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ORIGINAL ARTICLE

The Italian Dystonia Registry: rationale, design and preliminary findings

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Abstract The Italian Dystonia Registry is a multicenter data collection system that will prospectively assess the phenomenology and natural history of adult-onset dystonia and will serve as a basis for future etiological, pathophysiological and therapeutic studies. In the first 6 months of activity, 20 movement disorders Italian centres have adhered to the registry and 664 patients have been recruited. Baseline historical information from this cohort provides the first general overview of adult-onset dystonia in Italy. The cohort was characterized by a lower education level than the Italian population, and most patients were employed as artisans, builders, farmers, or unskilled

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workers. The clinical features of our sample confirmed the peculiar characteristics of adult-onset dystonia, i.e. gender preference, peak age at onset in the sixth decade, predominance of cervical dystonia and blepharospasm over the other focal dystonias, and a tendency to spread to adjacent body parts, The sample also confirmed the association between eye symptoms and blepharospasm, whereas no clear association emerged between extracranial injury and dystonia in a body site. Adult-onset dystonia patients and the Italian population shared similar burden of arterial hypertension, type 2 diabetes, coronary heart disease, dyslipidemia, and hypothyroidism, while hyperthyroidism was more frequent in the dystonia population. Geographic stratification of the study population yielded no major difference in the most clinical and phenomenological features of dystonia. Analysis of baseline information from recruited patients indicates that the Italian Dystonia Registry may be a useful tool to capture the real world clinical practice of physicians that visit dystonia patients.

Keywords Dystonia · Epidemiology · Risk factors

Introduction

Adult-onset dystonia (AOD), the most common form of dystonia [1], is characterized by a varying clinical expression, an onset that is often focal and includes blepharospasm (BSP), oromandibular dystonia, cervical dystonia (CD), laryngeal dystonia or limb dystonia, and a limited tendency to spread to adjacent body regions [2, 3]. In recent years, it has become increasingly evident that several non motor symptoms (including sensory, psychiatric and cognitive disturbances) may also contribute to the clinical spectrum of AOD [4–6]. At the etiological level, AOD is considered a multifactorial disorder, in which one or more unknown genes, along with poorly known environmental factors, combine to reach the threshold of disease [7].

Despite recent advances, significant gaps still remain in our knowledge of AOD, particularly as regards its frequency, natural history and risk factors for AOD. Uncertainties about the true prevalence of AOD are due at least in part to a high frequency of misdiagnosis/underdiagnosis, which often delays diagnosis of dystonia for several years [1, 8]. Longitudinal information about the natural history of motor and non motor manifestations is lacking. Moreover, little is known about possible factors that increase the risk of the most common forms of AOD and/or influence disease progression [9–11].

Owing to the relative rarity of AOD, a longitudinal multicenter collection of accurate and reliable clinical information would increase our understanding of the condition. Here we describe the Italian Dystonia Registry (IDR), a multicenter data collection system whose aim is to prospectively assess the phenomenology and natural history of AOD and serve as a basis for future etiological, pathophysiological and therapeutic studies. The IDR is also likely to facilitate the dissemination and implementation of best clinical practice among neurologists. In this paper, we present demographic and clinical information obtained from a large Italian cohort upon their baseline IDR assessment.

Methods

Registry design

The IDR has been proposed by the Department of Basic Medical Sciences, Neurosciences and Sense organs of the "Aldo Moro" University of Bari, Italy and by the Italian Academy for the Study of Parkinson's Disease and other Movement Disorders. The IDR aims to collect longitudinal clinical data covering motor, behavioural, and cognitive aspects of AOD; and to collect information, and possibly biologic samples, to identify factors that may influence AOD phenotype and progression. It is hoped that the pursuit of the two objectives will promote future etiological, pathogenetic and therapeutic studies, and will facilitate the dissemination and implementation of best clinical practices in the Italian National Health System.

Patients with AOD have been recruited from movement disorder centres that follow-up and treat people affected by dystonia and other movement disorders. To minimize underdiagnosis, people with dystonia will also be actively searched in other specialty clinics (ophthalmology, laryngology and orthopedics clinics). IDR study visits will take place at the time of the participant's routine clinical care visit. Baseline and annual follow-up visits include elements that are mandatory for all participants at all sites (core assessments) and elements that participating sites and participants may choose to perform (optional assessments).

Core assessments include demographic data (gender date and place of birth, years of schooling, address); working activities classified according with the criteria established by the Statistical Italian Institute [12]; year of onset and year of diagnosis of dystonia; time elapsing between dystonia onset and diagnosis; year of onset of dystonia in each body site; dystonia associated features (like pain, tremor, sensory trick, apraxia of eyelid opening, etc.); aetiology of dystonia coded according to the recently revised classification of dystonia [3]; lifetime diseases of

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the anterior segment of the eye (assessed by a brief validated questionnaire) [13]; injury at extracranial body sites severe enough to require medical survey, hospitalization or surgery (for each trauma information is collected about year and site of the trauma, and occurrence of wounds or bone fractures secondary to the trauma); medical diseases like arterial hypertension, type 2 diabetes, coronary heart disease, dyslipidemia and overt thyroid diseases associated with hypo/hyperthyroidism; other movement disorders, other neurological diseases, drug history, with particular reference to neuroleptic drugs; and treatment with botulinum toxin and/or deep brain stimulation. To be recorded in the IDR past medical and pharmacologic history needs to be supported by medical records or informed relatives.

Optional assessments include: family history of dystonia evaluated by a validated self-administered questionnaire and subsequent examination of subjects screening positive [14]; depression and anxiety assessments by self-administered questionnaires like Beck depression inventory and State-Trait Anxiety Inventory (STAI) Form Y-1 and Y-2; and cognitive assessment by the Wisconsin card sorting test [15]. Baseline demographic information and retrospective clinical data are collected at the assessment upon inclusion, while longitudinal clinical information will be collected in subsequent yearly assessment. The IDR does not include interventional procedures outside of normal clinical care, nor experimental therapies.

All participating sites are provided with a brief manual containing instructions for administering and scoring study instruments. Patients' information are recorded into a web-based encrypted anonymised system within the web site of the Italian Academy for the Study of Parkinson's Disease and other Movement Disorders (http://accademialimpedismov.it). The IDR web portal also contains an open section providing educational information to patients and physicians. The study has been approved by ethics committee throughout Italy. Informed consent is an unconditional prerequisite for patient participation in the study, and data protection and privacy regulations are observed in capturing, forwarding, processing, and storing participant data. Participants are free to withdraw from the registry at any time; unless otherwise requested by participant, all data obtained up to that point will be retained.

Analysis of baseline demographic and clinical characteristics of the enrolled population

Statistical analysis herein presented has been performed by STATA 11 package using descriptive statistics (*t* test, Chi-square test, Fisher's test, one-way ANOVA and post hoc test as appropriate). Data were expressed as mean and SD unless otherwise indicated. The reliability of retrospective information about year of dystonia onset and year of diagnosis was assessed by computing the intraclass correlation coefficient (ICC) upon information obtained from a sample of patients at the IDR baseline visit with information from prior medical records. P value ≤ 0.05 was considered statistically significant.

Information about education in the Italian population has been obtained by the website of the Italian Statistical Institute (ISTAT, http://www.istat.it) and referred to primary, secondary and tertiary education levels of Italian people aged 25–64 years. Activities at work were classified according to the criteria established by ISTAT [12]. Information about the prevalence of arterial hypertension, type 2 diabetes, coronary heart disease, and dyslipidemia in the Italian population aged 35–74 years were from the Italian Health Institute ("Istituto Superiore di Sanità"—ISS) [16]. Information about the prevalence of thyroid dysfunction in the adult European population was obtained by Garmendia Madariaga et al. [17].

Results

IDR started on January 2016. On 23rd August 2016, 20 movement disorders Italian centres (nine in northern Italy, four in central Italy, five in southern Italy, an two in Insular Italy—Sicily and Sardinia) have adhered to the IDR. Principal investigators who enrolled patients into the IDR were all neurologists.

Methodological issues

An average of 10–15 min was required to fill in the web form at the baseline visit. The reliability of the retrospective data about year of dystonia onset and year of diagnosis was assessed in a sample of 75 patients by comparing information obtained at the IDR baseline visit with information contained in prior medical records. The resulting ICC (year of dystonia onset: ICC 0.97, $p < 0.0001$; year of diagnosis: ICC 0.94, $p < 0.0001$) were highly significant and satisfactory.

Baseline features of the study population

By 23rd August 2016, 664 AOD patients have been recruited. Demographic and clinical information obtained at the baseline visit in the study population is reported in the following paragraphs.

Demographics

The patients enrolled consisted of 274 men and 390 women aged 64.3 years on average (SD 13.2; range 22–93); 157 individuals resided in Northern Italy, 108 in Central Italy,

307 in Southern Italy and 92 in Insular Italy (Sardinia and Sicily).

Education

Patients reported a mean of 9.3 years of schooling (SD 4.5; range 0–19). If compared with the Italian population aged 25–64 years (year of reference, 2015), the correspondent IDR population (n = 307) was characterized by a lower percentage of subjects with primary and tertiary education levels and a greater percentage of subjects with secondary education level (Fig. 1).

Activities at work

According with the ISTAT classification of activities at work, the frequency of employment of the study population in the various working categories was as follows: intellectual works 9.3%; technical work 4.3%; clerk 8.1%; trading and service activities 7.3%; artisan, worker, and farmer 32%; driver 2%; non qualified workers 27%; and army 9%.

Clinical features of dystonia

The mean age at dystonia onset was 52.9 years (SD 13.3; range 20–84) while the mean disease duration at the baseline visit was 23.3 years (SD 14.2). The time elapsing between onset and diagnosis of dystonia was 3.7 years on average (SD 7.4): 1 year or less elapsed between onset of dystonia and diagnosis in about half of the patients (350/664, 53%).

Out of the total number of 664 patients, 429 were affected by focal dystonia, 220 patients by segmental/multifocal dystonia, 12 patients by generalized dystonia, and three patients by hemidystonia. Overall CD (either focal or as part of a segmental dystonia) was the most frequent form of dystonia (n = 315 patients) followed by BSP (n = 296), OMD (n = 96), upper limb dystonia (n = 75), laryngeal dystonia (n = 27), lower limb (n = 24), and trunk dystonia (n = 12) (Fig. 2).

With regard to aetiology, idiopathic dystonia was diagnosed in 548 patients, secondary dystonia in 116 patients (n = 50 patients reported neuroleptic drugs before dystonia onset). Family history of dystonia was reported in 51 cases.

Eye symptoms

Eye symptoms (including burning sensation, dry eye) were present in 173 patients, 137 of whom suffered from BSP and 36 did not. BSP was present in 158 of the remaining 491 patients who did not have eye symptoms. There was thus a significant association between eye symptoms and BSP (Pearson's Chi-square 114.5, $p < 0.0001$).

Extra cranial injury

Fifty-eight patients reported extracranial injury involving upper limb (n = 23), lower limb (n = 25) and neck-trunk (n = 12). More than one site of injury was found in four patients. Among the 58 injured patients, 15 (26%) shared site of injury and site of dystonia whereas 43 (74%) had dystonia in a body site other than the site of injury.

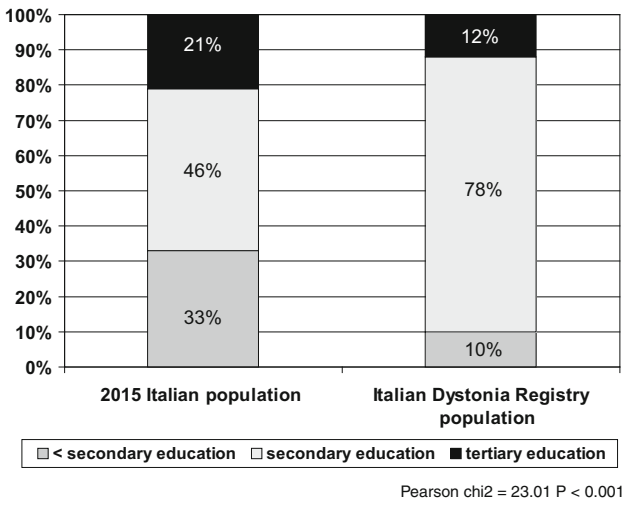

Fig. 1 Education levels in the Italian population aged 25–64 years (reference year, 2015) and in the Italian dystonia registry population of the same age range

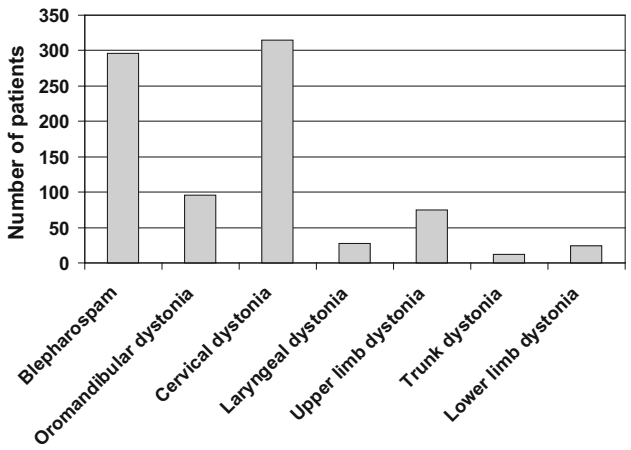

Fig. 2 Distribution of dystonia (either focal or as part of a segmental/multifocal dystonia) in 664 patients with adult-onset dystonia from the Italian dystonia registry

Comorbidity

Arterial hypertension was reported by 281/664 patients (42%), type 2 diabetes by 57/664 patients (8.5%), coronary heart disease by 74/664 patients (11%), dyslipidemia by 127/664 patients (19%), and thyroid diseases by 96/664 patients (14%). The prevalence of arterial hypertension, type 2 diabetes, coronary heart disease, and dyslipidemia, and hypothyroidism in the Italian population aged 35–74 years was similar to the frequency of these diseases observed in the IDR population of the same age range (Fig. 3). In AOD patients, the prevalence of overt thyroid dysfunction was significantly higher than the prevalence of both previously diagnosed and overt thyroid dysfunction assessed in nine European studies (see reference 17: mean 3.82%; 95% confidence interval 3.77–3.86%): (14 vs. 4%, $p = 0.05$) (Fig. 3).

Demographic and clinical characteristics of the study population according with geographic residence

Subgroups from Northern, Central, Southern, and Insular Italy shared most demographic and clinical characteristics, including age, sex, years of schooling, age at dystonia onset, clinical features of dystonia, aetiology of dystonia, and frequency of comorbid medical diseases (data not shown). However, the percent of patients who reported one year or less from the onset of dystonia to diagnosis was higher ($p = 0.05$) in the subgroup from Northern Italy (98/157, 62%) than in the subgroups from Central Italy (54/108, 50%), Southern Italy (153/307, 50%), and Insular Italy (45/92, 49%).

Discussion

Although several Italian multicenter clinical series of patients with AOD have been published between 1998 [18] and 2013 [19], data herein presented provides the first accurate overview of AOD in Italy.

Our AOD cohort was characterized by a lower education level than the overall Italian population, a finding confirmed by the fact that the majority of the AOD patients enrolled in the IDR were employed as artisans, builders, farmers, or unskilled workers. Since a person's education level and job may be related to socioeconomic status, the findings would suggest that environment may play a role in the risk of developing AOD; or, alternatively, that dystonia affects both education and job choice. It is worth noting that all recruiting centres belong to the national health system and no private center has been to date included in the registry. Therefore, a referral bias could contribute, at least in part, to the lower education we observed in our cohort.

The clinical features of our sample confirm the peculiar characteristics of AOD highlighted by the existing literature, i.e. women preference, peak age at onset in the sixth decade, and a relative tendency to spread to adjacent body parts [2, 3]. In the IDR sample, CD and BSP predominated over the other types of AOD, with a slight preponderance of CD. At variance with this finding, however, most studies from western countries reported a marked (two to three-fold) predominance of CD vs. BSP [1, 8]. By contrast, BSP seems to be the most frequent focal dystonia in East Asia countries like China and Japan [20]. The variable frequency relationships of CD and BSP may reflect geographic differences in risk factors or a referral bias. In Italy,

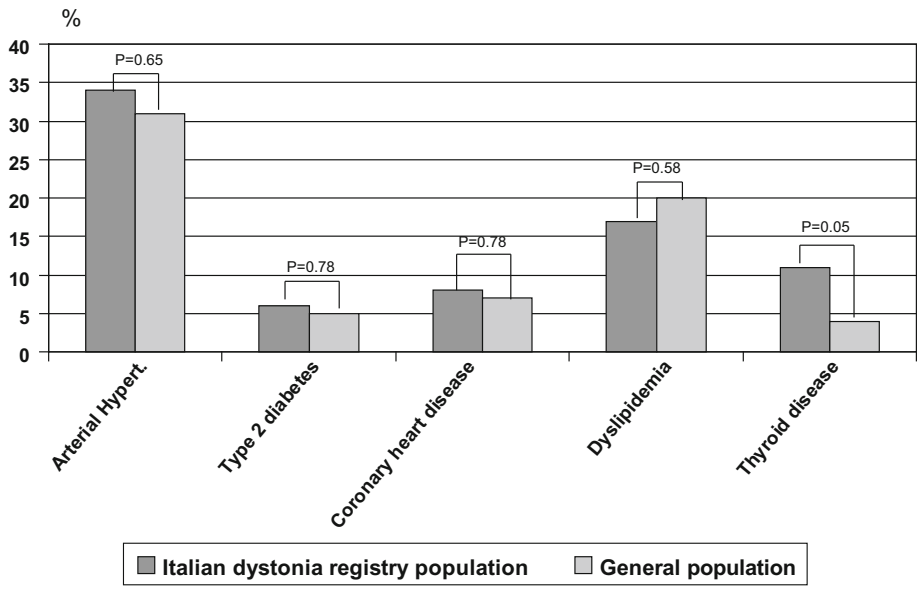

Fig. 3 Percent distribution of arterial hypertension, type 2 diabetes, coronary heart disease, dyslipidemia, and thyroid diseases in the Italian population and in the Italian Dystonia Registry population. Estimates refer to the age range 35–74 years

in fact, most BSP patients are diagnosed and followed up by neurologists, whereas ophthalmologists play a major role in the management of BSP in most western countries.

The IDR sample also confirmed the association between eye symptoms and BSP [13, 18]. It is worth noting that future prospective observation of the enrolled patients who had eye symptoms but lacked BSP would allow us to understand whether eye symptoms may be risk factors for spread of AOD to the orbicularis oculi muscles.

The role of focal peripheral injury in the development of topographically related focal dystonia is debated [21, 22]. In our cohort, 74% of injured patients had dystonia in a body site other than the site of injury. Prospective observation of this group might allow us to understand whether peripheral injury may increase the risk of dystonia spread to the injured part of the body.

IDR data suggests that the burden of the most relevant medical diseases (like arterial hypertension, type 2 diabetes, coronary heart disease, dyslipidemia) in AOD patients is similar to that observed in the Italian population [16]. There was, however, a tendency to a greater frequency of thyroid diseases in the AOD population than in the Italian population [17]. This finding adds to prior anecdotal data [23, 24] that pointed to the recurrence of thyroid diseases in cranial and cervical dystonia, and highlights the need for ad hoc powered controlled studies dealing with this issue.

When we stratified the study population according to the geographic residence, we did not observe any major difference in most clinical and phenomenological features of dystonia. However, the percentage of patients in whom the time interval between the onset of dystonia and diagnosis was one year or less was higher in the group from Northern Italy. A few single-center studies from Australia, Canada, USA, and Southern Italy [25, 26] have shown that diagnosis of AOD may be delayed for several years. The time elapsed from onset of dystonia to diagnosis may be an indicator of the quality of care reflecting factors associated with the patient or the health system. Since patients from the major geographic Italian subdivisions did not differ in regard to relevant dystonic features, then the faster diagnosis performed in Northern Italy probably reflects differences in the health system across Italy that need to be carefully addressed.

This study may have limitations. A potential referral bias is not just related to the lack of private centres but also to the fact that these are tertiary centres and dystonia diagnosis might be more difficult and delayed among general neurologist. In addition, this is not a case–control study and therefore comparing IDR patients with data from other sources carries important risks. In this regard, however, our findings only suggest the need for ad hoc future controlled studies.

Despite the foregoing limitations, the baseline results herein reported indicated that IDR may be a useful tool to capture the real world clinical practices of neurologists, and possibly of other specialists, that visit patients with AOD. The validity of the information provided by the IDR is strengthened by the simplicity of the recording form (data recording requires only 10–15 min on average) and by the use of validated self-administered questionnaires (like family history questionnaire, Beck depression inventory, eye symptoms questionnaire) that reduce the involvement, and consequently the effort, of medical personnel. Crucial information such as year of dystonia onset and year of diagnosis of dystonia diagnosis was characterized by a satisfactory reliability. The validity of other measures (such as extracranial injury and comorbid medical diseases) was supported by prior medical records or informed relatives.

On the basis of an analysis of data upon admission, the IDR is anticipated to provide clinically relevant prospective information about disease-specific outcomes, such as the frequency of dystonia, spread of dystonia, risk factors for spread of dystonia, geographic variations, and also to generate hypotheses for investigation and to answer a number of questions regarding health and economic aspects of AOD.

Compliance with ethical standards

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Conflict of interest The authors declare that they have no conflict of interest.

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