Test Specific Guidelines

Polymerase Gamma (POLG) Related Disorders Genetic Testing

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Procedures Addressed

The inclusion of any procedure code in this table is provided for informational purposes and is not a guarantee of coverage nor an indication that prior authorization is required.

Procedures addressed by this guideline	Procedure codes
POLG Known Familial Mutation Analysis	81403
POLG Full Gene Sequencing	81406
POLG Deletion/Duplication Analysis	81479

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.[1,2]

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.[1]

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):[3,4]

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.[2] When seizure etiology is unknown, valproic acid must be used with extreme caution, as it can precipitate liver dysfunction and/or failure in AHS.[5,6]

Childhood myocerebrohepatopathy spectrum (MCHS):[7]

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):[8]

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):[9]

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 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):[10]

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.[1,5,6]

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

POLG-related disorders can be inherited in an autosomal recessive or autosomal dominant pattern.

Autosomal dominant inheritance

In autosomal dominant inheritance, individuals have 2 copies of the gene and only one mutation is required to cause disease. When a parent has a mutation, each offspring has a 50% risk of inheriting the mutation. Males and females are equally likely to be affected.

Autosomal recessive inheritance

In autosomal recessive inheritance, individuals have 2 copies of the gene and an individual typically inherits a gene mutation from both parents. Usually only siblings are at risk for also being affected. Males and females are equally affected. Individuals who inherit only one mutation are called carriers. Carriers do not typically show symptoms of the disease, but have a 50% chance, with each pregnancy, of passing on the mutation to their children. If both parents are carriers of a mutation, the risk for each pregnancy to be affected is 1 in 4, or 25%.

AHS, MCHS, MEMSA, ANS, and arPEO are inherited in an autosomal recessive inheritance pattern, while adPEO is inherited in an autosomal dominant pattern. case of arPEO caused by digenic inheritance of POLG and TWNK mutations has been reported.[1]

Diagnosis

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

Management

Management 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

Introduction

Testing for POLG-related disorders may include known familial mutation analysis, next generation sequencing, or deletion/duplication analysis.

Known Familial Mutation (KFM) Testing

Known familial mutations analysis is performed when a causative mutation has been identified in a close biological relative of the individual requesting testing. Analysis for known familial mutations typically includes only the single mutation. However, if available, a targeted mutation panel that includes the familial mutation may be performed.

Next Generation Sequencing Assay

Next generation sequencing (NGS), which is also sometimes called massively parallel sequencing, was developed in 2005 to allow larger scale and more efficient gene sequencing. NGS relies on sequencing many copies of small pieces of DNA simultaneously and using bioinformatics to assemble the sequence. Sequence analysis detects single nucleotide substitutions and small (several nucleotide) deletions and insertions. Regions analyzed typically include the coding sequence and intron/exon boundaries. Promoter regions and intronic sequences may also be sequenced if disease-causing mutations are known to occur in these regions of a gene.

Sequence analysis for this group of disorders is typically limited to full sequencing of the POLG gene only, although POLG may appear on multigene panels for mitochondrial-related disorders.

Deletion and Duplication Analysis

Analysis for deletions and duplications can be performed using a variety of technical platforms including exon array, Multiplex ligation-dependent probe amplification (MLPA), and NGS data analysis. These assays detect gains and losses too large to be identified through standard sequence analysis, often single or multiple exons or whole genes.

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.

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

European Federation of Neurological Sciences/European Neurological Society

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:[13]

"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)."

"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)."

"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)."

Mitochondrial Medicine Society

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

"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."

US Food and Drug Administration

The Food and Drug Administration (FDA) states that Depakene (valproate) (2019) and Depakote ER (divalproex sodium) (2017) 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:[15,16]

"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."

"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."

Selected Relevant Publications

An expert-authored review (updated 2018) suggests the following testing strategy for those with a known or suspected diagnosis of a POLG related disorder:[1]

"POLG-related disorders have overlapping phenotypes. Suggestive findings can be identified through clinical investigations."

"Clinical diagnostic criteria do not exist. The diagnosis of most POLG-related disorders is established in a proband by identification of biallelic pathogenic variants in POLG by molecular genetic testing. The diagnosis of adPEO is established in a proband by identification of a heterozygous pathogenic variant in POLG by molecular genetic testing."

"Sequence analysis of POLG is performed first and followed by gene-targeted deletion/duplication analysis if no pathogenic variant is found."

"Sequence analysis of TWNK (formerly C10orf2 or PEO1) may be considered in persons with a suspected autosomal recessive POLG-related disorder but in whom only one POLG pathogenic variant was identified by single-gene testing, to investigate the possibility of digenic inheritance."

"A multigene panel that includes POLG, TWNK (formerly C10orf2 or PEO1), and other genes of interest may be considered."

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 that would detect the familial mutation, 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 POLG sequencing, and

No known POLG mutation in the family, AND

Diagnostic Testing for Symptomatic Individuals:

If adPEO is suspected:

Clinical examination is consistent with a diagnosis of adPEO, and

Genetic testing is needed to confirm the diagnosis, 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

Genetic testing is needed to confirm the diagnosis, OR

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

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