familial mutation testing

- Genetic Counseling:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND

- Previous Genetic Testing:
  - No previous genetic testing for NOTCH3 mutations, AND

- Predictive Testing:
  - Member has a first-degree relative (i.e. parent, sibling, child) with an identified NOTCH3 gene mutation, and
  - Member is at least 18 years of age, OR

- Diagnostic Testing for Symptomatic Individuals:
  - Member has a first-degree relative (i.e. parent, sibling, child) with an identified NOTCH3 gene mutation, and
o High index of suspicion for CADASIL diagnosis based on clinical findings, AND
• Rendering laboratory is a qualified provider of service per the Health Plan policy.

NOTCH3 targeted sequencing

• Genetic Counseling:
  o Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
• Previous Genetic Testing:
  o No previous genetic sequencing for NOTCH3 mutations, AND
• Diagnostic Testing for Symptomatic Individuals:
  o High index of suspicion for CADASIL diagnosis based on clinical findings, AND
• Rendering laboratory is a qualified provider of service per the Health Plan policy.

NOTCH3 deletion/duplication analysis

• Member meets the above criteria for NOTCH3 targeted sequencing, AND
• NOTCH3 targeted sequencing performed and detected no mutations, AND
• No previous NOTCH3 deletion/duplication analysis

References

Introduction

These references are cited in this guideline.


