To be submitted as a Case Report of BMC Neurology

Transient Ischemic Attack-like Episodes without Stroke-like Lesions on MRI in MELAS

Running Head: TIA-like Episodes in MELAS

Tadahiro Mitani, MD¹; Yoshimitsu Ohtsuka, MD¹; Noriko Aida²; Moyoko Tomiyasu, PhD³; Takayuki Obata, PhD³; Yoshihiro Watanabe¹; Megumi Tsuji¹; Mizue Iai, MD, PhD¹; Sumimasa Yamashita, MD, PhD¹; Takahito Wada MD, PhD¹; Hitoshi Osaka, MD, PhD¹

1. Division of Neurology, Kanagawa Children’s Medical Center
2. Division of Radiology, Kanagawa Children’s Medical Center
3. Research Center for Charged Particle Therapy, National Institute of Radiological Sciences

Number of words in the abstract and the manuscript: 82 and 1406,
respectively

Number of figures and tables: 2 figures and no tables

Key words: MELAS, MR spectroscopy, mitochondria, stroke-like episodes

Corresponding author: Takahito Wada

Mutsukawa 2-138-4, Minami-ku, Yokohama, Kanagawa, 232-8555 JAPAN

Tel.: +81-45-711-2351; Fax: +81-45-721-3324; E-mail: twada@kcmc.jp
Abstract

A stroke-like episode is a core symptom in mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS). Proton magnetic resonance spectroscopy (MRS) is diagnostically useful for mitochondrial diseases. We report an 8-year-old girl with MELAS, presenting with an atypical stroke-like episode, whose MRS showed a strikingly elevated lactate peak in a lesion where both T2-weighted and diffusion-weighted MRI showed no abnormal signals, and she recovered within a day. We propose to call this attack a “transient ischemic attack (TIA)-like episode” in MELAS.
Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) is a type of mitochondrial encephalopathy. Patients with MELAS present with a wide range of clinical expressions, of which stroke-like episodes represent a dominant phenotypic feature. In addition to these and other classical manifestations, including aphasia, hemianopsia, hemiparesis, hemineglect and hemihypethesia, stroke-like episodes are frequently associated with additional abnormalities, such as epileptic seizures, ataxia, migraine-like headaches, impaired hearing, visual impairment, amnesia, cognitive impairment, psychosis and a confusional state.

Proton magnetic resonance spectroscopy (\(^{1}\)H-MRS) is a new tool in brain biochemistry for studying abnormalities and is reported to be useful in diagnosis, therapeutic monitoring and for investigating the pathophysiology of mitochondrial encephalopathy.

Here, we present a case of stroke-like episodes in a MELAS patient, whose \(^{1}\)H-MRS showed extremely elevated lactate peak in the right occipital
lobe where no abnormal signals appeared on magnetic resonance imaging (MRI). The patient recovered completely within a day, and we propose to define this condition as a “transient ischemic attack (TIA)-like episode” in MELAS.

**Case report**

Our patient is an 8-year-old girl, who was born via vaginal delivery after a full-term gestation. Birth and development was apparently normal. She has no family history of endocrinological, ophthalmological or neurological disorders.

At five years of age, she was referred to our medical center for evaluation of elevated creatine kinase (524 IU/L). Upon physical examination, her muscle tone had been reduced and her deep tendon reflex was diminished. A laboratory test showed lactic acid elevation (7.4 mM) in her blood. A muscle biopsy of her biceps showed ragged-red fibers, and mitochondrial DNA testing detected heteroplasmy of mitochondrial mutation A3243G, which is
the most frequent pathogenetic mutation in MELAS. We suspected MELAS as her diagnosis, although she had no stroke-like episodes at that time.

At eight years of age, she manifested with fever and bilateral clonic seizure for a short time. Two days after onset, she was admitted to our center because of her first stroke-like episode, including gradually developing a severe headache and blindness. Upon physical examination, right homonymous hemianopia was present. Clinical routine MRI and MRS were examined using 1.5 or 3.0 T MR system (Siemens, Erlangen, Germany). For the quantification of single voxel $^1$H-MRS data (PRESS sequence[10], TE/TR = 30/5000ms), LCModel software (Stephan Provencher Inc., Oakville, Canada)[11] was used. After 60 h from the onset of her symptoms, both T2-weighted image (T2WI; echo time (TE)/repetition time (TR) = 80/5000 ms) and diffusion-weighted image (DWI: b=1000s/mm$^2$) showed high signal intensities in a left occipital lobe. ADC map showed mixed, or decreased and increased signal, in the same region, suggesting the mixture of cytogenic and vasogenic edema).[TO1] $^1$H-MRS showed an
elevated lactic acid (Lac), and the Lac to creatine and phosphocreatine (Cr) ratio was 0.43. Whereas N-acetylaspartate and N-acetylaspartylglutamate (NAA)/Cr ratio was 0.90. After the MR examination, she was treated with L-arginine, vitamin B1, edaravone and glycerin. One week from onset, she still complained of prolonged headaches, and a sequential MRI showed that T2WI and DWI revealed a left occipital high-signal lesion (Fig. 1 (a) and (c)). ¹H-MRS showed a strikingly-high Lac peak (Lac/Cr ratio of 3.17) and a large decrease in NAA/Cr ratio (0.30) at the same lesion (Fig. 2 (a)).

Another week after treatment, her symptoms disappeared. On Day 18, T2WI and DWI still showed a left occipital hyperintense lesion and ¹H-MRS showed Lac peak decreasing (Lac/Cr ratio of 0.94), although it was a fairly higher value than normal condition. It took about four weeks before her symptoms completely disappeared, and her ophthalmological examination showed right homonymous hemianopia on discharge. This first attack was considered to be a classical “stroke-like episode” in MELAS.

Eleven days after discharge, she had a second stroke-like episode,
complaining of complete blindness with severe headaches and repeated clonic seizure. An EEG showed no apparent seizure discharge. T2WI and DWI (b factor=1500) at 3T machine 8 h from onset showed a high-signal lesion in the left occipital region, which could be related to be a residual lesion of the first attack, but there were no apparent signal changes in other regions (Fig.1(c) and (d)). Her complete blindness led us to investigate her $^1$H-MRS in the right occipital region. Surprisingly, $^1$H-MRS showed a remarkable lactic acid peak (Lac/Cr ratio of 1.33) without a decreased NAA/Cr ratio of 0.93 on the right occipital lobe where no signal abnormalities had appeared on MRI (Fig.2 (c)). On the other hand, in the left occipital region where related to the first episode, an additional decreasing in Lac peak (Lac/Cr ratio of 0.37) and a recovering in NAA peak (NAA/Cr ratio of 0.58) were observed, and this might indicate a recovery of brain function (Fig.2 (b)).[12] She was treated as previously and her symptoms improved quickly in 24 h. Four days after the second attack, $^1$H-MRS showed a decline of Lac peak on the right occipital lobes (Lac/Cr ratios
of 0.44 and 0.16 in the left and right occipital lobes, respectively (Fig. 2 (d)).

Her ophthalmological examination showed no abnormalities.

**Discussion**

Here, we report a stroke-like episode of an 8-year-old girl with MELAS, whose right occipital lobe showed elevated lactate peak in $^1$H-MRS but appeared normal on MRI. Her symptoms improved more rapidly, compared with her typical stroke like episode, which showed abnormal lesions on MRI.

We propose that this stroke-like episode with an abnormal lactate peak on $^1$H-MRS in lesions showing no signal abnormalities on MRI be called a “transient ischemic attack (TIA)-like episode” in MELAS, because the episode is similar to the definition of TIA, “a sudden, focal neurologic deficit that lasts for less than 24 hours.”[13]

The previous papers reported that a patient who had never experienced a stroke-like episode showed a similar pattern in $^1$H-MRS, or elevated lactate and glucose as well as reduced NAA and glutamate in tissues appearing
normal on MRI.[14, 15] We emphasize that our case is different from previous cases, because the change of lactate peak in $^1$H-MRS during this TIA-like episode is consistent with her clinical course, which was much milder than that of her other typical “stroke like” episodes in MELAS. From this point, we consider that a TIA-like episode in this case is a mild type of a classical “stroke-like” episode, just like a transient ischemic attack vs. a stroke in cerebral infarction.

The pathogenesis and episodic nature of stroke-like episodes are so far unexplained, but there is consensus that a cerebral lesion represents a vasogenic edema.[9, 16-20] Three main hypotheses have been proposed to explain the pathogenic nature of stroke-like episodes: 1) an ischemic vascular mechanism, 2) a generalized cytopathic mechanism, and 3) a non-ischemic neurovascular cellular mechanism. Hypothesis 1) asserts that an ischemic change occurs because of hypoperfusion due to vascular abnormalities. Hypothesis 2) asserts that a generalized cytopathy is caused by an oxidative phosphorylation defect in neurons or glia cells or both.
Mitochondrial dysfunction results in anaerobic metabolism and neuronal death. Neuronal damage may lead to hyperperfusion, followed by vasogenic edema. Hypothesis 3) asserts that stroke-like episodes result from focal neuronal hyperexcitability (epileptic activity), which leads to increased energy demand, leading to a mismatch between demand and availability of ATP, and lastly to vasogenic edema and cortical necrosis.

The radiological features of stroke-like episodes are 1) a distribution of stroke-like lesions incongruent to a vascular territory, 2) preferential involvement of the cerebral cortex, 3) predilection to the posterior brain, 4) reversible vasogenic edema: a bright thickened cortical band on T2-weighted and FLAIR images, 5) a slowly progressive spread into the surrounding cortex, and 6) a T1-weighted cortical hyperintense signal during the subacute stage compatible with cortical laminar necrosis pattern.¹⁶

Our results indicate that an oxidative phosphorylation defect leads to an accumulation of lactic acid and neuronal functional loss. However, vasogenic edema and neuronal loss are not evident by imaging studies. Given the
proceeding seizure, this episode may be triggered by neuronal hyperexcitability (Hypothesis 3).

Our result suggests that recurrent symptoms of headache without any abnormal lesion on MRI may be a mild-type or TIA-like episode in MELAS or other mitochondrial diseases, and \(^1\)H-MRS can be useful for early diagnosis, leading to timely treatment with minimized brain damage, or differentiating stroke-like episodes from other causes of headache, such as migraine-like headaches and psychiatric conditions.

In summary, we present a case of stroke-like episodes in a MELAS patient with elevated lactate on MRS in a lesion without any signal abnormalities on MRI. These findings may represent another type of stroke-like episodes, or TIA-like attack in MELAS.

Consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written
consent is available for review by the Editor-in-Chief of this journal.
References


Figure Legend

Figure 1

T2-weighted (a) and diffusion-weighted (b) 1.5T MR images at the first classic “stroke-like” episode, showing high intensity signal at left occipital lesion. T2-weighted (c) and diffusion-weighted (d) 3T MR images at the second “TIA-like” episode, showing no abnormal intensity signal at right occipital lesion, and residual slight high intensity lesion at left occipital lesion due to the first episode.

Figure 2

Voxel positions and corresponding sequential 1H-MRS (single voxel PRESS sequence, TE/TR=30/5000ms) spectra in the left occipital lesion at the first classic “stroke-like” episode (a), and at the second “TIA-like” episode (b); in the right occipital lesion at the onset of the second “TIA-like” episode (c), and after 4days from the onset (d).
Figure 2

(a) Left occipital 1st episode
(b) Left occipital 2nd episode
(c) Right occipital 1st episode
(d) Right occipital 2nd episode

4 days after 2nd episode