Movement Disorders
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RESEARCH ARTICLE

Phenotypic Variability in Acquired and Idiopathic Dystonia

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Abstract: Background: To date, a few studies have systematically investigated differences in the clinical spectrum between acquired and idiopathic dystonias.

Objectives: To compare demographic data and clinical features in patients with adult-onset acquired and idiopathic dystonias.

Methods: Patients were identified from among those included in the Italian Dystonia Registry, a multicenter Italian dataset of patients with adult-onset dystonia. Study population included 116 patients with adult-onset acquired dystonia and 651 patients with isolated adult-onset idiopathic dystonia.

Results: Comparison of acquired and idiopathic dystonia revealed differences in the body distribution of dystonia, with oromandibular dystonia, limb and trunk dystonia being more frequent in patients with acquired dystonia. The acquired dystonia group was also characterized by lower age at dystonia onset, greater tendency to spread, lower frequency of head tremor, sensory trick and eye symptoms, and similar frequency of neck pain associated with CD and family history of dystonia/tremor.

Conclusions: The clinical phenomenology of dystonia may differ between acquired and idiopathic dystonia, particularly with regard to the body localization of dystonia and the tendency to spread. This dissimilarity raises the possibility of pathophysiological differences between etiologic categories.

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Dystonia, a movement disorder characterized by sustained or intermittent involuntary muscle contractions causing abnormal and often repetitive movements and postures, is classified along two axes.[1] The first axis refers to the clinical characteristics of patients. In adult patients, dystonia usually manifests as a focal form (such as blepharospasm [BSP], oromandibular dystonia [OMD], laryngeal dystonia [LD], cervical dystonia [CD], task-specific upper limb dystonia [TS-ULD], non-task-specific upper limb dystonia [NTS-ULD], lower limb dystonia [LLD], or trunk dystonia [TD]) or, less frequently, as a segmental/multifocal dystonia.[1] Clinical manifestations also encompass tremor and various non-motor features, including sensory trick and sensory symptoms.[2–4]

The second axis considers the etiology and classifies dystonia in inherited, acquired and idiopathic forms.[1] Acquired dystonias can follow infections, drugs, toxic insults, brain injury of a vascular or traumatic origin, or brain tumors.[1] Dystonia can also manifest in combination with neurodegenerative disorders such as parkinsonism, but it is unclear whether this association merely reflects comorbidity or implies some pathophysiological link between dystonia and parkinsonism.[5,6]

From a pathophysiological perspective, imaging and neuropathological studies have recognized the involvement of multiple brain regions (including the cerebral cortex, basal ganglia, cerebellum, thalamus, and brainstem) in several forms of idiopathic and acquired dystonia. This has led to the suggestion that dystonia may result from lesions in one or multiple nodes (network hypothesis), or from aberrant communication between network nodes, with specific regions possibly playing different roles in the various clinical manifestations of dystonia.[7–10] Several studies have also suggested that idiopathic and acquired forms of dystonia may have different neurophysiological mechanisms.[11,12] Differences in the pathophysiological mechanisms of idiopathic and acquired forms of dystonia may also cause differences in the clinical characteristics of both conditions. However, it has not been investigated whether there are differences in the clinical spectrum between acquired and idiopathic forms of dystonia.

For this purpose, we compared demographic data and clinical features (dystonia-associated features, body distribution of dystonia, and tendency to spread) in patients with adult-onset acquired and idiopathic dystonias. These comparisons can provide clues about the pathophysiology of acquired forms of dystonia.

Methods

Patients were identified from among those included in the Italian Dystonia Registry (IDR), a multicenter Italian dataset of patients with adult-onset dystonia.[13] On January 2022, the IDR contained 2342 records of dystonia patients from 44 secondary/tertiary referral centers for movement disorders located throughout Italy. Details of the demographic and clinical information included in the IDR are described elsewhere.[13] In brief, we collected information on sex, year of dystonia onset, year of dystonia diagnosis, year of onset of dystonia in each body site, dystonia-associated features like pain in CD patients, eye symptoms often preceding BSP (including burning sensation and grittiness in the eye, dry eye, or photophobia), tremor, and sensory trick, etiology of dystonia coded according to the most recent consensus update, drug history, and family history of dystonia/tremor in first-degree relatives. To be recorded in the IDR, clinical, pharmacologic, and family history data needed to be supported by medical records and/or informed relatives. Neuroleptic-induced tardive dystonia (NITD) was diagnosed when chronic neuroleptic drug treatment preceded the onset of dystonia by six months or less.

Patients included in the present study fulfilled the following inclusion criteria: age at dystonia onset ≥21 years and a diagnosis of acquired dystonia (defined as being non-inherited and with a known acquired or exogenous origin according to the dystonia classification) (1), or a diagnosis of isolated idiopathic dystonia. Exclusion criteria were: age at dystonia onset <21 years or a diagnosis of inherited or functional dystonia. With regard to idiopathic dystonia, we did not consider all patients with this etiology included in the IDR, but only those who were followed up at centers that also recruited patients with acquired dystonia. The study was approved by the local ethics committees; all participants gave their written informed consent.

Statistical analysis was performed using the Stata 11.0 package (Stata Corporation, College Station, TX, USA). Data were expressed as mean and standard deviation (SD), unless otherwise indicated. Differences across groups were analyzed by Fisher test (two-tailed), chi-squared test, Mann–Whitney *U* test, or one-way analysis of variance (ANOVA) with Newman–Keuls post hoc test, as appropriate. Dystonia spread was estimated by Cox regression analysis adjusted for age at dystonia onset and type of dystonia at onset. Study time was represented by the time elapsed between dystonia onset and spread. Patients in whom spread never occurred were included in the survival function for the duration of the observation, and their data were censored beyond that time. For the purpose of Cox analysis, hazard ratios (HRs), two-sided 95% confidence intervals (CIs), and *P* values were calculated. For all analyses, significance was set at 0.05.

Results

Study Population

The study population included 116 patients who were diagnosed with adult-onset acquired dystonia and 651 patients with isolated adult-onset idiopathic dystonia. The acquired dystonia group included 67 patients with NITD and 49 patients with acquired dystonia due to vascular brain injury (n. 31), traumatic brain injury (n. 10), brain tumors (n. 3), brain infection (n. 3), or brain surgery (n. 2).

Acquired versus Idiopathic Dystonia

The main demographic and clinical features of the two groups are reported in Table 1. Women predominated in both groups,

whereas age at dystonia onset was lower in the acquired group and dystonia duration was slightly but significantly longer in the acquired group.

Considering patients who had focal and segmental/multifocal dystonia, BSP and CD were the most frequent forms of dystonia and affected similar percentages of patients with acquired and idiopathic dystonia. TS-ULD was significantly less frequent in patients with acquired dystonia than in the idiopathic group (Table 1). In contrast, OMD, NTS-ULD, LLD, and TD were more frequent in the acquired dystonia group, with the frequency of limb and trunk dystonia being very low in the idiopathic group (Table 1).

Segmental/multifocal dystonia was more frequent in patients with acquired than idiopathic dystonia (Table 1), and the mean number of body parts affected by dystonia was also higher in the acquired dystonia group (2.5 ± 0.8 vs. 2.2 ± 0.3, $P < 0.0001$). Using idiopathic dystonia as a reference, Cox analysis confirmed a greater tendency to spread in the acquired dystonia group (HR = 1.86; 95% CI 1.2–2.84; $P = 0.005$), even though time to spread did not significantly differ between the two groups (acquired dystonia vs. idiopathic dystonia, 2.5 ± 4.4 vs. 2.8 ± 4.9 years, $P = 0.3$).

In the acquired dystonia group, there was a significantly lower frequency of tremor in the head, sensory trick, and eye symptoms related to BSP (Table 1). Neck pain associated with CD, tremor in the upper limb and a family history of dystonia/tremor in one or two first-degree relatives did not significantly differ between the two groups (Table 1). Dystonia phenotype within families was heterogeneous, with the same body part being affected in 5/7 familial patients with acquired dystonia and 35/64 familial patients with idiopathic dystonia.

Excluding patients with family history of dystonia from analysis did not substantially change the demographic and clinical features of patients with idiopathic and acquired dystonia (data not shown). As an illustrative example, including or excluding patients with family history of dystonia from analysis yielded no significant difference in the body distribution of dystonia in the acquired dystonia group (Fig. 1A: chi Square test, $P = 0.8$) and in the idiopathic group (Fig. 1B: chi square test, $P = 0.2$). Acquired Dystonia Subgroups.

TABLE 1 *Demographic and Clinical Features of Patients with Acquired and Idiopathic Dystonia*

	Idiopathic isolated dystonia (n. 651)	Acquired dystonia (116)	*P*
Sex (women/men)	375/276	65/51	0.7
Mean age at dystonia onset ± SD	56.9 ± 11.5	51.8 + 14.9	$P < 0.0001$
Mean dystonia duration ± SD	7.3 ± 5.3	9.8 ± 9.2	$P < 0.0001$
Body distribution of dystonia (%)			
Blepharospasm	271 (42%)	40 (34%)	0.15
Oromandibular-dystonia	67 (10.3%)	24 (21%)	0.001
Laryngeal distonia	45 (7%)	3 (2.6%)	0.1
Cervical Distonia	317 (49%)	61 (53%)	0.44
Limb dystonia			
- Upper limb (task specific)	37 (5.7%)	2 (1.7%)	0.05
- Upper limb (non task-specific)	4 (0.6%)	19 (16.4%)	<0.0001
- Lower limb	14 (2%)	19 (16.4%)	<0.0001
Trunk dystonia	6 (0.9%)	11 (9.5%)	<0.0001
Segmental/multifocal dystonia, n.pts (%)	163 (25%)	39 (34%)	0.05
Tremor, n. pts (%)			
- Head	165 (25%)	16 (13.8%)	0.007
- Upper limb	68 (10.4%)	8 (6.9%)	0.24
Sensory trick, n. pts (%)	352 (54%)	14 (12%)	<0.0001
Eye symptoms in BSP, n. pts/ n. BSP pts (%)	105/271 (39%)	8/40 (20%)	0.02
Neck pain in CD, n. pts/CD pts (%)	169/317 (53%)	35/61 (57%)	0.5
Family history of dystonia / tremor, n. pts (%)	64 (9.8%)	7 (6%)	0.2

Abbreviations: BSP, blepharospasm; CD, cervical dystonia.

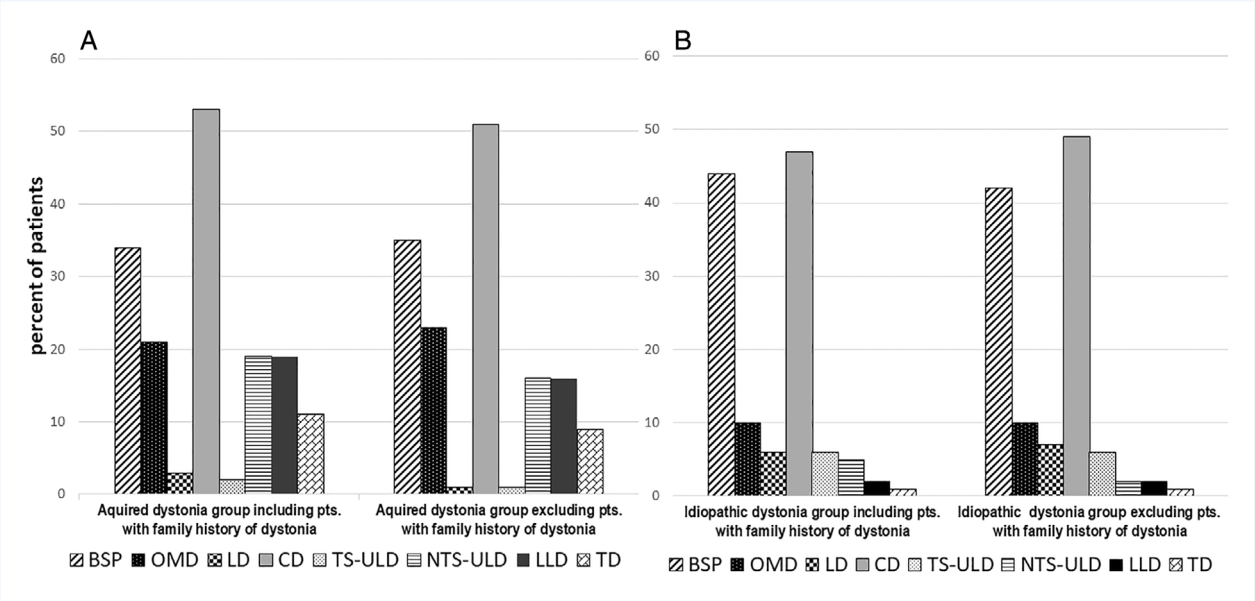

FIG. 1. Body distribution of dystonia in patients with acquired dystonia (**A**), and idiopathic isolated dystonia (**B**), either including or excluding patients with family history of dystonia. BSP, Blepharospasm; OMD, oromandibular dystonia; LD, laryngeal dystonia; CD, cervical dystonia; TS-ULD, task-specific upper limb dystonia; NTS-ULD, non-task-specific upper limb dystonia; LLD, lower limb dystonia; TD, trunk dystonia.

The acquired dystonia group could be stratified into two subgroups: 67 patients with NITD and 49 patients with non-drug-related dystonia due to brain lesions of variable etiology. The two subgroups were similar for most demographic and clinical features, even though males predominated in the non-drug-related subgroup (Table 2). With regard to body distribution of dystonia, there was a consistent presence of cranial and limb dystonias in both groups, though to a variable degree: BSP and OMD were more frequent in the NITD group whereas limb dystonia was more frequent in the non-drug-related subgroup (Table 2).

Using idiopathic dystonia as reference, Cox analysis indicated a greater tendency to spread in NITD (adjusted HR = 1.66; 95% CI 1.04–2.67; $P = 0.035$) and non-drug-related dystonia (adjusted HR = 1.81; 95% CI 1.07–3.07; $P = 0.028$). Among NITD patients, most of those who spread and those who did not (73% vs. 77%, $P = 0.7$) continued to be exposed to neuroleptic drugs even after dystonia onset. NITD and non-drug-related dystonia subgroups did not differ in time to spread (2.4 ± 4.5 vs. 2.5 ± 4.1 years, $P = 0.6$) or mean number of body parts affected by dystonia (2.5 ± 0.8 vs. 2.5 ± 0.8, $P = 1$).

Excluding patients with family history of dystonia from analysis did not substantially change the results of the comparison between drug and nondrug related acquired dystonia (data not shown).

Discussion

The results of this study indicate that the clinical phenomenology of dystonia may differ between etiologic categories. Clinical comparison of acquired and idiopathic dystonia revealed differences in the body distribution of dystonia (summarized in Fig. 1), with OMD, limb and trunk dystonia being more frequent in patients with acquired dystonia. In addition, the acquired dystonia group was characterized by a lower age at dystonia onset, a greater tendency to spread, a lower frequency of tremor in the head, sensory trick, and eye symptoms related to BSP, and a similar frequency of neck pain associated with CD and family history of dystonia/tremor. Patients with acquired dystonia due to NITD or brain lesions of variable etiology were similar for most demographic and clinical features, though males predominated in the non-drug-related subgroup. Cranial dystonia was more frequent in the NITD subgroup, while limb dystonia was more frequent in the non-drug-related subgroup.

The clinical differences we found across groups may have several explanations. Some differences may merely reflect the demographics of the conditions associated with dystonia. This probably explains the lower age at dystonia onset in NITD and acquired non-drug-related dystonia and the male preponderance in the acquired (non-drug-related) dystonia group. Other differences may arise from the variable body distribution of dystonia between groups. In this regard, the lower frequency of sensory trick in patients with acquired dystonia might depend, at least in part, on the greater frequency in this group of ULD, a form of dystonia usually characterized by a low frequency of sensory trick.[4,14] In contrast, the greater frequency of limb/trunk dystonia, the lower frequency of head tremor, and the greater tendency to spread in acquired than in idiopathic dystonia could not be easily explained by the conditions associated with dystonia development nor by the variable body distribution of dystonia in different etiological groups.

TABLE 2 *Demographic and Clinical Features of Patients with Acquired Dystonia Stratified in Two Subgroups: Neuroleptic Induced Tardive Dystonia (NITD) and Acquired (Non Drug-Related) Dystonia Associated to Brain Lesions*

	Neuroleptic induced tardive dystonia (n. 67)	Acquired (non drug-related) dystonia (n. 49)	*P*
Sex (women/men)	44/23	21/28	0.01
Mean age at dystonia onset ± SD	50.7 ± 14.4	53.4 ± 15.2	0.2
Mean dystonia duration ± SD	10 ± 9.2	9.6 ± 9.2	0.4
Body distribution of distonia			
Blepharospasm	29 (43%)	11 (22%)	0.02
Oromandibular-dystonia	19 (28%)	5 (10.2%)	<0.0001
Laryngeal distonia	1 (1.5%)	2 (4%)	0.4
Cervical distonia	36 (54%)	25 (51%)	0.4
Limb dystonia			
- Upper limb (task specific)	0	2 (4%)	0.2
- Upper limb (non task-specific)	4 (6%)	15 (31%)	0.001
- Lower limb	6 (8.9%)	13 (26%)	0.01
Trunk dystonia	6 (8.9%)	5 (10.2%)	1
Segmental/multifocal dystonia, n. pts (%)	23 (34%)	16 (33%)	0.8
Tremor, n. pts (%)			
- Head	12 (18%)	4 (8.2%)	0.2
- Upper limb	4 (6%)	4 (8.2%)	0.7
Sensory trick, n. pts (%)	6 (9%)	8 (16.3%)	0.3
Eye symptoms in BSP, n. pts/ n. BSP pts (%)	6/29 (21%)	2/11 (18%)	1
Neck pain in CD, n. pts/CD pts (%)	18/36 (50%)	17/25 (69%)	0.2
Family history of dystonia / tremor, n. pts (%)	3 (4.5%)	4 (8.2%)	0.4

Abbreviations: BSP, blepharospasm; CD, cervical dystonia.

Although some forms of idiopathic dystonia probably share common biological substrates,[14–16] the etiological and phenomenological heterogeneity herein highlighted raises the possibility that different etiological categories have different pathophysiological substrates. In support of this view, recent studies on the pathophysiology of the motor system have shown that the reduced sensorimotor inhibition and enhanced plasticity typically reported in idiopathic dystonia may not occur in secondary (acquired) dystonia.[11,12] It has also been hypothesized that several brain regions (including the cerebral cortex, cerebellum, thalamus, and midbrain/brainstem) are implicated in dystonia along with the basal ganglia, with the relative importance of brain regions possibly varying between different etiological categories.[7–10] If the underlying neurobiological basis is not shared by all etiological types of dystonia, then our findings would indicate that the pathophysiological differences between adult-onset acquired and idiopathic dystonia probably depend on the mechanisms underlying dystonia development outside the cranial and cervical area and spread of dystonia.

Acquired and idiopathic dystonias also showed similarities in the frequency of upper limb tremor and neck pain in CD patients; even the frequency of family history of dystonia was comparable in the study groups. In idiopathic dystonia, the occurrence of dystonia in one or two affected relatives in 10–20% of patients is well known and is generally regarded as a marker of a genetic predisposition that may be triggered by unknown genetic or environmental factors, leading to dystonia development.[15] To our knowledge, family history of dystonia has never been systematically investigated in acquired dystonia.[17] However, family history may reflect not only a shared genetic predisposition but also shared epigenetic factors. We have no information on whether cases with acquired dystonia and their affected relatives had comparable epigenetic/environmental exposure. Regardless of the explanation, occurrence of dystonia in relatives of patients with acquired dystonia of different origin is a novel finding that needs to be verified by independent studies since it may shed light on the mechanisms underlying the development of acquired dystonia. The observation that there

were more similarities than differences between etiological subgroups of acquired dystonia is also a novel finding that is in keeping with the current dystonia classification,[1] which considers all possible etiologies of acquired dystonia in only one group.

This study has strengths and limitations. As a service-based study, it could be affected by selection bias. However, we corrected for this bias by recruiting consecutive patients from several movement disorder centers throughout Italy. This allowed us to include a relatively large number of patients with acquired dystonia, whereas most previous series included fewer patients and could not provide detailed information on the phenomenology of dystonia in these conditions. Although there is no population-based study to be used for comparison, it is worth noting that our group of patients with acquired dystonia included those with several conditions that may cause acquired dystonia, with chronic neuroleptic treatment and vascular brain lesions being the most frequent, as reported.[1] Therefore, the acquired dystonia groups were probably representative of the corresponding conditions. The idiopathic case series also resembled the general population of cases in terms of demographic and clinical features. Patients with acquired dystonia were matched by the referral center to patients diagnosed with idiopathic dystonia. This methodology allowed us to obtain a clinical series that was matched as closely as possible in terms of the degree of medical surveillance required, to compare idiopathic and non-idiopathic groups in terms of demographic and clinical features, and to obtain as much power as possible for statistical comparison. Bias caused by the assessors being unblinded to dystonia etiology was unlikely since the assessors were unaware of the study hypothesis. Self-reported information was supported by medical records and/or informed relatives, thus minimizing the possibility of misclassification bias.

In conclusion, this study provided information on the expression of dystonia in acquired and idiopathic dystonia. We demonstrated that the clinical phenomenology of dystonia may differ between acquired and idiopathic dystonia, particularly with regard to the body localization of dystonia and the tendency to spread. These differences cannot be entirely explained by the conditions underlying dystonia development and, therefore, raise the possibility of pathophysiological differences between etiologic categories. Information about the clinical variability associated with different etiologies may be relevant to select specific patient subgroups and, to identify the most appropriate study design to better explore the unknown mechanisms underlying development of dystonia in different body parts and dystonia spread.

Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2)Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the first draft, B. Review and Critique.

G.D.: 1A, 1B, 1C, 2A, 2B, 3A
A.F.G.: 1B, 1C, 2B, 3B
R.E.: 1B, 1C, 3B
D.B.: 1B, 1C, 3B
T.E.: 1B, 1C, 2B, 3B
M.E.: 1B, 1C, 3B
A.T.: 1B, 1C, 3B
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M.T.: 1B, 1C, 3B
L.M.: 1B, 1C, 3B
M.Z.: 1B, 1C, 3B
A.B.: 1A, 1B, 2C, 3B

Disclosures

Ethical Compliance Statement: The study was approved by the ethics committee of the University Hospital of Bari, Italy (protocol number: v1/01/04/20/15). Informed consent was obtained by all participants.

The authors confirm that they have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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