ERN EURO-NMD Workshop MELAS Lay Summary

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Background and aims:

Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) is a rare and debilitating mitochondrial disease that mainly affects the brain and muscles. Because the mitochondria are responsible for producing energy, their dysfunction means that organs with high energy demands are particularly vulnerable. A key and severe feature of MELAS is the occurrence of stroke-like episodes (SLE). During these episodes, individuals may suddenly develop symptoms similar to those of a stroke, such as difficulty speaking, weakness on one side of the body, vision loss, or confusion. Some episodes may also include seizures. Unlike typical strokes, SLE are not caused by blocked or bleeding blood vessels, but by complex problems linked to mitochondrial energy failure. These episodes often lead to lasting disabilities — such as hemiparesis, hemianopia, sever cognitive impairment or even cortical blindness — and are a major contributor to illness severity and early mortality in MELAS. The underlying mechanisms are still not fully understood, and clear, internationally accepted treatment guidelines are lacking. As a result, clinical management varies widely across different countries and medical centers. Our workshop aimed to facilitate the derivation of recommendations by compiling expert opinions on the following points:

- definition of MELAS and SLE
- management of SLE
- management of cognitive and psychiatric issues
- management of headache and epilepsy
- management of comorbidities

Workshop outcomes:

Before this meeting, our group conducted a thorough review of the literature, focusing on the respective topic of the working group (see above), in patients with genetically confirmed MELAS syndrome. We included only peer-reviewed papers and searched the electronic databases MEDLINE via PubMed, ClinicalTrials.gov, and the European Clinical Trials Register.Both MeSH terms and open search were

performed. As preparatory work, we conducted an online surveyusing the “Delphi process” to prepare for the meeting and facilitate consensus-building.

At the workshop, the sessions began with an overview of the pre-workshop survey results, followed by a historical lecture on the origin and recent definitions of the MELAS syndrome by Prof. Michio Hirano, who first defined the diagnostic criteria for MELAS in 1992. Afterwards, the survey results that didn’t reach consensus were presented by the respective group leaders, and pro/contra arguments were illustrated. Based on these presentations, new statements were generated and subsequently voted on.

Definition of MELAS and SLE:

The experts reviewed all diagnostic criteria published over the past 30 years and examined additional scientific literature. Based on this evidence, the experts agreed that MELAS syndrome is a primary mitochondrial disease caused by a pathogenic mitochondrial DNA variant and is defined by the presence of one or more SLE with associated epileptic and/or encephalopathic features, together with genetic, biochemical, or muscle-based evidence of impaired oxidative phosphorylation.

Mitochondrial SLE were defined as acute or subacute evolving brain events that can occur at any age and present with neurological and/or psychiatric symptoms. These episodes typically show characteristic cortical or subcortical changes on MRI scans, with or without EEG abnormalities.

The experts confirmed that SLE are the key feature required for the diagnosis of MELAS. Even when a person carries a known mitochondrial DNA pathogenic variant, the diagnosis of MELAS should not be made unless they have experienced at least one SLE. Importantly, contrary to early diagnostic criteria, we now know that SLE can occur across the lifespan, even after the age of 40.

From a genetic perspective, although the m.3243A>G variant in the MT-TL1 gene is the most widely recognized cause, MELAS can result from several different pathogenic mitochondrial DNA variants. For this reason, the acronym MELAS should refer only to the clinical syndrome, not to a specific genetic variant. In addition, terms such as “MELAS-like” or “MELAS spectrum” should be avoided.

Finally, the experts emphasized that SLEcan arise from both mitochondrial and nuclear DNA mutations (such as POLG), meaning they can also occur in other mitochondrial syndromes.

Management of stroke-like episodes

The experts discussed the existing evidence and their own clinical experience to assess the current state-of-the-art use of various medications in the management of SLE. The detailed management of SLE will be presented in the full publication.

Management of Cognitive and Psychiatric Issues

Cognitive deficits are common in patients with MELAS. The experts recommend multi-domain cognitive assessments and cognitive rehabilitation when needed. Moreover, antipsychotic and antidepressive drugs can be used to manage acute psychiatric manifestations according to best psychiatric practices. Psychological support for both patients and caregivers should be provided if required.

Management of Headache and Epilepsy

Headache is common in patients with MELAS syndrome, and experts recommend that it should be routinely assessed during clinical visits. Regular monitoring helps ensure timely treatment and can significantly improve quality of life. Regarding epilepsy in MELAS outside of SLE, the experts support the recommendations of the

European InterERN Mitochondrial Working Group, which provide guidance on the safety and potential toxicity of anti-seizure medications in mitochondrial diseases.

Management of Comorbidities

The experts formulated statements on several comorbidities that occur in the acute phase of MELAS; including gastrointestinal dysmotility, cardiac symptoms, acute kidney injury and management of metabolic acidosis, that will be presented in the final full publication in the European Journal of Neurology (DOI: 10.1111/ene.70588).

Impact on the patients and their families (patient's words)

From the patient perspective, MELAS imposes substantial physical, neurological and cognitive consequences. Energetic failure particularly affects the brain and muscles, resulting in functional disability, loss of independence and the need for continuous support. Patients and caregivers consistently report life reorganisation, reduced social participation and uncertainty regarding disease trajectory. SLE are described as the most destabilising aspect of the disease. Their unpredictability, recurrent nature and potential for permanent deficits contribute to perceived vulnerability. Patients report variability in recognition and management, particularly outside specialist centres, highlighting the need for earlier detection and standardised care pathways.

Patients report anxiety related to future episodes, loss of skills and difficulty adapting to emerging disability. Caregivers experience sustained stress, role overload and risk of burnout, especially when structured psychological support is lacking. These observations reinforce the relevance of psychosocial components within care models.

Patients consistently emphasise the need for randomised trials addressing both acute and preventive treatment, given the current lack of proven interventions and reliance on empirical approaches. Variability in outcomes and treatment choices

reinforces the perception that robust evidence and shared protocols are urgently required.

Patient association's view on the MELAS consensus

Patient organisations acknowledge the MELAS consensus as a useful tool to reduce variability and support non-specialist clinicians. At the consensus meeting, patient delegates highlighted implementation gaps, particularly in SLE recognition, rehabilitation continuity and psychological support. Their contribution is intended not to replace clinical expertise but to ensure alignment between recommendations and lived realities.

Perceived care needs

Patient contributions identify core requirements for effective management:

- continuous, coordinated rehabilitation;
- integrated psychological support for patients and caregivers;
- formal recognition and protection of the caregiver role;
- improved preparedness of non-specialists for SLE recognition;
- explicit inclusion of nutritional management, perceived as relevant to energy, stability and metabolic vulnerability.

Language considerations

Patient associations offered targeted feedback on wording, requesting:

- clear, unambiguous terminology;
- translation into different languages
- explicit differentiation between acute and stable contexts;
- distinction between evidence-based recommendations and expert opinion;
- operational detail on monitoring and contraindications.

Terminological clarity is considered essential to facilitate accurate implementation, particularly in settings with limited MELAS expertise. Overall, the patient perspective highlights MELAS as a condition with substantial functional, organisational and psychological implications. Systematic incorporation of

patient-reported needs into consensus statements and care pathways is viewed as critical to improving the applicability of recommendations and the quality of care.