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## Original paper

### ***A rare case of idiopathic focal dystonia***

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#### Abstract

Our report is the case of a 43-year-old patient who has had several episodes of involuntary abnormal muscle contractions in the left upper limb. The medical history includes: asthma, non-neurological dysphonia, chronic laryngotracheitis and inconclusive family history. Paraclinical investigations performed do not show any relevant changes. In this context, we considered that the involuntary movements of the left arm represent idiopathic focal dystonia with a late onset.

**Keywords** Focal dystonia, idiopathic, spasmodic dystonia, clonazepam.

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## Introduction

Dystonia are a group of medical conditions characterized by involuntary muscle contractions with an intermittent or sustained tonic aspect, which produce twisting movements, torsion or abnormal postures in the involved body segments or regions. These pathological movements may be stereotyped or repetitive, may have variable speeds, from slow to fast, that are in close relationship with the degree of damage or the distribution of the affected muscular clusters [1-4]. In the light forms of illness, dystonia acts only as an exaggeration of the specific muscle group function, in the mild forms the disease signs are more augmented, with an aspect of rigidity or twisting and in the severe forms it appears as a fixed deformation [1, 5]. The contractions always have a directional character or a stable posture assuming one. The disease gets worse in the middle of a specific voluntary movement and may be improved temporarily by voluntary or specific gestures [4].

The disease affects approximatively 1% of the population and it seems women are more prone than men [6]. It is a disabling disorder with a large clinical aspect that can be associated with any other illness, present mainly in younger persons and can affect any region of the body: upper or lower limbs, torso, neck, face, eyes or the vocal cords, alone or in different combinations [1, 6].

The classification of dystonia was elaborated according the 4 affected aspects: the body region, the age of onset, the evolution in time and the other associated disorders, every one of these aspects having an important role in the diagnostic or treatment of the illness, as in the elaboration of an adequate disease management, prognostic and genetic counselling of the patients [1, 3, 7].

Although it is a rare condition, it occupies the 3<sup>rd</sup> place in the body movement disorders group, after the essential tremor and Parkinson's disease. In Romania it is underdiagnosed, the incidence being of 1/100.000 people. In the US, the prevalence of the idiopathic dystonia is around 250.000 and regarding the focal type of illness the prevalence is 300 per million, meaning that the prevalence is 9 times higher than the generalized form [8]. Because of the multitude of clinical signs and multifactorial aetiology, the diagnostic algorithm is very complex, without a group of tests that could lead to a certain diagnostic. The very expensive genetic tests, include a very scarce group of causes, therefore the probability of diagnosing a sporadic form of dystonia is very small, under 1%. Thereby, genetic testing for the DYT-1 gene should be conducted only in patients with age of onset under 30 years and with the primary form of illness, or in patients with age of onset over 30 years, with history of illness in family and constant torsional or directional movements or postures [9, 10].

Neuroimaging may be used in practice in diagnosing every type of dystonia, a normal brain MRI being an extra argument for a primary dystonia diagnostic. A functional brain MRI could reveal modifications in different profound brain structures or cortical areas as the cerebellum, basal

ganglia or the primary somatosensory cortex. Another strategy sometimes recommended for diagnosing purpose, is to do paraclinical test in strong relationship with the patients' clinical aspects [1, 9].

Electromyography is not a routine test for diagnosing primary dystonia, but it may be conducted in isolated cases with scarce or insufficient clinical signs [9].

The elected therapy, considered the first choice of treatment for every form of dystonia is the serotype A botulinum toxin (or serotype B if there is an actual resistance to serotype A botulinum toxin) [9].

Therefore, it was found that benzodiazepines are often prescribed to dystonia patients: Alprazolam, Clonazepam, and Diazepam. Clonazepam acts on the central nervous system by inhibiting the GABA receptors. The main indication is for generalized dystonia followed by cervical dystonia and secondary dystonia. The average dose used was 3.7mg/day. The secondary effects are represented by sedation, mental disorders, depression, and crisis in sudden interruption [1, 8, 11].

Baclofen, a gamma-amino butyric derived, is a GABA receptor agonist, with a role in lowering the excitability in the motor neurons in the central nervous system, may be used in various forms of dystonia, especially in younger patients at the beginning of the clinical signs of illness [12].

The daily dose of baclofen is 30-120 mg, fractioned in 3 or 4 parts, every 6-8 hours. The secondary effects are sedation, mental disorders, dizziness, or decrease in muscle tone [1, 8].

Surgical therapy: DBS – deep brain stimulation, myotomy/selective peripheral denervation, intrathecal baclofen administration, neurosurgical procedures with radiofrequency catheter [9].

## Case presentation

Next, we present the case of a 43-year-old woman, living in an urban area, with static, sedentary activity requiring manual skills (in a bank). Her medical history reveals allergic asthma, chronic laryngotracheitis, and dysphonia of non-neurological aetiology.

The condition started in full health, approximatively 1 year ago (2016), when the patient came to the hospital for involuntary movements at the left upper limb (Figure 1, A). They were characterized as torsion and twisting of the arm, forearm and hand palm, around the axis, or forced and alternating pronation and supination movements, accompanied by painful, simultaneous and sustained contractions of the involved muscular clusters with the appearance of an abnormal position of the left upper limb. The contraction of the muscle was slow at the beginning then it became faster, lasted for 30 minutes and after this the slow and full decontraction of the affected muscles occurred, without any other maneuver for stopping the muscle spasm. At the emergency room, the medical staff administered to her a diazepam vial, and at home she did not get any treatment. After approximatively 1 month, the episode repeats with the same characteristics therefore the patient is hospitalized.



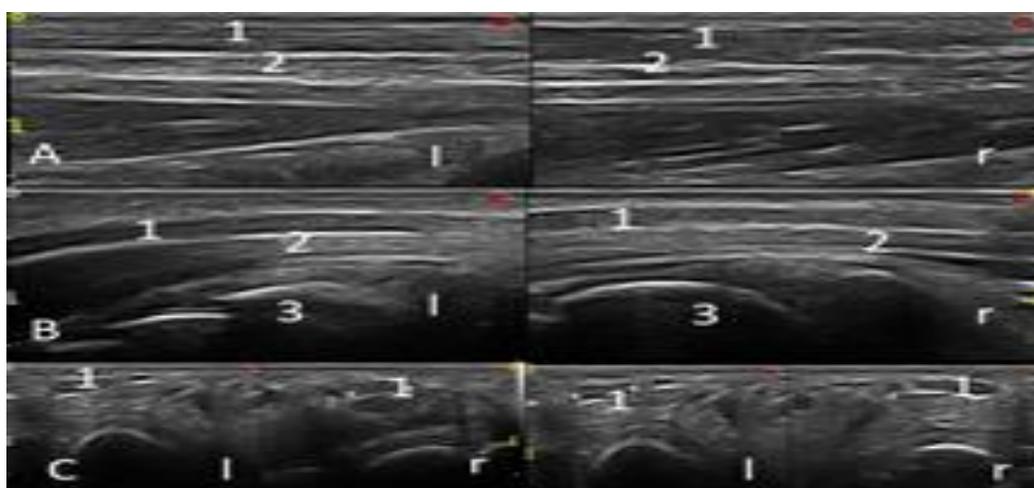
**Figure 1.** A. Involuntary movements and abnormal postures at the left upper limb, sagittal and frontal view. B. Normal Brain MRI, axial T2 weight of the posterior fossa and basal nucleus.

General and Neurological Clinical exam: no comparative motor deficits, walking could be performed but the patient presented a retro pulse tendency. The osteotonic reflexes were equal, also the abdominal skin reflexes, bilateral plantar flexion and normotonus. Romberg test positive consist in retro pulse and a tendency of lateral deflection, light left hemiataxia, normal superficial and profound sensitivity, conscious, cooperative.

Carried out laboratory tests: total cholesterol: 256 mg/dl, LDL Cholesterol : 180 mg/dl, triglycerides: 156 mg/dl, normal CBC, normal liver parameters, uric acid: 4,4 mg/dl, creatinine: 0,77 mg/dl,  $Ca^{2+}$  : 9,5 mg/dl, sideremia 82  $\mu$ g/l, Mg : 2.05 mg/dl, ceruloplasmin: 68 UI/ml, serum copper in normal parameters, serum potassium: 4,33 mmol/L, serum sodium: 144,4 mmol/L, C protein: 2,48 mg/dl, fibrinogen: 317 mg/dl, TSH: 3,726 UI/ml, T3: 2,73 ng/dl, T4: 0,81 ng/dl, ATPO: 0,77 UI/ml, alkaline phosphatase: 65U/L, prolactin:

33,79 ng/ml, ACTH: 28,6 pg/ml, serum cortisol: 17,3  $\mu$ g/dl, 25OH Vitamin D: 20.8 ng/ml, PTH: 56.7 pg/ml, normal values for antibodies anti acetylcholine receptors, normal values for anti-MUSK antibodies.

Imagistic evaluation using computerized tomography (CT) scan with contrast confirm normal brain; hereditary normal brain Magnetic Resonance Imagery-MRI with ANGIO MRI Magnetic resonance imaging performed in the skull, cervical and thoracic columns did not reveal morphological changes or structure in the brain or spinal cord. We used Philips Ingenia 3T, with weights of T2, T2Flair and T1. (Figure 1, B). Normal cervical and lumbar MRI. Normal left shoulder MRI. Also, musculoskeletal ultrasound performed at the involved limb as well as on the contralateral side revealed normal details concerning joint structures, median and ulnar nerves, flexor/extensor tendons and muscular compartment (Figure 2 - A, B, C).



**Figure 2.** Normal ultrasonographic structures. A, B – longitudinal, C – transversal aspects of the forearm and carpal tunnel. 1 – median nerve, 2 – flexor tendons, 3 – scaphoid bone, l – left, r – right.

EEG: alpha background rhythm, modulated in spindles, blocked at the opening of the eyes, accentuated by hyperventilation. Rare theta waves with diffuse distribution. No other paroxysmal graphic element.

EMG: conducted on the median and ulnar nerves at both upper limbs and on the peroneal, tibial sural and the superficial peroneal nerve on both lower limbs with normal aspect.

Genetic testing for DYT 1 gene was not conducted in this case inasmuch as the diagnostic and treatment guides for dystonia did not direct to this, because the illness debut was after the age of 30, and the patient had no familial history of dystonia.

## Discussions and Conclusions

Considering the age at the onset of the disease an important classification criteria of dystonia, having an important diagnostic and prognostic value, there are the following forms of the disease: infancy (birth to 2 years), childhood (3-12 years), and adolescence (13-20 years), early adulthood (21-40 years). At these age groups a possible cause can be identified and the disease can progress from a focal to a generalized form [1]. In the last form of the disease – adulthood (40 years and older) we can fit the patient, as she was 43 years old at the onset of the disease.

Depending on the body part affected the main types of dystonia include as subgroups the following forms: focal (one isolated region), segmental (2 or more contiguous regions), multifocal (2 or more non-contiguous regions), hemi-dystonia (half the body) and generalized (trunk plus 3 other sites) [1]. The blepharospasm, oro-mandibular dystonia, cervical dystonia, laryngeal dystonia, writer's cramp are types of focal forms of the disease, as cranial dystonia (blepharospasm with lower facial and jaw or tongue involvement) or bi-brachial dystonia are typical examples of segmental dystonia. So, the most affected by dystonia body parts are: the upper or lower cranial region, the cervical region, the larynx, the trunk, the upper or lower limbs, whether they are individually affected or in different combinations. The classification of dystonia is very important as it helps establishing both a correct diagnostic and an appropriate therapeutic strategy. It is well known, according to the guidelines, that segmental dystonia has as a first-aid therapeutic indication the botulinum toxin, while generalized forms of dystonia need both medical and surgical treatment [3]. Taking into account these classifications we can consider our case as being a focal form of dystonia. We also have to mention that a month before the onset of the involuntary movements of the left upper limb, the patient also presented an episode of dysphonia, described as a hoarseness suddenly occurred, that was labelled after investigations were performed, as having a non-neurological cause. Hypothetically speaking, one can think we are dealing with spasmodic dysphonia (SD), considered a focal laryngeal dysphonia, which appears as a consequence of some inadequate contractions of the laryngeal muscles, which also cause spasms of the vocal cords and lead to speaking dysphonia and swallowing

disabilities [8]. Sometimes, in what adults are concerned, SD can be the onset form of a focal dysphonia. So, from this point of view, we can consider that the patient has a multifocal form of dystonia, as she has two non-contiguous regions affected. The episode of dysphonia did not repeat, but the left upper limb dystonia appeared relatively fast in about one month, and from that moment on the patient received treatment. Taking into account that vocal disorders did not repeat, and the dystonic movements repeated at different time intervals, even after treatment was started, we would rather plead for the focal form of disease.

The temporal pattern has 2 subgroups:

1. Disease course can be static or progressive

2. Short-term variation can be:

- persistent-persist: the same extent throughout the day
- action-specific: occurs only during a particular activity or task;
- diurnal fluctuations: fluctuates during the day, with recognizable circadian variations in occurrence, severity and phenomenology;
- paroxysmal: sudden self-limited episodes of dystonia usually induced by trigger with return to pre-existing neurological state [1, 3].

According to the data existing in literature, the patient we presented can be considered as having a static form of dystonia, and if we take into account that the involuntary movements appear suddenly, have variable but limited duration (about 15-20 minutes) with total recovery to the initial state, we can consider it as a paroxysmal form of dystonia.

Clinical signs associated to this disease represent another classification criteria so, there are two forms: isolated (with or without tremor) and combined (with other neurological or systemic signs). Because, in our case the disease was not associated with other movements disorders such as myoclonus, parkinsonism tremor, etc. we can talk about an isolated form of dystonia. This type of isolated forms are also known as "pure" or "primary" forms of disease [1, 3].

The etiology of this disease is variate, there are different forms depending on the presence or absence of some neurological or systemic signs [1]:

- nervous system pathology: degenerative, structural (typically static) or no evidence for degenerative or structural lesions;
- heritability: inherited or acquired;
- idiopathic: sporadic or familial;

The patient we presented does not have antecedents of hereditary diseases and the neurological examination was normal, also the investigations performed did not show an eventual cause of dystonia, we can consider it an idiopathic dystonia.

According to the existing treatment guidelines the first treatment offered to the patients, as a first-line treatment, is the botulinum toxin that because of personal reasons she decides to refuse, so, as a consequence, we had to choose another type of therapy. The main classes of

drugs recommended in the treatment of different types of dystonia are: anticholinergics, dopaminergics, GABAergics (alprazolam, baclofen, chlordiazepoxide, clonazepam, and diazepam), muscle relaxants (baclofen, benzodiazepine, carisoprodol, chlorzoxazone, cyclobenzaprine, mataxolone, methocarbamol, orphenadrine) and others (carbamazepine, cannabidiol, cyproheptidine, gabapentin, lithium, mexilitine, nabilone, riluzole, tizanidine, zolpidem) [1]. At the beginning we administered in the evening 200 mg of carbamazepine, but after only three days of treatment we are forced to stop the treatment as the patient presented excessive drowsiness and she refused to continue the treatment. After this episode we administered 400 mg per day of Gabapentin, but from the same reasons we stopped this treatment too. Thus, we decided to administer 0.5 mg of clonazepam three times a day in association with 25 mg per day of Baclofen and we kept this treatment scheme until symptoms reappeared. Clonazepam is a benzodiazepine which exerts its action at the central level via GABA inhibition; important therapeutic benefits were obtained in cervical and secondary dystonia at drug doses of 3.7 mg/day for 10 months. Patients treated for five years with clonazepam had a better clinical evolution (Mitchell et al, 2004). In generalized forms of dystonia anticholinergics seem to be more efficient, but in our case the patient did not present a generalized form of dystonia. Clonazepam doses accepted for the generalized forms of dystonia are 1.5-12 mg/day [8, 13]. Baclofen is derived from gamma – aminobutyric acid (GABA), which decreases the excitability of the motor neurons in the central nervous system; because it attaches to the GABAs presynaptic receptors, the calcium influx is inhibited and also the release of glutamate and aspartate transmitters is reduced. So, Baclofen reduces spasticity in patients with dystonia and in those with spinal cord diseases. Important clinical results are obtained at a drug dose of 75 mg/day in patients with generalized form of dystonia. The recommended doses of Baclofen are 25-120 mg/day [8, 14]. After about 5 weeks, the patient had a new dystonic episode with the same clinical features, then we decided to increase the dose of Clonazepam to 1 mg three times a day still associated with 50 mg/day of Baclofen; this is a drug combination well tolerated by the patient. Because the patient presented another two shorter episodes, similar to those anteriorly described, we increased again the dose of Clonazepam, and thus, now, the treatment scheme is: 4.5 mg/day clonazepam and 50 mg/day Baclofen. Now the patient has a good evolution and she tolerates well the treatment. The most effective treatment consists of the injection of botulinum toxin. Considering that the patient refused this type of treatment we finally recommended Clonazepam and Baclofen because L-dopa is useful for the treatment of other forms of Dystonia (eg. Blepharospasm). As a particularity of the case, we can note the association with adjusted doses of baclofen in 50 mg/day to conventional clonazepam

therapy. Although there are quoted responses to clonazepam-only therapeutic doses, the particularity stems from the need for increasing the dose of clonazepam and the association with a central myorelaxant with effect on the dystonic muscles, in this case baclofen.

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