

Aggressive confusional state as a clinical manifestation of status epilepticus in MELAS

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Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS)¹ is caused by mutations in the mitochondrial DNA (mtDNA), the most common at nucleotide 3243 in the tRNA^{Leu(UUR)}.² Although early development is typically normal, stroke-like episodes and seizures may occur in childhood or young adult life. Patients also may have short stature, exercise intolerance, hearing loss, dementia, pigmentary retinal degeneration, and migraine-like headache.

Patients and methods. *Patient 1.* A 43-year-old man had bilateral sensorineural hearing loss since adolescence and focal epilepsy since age 42 years. Before admission he had had transient left arm paresthesias and his wife had noted confusion and aggressive behavior. Neurologic examination revealed mild left arm paresis. The patient was aggressive and confused. Brain CT showed an inhomogeneous hypodensity in the right parietal region. MRI revealed cortical and subcortical hyperintensities in T2- and perfusion/diffusion-weighted images in the right parietal region; these findings were recent and compatible with MELAS. The EEG during the status showed right parietal sharp waves at a frequency of 0.5 to 2 Hz and rhythmic theta and delta waves alternating with periodic polymorphic complexes in a waxing and waning manner at a frequency of 0.5 to 1.5 Hz in the same region. After a loading dose of phenytoin (PHT) 750 mg followed by the administration of PHT 400 mg/bid, the patient's clinical condition improved. An EEG 7 days later was free of epileptiform discharges. Muscle biopsy showed about 5% ragged red fibers. PCR analysis from muscle DNA revealed the MELAS mutation at bp3243 of the mtDNA.

Patient 2. A 57-year-old woman had migraine-like headache, aphasia, and confusion. Because of bilateral sensorineural deafness she had a left cochlear implant. Neurologic examination revealed bilateral gaze-induced horizontal nystagmus, apraxia, aphasia, and confusion. The EEG showed waxing and waning repetitive sharp waves and high amplitude polymorphic complexes in the left occipital region at a frequency of 0.7 to 2 Hz. ECD-SPECT performed during the status epilepticus revealed a left occipital to occipitoparietal hyperperfusion (figure). The left-sided cochlear implant caused artifacts in the CT scans. Analysis of the CSF revealed elevated levels of lactate (4.14 mmol/L). A muscle biopsy showed about 7% ragged red fibers and the typical MELAS mutation at position 3243 of the mtDNA. Status epilepticus ceased after the patient was started on PHT (750 mg loading dose followed by 100 mg/bid) and clonazepam (2 mg/bid) treatment.

One month later she was readmitted because of recurrence of confusion and aggressive behavior. Repeat EEG showed a pattern similar to the previous one, but in the right occipital region. CT scans revealed new hypodensities in the area of the right middle cerebral artery. The patient recovered after additional doses of lorazepam and PHT.

Discussion. The pathophysiology that leads to epileptic activity in the brains of patients with certain mitochondrial diseases—e.g., MELAS, myoclonus epilepsy with ragged red fibers (MERRF), and Leigh syndrome—is not well understood. In other mitochondrial diseases, chronic progressive external ophthalmoplegia, and Kearns-Sayre syndrome, epilepsy is not a common clinical finding. One distinct difference may be that gray matter involvement is an early feature of the disease in MELAS and MERRF.³ Impairment of the oxidative phosphorylation could make the membrane potential unstable or lead to the generation of free radicals, and a disruption in the calcium homeostasis system.³

No studies have yet addressed the question of which antiepi-

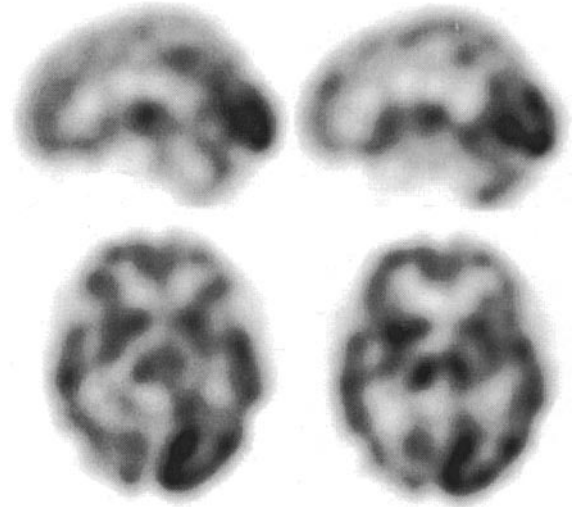


Figure. ECD-SPECT during status epilepticus reveals a left occipital parietal hyperperfusion in Patient 2.

leptic drug is best suited for chronic treatment of seizures in mitochondrial diseases. Valproate seems to be inappropriate, because it causes reduction of serum carnitine,⁴ inhibition of beta-oxidation and oxidative phosphorylation, and ultrastructural abnormalities of mitochondria with lipid deposition. Moreover, mitochondrial diseases may be considered a risk factor for valproate-induced liver failure.⁵ Although PHT also decreases serum carnitine levels,⁴ it is often used for treatment of status epilepticus. During status epilepticus the cerebral metabolism is increased. This has an even greater impact in patients with mitochondrial disease. In patients with MELAS, for example, neurons, which have to cope with an increased calcium influx during status epilepticus, are more likely to suffer from glutamatergic and calcium-induced excitotoxic cell damage, because their mitochondrial respiratory function and ATP availability are diminished. Impaired function of the calcium-ATPase results.⁶ Thus, rapid antiepileptic treatment of patients with MELAS with non-convulsive status epilepticus is important.

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Hypersensitivity pneumonitis possibly caused by riluzole therapy in ALS

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A 69-year-old man with sporadic amyotrophic lateral sclerosis (ALS) presented with complaints of increasing and disabling shortness of breath and dry cough for 3 months. A chest X-ray, taken for routine purposes 6 months before the start of symptoms, was normal.

The patient was diagnosed with ALS 33 months before presentation. Riluzole^{1,2} 50 mg twice daily was started 1 year later. He was treated with omeprazole 20 mg per day for more than 10 years, for a grade IV esophagitis. Ten days before the respiratory complaints started, omeprazole was switched to lansoprazole 15 mg per day.

After receiving antibiotics for a total of 20 days, without effect, the patient consulted a pulmonologist, who diagnosed him with pulmonary fibrosis. He was treated with methylprednisolone for 8 weeks (32 mg per day tapered every fortnight). This improved his general condition, but had only a minor effect on the coughing and dyspnea. After methylprednisolone was stopped, the complaints soon recurred and the patient presented himself to our clinic.

Clinical examination revealed ALS with predominant lower limb involvement: the patient was capable of walking with a walker, but was restricted to a wheelchair due to his dyspnea. The patient manifested an increased respiratory rate and use of accessory respiratory muscles. Lung auscultation was normal. Arterial blood gas at room air showed hypoxia (pH 7.49, oxygen tension 57 mm Hg, carbon dioxide tension 37 mm Hg). Laboratory tests revealed normal blood counts, normal liver and renal function and electrolytes, and increased erythrocyte sedimentation rate (63 mm/hour [normal value, 1 to 10 mm/hour]) and lactate dehydrogenase (701 U/L [normal value, 240 to 480 U/L]); antinuclear and antineutrophil cytoplasmic antibodies were negative. A chest X-ray was suggestive of interstitial lung disease (figure, A). Lung function measurements showed restrictive lung disease (forced vital capacity of 65% and total lung capacity of 57% of the predicted value) and a severe decrease of carbon monoxide diffusion (26% of the predicted value). Chest CT showed enlargement of the interlobular septa and bronchial structures (figure, C). Bronchoscopy results were normal. Broncho-alveolar lavage fluid stained negative for tuberculosis and contained no pathogenic bacteria or malignant cells. It contained 358 leukocytes per μL (normal value, 50 to 250 per μL), 51.5% of which were lymphocytes (normal value, 0.0 to 20.0%).

Thoracoscopic lung biopsy was performed, because less invasive technical investigations yielded no definite diagnosis and the patient was deteriorating. Anatomopathology revealed a picture suggestive of hypersensitivity pneumonitis (HP) (figure, E and F).

On the diagnosis of HP and exclusion of other potential causes, mainly by taking a detailed history of past and present exposures, riluzole and lansoprazole were discontinued and methylprednisolone 32 mg per day was restarted.

Three weeks later, the patient showed recovery from dyspnea and was walking with his walker again; the cough had disappeared. Control arterial blood gas showed complete normalization, control chest X-ray and CT showed significant resolution (figure 1, B and D), lung function showed partial recuperation (forced vital capacity of 78%), and carbon monoxide diffusion showed a significant increase to 40%.

Discussion. Neither the adverse events database of the distributor of riluzole (Aventis) nor the literature revealed reports of adverse events similar to the one reported here.^{3,4}

Omeprazole compromises the effect of riluzole by enhancing its metabolism, via induction of cytochrome p450 1A2, as can be read in the instruction leaflet of riluzole, supplied by Aventis. Lansoprazole does not have this effect. We hypothesize that the deleterious effect of riluzole in this patient only became apparent

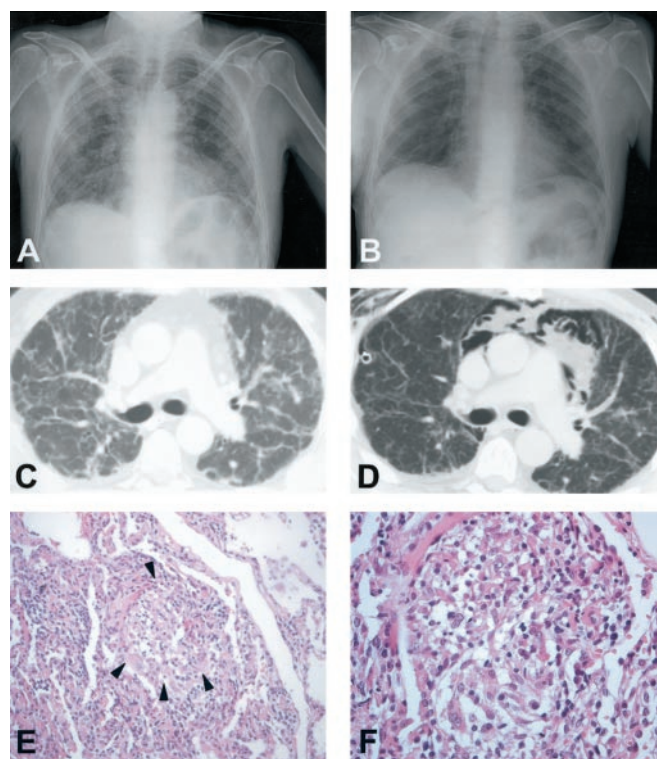


Figure. (A) Chest X-ray at presentation showed a normal mediastinum, normal lung hili, and a normal heart, but diffuse interstitial enhancement suggestive of interstitial lung disease. (B) Control chest X-ray, taken 3 weeks after cessation of riluzole therapy, showed resolution of the interstitial enhancement seen at presentation (see A). (C) Chest CT scan at presentation, at the level of the truncus pulmonalis, showed enlargement of the interlobular septa and bronchial structures (traction bronchiectasies). The lymph nodes are of normal size; there are no confluent alveolar infiltrates. (D) Control chest CT scan (level of the truncus pulmonalis), taken 3 months after cessation of riluzole, showed that the enlargement of interlobular septa and bronchial structures seen in C had diminished. (E) Pathologic examination of an open lung biopsy showed both the interstitial mononuclear infiltrate and loose epithelioid granulomas (a granuloma is delimited by the arrowheads), characteristic of hypersensitivity pneumonitis (hematoxylin-eosin [H-E], original magnification $\times 100$). (F) Detail of a loose epithelioid granuloma, as described in E (H-E, original magnification $\times 400$).

after switching omeprazole to lansoprazole, because this switch preceded the onset of symptoms in our patient by only 10 days. The prior 21 months of exposure to riluzole + omeprazole may have allowed the patient to develop a subclinical reaction to riluzole. That lansoprazole would be the cause of the HP is highly unlikely, in view of the short exposure to lansoprazole at the time of first symptoms (10 days) and the long-term widespread use of the compound without reports of similar adverse reactions.

The diagnosis of HP is supported by the biochemical, radio-

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