

Cervical dystonia: about familial and sporadic cases in 88 patients

Distonia cervical: considerações sobre casos esporádicos e familiares em 88 pacientes

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ABSTRACT

Cervical dystonia (CD) affects the musculature of the neck in a focal way or associated to other parts of the body. The aim of this study was to identify clinical differences between patients with dystonia patients without family history and with family history (sporadic). Eighty-eight patients with CD were recruited in a Movement Disorders Clinic between June of 2008 and June of 2009. Only patients with no etiological diagnosis were accepted for analysis. The age of onset of symptoms was later in patients with focal and segmental dystonia than in patients with generalized dystonia ($p < 0.001$). The severity of symptoms was higher in patients with sporadic dystonia than in familial patients ($p < 0.01$). Generalized cases were more severe in patients with a family history ($p < 0.01$). Sporadic patients had higher levels of pain than familial cases ($p < 0.05$). We expect soon to present the results of genetic analyzes of these patients.

Keywords: dystonia, cervical dystonia, DYT1, DYT6, genetic.

RESUMO

A distonia cervical (CD) afeta a musculatura do pescoço de modo focal ou em combinação com outras partes do corpo. O objetivo deste estudo foi identificar diferenças clínicas entre pacientes com distonia com história familiar e pacientes sem história familiar (esporádicos). Foram selecionados 88 pacientes com DC no Setor de Distúrbios do Movimento entre julho de 2008 e junho de 2009. Somente os pacientes sem diagnóstico etiológico foram admitidos para análise. A idade de início dos sintomas foi mais tardia em pacientes com distonia focal e segmentar do que em pacientes com distonia generalizada ($p < 0,001$). A gravidade dos sintomas foi maior em pacientes com distonia focal esporádicos do que naqueles com história familiar ($p < 0,01$). Os casos generalizados foram mais graves nos pacientes com história familiar ($p < 0,01$). Pacientes esporádicos tiveram níveis maiores de dor em relação aos casos familiares ($p < 0,05$). Esperamos apresentar em breve resultados de análises genéticas desses pacientes.

Palavras-chave: distonia, distonia cervical, DYT1, DYT6, genética.

The definition of dystonia was recently revisited. Currently, dystonia is a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both. Dystonic movements are typically patterned, twisting, and may be tremulous. Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation¹. Most voluntary muscles can be affected and, in the case of the neck muscles, the condition is referred to as cervical dystonia (CD), the most common form of dystonia. The term spasmodic torticollis was previously used for this movement, but it does not

stress the dystonic nature of the disease. CD can affect the musculature of the neck in a focal way or associated to other parts of the body².

Over the past 20 years, several loci (*DYT1* to *DYT25*) have been mapped in families with pure forms of dystonia, families with dystonia plus other movement disorders, or in sporadic cases of dystonia. The most different kinds of inheritance can be observed (autosomal dominant, autosomal recessive, and X-linked). However, only some genes for isolated (primary or pure) forms of dystonia were described until today³. Recently, *CIZ1* (*DYT23*), *ANO-3* (*DYT24*) and *GNAL* (*DYT25*)

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Conflict of interest: There is no conflict of interest to declare.

Received 02 October 2013; Accepted 09 October 2013.

genes were associated to families with CD^{4,5,6}. Before that, only *TOR1-A (DYT1)* and *THAP1 (DYT6)* genes were linked to isolated dystonia. Both are inherited as autosomal dominant traits, with reduced penetrance, and onset of clinical features commonly occurs during childhood or adolescence⁷⁻⁹.

Although these several loci and some genes were described in the last years, the presence of mutations in these genes in cohorts of patients with dystonia is low. For example, the presence of *THAP1* mutations in families with earlier “primary” dystonia is about 25%¹⁰. Regardless the monogenic inheritance, familial cases have lower mean age at disease onset than sporadic patients. Spread of dystonia to at least a second body site occurs more frequently in familial cases than in sporadic. The spread of symptoms is directly related to the duration of illness either in sporadic or in familial cases, however, in sporadic cases the most relevant spread occurs during the first 10 years; in familial patients, instead, progressive spread of dystonia occurs throughout the disease course¹¹.

To identify clinical differences among familial and sporadic cases of CD, we submitted patients at an evaluation in a Brazilian center for movement disorders.

METHOD

Standard protocol approvals, registrations, and patient consents.

All patients gave informed consent, and ethics approval was obtained from the medical joint and ethics committee at Federal University of Parana (UFPR) to perform this clinical and genetic study (CEP-UFPR ethical approval 1676.093/2008-06).

Subjects selection and clinical assessment

Subjects with CD who attended the Botulinum Toxin and Movement Disorders Outpatient Unit in the Neurology Service, *Clínicas Hospital*, UFPR, from June 2008 to June 2009, were selected for the study. Clinical diagnoses were made by means of history and examination by two neurologists. The patients were then assessed to identify clinical characteristics, an association with other movement disorders and neurological diseases, epidemiological data, the time during which the disease had evolved, a history of trauma, the use of medicines, signs and symptoms that might indicate a secondary cause and a family history of dystonia or other movement disorders. All the patients were submitted to brain computed tomography and cervical-spine radiography. Additional tests included complete blood count (CBC), TSH, VDRL, blood glucose test, ESR, electrolyte levels and liver and kidney function in all the patients. Computed tomography and magnetic resonance imaging of the cervical spine, magnetic resonance imaging

of the brain and other laboratory tests were requested according to the clinical assessment of each patient. The inclusion criterion was: (1) the presence of CD without an established cause (a “primary” or a idiopathic dystonia). The exclusion criteria were: (1) presence of a cause for the CD (2) refusal to submit to diagnostic investigation; (3) inability to attend reassessment; and (4) failure to sign the informed consent form. CD was classified in accordance with established schemes^{1,12}. The patients were assessed on admission to compare severity, disability and pain using the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) and visual analog pain scale (0=absence of pain, 1-3=mild pain, 4-6=moderate pain, 7-9=strong pain, 10=disabling pain).

Statistics

The distribution pattern for all the data was tested (normal or non-normal). The statistical differences between the means of the groups were measured using the one-tailed Student t-test for normal distributions and the Mann-Whitney test for non-normal distributions. For the differences between the expected values and the values actually found, the Fisher exact test was used. The results are given as mean \pm SD (standard deviation). The differences were considered significant if $p < 0.05$.

RESULTS

A total of 88 patients with CD were included, 56 were women and 32 men, a 1.75:1 ratio. Patients with familial history were called familial cases and those without familial history, sporadic cases. There were 16 families with 23 (26.74%) patients (Table 1).

Among the patients, 36 (40.91%) had focal CD. Other 22 (25%) patients had segmental dystonia, 6 (28.57%) with cranial-cervical dystonia, 13 (59.1%) with arms-cervical dystonia, 3 (13.67%) with arm-cranial-cervical dystonia, and one with laryngeal-cranial-cervical dystonia. Two (2.28%) patients with multifocal dystonia had abnormal movement in their left leg. A generalized dystonia was observed in 28 (31.81%) patients.

The mean age at onset of the group was 30.47 ± 21.16 years old (range, 5 months to 72 years old). The mean age at onset of focal dystonia (41.05 ± 16.87), and segmental dystonia patients (35.55 ± 24.13), was higher than the generalized dystonia group, 12.36 ± 9.10 ($p < 0.001$). The incidence of generalized dystonia decreases, progressively, from the first decade to the fifth of life. In the seventh and eighth decades of life, there was only the onset of focal and segmental dystonia (Figure 1). The gender did not affect the onset of symptoms. The mean of onset in men was 28.01 ± 21.66 years old, and in women was 32.28 ± 20.42 years old ($p = 0.175$).

Table 1. Families with cervical dystonia.

Family	Patient	Sex	Age (years)	Age of onset (years)	Clinical features and familial history
1	1	M	24	20	GD (CD, Meige syndrome, trunk, left leg).
	2	M	18	12	GD (CD, limbs, trunk and cranial dystonia). Several familial members with different forms of dystonia.
2	3	F	13	7	GD (CD, trunk and limbs). Father, a cousin, and an uncle with dystonia.
	4	M	35	11	GD (CD, limbs and trunk).
3	5	M	30	10	SD (right arm, left arm and neck). The parents had consanguinity. Two cousins had dystonia.
	6	M	92	70	SD (Cervical and right arm dystonia). He presented Parkinsonism.
4	7	M	68	56	FD (CD). No Parkinsonism No other familial members affected.
	8	M	10	4	GD (CD, trunk and limbs). Two twins brothers with dystonia.
5	9	F	47	30	SD (CD, Meige syndrome and head tremor). Father with dystonia.
	10	F	40	5	MD (left right and CD). She has a sister with dystonia in legs (most in right leg).
6	11	M	60	57	SD (CD, larynx, right arm and Meige syndrome). Sister and niece with oromandibular dystonia and CD.
	12	F	47	39	SD (CD and oromandibular). Several familial members with CD (focal form).
7	13	F	31	9	GD (CD, arms and trunk). A cousin had dystonia.
	14	F	33	12	GD (CD, limbs and trunk). Her father had CD.
8	15	F	17	2	GD (CD, limbs, cranial region and trunk). She had mental retardation. Her brother had CD without cognition features. The parents had consanguinity.
	16	M	49	27	GD (CD, larynx, left arm and trunk).
9	17	F	25	18	SD (right arm, cervical and oromandibular dystonia).
	18	F	16	6	GD (CD, oromandibular, larynx, limbs and trunk) The grandmother had mild face abnormal movements and speech disorder.
10	19	F	49	37	FD (CD and head tremor).
	20	F	27	25	FD (CD and head tremor).
11	21	F	25	24	FD (CD).
	22	M	18	17	FD (CD). Grandmother with CD and head tremor.
12	23	F	67	64	SD (blepharospasm and CD). She had Parkinsonism. Her niece had blepharospasm.

M: male; F: female; CD: cervical dystonia; GD: generalized dystonia; SD: segmental dystonia; MD: multifocal dystonia; FD: focal dystonia.

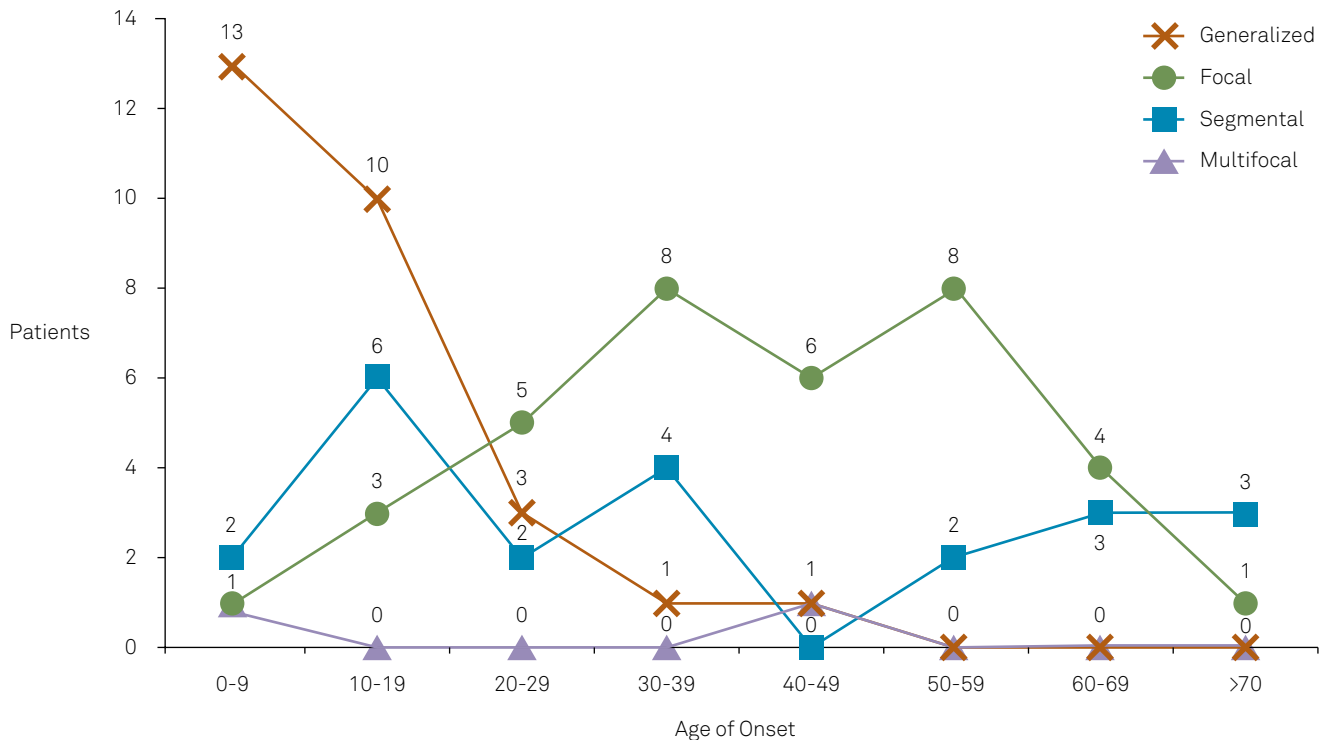


Figure 1. Incidence of cervical dystonia.

Table 2. Differences between sporadic cases and familial cases of cervical dystonia

Site of onset	Sporadic cases	Familial cases	Total	p
Patients	65	23	88	–
Male:female ratio	1:1.95	1:1.3	1:1.75	–
Age of onset*	32.37±21.09	24.78±20.48	30.47±21.16	p=0.07
Age of onset Focal dystonia	42.45±16.89 (23)	32.2±13.49 (5)	41.05±16.87 (28)	p=0.10
Age of onset: segmental dystonia	34±23.58 (15)	42±22.62 (7)	35.55±24.13 (22)	p=0.24
Age of onset: multifocal dystonia	42 (1)	5 (1)	24.5±24.75(2)	–
Age of onset: generalized dystonia	13.12±9.93 (18)	11±7.16 (10)	12.36±9.10 (28)	p=0.28
Focal dystonia: generalized dystonia ratio	1.83:1	1:2.2	1:1	p=0.227

* Years.

The main differences between sporadic and familial cases are in Table 2. The mean age at onset of dystonia in sporadic cases was 32.37±21.09 years old, and 24.78±20.48 years old in familial cases. Although there has not been any statistic difference, cases of generalized dystonia seen in the familial group were higher than in the sporadic group.

There was no difference, between familial and sporadic cases, related to the localization and the spreading of the dystonia. There was also no difference about the site of onset of symptoms among the patients with generalized dystonia (caudal or rostral, limbs or cranial-cervical) even in familial or sporadic cases (p=0.643 to p=1) (Table 3).

Regarding clinical presentations of CD (torticollis, laterocollis, retrocollis and anterocollis), one form was presented in 46 (52.27%) patients, two forms in 36 (40.9%) patients and three in 4 (4.54%). Among patients with generalized dystonia, 19 (67.86%) presented more than one form of dystonia. The most of patients with one form was found in a group with focal dystonia, 25 (65.8%) patients. The torticollis was the most common CD presentation, in

Table 3. Site of onset of generalized dystonia (sporadic cases X familial cases).

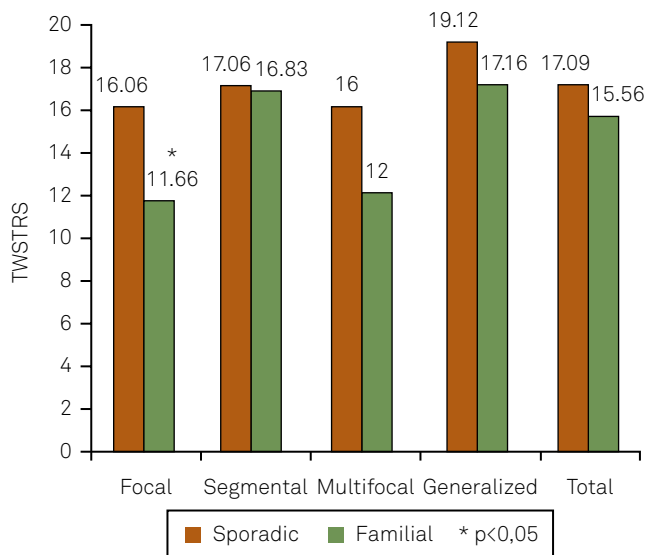
Site of onset	Sporadic cases	Familial cases	Total
Cranial-cervical	5	4	9
Cranial-facial	1	1	2
Cervical	4	3	7
Limbs	12	7	19
Arms	5	4	9
Legs	7	3	10

64 (72.73%) patients. The laterocollis was observed in 42 (47.73%) patients. The 17 (19.32%) patients with retrocollis, and the 11 (12.5%) patients with anterocollis were found mixed with other forms, no isolated cases were observed. The most common one presented was torticollis plus laterocollis (Table 4).

The severity caused by motor neck features, measured for TWSTRS scale, was higher in sporadic cases with focal dystonia (16.06±4.21) than in familial cases with focal dystonia

Table 4. Patients with cervical dystonia divided by clinical presentation.

Presentation	Sporadic cases (n=65)	Familial cases (n=23)	Total (n=88)	p
1 Type	34	12	46	1
Torticollis	23	9	32	
Laterocollis	11	3	14	
Retrocollis	0	0	0	
Anterocollis	0	0	0	
2 Types	27	10	37	1
Torticollis + Laterocollis	10	5	15	
Torticollis + Retrocollis	6	2	8	
Torticollis + Anterocollis	3	2	5	
Laterocollis + Retrocollis	6	0	6	
Laterocollis + Anterocollis	2	1	3	
3 Types	4	1	5	1
Torticollis + Laterocollis + Retrocollis	2	1	3	
Torticollis + Laterocollis + Anterocollis	2	0	2	



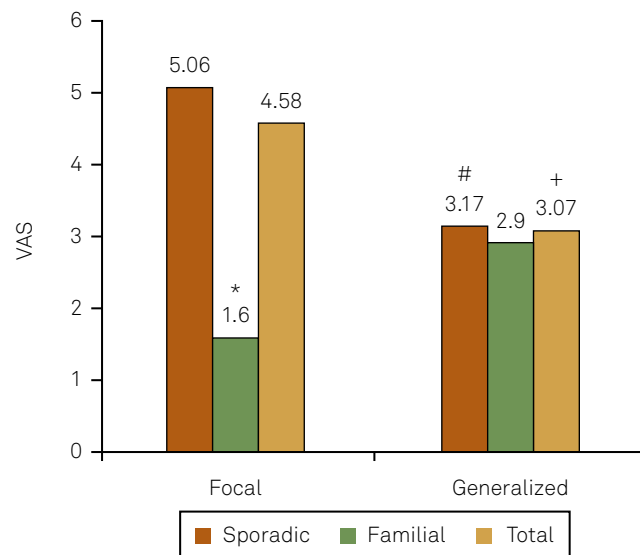
TWSTRS: Toronto Western Spasmodic Torticollis Rating Scale.

Figure 2. Differences of severity (TWSTRS) in cervical dystonia among patients with several clinical presentations.

(11.66±7.56) (p=0.03, Figure 2). There was no difference in severity between CD focal and CD segmental (p=0.13), and between CD segmental and CD generalized (p=0.19). When the same tool was used, patients with three or two forms of CD presented more severity than patients with one form of dystonia (p<0.001). The generalized cases had more severity than focal cases (p<0.05), mainly in familial patients (p<0.01).

Pain in neck area was related by 53 (60.23%) patients. 26 (49.06%) related a strong or a disability pain. The jerks and spasms, in 13 (14.77%) patients, were an aggravating factor to pain (p<0.001). The sporadic patients had higher pain levels than familial patients (p<0.05). There was more complaint of pain among patients with focal CD than patients with generalized CD (p<0.05). The familial patients with focal CD related less pain than the sporadic patients with focal CD (Figure 3). There was more intensity of the pain in patients with two and three cervical movements than patients with one movement (p<0.05).

Tremor (head tremor and arms postural tremor) was observed in 32 (36.37%) patients. Three patients, one with generalized and two with segmental dystonia presented parkinsonism. The patients with segmental dystonia were familial cases and started the features at 64 and 70 years old. The sporadic case started the symptoms at 17 years old by neck area with generalization in two years. No levodopa response was observed in these patients. Other four patients, two with segmental and two with generalized dystonia, had myoclonus. The mean age of onset was 15.5±5.07 (range, 12 to 23 years), without familial history or other movement disorders. A partial response with alcohol was achieved in two patients. A familial history of movement disorder (tremor, dystonia or parkinsonism) was related to 26 (29.55%) patients.



+ p<0.05 between the total of patients of focal dystonia and the total of patients of generalized dystonia;

p<0.05 between the sporadic patients with focal dystonia and sporadic patients with generalized dystonia;

* p<0.05 between the familial patients with focal dystonia and sporadic patients with focal dystonia.

VAS: visual analog scale.

Figure 3. Differences of pain level (VAS) in cervical dystonia among patients with several clinical presentations.

DISCUSSION

The total number of patients with familial history of movement disorders (29.55%, 26.14% with familial history of dystonia) was below the 44% found by Jankovic et al.¹³, probably due to the difficulty of the majority of patients to access their relatives, due to social and economic level conditions, and the presence of unusual ethnic-related genetic transmission of dystonia in our region.

The relationship of some ethnic groups with specific types of dystonia is known. The *DYT3* dystonia is a movement disorder of adult men from the Philippines. Dystonia *DYT3* has only been diagnosed in the Philippines¹⁴. The frequency of dystonia is estimated at 1/9000 in the Ashkenazi Jewish population¹⁵. Among other ethnic groups the prevalence is likely to be below, about 1/10000 to 1/30000, but has not been defined yet¹⁶. The *DYT6* gene was described in a study of three Amish-Mennonite families. The *DYT6* dystonia was initially associated with individuals of this ethnic group⁹. In 1880, the first Ashkenazi Jewish immigrants arrived in our region, mostly originating from Austrian Galicia. With the First and Second World War, new waves of Jewish immigrants arrived in Paraná¹⁷. The Mennonites formed an important wave of migration from Europe to the South of Brazil in XX century. Despite this fact, we cannot, by clinical history, establish a relationship of ancestry from any of the 88 patients evaluated with these ethnic groups.

In agreement with previous studies, we found a predominance of CD in whites and females (1:1.75)^{13,18-21}. There was an earlier onset of symptoms in men than in women at a mean of 5.18 years. Although statistical significance was not observed, these values were representative and higher than the difference of 2.2 years observed by Soland et al¹⁸.

The onset of symptoms occurred mainly between the fourth and the sixth decades of life (61.2 %) as demonstrated previously^{13,21}. There was a tendency of earlier onset when there was a family history, particularly in focal dystonias, however, this finding was not confirmed statistically significant. Previous studies also pointed to an earlier onset of familial cases than sporadic cases¹¹. Regardless family history, the generalized form started earlier, and focal and segmental forms later. In our study, patients started generalized dystonia mainly in childhood and adolescence, according previous studies^{11,13,21}.

There is a rule in the study of dystonias. The ones which begin in early childhood tend to start in lower limbs and spread to the rest of the body, while the dystonia starting in adults usually begins in the upper half of the body and tend to remain focal²². With increasing age, there is a caudal-rostal pattern of the site of onset in the following order: lower limb dystonia, writer's cramp, CD, spasmodic dysphonia, and blepharospasm/oromandibular dystonia²³. A study comparing the natural history of dystonia between sporadic and familial cases showed that the spread of symptoms to other sites could occur in both groups over time. However, a progression after five, 10, 15, 20 or 25 years were more pronounced in cases with familial history of dystonia¹¹. We observed a higher number of patients with generalized dystonia in familial patients and a significant number of patients with higher focal dystonia in sporadic group. These data confirm a higher tendency of earlier onset with faster spreading of dystonia in familial patients than sporadic patients^{11,23}.

The patients in our study who developed generalized dystonia began the symptoms in similar proportion by the limbs or the cranial-cervical region. There was not, unlike the previously published studies, a tendency of the familial generalized cases of starting their symptoms by legs^{11,23}. According to previous studies, *DYT1* dystonia has focal onset in the limbs, predominantly in the lower limbs, with subsequent generalization in childhood^{7,23}. *DYT3* dystonia has focal onset with secondary generalization in 2-5 years¹⁴. *DYT5* dystonia, or dopa-responsive dystonia, is a generalized dystonia, with onset in the lower limbs, typically in childhood. In *DYT7* and *DYT13* dystonia, the onset is later, and dystonia remains a focal form. When *DYT13* dystonia occurs in childhood, there is a greater tendency to generalize^{24,25}. Although the main presentation of *DYT6* dystonia is the onset in upper limbs in childhood spraying toward generalization, it may occur in the focal or segmental forms, having its onset in cranial-cervical region, and even occurring without a familial history¹⁰.

The most common presentation of CD was torticollis, followed by laterocollis, as demonstrated in previous studies^{13,20,21}. The presence of retrocollis was less common than the one reported in other series. In our study, patients with tardive dystonia were excluded. The retrocollis and involvement of other regions of the body in CD patients are more prevalent in patients with tardive dystonia. Torticollis and laterocollis, head tremor, *geste antagoniste*, and familial history are more common in dystonia "primary"²⁶. In previous study presented by our group, including patients with multiple etiologies (8.25% of cases secondary to the use of neuroleptics), the presence of retrocollis was higher (37.6%)²⁰.

Patients with two or three types of dystonic movements had severity and pain scores higher than those shown by patients with a single presentation. Generalized dystonia, with the majority of patients with more than one presentation, showed higher degrees of severity. Therefore, we reaffirm that a higher number of dystonic movements and extra-cervical sites of dystonia are factors of worsening to CD²⁰. Another important observed datum is when familial patients remain with CD in focal form, tending to have milder features than sporadic patients.

This tendency was repeated when the neck pain was evaluated. The familial patients with focal CD had lower pain scores, which was statistically significant for patients with the sporadic form and focal CD. The high incidence of pain contributes significantly to the disability of the patients in CD, and distinguishes it from other focal dystonias²¹. Different degrees of pain in the neck region were reported by 60.23% of patients, similar to 63% and 75% previously described^{27,28}.

CD can be diagnosed among the dystonia with gene loci known or not. Among the known loci with dystonia, CD can have early and familial onset with autosomal dominant inheritance (*DYT1*, *DYT6* and *DYT13*), or early onset with autosomal recessive inheritance (*DYT2* and *DYT17*), or late onset with autosomal dominant inheritance (*DYT7*, *DYT21*, *DYT23*, *DYT24* and *DYT25*). Currently, despite of the identification of several loci related with dystonia, the *TOR1A* (*DYT1*), *THAP1* (*DYT6*), *CIZ1* (*DYT23*), *ANO-3* (*DYT24*) and *GNAL* (*DYT25*) genes are the only ones linked to isolated ("primary") dystonias. The relationship of *CIZ1* (*DYT23*), *ANO-3* (*DYT24*) and *GNAL* (*DYT25*) genes with dystonia was described recently^{3-7,9}. In each monogenetic inheritance dystonia, CD may be more or less common, and the onset can be part of the spreading even of the generalization³. The *DYT23* dystonia, for example, has a pure latest onset CD⁴. Meanwhile, patients with *DYT6* dystonia have a huge range of phenotypes, and wide range of age of onset⁸⁻¹⁰. Therefore, it is expected that CD may have several levels of pain and severity within the same etiology, but especially among the different etiologies.

Currently, these clinical analyses among different etiologies are not possible due to poor clinical details of the presentations of CD reported in studies aimed genetic analysis.

Most likely, with the evolution of genetic studies of dystonia, it will be meaningless to compare clinical symptoms and pain of a familial group versus a sporadic group. In the future, the comparison of these parameters will be among groups with genetically defined etiology.

In conclusion, we described different clinical features, severity of symptoms and pain, between familial and sporadic patients with CD. This study was part of a continuous project. We expect to publish soon the first data about genetic evaluation of these patients to *DYT1* and *DYT6* genes.

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