

MELAS/SANDO overlap syndrome associated with POLG1 mutations

Niels Hansen · Thomas Zwarg · Isabel Wanke ·
Stephan Zierz · Oliver Kastrup · Marcus Deschauer

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Abbreviations

COX	Cytochrome oxidase
DNA	Deoxyribonucleic Acid
DWI	Diffusion weighted images
FLAIR	Fluid attenuated inversion recovery
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
NAA	<i>N</i> -Acetyl aspartate
PCR	Polymerase chain reaction
POLG	DNA polymerase gamma
SLE	Stroke-like episode
SLL	Stroke-like lesion

N. Hansen (✉)
Department of Neurology, Julius-Maximilians-University,
Josef-Schneider Strasse 11, 97080 Wuerzburg, Germany
e-mail: Hansen_N@klinik.uni-wuerzburg.de

T. Zwarg · O. Kastrup
Department of Neurology, University Duisburg-Essen,
Hufelandstrasse 55, 45122 Essen, Germany

I. Wanke
Department of Radiology and Neuroradiology,
University Duisburg-Essen, Hufelandstrasse 55,
45122 Essen, Germany

S. Zierz · M. Deschauer
Department of Neurology, Martin-Luther University
Halle-Wittenberg, Ernst-Grube-Strasse 40,
06120 Halle (Saale), Germany

Dear Editor,

Mitochondrial disorders are associated with various clinical presentations and an overlap between the syndromes. One typical mitochondrial syndrome is sensory ataxic neuropathy with dysarthria and ophthalmoparesis (SANDO) associated with mitochondrial DNA deletions [1, 2]. SANDO syndrome is frequently caused by nuclear recessive mutations in the POLG1 gene [3], or rarely by a dominant C10Orf2 (twinkle-helicase) mutation [2]. Another classic mitochondrial syndrome is mitochondrial encephalomyopathy with lactic acidosis, and stroke-like episodes (MELAS) syndrome presenting accessorially a stroke-like episode (SLE) based on a symptomatic stroke-like lesion (SLL) [4]. MELAS is typically due to the mtDNA mutations located in the tRNA^{Leu} (UUR), most frequently because of the 3243A>G mutation [5]. A patient with an SLE and an SLL in MRI due to a POLG1 mutation was recently identified, highlighting the complexity of the relationship between genotype and phenotype in mitochondrial disorders [6]. We present the case of a woman with SANDO syndrome and SLE characterised by acute hemiparesis and sensory disturbance of the right side resulting from a typical left-sided symptomatic SLL in MRI associated with POLG1 mutations, indicating a phenotype overlap between SANDO and MELAS syndrome due to a POLG1 defect.

This 48-year-old woman had a clinical history starting at age of 23 years with gait instability, manual coordination disorder, speech disturbance and secondary generalised motor seizures. From the age of 34 years, she had complained about tension-type headaches. At the age of 48 years, she presented with complete external ophthalmoplegia, cerebellar dysarthria and ataxia, sensory ataxia in Romberg-testing, areflexia of the lower extremities, loss of the sense of vibration in the legs, hypoalgesia of the legs

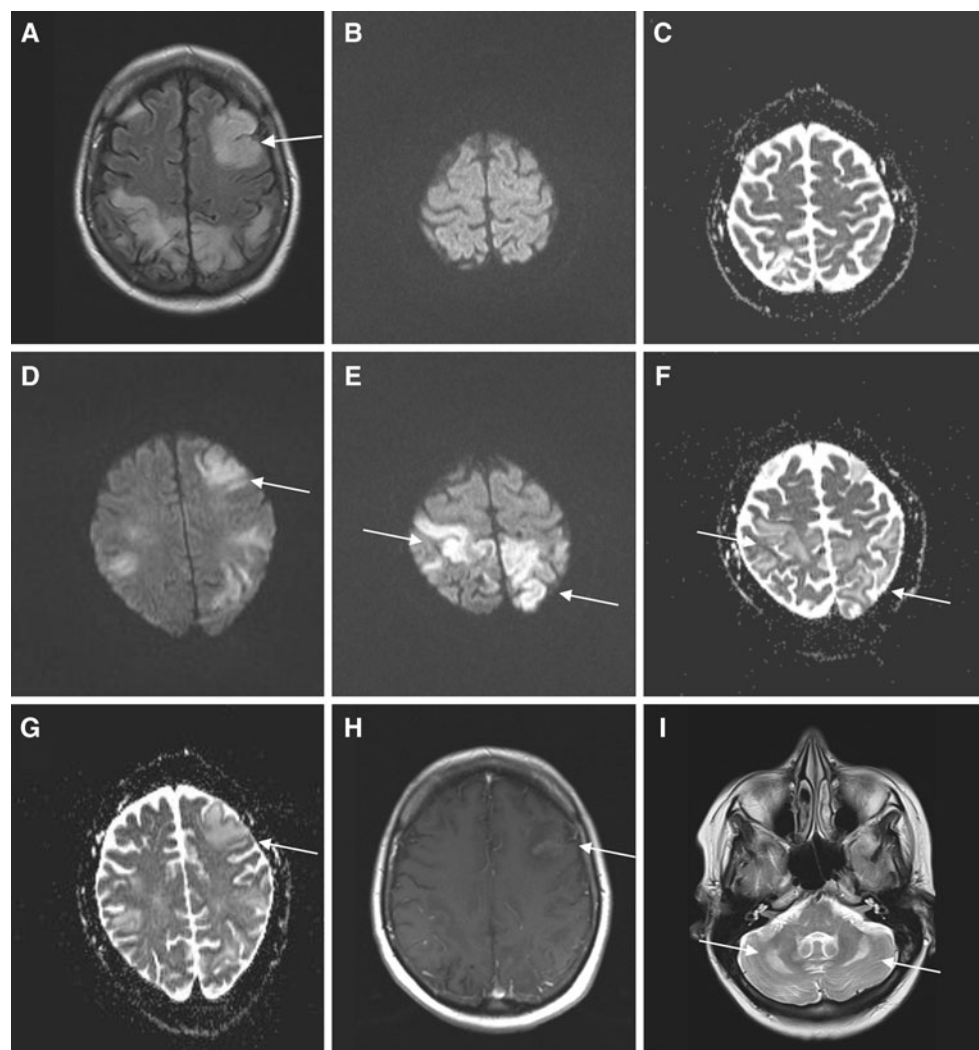
to the middle of the thighs, and mild cognitive dysfunction. Five months later, she was admitted to the hospital because of acute moderate hemiparesis and sensory disturbance of the right side. During subsequent hospitalisation, she also suffered generalised epileptic seizures and showed a worsening of cognitive function with memory and attention deficits. In clinical follow-up her hemiparesis and sensory disturbance regressed completely after 1 month. After combined anticonvulsant therapy with levetiracetam (2,500 mg/day), phenytoin (400 mg/day), and primidone (500 mg/day), the epileptic seizures resolved after 3 weeks and cognitive deterioration returned to the pre-hospitalisation level.

An MRI performed 1 day after admission revealed supratentorial signal alterations in the white matter and cortex including parts of the gyrus precentralis (Fig. 1a, d, g) and cerebellar hemispheres in MRI (Fig. 1i). Bihemispheric signal alterations were visible in MRI FLAIR (Fig. 1a), in axial ADC maps and diffusion-weighted images (DWI) (Fig. 1d, g) not apparent in an MRI

5 months earlier, revealing their episodic character. Furthermore, we detected the generalised cortical atrophy. An electroencephalography (EEG) 1 day after admission revealed frontotemporal delta deceleration.

An MRI performed 6 weeks after her admission revealed the minor progression of the parieto-occipital lesions with new, more cranially localised lesions (admission: Fig. 1b, c; 6 weeks after admission Fig. 1e, f). Furthermore, we verified a small, cortical garland-like haemorrhagic change in a left-sided frontal lesion (Fig. 1h). A proton magnetic resonance spectroscopy (MRS) was performed and added to the conventional MR imaging protocols using a 1.5-tesla scanner. A single-volume MRS of both frontal lesions (echo time 135 ms) was performed. We used the contralateral white matter as a reference. A marked decrease in *N*-acetyl aspartate (*N*-AA) (right-sided lesion: 23.3% and left-sided lesion: 15.9%) and high lactate peaks (the lactate peaks were twice as high as the choline peaks, values: 14–15) became apparent in MRS in the frontal lesions compared to the reference spectrum. Nerve conduction studies revealed

Fig. 1 Stroke-like episodes associated with SANDO syndrome. MRI axial FLAIR sequences revealed multiple, supratentorial, large, sharply-delineated and increased signal intensity areas in both the hemispheres affecting the cortex and white matter including parts of the gyrus precentralis (a). Corresponding lesions are demonstrated in axial DWI (d) and axial ADC maps (g). The symptomatic left frontal lesion with affection of the gyrus precentralis is marked by a *white arrow*. Progression of parieto-occipital lesions with new lesions in a more cranial distribution in axial DWI sequences (e) and axial ADC maps (f) 6 weeks later is denoted by *white arrows* compared to those performed 6 weeks before (b, c). In axial T1-weighted images (h) a small garland-like cortical hyperintense hemorrhagic change in the left frontal lesion is labelled by a *white arrow*. **i** Signal alterations in both the cerebellar hemispheres in T2-weighted images that are marked by *white arrows*



the signs of sensory axonal neuropathy. Repeated analyses of the cerebrospinal fluid (CSF) were normal. A muscle biopsy from the tibialis anterior muscle displayed 1% COX-negative fibres, but no ragged-red fibres. Spectrophotometric determination of mitochondrial enzymes in the muscle biopsy revealed elevated citrate-synthase activity (99 U/g non-collagen protein, normal 45–82) indicating the mitochondrial proliferation. Respiratory chain complexes activities related to citrate synthase showed a slight reduction in complex I and III. Molecular genetic analysis revealed the multiple mitochondrial DNA deletions in muscle tissue detected by the long range PCR technique. Sequencing of the POLG1 gene revealed the p.A467T mutation and p.W748S mutation in the heterozygous state. The mutations 3243A>G and 3271T>C in mtDNA were excluded.

This patient's clinical phenotype with chronic ophthalmoplegia, dysarthria and sensory ataxic neuropathy fulfils the SANDO triad [1]. Moreover, our patient had seizures and headache starting in young adulthood representing other typical symptoms of patients with POLG1 mutations [7, 8]. A study of 38 cases of POLG1 mutations demonstrated that POLG1 mutations reveal a wide clinical spectrum ranging from severe encephalopathy, liver failure, ophthalmoplegia, ataxia, myopathy, dysphagia, neuropathy to epilepsy [8]. However, SLEs are not a symptom typical of POLG1 defects, although there has been a single report [6]. SLEs in patients with classic MELAS syndrome often begin before the age of 40 [9]. Thus, our patient's SLE at the age of 48 years is uncommon for MELAS and she fails to fulfil the classical MELAS criteria [9]. Furthermore, typical symptoms, such as a hearing loss were not present. This SLE is based on a symptomatic SLL in our case—namely a left-sided frontal cerebral lesion with gyrus precentralis involvement—as the neuroimaging criteria are fulfilled, such as MRI FLAIR hyperintensities in a parieto-occipital location [10] concerning the white and grey matter, hyperintense lesions in ADC maps and DWI, as well as the MRS results showing a reduction in *N*-AA, and the elevated lactate of SLL in the lesion [11]. The hyperintense lesions in the DWI and the ADC sequence as in our findings (Fig. 1d, g) correspond to a vasogenic oedema [12, 13]. Moreover, MRI indicates an SLL because the cerebral lesions do not occupy vascular territories as do cerebral infarctions [12]. The remarkable MRI finding of gyrus haemorrhage in an SLL has been reported in a single patient [14]—this might have been the result of cortical laminar necrosis.

Cerebral lesions in MRI in patients with the common p.A467T and p.W748S POLG mutations were observed frequently in a study of 26 patients [7]. However, our patient's fronto-parietooccipital lesions in MRI FLAIR sequences are more pronounced and their distribution more

disseminated than those described by Tzoulis [7]. They did not describe SLE episodes in their patients, neither did they provide data on DWI nor MRS. A cortical occipital lesion was observed by MRI in T2-weighted images in a patient with an SLE and two other POLG1 mutations (p.R627Q and p.G848S), but no MRI DWI or MRS were performed [6]. In another study, POLG1 mutations resulted in SLLs and a syndromic epilepsy with occipital lobe predilection with an inconsistent correlation between unilateral occipital lesions, clinical activity and EEG [15]. The most favoured hypothesis so far proposed as an SLE mechanism is a defect of the oxidative phosphorylation in the neurons and glia cells with subsequent vasogenic oedema [16]. Progressive expansion of an SLL as seen in our patient and in many other MELAS cases [16] might reflect an ongoing neuronal metabolic derangement associated with concomitant vasogenic oedema. Prolonged epileptic seizure activity may promote the vasogenic oedema by altering the blood–brain barrier with consecutive pericapillary plasma extravasation [17].

In conclusion, this case highlights the phenotypic variability in mitochondrial disorders, demonstrating the difficulty of classifying patients into a specific syndrome, such as SANDO and MELAS due to overlapping manifestations.

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Conflict of interest The authors report no competing interests.

References

1. Fadic R, Russel JA, Vedanarayanan VV, Lehar M, Kuncl RW, DRI Johns (1997) Sensory ataxic neuropathy as the presenting feature of a novel mitochondrial disease. *Neurology* 49:239–245
2. Hudson G, Deschauer M, Busse K, Zierz S, Chinnery PF (2005) Sensory ataxic neuropathy due to a novel C10orf2 mutation with probable germline mosaicism. *Neurology* 64:371–373
3. Van Goethem G, Martin JJ, Dermaut B, Löfgren A, Wibail A, Ververken D et al (2003) Recessive POLG mutations presenting with sensory and ataxic neuropathy in compound heterozygote patients with progressive external ophthalmoplegia. *Neuromuscul Disord* 13:133–142
4. Tzoulis C, Bindoff LA (2009) Serial diffusion imaging in a case of mitochondrial encephalomyopathy, lactic acidosis and stroke like episodes. *Stroke* 40:15–17
5. Chinnery FP, Howell N, Lightowlers RN, Turnbull DM (1997) Molecular pathology of MELAS and MERRF. The relationship between mutation load and clinical phenotypes. *Brain* 120:1713–1721
6. Deschauer M, Tennant S, Rokicka A, He L, Kraya T, Turnbull DM et al (2007) MELAS associated with mutations in the POLG1 gene. *Neurology* 68:1741–1742
7. Tzoulis C, Engelsen BA, Telstad W, Aasly J, Zeviani M, Winterthun S et al (2006) The spectrum of clinical disease caused by the A467T and W748S POLG mutations: a study of 26 cases. *Brain* 129:1685–1692

8. Horvath R, Hudson G, Ferrari G, Fütterer N, Ahola S, Lamantea E et al (2006) Phenotypic spectrum associated with mutations of the mitochondrial polymerase gene. *Brain* 129:1674–1684
9. Hirano M, Ricci E, Königsberger R, Defendini R, Pavlakis SG, DeVivo DC et al (1992) MELAS: an original case and clinical criteria for diagnosis. *Neuromuscul Disord* 2:125–135
10. Clark JM, Marks MP, Adalsteinsson E, Spielman DM, Shuster D, Horoupian D et al (1996) MELAS: clinical and pathologic correlations with MRI, xenon/CT, and MR spectroscopy. *Neurology* 46:223–227
11. Bi WL, Baehring JM, Lesser RL (2006) Evolution of brain imaging abnormalities in mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes. *J Neuroophthalmol* 26:251–256
12. Ito H, Minato M, Naito E, Minato M, Naito E, Takeuchi M et al (2008) Serial brain imaging analysis of stroke-like episodes in MELAS. *Brain Dev* 30:483–488
13. Majole CB, Akkerman EM, Blank C, Barth PG, Poll-The BT, den Heeten GJ (2002) Mitochondrial encephalomyopathy: comparison of conventional MR imaging with diffusion-weighted and diffusion tensor imaging: case report. *AJNR Am J Neuroradiol* 23:813–816
14. Iizuka T, Sakai F, Suzuki N, Hata T, Tsukahara S, Fukuda M, Takiyama Y (2002) Neuronal hyperexcitability in stroke-like episodes of MELAS syndrome. *Neurology* 59:816–824
15. Engelsen BA, Tzoulis C, Karlsen B, Lillebo A, Lagreid LM, Aasly J, Zeviani M, Bindoff LA (2008) POLG1 mutations cause a syndromic epilepsy with occipital lobe predilection. *Brain* 131:818–828
16. Finsterer J et al (2009) Management of mitochondrial stroke-like episodes. *Eur J Neurol* 16:1178–1184
17. Iizuka T, Sakai F, Kan S, Suzuki N (2003) Slowly progressive spread of stroke-like lesions in MELAS. *Neurology* 61:1238