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ORIGINAL ARTICLE

The cortical excitability profile of patients with the G209A SNCA mutation versus patients with sporadic Parkinson's disease: A transcranial magnetic stimulation study

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Summary Mutations in the α-synuclein gene are a rare cause of Parkinson's disease. We investigated, by single-pulse TMS, the cortical excitability profile of nine α-synuclein patients in comparison with 24 idiopathic PD patients, subdivided into ''akinetic'' ($n=17$) and ''tremor-dominant'' ($n=7$) subgroups. The comparative assessment of rest motor threshold, active MEP and Silent Period Input/Output curves indicated that the cortical excitability of α-Synuclein patients is similar to patients with the ''akinetic'' form of PD. Both groups of patients exhibited differences in excitatory and inhibitory brain circuits from ''tremor-dominant'' patients indicating that varying clinical phenotypes are associated with differential profiles of corticospinal excitability.

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Introduction

In 1997, a heterozygous Ala53-to-Thr (A53T) mutation in the alpha-synuclein (SNCA) gene, resulting from a 209G-A transition, was identified in an Italian kindred and three unrelated Greek families with autosomal dominant Parkinson's disease (PD) [12]. Since then, approximately 70 cases from 22 unrelated families with this particular missense mutation have been reported [5]. Their clinical phenotype, neuropsychological features and neuropathological findings have been described in detail, and compared with that of patients suffering from sporadic PD [1,10,11]. However, the cortical excitability profile of this rare subtype of monogenic PD remains unexplored.

The present TMS study was designed to investigate the excitability of primary motor cortex in α-synuclein PD patients and compare findings to patients with sporadic PD.

Methods

We investigated a cohort of nine parkinsonian patients carrying the A53T mutation of the SNCA gene, a group of sporadic PD patients and a group of healthy controls (Table 1). The last two groups were age-and gender-matched with the first one.

Previous studies indicated that α-synuclein PD patients are characterized by absence or paucity of resting tremor compared to sporadic PD [1,11]. Since the clinical phenotype is expected to correlate with cortical excitability profiles [8], we dichotomized the sporadic PD control group into two subgroups. The former termed the ''akinetic'' type ($n = 17$), comprised patients who had a bradykinesia or rigidity UPDRS score one-grade higher than the tremor score. The latter, termed the ''tremor-dominant'' type ($n = 7$), was defined as patients who scored one-grade higher in tremor severity than both rigidity and bradykinesia scores. None of the participants was taking centrally acting drugs, save for L-dopa and dopaminergic agents and in all cases both hemispheres were examined in an OFF-drug condition.

Single-pulse TMS was performed with a Magstim 200 stimulator and a 70-mm diameter figure-of-eight coil [7] and MEPs were recorded with surface electrodes from FDI muscles.

Rest motor threshold (RMT) was defined at rest in 1% steps using the method of Mills and Nithi [6], which determines two stimulus intensity levels designated lower (LT) and upper (UT) threshold. Briefly, LT corresponds to the highest intensity, which evokes motor evoked potentials (MEPs) with a probability of zero, whereas UT is the lowest intensity, which evokes MEPs with a probability of unity. Mean threshold (MT) is the arithmetic mean of UT and LT.

The MEP and the SP input/output (I/O) curves were constructed using a wide range of SIs (from 5 to 100% maximum SI in 5% increments). At each SI, 4 SPs were obtained while subjects exerted an isometric contraction at 50% MVC and the average value of SP duration was used to construct the S/R curve. The duration of SP in individual trials was measured off-line and defined as the period between the onset of the MEP and the reoccurrence of EMG activity. Stimuli of different intensity were applied in random order to avoid serial order effects. The MEP data (peak-to-peak amplitude and area of MEPs) obtained concurrently with the aforementioned procedure were used to construct active MEP I/O curves.

Study participants provided informed consent for the procedures, which were approved by an institutional review board and performed in accordance with the ethical standards of the 1964 Declaration of Helsinki.

The SP and active MEP I/O curves were fitted to the Boltzman sigmoidal function using the Levenberg-Marquard non-linear least-mean-square algorithm [7]. This function is given by the equation:

$$Y = \text{Min} + (\text{Max} - \text{Min})/(1 + \exp((\text{V50} - X)/\text{Slope}))$$

where Y is SP duration or MEPs and X is the stimulus intensity (SI), Min and Max are the minimum and maximum values of SP duration or MEPs and V50 is the SI at which SP or MEPs are halfway between Min and Max. Slope is a measure of the steepness of the curve, with a larger value denoting a shallow curve. The SP and MEP S/R curves were statistically compared between the different groups for the parameters Max, V50 and Slope with an F-test.

RMT changes were explored using ANOVA and a Tukey post-hoc test to compare the groups in case of ANOVA significance. Age and gender differences were investigated with Kruskal-Wallis and the chi-square test. Normality of data distribution was tested with the Kolmogorov-Smirnov test. For all tests, $P < 0.05$ was the level of significance.

Statistical analysis was performed using GraphPad Prism version 6, San Diego, CA. USA and Statgraphics Centurion XV Manugistics, Rockville, MD, USA.

Results

In α-synuclein patients, UT, MT and LT ($x \pm SD$) were similar to the RMT values of the akinetic PD group (UT = 41.00 ± 6.14% versus 39.11 ± 5.81%, MT = 34.97 ± 5.99 versus 36.44 ± 5.81 and LT = 31.76 ± 5.79% versus 31.88 ± 5.63%, $P > 0.05$). Both of these groups had significantly lower MT compared to healthy controls (40.75 ± 5.23, $P < 0.01$) (Table 1).

The active MEP I/O curve of α-synuclein patients, constructed on the basis of peak-to-peak amplitude data, had a Max value of 7.43 ± 0.33 mV, V50 = 36.2 ± 1.32% and Slope = 4.30 ± 1.10 (Fig. 1a). Notably, the group of ''tremor-dominant'' patients had lower Max values (6.25 ± 0.19 mV) compared to α-synuclein patients and the ''akinetic'' group (Max = 7.99 ± 0.23 mV) ($P < 0.001$) and had significantly increased values of V50 (48.43 ± 1.31%) compared to α-synuclein patients ($P < 0.001$) whereas the ''akinetic'' group had intermediate values (46.45 ± 1.24%) (Table 1). All patient groups had significantly lower Max values compared to healthy controls (8.67 ± 0.15 mV).

A similar profile emerged from the I/O curves constructed on the basis of MEP area data (Table 1).

The SP I/O curve of α-synuclein patients had a Max value of 197.2 ± 6.91 ms, V50 = 46.18 ± 1.37% and Slope = 8.41 ± 0.97 (Fig. 1b). The Max values of SP duration in α-synuclein and ''akinetic'' (198.9 ± 4.47 ms), but not ''tremor-dominant'' patients (210.4 ± 4.35 ms), were significantly lower compared to healthy controls

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