

# The Syndrome of Mitochondrial Spinocerebellar Ataxia and Epilepsy caused by POLG mutations



## Charalampos Tzoulis,

is a resident in Neurology at Haukeland University Hospital and PhD student at the University of Bergen, Norway. He has a special interest in movement disorders, neurogenetics and in particular mitochondrial medicine.



## Laurence A Bindoff

received his medical training in Newcastle, UK. He is now Professor of Neurology, University of Bergen and a consultant at Haukeland University Hospital, Norway. His research interests include mitochondrial disease and neurogenetics, particularly inherited muscle disease and ataxias.

### Correspondence to:

Professor Laurence Bindoff,  
Department of Neurology,  
Haukeland University Hospital,  
5021 Bergen, Norway;  
Tel. +47 55975096  
Fax. +47 55975165  
Email. laurence.bindoff@  
nevro.uib.no

### Acknowledgments

The authors express their gratitude to Professor Bernt Engelsen for providing the EEG data.

## Introduction

DNA-polymerase  $\gamma$  (pol  $\gamma$ ) is the enzyme that replicates and repairs the mitochondrial DNA (mtDNA), the small, maternally inherited genome found inside mitochondria that encodes 13 subunits of the respiratory chain. Pol  $\gamma$  is a heterotrimer composed of one catalytic subunit (pol  $\gamma$ A), and two accessory subunits (pol  $\gamma$ B). Pol  $\gamma$ A comprises a polymerase (replicating) domain and an exonuclease (proof-reading) domain, separated by a large linker region. The linker domain is the binding site of the accessory subunits, which enhance substrate affinity and processivity of the catalytic subunit.<sup>1</sup>

Over 120 pathogenic mutations have been described in the gene encoding the catalytic pol  $\gamma$  subunit (POLG) and these are associated with a wide spectrum of neurological syndromes ranging from adult onset myopathies to severe infantile encephalopathies. Specific disorders include autosomal recessive and dominant progressive external ophthalmoplegia (PEO), Alper's syndrome, parkinsonism, and the syndrome of mitochondrial spinocerebellar ataxia and epilepsy (MSCAE).<sup>1,2</sup> This review will focus on MSCAE.

## Pathophysiology

MSCAE is inherited as a recessive disorder most commonly associated with the mutations c.1399G>A, p.A467T or/and c.2243G>C, p.W748S in the linker region of pol  $\gamma$ A. The A467T interferes with the catalytic subunit's intrinsic polymerase activity and binding to the accessory subunit, resulting in severely reduced efficiency of mtDNA synthesis.<sup>3</sup> The pathomechanism of the W748S mutation has yet to be revealed, but it is possible that this too has a similar effect. Irrespective of the mechanism, these mutations ultimately lead to secondary damage of the mtDNA in the form of point mutations, multiple deletions and quantitative depletion<sup>4,5</sup> making pol  $\gamma$  induced disease a paradigm for mtDNA disease.

## Epidemiology

The A467T and W748S were each introduced in the European populations by an ancient common founder. The reported carrier frequency for the A467T is 1% in Norway, 0.69% in the UK, 0.6% in Belgium, 0.5% in Sweden, and <0.2% in Finland. The carrier frequency of the W748S has been estimated to be 1% in Norway and 0.8% in Finland. Both sexes are equally affected by the disease.<sup>5,8</sup>

## History and clinical features

The age of onset varies between 1.5 and 45 years, with most patients presenting in their teens at a mean age of 19 years. The most common presenting features in order of decreasing frequency are progressive gait unsteadiness, epileptic seizures, and headache, often with migraine features. Ataxia is universally present and results from a combined cerebellar and peripheral sensory dysfunction, producing a clinical picture with nystagmus, scanning dysarthria, midline and appendicular ataxia. The vast majority of patients (98%) also develop features of a peripheral neuropathy with diminished tendon reflexes and glove and stocking sensory impairment. Ptosis and PEO develop late, at a mean age of 33 years. Progressive cognitive decline is common. A few patients develop gastrointestinal dysmotility with chronic abdominal pain, diarrhoea or pseudoobstruction (Table 1). Epilepsy affects the majority of patients (63%) and, although it usually manifests either at disease onset or shortly after, it may start as late as several decades after the onset of the ataxia. A variety of clinical seizure types are seen, including partial simple or complex visual and motor seizures and generalised tonic-clonic (GTC) seizures. Commonest are simple partial motor seizures involving an upper limb and the head/neck region and these often evolve into epilepsia partialis continua (EPC), which may last for up to several months. Visual seizures are common and patients usually describe flashing coloured lights in one or both visual hemifields. Primary and secondary GTC

**Table 1: Clinical features of MSCAE.<sup>1</sup>**

Liver failure was associated with the use of sodium-valproate in all but one patient.<sup>19,12</sup>

Sign/symptom	Present/evaluated	Percentage
Ataxia	68/68	100
Peripheral neuropathy	62/63	98
Headache	29/35	83
Epilepsy	43/68	63
PEO	35/68	51
Myoclonus	35/68	51
Liver failure	15/50	30 <sup>1</sup>
Gastrointestinal	6/68	9

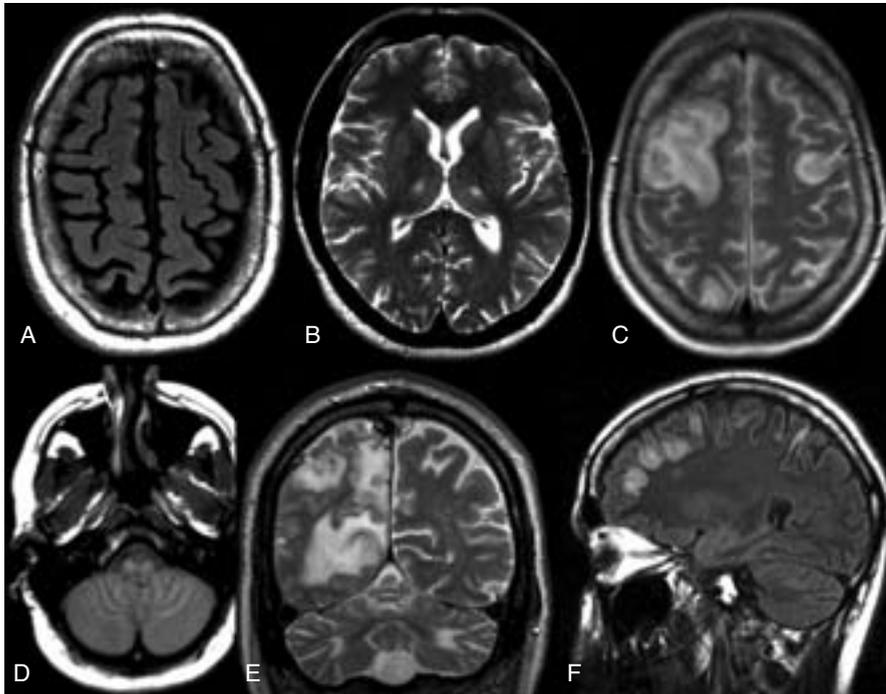


Figure 1: Common MRI findings in MSCAE. A: axial T2 FLAIR image showing cerebral atrophy. B: axial T2 image showing bilateral thalamic lesions. C: axial T2 image showing cortical lesions in both frontal lobes and the right parietooccipital area. D: axial proton weighted image showing bilateral olivary lesions. E: coronal T2 image showing a right occipital lesion and bilateral white matter hyperintensity in the cerebellum. F: sagittal T2 FLAIR image showing widespread frontal cortical lesions.

seizures are frequent as is GTC status epilepticus [914, unpublished data]. Patients with epilepsy experience episodes of clinical exacerbation with severe seizures and rapidly progressing encephalopathy (EE episodes). These start either acutely with epileptic seizures or insidiously with gradual mental and personality changes that may precede the onset of seizures by days to weeks. EE episodes may last from a few days up to several months (usually two to three months) and are clinically characterised by progressive encephalopathy, disturbed consciousness ranging from confusion to deep coma, and severe epilepsy with multiple daily seizures and frequent partial or generalised status epilepticus. EE episodes are associated with significant morbidity and mortality. In a series of 30 episodes in 26 patients, 14 proved fatal [unpublished data]. Survivors suffered severe and permanent disability as a result of accelerated decline of motor and cognitive skills and/or cortical visual loss. Liver involvement may occur ranging from asymptomatic biochemical findings to fulminate and fatal hepatic failure. Liver failure in MSCAE is usually, but not always, precipitated by exposure to the anti-epileptic drug sodium-valproate [1,914, unpublished data].

**Course and survival**

The course of MSCAE is invariably progressive. The rate of progression and mortality are highly variable and linked to two factors: genotype and epilepsy. Survival is worse in patients carrying the A467T and W748S mutations (compound heterozygous) and best in A467T homozygotes. The presence of epilepsy is the most important clinical prognostic factor as it is associated with significant morbidity and mortality as a result of EE episodes. In a study of 35 patients by the authors, mortality was 77% in patients with epilepsy (26 patients) with a median survival of 20 years, while no deaths occurred in the group without epilepsy (nine patients) [1, unpublished data].

**Investigations**

*Neuroimaging*

Magnetic resonance imaging (MRI) showing high T2 signal abnormalities in the thalamus, cerebellar cortex or white matter, and inferior olivary nuclei is highly suggestive of MSCAE (Figure 1, Table 2). During EE episodes, MRI may reveal hyperintense cortical lesions involving the occipital, frontal or parietal regions. These acute lesions evolve dynamically and may expand or regress reflecting the clinical course and severity of the episode (Figure 1C, E, F, Table 2). If performed early enough, diffusion imaging shows initially restricted cortical diffusion, which gradually increases, consistent with a transition from cytotoxic to extracellular cortical oedema. Progressive cerebellar and cerebral atrophy is commonly seen (Figure 1A). Magnetic resonance spectroscopy of fresh cortical lesions shows decreased N-acetyl aspartate spectra and high lactate levels [Unpublished data]

Table 2: When should the clinician suspect MSCAE? Common clinical features and associated MRI findings.	
Clinical features	MRI
Onset in teens	Cerebellar cortical atrophy, dentate atrophy, high T2 signal focal lesions in thalamus, cerebellar white matter and inferior olivary nuclei
Progressive spinocerebellar ataxia and sensory neuropathy	
Myoclonus may be present	
Late (ca 33 years) development of PEO	
Epilepsy: EPC in one side of the body, visual symptoms, GTC, SE	Acute, focal, T2 hyperintense cortical lesions, mostly occipital, but also frontal or parietal. Lesions evolve mirroring EE episode severity. Associated with bad prognosis
Episodes with epilepsy and progressive encephalopathy	



Figure 2: EEG findings in MSCAE. A: ictal EEG showing general slowing and epileptiform activity in the left occipital area (O1). During the recording the patient had a simple partial visual seizure with positive visual phenomena in the right visual hemifield. B: axial FLAIR-T2 MRI from the same period showing an old, retracted lesion in the patient's left occipital cortex.

## ABBREVIATED PRESCRIBING INFORMATION

Consult Summary of Product Characteristics before prescribing. **Uses:** The treatment of disabling motor fluctuations ("on-off" phenomena) in patients with Parkinson's disease which persist despite individually titrated treatment with levodopa (with a peripheral decarboxylase inhibitor) and/or other dopamine agonists. **Dosage and Administration:** Apomorphine hydrochloride is administered subcutaneously either as an intermittent bolus injection or by continuous subcutaneous infusion. Its rapid onset (5-10 mins) and duration of action (about 1 hour) may prevent an "off" episode which is refractory to other treatments. Hospital admission under appropriate specialist supervision is necessary during patient selection and when establishing a patient's therapeutic regime. Please refer to the Summary of Product Characteristics for full details before initiating therapy. Treatment with domperidone (typical dosage 20mg three times a day) before and during apomorphine HCl therapy is essential. The optimal dosage of apomorphine HCl has to be determined on an individual patient basis; individual bolus injections should not exceed 10mg and the total daily dose should not exceed 100mg. **Contraindications:** Children and adolescents (up to 18 years of age). Known sensitivity to apomorphine or any of its ingredients of the product. Respiratory depression, dementia, psychotic disease or hepatic insufficiency. Intermittent apomorphine HCl treatment is not suitable for patients who have an "on" response to levodopa which is marred by severe dyskinesia or dystonia. **Pregnancy and lactation:** Caution should be exercised if prescribing apomorphine to pregnant women and women of childbearing age. Breast-feeding should be avoided during apomorphine HCl therapy. **Interactions:** Patients should be monitored for potential interactions during initial stages of apomorphine therapy. Particular caution should be given when apomorphine is used with other medications that have a narrow therapeutic window. It should be noted that there is potential for interaction with neuroleptic and antihypertensive agents. **Precautions:** Use with caution in patients with renal, pulmonary or cardiovascular disease, or who are prone to nausea or vomiting. Extra caution is recommended during initiation of therapy in elderly and/or debilitated patients. Since apomorphine may produce hypotension, care should be exercised in patients with cardiac disease or who are taking vasoactive drugs, particularly when pre-existing postural hypotension is present. Neuropsychiatric disturbances are common in Parkinsonian patients. APO-go should be used with special caution in these patients. Apomorphine has been associated with somnolence and other dopamine agonists can be associated with sudden sleep onset episodes, particularly in patients with Parkinson's disease. Patients must be informed of this and advised to exercise caution whilst driving or operating machines during treatment with apomorphine. Haematology tests should be undertaken at regular intervals as with levodopa with given concomitantly with apomorphine. Pathological gambling, increased libido and hypersexuality have been reported in patients treated with dopamine agonists, including apomorphine. **Side Effects:** Local induration and nodules (usually asymptomatic) often develop at subcutaneous site of injection leading to areas of erythema, tenderness, induration and (rarely) ulceration. Pruritus may occur at the site of injection. Drug-induced dyskinesias during "on" periods can be severe, and in a few patients may result in cessation of therapy. Postural hypotension is seen infrequently and is usually intransient. Transient sedation following each dose of apomorphine may occur at the start of therapy, but this usually resolves after a few weeks of treatment. Nausea and vomiting may occur, particularly when APO-go treatment is initiated, usually as a result of the omission of domperidone. Neuropsychiatric disturbances (including transient mild confusion and visual hallucinations) have occurred during apomorphine therapy and neuropsychiatric disturbances may be exacerbated by apomorphine. Positive Coombs' tests and haemolytic anaemia have been reported in patients receiving apomorphine and levodopa. Local and generalised rashes have been reported. Eosinophilia has occurred in only a few patients during treatment with apomorphine HCl. Patients treated with dopamine agonists, including apomorphine, have been reported as exhibiting signs of pathological gambling, increased libido and hypersexuality (especially at high doses). Apomorphine is associated with somnolence. Breathing difficulties have been reported. *Prescribers should consult the Summary of Product Characteristics in relation to other side effects.* **Presentation and Basic NHS Cost:** Apo-go ampoules contain apomorphine hydrochloride 10mg/ml, as follows: 20mg in 2ml – basic NHS cost £37.96 per carton of 5 ampoules. 50mg in 5ml – basic NHS cost £73.11 per carton of 5 ampoules. APO-go pens (disposable multiple dosage injector system) contain apomorphine hydrochloride 10mg/ml, as follows: 30mg in 3ml – basic NHS cost £123.91 per carton of 5 pens. APO-go Pre-filled syringes contain apomorphine hydrochloride 5mg/ml, as follows: 50mg in 10ml – basic NHS cost £73.11 per carton of 5 syringes. **Marketing Authorisation Numbers:** APO-go Ampoules: PL04483/0064. APO-go Pens: PL04483/0065. APO-go Pre filled syringes: PL05928/0025. **Legal Category:** POM. **Date of last revision:** October 2008. For further information please contact: Britannia Pharmaceuticals, Park View House, 65 London Road, Newbury, Berkshire, RG14 1JN, UK.

**References:** 1. Pietz K, Hagell P, Odin P. 1998. Subcutaneous apomorphine in late stage Parkinson's disease: a long term follow up. *J Neurol Neurosurg Psychiatry*. 65:709-716. 2. Lees A, Turner K, Deleu D. 2002. Apomorphine for Parkinson's Disease. *Practical Neurology*, 2:280-287. 3. Deleu D, Hanssens Y, Norhway M G, 2004. Subcutaneous Apomorphine: An Evidence-Based Review of its Use in Parkinson's Disease. *Drugs Aging*, 21(11) 687-709. 4. Ellis C, Lemmens G et al 1997. Use of Apomorphine in Parkinsonian Patients with Neuropsychiatric Complications to Oral Treatment. *Parkinsonism & Related Disorders*, 3(2):103-107.

**Adverse events should be reported.**  
Reporting forms and information can be found  
at [www.yellowcard.gov.uk](http://www.yellowcard.gov.uk).  
Adverse events should also be reported to  
Medical Information on 0870 851 0207 or  
[drugsafety@britannia-pharm.com](mailto:drugsafety@britannia-pharm.com)

**Neurophysiology**

Electroencephalography in patients with epilepsy shows a primary occipital focus with generalisation during status epilepticus. Extra-occipital epileptogenic foci are also seen and these often correlate with extra-occipital frontal or parietal cortical lesions. Nerve conduction studies show a predominantly axonal sensory peripheral neuropathy (Figure 2).<sup>1,14</sup>

**Biochemistry and histology**

Elevation of lactate in blood or CSF is an inconsistent feature and blood chemistry is otherwise unremarkable with the exception of liver function tests in patients with liver involvement. Muscle histology may reveal cytochrome oxidase negative fibres, but is often normal, especially when taken early during the course of the disease.<sup>1</sup>

**Therapy**

No disease modifying treatment exists for MSCAE. The cornerstone of management is antiepileptic treatment. Achieving satisfactory seizure control in MSCAE is, however, a challenging task. Our experience suggests that monotherapy can be effective initially, but high dose polytherapy regimes are usually needed, particularly once the patient has an EE episode. No specific drug combination has shown an advantage and the choice of individual agents should be individualised for each patient and based on clinical response. Sodium-valproate is strongly contraindicated due to a significant risk for development of severe liver failure. Status epilepticus is often refractory to conventional treatment protocols and we have a low threshold for initiating generalised anaesthesia.<sup>1,11,14</sup> ♦

## REFERENCES

- Tzoulis C, Engelsen BA, Telstad W, Aasly J, Zeviani M, Winterthun S, Ferrari G, Aarseth JH, Bindoff LA. *The spectrum of clinical disease caused by the A467T and W748S POLG mutations: a study of 26 cases.* *Brain*. 2006 Jul; 129(Pt 7):1685-92. Epub 2006 Apr 25.
- NIEHS. Mitochondrial DNA replication group, Human DNA Polymerase Gamma Mutation Database: <http://tools.niehs.nih.gov/polg/>
- Chan SS, Longley MJ, Copeland WC. *The common A467T mutation in the human mitochondrial DNA polymerase (POLG) compromises catalytic efficiency and interaction with the accessory subunit.* *J Biol Chem*. 2005 Sep 9;280(36):31341-6. Epub 2005 Jul 16.
- Zsurka G, Baron M, Stewart JD, Kornblum C, Bös M, Sassen R, Taylor RW, Elger CE, Chinnery PF, Kunz WS. *Clonally expanded mitochondrial DNA mutations in epileptic individuals with mutated DNA polymerase gamma.* *J Neuropathol Exp Neurol*. 2008 Sep;67(9):857-66.
- Winterthun S, Ferrari G, He L, Taylor RW, Zeviani M, Turnbull DM, Engelsen BA, Moen G, Bindoff LA. *Autosomal recessive mitochondrial ataxic syndrome due to mitochondrial polymerase gamma mutations.* *Neurology*. 2005 Apr 12;64(7):1204-8.
- Hakonen AH, Davidzon G, Salemi R, Bindoff LA, Van Goethem G, Dimairo 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.* *Eur J Hum Genet*. 2007 Jul;15(7):779-83. Epub 2007 Apr 11.
- Craig K, Ferrari G, Tiangyow 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*. 2006 Jul; 129(Pt 7):1685-92.
- Van Goethem G, Martin JJ, Dermaut B, Löfgren A, Wibail A, Ververken D, Tack P, Dehaene I, Van Zandijck M, Moonen M, Ceuterick C, De Jonghe P, Van Broeckhoven C. *Recessive POLG mutations presenting with sensory and ataxic neuropathy in compound heterozygote patients with progressive external ophthalmoplegia.* *Neuromuscul Disord*. 2003 Feb;13(2):133-42.
- Kollberg G, Moslemi AR, Darin N, Nennesmo I, Bjarnadottir I, Uvebrant P, Holme E, Melberg A, Tulinius M, Oldfors A. *POLG1 mutations associated with progressive encephalopathy in childhood.* *J Neuropathol Exp Neurol*. 2006 Aug;65(8):758-68.
- Hakonen AH, Heiskanen S, Juvonen V, Lappalainen I, Luoma PT, Rantamäki M, Goethem GV, Löfgren A, Hackman P, Paetau A, Kaakkola S, Majamaa K, Varilo T, Udd B, Kaariainen H, Bindoff LA, Suomalainen A. *Mitochondrial DNA polymerase W748S mutation: a common cause of autosomal recessive ataxia with ancient European origin.* *Am J Hum Genet*. 2005 Sep;77(3):430-41. Epub 2005 Jul 27.
- Van Goethem G, Luoma P, Rantamäki M, Al Memar A, Kaakkola S, Hackman P, Krahe R, Löfgren A, Martin JJ, De Jonghe P, Suomalainen A, Udd B, Van Broeckhoven C. *POLG mutations in neurodegenerative disorders with ataxia but no muscle involvement.* *Neurology*. 2004 Oct 12;63(7):1251-7.
- Wong LJ, Naviaux RK, Brunetti-Pierri N, Zhang Q, Schmitt ES, Truong C, Milone M, Cohen BH, Wical B, Ganesh J, Basinger AA, Burton BK, Swoboda K, Gilbert DL, Vanderver A, Saneto RP, Maranda B, Arnold G, Abdenur JE, Waters PJ, Copeland WC. *Molecular and clinical genetics of mitochondrial diseases due to POLG mutations.* *Hum Mutat*. 2008 Jun 10;29(6):E150-E172. [Epub ahead of print]
- 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-gammaA.* *Brain*. 2005 Apr; 128(Pt 4):723-31. Epub 2005 Feb 2.
- Engelsen BA, Tzoulis C, Karlsen B, Lillebø A, Laegreid LM, Aasly J, Zeviani M, Bindoff LA. *POLG1 mutations cause a syndromic epilepsy with occipital lobe predilection.* *Brain*. 2008 Mar; 131(Pt 3):818-28. Epub 2008 Jan 30.