Tremor in multiple sclerosis: different patterns of long latency reflexes suggest different underlying pathophysiological mechanisms

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Introduction
Tremor is prevalent and disabling sign in multiple sclerosis (MS). Although many medications have been proposed to alleviate tremor in MS, treatment results are often disappointing. Anatomical basis and pathophysiology of tremor in MS are still poorly understood, this fact may partly accounts for low efficacy of treatment, which is still remain mainly empirical. Long latency reflexes (LLRs), elicited by electrical stimulation of mixed nerve, were useful in investigating pathophysiology of different hyperkinetic movement disorders [1], but little is known about their alterations in patients with tremor due to MS. Meanwhile, investigation of LLRs may provide important information about central pathways, presumably involved in MS tremor generation.

Aims
To evaluate LLRs in patients with MS associated tremor and to investigate whether there are any correlations between LLR changes and tremor clinical patterns, or lesions localization on brain MRI.

Patients and methods
124 MS patients (according to revised MacDonald’s 2005 diagnostic criteria) were evaluated. Group 1 included 58 patients with persisting (duration more than 3 months, not related to MS relapse), and interfering with daily activities (score no less than 2 in Tremor subscale of Kurtzke cerebellar functions scale) tremor. Group 2 included 66 MS patients without tremor. Main clinical characteristics of patient in groups are summed in table 1. LLRs elicited by stimulation of median nerve were recorded from thenar muscles as described by M. Naumann et al. [1997] [2] using Neuro-MVP-4 EMG machine (Neurosoft, Russia). MRI was performed on Magneton Symphony 1,5T (Siemens, Germany) using conventional sequences; in addition to visual analysis (localization of lesions in predefined areas), quantitative analysis of lesion load was performed using MIPAV 7.01 software.

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Discussion and conclusion
LLRs pattern 3 with relatively enhanced LLR1 is similar to those, previously demonstrated in many hyperkinetic disorders, including centrally driven tremors, such as parkinsonian and essential. Enhancement of LLR1 is thought to be hypothetical marker of desinhibition of thalamocortical projections [2]. In accordance with lesions localization, it is possible to suggest, that postural tremor in MS in some cases may be related to pathological central oscillator, located somewhere in thalamic area. Another hypothetical mechanism is pathological disorganization of cerebellar nuclei due to disruption of projections from cerebellar cortex (Purkinje cells) (fig. 4). Enhancement of LLR3 was previously reported in many cerebellar disorders [3], but in our study both LLR1 and 3 were relatively enhanced (LLRs pattern 4). Taking into account lesions localization in distal intentional tremor, it might be supposed, that this variant reflects abnormal functioning of pons-cerebellar-dentate nucleus-thalamus-cortical loop. More coarse distal and proximal intentional/postural tremor seems to be related to disruption of efferent projections of cerebral and spinal cerebellum (fig. 5). The value of enhanced LLR1 is hard to explain in both cases, but an additional role of central oscillator in some variants of intentional tremor might be proposed.

MRI: In MS patients with tremor lesions in medulla, pons, superior/inferior cerebellar peduncles, midbrain and thalamic area were found more frequently, as compared with patients without tremor (fig. 2). Quantitative analysis revealed higher lesion load in brainstem (but not in cerebellum or cerebral hemispheres) in patients with tremor (fig. 3). Some differences in predominant lesion locations were observed in various tremor clinical variants. Distal postural/intentional tremor was associated with lesions in medial cerebellar white matter (42,9%) and in (near) thalamus (42,9%). In distal intentional tremor lesions in pons, middle cerebellar peduncle (88,2%) and in lateral cerebellar white matter (70,6%) were observed. Lesions in midbrain or superior cerebellar peduncle (66,7%), along with lesions in pons (54,2%) and cerebral hemispheres (61,9%), prevailed in distal and proximal intention/intention-postural tremor. In Holmes tremor large midbrain lesions (100%), spreading to superior cerebellar peduncles and thalamic area (75%) was found.

References

Table 1. Clinical characteristics of MS patients with and without tremor (group 1 and 2 resp.)

<table>
<thead>
<tr>
<th>Age (M[SD]), years</th>
<th>Group 1 (n=58)</th>
<th>Group 2 (n=66)</th>
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<tr>
<td>Female/male (%)</td>
<td>34/24 (59/41)*</td>
<td>46/20 (70/30)</td>
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<tr>
<td>Disease duration (M[SD]), months</td>
<td>100,3 (68,1)*</td>
<td>128,7 (78,0)</td>
</tr>
<tr>
<td>Disease course (%)</td>
<td>42,9</td>
<td>42,9</td>
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| Relapsing-remitting | 34 (58,6)* | 27 (40,9) |
| Secondary progressive | 24 (41,4) | 32 (48,5) |
| Primary progressive | 0 (0)* | 7 (10,6) |
| EDSS (Me(0,0)) | 4,0 (3,5; 5,0) | 4,5 (3,5; 5,0) |

* Statistically significant differences

Fig. 2. Differences in lesion localization frequencies between MS patients with vs. without tremor. Only areas with statistically significant differences are indicated.

Fig. 3. Relative lesion load index for three cerebral areas in MS patients with and without tremor (group 1 and 2 resp.). Only for brainstem lesion load was statistically significant higher in patients with tremor.

Fig. 4. Hypothetical generation mechanism of postural tremor in MS: formation of central oscillator in thalamic area. Relative enhancement of LLR1 may reflect pathological activation of thalamocortical stimulating projections.

Fig. 5. Hypothetical generation mechanism of intentional tremor in MS: disruption of cerebellar-thalamocortical loops, or cerebellar efferent projections. Relative enhancement of LLR3 may reflect abnormal signal processing in pontocerebellum.

Fig. 1. Abnormal LLRs patterns in MS patients with (3, 4) and without (1, 2) tremor

Fig. 3. Relative lesion load index for three cerebral areas in MS patients with and without tremor (group 1 and 2 resp.). Only for brainstem lesion load was statistically significant higher in patients with tremor.