SHORT REPORT

Reversible brain dysfunction in MELAS: MEG, and ¹H 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 (¹H MRS) and auditory evoked magnetic fields (AEFs). The initial ¹H 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 ¹H MRS and AEFs reflected the neurological recovery very well. The stroke-like lesion was shown, using AEFs and ¹H MRS, to be able to function properly, although brain tissue of the lesion initially had severe damage due to mitochondrial dysfunction. (*J Neurol Neurosurg Psychiatry* 2001;70:675-678)

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biochemistry.⁵⁻⁷ Many authors have reported that in ischaemic stroke ¹H MRS shows characteristic prolonged increases in lactic acid (Lac) and lack of N-acetyl aspartate (NAA), indicating "neuronal loss".^{7,8} Acute stroke-like lesions of MELAS show similar findings to cerebral infarction, and tend to be normalised within a few months after onset.^{4,9,10} 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,^{11,12} 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 ¹H 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)

Mitochondrial encephalopathy with lactic acidosis and stroke-like syndrome (MELAS) is characterised by recurrent stroke-like episodes, headache, seizures, neurosensory hearing loss, and point mutations of mitochondrial DNA. Diffuse fibrillary gliosis with abundant reactive gemistocytes and focal evidence of ischaemic neuronal injury, which might be due to metabolic disturbances, are seen on light microscopy. Electron microscopic examination showed that bizarre enlarged mitochondria are markedly aggregated in smooth muscle cells and endothelium of the cerebral blood vessels. On the basis of these findings, the stroke-like episodes in MELAS are considered to result from defects in neuronal metabolism, as well as in cerebral vasculature.^{1,2} Neuroradiologically, MELAS is characterised by disappearance of the stroke-like lesions and their reappearance in another region.^{3,4}

Proton MR spectroscopy (¹H MRS) is a new tool for studying abnormalities in brain

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

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. Cho=choline containing compounds. (C and E) T2 weighted MRI showing a hyperintense lesion in the right superior temporal area and the regions of interest (white squared line) of ^1H MRS. T2 weighted MRI of an axial section and T1 weighted MRI of a coronal section showing the estimated dipoles of right N1m (white square) and P2m (white circle) of AEFs on the second admission (B) and at 4 months (D) after the second onset. The estimated current dipoles of both components (N1m and P2m) were finally located in the right superior temporal region.

ms and a repetition time of 1500 ms 1 day before the AEF measurements. Volumes of interest ($25 \times 25 \times 26 \text{ cm}^3$) were placed in the bilateral posterior temporal regions containing the primary auditory cortex.

On the second admission ^1H MRS showed a large Lac peak (Lac was not detected in normal tissue) and no NAA signal in the lesion of the right temporal lobe (fig 1 B). A clear NAA peak was found in the left temporal region and the NAA/Cr ratio was 1.88, which was slightly lower than the mean ratio of normal controls (2.76 (SD 0.48), $n = 10$). The range between the mean ± 2 SD of each metabolite in normal brain tissue was determined as the normal limit. The unaffected left parietal region that seemed normal on MRI showed a normal NAA/Cr ratio of 2.38. Mild accumulation of Lac, however, occurred in both the left parietal and the left temporal regions.

The AEF responses in the right hemisphere were too small in amplitude to identify peaks. In the contralateral left AEF responses, N1m and P2m peaks were identified at 83 ms and 178 ms, respectively, after their stimuli and ECDs were localised close together in the supratemporal cortex (fig 1 C).

The patient showed dramatic recovery from impairment of word discrimination with no audiographic changes in the next 2 months. T2 weighted imaging showed that the hyperintensity diminished in the right temporal lesion. The right temporal NAA/Cr ratio was increased to 1.38 and Lac was markedly decreased to 0.91 of the Lac/Cr ratio. The right AEF responses were demonstrated as clear N1m and P2m at 95 ms and 182 ms, respectively, and the ECD of P2m was located in the superior temporal region. The ECD of N1m was, however, localised in the middle temporal white matter, which was remote from the auditory cortex.

A follow up MEG-MRI examination 4 months after the second onset showed the patient to be almost free from the neurological symptoms except for mild sensorineural hearing loss with no audiographic changes. T2 weighted MRI detected no abnormal intensity in bilateral temporal regions. A low NAA/Cr ratio (1.42) and a small peak of Lac (Lac/Cr ratio 0.63) were still persistent, but gradually normalised (fig 1 D). The right AEF responses showed a clear N1m peak at 86 ms and a P2m peak at 182 ms. There were no obvious differences from the left AEF responses. The ECDs of the right and left N1m and P2m were localised in the auditory cortices (fig 1 E).

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.

N-acetyl aspartate is synthesised only in the mitochondria of neurons¹³ and it has been considered a neuronal marker.^{8,14} 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.^{4,9} 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.^{6,15,16} 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.¹⁷ Toyoda *et al* examined AEF responses of P50m and N100m in cases of ischaemic stroke, and reported that earlier responses were predominantly affected.¹⁸ These findings, including the results presented here, suggest that independent sources contribute to earlier and later responses and stress that the later responses could be a good index for detecting initial signs of neurological recovery.

The most striking finding in the present study was that the stroke-like lesion was able to function properly within a few months after onset using MEG and ^1H MRS, although the brain tissue involved in the lesion initially had severe damage due to mitochondrial dysfunction. Stroke-like lesions are difficult to treat and have different prognoses in individual patients with MELAS. However, we stress that some of these stroke-like lesions might show marked improvement. We think that this finding is encouraging for patients with untreatable stroke-like episodes of MELAS.

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- 1 Gilchrist JM, Sikirica M, Stopa E, et al. Adult-onset MELAS. Evidence for involvement of neurons as well as cerebral vasculature in strokelike episodes. *Stroke* 1998;27:1420–3.
- 2 Mizukami K, Sasaki M, Suzuki T, et al. Central nervous system changes in mitochondrial encephalomyopathy: light and electron microscopic study. *Acta Neuropathol (Berl)* 1992;83:449–52.
- 3 Abe K, Inui T, Hirono N, et al. Fluctuating MR images with mitochondrial encephalopathy, lactic acidosis, stroke-like syndrome (MELAS). *Neuroradiology* 1990;32:77.
- 4 Pavlakakis SG, Kingsley PB, Kaplan GP, et al. Magnetic resonance spectroscopy. Use in monitoring MELAS treatment. *Arch Neurol* 1998;55:849–52.
- 5 Kamada K, Houkin K, Iwasaki Y, et al. In vivo proton magnetic resonance spectroscopy for metabolic changes of human brain edema. *Neurol Med Chir (Tokyo)* 1994;34:676–81.
- 6 Graham GD, Kalvach P, Blamire AM, et al. Clinical correlates of proton magnetic resonance spectroscopy findings after acute cerebral infarction. *Stroke* 1995;26:225–9.
- 7 Houkin K, Kamada K, Kamiyama H, et al. Longitudinal changes in proton magnetic resonance spectroscopy in cerebral infarction. *Stroke* 1993;24:1316–21.
- 8 Negendank W, Sauter R, Brown TR, et al. Proton MR spectroscopy in patients with primary brain tumors: a multicenter study. *J Neurosurg* 1996;84:449–58.
- 9 Stefano ND, Matthews PM, Arnold DL, et al. Reversible decreases in N-acetylaspartate after acute brain injury. *Magn Reson Med* 1995;34:721–7.
- 10 Wilichowski E, Pouwels PJ, Frahm J, et al. Quantitative proton magnetic resonance spectroscopy of cerebral metabolic disturbances in patients with MELAS. *Neuropediatrics* 1999;30:256–63.
- 11 Ganslandt O, Steinmeier R, Kober H, et al. Magnetic source imaging combined with image-guided frameless stereotaxy: a new method in surgery around the motor strip. *Neurosurgery* 1997;41:621–7.
- 12 Kamada K, Takeuchi F, Kuriki S, et al. Functional neurosurgical simulation with brain surface magnetic resonance images and magnetoencephalography. *Neurosurgery* 1993;33:269–73.
- 13 Tallan HH. Studies on the distribution of N-acetyl-L-aspartic acid in brain. *J Biol Chem* 1956;224:41–5.
- 14 Miller BL. A review of chemical issues in ¹H NMR spectroscopy: N-acetyl-aspartate, creatine and choline. *NMR Biomed* 1991;4:47–52.
- 15 Kamada K, Houkin K, Iwasaki Y, et al. Metabolic and neurologic variations in patients with chronic cerebral infarction. A single voxel ¹H-MR spectroscopy study. *Neuroradiology* 1997;39:560–5.
- 16 Kamada K, Sauer M, Möller M, et al. Functional and metabolic analysis of cerebral ischemia using magnetoencephalography and proton magnetic resonance spectroscopy. *Ann Neurol* 1997;42:554–63.
- 17 Rossini PM, Tecchio F, Pizzella V, et al. On the reorganization of sensory hand areas after mono-hemispheric lesion: a functional (MEG)/anatomical (MRI) integrative study. *Brain Res* 1998;782:153–66.
- 18 Toyoda K, Ibayashi S, Yamamoto T, et al. Auditory evoked neuromagnetic response in cerebrovascular diseases: a preliminary study. *J Neurol Neurosurg Psychiatry* 1998;64:777–84.

NEUROLOGICAL STAMP

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 trypanosome 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 philatelically honoured in 1954, along with the German immunologist Behring (Stanley Gibbons 1123, Scott 722).

Among Behring's contributions was the demonstration that injections of blood taken from an animal with tetanus could confer immunity to the disease in other animals. He found the same for diphtheria and this led in collaboration with Paul Ehrlich to the development of an antitoxin for human patients. This treatment was first used in 1901 and subsequently caused a dramatic fall in mortality from diphtheria. Behring was 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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