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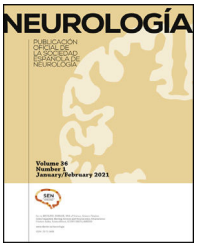

ORIGINAL ARTICLE

Alterations in dexterity and manual function in patients with focal hand dystonia

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KEYWORDS
Focal dystonia;
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Abstract
Introduction: Focal hand dystonia is a movement disorder whose symptoms cause alterations in the performance of tasks requiring a high level of dexterity. Currently, there is no model for interpreting the disease and few studies have identified the difficulties of patients with dystonia in carrying out activities of daily living (ADL). This study aims to describe manipulative dexterity and its influence on ADLs in patients with focal hand dystonia.
Materials and methods: We performed an observational, cross-sectional, case-control study including 24 participants (12 patients with focal hand dystonia and 12 controls). The patients were referred by the neurology department of Hospital Ramón y Cajal. We gathered sociodemographic data, as well as retrospective clinical data for patients. We subsequently administered evaluation tests, in the following order: Nine-Hole Peg Test (NHPT), Box and Blocks Test (BBT), Purdue Pegboard Test (PPT), and Jebsen-Taylor Test of Hand Function (JTTHF).
Results: The study sample included a total of 24 participants, 7 women and 17 men, with a mean age (standard deviation) of 50.79 (14.40) years. In the patient group, neuromuscular involvement or psycho-emotional problems were not detected in half of cases; smaller numbers of patients presented difficulties associated with the right shoulder (25%) and anxious state (33.3%).
Conclusions: Our results indicate that focal hand dystonia affects manipulative dexterity in these patients, who showed poorer performance and required more time to complete the tasks.

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PALABRAS CLAVE
Distonía focal;
Actividades de la vida diaria;
Destreza manipulativa;
Mano

Descripción de la afectación de la destreza y función manual en pacientes con distonía focal de la mano

Resumen
Introducción: La distonía focal de la mano es un trastorno del movimiento cuya sintomatología produce una alteración en el desempeño de tareas que requieren un nivel de destreza alto. Actualmente, no se dispone de un modelo de interpretación de la enfermedad y son escasos los estudios que identifican las dificultades de las personas con distonía al desempeñar las actividades de la vida diaria (AVD). Por todo ello, el objetivo del estudio es describir la destreza manipulativa y su influencia en las AVD de los pacientes con distonía focal de la mano.
Material y método: Se realizó un estudio observacional, transversal, tipo casos y controles. Se reclutaron 24 participantes: 12 pacientes y 12 sujetos control. Los pacientes fueron derivados por el Servicio de Neurología del Hospital Ramón y Cajal. Se obtuvieron datos sociodemográficos y datos clínicos retrospectivos en el grupo de casos. Posteriormente, se administraron pruebas de evaluación, en el siguiente orden: *Nine Hole Peg Test* (NHPT), *Box and Blocks Test* (BBT), *Purdue Pegboard Test* (PPT) y *Jebsen-Taylor Test of Hand Function* (JTTHF).
Resultados: En la muestra del estudio, participaron un total de 24 personas, 7 mujeres y 17 hombres, con una media de edad de 50,79 $\pm$ 14,40 años. Del total de participantes con distonía focal se observó que, aunque la mitad de la muestra no identificó signos de afectación neuromuscular, ni problemas psicoemocionales, un menor porcentaje de estos pacientes identificaron dificultades asociadas con el hombro derecho (25%) y el estado ansioso (33,3%).
Conclusiones: Los hallazgos encontrados en el presente trabajo señalan que la distonia focal de la mano afecta a la destreza manipulativa de estos pacientes, presentando una peor ejecución y requiriendo más tiempo para su ejecución.

Introduction

Focal hand dystonia is a movement disorder characterised by sustained or intermittent muscle contractions of the hand and arm, causing repetitive movements, abnormal postures, or both.[1]

The most typical symptoms are tension in the arm, rigidity of the hand during writing, or fatigue when performing an activity over a long period of time. Speed may also be decreased in some cases, which may be accompanied by tremor. Furthermore, dystonia is associated with a generalised alteration to sensorimotor integration; therefore, these patients may present an inefficiently high grip force, sometimes resulting in increased fatigue.[2] All these symptoms manifest during the performance of specific tasks requiring a high degree of dexterity, such as writing or playing an instrument.[3]

Such activities as writing involve precise, complex movements. This task requires the coordinated excitation and inhibition of the muscles involved. It also requires a high degree of manipulative dexterity, leading to a repetitive use of hand patterns. Individuals repeatedly performing manipulative tasks may develop symptoms resembling dystonia, due to the existence of risk factors associated with musculoskeletal disorders combined with repetitive movements.[4] Doshi et al.[5] observed that patients with focal hand dystonia, in addition to problems with writing, also presented problems dressing, undressing, and eating.

In the field of focal dystonia, further research is needed on the neuropathology,[6,7] prognosis,[8] and anatomical basis of the disease.[9] To establish a model for interpretating the disease and, more importantly, the optimal therapeutic management, we need to start from a solid understanding. Few studies have addressed not only manual dexterity but also how it affects hand functionality and even the activities of daily living (ADL).

Therefore, this study aims to describe the manipulative dexterity of patients with focal hand dystonia in comparison with healthy individuals, and to analyse how dystonia affects manipulative dexterity and function in ADL.

Material and methods

This is an observational, cross-sectional case-control study. We followed the methodological recommendations for the development of case-control studies established in the STROBE statement.[10]

We recruited 24 participants: 12 patients with dystonia and 12 controls. Patients were referred by the neurology department at Hospital Ramón y Cajal (Madrid, Spain).

Participants were consecutively selected by non-probability sampling, whereas controls were collected by convenience and matched with participants.

Inclusion criteria were the following: age between 18 and 75 years, diagnosis of occupational dystonia/focal or segmental dystonia (according to the 1894 classification of the Dystonia Medical Research Foundation) of the upper limb, progressing for more than one year. Participants also had to be under treatment with periodical botulinum toxin infiltrations and no other drug with effect in the central nervous system, with the last infiltration having been performed at least 4 months prior to inclusion. To ensure a more homogeneous sample, thus increasing the likelihood of obtaining reliable results, we included right-handedness as an inclusion criterion.

Exclusion criteria were diagnosis of secondary dystonia, any other neurological or neurodegenerative disease, or musculoskeletal disease or trauma involving the upper limbs.

Table 1 Sociodemographic characteristics of the sample.

	n = 24	Patients with dystonia (n = 12)	Controls (n = 12)
Diagnosis: dystonia/no dystonia, n (%)	12 (50)/12 (50)		
Age, mean (SD) (range)	50.79 (14.40) (25-76)	51.50 (16.80) (25-76)	50.08 (12.25) (25-65)
Sex: women/men, n (%)	7 (29.2)/17 (70.8)	3 (25)/9 (75)	4 (33.3)/8 (66.7)
Level of schooling: basic/medium/high, n (%)	2 (8.3)/5 (20.8)/17 (70.8)	2 (16.7)/5 (41.7)/5 (41.7)	0 (0)/0 (0)/12 (100)
Disease progression time in years, mean (SD) (range)	6.22 (11.95) (0—50)	13 (14.74) (1—50)	0 (0) (0-0)
Musculoskeletal problems: neck/right shoulder/lumbar spine/none, n (%)	2 (8.3)/3 (12.5)/1 (4.2)/18 (75)	2 (16.7)/ 3 (25)/1 (8.3)/6 (50)	0(0)/ 0 (0)/1 (9.1)/10 (90.9)
Psychoemotional problems: anxiety/frustration/both/none, n (%)	5 (20.8)/1 (4.2)/1 (4.2)/17 (70.8)	4 (33.3)/1 (8.3)/1 (8.3)/6 (50)	1 (8.3)/0 (0)/0 (0)/11 (91.7)

SD: standard deviation. $P < .05$ (t test).

The study was approved by the ethics committee at Universidad Rey Juan Carlos and Hospital Universitario Ramón y Cajal, in accordance with the principles of the Declaration of Helsinki on medical research involving human subjects, adopted at the 18th World Medical Assembly (Helsinki, Finland, June 1964), and subsequent revised versions. After recruiting the study participants, we obtained their written informed consent to participate in the study.

Testing was conducted at Universidad Rey Juan Carlos over a period of 5 months. We retrospectively obtained sociodemographic and clinical data. To collect sociodemographic and general health-related information associated with musculoskeletal involvement, psychosocial difficulties, and symptoms of depression and anxiety, we performed a subjective assessment using a semi-structured interview.

Tests were administered in the following order: Nine Hole Peg Test (NHPT), Box and Blocks Test (BBT), Purdue Pegboard Test (PPT), and Jebsen-Taylor Hand Function Test (JTHFT). All tests were selected due to their good psychometric properties, both in terms of validity and reliability and sensitivity for detecting alterations in hand function at different ages and in clinical conditions such as multiple sclerosis and occupational dystonia, among others.[11—15]

We used the NHPT to measure fine manual dexterity. The test consists of placing 9 pegs into their corresponding holes and subsequently removing them, as quickly as possible. The time taken to place and remove the pegs is recorded.[16]

With the BBT, we assessed unilateral gross manual dexterity. The test is easy and quick to administer. Patient are asked to move, one by one, the maximum number of blocks from one box to another in a period of 60 seconds, starting with the unaffected arm. Higher scores indicate better manual dexterity. The test has standardised instructions for administration and scoring.[17]

We used the PPT to measure motor dexterity of the hand, both unilaterally and bilaterally. The test uses a board with holes and 4 holders for pegs, washers, and collars. Patients perform 4 subtests: insertion with the dominant hand, with the non-dominant hand, with both hands simultaneously, and assembly. The time available for each subtest is 30 seconds, except for the assembly subtest, for which subjects are given 60 seconds. The test is quick and easy to administer (5 min).[18]

We used the JTHFT to assess a wide range of hand functions frequently used in ADL. It includes seven subtests (writing, simulated page-turning, lifting small objects, simulated feeding, stacking, lifting large lightweight objects, and lifting large heavy objects) to be performed first with the dominant hand and subsequently with the non-dominant hand. This is a timed test.[19,20]

Statistical analysis

We calculated descriptive statistics broken down by age, sex, level of education, disease duration, neuromusculoskeletal involvement, and psychoemotional problems (Table 1). We calculated the mean and standard deviation of normally-distributed quantitative variables, and the median and the 25th and 75th percentiles for non—normally-distributed variables.

Firstly, we tested for normal distribution using the Shapiro—Wilk test, and analysed the difference of mean scores between both groups using the t test or Mann—Whitney U test, according to the parametric or non-parametric distribution of variables. To analyse differences between groups, we calculated the effect size using Cohen's d for variables with parametric distribution and Rosenthal's r for variables with non-parametric distribution. Data interpretation was conducted according to the guidelines published by Cohen in 1988 for the interpretation of results (0.2: small effect; 0.5: medium effect; and 0.8 or more: large effect).[21,22]

Secondly, we analysed the possible correlations between variables for the dominant and non-dominant hand using the parametric Pearson test or the non-parametric Spearman test.

Statistical analysis was performed using the SPSS statistics software for Windows (© 2013, version 22.0; IBM SPSS Corp.).

Results

A total of 24 participants were included in the study: 7 women and 17 men, with a mean age of 50.79 (14.40) years (Table 1). We observed no significant differences between cases and controls in age and sex ($P > .05$); however, there were statistically significant differences in the remaining sociodemographic variables ($P < .05$).

Table 2 Descriptive statistics from the sample, differences in mean scores between groups, and effect size.

	Patients with dystonia (n = 12)	Controls (n = 12)	P^1	P^2	d	r
Nine Hole Peg Test						
NHPT_D, *median (q1-q3)*	24.56 (19.72-29.98)	18.94 (16.94-22.26)	—	.01*		0.48
NHPT_ND, *median (q1-q3)*	21.49 (19.34-24.36)	21.13 (18.97-23.13)	—	.72		-
Purdue Pegboard Test						
PPT_D, *median (q1-q3)*	13.50 (10.25-14)	15 (13-17)	—	.06	—	—
PPT_ND, *median (q1-q3)*	12.50 (10.25-14)	13.50 (12.25-15)	—	.09	—	—
PPT_B, *median (q1-q3)*	10.50 (7.25-18)	18 (14.50-22)	—	.01*	—	0.52
PPT_AT, *mean (SD)*	22.25 (4.73)	31.25 (8.70)	.00*	—	1.28	—
Box and Block Test						
BBT_D, *median (q1-q3)*	62 (48.75-65)	62.50 (56.25-72.50)	—	.49	—	—
BBT_ND, *mean (SD)*	61.50 (7.47)	62.33 (12.21)	.18	—	—	—
Jebsen Taylor Hand Function Test						
JTHFT_WR_D, *median (q1-q3)*	19.93 (13.04-44.88)	10.08 (9.50-12.83)	—	.00*	—	0.67
JTHFT_WR_ND, *mean (SD)*	38.31 (16.33)	30.08 (12.50)	.17	—	—	—
JTHFT_PT_D, *median (q1-q3)*	5.04 (4.31-6.97)	3.67 (3.39-4.09)	—	.00*	—	0.63
JTHFT_PT_ND, *median (q1-q3)*	5 (3.85-6.17)	4.07 (3.63-4.65)	—	.11	—	—
JTHFT_SO_D, *mean (SD)*	6.63 (1.24)	6.67 (2.32)	.96	—	—	—
JTHFT_SO_ND, *median (q1-q3)*	6.91 (6.25-7.79)	5.99 (5.83-6.58)	—	.02*	—	0.46
JTHFT_SF_D, *median (q1-q3)*	7.28 (5.79-15.05)	7 (5.12-9.78)	—	.41	—	—
JTHFT_SF_ND, *mean (SD)*	9.96 (1.69)	10.22 (3.98)	.83	.83	—	—
JTHFT_ST_D, *median (q1-q3)*	2.65 (1.84-5.32)	1.94 (1.55-2.30)	—	.13	—	—
JTHFT_ST_ND, *median (q1-q3)*	2.92 (2.42-4.53)	2.19 (1.74-3.07)	—	.03*	—	0.43
JTHFT_LO_D, *median (q1-q3)*	3.88 (3.41-5.10)	3.26 (2.67-3.57)	—	.00*	—	0.54
JTHFT_LO_ND, *median (q1-q3)*	4.07 (3.54-4.46)	3.50 (3.22-3.91)	—	.05*	—	0.38
JTHFT_HO_D, *median (q1-q3)*	3.44 (3.08-4.61)	3.38 (2.71-3.71)	—	.43	—	—
JTHFT_HO_ND, *median (q1-q3)*	3.65 (3.30-4.22)	3.52 (2.90-4.04)	—	.37	—	—

P^1: *t* test, statistical significance at $P < .05$; P^2: Mann—Whitney U test, statistical significance at $P < .05$; d: Cohen's d; r: Rosenthal's r. BBT_D: Box and Block Test with the dominant hand; BBT_ND: Box and Block Test with the non-dominant hand; JTHFT_HO_D: Jebsen-Taylor Hand Function Test, heavy objects subtest with the dominant hand; JTHFT_HO_ND: Jebsen-Taylor Hand Function Test, heavy objects subtest with the dominant hand; JTHFT_LO_D: Jebsen-Taylor Hand Function Test, lightweight objects subtest with the dominant hand; JTHFT_LO_ND: Jebsen-Taylor Hand Function Test, lightweight objects subtest with the dominant hand; JTHFT_PT_D: Jebsen-Taylor Hand Function Test, page turning subtest with the dominant hand; JTHFT_PT_ND: Jebsen-Taylor Hand Function Test, page turning subtest with the non-dominant hand; JTHFT_SF_D: Jebsen-Taylor Hand Function Test, simulated feeding subtest with the dominant hand; JTHFT_SF_ND: Jebsen-Taylor Hand Function Test, simulated feeding subtest with the non-dominant hand; JTHFT_SO_D: Jebsen-Taylor Hand Function Test, small objects subtest with the dominant hand; JTHFT_SO_ND: Jebsen-Taylor Hand Function Test, small objects subtest with the dominant hand; JTHFT_ST_D: Jebsen-Taylor Hand Function Test, stacking subtest with the dominant hand; JTHFT_ST_ND: Jebsen-Taylor Hand Function Test, stacking subtest with the non-dominant hand; JTHFT_WR_D: Jebsen-Taylor Hand Function Test, writing subtest with the dominant hand; JTHFT_WR_ND: Jebsen-Taylor Hand Function Test, writing subtest with the non-dominant hand; NHPT_D: Nine Hole Peg Test with the dominant hand; NHPT_ND: Nine Hole Peg Test with the non-dominant hand; PPT_AT: assembly tests of the Purdue Pegboard Test; PPT_B: Purdue Pegboard Test with both hands; PPT_D: Purdue Pegboard Test with the dominant hand; PPT_ND: Purdue Pegboard Test with the non-dominant hand.

We observed that, while almost half of the patients with focal hand dystonia showed no signs of neuromuscular involvement or psychoemotional problems, a smaller percentage did report difficulties associated with the right shoulder (25%) and anxiety (33.3%) (Table 1).

Descriptive data from the administered tests are presented in Table 2. We observed that patients with focal hand dystonia took longer than controls to perform the dexterity and manual function tests, with the exception of the PPT and the JTHFT simulated feeding subtest, performed with the dominant hand.

Table 2 shows the difference in mean score in both groups and the effect size. We observed statistically significant differences between groups in manual dexterity in the dominant hand measured with the NHPT ($P = .01$) and in the bilateral and assembly subtests of the PPT ($P = .00$; $P = .01$). We also observed statistically significant differences between groups in the hand function variables analysed with the writing ($P = .00$), simulated page-turning ($P = .00$), and lifting large lightweight objects ($P = .00$) subtests of the JTHFT for the dominant hand, and differences in the hand function of the non-dominant hand in the lifting small objects ($P = .02$),

Table 3 Correlations between dependent variables.

	Patients NHPT_D	Controls		Patients NHPT_ND	Controls
JTHFT_WR_D	0.659*	0.077	JTHFT_WR_ND	0.546	0.462
JTHFT_PT_D	0.330	0.450	JTHFT_PT_ND	0.434	0.004
JTHFT_SO_D	0.643*	0.713**	JTHFT_SO_ND	0.571	0.574
JTHFT_SF_D	0.404	0.004	JTHFT_SF_ND	0.235	0.350
JTHFT_ST_D	0.712**	0.650*	JTHFT_ST_ND	0.238	0.469
JTHFT_LO_D	0.846**	0.396	JTHFT_LO_ND	0.106	0.344
JTHFT_HO_D	0.809**	0.411	JTHFT_HO_ND	0.396	0.594*
	Patients BBT_D	**Controls**		**Patients BBT_ND**	**Controls**
JTHFT_WR_D	−0.501	−0.113	JTHFT_WR_ND	−0.600*	−0.417
JTHFT_PT_D	−0.145	−0.476	JTHFT_PT_ND	−0.336	−0.041
JTHFT_SO_D	−0.552	−0.190	JTHFT_SO_ND	−0.335	0.077
JTHFT_SF_D	−0.450	0.007	JTHFT_SF_ND	0.166	−0.039
JTHFT_ST_D	−0.763**	−0.455	JTHFT_ST_ND	−0.474	−0.024
JTHFT_LO_D	−0.698*	−0.708*	JTHFT_LO_ND	0.157	−0.452
JTHFT_HO_D	−0.795**	−0.701*	JTHFT_HO_ND	−0.419	−0.574
	Patients PPT_D	**Controls**		**Patients PPT_ND**	**Controls**
JTHFT_WR_D	−0.858**	−0.005	JTHFT_WR_ND	−0.307	−0.593*
JTHFT_PT_D	−0.664*	−0.447	JTHFT_PT_ND	−0.364	0.058
JTHFT_SO_D	−0.569	−0.769**	JTHFT_SO_ND	−0.404	−0.351
JTHFT_SF_D	−0.620	−0.034	JTHFT_SF_ND	−0.102	−0.242
JTHFT_ST_D	−0.546	−0.757**	JTHFT_ST_ND	−0.104	−0.477
JTHFT_LO_D	−0.821**	−0.623*	JTHFT_LO_ND	−0.010	−0.491
JTHFT_HO_D	−0.795**	−0.574	JTHFT_HO_ND	−0.007	−0.714**

* $P < .05$.
** $P < .01$.

stacking ($P = .03$), and lifting large lightweight objects ($P = .05$) subtests.

We found a large effect size in the assembly subtest of the PPT (d = 1.28). The subtests of the JTHFT performed with the dominant hand showed a medium effect size ($0.5 \geq r \leq 0.8$), whereas subtests performed with the non-dominant hand showed a small effect ($r < 0.5$).

Regarding the analysis of correlations between dependent variables (Table 3), the group of patients with focal hand dystonia showed significant positive correlations in the dominant hand between the NHPT and the hand function subtests of the JTHFT (writing, lifting small objects, stacking, lifting large lightweight objects, and lifting large heavy objects). Thus, shorter times in the NHPT were associated with shorter execution times and better hand function in the JTHFT.

In tests of gross manual dexterity with the dominant hand (BBT and the JTHFT stacking, lifting large lightweight objects, and lifting large heavy objects subtests), significant negative correlations were observed in the same group of patients. Therefore, smaller numbers of blocks moved in the BBT were associated with longer execution times and poorer hand function in the JTHFT (Table 3).

Patients with focal hand dystonia showed statistically significant negative correlations in manual dexterity tests with the dominant hand (PPT and the JTHFT writing, simulated page-turning, simulated feeding, lifting large lightweight objects, and lifting large heavy objects subtests), with smaller numbers of pegs inserted being associated with longer execution times and poorer hand function (Table 3).

Discussion

One of the aims of our study is to describe manual dexterity and hand function in patients with segmental or focal hand dystonia. According to our findings, patients with focal hand dystonia present poorer results in dexterity and manipulative function than individuals without dystonia, reflected in the longer execution times and poorer execution. These data corroborate the findings of the study by Alemán et al.[23]; despite their main objective being to study the cognitive sequelae of dystonia, these authors also studied its impact on hand function. Their results suggest significantly poorer performance in patients with dystonia than in controls. Furthermore, Allgöwer et al.[12] reported that patients with writer's cramp presented fine motor coordination problems in tasks requiring a high level of coordination and involving visual elements. This is consistent with the findings of other studies that support the presence of sensory processing alterations in this disorder and report abnormal size and organisation of brain areas involved in somatosensory representation.[24,25]

According to our findings, there are not significant differences in all variables; this may appear surprising, but is probably largely explained by the small sample size. However, taking into account

the effect size, we did find differences in some subtests. Allgöwer et al.[12] showed similar results, observing no significant differences in 2 tests of hand function, despite poorer results in patients than in controls. This seems to contradict previous results, such as those reported by Horstink et al.,[26] who found no differences in PPT results between patients with focal hand dystonia and controls, or the study by Bleton et al.,[27] who, despite identifying impaired force control, did not observe deficits in dexterity or sensory function. As mentioned previously, this is probably due to the number of study participants, as both studies had a small sample size, with the study by Bleton et al.[27] including only 6 patients with focal hand dystonia.

Another aim of our study was to analyse the impact of focal hand dystonia on dexterity and manipulative function in ADL. In this line, one of the considerations in the design of the JTHFT was the assessment of the hand function patterns generally used to perform everyday activities.[19] Lynch et al.[15] identified correlations between the JTHFT and the Klein-Bell scale in a cohort of patients with spinal lesions; therefore, the JTHFT may be useful in predicting the functional use of the hand in ADL. According to our results, execution time is one of the biggest predictors of hand function, and would translate into inadequate performance of ADL. Focal hand dystonia affects different motor tasks more generally than we may expect a priori. This impact on hand function, as reflected by the execution time observed in our results, is consistent with the findings of other studies, such as that conducted by Van Vugt et al.[28] in 2014. Their study focused on musician's dystonia in pianists and suggested that, in addition to presenting problems in their performance as musicians, they probably had difficulties in other motor tasks and fine motor skills in other contexts. The authors did not specifically assess these tasks, but conclusions were drawn from the improvements achieved with the therapies used.

Similarly, a review published in 2017 by Stahl et al.[29] found that although the abnormal motor activation occurs during the performance of a specific activity (which is related with the patient's work), severe symptoms affect the patient's life globally, decreasing their involvement and performance in ADL.

One of the limitations of our study is the small sample size and the fact that all participants came from the same region, which represents a difficulty for extrapolating results. However, considering the classification of focal hand dystonia as a rare disease, it is difficult to obtain larger homogeneous samples.

Regarding the clinical implications of the data obtained, given that patients with focal hand dystonia seem to present deficits in manipulative dexterity and, as a result, problems in ADL, specific emphasis should be placed on the rehabilitation of the upper limb, focusing on such aspects as force control, execution time, fine motor coordination, and functionality in everyday activities.

Conclusions

Our findings suggest that focal hand dystonia affects the manipulative dexterity of these patients, who show poorer execution and longer execution times.

Patients with focal hand dystonia also present impaired performance in ADL, requiring higher precision and coordination of the dominant hand.

Considering the limitations of our study, further studies in this line are needed to obtain more conclusive results.

Conflicts of interest

The authors have no conflicts of interest to declare.

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