Nabiximols and MS spasticity: neurophyisiological tests, walking performance and self-reported questionnaires

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Background:

Spasticity is one of the most reported disabling symptoms in multiple sclerosis (MS) patients, affecting more than 80% of them with increasing severity as the disease progresses.
Nabiximols, an oromucosal combination of delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), has been recently approved as a second-line therapy for spasticity treatment in MS patients who have not responded adequately to other antispastic medications. The drug efficacy, evaluated by the subjective measurement validated 11-point Numeric Rating Scale (NRS), was demonstrated in phase III trials [1] and confirmed in subsequent observational studies [2].
The degree of spasticity is usually measured via clinical evaluation with rating scales (such as modified Ashworth scale), but inter-observer variability and individual patient differences have raised concerns about reliability.
Modifications in neurophysiological parameters could reflect the altered spinal mechanisms involved in the generation of motoneuronal hyperexcitability, representing a possible parameter to monitor antispastic treatment response.
Another tool is to evaluate the variation on walking performance tests, as an indirect effect of spasticity on deambulation. Finally, there is a growing interest on self-reported questionnaires, assessing the impact of peculiar dimensions of disease in MS patients.

Aims:

To correlate neurophysiological tests, walking performance parameters and self-reported questionnaires with spasticity reduction, in a cohort of MS patients successfully treated with Nabiximols.

Materials and methods

Six MS patients were recruited to start a second-line antispastic treatment because of sustained spasticity with urinary dysfunction, sometimes associated with painful spasm, persistently occurring although full-dose treatment with standard antispastic therapy with baclofen (table 1). All of them resulted responders after 4 weeks of Nabiximols therapy, considering that at least 20% reduction in NRS was reported.
The cohort underwent neurophysiological tests (H reflex and H/M ratio, F wave of the lower limbs) before and after four weeks of Nabiximols therapy (time 1). The tests were repeated after eight weeks (time 2) of on-going cannabinoid therapy to monitor the evolution of the parameters.
Timed 25-foot walk (T25FW) and six-minute walk test (6MWT) were performed at baseline and at time 1, along with multiple sclerosis spasticity scale (MSSS-88), modified fatigue impact score (MFIS) and 12-item MS walking scale (MSWS-12).
Statistical analysis was based on t test for the comparison between groups with regards to walking performance tests and self-reported questionnaires, while ANOVA was used for the analysis of neurophysiological parameters.

Gender, n (%)	**Male: 4 (64%) Female: 2 (33%)**
Age, years (± SD)	47.5 ± 8.7
Disease duration, years (± SD)	13.2 ± 4
Disease form:	
RR, n	2
SP, n	2
PP, n	2
EDSS at baseline (± SD)	5 ± 1.5
NRS 0-10 at baseline (± SD)	6,83 ± 1.6
NRS 0-10 at follow-up (± SD)	4,83 ± 1
Painful spasm reported (%)	80%
Ambulation Index 1-9 (± SD)	2,8 ± 1

Table 1

Results

Nabiximols therapy induced a modification in neurophysiological parameters: a significant reduction of the latencies for both H (P = 0.01) and F (P = 0.002) waves was reported, more evident at time 2 (table 2).

		Baseline	Time 1	Time 2	P (bas vs T1)	P (bas vs T2)
H wave	**threshold, msec (± SD)**	9.6 ± 4.7	10.1 ± 2.9	9.00 ± 3.0	> 0.05	> 0.05
	latency, msec (± SD)	29.3 ± 1.7	28.2 ± 1.5	27.7 ± 1.6	**0.013**	**0.005**
	amplitude, msec (± SD)	5.0 ± 3.3	5.4 ± 2.7	4.9 ± 3.3	> 0.05	> 0.05
	H amp/ M amp	0.28 ± 0.14	0.29 ± 0.08	0.24 ± 0.92	> 0.05	> 0.05
F wave	**threshold, msec (± SD)**	21.1 ± 5.9	24.0 ± 8.8	18.1 ± 4.1	> 0.05	> 0.05
	min. latency, msec (± SD)	47.5 ± 4.3	47.3 ± 3.8	44.5 ± 3.1	**0.002**	**0.002**
	chronodispersion, msec (± SD)	4.54 ± 2.0	4.5 ± 1.9	4.9 ± 1.8	> 0.05	> 0.05
	amplitude, msec (± SD)	0.26 ± 1.60	0.24 ± 0.12	0.37 ± 0.23	> 0.05	> 0.05

Table 2

Considering walking performance tests, we observed 11.3% relative reduction of time to perform T25FW (baseline: 9,9 sec ± 5,4; time 1: 8,6 sec ± 4,1; P = 0,03). Better results in 6MWT, with 27.5% relative improvement in distance (baseline: 266,5 meters ± 109; time 1: 339,5 meters ± 150; P = 0,09) were reported, even if not statistically significant (figure 1).

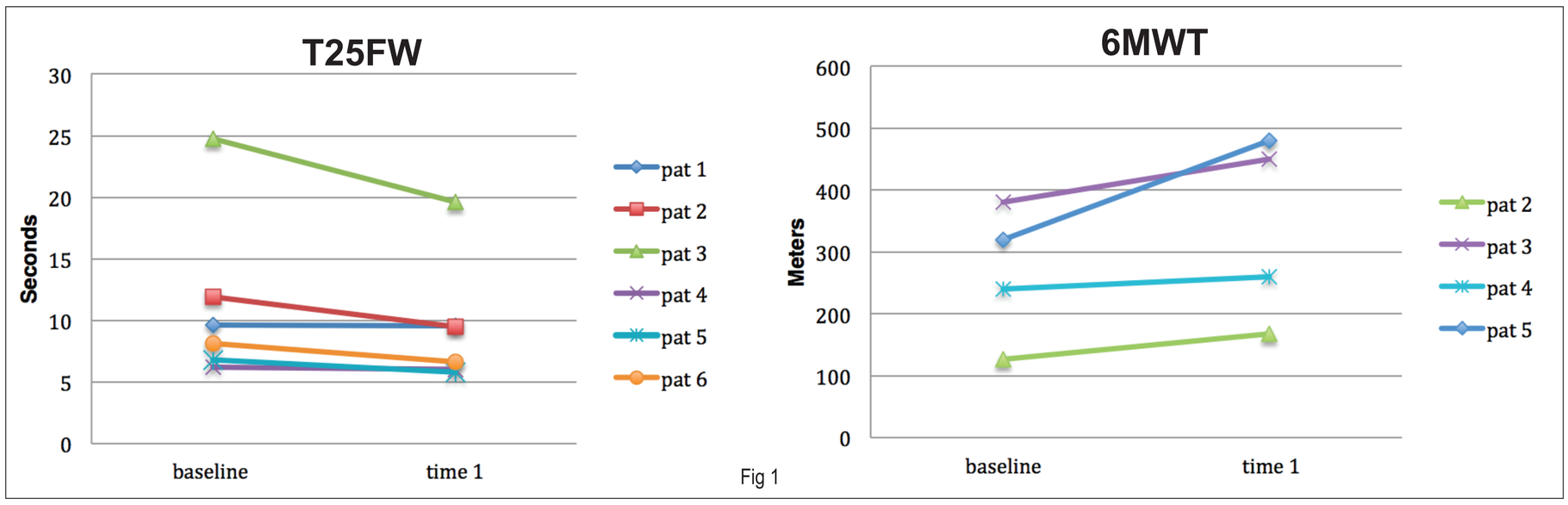

Fig 1

Regarding self-reported questionnaires, a trend in reduction of the MSSS-88 total score was reported (figure 2), confirming the subjective improvement after cannabinoid treatment.

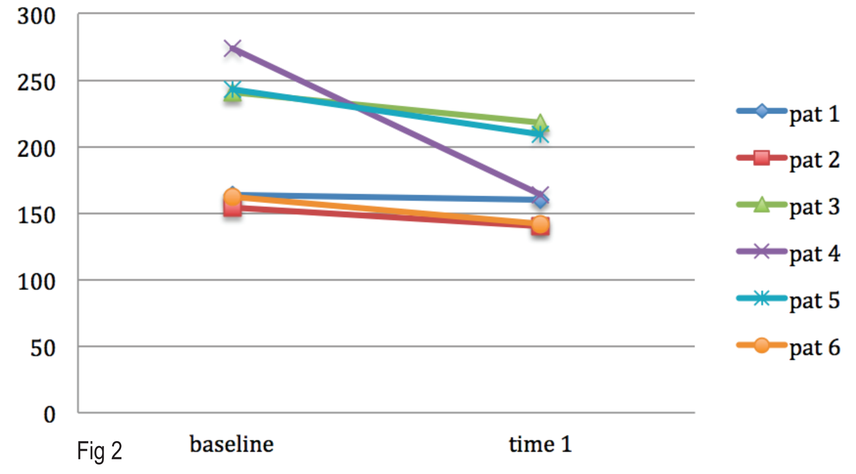

Fig 2

Discussion

Neurophysiological parameters have been already studied in the evaluation of spasticity, though correlation with clinical response to cannabinoids is controversial [3, 4]. Our findings of decreased latencies in H and F-waves may point out that there could be a modulation, exerted by Nabiximol therapy, of motoneuronal excitability and that it can also be used as a tool for measuring the degree of spasticity, as previously suggested by other studies [5]. However, the cohort is quite small to draw final conclusions and there are some concerns on the possible utilization in clinical settings.
Preliminary data of the present study suggest that walking parameters improvement correlate with spasticity reduction, due to Nabiximols therapy.
Spasticity is a complex phenomenon, which is only partially derived from altered spinal reflexes. It is in fact influenced by external conditions, including bio-mechanical factors. This is probably a reason of the difficulty in finding a single, objective marker of the phenomenon.

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