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Environmental Factors and Disease Progression in Adult-Onset Isolated Focal Dystonia: A Tertiary Center Cohort Study

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Abstract

Background: Adult-onset isolated focal dystonia (AOIFD) is the most common form of dystonia, being the third most common movement disorder. AOIFD has a heterogenous phenotype, etiopathogenesis being incompletely understood, both genetic and environmental factors playing a role.

Objective: The objective of this study was to characterize a cohort of Romanian patients with AOIFD and to explore the potential associations between environmental factors and disease progression.

Methods: We conducted an observational cross-sectional study on patients with AOIFD evaluated in a tertiary neurology referral centre in Romania, approved by the local Ethics Committee. Demographic, clinical, environmental, and treatment-related data were collected. Associations were assessed using univariable analyses and logistic regression models.

Results: 89 patients were included. The most common phenotypes were cervical dystonia (53.9%) and blepharospasm (36.0%). Disease progression was present in 75.3% of cases. No statistically significant associations were observed between disease progression and environmental or lifestyle factors. Isometric occupational activity was associated with acute onset (p=0.023). Evolution to Meige syndrome occurred exclusively in patients with late-onset blepharospasm.

Conclusions: AOIFD is a heterogeneous multifactorial disorder. While the assessed environmental factors were not significantly associated with disease progression, certain phenotype-specific patterns were observed.

Key words: blepharospasm, cervical dystonia, isolated focal dystonia, environmental factors, disease progression

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INTRODUCTION

Dystonia is defined by intermittent or sustained involuntary movements and/or postures[1]. The term refers both to a clinical syndrome that can be attributed to specific causes (e.g., structural lesions of the brain, neurological or systemic diseases, side effects of certain drugs), and to a group of primary movement disorders in which dystonia is the predominant clinical manifestation[1]. Although considered rare, it is the third most common movement disorder after Parkinson's disease and essential tremor.

Isolated focal dystonia refers to a condition in which dystonia is confined to a single body region and is the main or sole clinical manifestation[1]. Adult-onset isolated focal dystonia (AOIFD), either idiopathic or genetic, is the most common form[2]. It has a broad phenotypical spectrum and a prevalence of approximately 30 cases per 100,000 individuals[3,4]. The most common phenotypes of AOID are cervical dystonia (CD) and blepharospasm (BSP), immediately followed by writer's cramp, a task-specific dystonia[2]. All these phenotypes can be highly debilitating. Currently, no disease-modifying therapies are available. Symptomatic treatments, including botulinum toxin, provide only modest benefit[5,6].

AOIFD may be associated with specific genetic mutations, but in most cases, no known genetic mutation is found. Since some mutation carriers remain asymptomatic while others develop the disease, it is thought that environmental factors also influence the onset and the progression of the disease[3]. Within this framework, the theory of a complex gene-environment interaction, meaning that genetic predisposition may increase susceptibility to environmental factors that trigger and exacerbate the dystonia, was proposed[3,7].

Although initially only one body region is affected in AOIFD, over time dystonia can spread to contiguous or non-contiguous body regions, evolving from focal to segmental or multifocal dystonia, thereby increasing disability[8-11]. The rate of dystonia spread depends on the body distribution at onset. Among the phenotypes, BSP exhibits the highest rate of spread compared to CD or laryngeal dystonia[8-11]. The spread typically occurs within the first 5 years after disease onset, with BSP associated with a shorter interval to regional extension[10,11]. Moreover, studies have reported conflicting findings regarding the role of associated tremor as a predictor of dystonia spread, suggesting it may either increase or decrease the risk of disease extension[9,11,12]. Additionally, patients with older age at onset have a higher risk of spread to segmental or multifocal dystonia, in contrast to younger age at onset, where focal dystonia tends to progress to generalized distribution[10,13].

Some environmental and lifestyle factors have been repeatedly associated with various types of AOIFD. For example, it was suggested that increased sun exposure, which induces repetitive contraction of the orbicularis oculi muscles, could predispose to BSP[14,15]. While the relation between alcohol consumption and the development or progression of AOIFD is not clear yet, cigarette smoking was found to be a potentially protective factor in some studies[3,16]. Coffee intake was also found to confer a protective effect on developing BSP[17]. The latter correlation is biologically plausible, since caffeine acts on adenosine receptors, which are believed to influence dopaminergic circuitry in the basal ganglia[3]. Moreover, an increased caffeine intake was inversely associated with the age at onset in people with BSP[17].

However, data on the role of environmental exposures in AOIFD remain scarce, underscoring the need for further studies to assess potential correlations between specific environmental factors and clinical characteristics of dystonia, such as age at onset or disease progression. This could not only help clinicians better understand disease prognosis and progression but also identify modifiable environmental or lifestyle factors that may help prevent further disability.

MATERIALS AND METHODS

Study design

We conducted an observational cross-sectional study on patients with AOIFD evaluated between November 2017 and December 2018 at the Neurology Department of Colentina Clinical Hospital in Bucharest, a tertiary neurology referral center with extensive experience in botulinum toxin therapy for movement disorders. The study was part of the GENDYS project (Genomic Profiling of Adult-Onset Isolated Focal Dystonia in a Group of Romanian Patients), supported by a grant from the Romanian Ministry of Research and Innovation (PN-III-P4-ID-PCE-2016-0696). The study was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the Ethical Committee of Colentina Clinical Hospital (NO 17/04.09.2017). All participants provided written informed consent prior to inclusion, including consent for genetic testing and for the use of their anonymized data for research purposes. Here we present the correlations between the

AOIFD phenotype, demographic and environmental factors (including lifestyle), and disease progression. The genetic data obtained within the GENDYS project have been partially reported to date (e.g., the CACNA1B study by Cocos et al.) and are beyond the scope of the present analysis

Study population

All patients were evaluated by an experienced neurologist specialized in movement disorders who confirmed the diagnosis of AOIFD using internationally accepted classification criteria (i.e., IM; the diagnosis of AOIFD was also confirmed by BOP, who also performed the botulinum toxin injections). Patients were eligible for inclusion if they had AOIFD, declared Romanian descent, and were willing and able to provide written informed consent and complete the assessment procedures. Patients were excluded if they presented generalized, segmental, or multifocal dystonia at disease onset, if the dystonia was secondary to structural, metabolic, or pharmacological causes, and if they had major psychiatric or systemic comorbidities that could interfere with the study evaluation. The present analysis also excluded patients with a phenotype resembling hemifacial spasm at onset (included in the GENDYS cohort).

Variables

Demographic, clinical, environmental, and treatment-related variables were recorded. Demographic variables included sex and age at symptom onset. For descriptive analyses, age at onset was categorized into three groups (<30 years, 30–50 years, and >50 years).

The clinical phenotype of dystonia was classified according to the predominant anatomical distribution at diagnosis. The analyzed phenotypes included CD, BSP, and other focal dystonias, such as writer's cramp or oromandibular dystonia. Additional clinical characteristics recorded in the database included family history of dystonia, family history of other movement disorders, acute onset of symptoms, the presence of tremor, diurnal fluctuations, and phenotypic evolution of BSP to Meige syndrome.

Environmental and lifestyle exposures were evaluated as potential factors associated with disease characteristics and progression. Occupational variables were categorized based on the predominant type of muscular activity involved, as well as exposure to toxic agents. *Isometric professions* were defined as occupations requiring sustained muscle contraction with minimal joint movement, typically involving prolonged static postures. In contrast, *isotonic professions* were defined as occupations involving repetitive or dynamic muscle activity with continuous changes in muscle length and joint movement. Classification was performed based on the main occupational activity reported by each participant. Lifestyle-related exposures included smoking status, daily coffee consumption, and daily alcohol intake. For statistical analyses, smoking status was dichotomized as ever smoker (including both former and current smokers) versus never smoker.

Treatment-related variables included the administration of botulinum toxin within the first year from symptom onset and the use of oral medications commonly prescribed in dystonia management, including clonazepam, trihexyphenidyl, and dopaminergic drugs.

The dependent variable analyzed in this study was disease progression, defined as either as extension of dystonia to additional body regions - corresponding to a transition from focal to segmental or multifocal distribution, or as progressive worsening of symptoms over time, as determined from patient-reported disease history obtained through structured interviews.

Statistical analysis

Descriptive statistics were used to summarize the demographic, clinical, environmental, and treatment-related characteristics of the study cohort. Categorical variables were reported as absolute counts and percentages.

To explore the distribution of environmental and clinical variables across relevant patient subgroups, graphical visualization methods were employed. Heatmaps were generated to illustrate the distribution of environmental and lifestyle factors across dystonia phenotypes and across age-at-onset groups. Additional heatmaps were used to visualize the distribution of selected clinical characteristics and treatment exposures across dystonia phenotypes and age-at-onset categories. In these visualizations, cell values represented the percentage of patients within each subgroup presenting the respective characteristic.

Sankey diagrams were used as exploratory visualization tools to illustrate the distribution of dystonia phenotypes within the cohort and their relationship with selected clinical features, including tremor, diurnal fluctuations, and phenotypic evolution to Meige syndrome. The width of each flow represented the relative number of patients within each category.

Associations between disease progression and demographic, environmental, clinical, and treatment-related variables were evaluated using univariable comparisons. Categorical variables were compared using the chi-square test or Fisher's exact test when appropriate, depending on the expected cell counts.

To further investigate potential associations between environmental exposures and disease progression, logistic regression models were constructed. Univariable logistic regression analyses were first performed for each environmental exposure variable, including occupational factors (isometric profession, isotonic profession, toxic occupational environment) and lifestyle factors (ever smoking, daily coffee consumption, and daily alcohol consumption). Multivariable logistic regression models were subsequently fitted to estimate adjusted odds ratios while controlling for potential confounders, including gender, age at onset, and dystonia phenotype. Results were reported as odds ratios with corresponding 95% confidence intervals.

Statistical analyses were performed using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA) and Python statistical libraries. Graphical visualizations, including heatmaps, Sankey diagrams, and forest plots, were generated using Python-based tools based on author-defined specifications. All tests were two-tailed, with a significance level of $p < 0.05$.

RESULTS

The study included 89 patients with AOIFD (63 females and 26 males). At the time of study inclusion, the mean disease duration since diagnosis was 8.11 years, reflecting a cohort predominantly composed of patients with established disease undergoing follow-up and treatment with botulinum toxin in a tertiary movement disorders center. Most patients developed dystonia after the age of 50 (46.1%), while only 14.6% had onset before the age of 30. The most common phenotype was CD, observed in 48 patients (53.9%), followed by BSP in 32 patients (36.0%). A family history of dystonia was present in 7.9% of patients, while 6.7% reported a family history of other movement disorders. A total of 67 patients (about 75%) reported disease progression, from which all presented worsening of symptoms and 18 patients presented disease extension to other body regions (almost 27%).

Regarding occupational factors, 36.0% of patients had work-related activities predominantly involving isometric movements, while 21.3% reported predominantly isotonic activities. Only 23.6% of the patients reported working in a toxic environment, including approximately one third of patients with BSP (31.2%) and about one quarter of those with CD (22.9%). Interestingly, patients with predominantly isometric occupations had a higher frequency of acute symptom onset than the rest of the cohort (18.8% vs 3.5%; OR 6.35, 95% CI 1.20–33.61; p=0.023), while exposure to toxic environments was more common in patients with onset after 50 years (34.1%). For more details, see **Table 1.**

Table 1. Baseline characteristics of the study cohort (N = 89)

Variable	**n (%)**
Sex	
Female	63 (70.8)
Male	26 (29.2)
Age at onset	
<30 years	13 (14.6)
30–50 years	35 (39.3)
>50 years	41 (46.1)
Dystonia phenotype	
Cervical dystonia	48 (53.9)
Blepharospasm	32 (36.0)
Other focal dystonia	9 (10.1)
Occupational factors	
Isometric profession	32 (36.0)
Isotonic profession	19 (21.3)
Toxic occupational environment	21 (23.6)
Lifestyle factors	
Non-smoker	54 (60.7)
Former smoker	11 (12.4)
Current smoker	24 (27.0)
Daily coffee consumption	64 (71.9)
Daily alcohol consumption	13 (14.6)
Family history	
Family history of dystonia	7 (7.9)
Family history of movement disorders	6 (6.7)
Clinical characteristics	
Acute onset	8 (9.0)
Disease progression	67 (75.3)
Diurnal fluctuations	24 (27.0)
Tremor	
Absent	78 (87.6)
Present	8 (9.0)
Other/uncertain coding	3 (3.4)
Treatment exposure	
Botulinum toxin in first year after onset	20 (22.5)
No toxin in first year	66 (74.2)
Clonazepam treatment	25 (28.1)
Trihexyphenidyl treatment	28 (31.5)
Dopaminergic treatment	1 (1.1)
Phenotype evolution	
Evolution to Meige syndrome	8 (9.0)

Regarding lifestyle factors, most patients were non-smokers (60.7%), while 27.0% were current smokers and 12.4% former smokers. A higher percentage of smokers was reported among CD patients (45.8%) compared to BSP (37.5%) and other forms of AOIFD (11.1%). Daily coffee consumption was common, reported by 71.9% of patients, 78.1% for BSP and 68.8% for CD, whereas daily alcohol intake was reported by 14.6%. Daily coffee consumption was highly prevalent across all age groups, with the highest proportion observed among patients with onset after 50 years (75.6%). Ever smoking (defined as patients who were actively smokers or former smokers) was most frequent in the 30–50 years onset group (45.7%), with lower proportions observed in patients with onset before 30 years (30.8%) and those with onset after 50 years (36.6%). The distribution of environmental and lifestyle factors across dystonia phenotypes is illustrated in **Figure 1.**

A family history of dystonia was uncommon across the cohort, with similar proportions observed in CD and BSP (6.2%), while a higher proportion was noted in other focal dystonia (22.2%). Early treatment with botulinum toxin within the first year after symptom onset was most frequent in CD (31.9%), compared with BSP (16.7%), and was not observed among patients with other focal dystonias. Oral medications were used predominantly in CD, with clonazepam and trihexyphenidyl reported in approximately one third of cases.

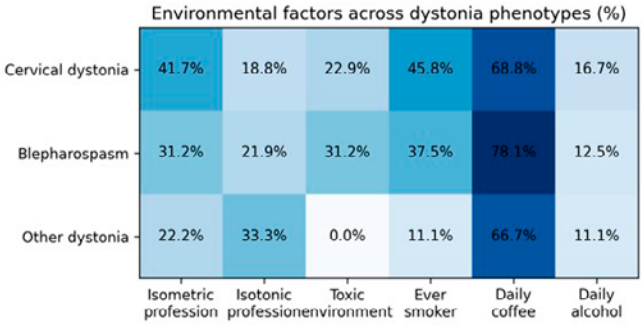

Figure 1. Heatmap of environmental and lifestyle factors across dystonia phenotypes. *(Heatmap illustrating the distribution of selected environmental and lifestyle factors across dystonia phenotypes in the study cohort. Rows represent dystonia phenotypes (cervical dystonia, blepharospasm, and other focal dystonia), while columns represent environmental exposures and lifestyle factors including isometric profession, isotonic profession, toxic occupational environment, ever smoking (former or current), daily coffee consumption, and daily alcohol consumption. Values indicate the percentage of patients within each dystonia subtype presenting the respective exposure. Darker shades of blue correspond to higher prevalence of the factor within the subgroup.)*

Oral therapies varied across age groups: clonazepam was most frequently reported in the 30–50 years onset group (31.4%), while trihexyphenidyl use was particularly common among patients with onset before 30 years (53.8%). Dopaminergic therapy remained rarely used in the cohort. Acute onset was relatively infrequent across all phenotypes, however it appeared more frequent among patients with onset before 30 years of age (23.1%) compared with older age groups. The distribution of age at onset and treatment exposure across dystonia phenotypes is shown in **Figure 2**.

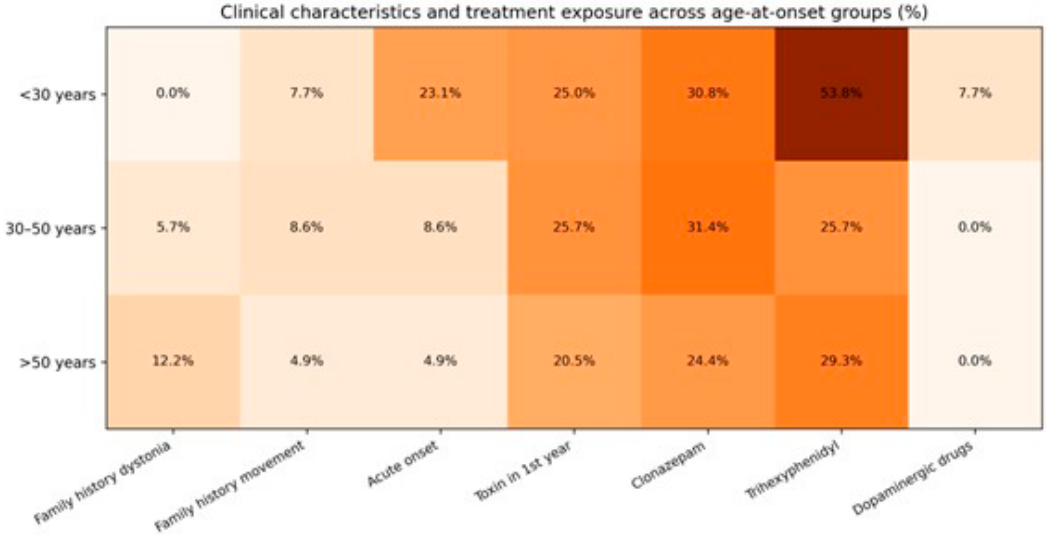

Figure 2. Heatmap of clinical characteristics and treatment exposure across age-at-onset groups. *Heatmap illustrating the distribution of selected clinical characteristics and treatment exposures according to age at dystonia onset within the study cohort. Rows represent age-at-onset groups (<30 years, 30–50 years, and >50 years), while columns represent family history of dystonia, family history of movement disorders, acute onset, botulinum toxin treatment within the first year after symptom onset, and use of oral medications (clonazepam, trihexyphenidyl, and dopaminergic drugs). Values indicate the percentage of patients within each age group presenting the respective characteristic. Darker shades of orange correspond to a higher prevalence within the subgroup.*

Most patients experienced disease progression as defined above (75.3%), and 27.0% reported diurnal fluctuations. However, in most of the patients the dystonia remained focal – see Figure 3. Tremor was present in 9.0% of cases. Univariable analyses did not identify any statistically significant association between disease progression and the examined demographic, lifestyle, or occupational variables. No statistically significant differences were observed in demographic characteristics, dystonia phenotype, environmental exposures, clinical features, or treatment-related variables between the two groups. Environmental factors, including occupational exposures, smoking status, daily coffee consumption, and daily alcohol use, showed similar distributions among patients with and without disease progression. Specifically, progression rates were comparable across sex categories and did not differ significantly according to daily alcohol consumption or daily coffee consumption. Similarly, no significant relationship was found between progression status and occupational profile, whether defined by predominantly isometric or isotonic professional activity. Likewise, family history of dystonia or other movement disorders, acute onset, and early treatment exposure did not differ significantly between groups. Taken together, these results suggest that, within this cohort, disease progression was not significantly influenced by sex, caffeine or alcohol exposure, or job-related physical activity characteristics. Overall, the univariable analysis did not identify any individual factor significantly associated with disease progression in this cohort.

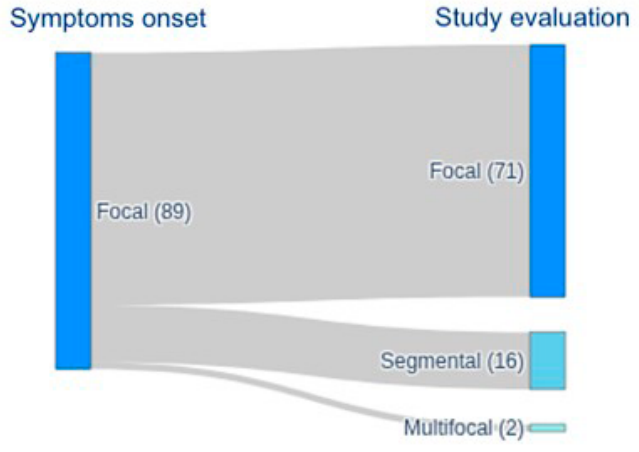

Figure 3. Sankey diagram showing disease extension from symptom onset to study evaluation. Node labels indicate patient counts. Most patients kept a focal distribution over time, whereas only a minority evolved toward segmental or multifocal distribution, indicating relative longitudinal stability of disease topography in the cohort.

Logistic regression analysis examining environmental factors and disease progression is presented in Table 2. In univariable analyses, none of the environmental exposures showed a statistically significant association with disease progression. Similar findings were observed in the multivariable model adjusted for gender, age at onset, and dystonia phenotype. Daily alcohol consumption showed a trend toward a lower likelihood of disease progression (adjusted OR 0.36, 95% CI 0.03–1.16, p = 0.07), although this did not reach statistical significance. Overall, occupational exposures, smoking status, and daily coffee consumption were not independently associated with disease progression in this cohort.

Variable	Univariable OR (95% CI)	p-value	Adjusted OR (95% CI)*	p-value
Isometric profession	1.28 (0.46–3.56)	0.63	1.43 (0.46–4.50)	0.54
Isotonic profession	1.30 (0.38–4.42)	0.67	1.30 (0.30–5.61)	0.73
Toxic environment	1.53 (0.45–5.16)	0.49	1.57 (0.37–6.78)	0.54
Ever smoker	1.18 (0.44–3.19)	0.74	1.10 (0.37–3.32)	0.86
Daily coffee	0.69 (0.22–2.13)	0.52	0.86 (0.23–3.25)	0.83
Daily alcohol	0.46 (0.13–1.59)	0.22	0.36 (0.03–1.16)	0.07

Table 2. Logistic regression analysis of environmental factors associated with disease progression in adult-onset focal dystonia. *(Logistic regression analysis evaluating the association between environmental exposures and disease progression. Univariable odds ratios (OR) were calculated for each environmental factor individually. Multivariable models were adjusted for gender, age at onset, and dystonia phenotype. Smoking status was analyzed as ever smoker (former or current) versus never smoker. Odds ratios are presented with 95% confidence intervals (CI).)*

When patients were stratified by age at onset, disease progression was observed in 69.2% of those with onset before 30 years, 77.1% of those with onset between 30 and 50 years, and 75.6% of those with onset after 50 years, with no statistically significant difference across groups (p=0.8507). Likewise, no significant association was found between late onset (>50 years) and disease progression compared with the rest of the cohort (OR 1.03, 95% CI 0.39–2.72; p=1.000). These findings suggest that age at onset was not a major determinant of overall clinical progression in this cohort.

Considering Meige syndrome is generally regarded as a phenotypic extension of blepharospasm, its distribution was examined within the study group. From the total of 32 blepharospasm patients, the development of the Meige phenotype was observed in 8 patients, all from the group with the onset of the disease after the age of 50. This corresponded to a rate of 33.3% (8/24) among patients with blepharospasm whose disease

onset occurred after the age of 50, whereas no progression to Meige syndrome was observed in those with onset before the age of 50 (0/8). Although not statistically significant, this distribution may be interpreted as suggesting a trend toward a higher likelihood of Meige syndrome development among patients with later-onset blepharospasm.

Acute onset was more frequent in patients with onset before 30 years (23.1%) than in those aged 30–50 years (8.6%) or above 50 years (4.9%), although this difference did not reach statistical significance (p=0.1348). A trend toward association between early onset and acute presentation was observed (OR 4.26, 95% CI 0.88–20.62; p=0.089).

Although age at onset was not significantly associated with overall disease progression, several significant phenotype-related associations were identified. Patients with late-onset disease were significantly more likely to present with BSP, whereas CD was more frequent among those with earlier onset. Specifically, BSP was observed in 7.7% of patients with onset before 30 years, 20.0% of those with onset between 30 and 50 years, and 58.5% of those with onset after 50 years (p=0.00016). Conversely, CD was present in 76.9%, 62.9%, and 39.0% of these groups, respectively (p=0.0229).

Regarding treatment-related variables, the database allowed assessment of treatment exposure rather than treatment response. No significant associations were identified between environmental factors and early treatment with botulinum toxin, clonazepam, or trihexyphenidyl, although some numerical trends were observed. Moreover, no statistically significant correlations were found between early treatment exposure (botulinum toxin injections, clonazepam, or trihexyphenidyl within the first year after onset) and disease progression.

DISCUSSION

In this study we describe the demographic and clinical characteristics of a cohort of patients with AOIFD evaluated at a tertiary neurology referral center in Romania. Our results show a higher prevalence of CD (53.9%), followed by BSP (36%), other forms of dystonia representing a lower percentage (10.1%). These findings are consistent with the literature, CD and BSP representing the most common forms of AOIFD[1,2,19]. Most patients had a later age of onset (>50 years, mean age at onset of 46.25 ± 13.91 years), which is in line with the available literature showing that AOIFD usually occurs after the fourth decade of life[19]. Regarding occupational exposure, in our study, work-related isometric muscle activity (characterized by prolonged sustained contractions), was more prevalent (36%), especially among patients with CD (41.7%). Additionally, isometric activity correlated with a higher frequency of acute symptom onset compared with the rest of the cohort (p=0.023). These findings could support the theory of sensorimotor integration impairment[7,20].

Regarding environmental and lifestyle factors, including cigarette smoking, coffee intake, and alcohol consumption, we did not found statistically significant correlations. However, a higher incidence of smoking was found among CD patients (45.8%), compared to BSP (37.5%). Literature data are controversial in this specific topic, some studies suggesting a protective effect of cigarette smoking, while others report no significant association[3,16,17]. Regarding caffeine consumption, despite some studies showing an inverse correlation between certain forms of AOIFD and caffeine intake, in our cohort, daily coffee consumption was common among all age groups, with a slightly higher prevalence in BSP patients (78.1%) than CD (68.6%). The hypothesis that caffeine exerts a protective role on the development and progression of AOIFD needs further assessment[3,16,17].

Additionally, in our cohort, 75.3% of patients exhibited disease progression; however, no statistically significant correlations were found between environmental or lifestyle factors, sex or age at onset. Meige syndrome was identified exclusively in the BSP subgroup with a later onset (>50 years), which suggest, even though not statistically relevant, trend toward a higher likelihood of Meige syndrome development among patients with later-onset BSP, in line with the literature[21,22].

Regarding the symptomatic treatment, oral pharmacological therapies, such as clonazepam and trihexyphenidyl, were widely used across the entire cohort, particularly among patients with CD (approximately one-third of cases). In contrast, botulinum toxin injections were rarely initiated within the first year following the diagnosis, possibly due to limited availability in Romania at the time.

Our study has several limitations, mainly related to the cross-sectional design, which means that variables such as lifestyle factors were assessed solely from patient history, potentially introducing recall bias or reporting inaccuracies, and preventing the assessment

of temporal relationships between variables. Although this is, to the best of our knowledge, the largest cohort of Romanian patients with AOIFD reported to date, the relatively small number of participants remains a limitation.

CONCLUSION

Overall, our findings suggest that AOIFD in this Romanian tertiary-center cohort follows a clinical pattern largely consistent with previously reported data, with CD and BSP representing the predominant phenotypes and late-onset disease being common[1,2,18,19]. Although no statistically significant associations were identified between environmental factors and disease progression, our study showed a potential link between isometric occupational activity and acute-onset disease, and an association between late-onset BSP and phenotypic evolution to Meige syndrome. These findings may indicate clinically relevant patterns that warrant further investigation.

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Author Contributions
IM drafted and revised final the manuscript; she also conceptualized the study protocol, as part of her Ph.D., under the supervision of BOP, and contributed to the ethics submission and statistical analysis; she was the main responsible for the recruitment and clinical evaluation of the study participants and she did most of the data collection, and processing, being part of the GENDYS team; TCB and MCZ contributed to the draft of the manuscript, critically appraised the statistical methods and did most of the statistical analysis; AFT significantly contributed to the manuscript draft, data processing and statistical analysis; LD contributed to the conceptualization, ethics submission and implementation of the GENDYS project, and revised the draft of the manuscript; BOP coordinated and critically revised all aspects related to the GENDYS project, the present study and the manuscript; he also obtained the funding required for this work (GENDYS, PN-III-P4-ID-PCE-2016-0696), was the PI of the study, and the supervisor of IM's Ph.D. All authors revised and approved the final version of the manuscript

All authors have read and agreed to the published version of the manuscript.

Institutional Review Board Statement. The study was conducted in accordance with the Declaration of Helsinki, and approved by the Local Ethics Committee of Colentina Clinical Hospital (No. 17/04.09.2017).
Informed Consent Statement. Informed consent was obtained from all subjects involved in the study.
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IM, LD, and BOP were part of the project team and received payment for their work.

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