Defazio *et al. Ageing Neur Dis* 2023;3:23
DOI: 10.20517/and.2023.32

Ageing and Neurodegenerative Diseases

Review

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Adult-onset idiopathic dystonia: phenotype and mechanism changes "as time goes by"

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How to cite this article: Defazio G, Muroni A. Adult-onset idiopathic dystonia: phenotype and mechanism changes "as time goes by". *Ageing Neur Dis* 2023;3:23. https://dx.doi.org/10.20517/and.2023.32

Received: 21 Jul 2023 **First Decision:** 25 Oct 2023 **Revised:** 8 Nov 2023 **Accepted:** 24 Nov 2023 **Published:** 4 Dec 2023

Academic Editor: Weidong Le **Copy Editor:** Dong-Li Li **Production Editor:** Dong-Li Li

Abstract

Adult-onset idiopathic dystonia is thought to be an autosomal dominant disorder with markedly reduced penetrance and heterogeneous clinical presentation. It has been known for a long time that age may affect the clinical phenomenology of the condition, at least in terms of the site of dystonia onset. The aim of this paper is to understand whether age and aging may play a role in the natural history of adult-onset idiopathic dystonia and in the mechanisms underlying its development and progression. Aging may increase abnormalities in cortical/subcortical excitability manifested by patients with different forms of adult-onset idiopathic dystonia, thus enhancing susceptibility to dystonia development, worsening spasm severity, at least in blepharospasm, and favoring perhaps the spread of dystonia to near body sites. The relationship between age of onset and site of onset in adult-onset idiopathic dystonia (AOID) might reflect age- and body-site-specific environmental risk factors that would drive the variable clinical expression of individuals carrying dystonia-susceptibility gene(s).

Keywords: Adult-onset dystonia, aging, spread

INTRODUCTION

Adult-onset idiopathic dystonia (AOID), the most common form of dystonia, is a relatively frequent movement disorder characterized by heterogeneous clinical presentation such as focal blepharospasm

(BSP), oromandibular dystonia (OMD), laryngeal dystonia (LD), cervical dystonia (CD), upper limb dystonia (ULD)[1]. In a proportion of patients, focal dystonia may spread to neighboring body sites, thus resulting in segmental/multifocal forms[1]. In the clinical phenomenology of AOID, motor aspects are integrated by several non-motor symptoms, including psychiatric, cognitive, and sensory symptoms[2-6]. To date, only a few studies have examined the contribution of sleep disturbances to the phenotype spectrum of AOID, but the results have been inconsistent[7].

The cause and mechanisms underlying AOID are poorly known. AOID is thought to be an autosomal dominant disorder with markedly reduced penetrance of 10%-12%. Most patients are sporadic, whereas up to 20%-25% have at least one other affected relative, often with a different phenotype[8,9]. The different phenotypes are not caused by different genetic mutations since discordant phenotypes are seen in 50% of affected proband-relative pairs and are also seen in multiplex families[10]. Environmental factors probably determine both disease penetrance and expression[11]. The few available controlled studies to date suggest that environmental risk factors may differ from one form of focal dystonia to another and may be site-specific[12]. Eye diseases may be risk factors for BSP[13], scoliosis and neck trauma for CD[14], and activities at work for ULD[15]. The site-specificity of environmental risk factors may partly account for the clinical heterogeneity of AOID.

The age of onset is one of the prominent clinical features used in the current reference classification of dystonia to summarize genotype-phenotype relations for isolated dystonia[1]. On the other hand, the well-known relationship between the age of onset of dystonia and phenotype expression in isolated AOID[16] would suggest a contribution of aging to the clinical phenomenology of the condition. The aim of this paper is to understand whether aging may play a role in the natural history of AOID and in the mechanisms underlying AOID development and progression.

SEARCH STRATEGY AND SELECTION CRITERIA

The search was carried out in the PubMed database, with reference to publication time ranging from January 1st, 1971, to October 31st, 2023. The MeSH terms "age" and "adult" and "blepharospasm/cervical dystonia/oromandibular dystonia/laryngeal dystonia/hand dystonia/writer's cramp/dystonia spread/dystonia severity/dystonia endophenotype/non-motor symptoms" included in title and/or abstract were used for the search. The search yielded 203 papers that were subsequently analyzed by a two-stage process. In the first stage, we screened by title/abstract to select only peer-reviewed, English language, original research studies that enrolled individuals aged 18 years or above. This results in the exclusion of 37/203 papers belonging to the categories of review articles, case reports, and studies on genetic forms of dystonia. In the second stage of screening, titles/abstracts of the remaining 176 papers were reviewed for potential relevance by one reviewer (GD). Papers including patients with idiopathic, isolated dystonia and assessing clinical/instrumental parameters at different ages were selected and their full texts were reviewed to check for adherence to the study objective. If several papers referred to the same population, then only the most informative paper was considered. The final list included 13 articles[9,16-27].

AGE AND PHENOTYPE EXPRESSION OF DYSTONIA AT ONSET

Several earlier clinical papers raised the possibility that the ages of onset of the various AOID phenotypes vary significantly. Meta-analysis of 83 published series[16] assessing more than 5,000 patients confirmed significant differences in the mean age of onset of four AOID phenotypes, including writer's cramp (mean age of onset 38.4 years; 95%CI, 36.9-39.9 years), CD (mean age of onset. 40.8 years; 95%CI, 40.3-41.3 years), LD (mean age of onset 43.0; 95%CI, 42.2-43.9 years), and BSP/OMD (mean age of onset, 55.7 years; 95%CI,

55.1-56.4 years). Likewise, family studies are characterized by intrafamilial phenotypic heterogeneity[9-17], and more recent clinical series[18,19] demonstrated a tendency to a caudal-to-rostral shift of the site of dystonia onset with increasing age: writer's cramp developed earlier than CD, LD, and BSP/PMD in the order. Recently, non-task-specific ULD at onset, a neglected form of dystonia, was shown to develop at an age similar to that of cranial dystonia[20].

Overall, these findings indicate that age may, at least in part, contribute to the phenotypic variability in AOID presentation.

Age and disease progression

Two aspects cover the issue of progression of AOID over time. The first relates to the severity of motor and non-motor symptoms, and the second to the spread of dystonia to neighboring body sites.

Severity of motor symptoms

Only a few longitudinal prospective studies assessed motor symptoms over time in AOID[21,22]. In patients with BSP, the severity of motor symptoms may increase in the early years of disease[14], but also subsequently. In fact, a recent prospective study on 60 patients suffering from BSP from 11.5 years (SD, 7.7) showed that, motor symptoms could further worsen over the next 5 years in 85% of study patients[22]. Worsening was mainly due to the appearance or the increased duration and frequency of prolonged orbicularis oculi spasms (i.e., spasms lasting three seconds or more)[22]. The worsening of BSP severity was independent of baseline disease duration, thus raising the possibility that aging plays a role in the progression of motor severity.

In 1971, Meares provided a longitudinal observation on 41 CD patients and showed that unoperated cases generally deteriorated during the first five years of history but then became static or tended to improve[23]. Longitudinal studies dealing with the severity of motor symptoms in other forms of focal AOID such as OMD, LD, and ULD are lacking. In task-specific ULD, however, it was recently shown that 9/70 writer's cramp patients (13%) lost task specificity after 9.1 ± 8.9 years[20]. Although loss of task specificity may reflect an increasing severity of dystonia over time, the possible role of symptomatic treatments (botulinum toxin and retraining) in preventing loss of task specificity should also be considered.

Owing to the paucity of longitudinal prospective studies, it remains unclear whether the motor severity of AOID can get worse and worse over time. Available information provides some support only to the notion that BSP in elderly patients can get worse with age, at least in a proportion of cases.

Severity of non-motor symptoms

In the last decades, several non-motor symptoms (including psychiatric, sleep, cognitive, and pain symptoms) have been shown to probably contribute to the clinical spectrum of AOID. Prospective studies assessing changes in the non-motor symptoms over time are lacking. However, a few cross-sectional studies performed in BSP patients failed to find any correlation between the severity of non-motor symptoms/the number of affected non-motor domains per patient and age, disease duration, and severity of motor symptoms[2,24]. These findings raise the possibility that the variable expression of non-motor symptoms is correlated to the natural history of the disease rather than to aging.

Spread of dystonia

The spread of AOID to adjacent body sites has been well characterized[25-29]. Both retrospective and prospective studies have shown that dystonia presenting as focal BSP spreads to cranial and extracranial

sites more often and earlier (typically over the first 5 years of history) than focal CD and task-specific ULD. It was also shown that the variable tendency of the spread of AOID presenting in different body sites is independent of age at dystonia onset[2,20-29]. Interestingly, a study in a large population of patients presenting with the most common forms of AOID, i.e., BSP and CD, showed that spread may develop over a similar period of age (i.e., around age 50), regardless of the site and the age of dystonia onset[25]. This would suggest a link between aging and the spread of AOID. The convergent age of spread in patients presenting with BSP and CD points to the existence of an age period (starting at approximately 40-50 years) in which AOID patients are "vulnerable" to spread. It is worth noting that the beginning of this age period is close to the peak age of BSP onset. Because CD develops earlier than BSP[16], the convergent age of spread in the two groups is in keeping with a longer time to spread (the time elapsing between the onset of focal dystonia and the development of dystonia in a second body site) in CD. The existence of an age period of vulnerability to dystonia spread is also reflected in the inverse correlation between age of dystonia onset and time to spread that has been observed even in other forms of AOID: in both non-task-specific ULD[20] and LD[26], the earlier the onset of focal dystonia the longer the time to spread.

AGING AND DYSTONIA MECHANISMS

If age and aging affect the clinical phenomenology of AOID in terms of site of onset and spread, then aging should influence the mechanisms leading to dystonia appearance and progression. Dystonia is now thought to be a network disorder in which different neurophysiological mechanisms have been consistently reported[30,31]. Both the motor and sensory systems show abnormalities in dystonia.

In the motor system, dystonia is characterized by loss of inhibition at multiple levels in the central nervous system. In the motor cortex, both inhibitory cortical circuits and surround inhibition are reduced in dystonia[32], while in the midbrain, blink reflex excitability is consistently enhanced in BSP[33]. Since cortical plasticity mechanisms rely on a dynamic balance between excitatory and inhibitory interneurons, it is conceivable that altered inhibitory interneuron activity may concur to give rise to other pathophysiological mechanisms reported in dystonia, such as aberrant cortical plasticity mechanisms[34]. Interestingly, the reported increasing severity of BSP over a 5-year follow-up period was accompanied by a worsening of the blink reflex recovery cycle at follow-up in comparison with the baseline[22]. This would support aging-related effects on the pathophysiological mechanisms underlying blepharospasm.

The sensory system is also involved in dystonia. Patients with focal ULD exhibit abnormal somatotopy with overlapping digit representations in primary somatosensory cortex, together with diminished temporal and spatial tactile acuity[35]. Abnormal somatosensory temporal discrimination threshold (STDT) has been consistently demonstrated in several forms of AOID[36,37] and possibly reflects abnormal inhibitory interneuronal activity at different levels of the central nervous system, including cortical and subcortical structures. The abnormal STDT is thought to be a mediational endophenotype in AOID. This implies that the endophenotype and the disease are both caused by a genetic disorder and that gene(s) are linked to disease by an endophenotype, which therefore reflects disease susceptibility.

Aging may modulate several basic mechanisms that appear to be dysfunctional in dystonia[38,39], including intracortical inhibitory pathway, and the organization of cortical body maps in the primary sensorimotor cortices[40-41]. Healthy elderly subjects displayed enlarged hand representations in the primary somatosensory cortex, possibly related to an age-related reduction in intracortical inhibition. Likewise, even the excitability of the blink reflex recovery cycle increases over time in healthy individuals[42]. Finally, aging could also affect STDT. An early study on 80 healthy volunteers aged from 18 to 82 years found that STDT increased in subjects older than 65 years[43], while an increase in the STDT by 0.66 ms for every year increase in age was observed in a later study assessing 100 healthy volunteers aged 18-79 years[44].

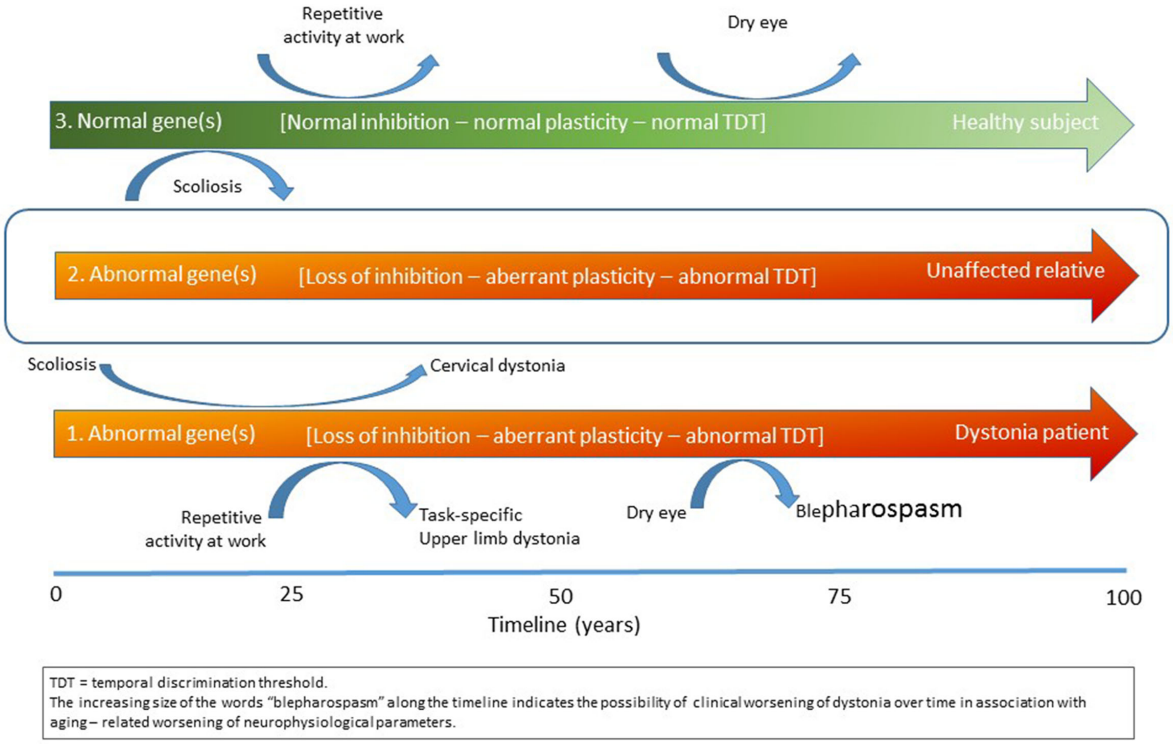

Figure 1. The figure summarizes the mechanisms possibly underlying the variable age at onset and clinical expression of idiopathic adult-onset focal dystonia. The genetic abnormality (Tracks 1 and 2) causes neurophysiologic changes lowering the threshold for disease susceptibility that tends to worsen over time. Age- and site-specific environmental factors capable of acting on dystonia-related mechanisms may thus trigger specific focal dystonias with variable age at onset (Track 1). It is also speculated that further deterioration of dystonia-related mechanisms by aging would worsen motor symptoms over time in blepharospasm and possibly make patients with adult-onset idiopathic dystonia more susceptible to spread of dystonia (Track 1). Subjects who carry the genetic mutation but are not exposed to any environmental factor affecting the neurophysiological mechanisms of dystonia do not manifest the clinical disease (Track 2). Environmental factors do not trigger dystonia in subjects who do not carry the genetic abnormality (Track 3) and have normal dystonia-related mechanisms. In healthy subjects, changes in dystonia-related mechanisms by aging do not approach the threshold for disease susceptibility.

AGING AND EPIGENETIC RISK FACTORS

The body of work on the environmental risk factors possibly leading to focal dystonia in predisposed subjects is not large. Nevertheless, available evidence suggests that such factors can differ from one form to the other. It is worth noting that the frequency of environmental factors thought to trigger different focal dystonias may vary with age. For instance, dry eye syndrome possibly triggering BSP[5] is characterized by an increasing prevalence with increasing age[45,46]; idiopathic scoliosis that may precede CD usually develops before or at around puberty[47]; and certain activities at work that may contribute to ULD can be more frequently performed by younger adults. The epidemiological differences in prevalence among clinical AOID subtypes and the variable relationship between age of onset and site of AOID onset might therefore reflect age- and body-site-specific environmental risk factors that would drive the variable clinical expression of individuals carrying dystonia-susceptibility gene(s) [Figure 1].

CONCLUSIONS

Despite the well-known and accepted relationship between age and body site of AOID onset, studies specifically addressing the contribution of aging to the natural history of AOID and to the mechanisms underlying its development and progression are lacking. Theoretically, aging may increase abnormalities in cortical/subcortical excitability that manifest in patients with dystonia, thus enhancing susceptibility to dystonia development. However, aging-related effects on the pathophysiological mechanisms underlying AOID have been demonstrated only for BSP. Likewise, convincing evidence suggesting an influence of aging on the severity of motor symptoms has been provided only in BSP patients. By contrast, an isolated earlier study observed that CD can get worse in the first years of history but then stabilize. Owing to the lack of longitudinal studies assessing motor severity in other forms of AOD, it is not known whether aging can play a role in the severity progression of AOID other than BSP and CD. Studies assessing the trend of AOID-related non-motor symptoms over time are also lacking. Several observations from our group indicated that patients presenting with different forms of focal AOID (characterized by variable age of onset) may have a convergent age of spread at around 40-50 years. The existence of an age period in which AOID patients are more "vulnerable" to spread raises the possibility of an age-related deterioration of the mechanisms limiting spread in most AOID patients. This paper highlights the need for future clinical and neurophysiological studies aimed at investigating the complex relationship between AOID and aging.

DECLARATIONS

Authors' contributions

Creating the work plan: Defazio G
Searching the bibliography: Muroni A
Writing and revision: Defazio G, Muroni A

Availability of data and materials

Not applicable.

Financial support and sponsorship

None.

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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