

# Regression of stroke-like lesions in MELAS-syndrome after seizure control

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**ABSTRACT** – There are some indications that seizure activity promotes the development of stroke-like episodes, or vice versa, in patients with mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS) syndrome or other syndromic mitochondrial disorders. A 41-year-old Caucasian female with MELAS syndrome, presenting with short stature, microcytic anaemia, increased blood-sedimentation rate, myopathy, hyper-gammaglobulinaemia, an iron-metabolism defect, migraine-like headaches, and stroke-like episodes, developed complex partial and generalised seizures at age 32 years. Valproic acid was ineffective but after switching to lamotrigine and lorazepam, she became seizure-free for five years and stroke-like episodes did not recur. Cerebral MRI initially showed enhanced gyral thickening and a non-enhanced T2-hyperintensity over the left parieto-temporo-occipital white matter and cortex and enhanced caudate heads. After two years without seizures, the non-enhanced hyperintense parieto-temporo-occipital lesion had disappeared, being attributed to consequent seizure control. The caudate heads, however, remained hyperintense throughout the observational period. This case indicates that adequate seizure control in a patient with MELAS syndrome may prevent the recurrence of stroke-like episodes and may result in the disappearance of stroke-like lesions on MRI.

**Key words:** epilepsy, seizures, mitochondrial disorders, metabolic disease, antiepileptics, MELAS

Stroke-like episodes (SLEs) and concomitant stroke-like lesions (SLLs) on MRI are dominant features in patients with mitochondrial encephalopathy, lactacidosis and stroke-like episodes (MELAS) syndrome (Testai and Gorelick, 2010). Additionally, SLEs occur in a number of other syndromic and non-syndromic mitochondrial disorders (Finsterer, 2007). Although there is no consensus on the treatment of SLEs, there is some evidence that antioxidants, cofactors, L-arginine, steroids, glycerol, edaravone, or

dichloroacetic acid may have a beneficial effect. There are also some indications that seizure activity promotes the development of SLEs (Iizuka *et al.*, 2002) and that effective seizure control may prevent the development and recurrence of SLEs and even resolve stroke-like lesions, as in the following case.

## Case report

The patient was a 41-year-old Caucasian female, height 160 cm,

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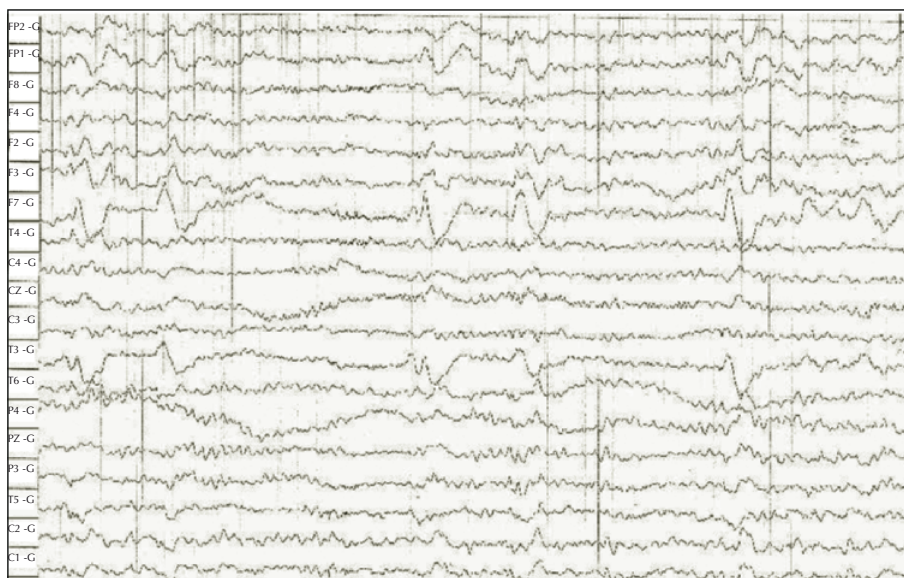
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weight 55 kg, with a normal developmental history. She was diagnosed at 32 years with MELAS syndrome based on: the family history, clinical manifestations such as growth retardation, short stature, increased blood-sedimentation rate, microcytic anaemia, migraine-like headaches, SLEs, epilepsy, myopathy, hyper-gammaglobulinaemia, an iron-metabolism defect, and increased lactate-peaks on cerebral H-MR-spectroscopy. Muscle biopsy at age 32 showed fibre atrophy and some ragged-red muscles fibres. Screening for tRNA(Leu), tRNA(Ser), and tRNA(Lys) mtDNA gene mutations by single-strand conformational polymorphism (SSCP), for the m.3243A>G and the m.8344A>G mutations by restriction fragment length polymorphism (RFLP), and further sequencing of the tRNA(Seer) gene, failed to confirm the presence of a pathogenic mutation, thus MELAS syndrome was assumed to have been caused by other mtDNA or nDNA mutations. Her sister, who had a history of migraine, aseptic pleocytosis, encephalopathy, slight anaemia, and bilateral temporal calcifications and had died from cerebral oedema and intractable epileptic seizures at age 19, was assumed to have also suffered from MELAS syndrome. Her mother had died from colon cancer.

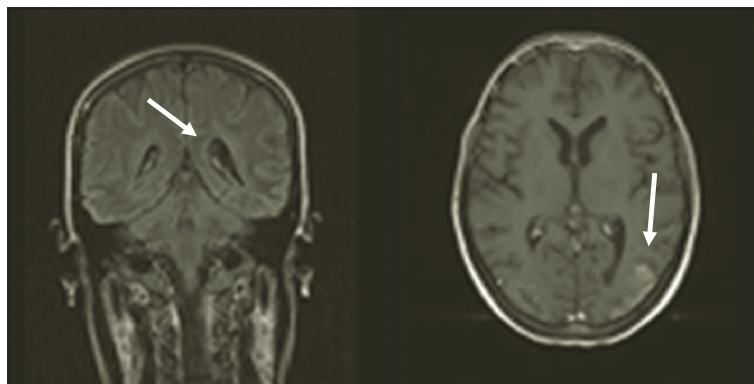
At 32 years old, the index patient experienced a first tonic-clonic seizure with aura. The EEG showed focal slowing and sporadic sharp waves and spikes over the left and right fronto-temporal projections with left-sided predominance (*figure 1*). The MRI showed slight focal atrophy (*figure 2*), bilateral hyperintense lesions in the temporo-occipital region with gyral thickening, and enhancement of the temporo-occipital cortex and the caudate heads. Valproic acid treatment (600 mg/d) was started. One month later, she experienced a similar aura without cloni. One year after the first tonic-clonic seizure

she presented with an episode of hemianopsia to the right and simple and complex optic hallucinations. The EEG showed high-amplitude spikes, sharp waves, polyspikes, and spike-wave complexes over the left occipital projections with paroxysmal tendency to generalise. Valproic acid treatment was increased. Six months later, a similar episode occurred. The MRI showed, in addition to the previous one, a more pronounced thickening of the gyri in the temporo-occipital region (*figure 2*). Since valproic acid is mitochondrion-toxic, the antiepileptic drug (AED) treatment was changed to lamotrigine (slowly increasing to 400 mg/d). At age 35 years, she experienced the next stroke-like episode manifesting as a visual field defect, with visual hallucinations, kakosmia, disturbed taste, headache, and speech disturbance. The MRI disclosed a left-sided occipito-temporal hyperintense lesion with cortical enhancement and enhanced caudate heads. The EEG showed spikes and sharp waves over the left temporal projections shortly after onset of hyperventilation. Lorazepam (1 mg/d) was added. One month later, a similar episode occurred. A further SLE with vertigo, dysosmia, and seizures occurred at age 36 years. Since then, no further SLE occurred except for a tonic-clonic seizures at 40 years, triggered by a bronchial infection. After the last seizure, lamotrigine was increased to 600 mg/d but levetiracetam was refused by the patient because of tiredness.

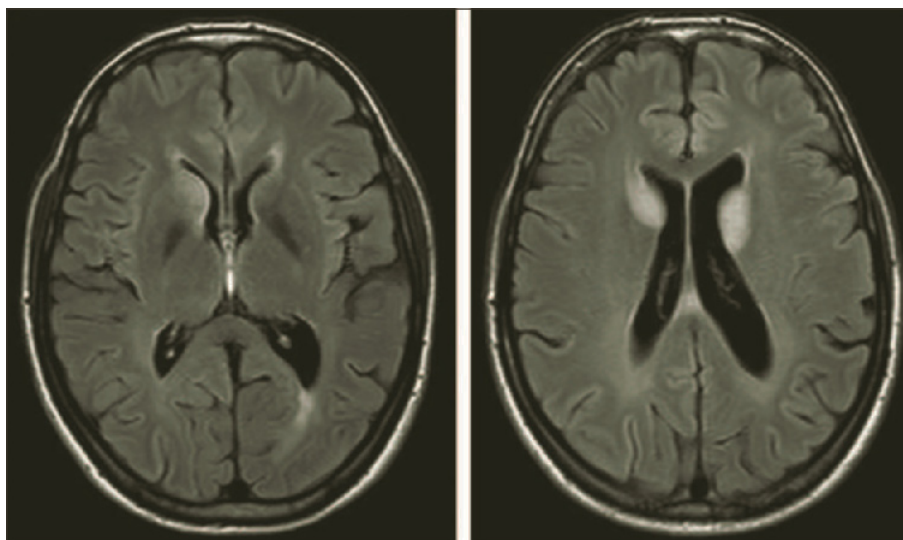
After switching to lamotrigine and lorazepam, she became seizure-free at age 36 years. Repeated cerebral MRI studies between age 32 and 37 years showed enhanced, gyral thickening and initially a non-enhanced T2-hyperintensity over the left and right parieto-temporo-occipital white matter and cortex and enhanced lesions over the caudate heads (*figure 3*). At the age of 35 years, the right-sided



**Figure 1.** EEG recordings showing intermittent sharp waves over the left fronto-temporal projections.



**Figure 2.** Coronal TIRM-sequence, showing slight inner atrophy of the left temporo-parietal region at age 33 years (left). An axial T1-sequence of the same investigation shows gyral enhancement in the left temporo-occipital region (right).



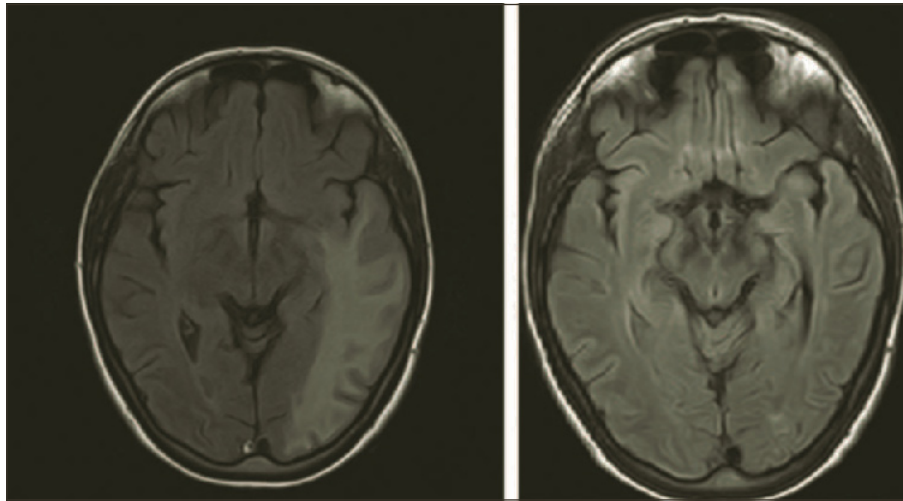
**Figure 3.** TIRM-sequences, showing normal basal ganglia (left) and hyperintense heads of the caudate nucleus (right).

parieto-temporo-occipital white matter lesion had disappeared (*figure 4*). After a two-year seizure-free period, at the age of 38 years, the MRI surprisingly showed further improvement with complete disappearance of the left occipito-temporo-parietal lesion without any volume loss, but with the remaining caudate lesions (*figure 4*). L-arginine, which has been also shown to have a beneficial effect on SLLs in single cases (Kubota *et al.*, 2004), was not administered. Screening for mutated genes other than the tRNA genes, such as *ND1*, *ND4*, *ND5*, *COX2*, *COX3*, or *POLG1*, which may also cause MELAS (Deschauer *et al.*, 2007), was not performed due to a lack of funding.

## Discussion

In this case study of MELAS syndrome, it remains inconclusive whether regression of the stroke-like lesions (SLLs)

occurred spontaneously or due to the AED treatment. However, previous studies have shown that effective, long-term seizure control with non-mitochondrion toxic AEDs in MELAS syndrome may not only prevent the development of new SLLs but may also result in their disappearance, suggesting a pathogenetic role for epileptic activity in the development, maintenance, and recurrence of SLLs (Kubota *et al.*, 2004). According to this hypothesis, epileptic activity results in metabolic dysfunction of neurons with consecutive development of typical focal lesions seen on MRI in MELAS patients (Iizuka *et al.*, 2003; Iizuka *et al.*, 2002). On MRI, SLLs present with variable appearance, particularly in the acute stage. Most commonly, a SLL represents a vasogenic oedema, which shows up on MRI as hyperintensity on T2 and an elevated apparent diffusion coefficient (ADC) (Ohshita *et al.*, 2000; Ito *et al.*, 2008). The hypersignal on DWI, in the case of



**Figure 4.** Axial T2-weighted MRI at 35 years old in the described patient showing a left temporo-parieto-occipital hyperintensity, being interpreted as a stroke-like lesion (left). This lesion had disappeared within one year after having become seizure-free at 37 years (right).

elevation of ADC, corresponds to a T2 shine-through effect. SLLs remain hyperintense on T2-weighted images for months after onset but become hypointense or isointense in the chronic stage. On ADC maps, which reflect the underlying pathophysiology better than DWI, SLLs show up as elevation over months (Ohshita *et al.*, 2000; Ito *et al.*, 2008) to become hypointense or alternatively hyperintense in the chronic stage (Ohshita *et al.*, 2000). Only for a short period during the initial stages may a SLL show up as hypointensity on T2-weighted images and reduced on the ADC map (Ito *et al.*, 2008). Although classical SLLs may exclusively present as vasogenic, reversible oedema, cytotoxic and vasogenic oedema may coexist within the same lesion (Ishikawa *et al.*, 2009), particularly at onset of the SLE (Tzoulis and Bindoff, 2009).

According to the epilepsy hypothesis, SLLs represent regions of neuronal hyperactivity, resulting in increased focal energy demand and a mismatch between impaired energy production and increased energy requirement (Kubota *et al.*, 2004). An argument for a beneficial role of AEDs in the presented patient is based on the observation that SLLs did not disappear on MRI as long as the patient experienced seizures. Under valproic acid, seizures were not only poorly controlled but SLLs also remained unchanged on MRI since their first recognition. Valproic acid inhibits oxidative phosphorylation, induces apoptosis of microglia, and sequesters carnitine (Toth *et al.*, 2001), which explains why it is contraindicated in mitochondrial disorders and may even worsen cerebral manifestations of the disease (Lin and Thajeb, 2007). In addition to valproic acid, other mitochondrion-toxic AEDs include barbiturates and phenytoin (Finsterer and Segall, 2010). To ultimately assess the role of AEDs on

the dynamics of SLLs, however, larger series with similar patients and the development of experimental studies are mandatory.

This case indicates that prevention of seizures by effective AED therapy in patients with MELAS syndrome may prevent the recurrence of SLEs and may also result in the disappearance of SLLs on cerebral MRI. AEDs, such as lamotrigine or lorazepam, should be considered as a supportive therapy in patients with acute or chronic SLLs. □

#### Disclosure.

None of the authors has any conflict of interest or financial support to disclose.

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