Cortical silent period prolongation in spinocerebellar ataxia type 2 (SCA2)

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Summary

Spinocerebellar ataxia type 2 (SCA2) is an autosomal dominant neurodegenerative disorder mapped on chromosome 12. Different results have been reported in spinocerebellar ataxias following transcranial magnetic stimulation (TMS). TMS-induced cortical silent period (CSP) was prolonged in different cerebellar disorders. Here we evaluate the duration of the TMS-induced CSP following a single magnetic stimulus in a large homogeneous group of SCA2 patients compared with idiopathic cerebellar ataxia (IDCA) patients with similar disease duration and severity, and in 20 healthy controls. The CSP duration in both arm and leg muscles was significantly (p<0.005) longer in patients than in controls. A significant positive correlation between disease duration and CSP prolongation in both SCA2 and IDCA was found. No correlation between age, onset and CSP duration emerged in either group.

This study shows a prolongation of the TMS-induced silent period in both SCA2 and IDCA indicating that the cortical inhibitory mechanism is dependent on the disease duration and severity. Thus, the cerebellum seems to exert a pliable physiological influence on the cortico-spinal system through control of inhibitory cortical interneurons.

KEY WORDS: cortical silent period, idiopathic cerebellar ataxia, spinocerebellar ataxia type 2, transcranial magnetic stimulation.

Introduction

Spinocerebellar ataxia type 2 (SCA2) is an autosomal dominant neurodegenerative disorder which has been mapped on chromosome 12, with expanded cytosine-adenine-guanine (CAG) repeats being identified as the mutational cause of the disease (1-5). SCA2 is clinically characterised by stance and gait ataxia variably associated with slow saccades, dysarthria, dysphagia, postural or action tremor, double vision, muscular atrophy, cramps, and pyramidal signs (clonus, spasticity, and increased tendon reflexes) (2-4). Clinical signs due to involvement of the pyramidal system are also present in other types of hereditary or sporadic spinocerebellar ataxias.

Different results have been reported in spinocerebellar ataxias following transcranial magnetic stimulation (TMS) (6-11). Some authors have reported an abnormal increase of the threshold (MT) (9) for evoking motor evoked potentials (MEPs), whereas findings of normal threshold in cerebellar disorders, other than SCA2, have been observed by other authors (8,10,12). However, only few studies have assessed the excitatory and inhibitory circuits in autosomal spinocerebellar ataxias (11,13-15). The TMS-induced cortical silent period (CSP), a tool which has proven to be useful in evaluating cortical inhibitory activity, has been reported to be prolonged in duration in cerebellar disorders of differing origin (16,17).

To our knowledge, there are at present only few studies evaluating CSP duration in SCA2 (10,11). Moreover none of these studies was focused specifically on CSP behaviour. To investigate CSP duration in SCA2 might give further insight into the pathophysiology of this disease. If the duration of TMS-induced CSP differs between sporadic and hereditary cerebellar ataxias, this may be considered a marker to differentiate these different types of disease. Were SCA2 and idiopathic spinocerebellar ataxia (IDCA) patients with similar clinical conditions to show different CSP durations, then different pathophysiological behaviour of the cortical inhibitory circuit degeneration could be hypothesised. If, on the other hand, they showed comparable CSP durations, this might confirm that the cortical inhibitory cir-
cuit degeneration is the consequence solely of the progression of the cerebellar involvement and that it is independent of the type of cerebellar ataxia. The aim of the present study was to assess the duration of the CSP following a single magnetic stimulus in a large and homogeneous group of SCA2 patients and to compare the results with those obtained from a group of patients with sporadic cerebellar ataxia with similar disease duration and severity.

Materials and methods

Patients and controls

Twenty-six patients with clinical signs of spinocerebellar ataxia were enrolled in the study. Sixteen patients with autosomal dominant ataxia (11 men and 5 women; mean age 48.5 years, range 26-72 years, mean age at disease onset 38.9 years, mean disease duration 13.6 years) were diagnosed as having IDCA type I according to the following criteria: autosomal dominant inheritance; progressive cerebellar ataxia variably associated with dysarthria, pyramidal or extrapyramidal signs; decreased vibration sense; and ophthalmoplegia. Molecular analysis revealed that all the patients were affected by SCA2 (1). The patients’ clinical, molecular, and neuroradiological data are reported in detail elsewhere (3-5,9). The remaining 10 patients (7 men, 3 women, mean age 50.3 years, age range 29-71 years) had neither positive family history of neurodegenerative diseases, nor molecular evidence of hereditary spinocerebellar ataxias and were thus classified as IDCA. All patients underwent neurological examination: 15 patients (10 SCA2 and 5 IDCA) had clinical symptoms and signs of pyramidal tract involvement (positive Babinski’s sign, spasticity and increased deep tendon reflexes). The severity of disability was evaluated by the inherited ataxia progressive scale (IAPS) (2). This is a 4-point severity scale in which: grade 1=asymptomatic (1 SCA2, no IDCA patients), grade 2=mild ataxia (7 SCA2, 4 IDCA), grade 3=severe ataxia (5 SCA2, 4 IDCA); grade 4=patient confined to wheelchair (3 SCA2, 2 IDCA). Although IAPS was originally proposed for inherited ataxias (2), it measures only severity and is not influenced by the type (inherited or sporadic) of ataxia. For this reason it can also be used to score ataxia progression in patients with sporadic (idiopathic) ataxia. Patients were enrolled and retrospectively evaluated by neurologists (S.G., F.L.) from a single hospital. TMS results were compared with the data obtained from 20 controls (12 men, 8 women; mean age 46.8 years; range 23-70 years) with no history of neurological disease and no abnormalities on neurological and physical examination. All the subjects enrolled in the control group belonged to the hospital staff. Both patients and controls gave their informed consent and the protocol was approved by the local ethics committee.

Methods

Surface EMG recordings were performed using surface electrodes from the right first dorsal interosseus (FDI) and tibialis anterior (TA) muscles. A ground electrode was placed proximally to the recording site. Filters were set at 100 Hz to 3 KHz. TMS was performed via a round magnetic coil (9 cm in diameter) connected with a Magstim 200 two tesla stimulator (The Magstim Company, Dyfed, Wales, UK). The coil was applied to the scalp with the centre over the vertex so that the current flowed in an anti-clockwise direction. After achieving the cortical motor threshold, which was defined as the stimulus intensity required to produce a motor evoked potential (MEP) of at least 50 µV in 3 out of 5 consecutive trials, the coil was moved over the vertex in order to use the optimal stimulation site in the hand and leg motor area so as to record reproducible, maximal amplitude MEPs in the target muscles. The subjects were seated in a reclining chair with their arms or legs restrained in a device that allowed measurement of the isometric force produced by foot dorsiflexion or extension. The force level was indicated by an oscilloscope. The EMG signal was also played through a loudspeaker. This visual and auditory feedback enabled subjects to produce a constant EMG signal when muscle contraction was required and helped them to maintain complete relaxation at other times. Trials with incorrect relaxation or voluntary contractions were discarded. The CSP duration was recorded in FDI and TA muscles while the subject exerted a tonic voluntary activation of approximately 10% of maximal voluntary contraction (MVC) at 70%, 80%, and 90% of the maximum stimulator output. Audio-video feedback was used to help subjects to maintain the correct level of activity throughout the trials. The traces were digitalised with an analogic-digital converter and stored on a personal computer. For each subject, 5 EMG responses were collected and the mean CSP was calculated. The duration of the silent period was measured from the MEP onset to 80% of return of background EMG. In patients with clinically asymmetric involvement, testing was carried out on the more symptomatic side, otherwise the right side extremities were preferred. Although this may introduce a bias, we choose to record the CSP in the more symptomatic side because we believe that recordings from the more affected district could be more appropriate for a correlation study with disability severity and progression.

Statistical analysis

Values are expressed as mean±SD. Student’s t tests were used to compare measurements between the patients and the control group and, within the patient group, to compare SCA2 and IDCA. Statistical significance was set at p<0.05. Pearson’s correlation analysis was used to compare clinical and genetic data to CSP duration at 90% stimulator output. Results

In SCA2 patients, the mean age at onset and the mean disease duration were 36.1±13.2 years and 12.3±7.1 years, respectively. The mean IAPS was 2.7±0.9 For IDCA the mean score of the disease progression was 2.8±0.5 No significant differences between these two scores were found. The mean CAG repeat expansion was 40.6±2.9. Data of patients and controls are shown in Table I. The CSP duration in both FDI and TA mus-

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cles was significantly (p<0.005) longer in patients than in controls (Table I; Figures 1 and 2) at all the stimulation intensities evaluated. No significant difference (p>0.05) was found between SCA2 and IDCA. Pearson’s correlation analysis showed a significant positive correlation between disease duration and CSP prolongation in both SCA2 (FDI: r=0.68; TA: r=0.72) and IDCA (FDI: r=0.66 at 90%; TA: r=0.70 at 90%). In SCA2 patients, a significant positive correlation (r=0.65) between CSP prolongation and IAPS was also found. In both groups of patients, Pearson’s correlation analysis showed no correlation between age, and age at onset and CSP duration. In SCA2 patients, CAG repeat expansion did not correlate with CSP duration.

Table I - Data of patients and controls.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>CSP (ms) (% suprathreshold intensity stimulation) lower limbs</th>
<th>CSP (ms) (% suprathreshold intensity stimulation) upper limbs</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCA2 (n=16)</td>
<td>49±14</td>
<td>232±73 (70%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>237±74 (80%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>244±73 (90%)</td>
</tr>
<tr>
<td>IDCA (n=10)</td>
<td>50±11</td>
<td>223±65 (70%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>229±65 (80%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>235±66 (90%)</td>
</tr>
<tr>
<td>Controls (n=20)</td>
<td>44±15</td>
<td>156±10 (70%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>162±11 (80%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>167±11 (90%)</td>
</tr>
</tbody>
</table>

Abbreviations: SCA2=spinocerebellar ataxia type 2; IDCA=idiopathic cerebellar ataxia; CSP=cortical silent period.

Figure 1 - Means with standard deviation of the CSP durations obtained at different intensities of stimulation (70%, 80%, and 90% of the maximum stimulator output) from FDI (A) and TA (B) muscles in SCA2, IDCA, and control subjects.

Figure 2 - Representative rectified EMG response from the TA muscle of a control subject (A) and from a patient with SCA2 (B). It is possible to note a shorter silent period duration in the control subject as compared to the SCA2 patient.
Discussion

The primary observation in this study was a significant prolongation of the CSP duration in both SCA2 and IDCA patients as compared to the control group. Statistically significant correlations between silent period prolongation, disease duration and IAPS were found in both groups of patients. The cerebellar dysfunction present in SCA2 may be attributed to pathology in the cerebellum and in its connecting pathways (18). Cortical structures other than the cerebellum can be involved to a greater or lesser extent in S2C (5,19).

Silent period is defined as the suppression of the ongoing EMG activity while the stimulated subject is trying to maintain a sustained muscular contraction (20). Its physiology, however, is not fully understood. Probably it involves spinal inhibitory mechanisms during its first part and cortical inhibitory circuits during its latter part (21). A prolonged CSP duration has been reported in patients with cortical and subcortical ischaemic infarction (22) and in patients with lesions of the internal capsule, thalamus premotor cortex, and temporal parietal lobe (23). The shortening of the CSP, seen in lesions of the primary motor cortex, has been interpreted, by some authors as hypoactivity of cortical inhibitory neurons following excitation of cortico-spinal cells due to the higher vulnerability of γ-amino-butyric acid (GABA)-ergic neurons to hypoxia (23). Conversely, the prolongation of the CSP duration, observed in lesions outside the motor cortex, has been interpreted as a disinhibition of cortical neurons (23).

There are only a few reports regarding cortical excitability in cerebellar disorders (9-17). An increased motor threshold was observed in patients with cerebellar ataxia (9,12,13).

In a previous study, Restivo et al. (9) reported an increased motor threshold to lower limbs in SCA2. These alterations were hypothesised to be related to a primary cerebellar pathway involvement with a subsequent negative influence on the excitatory state of the primary motor cortex. Spino-cerebellar motor dysfunction, in fact, might be caused by an insufficient activation of the cerebellar output to the motor cortex, consequently influencing its excitatory state (17).

It has been reported that magnetic or electrical stimulation over the basal occiput is able to reduce excitability of the human motor cortex to a test magnetic stimulus applied 5-7 ms later (24-26). This inhibition was lacking in patients with cerebellar degeneration or involvement of the cerebello-thalamic-cortical pathway (14,27) or cerebellar hemispheric lesions (13,28). These findings seem to point to a cerebellar influence on inhibitory cortical interneurons.

Wessel et al. (17) studied a heterogeneous group of 24 ataxic patients and they observed an abnormal CSP prolongation, and an abnormal refractory period after double magnetic stimulation in 10 and in 2 out of 24 patients, respectively. These authors found no correlation between the duration of the silent period and the severity of the ataxia (17). They concluded that prolonged post-excitatory inhibition and refractory period could be due to the loss of Purkinje cells with release of cerebellar nuclear cells from inhibition leading to a transient facilitation of cortical inhibitory interneurons and consequent decreased excitability of the primary motor cortex. No correlation was found between the duration of the CSP and the severity of the ataxia (17).

In a recent report, Liepert et al. (15) found a reduced intracortical facilitation after paired TMS in 15 patients with autosomal dominant and idiopathic cerebellar ataxia of different origin. A significant increase of CSP was also seen after single TMS in the patient group (15). These authors concluded that the cerebellum may exert a physiological facilitatory influence on the motor cortex which is decreased in cerebellar degeneration. Similar results were reported by Restivo et al. (11) in a large group of SCA2 patients. The latter authors also reported a significant correlation between the disease duration, IAPS and electrophysiological abnormalities (11).

Oechsner and Zangemeister (16) studied 5 patients with sporadic cerebellar ataxia and they found a significant prolongation of the CSP after TMS (16). These authors concluded that cerebellar lesions may activate indirect inhibitory cortical interneurons or cause an alteration of the normal tonic cerebellar excitation to the motor cortex (16). Our data confirm the findings of an increased CSP duration in cerebellar hereditary or idiopathic dysfunction. In our patients, silent period duration after cortical stimulation was prolonged in both upper and lower limbs. In conclusion, first, this study showed a prolongation of the TMS-induced silent period in both SCA2 and IDCA. This strongly indicates that the involvement of cortical inhibitory mechanisms is dependent on the duration and severity of the disease, and it is very likely unrelated to the genotype. Second, these results seem to support the hypothesis that the cerebellum exerts a pliable physiological influence on the cortico-spinal system by a control on inhibitory cortical interneurons.

References

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