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Mini Review

Treatment Avenues for the Juvenile and Adult Onset Mitochondriopathies Alpers Syndrome, Ataxia Neuropathy Spectrum, MEMSA and PEO Caused by Polymerase-Gamma Mutations Ala467Thr and Trp748Ser

Hans Zempel[1-3]*, Bernard Sadzot[3] and Natja Haag[4]*

[1]*German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany*
[2]*University of Bonn, Germany*
[3]*Department of Neurology, University Hospital of Liège, Belgium*
[4]*Institute of Human Genetics, RWTH Aachen University, Germany*

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***Corresponding author(s)**

Hans Zempel, German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany,
Tel: +49 (0) 228 / 43302-0;
Email: HansZempel@hotmail.com

Natja Haag, Institute of Human Genetics, Medical Faculty, RWTH Aachen University, Aachen, Germany,
Tel: +49 241 80723;
Email: nhaag@ukaachen.de

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Abstract

Defects in the only human mitochondrial polymerase, the Polymerase Gamma (Polγ) encoded by the POLG gene, cause mitochondriopathies like Alpers Syndrome or MEMSA typically leading to medication resistant fatal seizures. Pathomechanistically, depletion of mitochondrial DNA leads to mitochondrial malfunction. Depending on the mutation and the degree of mitochondrial DNA depletion, age of onset can vary between 30 days and 64 years, but most children affected decease within infancy (overall median age of death 3.5 years). Here we review therapeutic avenues for patients with the two most frequent mutations, Ala467Thr and Trp748Ser. In these patients symptoms appear at a relatively late age (median 14 and 17 years, respectively) and patients also decease at a relatively late age (median 20 and 25 years, respectively) when homozygous for one of these mutations.

Proposed treatments may also be beneficial for other mitochondriopathies like Friedreich Ataxia.

Introduction

POLG encodes for the catalytic subunit of the heterotrimeric Polymerase-gamma (Polγ), the only mitochondrial polymerase in humans. Polγ consists of a catalytic subunit of 140 kDa, p140, and two identical accessory subunits of 55 kDa in size, p55. Polγ possesses synthesizing, lyase and proofreading functions.

More than 300 pathological mutations are described [1], but two mutations, namely Ala467Thr and Trp748Ser, make up the majority of cases with estimated carrier prevalence in the Caucasian population between 0.5 and 1% [2].

Clinical features of Alpers (or Alpers-Huttenlocher) Syndrome and related syndromes like myoclonic epilepsy myopathy sensory ataxia (MEMSA), ataxia neuropathy spectrum (ANS), progressive external ophthalmoplegia (PEO) or MELAS (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episode) caused by *POLG* mutations have been extensively described [2]. Briefly in Alpers Syndrome, the predominant features are early predilection of epileptiform discharges over occipital brain regions with generalization upon disease progression. As the disease progresses, seizures become resistant to medication. Myoclonuses appear and can become so rapid that they are indistinguishable from myoclonic seizures. In fully developed Alpers Syndrome, liver failure (also, but not necessarily, due to liver toxicity of anti-epileptic medication such as Valproic Acid, which should be avoided) and cortical blindness become apparent. Death occurs mainly due to status epilepticus and liver failure [2].

The age of onset of *POLG* caused syndromes ranges from 30 days to 64 years, with a median age of 1.83 years for males and 4 years for females (overall 2 years). The median age of death is 3.5 years, with the median interval between onset and death being 1 year. Two common mutations, Ala467Thr and Trp748Ser, result in a relatively late age of onset (median 14 and 17 years, respectively) and a late age of death (median 20 and 25 years, respectively) for homozygous cases [3,4] (Figure 1).

Therefore, a residual activity of Polγ can be assumed. Indeed, biochemical studies showed that there is residual activity of ~5% for both mutations, modulated by the presence of p55 [5,6]. In the

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Table 1: Summary of possible treatments, ordered by availability. All treatments target pathways that increase mitochondrial function (if not indicated otherwise).

•	**Dietary measures**
o	Ketogenic diet
•	**Lifestyle measures**
o	Endurance exercise
o	Exposure to cold
•	**Dietary supplements commercially available**
o	NAD+
o	Quercetin
o	MitoQ (mitochondrially targeted antioxidant)
•	**Future therapy options**
o	Enzyme replacement therapy

presence of other factors, processivity *in vivo* might be even better. Conversely, mutations leading to even less processivity, e.g. the G848S mutation, which lies within the polymerase domain (Figure 1) and shows only <1% processivity, result in infant death when compound heterozygous with another mutation [2,3]. Also, pathological analysis confirmed that adult patients show higher relative mitochondrial DNA (mitoDNA) copy number than infants (40-50% loss vs. 80% loss) at the time of death [7], indicating that processivity directly correlates with mitoDNA content and age of death.

MitoDNA content is usually considered pathological when it drops below 70% [8], which can be assumed to correlate best with onset of disease. In post-mortem studies, neuronal mitoDNA content in patients showed a decrease to 50-60% [7], whereas mitoDNA content in other tissues was often normal, with the exception of the liver [3]. As disease duration is roughly half the age of onset, a linear depletion of mitoDNA could be assumed. In some *POLG*-caused syndromes mitoDNA damage or deletions might accumulate progressively, however, the total content of mitoDNA or depletion of mitoDNA-encoded proteins correlates best with patient's time of death (Table 1).

Dietary and Life-Style Considerations

A ketogenic diet increases mitochondria mass, mitochondria function and mitochondria respiration. Ketogenic diets have been employed previously and can ameliorate seizure severity and functional outcomes [10,11].

Mitochondrial function is strongly stimulated by exercise; in particular endurance based exercise, but of course the patient still has to be able to perform exercises [12]. Also, exposure to cold increases mitochondria mass at least in the periphery and muscles [13], but great care must be applied as infections are common in patients with mitochondriopathies.

Dietary supplements

Mitochondrial mass was shown to be increased by resveratrol, epicatechins, curcumin, phytoestrogens like Polyrroloquinoline quinone (PQQ) (also contained in vegetables like soybeans) and NAD+ supplements [9], all of which are commercially available

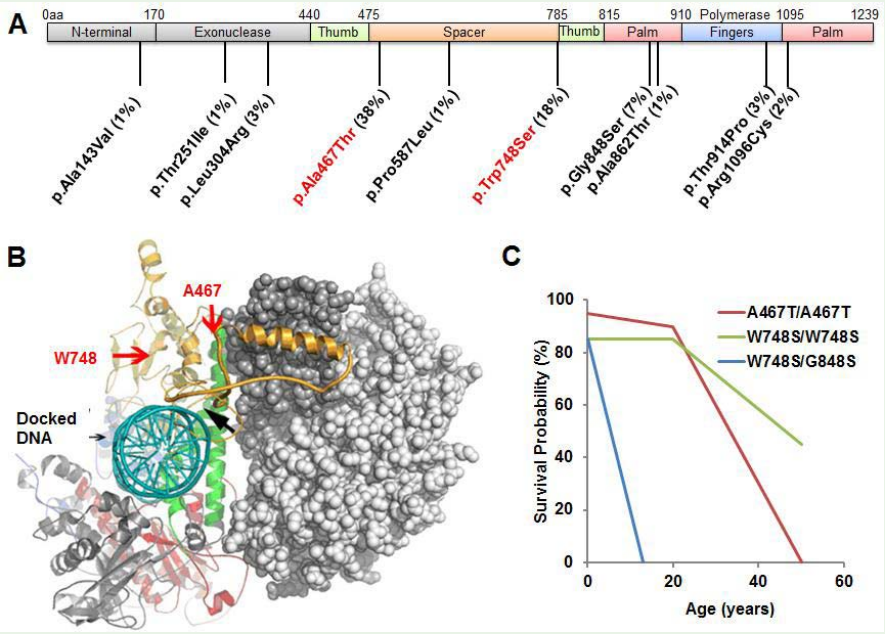

Figure 1: A) Domain diagram of Polymerase Gamma (Polγ) with the most common mutations. Note the two most frequent mutations discussed here (Ala467Thr and Trp748Ser) lie within the spacer/thumb domains.
B) Modeled Polγ complex with docked DNA (DNA-helix lies sagittal, turquois; dimeric subunit B is represented in grey, right half). Black arrow indicates region of DNA interkalation by Polγ, red arrows indicate the position of the discussed mutations.
C) Kaplan-Meier survival curves based on genotype. Patients with the two most prevalent mutations (A467T and W748S) have a higher survival probability, likely due to residual Polγ activity, compared to more severe mutations, e.g. shown here the third most frequent mutation G848 in combination with W748S. Adapted from (and see details for) [3,4].

even without prescription and even combined at commonly used dosages for less than 1€/day. So is the antioxidants quercetin [13]. The mitochondrially targeted antioxidant MitoQ might help to maintain mitochondrial function and to protect mitoDNA [14,15].

Future therapy options

In many cases of Alpers Syndrome and related mitochondriopathies caused by *POLG* mutations, children die in their infancy due to almost complete lack of enzyme activity [2]. For these patients and also for long-term treatment of milder cases or in case of therapy resistance, enzyme replacement therapy of Polγ has to be considered. Biotechnological procedures to tag recombinant proteins for mitochondrial targeting are available and could be adapted for transporting recombinant proteins (tagged with mitochondria targeting and membrane penetrating sequences) across the blood brain barrier and even the placenta barrier [16]. For mitochondriopathies with milder phenotypes the same strategy could be employed.

Follow-up of treatments

Apart from classical diagnostics for neurodegenerative mitochondrial diseases like clinical assessment, EEG and mitochondrial mass measurements [17], noninvasive and repeatable diagnostic tools able to detect subtle changes specific for *POLG*-caused Alpers and associated syndromes might be necessary. As sleep pathology may be a complication of primary mitochondrial diseases, it could be employed to measure the typically arising central neurological and peripheral neuromuscular degenerative changes that commonly present as central sleep apnea and poor ventilatory response to hypercapnia [18].

Classically, neuroimaging can assist in the diagnosis of mitochondriopathy-caused brain pathological changes, such as e.g. ischemic strokes in brain regions untypical for vascular lesions, but most changes detectable by neuroimaging are unspecific for Alpers syndrome. Yet, successful treatment could be confirmed via measuring brain metabolites via MRS, such as lactate, creatine, and N-acetyl aspartate in a single- or multi-voxel distribution, but more research needs to be done in this respect [17,19].

Discussion

In *POLG*-caused mitochondriopathies, there is a direct genotype-phenotype relationship. In case of heterozygosity, or for mutations of Polγ that cause mild deficits in processivity, patients present with milder clinical manifestations, such as Progressive External Ophthalmoplegia (PEO) with little or no decreased life expectancy, or symptoms can be totally absent. Between absence of symptoms and full blown Alpers Syndrome, patients may present with Ataxia Neuropathy Spectrum (ANS) or Myoclonus, Epilepsy, Myopathy and Sensory Ataxia (MEMSA). In contrast, more severe mutations with total loss of enzyme activity lead to infant/neonatal onset of disease and to myocerebrohepatopathy spectrum (MCHS), and to death within 0-3 years (for review see [2], for a detailed listing of mutations and associated syndromes see https://tools.niehs.nih.gov/polg/). Thus, even slightly increasing enzyme efficiency (or amount) might lead to less severe symptoms. The clinical manifestations of the two mutations discussed here do not differ significantly, despite the different average age of onset. Biochemically, the processivity of Polγ with the A467T mutation is slightly worse than in case of the W748S mutation (4% vs. 6%, respectively, including interaction with the p55 subunit) [5,6]. Here, too, decreased biochemical activity correlates with early average onset of disease (14 vs. 17 years) and early time of death (20 vs. 25 years) (see above). This also clearly indicates that even slightly increasing activity or amounts of Polγ might have significant clinical effects.

The summary of all possible side effects and pharmaceutical interactions is not within the scope of this review. Despite the fact that treatments outlined above are usually well tolerated and have tolerable side effects, severe side effects cannot be excluded as there are no previous reports for any of these medications or supplements for the treatment of *POLG*-caused mitochondriopathies to the best of our knowledge. Thus, minimal dosage and no polymedication are advised. Special consideration for each medication and close monitoring is advised, especially for neurological and hepatic syndromes.

Conclusion

This review aims to provide clinicians treating patients with Alpers Syndrome and related mitochondriopathies caused by Polγ-mutations with treatment options. Side effects and gain vs. risk of treatments outlined above should be carefully considered for each case individually. Particular attention should be given to potential interactions in case of polymedication.

Proposed treatments might be applicable also for other mitochondriopathies, even though pathomechanisms are completely different. Indeed, a phase II clinical trial showed that high dose resveratrol did improve neurological outcome in patients suffering from Friedreich Ataxia [20]. In Friedreich Ataxia, iron overload of mitochondria due to deficient frataxin leads to increased ROS production.

Enhancing mitochondrial biogenesis leads to enhanced mitochondria mass turnover and might thereby reduce disease severity also in other mitochondriopathies, however, there is need for more human data.

Methods

Literature search was conducted using Pub Med database with the following search terms: “Polymerase Gamma”, “Polymerase-γ”, “*POLG*”, “Alpers Syndrome”, “A467T”, “W748S”, “mitochondrial DNA replication”, “MELAS”. Results were then screened for relevance with respect to relevance for the mutations discussed here and clinical applicability. Other sources (neurology textbooks, Google, etc.) were only considered for overall orientation, but were in general little helpful for the creation of this article. Figures were created by using Adobe Photoshop and Adobe Illustrator.

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