Subtle upper limb impairment in asymptomatic multiple sclerosis subjects

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Subtle upper limb impairment in asymptomatic multiple sclerosis subjects

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We evaluated upper limb function in multiple sclerosis (MS) subjects (11 clinically definite MS patients and seven clinically isolated syndrome (CIS) subjects), with a normal upper limb standard neurological examination. Subjects performed center-out reaching movements under visual control, with and without vision of the hand. Their movements were recorded through a digitizing tablet. Motor performance was also related to lesion load, estimated from magnetic resonance imaging (MRI). We found that in MS and CIS subjects, under the hand vision condition, movements were significantly less smooth, and had a less symmetric speed profile. However, the observed impairment did not correlate with MRI findings. This result may be interpreted as evidence of a compensatory strategy, elicited by subtle alterations in sensorimotor control. Multiple Sclerosis 2007; 13: 428–432. http://msj.sagepub.com

Key words: asymptomatic; digitizing tablet; multiple sclerosis; upper limb; sensorimotor control

Introduction

The identification of new methods or techniques which might help in monitoring clinical progression and quantifying pathological disturbances in patients with mild or no clinical symptoms, could be of importance in the management of demyelinating diseases.

Conventional magnetic resonance imaging (MRI) is a sensitive tool for detecting abnormalities in subjects with multiple sclerosis (MS), and is a key to diagnosis, but lacks substantial correlation with clinical impairment and disability, as measured through commonly-used clinical scales, such as the Expanded Disability Status Scale (EDSS) [1]. Actually, the computer-assisted analysis of the movement in the arms might be able to detect minimal abnormalities and to quantify the degree of involvement, thereby obtaining objective data, which could be then utilized for the evaluation of the course of the disease or the response to particular therapeutics strategies.

It has been applied in the detection of central nervous system (CNS) damage in a number of neurological disorders, such as degenerative ataxia or Huntington’s disease [2–4]. However, this approach has not been extensively applied to the study of MS, if not for very peculiar patient subpopulations [5–7].

The aim of the study was: (i) to test whether movement analysis was capable of detecting subclinical abnormalities in motor control in asymptomatic MS subjects; and (ii) to evaluate the possible correlation between such abnormalities’ clinical data or total lesion load determined by MRI examination.

Materials and methods

Subjects

Eighteen subjects with demyelinating disease (15 female, three male), mean age 36 years (21–48), mean disease duration five years (0–13), were
included in the study. Out of this group, seven patients had monosymptomatic disease suggestive of MS (clinically isolated syndromes; CIS) [8], and 11 fulfilled Poser criteria [9] for clinically definite, relapsing-remitting (RR) MS. Patients were recruited at the Department of Neurology of the Hospital ‘P Antero Micone’, and the Department of Neuroscience, Ophthalmology and Genetics, University of Genova.

Patients with CIS had a first acute neurological event suggestive of CNS demyelination, and no alternative diagnosis was identified upon deep investigation. All CIS subjects showed T2 MRI focal abnormalities suggestive of demyelination, and oligoclonal bands at CSF analysis. Inclusion criteria were: EDSS less than or equal to 1 (presence of only neurological signs, but no sign or symptoms at upper limbs), and a ‘normal’ score for the ‘arm’ portion of the Scripps Neurological Rating Scale (NRS) [10], for the sensory, motor and cerebellar systems. Exclusion criteria were: relapses within the last three months, treatment with corticosteroids within the previous three months, and Mini Mental State Examination (MMSE) < 24.

Eight healthy, age-matched, subjects, with a normal neurological examination and no history of neurological diseases were used as controls. Informed consent was signed by all participants.

Clinical assessment

Patients underwent clinical examination to estimate their disability using the EDSS score, Scripps NRS and the Nine-Hole Peg Test (9HPT) [11] (average of four trials for each hand). Each patient was examined by the same neurologist.

MR imaging

Brain MRI scans were obtained using the same MR scanner (1T, Picker). During each session, the following scans were performed: DP/T2 (TR = 2400 ms, E = 30/80 ms); T1-weighted SE (TR = 768 ms, TE = 15 ms); FLAIR (TR = 7000 ms, TE = 96 ms, TI = 2200 ms).

Thick slices (5 mm), with no gap, were positioned parallel to a line that joins the most infero-anterior and the infero-posterior parts of the corpus callosum.

Lesions were first identified by the agreement of two experienced observers, on the first echo of the dual-echo scans, and on the T1-weighted scans; the second echo of the dual-echo scans or FLAIR images were always used to confirm the presence of lesions. For T1-weighted scans, hypointense lesions had a corresponding signal alteration on both echoes of the dual-echo images. Lesions were then segmented using a semi-automated segmentation technique with commercially available image analysis program (Analyze 6.0; AnalyzeDirect, Inc. Lenexa, KS, USA). Infratentorial brain T1 and T2 lesion load, supratentorial brain T1 and T2 lesion load, and total brain T1 and T2 lesion load were calculated.

Visuo-motor task

Subjects performed center-out reaching movements with their dominant hand on a digitizing tablet (CalComp 2500; GTCO CalComp, Columbia, MD, USA). Belts and a splint restrained the movements of the torso, wrist and fingers. The forearm was suspended to balance the effect of gravity, and the height of the seat was adjusted so that the shoulder, elbow and hand lay on the same horizontal plane. For each subject, shoulder position was adjusted so that, with the hand at the center of the tablet, the elbow and shoulder joints were flexed about 90° and 45°, respectively.

Subjects were requested for fast and accurate movements (amplitude 10 cm), in one of eight (0°, 45°, 90°, 135°, 180°, 225°, 270°, 315°) randomly selected directions on the horizontal plane. Target and hand position were continuously displayed (as a 1-cm circle and a 0.5-cm dot, respectively, both black against a white background), on a 17” computer screen, placed about 1 m away, at eye level.

The experimental task involved two conditions: (i) VISION, ie, subjects could see on the computer screen both the target position and the instantaneous hand position; and (ii) NO VISION, ie, no display of hand position. For each condition, each subject performed three blocks of five trajectories for each direction, but only the last two blocks were considered for analysis.

Kinematic analysis

Hand trajectories were sampled at 125 Hz, and smoothed (fourth order Savitzky–Golay, equivalent cut-off frequency: about 6 Hz). The same filter was used to estimate all subsequent derivatives (speed, acceleration, jerk). A number of indicators were then estimated:

- Aiming error: difference between target and actual initial trajectory direction (first 100 ms of movement);
- Path curvature: percent increase of the length of the actual hand path, relative to the straight line connecting initial and target position;
- Symmetry: ratio between the durations of acceleration and deceleration phases;

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Smoothness: computed as the logarithm of the normalized time integral of the squared norm of the jerk (third time derivative of hand trajectory). This indicator is motivated by the observation that in normal subjects, hand trajectories are maximally smooth, i.e., they appear to minimize the jerk integral. The jerk integral was normalized with respect to movement amplitude and duration.

Statistical analysis

We ran a two-way ANOVA with two factors: disease (MS, CIS, or controls) and vision (yes, no); post-hoc analysis (Tukey) was used wherever appropriate.

The relationship between MRI parameters (T2 and T1 total lesion load), kinematic parameters and clinical scores were assessed using Spearman’s Rank Correlation.

Results

Typical trajectories and speed profiles observed in the VISION condition are displayed in Figure 1.

Movement analysis

We found a significant effect of disease in smoothness ($F(2,21) = 4.176; P = 0.0297$) (Figure 2). In contrast, no statistically significant effects of disease were observed for aiming error ($F(2,21) = 1.2214; P = 0.315$), curvature ($F(2,21) = 1.4269; P = 0.262$), and symmetry ($F(2,21) = 0.2776; P = 0.760$).

Furthermore, post-hoc analysis of the smoothness indicator revealed that CIS patients differed from controls ($P < 0.024$, smoothness), whereas MS patients did not differ from both control and CIS subjects.

Regarding the effect of vision, we found significant effects on curvature ($P < 0.0001$) and symmetry ($P < 0.0001$). Post-hoc analysis showed that MS and CIS subjects, but not controls, showed significant effects of vision on speed profile symmetry ($P = 0.019, 0.001$ and $0.129$, respectively).

As regards curvature, only CIS subjects revealed a significant vision effect ($P = 0.00252$). Figure 2 suggests that CIS subjects display a marked increase in trajectory curvature when vision of the hand is available.

Moreover, no indicators displayed a significant interaction between vision and disease.

9HPT evaluation

The results of 9HPT evaluation are reported for each subject in Table 1. Overall, the 9HPT score did not differ between patients and controls (19.68 ± 0.75 and 18.75 ± 0.60 s, respectively; mean ± SE, dominant hand; $P > 0.05$). More specifically, the score was 19.55 ± 0.75 and 19.94 ± 0.50 s, respectively, in CIS and MS subjects.

Lesion load

Estimates of lesion load are reported in Table 1. The lesion load found in both CIS and MS patients was significantly > 0 ($T1$: 703.38 ± 214.80 mm$^3$; $T2$: 8767.74 ± 2551.32 mm$^3$). However, no correlation was found between lesion load (both $T2$ and $T1$) and the abnormalities in kinematic parameters.

Discussion

We analysed subjects with brain MRI suggestive of demyelinating disease, either CIS or definite MS, but no observable impairment upon neurological examination. We found that these patients indeed displayed subtle symptoms, that could be detected (and quantified) through movement analysis in a reaching task. More specifically, their movements showed a significant increase in the jerk integral and a trend for asymmetry with abnormal large duration of the deceleration phase. These effects can be interpreted in terms of optimal feedback control [12], as the result of a compensation
strategy, due to an abnormally large variability in either motor commands, or sensory afferences. According to this interpretation, variability in motor commands, which increases with command magnitude, may result in a compensation strategy to keep the endpoint error low, which consists of accelerating the arm (therefore applying strong muscle activation) early in the movement, so that more time is allowed for gradual corrections in its final part (ie, during the deceleration phase). A deficit during the visual-guidance condition, ie, eye–hand co-ordination, may not be excluded.

Eye movement disorder has not been evaluated with instrumental tools, such as electro-oculography, but all subjects were clinically asymptomatic for any oculomotor disturbances. Additionally, the utilized method could be a useful tool in order to plan rehabilitation programs for the upper limb, based on kinematic alteration, in symptomatic MS subjects.

It should be noted that the 9HPT, commonly used for scoring upper limb function, and recently proposed as an outcome measure in clinical trials, was unable to distinguish differences between the three groups.

In addition, no correlation between MRI data and kinematic parameters was found. This is not entirely surprising, as the total lesion load is a measure of cumulative CNS damage, not specific to a neural pathway, whereas kinematic findings

Table 1 Lesion load (T1 and T2) and 9HPT scores for controls, CIS and MS subjects (mean ± SE)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Lesion load (mm³)</th>
<th>9HPT (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T1</td>
<td>T2</td>
</tr>
<tr>
<td>Controls</td>
<td>0 ± 0</td>
<td>0 ± 0</td>
</tr>
<tr>
<td>CIS</td>
<td>785.57 ± 460.39</td>
<td>6313.57 ± 2672.74</td>
</tr>
<tr>
<td>MS</td>
<td>648.27 ± 248.55</td>
<td>10517.18 ± 4096.58</td>
</tr>
</tbody>
</table>
reflect compensation strategies that have a complex relationship to anatomical damage. Further study is needed in order to determine the consistency of results on a larger cohort of subjects, and possible correlations with non-conventional MRI parameters.

Acknowledgements

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References