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Research report

Brain magnetic resonance metabolic and microstructural changes in adult-onset autosomal dominant leukodystrophy

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ABSTRACT

Introduction: adult-onset autosomal dominant leukodystrophy (ADLD) is a rare inherited disorder due to a duplication of lamin-B1 (LMNB1) gene. The aim of this study was to investigate brain metabolic and microstructural alterations by using advanced MR techniques.
Methods: we performed brain MR scans including single-voxel proton-MR Spectroscopy (^{1}H-MRS) of the lateral ventricles and parietal white matter and diffusion tensor imaging (DTI) in 4 subjects with LMNB1 gene duplication, 6 non-mutated relatives and 7 unrelated healthy controls. Cervical and thoracic spinal cord MR was performed in three symptomatic subjects with LMNB1 mutation. All participants underwent clinical and neuropsychological evaluation.
Results: all subjects with LMNB1 gene duplication presented pathological accumulation of lactate in lateral ventricles CSF and no alterations of brain white matter absolute metabolites concentrations or metabolites/Cr ratios. We found increased white matter intra- and extracellular water transverse relaxation times. Tract-based spatial statistics analysis detected a significantly reduced fractional anisotropy in the genu of the corpus callosum in mutated cases compared to unrelated healthy controls and non-mutated relatives. Moreover, we detected different degrees of the typical white matter signal intensity alterations and brain and spinal atrophy at conventional MRI in symptomatic subjects with LMNB1 mutation. A mild impairment of executive functions was found in subjects with LMNB1 gene mutation.
Conclusion: in subjects with LMNB1 gene duplication, we found a pathological increase in CSF lactate, likely due to active demyelination along with glial activation, and microstructural changes in the genu of the corpus callosum possibly underpinning the mild neuropsychological deficits.

1. Introduction

Lamins are components of nuclear membrane regulating nuclear architecture, chromatin organization and cellular senescence (Cortelli et al., 2012; Dreesen et al., 2013). Increased production of lamin-B1 (LMNB1) leads to abnormal oligodendrocytes and myelin development (Cortelli et al., 2012). Adult-onset autosomal dominant leukodystrophy (ADLD) is a rare inherited laminopathy due to a duplication of LMNB1 gene on chromosome 5q31 (Cortelli et al., 2012; Eldridge et al., 1984; Coffeen et al.,

Abbreviations: ^{1}H-MRS, proton MR spectroscopy; AAE, age at evaluation; ADLD, adult-onset autosomal dominant leukodystrophy; BET, brain extraction tool; BMDB, brief mental deterioration battery; CC, corpus callosum; Cho, choline containing compounds; Cr, creatine plus phosphocreatine; CSF, cerebro-spinal fluid; DTI, diffusion tensor imaging; EPI, echo planar image; FA, fractional anisotropy; FAB, frontal assessment battery; FDT, FMRIB's diffusion toolbox; FLAIR, fluid attenuated inversion recovery; FNIRT, FMRIB's non-linear image registration tool; FR, final result; FSE, fast spin-echo; FSL, FMRIB's software library; FSPGR, fast spoiled gradient echo; GLX, glutamine-glutamate complex; IR, interquartile range; IVM, immediate visual memory; LMNB1, lamin B1; med, median; mI, myo-inositol; MMSE, mini-mental state evaluation; NAA, *N*-acetyl-aspartate; ppm, parts per million; ROI, region of interest; TBSS, tract based spatial statistics; VOI, volume of interest.

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2000; Padiath et al., 2006). Main clinical features include autonomic failure associated with pyramidal and cerebellar involvement leading to severe motor impairment, and various degrees of cognitive deficits (Cortelli et al., 2012; Brussino et al., 2009; Potic et al., 2013). Conventional MR typically shows different degrees of signal alterations and atrophy in brain and spinal white matter with a relative sparing of periventricular areas and U-fibers (Melberg et al., 2006; Sundblom et al., 2009). Moreover, MR-signal alterations in the corticospinal tract and corpus callosum (CC) have also been detected in asymptomatic mutated subjects (Melberg et al., 2006). Two recent studies evidenced altered brain white matter metabolism in vivo using proton MR spectroscopy (^{1}H-MRS) in ADLD families (Finnsson et al., 2013; Potic et al., 2013). To date, in the only diffusion tensor imaging (DTI) study in ADLD, reduced fractional anisotropy (FA) values in the internal capsule and CC were reported (Potic et al., 2013). The limited post-mortem studies showed rarefaction and vacuolation of myelin with relative sparing of brain cortex and U-fibers (Coffeen et al., 2000; Melberg et al., 2006). In addition, glial compartment appeared relatively preserved with signs of mild reactive astrogliosis and without evidence of active inflammation (Coffeen et al., 2000; Melberg et al., 2006).

The aim of our study was to assess brain metabolic and microstructural changes in four subjects with LMNB1 gene duplication from one Italian family with ADLD, using ^{1}H MRS and DTI and to correlate neuropsychological findings with white matter alterations.

2. Materials and methods

2.1. Subjects

We enrolled four subjects with LMNB1 gene duplication (2 males; age, mean ± standard deviation = 46.0 ± 16 years; range: 23–58 years) belonging to the same Italian family. We also enrolled six asymptomatic non-mutated relatives (6 males; age = 37.0 ± 3 years; range = 32–39 years) and seven unrelated healthy volunteers (6 males, age = 45.0 ± 3 years, range = 41–49 years) as control-groups. All participants underwent extensive neurological assessment and mutated cases performed also neuropsychological testing including mini-mental state examination (MMSE) (Folstein et al., 1975; Measso et al., 1993), frontal assessment battery (FAB) (Apollonio et al., 2005), short and long term verbal memory test (Carlesimo et al., 1996), visual search test (barrage test) (Gallassi et al., 1986), simple copy design test (Carlesimo et al., 1996), simple verbal analogies test (Gallassi et al., 2014), selective visual attention test (stroop test) (Caffarra et al., 2002), immediate visual memory test (Carlesimo et al., 1996), phonemic and semantic verbal fluency test (Novelli et al., 1986) and brief mental deterioration battery (BMDB) resulting in a score, called final result, a measure of global cognitive functioning (Gallassi et al., 1986; Gallassi et al., 2008). All test results were corrected for age and education according to Italian standardizations.

All participants underwent a standardized brain MR protocol, and three symptomatic ADLD subjects were also subjected to cervical and thoracic spinal cord MR scans. The study protocol was approved by the local ethical committee. We obtained informed consent from all participants prior to their inclusion in the study, according to the Declaration of Helsinki.

2.2. Magnetic resonance imaging and proton MR spectroscopy acquisition

MR studies were performed using a 1.5 Tesla (Signa Horizon LX, General Electrics Medical Systems Milwaukee, Wisconsin) system equipped with a quadrature birdcage head coil. In all recruited participants structural imaging protocol included: T_1w volumetric FSPGR (TR = 12.5 ms, TI = 600 ms, TE = 5.1 ms, FOV = 25.6 cm^2; 1 mm isotropic voxels), axial and coronal FLAIR T_2w (TR = 8000 ms, TI = 2000 ms, TE = 93.5 ms, 3 mm slice thickness with no inter-slice gap), and FSE axial T_2w (TR = 7000 ms, TE = 100 ms, 3 mm slice thickness) sequences. We also obtained axial DTI images of contiguous 3 mm slices using a single-shot spin echo-EPI sequence (TR = 10 s, TE = 85.4 ms, FOV = 32 × 32 cm, in-plane resolution = 2.5 × 2.5 mm, 64 diffusion-weighted directions and 7 unweighted scans, *b*-value = 900 s/mm^2).

Three symptomatic patients with LMNB1 mutation also underwent cervical and thoracic spinal cord MR scans, consisting of sagittal (cervico-thoracic level) and axial (cervical level) spinal cord FSE T_2w (TR = 3500 ms, TE = 108 ms; 3.5 mm slice thickness) and FSE T_1w (TR = 620 ms, TE = 10 ms; 3.5 mm slice thickness).

Proton MR spectra were acquired using the point-resolved spectroscopy (PRESS) single voxel localization sequence with chemical shift selective water suppression (CHESS). Careful localization of two ^{1}H-MRS volumes of interest (Fig. 1) was performed using the three orthogonal projections of the 3D T_1w FSPGR and the T_2w images.

One voxel was selected to include the parietal white matter (Fig. 1), (TR = 4000 ms; TE = 35 ms, volume = 20 × 20 × 20 mm; number of acquisitions = 128; acquisition time = 4 min 16 s). For this localization we also acquired unsuppressed water spectra at TE = 26, 30, 40, 50, 60, 80, 100, 300, 600, 900, and 1000 ms, with TR = 15000 ms to evaluate the intra and extracellular water content in the white matter with the aim of absolute metabolite quantification using water as an internal reference. The long TR was chosen to minimize the effect of T_1 relaxation on the water signal. The total acquisition time for unsuppressed water spectra was about 3 min.

A second volume of interest was selected in the lateral ventricles (Fig. 1), to include mostly CSF in order to maximize the detection of lactate (TR = 1500 ms, TE = 288 ms, volume range = 6.4–9.6 cm^3, number of acquisitions = 384, acquisition time = 10 min 12 s) (Grimaldi et al., 2010). We did not perform MRS acquisition in lateral ventricles in healthy unrelated controls because lactate content in the CSF in both the intracellular and extracellular compartments in resting conditions is far below the threshold of detectability for 1.5 T single voxel MRS (about 1.0 μmol/g) (Dienel, 2012). The total acquisition time for MRS evaluation was about 18 min.

2.3. Proton MR Spectroscopic data analysis

2.3.1. Lactate content detection in the lateral ventricles localization

Suppressed-water proton MR spectra from the lateral ventricles were pre-processed with Gaussian filtering of 2 Hz followed by exponential filtering of −1 Hz, and lactate fitted using the time domain semi-parametric algorithm QUEST (Ratiney et al., 2005). The amount of lactate was assessed using unsuppressed water signal acquired by PROBE as an internal standard (La Morgia et al., 2008) to convert the value in arbitrary units derived from the fitted lactate spectra to ratio relative to water, since Cr is useless as a reference in a lateral ventricle localization.

2.3.2. Metabolites' quantification

In order to obtain an absolute metabolite quantification for the white matter localization, both suppressed and unsuppressed water spectra were processed with version 6.3 of the fitting program LCModel (Provencher, 1993; Provencher, 2001), that analyzes spectra as a linear combination of complete model spectra of metabolite solutions in vitro. For both water and metabolite acquisitions, LCModel yields a value for fitted signals in arbitrary units, which is nevertheless corrected for transmitter and receiver gain, for the number of excitations, proton number and acquisition