

PATHOPHYSIOLOGIC EVALUATION OF CEREBRAL BLOOD FLOW, ENERGY STATUS AND OXIDATIVE STRESS DURING STROKE-LIKE EPISODES IN MELAS PATIENTS BY MRI AND PET.

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Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS) syndrome is the most common mitochondrial disorder, which is mainly caused by an A-to-G transition at nucleotide position 3243 (A3243G) in mitochondrial DNA (mtDNA). The clinical features of MELAS syndrome consist of stroke-like episodes, hearing-loss, myopathy, cardiomyopathy and diabetes mellitus. Stroke-like episodes are the main symptom in MELAS patients and provoke neurological symptoms (e.g. headache, epilepsy, hemiparesis and dementia). Although several causative hypotheses of stroke-like episodes have been proposed to date, the pathophysiology remains obscure. Using magnetic resonance imaging (MRI) and positron emission tomography (PET), we performed *in vivo* serial functional imaging of regional cerebral blood flow (rCBF), energy status and oxidative stress during stroke-like episodes in MELAS patients demonstrating A3243G mutation. The following techniques were used to obtain images: (a) Apparent diffusion coefficient (ADC) mapping on diffusion-weighted MRI; ADC can detect proton mobility in brain tissue and discriminate between vasogenic and cytogenic edema. (Yoneda M, et al, Neurology 1999). (b) MR spectroscopy (MRS) and continuous arterial spin labeling (CASL); MRS is used to evaluate energy metabolism (lactate) in the brain, while CASL is a non-invasive method of quantifying of rCBF during the process of stroke-like episodes *in vivo* (Tsujikawa T, et al. Brain Dev. 2009). (c) PET with [¹⁸F]-fluorodeoxyglucose (¹⁸FDG) and [⁶²Cu]-diacetyl-bis(N4-methylthiosemicarbazone) (⁶²Cu-ATSM); ¹⁸FDG can detect glucose metabolism in the brain. ⁶²Cu-ATSM has a high permeability allowing it to cross the blood-brain barrier, where it accumulates in sites of impaired mitochondrial respiratory chain with excess electrons (*i.e.* over-reduction state). This enables imaging of regional oxidative stress in the patient's brain in order to clarify the role of oxidative stress and mitochondrial dysfunction *in vivo*. (Ikawa M, et al. Mitochondrion 2009). Using the imaging techniques described above, we evaluated serial changes in rCBF, energy status and oxidative stress during stroke-like episodes in MELAS patients, and suggested that the process of MELAS strokes is as follows; (i) increased energy demand in brain cells with respiratory chain defect (*i.e.* neuronal hyper-excitability proposed by Iizuka et al. T [Neurology 2002]), (ii) vasodilatation and hyperemia caused by impaired cerebral blood-vessel cells leading to vasogenic edema (*i.e.* angiopathy), (iii) overloading of oxygen and enhanced glucose metabolism in the neurons and glial cells through hyperemia, (iv) over-reduction state in impaired respiratory chains burdened with excess electrons due to glycolytic hyper-metabolism, (v) enhanced reactive oxygen species (ROS) generation (oxidative stress) (*i.e.* cytopathy), (vi) neuronal cell death caused mainly by oxidative damage.

Key words:

MELAS, rCBF, energy status, oxidative stress, PET, MRI