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# POLG Gene Mutation and Alpers - Huttenlocher Syndrome: A Case Report and Review of Literature

**Dr. Varnit Shanker[1], Dr. Praveen Kumar[2]**

[1]Consultant, DACH Institute of Child Neurosciences, Jaipur

[2]Senior Consultant, Department of Child Neurology, Sir Gangaram Hospital, New Delhi

**Abstract:** ***Alpers - Huttenlocher syndrome (AHS) is an autosomal recessive inheritance condition associated with POLG and is characterized by the classic triad of epilepsy refractory to treatment. In this study, a clinical case of a 10 - month - old female patient with a provisional diagnosis refractory epilepsy is reported. Subsequently, the paper describes the clinical features, natural history of Alpers - Huttenlocher syndrome, and treatment of PLOG - related disorders, focusing particularly on the neurological manifestations of these conditions.***

**Keywords:** PolG gene mutation, Neuroregression, Super - refractory seizures

## 1. Introduction

The term mitochondrial diseases refers to a group of disorders related to the respiratory chain and oxidative phosphorylation (OXPHOS) dysfunction. Mitochondrial diseases are caused by mutations in the nuclear gene POLG. The POLG gene encodes the mitochondrial DNA (mtDNA) polymerase gamma catalytic subunit (*174763), which is responsible for the replication and repair of the mitochondrial genome. One of the mitochondrial diseases with an uncharacteristic and varied neuropathological picture is the Alpers - Huttenlocher syndrome – progressive neuronal degeneration with liver failure [1, 2].

The most common POLG gene variant in Alpers - Huttenlocher syndrome replaces the amino acid alanine with the amino acid threonine at position 467 (written as Ala467Thr or A467T). This variant blocks the ability of the alpha subunit to attach to the beta subunits and reduces pol γ's ability to synthesize DNA. Due to the high energy demand and the proportional need for mitochondria, the brain and liver are the classic organs that are affected by this disease. Decreased mitochondria in these organ systems lead to various symptoms, with seizures and liver failure being the most common. This pathology is a rapidly progressive disease that occurs early in life and invariably ends in a fatality [3, 4]. Herein, the study described a child with PolG gene mutation present with neuroregression and super - refractory seizures.

## 2. Case Description

A 10 - month - old female patient was admitted for status, persistent hepatitis, epilepsy and neuroregression possibly secondary to epilepsy. Before admitting to this hospital, the patient was admitted multiple times to several hospitals for the treatment of seizures. Apart from hospitalization for seizures, the patient did not have any familial, perinatal, or past history. Because of the patient's liver dysfunction and clinical history, the patient's AST and ALT were elevated upon admission, and reactive hepatitis was suspected. The initial laboratory finding suggested acute liver failure with AST and ALT levels of 386 IU/L and 176 IU/L, glutamyl transpeptidase of 201 IU/L, ammonia of 106 µg/dL, total and direct bilirubin of 7.1 mg/dL and 6.1 mg/Dl. From the test analysis of the patient initial blood gas, the lactate level was slightly elevated to 3.1 mmol/L.

However, the autoimmune conditions and endocrinological conditions were found to be normal. Meanwhile, during the course of hospitalization, the patient's mental status became altered with hyperammonemia, with GCS scores falling from 11/15 to 08/15. After initial stabilization, there was re - occurrence of seizures - mixed in presentation, which ranged from myoclonic seizures to generalized tonic - clonic seizures. The patient was started on IV Sodium Valproate at 30 mg/kg/day in two divided doses. After the initial response, the patient progressed to super refractory status. In addition to IV phenobarbital (7mg/kg/day in two divided doses), she received an infusion of IV midazolam and IV ketamine.

## 3. Management and Outcome

The bilateral periodic discharges of epileptiform were determined by Electroencephalogram (EEG**).** Thus, the multifocal diffusion restriction area in the left insula and deep gray matter area are shown in below Figure 1,

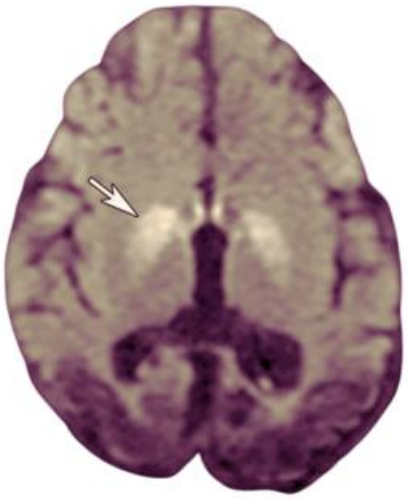

**Figure 1:** Brain Magnetic resonance imaging (MRI)

However, the patient's continuous myoclonic seizure and other symptoms were not improved with the use of a combination therapy of six antiepileptic drugs. WES revealed the heterozygous mutation of the *POLG* gene (p. Arg807His and p. Arg627Trp), confirming Alpers–Huttenlocher syndrome AHS, which is represented in below Table 1.

**Table 1:** Genetic report

| Gene | HGVS | Patient | Parent A |
|---|---|---|---|
| POLG | NP_002684.1: p. Arg807His | O, hetero | X |
| POLG | NP_002684.1: p. Arg627Trp | O, hetero | O, hetero |

A heterozygous mutation of the POLG gene (p. Arg807His and p. Arg627Trp) was noted in the Whole exam Sequencing. A pattern of EEG was evolved to generalize the slow spike and paroxysmal fast activities, particularly on the right posterior quadrant. Then, the mitochondrial cocktail therapy comprised the coenzyme Q10 (CoQ10), thiamine, and L - carnitine after the discontinuation of valproate. Further, the motion function has been enhanced, and the number of apnea events has been significantly reduced after the three weeks of this cocktail therapy. After the gastrostomy, the feeding problem was solved. However, the patient was not able to feed orally. At this stage, the patient was discharged.

## 4. Discussion with Review Of Literature

To find out the most comprehensive and updated recommendations for the prevention and treatment of tetanus, a targeted literature study was carried out. A case study of a child with PolG gene mutation is described above. Chronologically, the next presentation of biallelic POLG mutations is AHS, which was initially described as a triad of neurodevelopmental regression, intractable seizures, and liver failure [5, 6]. In RSE, neuroregression, and super - refractory seizures, mechanisms responsible for seizure termination failure and additional pathophysiologic processes are developed, leading to the persistence of SE. Refractory Status Epilepticus (RSE) and super - refractory status epilepticus (SRSE) are neurological emergencies with considerable mortality and morbidity. Therefore, Table 2 represents the most common pharmacological and non - pharmacological therapies for neuroregression, RSE, and Super - refractory seizures and their corresponding level of evidence.

**Table 2:** Pharmacological and non - pharmacological therapies

| Authors | Treatment of neuro - regression, RSE, and Super - refractory seizures | Mechanism of action | Dose | Adverse Events | Clinical Considerations | Level of evidence |
|---|---|---|---|---|---|---|
| Nicolas Gaspard *et al.* [7] | Ketamine | Noncompetitive NMDA glutamate receptor antagonist reduces neuronal excitability. | Infustion rate: 1–10 mg/kg/h | ICP elevation, hypertension, tachycardia | Ketamine is an enzyme inducer and inhibitor. | Class IV |
| Gretchen M. Brophy *et al.* [8] | Benzodiazepines Midazolam | Enhances the frequency of CI channel opening and allosteric modulation of GABA - A receptors | Infusion rate: 0.05– 2 mg/kg/h Loading dose: 0.2 mg/kg; administer | Hypotension, respiratory depression | Prolonged use may caus drug accumulation and tachyphylaxis. | Class IIA, Level B |
| Uri Kramer *et al.* [9] | IVIG | Alteration of IgG - specific receptors (FcgR) expression and function of complement - mediated cell damage | Over 3 to 5 days, 1 to 2g/kg was divided. | Transfusion - related to acute lung injury, renal dysfunction with concentrated solutions | With cryptogenic and autoimmune etiologies o RSE/SRS, immunomodulatory therapies may be considered in patients. | Class IV |
| D. Caputo *et al.* [10] | Prednisone | Inhibition of immunosuppressive action | 60 mg daily | Adrenal suppression, altered immune function, and glucose intolerance | - | Class IV |
| Tomohiro Yamazoe *et al.* [11] | Vagus nerve stimulation | Elevation of GABA levels in the brainstem | Surgical implantation | Surgical infection and Hoarseness | - | Class IV |
| Roberto H. Caraballo *et al.* [12] | Plasmapheresis | Immune factors and removal of circulating | 5 exchanges over 5 days | - | - | Class IV |
| Hae W. Shin *et al.* [13] | Electroconvulsive therapy | Development of seizure threshold and neurotransmission of GABA | Variable protocols | After treatment, seizures and non - convulsive SE may be induced. | Patients with cardiovascular condition require EEG monitoring | Class IV |
| Kristin Guilliams *et al.* [14] | Hypothermia | Decreased K+ conductance and Na+ exchange | 32–35◦C x 24h Rewarming ≤0.5 ◦C/ h | Coagulation disorders and electrolyte disturbances | Requires EEG monitorin | Class IV |
| Raquel Farias - Moeller *et al.* [15] | Ketogenic diet | Stabilization of neuronal membrane, decrease in glycolysis, and increase in | 4: 1 ratio (fat to carbohydrates and proteins) | Metabolic acidosis and hyperlipidemia | Contraindicated in pyruvate carboxylase deficiency | Class IV |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | polyunsaturated fatty acids | | | | |
| Michael Barberio *et al.* [16] | Pentobarbital | Inhibition of NMDA receptors, | Breakthrough SE: 5 mg/kg bolus | - | Drug accumulation with prolonged use | Class IV |

EEG might provide a diagnostic clue in patients having seizures. Although later EEG can be nonspecifically abnormal, children with AHS usually have Rhythmic High - Amplitude Delta With Superimposed polyspikes (RHADS) on EEG performed early in the disease course.

**Prevalence**

Approximately, 151, 000 people were affected by AHS. The commonest type is the infantile form with its onset usually before 2 years of age but it can range between 3 months to 8 years. It exhibits recurrent vomiting, failure to thrive, hypotonia, and developmental delay, typically following a short period of normal development. Age at onset is influenced, in part, by specific mutations within the polymerase - g gene, other genes, environmental factors like intercurrent viral infections, and certain medications like valproic acid. The predominance of reports with POLG - proven Alpers–Huttenlocher syndrome strongly suggests that the majority of patients presenting with seizures have predominant occipital lobe discharges. The most common *POLG* variants are shown in Table 3.

**Table 3:** *POLG* Pathogenic Variants

| Reference | Prevalence | POLG pathogenic variant |
|---|---|---|
| Hakonen et al. [17], Nurminen et al. [18] | 0.016% (likely European) | p. Gly848Ser |
| Craig et al. [19] | 0% (Italian) | p. Ala467Thr |
| Van Goethem et al. [20] | 0.6% (Belgian) | |
| Horvath et al. [21] | 0.17% - 0.69% (European) | |
| Craig et al. [19] | 0.69% (United Kingdom) | |
| Ferrari et al. [22], Scuderi et al. [23] | 1% (Italian) | p. [Thr251Ile; Pro587Leu] |
| Craig et al. [19] | 0% (Italian) | p. Trp748Ser |
| Hakonen et al. [24] | 0.8% (Finnish) | |

The most common POLG mutation named p. Ala467Thr also exhibits considerable phenotypic heterogeneity. The clinical, neuropathological, and mitochondrial genetic features in unrelated patients with homozygous p. Ala 467Thr mutations considered the mechanisms by which homozygous p. Ala467Thr mutations gave rise to such diverse phenotypes.

**Palliative care/hospice care strategies for children**

Involvement of palliative care/hospice care services is essential. Earlier, in the course of the disorder, rehabilitation medicine and GI and respiratory services are important for the care and treatment of GI tubes, ventilator support, and therapies. However, a global perspective of care to maximize quality of life should involve palliative care early in the course of the disorder. “Quality of life” varies between ethnic, religious, personal, and community standards, and is thus very subjective. Open discussion concerning the issues and feelings of the family needs to be addressed by the caring “team”, together with the family, and the palliative/hospice team [25]. Palliative epilepsy surgery can improve outcomes beyond what is captured with available surgical outcome measures, such as QOL in patients undergoing palliative hemispherectomy. Some palliative surgical procedures also have a diagnostic utility that may lead to more definitive surgery later [26]. With various mechanisms of supervision, the palliative care team signposts families to comprehensive bereavement care [27].

## 5. Conclusion

In conclusion, POLG mutations have a high prevalence and are hence a potentially important cause of severe intractable epilepsy. POLG - related disorders are considered an overlapping spectrum of diseases, presenting from early childhood to late adulthood. Since the molecular, clinical, and biochemical elucidation of Alpers - Huttenlocher syndrome more than a decade ago, an enlarging body of information has described the genetic and environmental elements of Alpers - Huttenlocher syndrome. Current clinical practice is challenged by the heterogeneous etiologies and multiple factors involved in the progression from SE to RSE and SRSE. Whenever possible, early and ongoing palliative care helps in building trust with the medical team and partnering with the family to support their goals.

## References

[1] Tarka S, Laure - Kamionowska M, Wierzba - Bobrowicz T, et al. POLG gene mutation. Clinico - neuropathological study. Folia Neuropathologica 2020; 58 (4): 386 - 92.
[2] Russo SN, Shah EG, Copeland WC, Koenig MK. A new pathogenic POLG variant. Molecular Genetics and Metabolism Reports.2022; 32: 1 - 6.
[3] POLG gene DNA polymerase gamma, catalytic subunit. Medline Plus 2023; 1 - 6. https: //medlineplus. gov/download/genetics/gene/polg. pdf
[4] Barzegar M, Mazyar Hashemilar. Alpers Disease: Report of Two Familial Cases. Pakistan Journal of Medical Science.2007; 23 (4): 643 - 646.
[5] Samanta D, Garrity L, Arya R. Refractory and super - refractory status epilepticus. Indian pediatrics.2020; 57: 239 - 53.
[6] Saneto RP, Cohen BH, Copeland WC, Naviaux RK. Alpers - huttenlocher syndrome. Pediatric Neurology.2013; 48 (3): 167 - 78.
[7] Gaspard N, Foreman B, Judd LM, Brenton JN, Nathan BR, McCoy BM, Al-Otaibi A, Kilbride R, Fernández IS, Mendoza L, Samuel S. Intravenous ketamine for the

treatment of refractory status epilepticus: a retrospective multicenter study. Epilepsia.2013; 54 (8): 1498 - 503.
[8] Brophy GM, Bell R, Claassen J, Alldredge B, Bleck TP, Glauser T, LaRoche SM, Riviello JJ, Shutter L, Sperling MR, Treiman DM. Guidelines for the evaluation and management of status epilepticus. Neurocritical care.2012; 17: 3 - 23.
[9] Kramer U, Chi CS, Lin KL, Specchio N, Sahin M, Olson H, Nabbout R, Kluger G, Lin JJ, van Baalen A. Febrile infection–related epilepsy syndrome (FIRES): pathogenesis, treatment, and outcome: a multicenter study on 77 children. Epilepsia.2011; 52 (11): 1956 - 65.
[10] Caputo D, Iorio R, Vigevano F, Fusco L. Febrile infection - related epilepsy syndrome (FIRES) with super - refractory status epilepticus revealing autoimmune encephalitis due to GABAAR antibodies. European Journal of Paediatric Neurology.2018; 22 (1): 182 - 5.
[11] Yamazoe T, Okanishi T, Yamamoto A, Yamada T, Nishimura M, Fujimoto A, Enoki H, Yokota T, Sato K, Yamamoto T. New - onset refractory status epilepticus treated with vagus nerve stimulation: a case report. Seizure.2017; 47: 1 - 4.
[12] Caraballo RH, Reyes G, Avaria MF, Buompadre MC, Gonzalez M, Fortini S, Cersosimo R. Febrile infection - related epilepsy syndrome: a study of 12 patients. Seizure.2013; 22 (7): 553 - 9.
[13] Shin HW, O'Donovan CA, Boggs JG, Grefe A, Harper A, Bell WL, McCall WV, Rosenquist P. Successful ECT treatment for medically refractory nonconvulsive status epilepticus in pediatric patient. Seizure.2011; 20 (5): 433 - 6.
[14] Guilliams K, Rosen M, Buttram S, Zempel J, Pineda J, Miller B, Shoykhet M. Hypothermia for pediatric refractory status epilepticus. Epilepsia.2013; 54 (9): 1586.
[15] Farias - Moeller R, Bartolini L, Pasupuleti A, Brittany Cines RD, Kao A, Carpenter JL. A practical approach to ketogenic diet in the pediatric intensive care unit for super - refractory status epilepticus. Neurocritical care.2017; 26: 267 - 72.
[16] Barberio M, Reiter PD, Kaufman J, Knupp K, Dobyns EL. Continuous infusion pentobarbital for refractory status epilepticus in children. Journal of Child Neurology.2012; 27 (6): 721 - 6.
[17] Hakonen AH, Davidzon G, Salemi R, Bindoff LA, Van Goethem G, DiMauro S, Thorburn DR, Suomalainen A. Abundance of the POLG disease mutations in Europe, Australia, New Zealand, and the United States explained by single ancient European founders. European journal of human genetics.2007; 15 (7): 779 - 83.
[18] Nurminen A, Farnum GA, Kaguni LS. Pathogenicity in POLG syndromes: DNA polymerase gamma pathogenicity prediction server and database. BBA clinical.2017; 7: 147 - 56.
[19] Craig K, Ferrari G, Tiangyou W, Hudson G, Gellera C, Zeviani M, Chinnery PF. The A467T and W748S POLG substitutions are a rare cause of adult - onset ataxia in Europe. Brain.2007; 130 (4): E69.
[20] Van Goethem G, Dermaut B, Löfgren A, Martin JJ, Van Broeckhoven C. Mutation of POLG is associated with progressive external ophthalmoplegia characterized by mtDNA deletions. Nature genetics.2001; 28 (3): 211 - 2.
[21] Horvath R, Hudson G, Ferrari G, Fütterer N, Ahola S, Lamantea E, Prokisch H, Lochmüller H, McFarland R, Ramesh V, Klopstock T. Phenotypic spectrum associated with mutations of the mitochondrial polymerase γ gene. Brain.2006; 129 (7): 1674 - 84.
[22] Ferrari G, Lamantea E, Donati A, Filosto M, Briem E, Carrara F, Parini R, Simonati A, Santer R, Zeviani M. Infantile hepatocerebral syndromes associated with mutations in the mitochondrial DNA polymerase - γA. Brain.2005; 128 (4): 723 - 31.
[23] Scuderi C, Borgione E, Castello F, Giudice ML, Santa Paola S, Giambirtone M, Di Blasi FD, Elia M, Amato C, Città S, Gagliano C. The in cis T251I and P587L POLG1 base changes: description of a new family and literature review. Neuromuscular Disorders.2015; 25 (4): 333 - 9.
[24] Hakonen AH, Heiskanen S, Juvonen V, Lappalainen I, Luoma PT, Rantamäki M, Van Goethem G, Löfgren A, Hackman P, Paetau A, Kaakkola S. Mitochondrial DNA polymerase W748S mutation: a common cause of autosomal recessive ataxia with ancient European origin. The American Journal of Human Genetics.2005; 77 (3): 430 - 41.
[25] Radbruch L, De Lima L, Knaul F, Wenk R, Ali Z, Bhatnaghar S, Blanchard C, Bruera E, Buitrago R, Burla C, Callaway M. Redefining palliative care—a new consensus - based definition. Journal of pain and symptom management.2020; 60 (4): 754 - 64.
[26] Jeno M, Zimmerman MB, Shandley S, Wong - Kisiel L, Singh RK, McNamara N, Romanowski EF, Grinspan ZM, Eschbach K, Alexander A, McGoldrick P. Pediatric palliative epilepsy surgery: a report from the Pediatric Epilepsy Research Consortium (PERC) Surgery Database. Pediatric Neurology.2024; 157: 70 - 8.
[27] Tumienė B, Del Toro Riera M, Grikiniene J, Samaitiene - Aleknienė R, Praninskienė R, Monavari AA, Sykut - Cegielska J. Multidisciplinary care of patients with inherited metabolic diseases and epilepsy: Current perspectives. Journal of Multidisciplinary Healthcare.2022; 25: 553 - 66.