Mitochondrial encephalopathy with CADASIL-Like MRI

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Dear Sir,

Mitochondrial cytopathies due to mitochondrial DNA (mtDNA) mutations represent a heterogeneous group of respiratory chain disorders associated with variable systemic, muscular, peripheral and central nervous system involvement. Heteroplasmy and a threshold effect are responsible for the variability of clinical manifestations. Prototypic neurological phenotypes include mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS), myoclonus ataxic encephalopathy (MERRF), epileptic with ragged-red fibers (MERRF), stroke-like episodes (MELAS), myoclonus ataxic encephalopathy (MERRF), and Leigh’s syndrome [1].

Herein we describe a patient with molecular genetically diagnosed mitochondrial cytopathy with MRI findings strongly resembling CADASIL.

Case Report
A 48-year-old woman was admitted to our department for the evaluation of bilateral ptosis and restricted eye movements. Her personal medical history was uneventful, and there were no neurological disorders reported from other family members. At the age of 45 years she noticed drooping eyelids, impaired visual ability at night, exercise-dependent leg weakness and fatigability. Over the following years, symptoms deteriorated and she had to give up her job as a sewer. In addition, she reported pulsating headaches without accompanying vegetative symptoms. She had no complaints regarding her memory, and she did not report epileptic seizures or stroke-like episodes.

General examination revealed short stature (1.48 m) and obesity. Neurological examination showed bilateral right-dominant ptosis and external ophthalmoplegia. Funduscoppy as well as cranial nerve functions were normal. There was no atrophy, muscle tone was normal, but there was moderate proximal paresis of the legs (M4 to M5; MRC grading). There was a slight bilateral brady-dysdiadochokinesia, and walking with closed eyes was slightly ataxic. Tendon reflexes were bilaterally weak, and plantar responses were flexor.

Laboratory workup showed elevated creatine kinase (190 U/l; normal for our laboratory <167) and serum lactate levels (3.4 mmol/l; normal <2.4), while serum glucose and pyruvate were within the normal range. EEG demonstrated slight general slowing with theta activity. Electroencephalography and cardiolologic investigations including echocardiography were normal. Biopsy of the left quadriceps revealed mild myopathic changes consisting of variability of fiber diameter, elongated fibers, and some internalized nuclei. Immunohistochemistry revealed no red ragged fibers (trichrome stain), and normal staining for mitochondrial enzyme activity (COX, NADH, and SDH stains). Electron microscopy of multiple skin and muscle vessels did not demonstrate granular osmiophilic deposits in the vascular smooth muscle cells.

Neuroradiology
MRI and magnetic resonance spectroscopy (MRS) were performed on a 3T Philips Achieva whole-body MRI system (Philips Achieva whole-body MRI system (Philips Achieva whole-body MRI system (Philips Achieva whole-body MRI system (Philips Achieva whole-body MRI system (Philips Achieva whole-body MRI system (Philips Achieva whole-body MRI system (Philips Achieva whole-body MRI system (Philips Achieva whole-body MRI system (Philips Achieva whole-body MRI system (Philips Achieva whole-body MRI system...
ips Medical Systems, Best, The Netherlands) using a transmit/receive head coil. T₂-weighted MRI sequences showed pronounced confluent hyperintense lesions in the white matter of the anterior temporal poles and marked hyperintense lesions in the capsula extrema bilaterally. In addition, there were some circumscribed hyperintense lesions in the subcortical white matter as well as confluent subcortical lesions in the frontal regions (fig. 1A–C). No lesions suspicious for microhemorrhages were detected and there was no pathological contrast enhancement. Diffusion-weighted imaging and ADC mapping have not been performed.

'H-MRS data were acquired using high-resolution multi-spin echo spectroscopic imaging (TSI; TE = 288 ms, slice thickness = 1.5 cm, resolution 28 × 28, FOV = 220 mm) [7] and conventional chemical shift imaging (CSI; TE = 35 ms, resolution 16 × 16 and TE = 288 ms, resolution 12 × 12, NSA = 2; slice thickness = 2 cm, FOV = 220 mm). For all measurements the bandwidth was 2,500 Hz and the repetition time TR = 1,520. The data were received from axial slice, which was adjusted parallel to the calcarine fissure including the visual cortex. Regions of interest were selected in the subcortical white matter. Signal localization was achieved by use of point-resolved spectroscopy, and chemical shift selective excitation in combination with a dephasing gradient was used for water suppression. Spectral data were postprocessed using a constant baseline correction, B₀ correction, exponential spectral filtering by 2 Hz and Gaussian filtering of 3 Hz as well as linear phase correction. Relative metabolite concentrations were determined using LC Model. CSI showed a lactate double peak in the occipital cortical and subcortical brain regions bilaterally (fig. 2A). TSI revealed an alanine double peak in the frontal cortical brain regions (fig. 2B).

Molecular Genetic Analysis
Total DNA was extracted from EDTA-blood and skeletal muscle according to standard isolation protocols (Qiagen, Hilden, Germany). Screening for large-scale mtDNA rearrangements and point mutations was performed by long template polymerase chain reaction and single-strand conformation polymorphism, respectively. Abnormal conformers were directly sequenced on an ABI 377 DNA Sequencer (Applied Biosystems, Forster City, Calif., USA). No pathogenic point mutations but an 8.3-kb deletion in 28–36% of the mtDNA population of the muscle was detected. No deleted mtDNA was found in the blood. Amplification and sequencing of the entire Notch3 gene on both strands and including exon-intron boundaries were performed using standard methods (Dr. R. Spiegel, Genetica, Human Genetic Laboratory, Zurich, Switzerland). No mutations were detected.

Discussion
A mitochondrial cytopathy in our patient was strongly suggested by the clinical pattern including short stature, progressive external ophthalmoplegia, and myopathy, as well as by the laboratory findings of elevated serum lactate and creatine kinase levels. The diagnosis was finally confirmed by molecular genetic analysis of the mitochondrial genome revealing a heteroplasmic 8.3-kb deletion in the skeletal muscle.

The CSI MRS results were in line with the diagnosis of a mitochondrial cytopathy and demonstrated a lactate doublet peak in occipital areas, reflecting a dysbalance between glycolysis and oxidative respiration. In addition, TSI MRS revealed a high alanine peak in the frontal lobe. Elevated alanine levels may be seen in patients with mitochondrial encephalopathy [8].

Fig. 1. MRI. A, B T₂-weighted MR images demonstrate confluent hyperintense signal alterations in the subcortical white matter of the anterior temporal poles (A) and the capsula extrema (B) bilaterally. C In addition, there are circumscribed hyperintense signal alterations in the subcortical cerebral white matter which are confluent in the frontal regions.
However, elevated alanine has also been described in animal models of ischemic brain injury, where it was interpreted as a general marker of ischemia [9, 10]. In contrast, main cerebral MRS findings in CADASIL patients included decreased N-acyetyl aspartate, creatine and choline in pathological as well as normal-appearing white matter, whereas lactate was hardly visible in individual patient spectra and no alanine was detected [11].

Cerebral MRI alterations in mitochondrial encephalopathies are usually expected to be homogeneous and equally distributed in cortical and subcortical areas [12]. In our patient, however, there were circumscribed alterations in the anterior temporal poles, the capsula extrema and the subcortical white matter. This particular lesion pattern has been proposed to be suggestive of CADASIL [6, 13]. Compared to MRI alterations of patients with presumably sporadic cerebral small vessel disease without Notch3 mutations, involvement of the temporal pole had a sensitivity of 89% and a specificity of 86% for the diagnosis of CADASIL [6]. Involvement of the external capsule was less specific and had a sensitivity of 93% and a low specificity of 45% [6].

Fig. 2. MRS. A 1H-MR spectrum, corresponding to the voxel shown in the right occipital region, obtained by CSI measurement, TE = 288 ms. The arrow indicates the lactate double peak at 1.33 ppm. B 1H-MR spectrum, corresponding to the voxel shown in the left frontal region, obtained by TSI measurement, TE = 288 ms. The arrow indicates the alanine double peak at 1.48 ppm.

Based on the negative skin biopsy and Notch3 gene analysis, coincidental CADASIL in our patient can be practically excluded. Our findings therefore demonstrate an overlapping neuroradiological presentation of the two disorders. CADASIL and some phenotypes of mitochondrial encephalopathies also share several clinical characteristics such as migraine and stroke-like episodes, raising the question of common pathogenetic mechanisms. Clinical peripheral nerve or muscle involvement, a hallmark of mitochondrial cytopathies, is not evident in CADASIL. However, several independent CADASIL families carrying different Notch3 mutations had muscle mitochondrial abnormalities [14–16]. In a morphological study, abnormal mitochondria containing paracrystalline inclusions were detected, but these abnormalities were not associated with mitochondrial dysfunction or mtDNA mutations [16]. Another CADASIL patient had coincident mtDNA and Notch3 mutations [14], and a recent study demonstrated an increased rate of mtDNA sequence variations within CADASIL pedigrees [17]. In addition, experimental data of a lethal mutation of the Drosophila Notch3 gene revealed a significantly decreased activity of two respiratory chain complexes, NADH dehydrogenase and ATP synthase [15].

In conclusion, mitochondrial encephalopathy may be associated with anterior temporal lobe changes thought to be specific of CADASIL. MRI and MRS studies might be useful tools in identifying overlap and co-occurrence of these two disorders, and might contribute to a better understanding of their pathophysiological intersections.

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References