Polymerase Gamma (POLG) Related Disorders Genetic Testing

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 are POLG-related disorders

Definition

“POLG-related disorders” is a term used to describe medical conditions caused by mutations in the POLG gene. This is a wide spectrum of conditions that may involve multiple organ systems and have variable severity and age at onset.

Incidence and Prevalence

Although Alpers-Huttenlocher syndrome (AHS) is clinically reported to occur in 1/51,000 individuals, disease frequency calculated based on prevalence of the most common POLG mutations may be as high as 1/10,000.

Symptoms

There are 6 main phenotypes attributed to POLG mutations. Most affected individuals have some features ascribed to each phenotype, but rarely have all.

- **Alpers- Huttenlocher syndrome (AHS):**
  - Most common symptoms
  - refractory seizures
  - psychomotor regression
  - liver disease
Other possible symptoms
- migraine with visual auras
- cortical blindness
- hypotonia
- ataxia
- extrapyramidal movements
- peripheral neuropathy
- progressive spastic paraparesis
- renal tubular acidosis
- hearing loss
- cyclic vomiting
- pancreatitis

Development is often normal until disease onset, which is typically before 4 years of age. However, congenital static encephalopathy and juvenile-onset have also been described. When seizure etiology is unknown, valproic acid must be used with extreme caution, as it can precipitate liver dysfunction and/or failure in AHS.

Childhood myocerebrohepatopathy spectrum (MCHS):
- Most common / presenting symptoms
  - failure to thrive
  - lactic acidosis
  - developmental delay
  - encephalopathy
  - dementia
  - myopathy
  - hypotonia

- Other possible symptoms
  - liver failure
  - renal tubular acidosis
  - pancreatitis
  - cyclic vomiting
  - hearing loss
- MCHS is a rapidly progressive disease with a fatal outcome that usually presents between the first few months of life and 3 years. MCHS has a similar presentation to AHS, however severe myopathy, specific liver pathology, and nonspecific brain MRI brain findings (diffuse atrophy) help differentiate MCHS from AHS. In addition, seizures are less prominent and more easily controlled in MCHS compared to AHS.

- **Myoclonic epilepsy myopathy sensory ataxia (MEMSA).**
  - Common symptoms
    - epilepsy
    - myopathy
    - ataxia without ophthalmoplegia
  - MEMSA has also been known as spinocerebellar ataxia with epilepsy (SCAE). Disease onset typically occurs in adolescence and presents with cerebellar and sensory ataxia. Epilepsy usually follows, with refractory seizures leading to a progressive encephalopathy.

- **Ataxia neuropathy spectrum (ANS).**
  - Common symptoms
    - migraine headaches
    - ataxia
    - neuropathy (sensory, motor, or mixed)
    - encephalopathy with seizures
    - psychiatric disturbance
  - Other possible symptoms
    - myoclonus
    - blindness
    - hearing loss
    - liver failure (varying severity)
  - Disease onset ranges between adolescence and adulthood. Migraine headaches may be the first presenting symptom and precede the other symptoms by many years. Clinical myopathy is very rare. The encephalopathy is often milder than AHS and more slowly progressive. ANS was previously referred to as mitochondrial recessive ataxia syndrome (MIRAS) and sensory ataxia neuropathy dysarthria and ophthalmoplegia (SANDO).

- **Autosomal recessive progressive external ophthalmoplegia (arPEO).**
Common symptoms
- Progressive weakness of the extraocular eye muscles resulting in ptosis and ophthalmoparesis without associated systemic involvement.
- Apparently isolated PEO can present with additional symptoms later in life.

Onset is typically in adulthood.

- Autosomal dominant progressive external ophthalmoplegia (adPEO):\(^1,9\)
  - Common symptoms
    - Progressive weakness of the extraocular eye muscles resulting in ptosis and ophthalmoparesis
    - Generalized myopathy
    - Sensorineural hearing loss
    - Axonal neuropathy
    - Ataxia
    - Depression
    - Parkinsonism
    - Hypogonadism
    - Cataracts
  - Previously, adPEO was called Chronic Progressive External Ophthalmoplegia plus (CPEO+).

Onset of the POLG-related disorders can range from infancy to late adulthood. Younger patients typically present with seizures and lactic acidosis.\(^11\) Later in life, the most common presenting symptoms are myopathy, chronic progressive external ophthalmoplegia (CPEO), and sensory ataxia.\(^11\) Liver failure may also occur, particularly with exposure to the antiepileptic drug, valproic acid.\(^1\)

**Cause**

POLG-related disorders are caused by mutations in the POLG gene. POLG codes for a subunit of DNA polymerase protein that replicates and repairs mitochondrial DNA (mtDNA). Disease-causing mutations can affect polymerase activity, processing, DNA binding, or subunit association.\(^1\)

**Inheritance**

Inheritance patterns of the 6 main POLG-related disorders varies.

- AHS, MCHS, MEMSA, ANS, and arPEO are inherited in an autosomal recessive inheritance pattern. Males and female are equally likely to be affected. If both
parents are carriers of one of these conditions, the risk for a pregnancy to be affected is 1 in 4 (25%).

- adPEO is inherited in an autosomal dominant pattern. When a parent has this condition, each of her/his offspring have a 50% risk of inheriting the mutation. First degree relatives of an affected individual are at 50% risk of inheriting the mutation.

**Diagnosis**

As no clinical diagnostic criteria exist, genetic testing of POLG is required to confirm clinical suspicion of a disorder in this spectrum.

**Treatment**

Treatment is supportive and based on presenting symptoms and typically involves referral for speech therapy, physical therapy, and occupational therapy. Respiratory and nutritional support are provided as needed.

Any medications metabolized by hepatic enzymes should be carefully dosed to avoid liver toxicity. Certain antiepileptic drugs should be avoided due to the risk for precipitating or accelerating liver disease.\(^1\)

Occurrence of dehydration, fever, anorexia and infection can create physical stress and hasten medical deterioration. These events should be avoided as much as possible.

**Survival**

The range of survival is broad and is largely dependent on the presenting phenotype, age at onset, and the occurrence of secondary complications.

**Test information**

- Given that clinical diagnostic criteria do not exist, genetic testing of POLG is required in order to confirm the diagnosis of a POLG-related disorder.\(^1\)
  - For individuals with suspected adPEO, identification of one POLG mutation is required to confirm the diagnosis.
  - For individuals presenting with clinical features consistent with one of the five other phenotypes, identification of two (biallelic) mutations is required to confirm the diagnosis.

- **POLG Full Gene Sequencing** can be performed to identify mutations in individuals with POLG-Related Disorders. Full sequencing is typically needed given that POLG-related disorders are mainly autosomal recessive conditions and the identification of two mutations in necessary for the diagnosis.

- **POLG Deletion/Duplication Analysis** can be performed if no mutations or only one mutation is found on targeted mutation analysis and/or full gene sequencing.
• **Multi-Gene Panels** - A number of large panels are available that sequence numerous nuclear-encoded mitochondrial genes for a broad approach to testing. Multi-gene panel tests, even for similar clinical scenarios, vary considerably laboratory by laboratory in the genes that are included and in technical specifications (e.g. depth of coverage, extent of intron/exon boundary analysis, methodology of large deletion/duplication analysis).

• While biochemical analyses of an affected tissue may be informative, they are not sensitive or specific enough to definitively diagnose a POLG-related disorder. Muscle biopsy can be completely normal in children and adults with a POLG-related disorder and in clinically unaffected tissue.¹²

**Guidelines and evidence**

• The Food and Drug Administration (FDA, 2017) states that Depakene (valproate) and Depakote ER (divalproex sodium) are contraindicated for patients known to have mitochondrial disorders caused by POLG mutations and children under two years of age who are clinically suspected of having a mitochondrial disorder.¹³

  o “Valproate-induced acute liver failure and liver-related deaths have been reported in patients with hereditary neurometabolic syndromes caused by mutations in the gene for mitochondrial DNA polymerase γ (POLG) (e.g., Alpers-Huttenlocher Syndrome) at a higher rate than those without these syndromes. Most of the reported cases of liver failure in patients with these syndromes have been identified in children and adolescents.”

  o “POLG-related disorders should be suspected in patients with a family history or suggestive symptoms of a POLG-related disorder, including but not limited to unexplained encephalopathy, refractory epilepsy (focal, myoclonic), status epilepticus at presentation, developmental delays, psychomotor regression, axonal sensorimotor neuropathy, myopathy, cerebellar ataxia, ophthalmoplegia, or complicated migraine with occipital aura. POLG mutation testing should be performed in accordance with current clinical practice for the diagnostic evaluation of such disorders. The A467T and W748S mutations are present in approximately 2/3 of patients with autosomal recessive POLG-related disorders.”

• Although not specific to genetic testing for POLG, the Mitochondrial Medicine Society (2015)¹⁴ developed consensus recommendations for the diagnosis and management of mitochondrial disease. Testing strategies, including strategies for genetic testing, were discussed.

  o Recommendations for DNA testing include the following:

    - “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/European Neurological Society (EFNS/ENS) 2014 consensus guidelines on the diagnosis and management of chronic ataxias in adulthood recommend POLG testing in the following evaluation of individuals with autosomal recessive cerebellar ataxia: 15
  
  o “Step 1: mutation analysis of the FRDA gene for Friedreich’s ataxia (although one can refrain from this in the case of severe cerebellar atrophy), and biochemical testing that includes cholestanol, vitamin E, cholesterol, albumin, creatine kinase (CK) and a-fetoprotein. Also consider doing nerve conduction studies/EMG (presence versus absence of peripheral neuropathy, axonal versus demyelinating) and referral to an ophthalmologist (retinitis pigmentosa, cataract, cherry red spot etc.) (Table S2) (good practice point).”
  
  o “Step 2: mutation analysis of the SACS, POLG, Aprataxin (APTX) and SPG7 genes (taking into account specific phenotypes, as given in Table S2), and biochemical testing for white cell enzymes, phytanic acid and long chain fatty acids (good practice point).”
  
  o “Step 3: referral to a specialized centre, e.g. for skin or muscle biopsy targeted at diagnoses such as Niemann - Pick type C, recessive ataxia with coenzyme Q deficiency [aarF domain containing kinase 3 (ADCK3)/autosomal recessive spinocerebellar ataxia 9 (SCAR9)] and mitochondrial disorders, or for extended genetic screening using gene panel diagnostics (good practice point).”

- A 2014 expert-authored review suggests the following testing strategy for those with a known or suspected diagnosis of a POLG related disorder: 1
  
  o “Standard clinical investigations can identify findings that, in the context of an appropriate family history, can suggest one of the POLG-related phenotypes.”
  
  o “Confirmation of the diagnosis of a POLG-related disorder requires identification of POLG pathogenic variants by molecular genetic testing.”
  
  o “One of the following two approaches can be used:”
  
  ▪ “Direct sequencing of POLG”
  
  ▪ “Two tiered analysis: targeted analysis for the common POLG pathogenic variants p.Ala467Thr, p.Trp748Ser, and p.Gly848Ser, followed by sequence analysis of the entire coding region if no pathogenic variants or only one pathogenic variant is found.”
  
  o “In persons meeting the diagnostic criteria of an autosomal recessive POLG-related disorder but in whom sequence analysis identifies only one disease-causing ‘POLG’ allele, further testing may be considered to search for a second pathogenic variant in regulatory regions (e.g., the POLG promoter) or in related mitochondrial DNA replication genes such as C10orf2 (formerly PEO1; (encodes...
the twinkle helicase) and POLG2 to investigate the possibility of digenic inheritance."

- "Digenic inheritance has been reported in arPEO in a simplex case with pathogenic variants in POLG and C10orf2."
- "Oligonucleotide array should be strongly considered as microdeletions involving intragenic regions of POLG are reported and therefore relevant in a symptomatic individual with a single heterozygous pathogenic variant."
  - "An alternative genetic testing strategy is use of a multi-gene panel that includes POLG and other genes of interest."

Criteria

Known POLG Family Mutation Testing

- Genetic Counseling:
  - Pre and post-test counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Diagnostic Testing for Symptomatic Individuals
  - No previous genetic testing of POLG, and
  - If adPEO is suspected:
    - Clinical examination is consistent with a diagnosis of adPEO, and
    - POLG mutation identified in 1st degree biological relative, OR
  - If AHS, MCHS, MEMSA, ANS, or arPEO is suspected:
    - Clinical examination is consistent with a diagnosis of AHS, MCHS, MEMSA, ANS, or arPEO, and
    - Two POLG mutations identified in a sibling, or
    - One POLG mutation identified in both parents

POLG Full Gene Sequencing

- Genetic Counseling:
  - Pre and post-test counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - No previous genetic testing for POLG, and
o No known POLG mutation in the family, AND

• Diagnostic Testing for Symptomatic Individuals:
  o If adPEO is suspected:
    ▪ Clinical examination is consistent with a diagnosis of adPEO, and
    ▪ Genetic testing is needed to confirm the diagnosis, OR
  o If AHS, MCHS, MEMSA, ANS, or arPEO is suspected:
    ▪ Clinical examination is consistent with a diagnosis of AHS, MCHS, MEMSA, ANS, or arPEO, and
    ▪ Genetic testing is needed to confirm the diagnosis, OR
  o If evaluating the risk for valproate-induced hepatic toxicity:
    ▪ The member has epilepsy, and
    ▪ There is suspicion for a POLG-related disorder based on the presence of at least one of the following:
      • unexplained encephalopathy, or
      • refractory epilepsy, or
      • status epilepticus at presentation, or
      • developmental delays, or
      • psychomotor regression, or
      • axonal sensorimotor neuropathy, or
      • myopathy and/or hypotonia, or
      • progressive spastic paraparesis, or
      • renal tubular acidosis, or
      • sensorineural hearing loss, or
      • cyclic vomiting, or
      • pancreatitis, or
      • cerebellar ataxia, or
      • ophthalmoplegia and/or ptosis, or
      • complicated migraine with occipital aura, and
    ▪ The member is currently on Depakene (valproate) or Depakote ER (divalproex sodium) therapy, or the use of one of these medications is being proposed.
POLG Deletion/Duplication Analysis

- Genetic Counseling:
  - Pre and post-test counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Criteria for POLG Full Gene Sequencing is met, AND
- If adPEO is suspected:
  - No mutations found on POLG Full Gene Sequencing, OR
- If AHS, MCHS, MEMSA, ANS, or arPEO is suspected:
  - No mutations or only one mutation found on POLG Full Gene Sequencing, OR
- If evaluating the risk for valproate-induced hepatic toxicity:
  - No mutations or only one mutation found on POLG Full Gene Sequencing

References


13. FDA label: Depakote ER. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021168s038lbl.pdf.
