Canavan Disease Testing

Introduction

Canavan disease 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 Canavan disease

Definition

Canavan disease is a genetic disorder leading to progressive damage to the brain’s nerve cells.¹⁻²

Prevalence

Canavan disease is most often found in Ashkenazi Jewish populations.¹⁻²

- Between 1 in 40 and 1 in 82 people of Ashkenazi Jewish descent are carriers for Canavan disease.² Because of this relatively high carrier rate, population based screening in the Ashkenazi Jewish population is available. (See Ashkenazi Jewish Carrier Screening).

- Between 1 in 6,400 and 1 in 13,500 Ashkenazi Jews have the disease.¹

Canavan disease occurs in all ethnic groups, and the prevalence among the general population is significantly lower than that in the Ashkenazi Jewish population.²

Symptoms

Signs and symptoms of Canavan disease usually begin in infancy and include:¹
• developmental delays including motor skills, learning disabilities, or problems sleeping
• weak muscle tone (hypotonia)
• large head size (macrocephaly)
• abnormal posture
• leukodystrophy on neuroimaging, and
• seizures.

Cause

Canavan disease is caused by changes, or mutations, to the ASPA gene. ASPA helps make an enzyme called aspartoacylase. This enzyme is essential to maintain the health of myelin, the nerve cells’ protective covering, by breaking down harmful compounds that would otherwise degrade myelin. The most significant of these compounds that break down myelin is called N-acetylaspartic acid (NAA).

In the absence of aspartoacylase, the myelin protective covering of the nerve is eventually destroyed. Without this protective covering, nerve cells malfunction and die.

Inheritance

Canavan disease is an autosomal recessive disorder, meaning that an affected individual must inherit two ASPA gene mutations - one from each parent.

Individuals with only one mutation are called carriers. Carriers do not show symptoms of Canavan disease, but have a 50% chance of passing on the mutation to their children who will also be carriers.

If two unaffected carriers have children, each of their pregnancies has a 1 in 4 (25%) chance of being affected with Canavan disease.

Diagnosis

Canavan disease is suspected when a patient presents with classic signs and symptoms. Diagnosis is confirmed by biochemical or genetic testing or both. Biochemical tests analyze either NAA levels or aspartoacylase enzyme activity in someone with suspected Canavan disease.

• Affected individuals cannot break down NAA, so it accumulates in the blood or urine.
• Affected individuals will have severely reduced or nonexistent aspartoacylase enzyme activity.
Molecular genetic testing can be used for confirmation of the diagnosis and to help family planning by identifying individuals at risk of being carriers.\textsuperscript{2}

**Survival**

Canavan disease does not usually allow survival beyond childhood.\textsuperscript{1}

**Test information**

**Introduction**

Testing for Canavan disease may include targeted mutation analysis, sequence analysis, deletion/duplication analysis, or known familial mutation analysis.

**Targeted mutation analysis**

Targeted mutation analysis is the most common genetic test for Canavan disease. The panel looks for up to four of the most common mutations in the ASPA gene linked to Canavan disease, including the Glu285Ala and Tyr231X mutations, which account for 98\% of all Ashkenazi Jewish cases.\textsuperscript{2,3} The panel also includes the p.Ala305Glu mutation, which accounts for between 30\% and 60\% of all non-Ashkenazi Jewish cases.\textsuperscript{2,3}

**Sequence analysis**

Sequence analysis looks for mutations across the entire coding region of the ASPA gene. In addition to the more common mutations found in the Ashkenazi Jewish population, sequencing is also able to find less common mutations found in non-Ashkenazi Jews.\textsuperscript{2,3} Sequence analysis has a detection rate of about 99\% in all populations.\textsuperscript{2}

**Deletion/duplication analysis**

Deletion/duplication analysis will find gene rearrangements that are too large to be detected by sequencing. Large deletions in the ASPA gene have been reported but are believed to be uncommon.\textsuperscript{2} Therefore, deletion/duplication analysis is unlikely indicated in most cases.

**Known familial mutation analysis**

Once mutations have been identified in a symptomatic individual, carrier testing can be performed on at-risk relatives using this same targeted mutation panel or perhaps known familial mutation analysis for the specific mutation identified in the affected individual.
If both members of a couple are carriers with identified mutations, prenatal diagnosis of an at-risk pregnancy is possible using this same targeted mutation panel or known familial mutation analysis for the specific mutations identified in the parents.

Guidelines and evidence

Introduction

This section includes relevant guidelines and evidence pertaining to Canavan disease testing.

2018 expert-authored review

A 2018 expert-authored review states the following regarding molecular genetic testing for diagnostic purposes:

- The targeted mutation panel may be used to confirm a clinical diagnosis, biochemical diagnosis, or both.
- “Targeted analysis for the pathogenic variants p.Glu285Ala, p.Tyr231Ter, and p.Ala305Glu can be performed first in individuals of Ashkenazi Jewish ancestry.”
- “Targeted analysis for the pathogenic variant p.Ala305Glu can be performed first in individuals of non-Ashkenazi Jewish ancestry.”
- “Sequence analysis of ASPA detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. Perform sequence analysis first. If only one or no pathogenic variant is found perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications.”

American College of Medical Genetics

The American College of Medical Genetics (ACMG, 2008) supports offering carrier testing for Canavan disease to individuals of Ashkenazi Jewish descent for the two common mutations. It is anticipated that the detection rate will be ~97%. This test should be offered to individuals of reproductive age, preferentially prior to pregnancy, with genetic counseling performed by a geneticist or genetic counselor. ACMG supports the testing of individuals of Ashkenazi Jewish descent, even when their partner is non-Ashkenazi Jewish. In this situation, testing would start with the individual who is Ashkenazi and reflex back to the partner if necessary.

American College of Obstetrics and Gynecologists

The American College of Obstetrics and Gynecologists (ACOG, 2009) recommends that individuals who are considering a pregnancy or are pregnant should consider testing if at least one member of the couple is Ashkenazi Jewish or has a relative with
Canavan disease. If the woman is pregnant, testing may need to be conducted on both partners simultaneously in order to receive results in a timely fashion. If one or both partners are found to be carriers of Canavan disease, genetic counseling should be provided, and prenatal testing offered, if appropriate.\textsuperscript{5}

Criteria

Introduction

Requests for Canavan Disease testing are reviewed using these criteria.

ASPA Known Familial Mutation Analysis

- 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 of ASPA, AND

- Carrier Screening for Asymptomatic Individuals:
  - Known family mutation in ASPA in 1\textsuperscript{st}, 2\textsuperscript{nd}, or 3\textsuperscript{rd} degree biologic relative, OR

- Prenatal Testing for At-Risk Pregnancies:
  - ASPA mutations identified in both biologic parents

ASPA Targeted Mutation Analysis for Common Mutations

- 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 ASPA genetic testing, including Ashkenazi Jewish screening panels containing targeted mutation analysis for Canavan disease, AND

- Diagnostic Testing or Carrier Screening:
  - Ashkenazi Jewish descent, regardless of disease status and N-acetylaspartic acid (NAA) levels, OR

- Prenatal Testing for At-Risk Pregnancies:
  - ASPA Ashkenazi mutations identified in both biologic parents.
ASPA Sequencing

- 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 ASPA gene sequencing, and
  - No known ASPA mutation in family, and
  - No mutations or one mutation detected by common mutation panel, AND

- Diagnostic Testing for Symptomatic Individuals:
  - Increased levels of N-acetylaspartic acid (NAA) in urine, and
  - An individual age three to five months of age with a triad of hypotonia, macrocephaly and head lag, or
  - Failure to attain independent sitting, walking or speech, OR

- Testing for Individuals with Family History or Partners of Carriers:
  - 1st, 2nd, or 3rd degree biologic relative with Canavan disease clinical diagnosis, family mutation unknown, and testing unavailable, or
  - Partner is monoallelic or biallelic for ASPA mutation, and
    - Have the potential and intention to reproduce

References

Introduction

These references are cited in this guideline.


