Correlations of brain 1H-MRS, DTI, and post-mortem findings in patients with mitochondrial neurogastrointestinal encephalomyopathy (MNGIE).

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Introduction

Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) is a rare autosomal recessive disorder caused by loss of function mutations in the nuclear gene encoding tymidine phosphorylase (TP) that generate mitochondrial nucleotide pool imbalances and subsequent mitochondrial DNA (mtDNA) defects [1]. The presence of brain diffuse white matter (WM) hyperintensities on T2- weighted sequences is typical, even if the gastrointestinal involvement is more severe than the neurological, leading to cachexia and adverse outcome in early adulthood [2]. The aim of this study was to characterise in five MNGIE patients the leucoencephalopathy combining ^{1}H-MRS and DTI in order to clarify its pathophysiology, correlating MR findings with post-mortem study obtained in one patient.

Methods

Five patients with a molecular diagnosis of MNGIE and 12 sex- and age- matched healthy controls were studied. Informed consent was obtained from all the subjects. Neuropathological examination was carried out in patient 1. Brain MR studies were performed using a 1.5T GE Signa Horizon LX whole-body scanner. Spectra were acquired using the PRESS localisation sequence (TE=35 ms; TR=4000 ms, number of acquisitions=64) from the left parietal WM (volume=2x2x2 cm^3). Absolute concentrations of N-acetylaspartate (NAA), creatine-phosphocreatine (Cr), and choline (Cho) were calculated by acquiring spectra of unsuppressed water (TE from 25 to 1000ms; TR=15000ms) [3] and using a T2 for metabolites (for NAA=742 ms; Cho=293 ms, Cr=211 ms) derived from 15 healthy subjects. Spectra were analyzed with the LCModel software package [4]. Diffusion-weighted EPI images (matrix=128x128, FOV=24 cm, slice separation= 6 mm, TE= 98.8 ms, TR=10 s, b= 0, 900 mm^2/s, in 6 directions) were acquired. Diffusion images were eddy-current corrected and maps of the fractional anisotropy (FA) and mean diffusivity (MD) were calculated using FSL 3.2 (FMRIB Software Library, Oxford, U.K.). An ROI covering the spectroscopy voxel was generated in the DTI volume, using the location information in the voxel header, and mean FA, MD, axial and radial components of MD (AD and RD) values were calculated in this ROI, after excluding pixels with MD > $2.0x10^{-3}$ mm^2/s, considered to be CSF. Group differences between patients and controls were calculated for MRS and DTI parameters, using the Student T-test. Correlations were performed between MRS, DTI and clinical parameters, using the Pearson test 1-tailed. Statistical significance was taken as $p<0.05$.

Results

Conventional brain MRI demonstrated the typical diffuse confluent cerebral and cerebellar increased signal intensity on T2-w sequences in all five patients.

WM [NAA], [Cr], and [Cho] were significantly lower in patients than in controls (Table 1) .

WM MD, AD, and RD were significantly higher than controls and FA significantly lower (Table 1).

Case 1 and 4, studied 10 and 12 months before the decease respectively, showed the greatest increase in WM MD, AD and RD values (Table 1).

WM MD, AD and RD values were negatively correlated only with WM [NAA] and positively correlated with the age of patients (Table 2).

There was a significant negative correlation between WM [NAA] and age, that was not found for the other metabolites (Table 2).

Brain pathological examination of case 1 did not detect demyelination, neuronal loss or gliosis.

Table 1. Demographic, ^{1}H-MRS, and DTI findings from WM of 5 MNGIE patients compared to healthy controls.

	Age/sex	[NAA] mM	[Cho] mM	[Cr] mM	FA	MD ($x10^{-3}$ mm^2/s)	AD ($x10^{-3}$ mm^2/s)	RD ($x10^{-3}$ mm^2/s)
Case 1	36/M	6.38	4.70	2.02	0.23	1.28	1.59	1.12
Case 2	29/F	7.48	4.95	1.75	0.32	0.91	1.22	0.76
Case 3	28/M	6.51	3.74	1.59	0.33	0.99	1.33	0.83
Case 4	38/M	5.75	3.28	1.25	0.22	1.38	1.70	1.23
Case 5	27/F	7.19	4.18	1.34	0.22	1.04	1.30	0.92
Mean±Sd	31±5	6.66±0.69	4.17±0.69	1.59±0.31	0.26±0.05	1.12±0.20	1.43±0.21	0.97±0.20
Controls	38±5	9.44±0.64	6.02±0.49	1.97±0.22	0.41±0.02	0.84±0.04	1.22±0.06	0.65±0.04
***p* value**		*<0.01*	*<0.01*	*<0.05*	*<0.01*	*<0.01*	*<0.01*	*<0.01*

Table 2. Correlations between age, ^{1}H-MRS, and DWI findings from WM of 5 MNGIE patients.

		Age (years)	[NAA] mM	MD ($x10^{-3}$ mm^2/s)	AD ($x10^{-3}$ mm^2/s)	RD ($x10^{-3}$ mm^2/s)
Age	Coefficient of correlation		-0.838	0.952	0.972	0.935
	p		0.038	0.006	0.003	0.010
[NAA]	Coefficient of correlation	-0.838		-0.871	-0.915	-0.841
	p	0.038		0.027	0.015	0.037

Discussion

The reduction in all ^{1}H-MRS metabolites in the brain WM of our MINGIE patients can be explained by a dilution effect due to increased brain water content demonstrated by the increased of WM MD values. This MR pattern represents a distinctive finding in the wide family of leukoencephalopathies and also among other forms of mitochondrial disease [5]. On the basis of the correlation between the elevation of MD and the decrease of WM [NAA], not found for the other metabolites, we hypothesize that the brain damage in MNGIE is compartmentalised and mediated by the impairment of the complex system of osmoregulation where also NAA has been implicated as neuronal osmolyte. NAA acting as a molecular water pump, removes metabolic water from myelinated neurons by transporting water against a water gradient into extracellular fluids as NAA is transported down its gradient; and the released NAA is recycled and the water is transported via astrocytes or extracellular fluids to the blood–brain barrier and then to the vascular system for its removal [6]. Our results are consistent with the functional alteration of the blood–brain barrier demonstrated in a previous post-mortem study of two MNGIE patients [7] and the absence of detectable brain axonal/neuronal loss, demyelination, and gliosis in the same cases and in one of our patient [7]. The correlations between ^{1}H-MRS, and DTI changes and the age of patients suggest that these MR parameters are robust bio-markers of diagnosis and progression of disease, and that can be usable for monitoring therapeutic trials [8].

References

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