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Long-term follow-up study with repetitive transcranial magnetic stimulation (rTMS) in Parkinson's disease

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Abstract

Several studies have claimed the effectiveness of repetitive transcranial magnetic stimulation (rTMS) in Parkinson's disease (PD). The rTMS therapy has to be repeated regularly to achieve a permanent effect but the side effects of long-term administration of low frequency rTMS are not known. Further, there is no information about its influence on the development of Parkinson's disease. Two different groups of patients with PD were compared in a retrospective study for 3 years. The first group (A) was treated with drugs, the second group (B) was treated with drugs + rTMS (1 Hz, 0.6 T, 100 stimuli per day for 7 days using a round coil). rTMS was repeated at least twice each year for 3 years. Symptoms of PD were assessed using the Graded Rating Scale. Although at the onset of the study group B patients had greater disease severity and were receiving higher doses of levodopa, this group (receiving rTMS) showed no deterioration in these parameters, whereas those in group A receiving drugs alone showed a marked deterioration. Hoehn–Yahr (H–Y) stages at the onset of the study and 3 years later were: group A: 1.93 ± 0.75, 3.03 ± 1.01; group B: 2.50 ± 0.83, 2.45 ± 0.62. The dose of levodopa (mg/day) was at the onset of trial and 3 years later was: group A: 124.4 ± 144.0, 555.5 ± 247.2; group B: 287.7 ± 217.1, 333.4 ± 181.0. The yearly increment in the scores was: group A: 1.308 ± 0.307 ($P < 0.001$), group B: 0.642 ± 0.389 ($P < 0.1$). Accordingly, this retrospective study using regularly repeated rTMS with 1 Hz for 7 days, at least twice yearly for 3 years, significantly slowed the development of Parkinson's disease. Unwanted side effects were not observed during the 3 years.

Keywords: Parkinson's disease; Transcranial magnetic stimulation; Levodopa

1. Introduction

Parkinson's disease (PD) is a chronic, degenerative disease that shows a fast progression rate in the early phase of PD and that slows in the later phase of the disease. This observation is based on the followed clinical scores of the parkinsonian symptoms [5] and ^{18}F-dopa uptake in the putamen [9]. It is supposed that two drugs, namely selegiline [10,16] and ropirinole [12,21], have favorable influence on the development of PD. Although selegiline adding to levodopa decreased the decline in motor performance and freezing of gait, but induced more dyskinesias during the 2-year follow-up [16]. Patients with ropirinole intake showed decreased decline in dopamine uptake assessed by ^{18}F-dopa than that with levodopa, although their motor control was worse and the side effects appeared more frequently in the group with ropirinole [21]. The dopamine uptake did not correlate with the change in clinical symptoms. The applied drugs in the treatment of PD have negligible influence on the development of the disease.

It was published that microelektroshock induced by transcranial magnetic stimulation (TMS) decreased the reaction time in PD [11], increased the speed of active movement [17]

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and improved the parkinsonian symptoms [2,7,8,15]. Opposite to the low frequency repetitive transcranial magnetic stimulation (rTMS), the high frequency of it destroyed the spiral drawing [1] and the repetitive stimulation under the finger tapping did not change the reaction time [4]. The favorable effect of low frequency rTMS lasted a few months and it needed to be repeated to keep a balanced moving state on a day long. It is supposed according to the short-term studies with low frequency stimulation of rTMS that it has no side effect, but the unwanted effects of long-term, regularly repeated stimulation are not known; further, the effect of rTMS on the progression of PD has not been detected yet. The aim of our more than 3-year follow-up retrospective study was to compare two groups of patients with PD. Between them, the main difference was the applied 1 Hz rTMS therapy for 7 days.

1.1. Patients and methods

In the group A, 29 patients (age: group A, 66.3 ± 8.2 years; duration of disease, 4.1 ± 3.3 years) with PD were recruited. They visited the outpatient clinic from 1986 to 1995. Every patient, who was followed for at least 3 years, was involved in this retrospective study. Parkinsonian symptoms were assessed by Graded Rating Scale [6] which mainly focuses on the parameters of waking, rigidity and fast alternating movement on both the upper and lower extremities. Patients with PD were tested monthly. From 1996 to 2001, the rTMS was introduced in the treatment of patients with PD in another town. Forty-six patients with PD were recruited into the group B (age: 63.9 ± 9.0 years, duration of the disease: 4.5 ± 3.0 years). Group B was given the same drugs as the group A (10 mg selegiline, Jumex; Sanofi-Synthelabo, standard levodopa + benzerazid Madopar 250 mg; Hoffmann La Roche and slow-release levodopa wirh carbidopa given as Sinemet CR 250 MSD). These patients were selected because they had received at least two 1-week session of treatment with rTMS each year (using an average of 2.42 ± 0.11). Parkinsonian symptoms were detected before and after the treatment for 7 days and 1 month after rTMS then every 3 months. Those were assessed by Graded Rating Scale and Unified Parkinsonian Disability Scale (UPDRS). The two scores correlated well with each other ($r = 0.8$).

Patients gave their informed consent and the local Ethical Committee gave permission for the study to proceed.

1.2. Treatment protocol with rTMS

Repetitive TMS was given twice a day for 7 days. Each session involved 50 stimulus applied 1 Hz and an intensity of 25% of the maximal output of the device (2.3 T). The equipment used was a Dantec Maglite transcranial magnetic stimulator with a 14 cm diameter coil. The coil was positioned over vertex of the skull.

1.3. Statistical analysis

The association between initial score, rTMS treatment and rate of change in score was assessed by repeated measures regression models with random effects error structures (linear mixed model). The fixed effects part of the model included estimates of the mean overall level of score at the baseline and the mean rate of decline per day during the follow-up and the interaction between the rate of decline and the treatment. The random part of the model is assumed that each person's individual path then followed the mean path, except for random effects, which modified the overall level to be higher or lower, and the rate of change to be faster or slower depending from

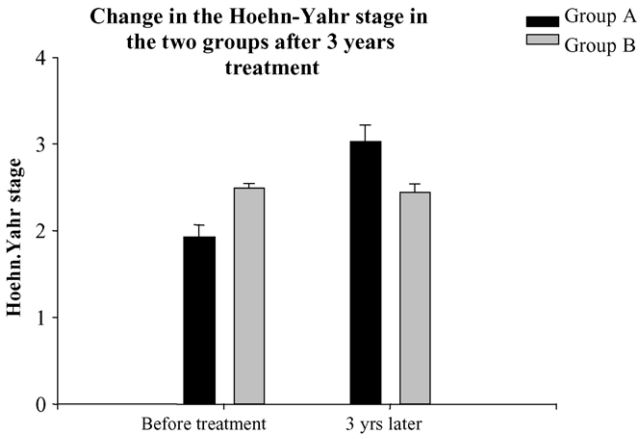


Fig. 1. The dose of levodopa in the group A (selegiline, standard levodopa, slow-release levodopa) ($n = 29$) was increased highly significantly ($P < 0.001$) during the 3 years of the retrospective study. Opposite to it, the dose of levodopa in the group B (drugs plus rTMS with 1 Hz for 7 days) ($n = 46$) was not elevated significantly comparing before and after the followed period.

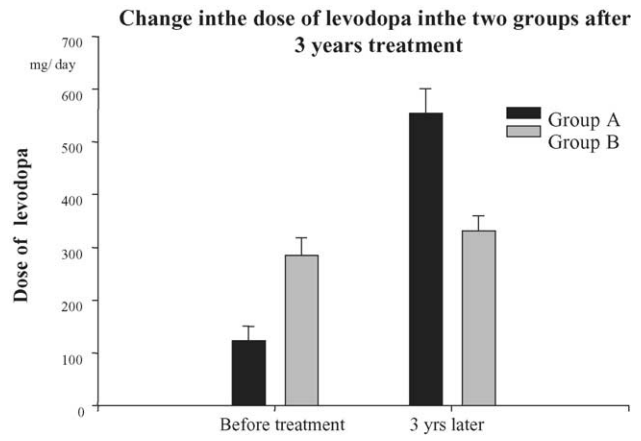


Fig. 2. The deterioration in Hoehn–Yahr stages was highly significant ($P < 0.001$) in the group A treated with drugs alone (selegiline, standard levodopa, slow release levodopa). The regularly repeated rTMS with 1 Hz for 7 days at least twice for years decreased the progression of Parkinson's disease. The Hoehn–Yahr stage did not change significantly comparing the stage before and after 3-year follow-up.

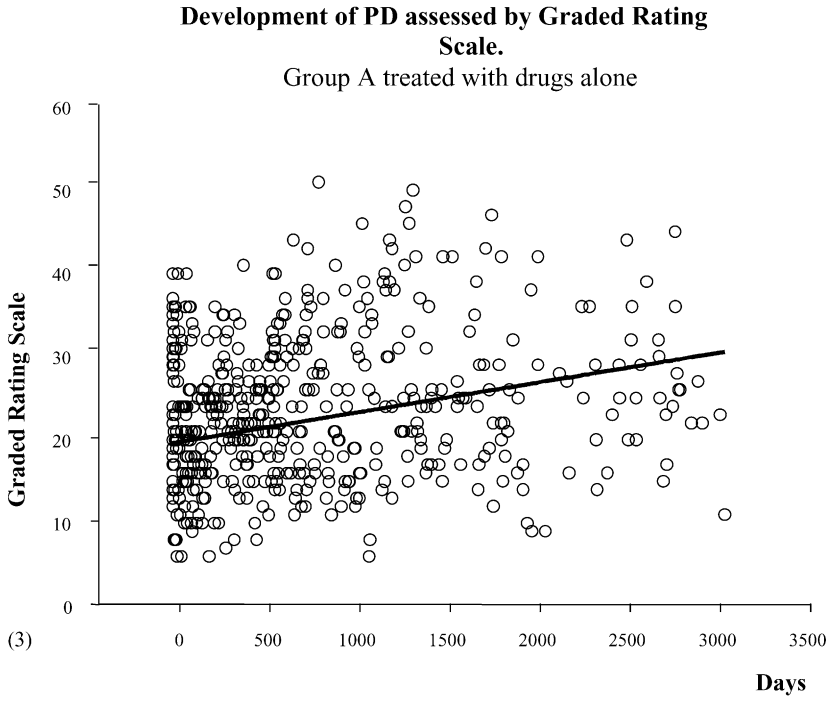
the subject initial score. The model was validated graphically for assumptions of linearity and homoscedasticity. A similar model was applied in Wilson's study [21].

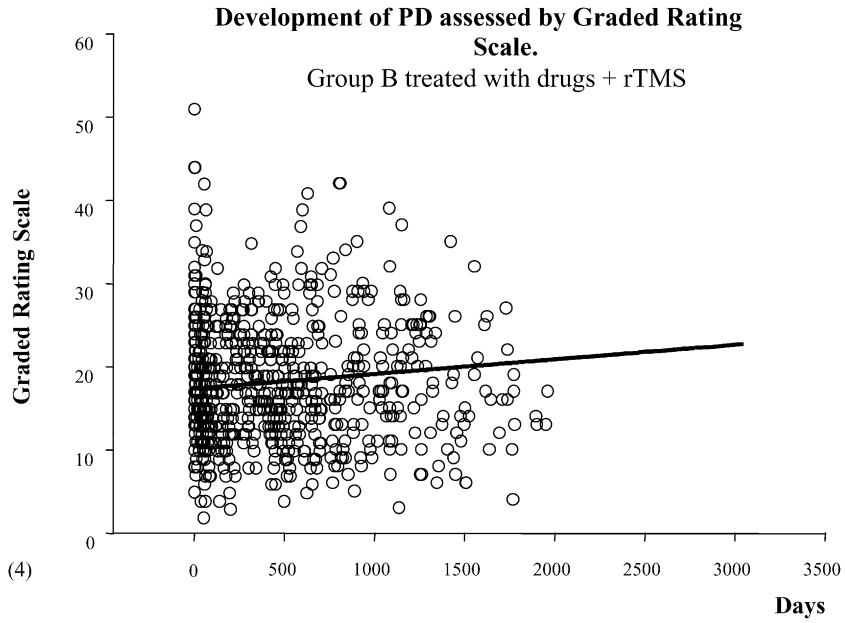
Other characteristics of the two groups were compared by mean values using Wilcoxon's rank sum test and unpaired *t*-tests, as appropriate.

All statistical calculations were performed using commercially available statistical software (Splus v. 6.1, Insightful, Seattle, WA).

2. Results and discussion

At the beginning of our retrospective study, there was no difference between the groups in their age and in the duration of the disease. At the onset of the trial, the dose of levodopa in the group B was significantly higher ($t = 3.5$, $P < 0.001$) than that in the group A (Fig. 1). Similarly, the Hoehn–Yahr (H–Y) stage of the group B was significantly worse than that of the counterpart group ($z = 2.57$, $P < 0.001$) (Fig. 2). Conversely,





Figs. 3 and 4. The values of Graded Rating Scale (GRS) were plotted in the above figures. Fig. 3. Group A treated with drugs alone was followed more than 3 years, but there were data up to 9 years. The regression line was fitted to them. The yearly increment was 1.308 ± 0.307. Fig. 4. Results of group B (drugs plus rTMS) are demonstrated in the. The longest follow-up period was 5 years. The yearly increment was 0.642 ± 0.389, which significantly differed from the group A ($P < 0.05$).

after 3 years, the dose of levodopa was significantly less in the group B ($t = 4.48$, $P < 0.001$) and lower HY stage was detected in the group B than in the group A ($z = 3.25$, $P < 0.01$) (Figs. 1 and 2).

There was a statistically significant difference ($P < 0.05$) between the rates of progress of PD in the two groups. In both groups, the deterioration continued and the yearly increase in scores (mean slope parameter of the regression model) was 1.308 ± 0.307 ($P < 0.001$) in the group A, while 0.642 ± 0.389 ($P < 0.1$) in the group B (Figs. 3 and 4).

Other factors as age, duration of illness, dominant symptom (tremor or hypokinezis) had not reached significant effect and they were not included in the final regression model.

In the final model, the mean intercept parameter included a constant C plus an effect depending from the initial score of the patient (F), i.e. we used the estimated rather then the directly measured score at the first visit. The estimated parameters are: $C = 5.55 \pm 0.95$ and $F = 0.60 \pm 0.043$, both highly significant ($P < 0.001$), meaning the measured score at the given time depends from initial value. In the group A, 20.69% of the patients had the same or better HY stage after 3 years of the start of the trial while the same values in the group B is 71.7% which corresponds to OR = 0.1 [CI 95% 0.03–0.31] (OR = odds ratio, CI 95% = 95% confidence interval).

The correlation between the two scores (GRS and UPDRS) is $r = 0.8$.

In our present retrospective study, two different groups of patients with Parkinson's disease were compared and they were followed for 3 years. The main difference between the two groups was that the group B, besides the drugs, was regularly treated with rTMS for a week. Our long-term follow-up study based on the clinical rating scales of patients with PD as it was published by Lee et al. [5]. Our main conclusions from the present retrospective study are that the progression of PD with regularly repeated rTMS is going ahead slower than that of it with selegiline + levodopa. The elevation of the dose of levodopa showed significantly higher increment in the group A with drugs alone. MAO-B inhibitors and dopamine agonists have been claimed that they can favorable modify the development of Parkinson's disease. The trial of DATATOP after 1 year proposed a better life expectancy in the group with selegiline compared with tocoferol [10]. Later, it was also confirmed in a 2-year follow-up study that the decline in motor performance was less in the group with selegile completed with levodopa, although the dyskinesia appeared more frequently than in the group with levodopa alone [16]. If any effect was responsible for this drug, it appeared in our both groups because every subject recruited in the study was treated with selegiline. It is also supposed that dopamine agonists decrease the apoptosis of dopaminerg neurons in substancia nigra assessed by PET study [20]. By the end of the 2-year trial with ropirinol versus levodopa, the dopamine uptake was better preserved in the group treated with dopamine agonist. Importance of this 8% difference is not known because the decline in dopamine uptake and the clinical state did not correlate with each other; further, the levodopa group showed superior motor control assessed by UPDRS, less side effects and the drop-out was fewer [20]. In our study, we focused on the motor disability caused by the disease and influenced by drugs or drugs plus rTMS. According to our results, the yearly increment was half in the motor scores in the group B with rTMS opposite to the group A with drugs alone. Both the electrophysiological and biochemical changes may play role in the long-term effect of rTMS; however, the proper explanation is not known. The importance of the change in the intracortical inhibition with different state of diseases was supposed according to TMS studies. The rTMS with 1 Hz causes a prolonged inhibition in intracortical connections which decreased in PD [3]. Off state of PD was characterized by impaired short interstimulus interval intracortical inhibition assessed by double-stimulation of TMS, while the 'on' state of PD was not differed significantly from controls [14]. Restoration of intracortical inhibition by dopaminergic drugs correlated with the therapeutic effect [18]. The reduction of the activity in corticostriatal pathway by rTMS may contribute to the elevated concentration of dopamine in the striatum [19]. The protective effect of rTMS against different toxins was suggested in animal studies [13]. The cerebrospinal fluid from rats treated with rTMS for 11 weeks increased the overall viability of mouse monoclonal hippocampal HT 22 cells and had a neuroprotective effect against oxidative stressors, namely amyloid beta and glutamate [13].

The balance between the inhibition and the facilitation in the cortex, the surveillance of neuron populations because of increased production of grows factors altogether may lead to the favorite effect of rTMS on the progression of PD.

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