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Review Article

POLG Related Neurological Disorders and Their Mimics

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Abstract

The POLG gene is responsible for production of alpha subunit, of a protein called polymerase gamma (pol γ). Pol γ is a mitochondrial DNA polymerase, responsible for replication of the mitochondrial genome. POLG-related disorders comprise a continuum of broad and overlapping phenotypes that can be distinct clinical entities or consist of a spectrum of overlapping phenotypes. Presentations within a given family are usually similar. Although almost any organ system can be involved, evidence to date suggests that diabetes and cardiomyopathy are not very common in POLG-related disorders, distinguishing them from other multisystem mitochondrial diseases. Mutations in POLG can cause early childhood mitochondrial DNA (mtDNA) depletion syndromes or later- onset syndromes arising from mt DNA deletions. POLG mutations are the most common cause of inherited mitochondrial disorders, with as many as 2% of the population carrying these mutations. Clinical features may include hypotonia, developmental delay, seizures, movement disorder (e.g., myoclonus, dysarthria, choreoathetosis, parkinsonism), Myopathy(e.g., ptosis, ophthalmoplegia, proximal > distal limb weakness with fatigue and exercise intolerance), Ataxia, Peripheral neuropathy, Episodic psychomotor regression, Psychiatric illness (e.g., depression, mood disorder),Endocrinopathy (e.g., premature ovarian failure).Most common disorders caused by POLG mutations are Alpers-Hutten ocher syndrome (AHS),Childhood myocerebrohepatopathy spectrum(MCHS),Myoclonic epilepsy myopathy sensory ataxia (MEMSA),Ataxia neuropathy spectrum (ANS),Autosomal recessive progressive external ophthalmoplegia (arPEO), Autosomal dominant progressive external ophthalmoplegia (adPEO). This review will summarize POLG related disorders and their mimics focusing mainly on the neurological manifestations of these conditions.

Keywords: POLG; Mimics; Mitochondrial DNA; mtDNA polymerase; Syndromes

Abbreviations

POLG: DNA Polymerase Subunit Gamma; MNGIE: Mitochondrial Neurogastrointestinal Encephalomyopathy; MERRF: Myoclonic Epilepsy with Ragged-Red Fibers; MELAS: Mitochondrial Encephalomyopathy, Lactic Acidosis, And Stroke-Like Episodes; ADEM: Acute Disseminated Encephalomyelitis; NGS: Next Generation Sequencing.

Introduction

ATP is the major supplier of energy to development and normal functioning of the central nervous system [1]. In neurons, the majority of ATP is generated in the mitochondria by oxidative phosphorylation (OXPHOS) via the electron transport chain (ETC) and ATP synthase. OXPHOS system comprises of 90 proteins and around 13 are derived from the mitochondrial genome. In human genome, mitochondria is a closed circular DNA molecule of 16,569 bp that also encodes 22 tRNAs and 2 ribosomal RNAs that are required for synthesis of the 13 polypeptides. The mitochondrial DNA (mtDNA) is located in discrete nucleoids localized within the inner matrix of the mitochondrion, each of which contains one or two copies of the mtDNA [2,3].

DNA polymerase subunit gamma (POLG or POLG1) is an enzyme that in humans is encoded by the POLG gene [4]. The maintenance

of mitochondrial DNA (mtDNA) is critically dependent upon polymerase-γ (pol-γ),encoded by the nuclear gene POLG. In humans, mtDNA is copied by a 195 kDa heterotrimer consisting of a catalytic subunit (p140, coded by POLG on chromosome 15q25) and two identical accessory subunits (p55, coded by POLG2 on chromosome 17q).The catalytic subunit (p140) possesses DNA polymerase, 3′→5′ exonuclease and 5′dRP lyase activities, whereas the accessory subunit (p55) is a DNA binding factor that confers high processivity by increasing the affinity of the heterotrimer for template DNA. Pol-γ has a high base-substitution fidelity (<2×10 - 6 errors per nucleotide) and is relatively accurate over short repeat sequences, but longer homopolymeric tracts (> 4 bp) lead to slippage during replication [5-8].

There is a close relationship between the mitochondrial transcription factor A (mtTFA) and mtDNA levels [9], suggests that mtTFA binds to mtDNA as a chaperone, protecting against oxidant damage [10]. Nuclear respiratory factor-1 (NRF-1) is a transcription factor that regulates the expression of many mitochondrial proteins, NRF-1 expression is related to cellular ATP levels and binds to promoter regions of POLG, POLG2 and mtTFA [11]. Graziewicz., *et al.* described about the proteins involved in mtDNA replication and repair [12]. The first pathogenic mutations in POLG were identified in families with autosomal dominant chronic progressive external ophthalmoplegia [13]. several reports identified POLG mutations in patients with ataxia specially in the Norwegian and Finnish populations [14,15].

In one large Australian Cohort, mutations in POLG represented the most prevalent single gene cause of mitochondrial disease, accounting for 10% of adult mitochondrial disease cases [16]. POLG mutations are the most frequent cause of mitochondrial epilepsy at all ages [17], and also account for 10 - 25% of PEO [18] and > 10% of ataxia cases [19]. Age of onset of the POLG-related disorders ranges from infancy to late adulthood, however those with adolescent- onset or adult- onset disorders, do not present with a discrete clinical syndrome. Neurological findings in this type of disorders can be cortical [20,21,22], seizures [22], cerebrovascular involvement [21,22], extrapyramidal movement disorder [23,24], peripheral neuropathy [21,25], cerebellar involvement [21], dementia [21], sensorineural deafness [21], ptosis and external ophthalmoplegia [26].

Typical POLG related disorders

Alpers-huttenlocher syndrome (AHS)

AHS, one of the most severe phenotypic manifestations in the spectrum of POLG-related disorders, is characterized by a progressive and ultimately severe encephalopathy with intractable epilepsy, neuropathy, and hepatic failure. While AHS is usually fatal, the age of onset, rate of neurologic degeneration, presence of hepatic failure, and age of death vary [27-29].

Childhood myocerebrohepatopathy spectrum (MCHS)

MCHS presents between the first few months of life and about age three years with developmental delay or dementia, lactic acidosis, and a myopathy with failure to thrive. Other features of a mitochondrial disorder that may be present include liver failure, renal tubular acidosis, pancreatitis, cyclic vomiting, and hearing loss. Seizures are not present, at least early in the disease course [30].

Myoclonic epilepsy myopathy sensory ataxia (MEMSA)

Previously referred to as spinocerebellar ataxia with epilepsy (SCAE),MEMSA now describes the spectrum of disorders with myopathy, epilepsy, and ataxia without ophthalmoplegia. Cerebellar ataxia, generally the first sign, begins in young adulthood as a subclinical sensory polyneuropathy. Epilepsy develops in later years, often beginning focally in the right arm and then spreading to become generalized. The seizures may be refractory to conventional therapy, including anesthesia. Recurrent bouts of seizure activity are accompanied by progressive interictal encephalopathy. The myopathy in MEMSA may be distal or proximal, and, as in the other POLG-related disorders, it also may present as exercise intolerance [31].

Ataxia neuropathy spectrum (ANS)

ANS includes mitochondrial recessive ataxia syndrome (MIRAS) and a separate entity known as sensory ataxia neuropathy dysarthria and ophthalmoplegia (SANDO) [32]. ANS is characterized by ataxia, neuropathy, and (in most but not all affected individuals) an encephalopathy with seizures. The encephalopathy is similar to that seen in AHS but tends to be more slowly progressive and can even be mild. The neuropathy may be sensory, motor, or mixed and can be severe enough to contribute to ataxia – so-called sensory ataxia. About 25% of affected individuals have cramps, but clinical myopathy is rare. Other features may include myoclonus, blindness,

and liver dysfunction [20,33].

Autosomal recessive progressive external ophthalmoplegia (arPEO)

Progressive PEO without systemic involvement is the hallmark of arPEO. Caution needs to be exercised, however, when making the diagnosis of arPEO, as some POLG pathogenic variants associated with arPEO are also associated with ANS and other POLG-related disorders with systemic involvement. Thus, many individuals who have no other clinical findings at the time of diagnosis with isolated arPEO develop other manifestations of POLG-related disorders over subsequent years or decades [34-36].

Autosomal dominant progressive external ophthalmoplegia (adPEO)

The universal manifestation of this adult-onset disorder is progressive weakness of the extraocular eye muscles resulting in ptosis and strabismus [37]. A generalized myopathy is present in most affected individuals, leading to early fatigue and exercise intolerance. Some affected individuals(in what has been called "chronic progressive external ophthalmoplegia plus," or CPEO+) have variable degrees of sensorineural hearing loss, axonal neuropathy, ataxia, depression, parkinsonism, hypogonadism, and cataracts [38,39]. Cardiomyopathy and gastrointestinal dysmotility are less common [40-42].

Atypical POLG related disorders

MNGIE- like disorder

Recently Huang., *et al.* reported a 49-year-old Chinese man with MNGIE-like syndrome involved leukoencephalopathy and was associated with novel POLG mutations [43]. Tang S., *et al.* supported the fact that POLG1 mutations may cause MNGIE-like syndrome, but the lack of leukoencephalopathy and the normal plasma thymidine favor POLG1 mutations as responsible molecular defect [44]. Prasun., *et al.* also reported mitochondrial neurogastrointestinal encephalomyopathy (MNGIE)-like phenotype in a patient with a novel heterozygous POLG mutation [45]. Van Goethem., *et al.* also reported novel POLG mutations in progressive external ophthalmoplegia mimicking mitochondrial neurogastrointestinal encephalomyopathy [46].

Movement disorder syndromes

In a cohort of adult patients with mitochondrial movement disorders, 5 of 42 (12%) had POLG mutations. These five patients all had parkinsonism, and three also had restless legs syndrome [47]. POLG- related parkinsonism has an earlier onset than idiopathic Parkinson disease, typically ~40 years but as early as the third decade in some families [48], and is associated with initially asymmetric clinical and imaging features and a good response to levodopa [47]. Palatal tremor also seems to be a characteristic feature in some patients with POLG mutations, occurring together with facial dyskinesia and progressive ataxia in the so- called progressive ataxia palatal tremor (PAPT) syndrome [49] however recently reported 2 cases was due to novel tauopathy [50]. Dystonia, the most frequent movement disorder in other mitochondrial disorders such as Leigh syndrome, is rarely observed in patients with POLG mutations [51,52].

Mimics to POLG related disorders

Few disorders are reported in literature supported by neuroimaging, CSF findings, neuropathological and even symptoms which can easily confuse with this type of disorderss when patient presents to clinic for the first time. Clinicians should bear in mind few important features which can help to differentiate this disorders.

MERRF and MELAS

POLG- related epilepsies can mimic classic mitochondrial syndromes, including myoclonic epilepsy with ragged- red fibres [53] and mitochondrial encephalomyopathy, lactic acidosis and stroke- like episodes [54] or overlap syndrome [55].

ADEM

A viral prodrome can sometimes be observed, which might arouse clinical suspicion of encephalitis [56]. Some individuals were reported to have oligoclonal bands in their cerebrospinal fluid (CSF). In one case, neuropathology revealed features of acute disseminated encephalomyelitis (ADEM), again suggesting an underlying immune- mediated pathology [57].

Multiple sclerosis (MS)

Laguna., *et al.* reported POLG1 variations presented as MS [58].

Discussion

POLG encodes the catalytic subunit of DNA polymerase γ, the enzyme responsible for replicating the mitochondrial DNA

(mtDNA).Mutations in POLG are associated with a clinical continuum of heterogeneous syndromes, ranging from infantile-onset epilepsies and liver failure to late- onset ophthalmoplegia, muscle weakness, parkinsonism. Mitochondrial DNA defect can be either depletion or deletions. Full clinical assessment should encompass a multisystem evaluation, including vision and hearing, and cardiac, hepatic, renal, gastrointestinal and respiratory function as it can involve multiple organs at cellular level. Diagnostic modalities can range from basic EEG, Neuroimaging, blood and CSF biomarkers to complex strategies like histopathology, respiratory chain enzymology and whole exome sequencing or next generation sequencing(NGS) as part of molecular genetics.

Conclusion

POLG-related disorders comprise a continuum of overlapping phenotypes that were clinically defined long before their molecular basis was known. Most affected individuals have some, but not all of the features of a given phenotype. It is associated with numerous clinically heterogeneous syndromes characterized by a quantitative and/or qualitative mtDNA defect as discussed in this review. Seizures dominate the clinic picture from childhood to even ataxia and parkinsonism in adulthood which indicate poor prognosis. Multiple organs can be involved at a single time or at the time of presentation. Treatment is mainly in the form of antiepileptic, liver transplant and conservative most of the times as there is no effective disease modifying therapies, despite tremendous advances in mitochondrial disease diagnostics in recent years. Future research should focus on inventing novel agents which can target the disease at the grass root level.

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