Reversible brain dysfunction in MELAS: MEG, and $^1$H MRS analysis

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Abstract
This case report describes a follow up investigation of a patient with impaired word discrimination due to mitochondrial encephalopathy with lactic acidosis and stroke-like syndrome (MELAS) using proton magnetic resonance spectroscopy ($^1$H MRS) and auditory evoked magnetic fields (AEFs). The initial $^1$H MRS showed no N-acetyl aspartate (NAA) and marked accumulation of lactate (Lac) in the stroke-like lesion of MELAS, which was silent in neural activity according to AEFs. The follow up investigations, however, demonstrated that NAA reappeared, that the formerly increased Lac signal was significantly reduced, and that the magnitude of AEFs of the lesion was markedly increased. Metabolic and functional changes in $^1$H MRS and AEFs reflected the neurological recovery very well. The stroke-like lesion was shown, using AEFs and $^1$H MRS, to be able to function properly, although brain tissue of the lesion initially had severe damage due to mitochondrial dysfunction.

Keywords: magnetic resonance spectroscopy; magnetoencephalography; MELAS

Mitochondrial encephalopathy with lactic acidosis and stroke-like syndrome (MELAS) is characterised by recurrent stroke-like episodes in MELAS are considered to result from defects in neuronal metabolism, as well as in cerebral vasculature. Acute stroke-like lesions of MELAS show similar findings to cerebral infarction, and tend to be normalised within a few months after onset. However, it is still unclear whether metabolically improved brain tissue is still able to function in MELAS.

Magnetoencephalography (MEG) reflects intracellular electric current flow in the brain, providing direct information on neural activity. Since it was used for functional brain mapping of the primary sensory cortex by measuring somatosensory evoked magnetic fields, the accuracy of MEG source localisation has become accepted for clinical use.

The present case report describes the follow up of a patient with impaired word discrimination due to stroke-like lesions in bilateral temporal areas, using $^1$H MRS and auditory evoked magnetic fields (AEFs). Metabolic and functional changes of a stroke-like lesion of MELAS were analyzed and are discussed in comparison with the neuroradiological findings and clinical symptoms.

Case report
A 32 year old right handed man had severe headache and difficulties in communicating with others and was admitted to the outpatient clinic of Hokkaido Neurosurgical Memorial Hospital on 3 March 1999. Neurological examination showed severe sensory dominant aphasia. T2 weighted MRI showed a left temporal lobe hyperintense lesion involving the superior temporal region and Heschl's gyrus (fig 1 A). Angiography showed no abnormalities and the neuroradiological findings did not correspond to the vascular supply territory. The presence of mitochondrial mutations of mtDNA 3243 in blood samples and muscle biopsy showing ragged-red fibres confirmed the diagnosis of MELAS. As he became free of neurological symptoms within the next 2 months, he was discharged.

Four months after discharge, he was readmitted because of headache and a new onset of auditory hallucinations. Although he showed only mild sensorineural hearing loss (>15 dB)
at frequencies of 8 to 12 kHz, word discrimination acuity was markedly impaired. T2 weighted MRI on the second admission demonstrated a hyperintense lesion in the right posterior temporal area involving the superior temporal lobe and Heschl’s gyrus although the left temporal lesion that was involved in the first episode appeared normal (fig 1C).

The AEFs were measured with a sampling rate of 600 Hz by a MEG system (VectorView, Neuromag, Finland) on the second admission, at 2 months and 4 months after the onset. Tone bursts of 1 kHz with a sound pressure level of 85 dB and duration of 200 ms were presented separately to the left or right ear via air tubes and inserts. Equivalent current dipoles (ECDs) were calculated using a single current dipole model and only the ECDs with a minimum correlation value exceeding more than 0.90 between the measured and the calculated fields were accepted.

Brain MR examinations were performed using a whole body 1.5T MR system (Signa, HiSpeed, General Electric, Milwaukee). Single voxel 1H MRS with point resolved spectroscopy was performed with an echo time of 270

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**Figure 1**  (A) T2 weighted MRI showing a hyperintense lesion in the left superior temporal region on the first admission. (B) Proton MR spectroscopy (1H MRS) of the stroke-like lesion in the right temporal region on the second admission, and (D) at 4 months after the second onset showing the dramatic recovery in NAA/creatine+phosphocreatine (Cr) intensity ratio and the decline in Lac concentration. Vertical scales are the same over all 1H MRS.

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N-acetyl aspartate is synthesised only in the mitochondria of neurons and it has been considered a neuronal marker. As neurons in the CNS have an extremely limited capacity for regeneration, a decrease in NAA is usually interpreted as a sign of irreversible neuronal loss. A few previous 1H MRS studies of MELAS, however, reported that decreased NAA signals could recover, as in our patient, and speculated that mitochondrial dysfunction that caused the NAA decrease was reversible. Although the role of NAA is still unclear, a few authors have shown that the NAA concentration could predict clinical prognosis of patients with stroke and reflect neurological symptoms. Metabolic recovery of 1H MRS in our patient was well correlated with functional recovery of AEFs as well as clinical symptoms. The findings suggested that the residual NAA signal in the lesions indicates surviving viable neurons, which produce NAA and which can remain functioning. The NAA signal might, therefore, reflect neuronal function as well as the numbers of damaged but still surviving neurons.

We found increased amplitudes of N1m and P2m responses from the right hemisphere during the recovery period. As the P2m recovered before the N1m, later responses might revert to normal faster than early responses. Although there have been no studies of MEG signal recordings in patients with MELAS, a few reports described relations between evoked magnetic fields and cerebral infarction. Rossini et al investigated N20m and P30m responses from the sensory cortical hand area after a monohemispheric lesion. They demonstrated independent changes of N20m and P30m, where the later response (P30m) became excessively larger in the affected hemisphere. They speculated that the later response tends to be preserved as it might be strongly related to more synaptic relays than earlier responses.

Discussion
This patient presented twice with acute cerebral focal mitochondrial decompensation and had auditory hallucinations and difficulties in word discrimination due to the bilateral temporal lobe lesions. The initial 1H MRS suggested that the lesion produced severe anatomical as well as metabolic alterations, and gave the impression that the tissue would hardly survive and regain active metabolic and functional states.

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Paul Ehrlich (1854–1915) and Emil Adolf Von Behring (1854–1917)

The German physician, bacteriologist, and chemist Paul Ehrlich shared with Ilya Metchnikoff the Nobel Prize in 1908 for his contributions to immunity. The climax of the 19th century’s united attack on microbes was Paul Ehrlich’s discovery of Salvarsan, which gave rise to the concept of a chemotherapeutic “magic bullet” against specific infectious organisms. Beginning with dyes and later expanding his studies to include arsenical compounds, Ehrlich and his coworkers modified the chemical structure of numerous molecules to produce effective drugs against trypanosomiasis and later spirochete infections. They tested hundreds of compounds before they came on one, number 606, that Ehrlich thought was the chemotherapeutic agent he was searching for. Clinical tests confirmed the potential of the drug in treating syphilis and trypanosomiasis. The discovery was announced in 1910. Ehrlich named the drug Salvarsan.

In 1905 Treponema pallidum was discovered by Schaudinn and Hoffman in Berlin. They showed it to be the cause of syphilis. Ehrlich synthesised the chemical, which would destroy the causative organism but spare the patient. About 3 decades later, the advent of sulphonamides for the treatment of bacterial infections was a direct, although delayed outgrowth of Ehrlich’s demonstration that dyes could be antibacterial agents. When penicillin was introduced, Ehrlich’s drugs against syphilis were abandoned, but he had set in motion the activities of the 20th century that were to revolutionise the therapy of microbial diseases.

Ehrlich was nominated again for a Nobel Prize in 1912 and 1913 for his contributions to chemotherapy. The value of Salvarsan was still, however, in dispute at that time, and then in 1915 Ehrlich died. Ehrlich was posthumously awarded the first Nobel Prize in physiology or medicine in 1901. In 1913 he introduced a refinement of the immunisation technique by using toxin-antitoxin mixtures to immunise against diphtheria.

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