

Idiopathic Non-Task-Specific Upper Limb Dystonia, a Neglected Form of Dystonia

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ABSTRACT: Objective: The objective of this study was to describe the clinical and demographic features of idiopathic non-task-specific upper limb dystonia compared with the task-specific form.

Methods: In this retrospective study, adult patients with idiopathic upper limb dystonia, either focal or as part of a segmental/multifocal dystonia, from the Italian Dystonia Registry were enrolled. In patients with focal upper limb dystonia, dystonia spread was estimated by survival analysis.

Results: Of the 1522 patients with idiopathic adult-onset dystonia included in the Italian Dystonia Registry, we identified 182 patients with upper limb dystonia. Non-task-specific dystonia was present in 61.5% of enrolled cases. Women predominated among non-task-specific patients, whereas men predominated in the task-specific

group. Peak age of upper limb dystonia onset was in the sixth decade in the non-task-specific group and in the fourth decade in the task-specific group. In both groups, upper limb dystonia started as focal dystonia or as part of a segmental dystonia. Segmental onset was more frequent among non-task-specific patients, whereas focal onset predominated among task-specific patients. Dystonic action tremor was more frequent among non-task-specific patients. No significant differences between groups emerged in terms of sensory trick frequency, rest tremor, or family history of dystonia. In patients with focal upper limb dystonia, dystonia spread was greater in the non-task-specific group.

Conclusion: Novel information on upper limb dystonia patients suggests that non-task-specific and task-specific upper limb dystonia have different demographic and

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Italian Dystonia Registry participants are listed in the Appendix.

Giovanni Defazio and Tommaso Ercoli contributed equally to this work.

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clinical features. However, it remains to be determined whether these differences also reflect pathophysiological differences. © 2020 International Parkinson and Movement Disorder Society

Key Words: dystonia; non-task-specificity; task-specificity; upper limb; writer's cramp

Idiopathic adult-onset upper limb dystonia (ULD) is characterized by the presence of abnormal patterned movements and dystonic postures in the upper limbs.^{1,2} A remarkable feature of ULD is its task specificity, meaning that dystonia appears only during the execution of specific motor activities (eg, writer's cramp [WC]),^{3,4} although over time task-specific ULD may lose its specificity and thus become a non-task-specific dystonia.¹ ULD may also begin as a non-task-specific dystonia that manifests during different types of voluntary movement or even at rest.^{1,5}

Since Marsden's⁴ original observation about 40 years ago that WC may be a task-specific form of adult-onset dystonia, only a few studies have investigated the demographic and clinical features of idiopathic ULD.^{6–11} Most reports have included a relatively small number of patients with upper limb dystonia or they have focused on specific subtypes, such as WC⁶ or musician's dystonia.¹² No studies have specifically examined the clinical features of idiopathic non-task-specific dystonia or the possible differences between non-task-specific and task-specific ULD. Non-task-specific ULD has often been considered to be secondary to lesions in the basal ganglia and other brain areas.¹³

Knowledge about the clinical phenomenology of idiopathic non-task-specific ULD may be essential for design and implementation of future studies that aim to treat or modify disease course in those with idiopathic isolated ULD. We therefore performed a retrospective cross-sectional study to determine the frequency of non-task-specific ULD in a large cohort of Italian patients with adult-onset idiopathic dystonia and compared their main clinical and demographic features with those with a task-specific ULD (WC).

Methods

Data were obtained from the Italian Dystonia Registry, a database established in 2016 that stores demographic and clinical information of dystonia patients.¹⁴ The study was based on entirely retrospective data collection. A total of 37 Italian institutions contribute to the database using a common clinical protocol. Italian Dystonia Registry inclusion criteria include a diagnosis of dystonia according to published criteria,¹⁵ and an age of dystonia onset ≥ 18 years. Assessment included a standardized collection of historical data (demographic data, age of onset, age of dystonia diagnosis, and age

of dystonia onset in each body site, etc.) as supported by informed family members and/or prior medical records and clinical examination of all body sites potentially affected by dystonia (including less frequent sites such as the lower limbs). For each affected body region, the age of dystonia onset was recorded. With regard to ULD, it was recorded whether ULD was task specific at onset (ie, dystonia that manifested during only 1 specific motor activity such as writing, typing, playing a musical instrument, etc.) and whether and when (year) task specificity was lost. Magnetic resonance imaging or computed tomography of the head was performed in all patients and did not show any lesions in the basal ganglia, thalamus, cerebellum, or in any other areas possibly causing acquired forms of ULD.^{1,13} Tests for Wilson's disease and common pathogenetic variants (eg, *TOR1A*, *THAP1*) were performed as appropriate.

Patients included in the present study fulfilled the following eligibility criteria: (1) age of dystonia onset ≥ 18 years; (2) a diagnosis of ULD, either focal or as part of a segmental/multifocal dystonia; and (3) idiopathic etiology. The local ethical review board approved the study (identification no. PG/2018/11698). The requirement for informed consent was waived because the study was register based and individuals were not identifiable at any time.

Statistical analysis was performed with the Stata 11.0 package (StataCorp LP, College Station, TX). Data were expressed as mean $\pm$ standard deviation unless otherwise indicated. Differences between groups were examined by chi-square test, Fisher's exact test, or the Mann-Whitney *U* test as appropriate. In patients with focal ULD at dystonia onset, the relationship between later dystonia spread task specificity at onset was estimated by Kaplan-Meier survival curves and multivariable Cox regression analysis using 2 models. In the first model, study time was represented by the time elapsed between dystonia onset and spread. In the second model, study time was represented by age at spread. Patients in whom spread never occurred were included in the survival functions for the duration of the observation. Kaplan-Meier survival curves were compared by log-rank test. Multivariable Cox proportional hazard regression analysis was adjusted for age of dystonia onset and years of schooling as continuous variables and for female sex, task specificity at onset, dystonic tremor, sensory trick, family history of dystonia, and comorbidity as categorical variables (1 if present, 0 if not). For the purpose of Cox analysis, hazard ratios, 2-

sided 95% confidence intervals, and *P* values were calculated. For all analyses, significance was set at 0.05.

Results

In December 2019, the Italian Dystonia Registry contained data from 1522 patients with adult-onset idiopathic dystonia, of whom 182 were eligible for this study. A total of 112 patients presented with non-task-specific ULD, whereas 70 presented with task-specific ULD. In the task-specific ULD group, all patients had WC and 9 lost task specificity after 9.1 ± 8.9 years.

Clinical Phenomenology of Patients with Non-Task-Specific ULD and WC

When we investigated the demographic and clinical features of patients with non-task-specific ULD and WC (Table 1), we found that women were slightly more frequent in the non-task-specific ULD group (59/112), whereas men were slightly more prevalent in the WC group (39/70), although intergroup differences were not statistically significant (Table 1). Non-task-specific ULD patients reported less years of schooling than WC patients. Age of ULD onset ranged from 20 to 80 years in both groups, although it was significantly higher in the non-task-specific group. The peak age of ULD onset was in the sixth decade in the non-task-specific ULD group, whereas it was in the fourth decade in the WC group (Fig. 1). In both groups, ULD began as a

focal dystonia or as part of a segmental dystonia. The latter group included 2 subgroups: (1) patients with segmental upper limb onset and another body region involved at the same time and (2) patients with focal onset in another body region that later spread to the upper limb. These subgroups were characterized by a greater frequency of patients with non-task-specific ULD, whereas a focal ULD onset predominated among task-specific ULD patients. Likewise, dystonic action tremor was more frequent in the non-task-specific group. Among comorbid diseases, cardiovascular disease was significantly more prevalent in the non-task-specific ULD group. No significant differences between groups emerged in terms of frequency of sensory trick, rest tremor, or family history of dystonia.

Excluding the 30 ULD patients who had a focal onset in a body region other than the arm, significant differences were found between the remaining 82 patients with non-task-specific ULD at onset and the 70 patients with WC at onset in terms of age of ULD onset (49.1 ± 16.1 vs. 43.8 ± 15.9 years, $P = 0.04$), years of schooling (10.3 ± 4.1 vs. 13.3 ± 4.2 years, $P < 0.001$), dystonic action tremor frequency (36/82 vs. 18/70, $P = 0.03$), and cardiovascular disease frequency (43/82 vs. 18/70, $P < 0.001$).

In addition, the analysis limited to the comparison of the 51 patients with focal non-task-specific ULD at onset and the 56 patients with focal WC at onset yielded differences between groups in terms of age of ULD onset (51.2 ± 15 vs. 41.7 ± 14.7 years,

TABLE 1 Demographic and clinical features of patients with upper limb dystonia according to task specificity at onset

Demographic and clinical features	Writer's Cramp at Onset (n = 70)	Non-Task-Specific Upper Limb Dystonia at Onset (n = 112)	<i>P</i>
Males, n (%)	39 (55.7)	53 (47.3)	0.29
Mean years of schooling $\pm$ SD, y	13.31 ± 4.18	9.97 ± 4.28	$<0.001^a$
Patients with tertiary education, n (%)	43 (61)	36 (32)	$<0.001^a$
Mean age of upper limb dystonia onset $\pm$ SD, y	43.83 ± 15.90	51.63 ± 16.66	0.002^a
Presentation of ULD, n (%)			$<0.001^a$
Focal upper limb dystonia at onset	56 (80)	51 (46)	
Segmental upper limb dystonia at onset, with another body region involved at the same time	4 (6)	31 (28)	
Focal onset of dystonia elsewhere that later spread to the upper limb	10 (14)	30 (27)	
Patients with dystonic, n (%)			
Rest tremor, either alone or associated with action tremor	6 (9)	13 (12)	0.622
Action tremor, either alone or associated with rest tremor	18 (26)	54 (48)	0.003^a
Sensory trick, n (%)	3 (4.3)	11 (9.8)	0.254
Patients with a family history of dystonia, n (%)	10 (14.3)	21 (18.8)	0.544
Comorbidity, n (%)			
Overall	17 (24.3)	64 (57.1)	$<0.001^a$
Cardiovascular	11 (15.7)	55 (49.1)	$<0.001^a$
Thyroid disorders	3 (4.3)	6 (5.4)	1
Other medical conditions	3 (4.3)	3 (2.7)	0.677

SD, standard deviation; ULD, upper limb dystonia.

^aSignificant at $P < 0.05$.



FIG. 1 Frequency distribution of age at upper limb dystonia onset in 70 patients presenting with writer's cramp (gray bars) and 112 patients presenting with non-task-specific upper limb dystonia (black bars).

$P < 0.0001$), years of schooling (10.1 ± 4.1 vs. 13.7 ± 4.2 years, $P < 0.0001$), dystonic action tremor frequency (26/51 vs. 14/56, $P < 0.01$), and cardiovascular disease frequency (22/51 vs. 9/56, $P = 0.002$).

Dystonia Spread in Patients with Focal ULD at Onset

In the 107 patients with focal ULD at onset, 10/56 patients with WC (18%) and 25/51 patients with non-task-specific ULD (49%) had dystonia spread.

The overall disease duration was 14.6 ± 10.8 years in the non-task-specific group and 15.1 ± 9.9 years in the task-specific group ($p = 0.4$). The body sites involved in dystonia spread were the cranial region in 8 patients (6 were from the non-task-specific group), the neck in 24 patients (18 were from the non-task-specific group), the larynx in 4 patients (2 were from the non-task-specific group), and the lower limb in 4 patients (2 were from the non-task-specific group) over 13.5 ± 13.7 years. Four patients had 3 or more affected body regions.

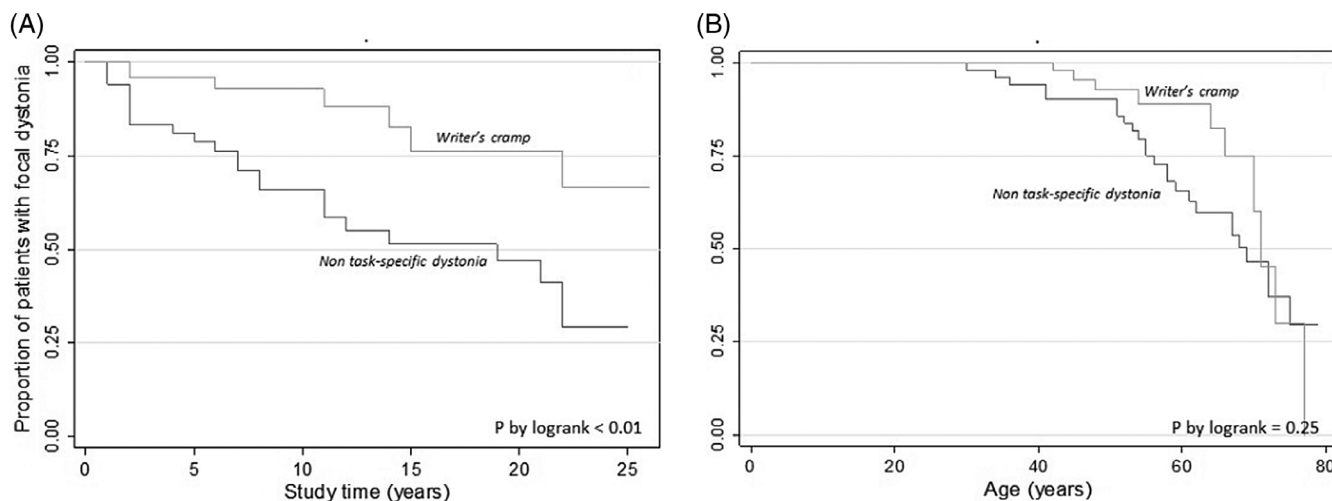


FIG. 2 Kaplan-Meier's survival analysis of spread of dystonia in patients with focal upper limb dystonia at onset. **(A)** Study time was represented by the time elapsed between dystonia onset and spread, and patients in whom spread never occurred were included in the survival functions for the duration of the observation: in the non-task-specific group, the number of at-risk patients was 51 at time 0, 32 at 5 years, 18 at 10 years, 14 at 15 years, and 8 at 20 years; in the task-specific group, there were 56 patients at time 0, 31 at 5 years, 20 at 10 years, 11 at 15 years, and 8 at 20 years. **(B)** Study time was represented by age at spread, and patients in whom spread never occurred were censored at age at data collection: in the non-task-specific group, the number of at-risk subjects was 51 at age 20, 47 at age 40, 23 at age 60, and 12 at age 70; in the writer's cramp group, the number of at-risk subjects was 56 at age 20, 46 at age 40, 17 at age 60, and 5 at age 70 group.

The Kaplan-Meier survival model based on the elapsed time between ULD onset and spread over time in patients with this feature indicated that dystonia spread more frequently (P by log rank <0.01) in the non-task-specific ULD group than in the WC group (Fig. 2A). The mean time it took for dystonia to spread was significantly lower in the non-task-specific ULD group than in the WC group (11.4 ± 11.8 vs. 19.7 ± 16 years; $P < 0.01$). The greater tendency to spread in the non-task-specific ULD group was confirmed by multivariable Cox analysis adjusted for gender, years of schooling, age of ULD onset, family history of dystonia, and comorbidity (adjusted hazard ratio = 2.5; 95% confidence interval, 1.1–5.1; $P = 0.03$). No adjustment factor was significantly associated with spread on multivariable analysis (data not shown).

The survival curves based on age at spread (Fig. 2B) did not significantly differ between the non-task-specific ULD and WC groups (P by log rank = 0.25). Visual inspection of the curves suggested that the 2 groups developed spread during a similar age range. The minimum age at spread was 30 years in the non-task-specific ULD group and 42 years in the WC group, whereas most patients in both groups developed spread after the age of 45 (20/25 patients in the non-task-specific ULD group and 9/10 patients in the WC group, $P = 0.65$). Mean age at spread did not significantly differ between the non-task-specific ULD and WC groups (61 ± 12.7 vs. 55.9 ± 12.2 , $P = 0.14$). Correlation analysis yielded a significant inverse relationship between time to spread and age of dystonia onset in the WC group (Spearman ρ , -0.76 , $P = 0.01$), but not in the non-task-specific ULD group (Spearman ρ , -0.32 , $P = 0.14$).

Discussion

Our study provides novel information on the demographic and clinical features of idiopathic non-task-specific ULD patients. In the large sample of 1522 patients with idiopathic adult-onset dystonia from the Italian Dystonia Registry,¹⁴ we identified idiopathic ULD in 12% of cases, the majority of whom (61.5%) had non-task-specific ULD at onset. Although the frequency data herein provided were from neurological services and therefore not necessarily representative of the general patient population, our findings nevertheless suggest that idiopathic non-task-specific ULD is more frequent than has been suggested by previous observations.

Non-task-specific ULD tends to manifest more frequently in subjects with lower levels of education and to develop in late adulthood, with a peak age of onset in the sixth decade. Non-task-specific ULD may be a manifestation of dystonia spread or start focally. The

late peak age of onset of non-task-specific ULD may be reflective of the large number of participants with ULD as part of a segmental dystonia (55% of study participants) that began as blepharospasm or cervical dystonia (dystonia subtypes that predominate in women and typically develop in the fifth and sixth decades of life).¹¹ However, a peak age of onset in the sixth decade was also observed in patients with focal non-task-specific ULD at onset. The late age of onset and the relatively high tendency to spread of non-task-specific ULD are clinical features similar to those also reported in blepharospasm and differ from those reported in cervical dystonia and task-specific ULD.^{10,16}

The presence of dystonic tremor in non-task-specific and task-specific ULD supports the observation that tremor is a phenotypic feature of dystonia.¹⁷ Although we did not have data on the time of appearance of tremor and dystonia, the higher frequency of tremor among non-task-specific patients may reflect the greater frequency of segmental dystonia in this group, supporting previous reports that suggest that dystonia spreads more commonly in patients with tremor.^{17,18} The frequent association of non-task-specific ULD with tremor, together with the lack of task specificity at onset, may partially explain the prior under recognition of idiopathic non-task-specific ULD.

Patients with non-task-specific ULD did not significantly differ from patients with task-specific ULD in terms of sex, sensory trick frequency, or family history of dystonia. The overall low frequency of sensory trick in ULD compared with blepharospasm and cervical dystonia is consistent with prior reports and indicates a probable underreporting of this sign by patients with ULD themselves.¹⁹ The frequency of family history of dystonia in the non-task-specific ULD group was consistent with the percentages observed in other forms of adult-onset dystonia.^{20,21} Finally, the association of non-task-specific ULD with cardiovascular disease probably reflects the older age of patients in this group.

Our current data confirm the main known demographic/clinical features of task-specific ULD, that is, male predominance, high levels of education, peak age of onset in the fourth decade, more frequent presentation as a focal dystonia (80% of cases in the task-specific ULD group vs. 46% of cases in the non-task-specific ULD group), and a low tendency to spread.^{10,16} The association between task-specific ULD and higher education supports previous reports that have suggested that higher education may be a risk factor for task-specific ULD.²² Further novel information from our study indicates that patients with non-task-specific ULD experience dystonia spread during a similar age range as patients with task-specific ULD. Because task-specific ULD develops earlier, the convergent age of spread in the 2 groups is consistent with a longer time to spread in task-specific ULD patients. These data point to the

existence of an age range (starting approximately in the fifth decade) in which patients are more prone to spread, as already documented in other forms of dystonia such as cervical dystonia, blepharospasm and laryngeal dystonia.^{23,24} The existence of an age range of heightened vulnerability to dystonia spread is also reflected in the inverse relationship between age of dystonia onset and time to spread in the task-specific group. The increased vulnerability of certain age groups to spread may reflect an aging-induced rearrangement of brain networks relevant to dystonia. Aging modulates basic mechanisms that are abnormal in dystonia, including intracortical inhibition and cortical body maps in the primary sensorimotor cortex.^{25,26} Healthy elderly subjects displayed enlarged hand representations in the primary somatosensory cortex, possibly related to an age-related reduction in intracortical inhibition.²⁷ Aging may thus enhance the cortical excitability abnormalities present in dystonia patients, thus increasing susceptibility to spread.

Overall, information from our study suggests that the age of ULD onset, site of dystonia presentation, frequency of action tremor, and tendency to spread differ in patients with idiopathic non-task-specific ULD and WC. One possible explanation for the differences we found between the 2 groups is that in retrospective clinical cohorts, task specificity is a feature defined by history and relies on the patient's subjective judgment. The variability in educational levels between groups may thus reflect differences in the use of handwriting, although there is not always a close relationship between educational level and exposure to handwriting. However, it is possible that if handwriting is used less, ULD may be perceived later by the patient as a "non-task-specific" form. Under this hypothesis, non-task-specific ULD would have a later onset, as observed in our study. Nevertheless, there is no direct evidence linking exposure to complex manual activities with the other observed clinical differences between the 2 ULD subtypes, that is, tremor frequency and tendency to spread. Likewise, there is no relationship between age of onset and tremor frequency^{17,18} or between age of onset and tendency to spread in patients with different focal adult-onset dystonias.^{10,16} The findings of the present study also introduce the possibility that non-task-specific and task-specific ULD are distinct clinical subtypes. In a previous article, we reported that patients with different forms of focal adult-onset dystonia show differences in several clinical, demographic, and neurophysiological features.²⁸ However, despite these differences, adult-onset focal dystonias have common clinical features and share several pathophysiological mechanisms.²⁸ We believe that, similar to the various forms of adult-onset focal dystonias, non-task-specific ULD and task-specific ULD (WC) share some common clinical and pathophysiological features, although they

differ with respect to other clinical and demographic features. Neurophysiological testing or other specific markers able to differentiate between the 2 possible ULD subtypes would confirm whether the 2 types of ULD are truly distinct entities.

This study has limitations. Because our series was not population based and ULD was diagnosed by several clinical examiners from the various participating centers, we could not rule out selection bias. This limitation notwithstanding, the consecutive recruitment of patients from participating centers during the study period, as well as the diagnosis of dystonia made by experts in movement disorders, yielded a clinical series resembling the general Italian population of adult-onset idiopathic dystonia.¹⁴ Another possible limitation that may render our series poorly representative of idiopathic adult-onset ULD is the lack of information about levodopa trials that would have permitted us to exclude dopa-responsive dystonia, although none of the clinical presentations suggested this condition. Bias caused by the examiners being unblinded to the case status was unlikely because they were unaware of study hypotheses. The retrospective data collection might have biased the accuracy of information regarding age of onset and spread. However, we have previously demonstrated a high test-retest reliability of idiopathic adult-onset focal dystonia patients in self-reporting age at dystonia onset.¹⁶ The lack of statistically significant differences in age at spread between ULD subtypes (61.1 ± 12.7 vs. 55.9 ± 12.2 , $P = 0.14$) could also reflect low study power. Despite these limitations, the observation that our task-specific ULD series shared relevant clinical features with corresponding cases from the literature supports the validity of our results, even in the absence of prior reference studies on non-task-specific ULD.

In conclusion, information on idiopathic ULD patients from the largest standardized multicenter registry study to date confirms that ULD phenomenology may vary and demonstrated for the first time that clinical characteristics across groups may differ significantly based on whether dystonia is task specific at onset. Novel information from our study therefore introduces the possibility that non-task-specific ULD and task-specific ULD (namely WC) may be considered 2 stages of the same condition or even distinct clinical subtypes. However, it remains to be determined whether the clinical differences between non-task-specific ULD and WC also reflect pathophysiological differences. ■

APPENDIX

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Full financial disclosures for the previous 12 months: