Letter to the Editor

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Rare Phenotypic Manifestations of MELAS

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To the Editor,

Mitochondrial Encephalopathy, Lactic Acidosis, and Stroke-like episodes (MELAS) syndrome is one of the most frequent syndromic mitochondrial disorders (MIDs).[1] It is diagnosed according to the Japanese criteria if at least two features of category A [headache with vomiting, seizures, hemiplegia, cortical blindness, stroke-like lesion (SLL)] and at least two features of category B (elevated lactate in serum or cerebro-spinal fluid, mitochondrial myopathy on muscle biopsy, MELAS-related mutation) being present.[2] MELAS is diagnosed according to the Hirano criteria if all three of the canonical features [stroke-like episode (SLE) before age of 40 years, encephalopathy (seizures or dementia), and mitochondrial myopathy on biopsy] and at least two of the other features (normal early psychomotor development, recurrent headache, or recurrent vomiting) are present.[3]

Eighty percent of the MELAS cases are due to the variant m.3243A>G in *MT-TL1*.[1] Other mutated genes associated with MELAS include *MT-ND5*, *MT-TC*, *MT-TF*, *MT-TH*, *MT-TK*, *MT-TL2*, *MT-TQ*, *MT-TV*, *MT-TW*, *MT-TS1*, *MT-TS2*, *MT-ND1*, *MT-ND6*, *MT-CO2*, *MT-CO3*, and *MT-CYB*.[1] The most frequent phenotypic manifestations of MELAS include seizures (76% of patients), headache (50% of patients), SLEs (>90%), visual loss (52% of patients), muscle weakness (48% of patients), vomiting (55%), as well as short stature (>25% of cases), impaired consciousness, impaired cognition, hearing loss, or diabetes (10–24% of patients).[1] Although the phenotypic spectrum of MELAS is broader than anticipated (Table 1), most of these features are rare and often reported only in a single patient or family. This is why it is sometimes questionable if these rare features are truly attributable to the MID or due to a secondary problem.

Rare phenotypic manifestations occurring in <10% of the MELAS cases include cerebral manifestations (dystonia, chorea, parkinsonism), psychiatric abnormalities (delirium, confusion, mutism, hallucinations, delusions, dysexecutive syndrome), ophthalmologic manifestations (cataract, retinal detachment, maculopathy, polymegathism), otologic disease (vestibular dysfunction), endocrine abnormalities (hypoaldosteronism, Addison's disease, hyperthyroidism, hypopituitarism, osteoporosis), cardiac manifestations (noncompaction, arterial hypertension), lungs (pulmonary hypertension, chronic obstructive pulmonary disease), gastrointestinal compromise (pancreatitis, odynophagia), kidneys (Fanconi syndrome), and vascular involvement (artery dissection, aneurysm formation, aortic rupture). Rare non-specific manifestations include developmental delay or fever (<10% of cases).[4,5] Non-specific manifestations of MELAS may also include dysmorphism (hypertelorism, protruding ears).[6] Knowing the entire spectrum of the phenotype is crucial, as prospective investigations may also be carried out for these rare features and some of them may strongly determine the prognosis and outcome.

Although SLLs, the morphological equivalent of SLEs on MRI,[7] develop predominantly in the cortex and subcortical white matter, they can rarely occur ubiquitously in the central nervous system, including the cerebellum, brainstem, the spinal cord, or the optic nerve. Though epilepsy is frequent in MELAS, certain seizures have only been infrequently reported. These include non-convulsive status epilepticus,[8] epilepsia partialis continua,[9] occipital status epilepticus, and myoclonic seizures.[10]

Overall, although MELAS is a frequent phenotype, we still do require more comprehensive evaluations of the phenotype to assess which features are truly attributable to a MELAS mutation to encompass the entire phenotypic spectrum of the disease. Rare phenotypic features should be regarded as part of the phenotype only if the diagnostic criteria for MELAS are met, if a MELAS-associated mutation is present, and if there is no other plausible explanation for a particular feature. It is important to describe the pathophysiological relationship between a rare phenotypic feature and the underlying mitochondrial

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Table 1. Rare Phenotypic Features of MELAS

Organ	Abnormality	Mutation	Reference
CNS	Dystonia	m.3243A>G	11
	Chorea-ballism	m.3243A>G	11
	Parkinsonism	m.14787del4	12
	Cerebellar tremor	m.14864T>C	8
	Focal NCSE	m.14864T>C	8
	Epilepsia partialis continua	m.3271T>C	9
	Lennox-Gastaut syndrome	m.3243A>G	13
	Myoclonic seizures	m.3243A>G	10
Psychiatric	Confusion, mutism	m.3243A>G	14
	Hallucinations, delusion	m.3243A>G	15
	Delirium	m.4450G>A	16
	Dysexecutive syndrome	m.12015T>C	17
Eyes	Cataract	m.9957T>C	18
	Retinal detachment	m.3243A>G	19
	Maculopathy	m.3243A>G	20
	Polymegathism	m.3243A>G	21
Ears	Vestibular dysfunction	m.3243A>G	22
Endocrine	Hypoaldosteronism	m.3243A>G	23
	Addison syndrome	m.8344A>G	24
	Hyperthyroidism	m.3243A>G	25
	Hypopituitarism	nr	26
	Osteoporosis	m.3243A>G	27
Cardiac	Noncompaction	m.3243A>G	28
	Pulmonary hypertension	m.3243A>G	29
	Arterial hypertension	m.3243A>G	30
Lungs	COPD	m.3243A>G	31
Arteries	Carotid artery dissection	m.3243A>G	32
	Aortic rupture	m.3243A>G	33
	Aneurysm	m.3243A>G	34
Gastrointestinal	Pancreatitis	m.3243A>G	35
	Odynophagia*	m.3243A>G	31
Kidneys	Fanconi syndrome	nr	36
Skin	Focal melanoderma	m.3243A>G	6
Non-specific	Dysmorphism	m.3243A>G	6
	Fever	m.3243A>G	5
	Developmental delay	m.10158T>C	37
	Pseudobulbar syndrome	m.3243A>G	38
	Occipital status epilepticus	m.3243A>G	39

COPD, chronic obstructive pulmonary disease; MELAS, Mitochondrial Encephalopathy, Lactic Acidosis, and Stroke-like episodes; NCSE, non-convulsive status epilepticus; nr, not reported.
*Pain when swallowing.

dysfunction in each case.

Informed consent was obtained. The study was approved by the institutional review board.

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