MELAS and its peculiarities

Journal of Medical Biomedical And Applied Sciences
Doi : 10.15520/jmbas.v6i10.160
Received : 5 October 2018
Accepted : 10 October 2018

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Keywords
encephalopathy, mitochondrial DNA, cerebrum, brain, stroke, electroencephalography

Letter to the Editor

In a recent article, Tatlisumak et al. reported about a study on 238 stroke patients of whom 4 carried the m.3243A>G mutation in the *tRNA(Leu)* gene[1]. We have the following comments and concerns.

Stroke-like episodes (SLEs) do not only occur in patients with MELAS, MERRF, KSS, Leigh-syndrome, MIRAS, or triple-H syndrome but also in patients with LHON[2], CPEO[3], CMTX1[4], patients carrying *POLG1* mutations[5], and particularly in non-syndromic mitochondrial disorders (MIDs)[6–8].

Epilepsy should be included as a red flag of MELAS-syndrome or the m.3243A>G mutation since it can be a dominant feature of the phenotype[9,10]. In a study of 165 patients with a MID, 61% had an abnormal EEG and among these 85% had epileptiform discharges[11]. In a study of 182 adult MIDs the prevalence of epilepsy was 23% with a mean age at onset of 29y[12]. Epilepsy in MELAS-syndrome may not only manifest with motor manifestations but also with visual hallucinations[13] or psychosis[14]. Recognising epilepsy in MELAS is important since it is regarded by some authors to be involved in the pathogenesis of SLEs[15]. Furthermore, epilepsy is accessible to treatment in two thirds of the cases whereas a SLE without epilepsy is hardly accessibly to any conventional therapy except L-arginine[15]. There are even reports showing the ketogenic diet may reduce the severity and duration of SLEs[16]. How many of the four included patients had epilepsy and how many required antiepileptic drug (AED) treatment? AED treatment of MID is crucial since AEDs can be highly mitochondrion-toxic and may deteriorate the clinical manifestations in MELAS. Mitochondrion-toxic AEDs include VPA, CBZ, PHT, and PB. Less mitochondrion-toxic are LEV, LTG, ZNS, and PGB.

In how many of the four included patients was MR-spectroscopy, PWI, or MR-angiography carried out? In how many of the 4/238 stroke patients carrying the m.3243A>G mutation did the work-up provide indications for an ischemic stroke and in how many was the stroke in fact a SLE? These two entities need to be differentiated not only because of the variable pathogenesis but also with regard to the different manifestations on cerebral MRI (Table1) and the variable therapeutic approaches. It has to be also stressed that stroke-like lesions and ischemic stroke may coexist.

MELAS patients may develop ischemic stroke in case of atrial fibrillation, a therosclerosis, s ystolic dysfunction, ventricular arrhythmias, arterial hypertension, smoking, or low output failure. Furthermore, it has to be highlighted that in a classical stroke-like lesion also regions with a cytotoxic edema, particularly in the cortical sections, may occur (Table1)[17]. Rarely, MELAS may be associated with reversible vasoconstriction syndrome and thus cause cerebral ischemia via this mechanism[18].

The mutation load was low in all four patients with heteroplasmy rates of 4, 10, 41, and 52% respectively[1]. The discrepancy between the absence of classical SLEs and stroke-like lesions on imaging could be explained by this low mutation loads. Did the authors consider that their findings were just incidental and not causally related to the occurrence of classical ischemic stroke in at least three of the included patients? Since stroke-like lesions may disappear on imaging over time, it would be interesting to know if any of the four patients carrying the m.3243A>G variant ever had an episode attributable to a SLE or follow-up MRIs.

Overall, the highly variable manifestations of SLEs on imaging must be well appreciated and SLEs must be clearly distinguished from ischemic stroke, since management of these two entities is distinct. Clinical and EEG manifestations of SLEs must be recognised since they are usually accessible to treatment. The complexity of MID patients requires a differentiated and multidisciplinary approach with regard to diagnosis and treatment.

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Table 1. Differences between vascular ischemic stroke andmitochondrial stroke-like episode on imaging studies and EEG

Imaging method	Ischemic stroke	Stroke-like episode	Reference
T1-weighted	Isointense	Hyperintensity (cortical necrosis)	17
DWI	Hyperintensity	Hyperintensity	19
ADC	Hypointensity	Hyperintensity (cortical hypointensity)	18
PWI	Hypoperfusion	Hyperperfusion (hypoperfusion)	16,20
MRA	Stenosis, occlusion	Patent arteries	15
FLAIR	Hyperintensity after 8h	Hyperintensity	21
HMPAO-SPECT	Hypoperfusion	Hyperperfusion	6,10
Isomazenil (IMZ)-SPECT	Reduced uptake	Reduced tracer uptake	14
EEG	Usually normal	Epileptiform discharges	1
Tendency to progress/recur	No	Yes	22

DWI: diffusion weighted inaging, ADC: apparent diffusion coefficient, PWI: perfusion-wighted imaging, MRA: MR angiography, FLAIR: fluid-attenuated inversion recovery, HMPAO-SPECT: single-photon emission computed tomography, EEG: encephalography

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