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

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Introduction

DNA-polymerase γ (pol γ) 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 γ is a heterotrimer composed of one catalytic subunit (pol γA), and two accessory subunits (pol γB). Pol γA 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.[1]

Over 120 pathogenic mutations have been described in the gene encoding the catalytic pol γ 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).[1,2] 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 γA. 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.[3] 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[4,5] making pol γ 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.[5,8]

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.[1]
Liver failure was associated with the use of sodium-valproate in all but one patient.[9,12]

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[1]
Gastrointestinal	6/68	9

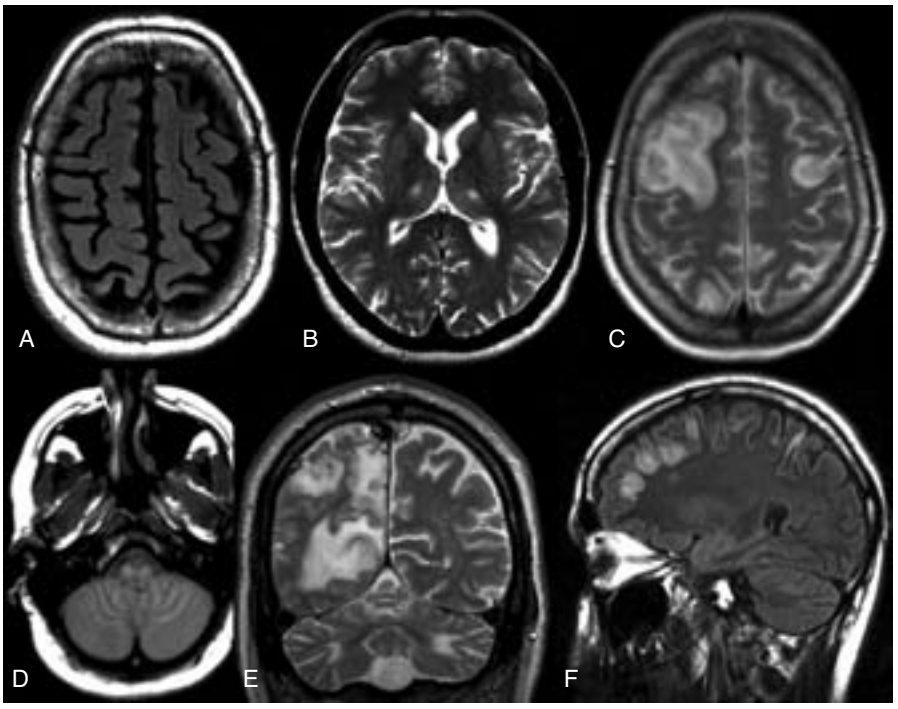

Figure 1: Common MRI findings in MSCAE. A: axial T2 FLAIR image showing cerebral atrophy. B: axial T2 image showing bilateral thalamic lesions. C: axial T2 image showing cortical lesions in both frontal lobes and the right parietooccipital area. D: axial proton weighted image showing bilateral olivary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

Table 2: When should the clinician suspect MSCAE? Common clinical features and associated MRI fndings.

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	

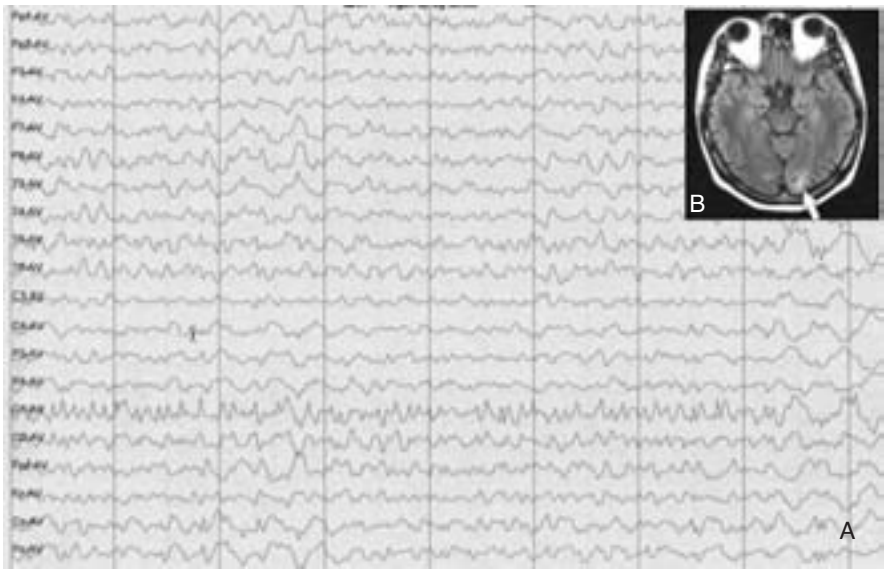

Figure 2: EEG findings in MSCAE. A: ictal EEG showing general slowing and epileptiform activity in the left occipital area (O1). During the recording the patient had a simple partial visual seizure with positive visual phenomena in the right visual hemifield. B: axial FLAIR-T2 MRI from the same period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

seizures are frequent as is GTC status epilepticus [9 14, 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, 9 14, 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'

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).[1,14]

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.[1]

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.[1,11,14] ◆

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