Investigating bioenergetic dysfunction in motor neurone disease using 31 phosphorus magnetic resonance spectroscopy: a feasibility study

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Background: Motor neurone disease (MND) is an inexorably fatal neurodegenerative condition. An emerging role for the importance of bioenergetic dysfunction in the pathophysiology of MND is recognised and characterised by deficits in energy metabolites such as adenosine triphosphate (ATP) and phosphocreatine (PCr). Phosphorus magnetic resonance spectroscopy (^{31}P-MRS) allows detection of ATP and PCr and represents a non-invasive tool to probe cellular bioenergetics *in vivo*. There are technical challenges and, although a few previous muscle studies exist, no ^{31}P-MRS brain study has yet been conducted in MND.

Objectives: The objective of this pilot study is to demonstrate feasibility of a ^{31}P-MRS protocol to study bioenergetics in both brain and muscle in patients with MND.

Methods: ^{31}P-MRS spectra were acquired from 12 healthy volunteers, each scanned three times, from a coronal acquisition centred on motor tracts. Quality of spectra was evaluated using signal to noise ratios. Repeatability and reproducibility were assessed using coefficients of repeatability (CR), coefficients of variability (CV), and Bland-Altman upper and lower limits of agreement (ULOA and LLOA); measurement bias was evaluated; and feasibility in terms of participants' tolerance was assessed. In muscle, a dynamic protocol to measure changes in PCr during contraction of lower leg muscles was developed and tested in four healthy volunteers. Pilot brain and muscle ^{31}P-MRS spectra have been acquired employing the developed protocol from four MND patients, to date.

Results: In healthy volunteers, signal to noise ratios for brain PCr and γATP were 138.0 (±30.9) and 37.9 (±7.8), respectively; deep white matter PCr/γATP was 1.11 (±0.07) and was characterised by CR=0.34, CV=6.1%, ULOA=0.31, and LLOA= -0.31. No systematic bias was detected. Mean muscle PCr/total phosphorus signal was 0.51 (±0.02) at rest and 0.41 (±0.02) at the end of muscle contraction in healthy volunteers. In patients, deep white matter PCr/ γATP was 1.30 (±0.07) and mean muscle PCr/total phosphorus signal results were 0.45 (±0.16) at rest and 0.18 (±0.11) following exercise. Spectra acquisition was well tolerated by healthy participants and MND patients in all cases.

Discussion: We have demonstrated feasibility of applying ^{31}P-MRS in healthy participants and people living with MND in both brain and muscle. The technique yields good quality spectra (as shown by the relatively high signal to noise ratio), is repeatable and reproducible (as exemplified by low CR, CV, and relatively narrow limits of agreement), and was well tolerated by participants even in the presence of significant disability. The technique has potential to identify patients with abnormal bioenergetics, decipher mechanisms underpinning energy dysmetabolism, and merits further investigation as a biomarker for future clinical trials.