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Central Motor Conduction Time and Diffusion Tensor Imaging metrics in children with complex motor disorders

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HIGHLIGHTS

- Both measurement of Central Motor Conduction Time (CMCT) and Diffusion Weighted Imaging (DWI) may aid with the clinical assessment of children and young people with complex motor disorders.
- Diffusion Tensor Imaging (DTI) metrics in a group of children with complex motor disorders did not correlate with CMCT, nor were group wise differences in DTI metrics identified when children with normal and abnormal CMCT where compared.
- Children and young people with acquired dystonia were frequently found to have normal CMCT values.

ABSTRACT

Objectives: To explore potential correlations between Diffusion Tensor Imaging (DTI) metrics and Central Motor Conduction Time (CMCT) in a cohort of children with complex motor disorders.
Methods: For a group of 49 children undergoing assessment for potential Deep Brain Stimulation (DBS) surgery, CMCT was derived from the latency of MEPs invoked by transcranial magnetic stimulation of the contralateral motor cortex and from peripheral conduction times. Tract-Based Spatial Statistics (TBSS) was used to compare Diffusion Tensor Imaging (DTI) metrics between children with normal and abnormal CMCT. TBSS was also used to look for correlations between these metrics and CMCT across the group.
Results: Median age at assessment was 9 years (range 3–19 years). For 14/49 children a diagnosis of primary dystonia had been made. No correlation could be found between DTI metrics and CMCT, with no difference in metrics found between children with normal and abnormal CMCT.
Conclusions: DTI metrics did not differ between children with normal and abnormal CMCT. Tissue properties determining CMCT may not be explained by existing DTI metrics.
Significance: DTI and CMCT measurements provide complementary information for the clinical assessment of children with complex motor disorders.

1. Introduction

Hypertonic motor disorders in childhood may arise from a diverse range of pathological processes, often affecting more than one motor region of the central nervous system. An important distinction to be made in clinical practise is the relative integrity of the corticospinal tract (CST) in children with hypertonic motor disorders, influencing understanding of the underlying disease process and, more importantly, the choice of clinical intervention (Lin, 2003, 2011; McClelland et al., 2011). Dystonia and spasticity are often seen coincidently in the child with pathological hypertonicity, particularly in the context of cerebral palsy (Sanger et al.,

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2003). Clinical evaluation of the child with hypertonia is challenging, and concerns exist that the relative contributions of dystonia and spasticity may be under- and over-estimated respectively (Lin, 2011). Transcranial Magnetic Brain Stimulation (TMS) is a well-established tool for probing the integrity of the CST, and has been used to demonstrate the maturation of Central Motor Conduction Time (CMCT) in children (Eyre et al., 1991; Koh and Eyre, 1988). Prolonged CMCT has been demonstrated in a number of disorders known to affect the CST, including stroke, Multiple Sclerosis (MS) and Motor Neuron Disease (MND) (Berardelli et al., 1991; Heald et al., 1993; Hess et al., 1986). We have previously reported our own experience of using CMCT as a clinical tool for assessing CST integrity in children with dystonia undergoing assessment for deep brain stimulation (DBS), demonstrating normal CMCT time in the majority of patients for whom structural Magnetic Resonance Imaging (MRI) would be suggestive of CST damage (McClelland et al., 2011).

In recent years Diffusion Tensor Imaging (DTI) has become widely used in the investigation of children with movement disorders. DTI exploits the fact that the diffusion of water has different characteristics within different types of brain tissue to provide information about the microstructure of the brain, potentially providing a window into the relationship between structure and function (Le Bihan et al., 2001). Diffusion which is unrestricted and equal in any direction is termed isotropic, whereas diffusion which is restricted more in one plane than another is termed anisotropic. For example, anisotropic diffusion is seen in white matter pathways because water diffuses relatively freely along the longitudinal axis of a coherent axonal bundle, compared with relatively restricted diffusion in a direction perpendicular to this. One commonly used parameter is Fractional Anisotropy (FA), a measure of the directionality of water movement with values from 0 to 1, higher values indicating greater directionality which in turn is thought to reflect the integrity of white matter pathways. DTI has considerably advanced our understanding of the pathophysiology in cerebral palsy, and in particular the relative contributions of disruptions to motor and sensory pathways (Scheck et al., 2012). In the context of MND correlations have been demonstrated between the severity of motor disability, increasing delay in CMCT and reduction in FA (Ellis et al., 1999; Iwata et al., 2008; Mitsumoto et al., 2007; Sach et al., 2004). Taken together, these and other studies raise the possibility that FA could potentially be used as a biomarker for CST integrity.

Only one reported study to date has investigated possible correlations between DTI metrics and CMCT in healthy subjects, finding no areas of correlation (Hübers et al., 2012). This study applied a voxelwise approach, utilising Tract Based Spatial Statistics (TBSS) (Smith et al., 2006) to explore possible relationships between DTI metrics and a number of TMS measures, concluding that FA alone may be a poor marker of the biophysical tissue properties underlying CMCT.

We aimed to explore the relationship between CMCT and DTI metrics in a sample of children with motor disorders undergoing assessment for DBS. We utilised a TBSS approach, including FA and other DTI metrics, namely Mean Diffusivity (MD), Radial Diffusivity (RD) and Axial Diffusivity (PD).

2. Methods

A retrospective analysis was performed, using data collected during the routine clinical assessment of 49 children with complex motor disorders undergoing assessment for possible DBS surgery. These children currently undergo MRI, including diffusion weighted imaging (DWI) sequences, and CMCT in order to assess the integrity of the corticospinal tract, given that evidence of significant CST dysfunction would be considered a contraindication to DBS.

Inclusion criteria for cases involved in this study were assessment at our centre between July 2008 and January 2012, inclusion of DWI sequences (see below) during routine clinical assessment and measurement of CMCT to the right upper limb performed during routine clinical assessment. All children presented with severe dystonic movement disorders, refractory to medical therapy. No child had signs suggestive of peripheral neuropathy on clinical examination.

2.1. Clinical features

In all 49 children the predominant motor phenotype was dystonia, with additional clinical features of spasticity in 8 (16.3%) cases. Median age at assessment was 9 years (range 3–19 years). For 14 children dystonia was classified as primary on aetiological grounds (none of whom were found to have clinical features of spasticity). In the remaining 35 children dystonia was classified as secondary on an aetiological basis (Bressman, 2004). In the primary dystonia group 3 children had a confirmed mutation in the *torsin A* gene (DyT1 +ve dystonia), 1 child a confirmed mutation in the epsilon sarcogylcan gene (DyT11 +ve dystonia), with the remaining 10 children classified as having idiopathic primary dystonia. In the secondary dystonia group 19 children had a diagnosis of cerebral palsy, 4 glutaric aciduria, 1 Lesch Nyhan disease, 1 hypomyelination, 3 pantothenate kinase associated neurodegeneration, 1 methylmalonic acidaemia, 1 a genetically confirmed mitochondrial disorder and 5 children had undiagnosed presumed neurometabolic disorders.

2.2. Measurement of CMCT

Measurement of CMCT was conducted according to standard neurophysiological methodology (Mills, 1999). Distal M- and F-wave latencies were measured in the ulnar nerves, bilaterally or unilaterally according to the child's ability to cooperate with testing. TMS (MagStim 200; Magstim Company, Carmarthenshire, UK) was applied over the contralateral motor cortex using a circular coil (90 mm, maximum magnetic field strength 2.0 T). Motor Evoked Potentials (MEPs) were recorded in the activated abductor digiti minimi. Active contraction was chosen because TMS does not evoke MEPs in relaxed muscle in children below the age of 6, and consistent MEP responses are not recorded in relaxed muscle until adolescence (Eyre et al., 1991; Koh and Eyre, 1988).

Magnetic stimulus intensity was progressively increased in steps of 10% maximum stimulator output until reproducible MEPs were obtained. It was not possible to measure precise resting or active corticomotor threshold because of ongoing involuntary muscle activity. The level of muscle contraction is difficult to standardise in a child with dystonia, owing to involuntary movement. However, above a level of 15% maximum voluntary contraction, the latency of MEP has been shown to stabilize (Mills, 1999). Therefore, the MEPs were recorded during activity estimated to be greater than 15% of maximum voluntary contraction. Three to eight suprathreshold MEP responses were recorded and superimposed to identify the earliest onset latency. CMCT was then calculated from the measured latencies according to the equation

$$\mathrm{CMCT} = \mathrm{MEP} - (\mathrm{F} + \mathrm{M} - 1)/2.$$

The upper limit of normal for CMCT to the hand muscle was taken as 7.9 ms (Mills, 1999). CMCT values were classed as either normal or prolonged based on established data showing that CMCT reaches normal adult values by the age of 2–4 years for upper