Mitochondrial Neurogastrointestinal Encephalopathy (MNGIE)

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 MNGIE

Definition

Mitochondrial Neurogastrointestinal Encephalopathy (MNGIE) is a multisystem mitochondrial disease.\(^1\) MNGIE is typically characterized by progressive gastrointestinal dysmotility, which may present with nausea, dysphagia, reflux, early satiety, vomiting after a meal, episodic abdominal pain, bloating, and/or diarrhea. Additionally, individuals may present with cachexia (a wasting syndrome), ptosis/ophthalmoplegia (drooping/weakness of the eyelid), leukoencephalopathy on brain MRI, or peripheral neuropathy (tingling, numbness, and/or pain in the extremities).\(^1\) Symptoms may first occur between the first and fifth decade of life and may not appear in any particular order.\(^1\)

- MNGIE is caused by biallelic mutations in the nuclear TYMP gene on chromosome 22 and is inherited in an autosomal recessive pattern, meaning parents of an affected individual must be obligate carriers. The chance of having another child with MNGIE to the same parents is 25%.
- Prevalence of MNGIE is largely unknown but the condition appears to be rare. Approximately 120 cases have been reported. No ethnic predilection for MNGIE disease has been observed. Parental consanguinity is common.\(^1\)
- Management can be supportive, and may include assistance with swallowing difficulties, medication for nausea and vomiting, gastrostomy and parenteral nutrition for nutritional support, pain medications for neuropathy, and physical therapy and occupational therapy.\(^1\)
In individuals with advanced illness, liver transplant or allogeneic hematopoietic stem cell transplant, have been suggested as possible curative treatment options, although risks and benefits of these procedures must be properly weighed.\(^2,3\)

Peritoneal dialysis has also been suggested as a method of reduction of the thymidine concentration and should be considered as an additional or alternative form of treatment.\(^4\)

**Test information**

- "The TYMP gene encodes thymidine phosphorylase, a cytosolic enzyme that catalyzes the phosphorylation of thymidine or deoxyuridine to thymine or uracil, and is thus essential for the nucleotide salvage pathway." \(^5\)
- Mutations that disrupt the function of TYMP will therefore disrupt the enzyme activity causing it to decrease and levels of thymidine or deoxyuridine to increase.
- Reduced thymidine phosphorylase enzyme activity or elevated thymidine and deoxyuridine levels are consistent with a diagnosis of MNGIE.\(^1\)
- Genetic testing of the TYMP gene can help to diagnosis a person with MNGIE.
  - The overwhelming majority (nearly 100%) of TYMP mutations are detected by gene sequencing. TYMP deletions and duplications are less common (prevalence unknown).
    - Complete sequencing of TYMP for pathogenic mutations is necessary to diagnosis MNGIE.
    - If only one TYMP mutation is identified or variant of uncertain significance results are returned, pursue gene TYMP deletion/duplication analysis.\(^1\)

**Guidelines and evidence**

- No specific evidence-based U.S. testing guidelines were identified.
- Although not specific to genetic testing for MNGIE, the Mitochondrial Medicine Society (2015) \(^6\) developed consensus recommendations for the diagnosis and management of mitochondrial disease. Testing strategies, including strategies for genetic testing, were discussed.
  - Recommendations for DNA testing include the following:
    - "Massively parallel sequencing/NGS of the mtDNA genome is the preferred methodology when testing mtDNA and should be performed in cases of suspected mitochondrial disease instead of testing for a limited number of pathogenic point mutations."
“Patients with a strong likelihood of mitochondrial disease because of a mtDNA mutation and negative testing in blood, should have mtDNA assessed in another tissue to avoid the possibility of missing tissue-specific mutations or low levels of heteroplasmy in blood; tissue-based testing also helps assess the risk of other organ involvement and heterogeneity in family members and to guide genetic counseling.”

“Heteroplasmy analysis in urine can selectively be more informative and accurate than testing in blood alone, especially in cases of MELAS due to the common m.3243 A>G mutation.”

“When considering nuclear gene testing in patients with likely primary mitochondrial disease, NGS methodologies providing complete coverage of known mitochondrial disease gene is preferred. Single-gene testing should usually be avoided because mutations in different genes can produce the same phenotype. If no mutation is identified via known NGS panels, then whole exome sequencing should be considered.”

- The European Federation of Neurological Sciences (2009) provided molecular diagnostic consensus-based guidelines based on literature reviews: “Sequencing of TYMP should be performed only if serum thymidine is elevated.”

- Evidence from peer reviewed journals provide symptoms, clinical findings, imaging, and family history suggestive of MNGIE.8,9
  - Severe gastrointestinal dysmotility, cachexia, ptosis, external ophthalmoplegia, and sensorimotor neuropathy.
  - Brain MRI that demonstrates abnormal brain white matter (increased FLAIR or T2-weighted signal) consistent with asymptomatic leukoencephalopathy. In the absence of leukoencephalopathy, MNGIE disease is very unlikely.1
  - Family history consistent with autosomal recessive inheritance.

Criteria

TYMP Known Familial Mutation Testing

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

- Previous Genetic Testing
  - No previous genetic testing in the individual for MNGIE, and
  - TYMP pathogenic variant(s) identified in parents and/or sibling(s), AND

- Predictive Testing for Asymptomatic Individual:
• 18 years of age or older, OR
• Diagnostic Testing for Symptomatic Individual:
  o Clinical exam and/or biochemical testing suggestive, but not confirmatory, of a
diagnosis of MNGIE, AND
• Rendering laboratory is a qualified provider of service per the Health Plan policy

TYMP Sequencing

• Genetic Counseling
  o Pre and post-test counseling by an appropriate provider (as deemed by the
    Health Plan policy), AND
• Previous Testing:
  o No previous genetic testing for MNGIE, and
  o No known TYMP pathogenic variants in the family, AND
• Diagnostic Testing for Symptomatic Individuals:
  o Clinical exam and/or biochemical testing suggestive, but not confirmatory, of a
diagnosis of MNGIE, and
  o Genetic testing is needed to confirm the diagnosis, AND
• Rendering laboratory is a qualified provider of service per the Health Plan policy

TYMP Deletion/Duplication

• Genetic Counseling
  o Pre and post-test counseling by an appropriate provider (as deemed by the
    Health Plan policy), AND
• Criteria for TYMP sequencing is met, AND
• No pathogenic variants or only one pathogenic variant identified in TYMP
  Sequencing.

References

1. Hirano M. (Updated January 2016). Mitochondrial Neurogastrointestinal
Information Resource (database online). Copyright, University of Washington,


