Progressive external ophthalmoplegia

Progressive external ophthalmoplegia is a condition characterized by weakness of the eye muscles. The condition typically appears in adults between ages 18 and 40 and slowly worsens over time. The first sign of progressive external ophthalmoplegia is typically drooping eyelids (ptosis), which can affect one or both eyelids. As ptosis worsens, affected individuals may use the forehead muscles to try to lift the eyelids, or they may lift up their chin in order to see. Another characteristic feature of progressive external ophthalmoplegia is weakness or paralysis of the muscles that move the eye (ophthalmoplegia). Affected individuals have to turn their head to see in different directions, especially as the ophthalmoplegia worsens. People with progressive external ophthalmoplegia may also have general weakness of the muscles used for movement (myopathy), particularly those in the neck, arms, or legs. The weakness may be especially noticeable during exercise (exercise intolerance). Muscle weakness may also cause difficulty swallowing (dysphagia).

When the muscle cells of affected individuals are stained and viewed under a microscope, these cells usually appear abnormal. These abnormal muscle cells contain an excess of cell structures called mitochondria and are known as ragged-red fibers. Although muscle weakness is the primary symptom of progressive external ophthalmoplegia, this condition can be accompanied by other signs and symptoms. In these instances, the condition is referred to as progressive external ophthalmoplegia plus (PEO+). Additional signs and symptoms can include hearing loss caused by nerve damage in the inner ear (sensorineural hearing loss), weakness and loss of sensation in the limbs due to nerve damage (neuropathy), impaired muscle coordination (ataxia), a pattern of movement abnormalities known as parkinsonism, and depression.

Progressive external ophthalmoplegia is part of a spectrum of disorders with overlapping signs and symptoms. Similar disorders include ataxia neuropathy spectrum and Kearns-Sayre syndrome. Like progressive external ophthalmoplegia, the other conditions in this spectrum can involve weakness of the eye muscles. However, these conditions have many additional features not shared by most people with progressive external ophthalmoplegia.

Frequency

The prevalence of progressive external ophthalmoplegia is unknown.

Causes

Progressive external ophthalmoplegia is a condition caused by defects in mitochondria, which are structures within cells that use oxygen to convert the energy from food into a form cells can use. This process is called oxidative phosphorylation. Although most
DNA is packaged in chromosomes within the nucleus (nuclear DNA), mitochondria also have a small amount of their own DNA, called mitochondrial DNA or mtDNA. This DNA contains genes essential for oxidative phosphorylation.

Progressive external ophthalmoplegia can result from mutations in one of several different genes. In some cases, mutations in nuclear DNA are responsible for the condition, including mutations in the POLG, TWNK, RRM2B, and SLC25A4 genes, among others. These genes are critical for the production and maintenance of mtDNA. Although the mechanism is unclear, mutations in these genes lead to the deletion of large segments of mtDNA in muscle cells. The size of the deleted region can range from 2,000 to 10,000 DNA building blocks (nucleotides).

In other cases, the condition is caused by a single large deletion of mtDNA that is not associated with a mutation in a nuclear DNA gene.

Less commonly, mutations that change single nucleotides in genes found in mtDNA, such as the MT-TL1 gene, cause progressive external ophthalmoplegia. These mutations occur in genes that provide instructions for making molecules called transfer RNAs. Transfer RNAs help assemble protein building blocks (amino acids) into functioning proteins. The transfer RNAs associated with progressive external ophthalmoplegia are present in mitochondria and help assemble the proteins that carry out the steps of oxidative phosphorylation.

Researchers have not determined how deletions of mtDNA or mutations in mtDNA genes lead to the specific signs and symptoms of progressive external ophthalmoplegia, although the features of the condition are probably related to impaired oxidative phosphorylation. It has been suggested that eye muscles are commonly affected by mitochondrial defects because they are especially dependent on oxidative phosphorylation for energy.

**Inheritance Pattern**

Progressive external ophthalmoplegia can have different inheritance patterns depending on the gene involved.

When the nuclear genes POLG, TWNK, RRM2B, or SLC25A4 are involved, progressive external ophthalmoplegia is usually inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to cause the disorder.

Certain mutations in the POLG or RRM2B gene can also cause a form of the condition that is inherited in an autosomal recessive pattern, which means both copies of the gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition.

When this condition is caused by mutations in the MT-TL1 gene and other mitochondrial transfer RNA genes, it is inherited in a mitochondrial pattern, which is also known as maternal inheritance. This pattern of inheritance applies to genes contained in mtDNA. Because egg cells, but not sperm cells, contribute mitochondria to
the developing embryo, children can inherit disorders resulting from mtDNA mutations only from their mother. These disorders can appear in every generation of a family and can affect both males and females, but fathers do not pass traits associated with changes in mtDNA to their children.

Single, large deletions of mtDNA are typically not inherited but occur during the formation of a mother’s egg cells or in early development of the embryo. Individuals with these mutations usually have no history of the disorder in their family.

Other Names for This Condition
- chronic progressive external ophthalmoplegia
- CPEO
- PEO

Diagnosis & Management

Genetic Testing Information
- What is genetic testing?
  /primer/testing/genetictesting
- Genetic Testing Registry: Autosomal dominant progressive external ophthalmoplegia with mitochondrial DNA deletions 1
- Genetic Testing Registry: Autosomal dominant progressive external ophthalmoplegia with mitochondrial DNA deletions 2
- Genetic Testing Registry: Autosomal dominant progressive external ophthalmoplegia with mitochondrial DNA deletions 3
- Genetic Testing Registry: Progressive external ophthalmoplegia

Research Studies from ClinicalTrials.gov
- ClinicalTrials.gov
  https://clinicaltrials.gov/ct2/results?cond=%22progressive+external+ophthalmoplegia%22+OR+%22CPEO%22+OR+%22PEO%22+OR+%22chronic+progressive+external+ophthalmoplegia%22

Other Diagnosis and Management Resources
- GeneReview: Mitochondrial DNA Deletion Syndromes
  https://www.ncbi.nlm.nih.gov/books/NBK1203
- GeneReview: POLG-Related Disorders
  https://www.ncbi.nlm.nih.gov/books/NBK26471
• GeneReview: RRM2B-Related Mitochondrial Disease
  https://www.ncbi.nlm.nih.gov/books/NBK195854

• United Mitochondrial Disease Foundation: Getting a Diagnosis
  https://www.umdf.org/what-is-mitochondrial-disease/getting-a-diagnosis/

**Additional Information & Resources**

**Health Information from MedlinePlus**

- Encyclopedia: Eyelid Drooping
  https://medlineplus.gov/ency/article/003035.htm

- Encyclopedia: Ptosis
  https://medlineplus.gov/ency/article/001018.htm

- Health Topic: Degenerative Nerve Diseases
  https://medlineplus.gov/degenerativenervediseases.html

- Health Topic: Eye Movement Disorders
  https://medlineplus.gov/eyemovementdisorders.html

- Health Topic: Eyelid Disorders
  https://medlineplus.gov/eyeliddisorders.html

- Health Topic: Mitochondrial Diseases
  https://medlineplus.gov/mitochondrialdiseases.html

**Genetic and Rare Diseases Information Center**

- Chronic progressive external ophthalmoplegia

**Additional NIH Resources**

- National Institute of Neurological Disorders and Stroke: Mitochondrial Myopathies
  https://www.ninds.nih.gov/Disorders/All-Disorders/Mitochondrial-myopathy-Information-Page

- National Institutes of Health Rare Diseases Clinical Research Network: North American Mitochondrial Disease Consortium
  https://www.rarediseasesnetwork.org/cms/NAMDC

**Educational Resources**

- Mayo Clinic: North American Mitochondrial Disease Consortium Patient Registry and Biorepository (NAMDC)
  https://www mayo.edu/research/clinical-trials/cls-20409244

- Muscular Dystrophy Association: Facts About Mitochondrial Myopathies
• Orphanet: Mitochondrial DNA-related progressive external ophthalmoplegia
  https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=663

• University of Iowa: Chronic Progressive External Ophthalmoplegia - Kearns-Sayre Syndrome
  http://webeye.ophth.uiowa.edu/eyeforum/cases/case24.htm

• University of Virginia Health System: Myopathy
  https://uvahealth.com/services/neurology/myopathy

Patient Support and Advocacy Resources
• MitoAction
  http://www.mitoaction.org/

• United Mitochondrial Disease Foundation: What is Mitochondrial Disease?
  https://www.umdf.org/what-is-mitochondrial-disease/

Clinical Information from GeneReviews
• Mitochondrial DNA Deletion Syndromes
  https://www.ncbi.nlm.nih.gov/books/NBK1203

• POLG-Related Disorders
  https://www.ncbi.nlm.nih.gov/books/NBK26471

• RRM2B-Related Mitochondrial Disease
  https://www.ncbi.nlm.nih.gov/books/NBK195854

Scientific Articles on PubMed
• PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28Ophthalmoplegia,+Chronic+Progressive+External%5BMAJR%5D%29+AND+%28progressive+external+ophthalmoplegia%5BTIAB%5D%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1440+days%22%5Bdp%5D

Catalog of Genes and Diseases from OMIM
• PROGRESSIVE EXTERNAL OPHTHALMOPLEGIA WITH MITOCHONDRIAL DNA DELETIONS, AUTOSOMAL DOMINANT 1
  http://omim.org/entry/157640

• PROGRESSIVE EXTERNAL OPHTHALMOPLEGIA WITH MITOCHONDRIAL DNA DELETIONS, AUTOSOMAL DOMINANT 2
  http://omim.org/entry/609283
- PROGRESSIVE EXTERNAL OPHTHALMOPLEGIA WITH MITOCHONDRIAL DNA DELETIONS, AUTOSOMAL DOMINANT 3
  http://omim.org/entry/609286
- PROGRESSIVE EXTERNAL OPHTHALMOPLEGIA WITH MITOCHONDRIAL DNA DELETIONS, AUTOSOMAL RECESSIVE 1
  http://omim.org/entry/258450

Sources for This Summary


Reprinted from Genetics Home Reference:

Reviewed: May 2016
Published: October 1, 2019

Lister Hill National Center for Biomedical Communications
U.S. National Library of Medicine
National Institutes of Health
Department of Health & Human Services