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Review Article

Dystonia and its Treatment in Ehlers-Danlos Syndrome

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Abstract

Ehlers-Danlos syndrome (EDS) is an inherited connective tissue disorder whose genetic defect is responsible for multiple clinical manifestations. Its physiopathology is explained by the mechanical characteristics of these tissues. They are very fragile. Their peculiar characteristics disrupt the signals sent to neurological centers by sensors scattered throughout the body. The consequence is a generalized proprioceptive disorder. One of the causes of this disorder is the fact that the basal ganglia do not regulate motor function correctly. This results in dystonia that has very important functional consequences. This dystonia is accessible to treatments with L-Dopa but also to oxygen and compression therapy.

Keywords: Hypermobility, Hereditary disease, Chronic pain, Fatigue, Parkinson's disease, Parkinsonism, disability, L-Dopa, Amantadine, Oxygen therapy.

Introduction

Over a time period of 23 years, we have examined more than 5,000 patients with EDS. We observed [1] clinical manifestations of dystonia in 66% of the cases. Its clinical pictures are misinterpreted, usually mistaken with psychiatric manifestations. Dystonia is almost never mentioned in the clinical descriptions of EDS Grahame [2], Malfait [3], Castori [4]. Pradeep Chopra [5] Chopra, Rhodes Island in the USA is an exception. Functional consequences of dystonia in EDS are important, contributing strongly to disabilities which often affect these patients, going against a widespread misconception of benignity which unfortunately remains attached to this pathology currently neglected and under diagnosed. A better knowledge of dystonia helps to better understand this syndrome and to make it better known and treated. General understanding of the mechanisms of symptoms of EDS has progressed considerably and allows for the implementation of more effective therapeutic strategies, including the treatment of dystonia and its functional consequences. We reported the first results in 2015 [6] and in 2016 (7). Since then, our experience has been considerably enriched, notably by the observation of spectacular, diffuse and violent demonstrations, dystonic crises that intrigue many neurologists and emergency physicians. This contribution is part of a worldwide movement of a new description of this disease which, for historical reasons, was poorly described, misnamed [8] and remains, very often, completely ignored in diagnostic discussions despite its frequency [9].

Semiological context of Ehlers-Danlos disease in 2018

EDS' Semiological context has evolved considerably over the last 20 years. The most apparent manifestations, those of the skin, first attracted the attention of the doctors. The dermatologist Nicolai Alexandrovich Tchernogoubov describes two cases at the Society of Dermatology and syphiligraphy of Moscow in 1882 [10]. The Russian will give his name to the disease. In 1900 [11] in Copenhagen, Edward Ehlers presented to the Society of Dermatology and Syphiligraphy in Copenhagen the case of a law student. Today, Ehlers-Danlos Syndrome (EDS) is defined as a generalized involvement of connective tissue. The lesion responsible for EDS is a hereditary modification of collagen, the armature which provides resistance and elasticity to all tissue. These two properties are essential for them to fulfill their role of protection against aggression and production of information from the sensors implanted within them and subjected to mechanical constraints at the origin of this information. The clinical expression of this syndrome is very variable from one individual to another, in the same family but also, in the same individual, from one moment to another,

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influenced by internal factors, particularly hormonal whence the greatest severity in women) and external, environmental (climate, trauma). The two historical symptoms, excessive skin stretchiness (73%) and joint hypermobility (96%), if common, have, in fact, little functional impact. The numerous other handicapping manifestations of the disease have long been obscured or considered as co-morbidities [12] whereas they contribute largely, by their diversity, to the diagnosis. These signs are the following: multiple pain (93%), fatigue (95%), sleep disorders (85%), motor proprioceptive disorders (87%), dystonia (66%), skin fragility (69%),dysautonomia (76%), hemorrhagic tendency (83%) respiratory dysfunction (79%), cutaneous hypersensoriality (69%) auditory (75%), olfactory (71%), vestibular (89%), binocular disorders (80%) %), significant digestive disorders (70%), significant oral changes (70%), bladder-sphincter system disorders (59%), dyspareunia (61%), obstetric (66%) and cognitive disorders (68%) contrasting with a clearly developed intelligence, affectivity and behavior disorders, some of which are related to the autistic spectrum. There is a link with learning difficulties (memory, attention, concentration, dysgraphia, dyspraxia, dyslexia) that are particularly common. These memory disorders are of great concern to patients who fear Alzheimer's disease with which they are very familiar because of its media coverage. In our experience, we have never seen an evolution from a patient with Ehlers-Danlos syndrome to an array of Alzheimer's disease and we reassure them on this point. The most common clinical presentation is "astheno-algic" associating a very important fatigue and multiple and rebellious pains. Women are significantly more symptomatic than men and represent 80% of patients in consultations dedicated to this syndrome. The presence of five of these 9 signs is sufficient to assert the diagnosis of Ehlers-Danlos with a specificity of 99.10% and a sensitivity of 98.63% [13,14]. Absence of a criterion (including hypermobility) cannot eliminate it [15,16]. They vary from birth to the end of life. Some may disappear, others may occur, more or less quickly, on the occasion of traumatic events (road accident for example) or hormonal events (puberty, pregnancy). Observation of identical family cases, with symptoms expressed to a greater or lesser degree, is the proof of this disease's hereditary nature, which, in our experience, is found in all children of an affected patient. Several classifications have been successively proposed by the geneticists, distinguishing 5 forms according to Beighton [16], 11 in Berlin [17], 6 in Villefranche [18] and, finally, 13 recently in New York (12), according to collagens' mutations. In practice, the found mutations relate to forms considered rare or very rare, clinically difficult to distinguish. In the common form (wrongly reduced to a so-called hypermobile form) which represents, in our experience, all our cases, there is no genetic test. Skin histology, especially electron microscopic examinations, widely used in Belgium [19] can contribute to a diagnosis that remains primarily clinical.

Dystonia in Ehlers-Danlos syndrome

Its clinical expression varies and is probably only the visible part of more diffuse, deeper muscle manifestations. To illustrate this for our patients, we compare the phenomenon of an iceberg of which we see the emerging part but, whose essence is immersed and invisible.

Figure 1: North pole: Gulls on an iceberg emerging very little (picture Claude Hamonet)

North Pole: Gulls on an iceberg emerging very little

Its detection by way of questioning the patient is not always easy, because often accustomed to these "muscular jerks" since childhood they consider it "normal". The presence of a parent or relative at the time of the exam is very important. In EDS, we have identified the following dystonia signs:

- •Involuntary segmental muscle contractions: hemiface contractions by jerks or persistent with tension, and blepharospasm. They can also occur on the anterior thigh (reminding the vibration of a mobile phone in the pocket of pants), the forearms but also to the hands (short muscles and long muscles), the shoulders, the neck or the back.
- Abrupt movements such as bursts of the shoulders, forearms, hand, head, lower limbs or larger movements with collision with an obstacle or imbalance, which may cause falls.
- Trembling fingers, at rest, hands outstretched.
- Trembling movements or jerky hands, resulting in clumsiness or ineffectiv gestures, sometimes occurring in overwhelming crisis during several minutes at the level of both hands, for example;
- When holding a pen or pencil to write or draw, the fingers are tense and curled up, both because of dystonia and to stabilize hypermobile fingers. W.
- Intermittent muscle contractures described as a feeling of painful hardening, rigidity, curbing movement, cramps, being "stiff".
- Permanent contractures, forced flexion of the wrist and fingers, flexion and adduction of the foot, very difficult to reduce and resistant to physiotherapy posture sessions, sometimes receding at night.
- Repetitive, incessant movements of flexion extension of the foot and knee while seated if feet are in contact with the ground.
- Repeated alternating movements of great amplitude,

flexion-extension of the trunk and lower extremities, occurring by seizures, as we observed in a 6-year-old girl. They disappeared completely under treatment with L-Dopa.

- Diffuse contracture attacks associated with neurovegetative type manifestations, often referred to as "spasmophilia";
- Diffuse tonic seizures in the lower extremities with alternating violent movements, increased by attempts of forced immobilization;
- Hemi-body or whole-body tonic seizures with, sometimes, attitudes in opisthotonos and possibility of wounds or hematomas facilitated by the delicacy of the skin and the vessels' great fragility.
- At night, there is the "Restless Legs Syndrome" with movements, sometimes wide and violent, especially of lower limbs.
- Bruxism, which we often encounter in Ehlers-Danlos syndrome.

There is, on the contrary no phenomenon of the gear wheel and gait is very different from the "small steps" with difficulty starting and trampling seen in Parkinson's disease.

We observe, in current practice, three types of clinical pictures: discrete forms, inconstant and without apparent functional consequence, forms of average intensity, almost permanent in their clinical expressions accentuated during crises, with functional repercussions and, finally, forms that we will describe as spectacular and severe. These may be resolutive transient episodes, this is the most common case, elsewhere, they persist for a long time, sometimes over several years, in some of our patients. These manifestations can be triggered by the occurrence of pain during a painful EDS attack or by contact with the needle during the intramuscular injection of a "trigger zone" such as we have often observed during treatment with local injections of lidocaine. Palpation during clinical examination can cause the same effects. These dystonic contractions may cause partial or complete dislocations of the shoulder, fingers, hip (when walking with painful blockages indicating a walking orthosis with articulation at the hip), of the patella or jaw. The duration of these manifestations of dystonia is usually brief, but they can last for days, weeks, months or, very exceptionally, years, as we have seen in a few cases. In other cases, they persist more and may appear as definitive, without solution for the moment, escaping the effects of anti-spasmodic. Role of dystonia and generalized dysproprioception, is difficult to distinguish in clinical tables of pseudo-paralysis that we regularly observe in these patients. Transient, sometimes accompanied by tingling, diffuse or persistent, pseudo-paralysis may sometimes be definitive. They are segmental, interesting a hand, for example, or have paraplegic topography, hemiplegic, even quadriplegic. In some patients, wearing of compression garments specially adapted for this syndrome, removes the functional discomfort.

New survey on the prevalence of dystonia in Ehlers-Danlos syndrome

We have, using previous clinical criteria, looked for signs of dystonia in the 88 patients examined between September 8, 2017 and December 13, 2017 and diagnosed with EDS. 80 of them were women, which confirms the greater severity for them. They ranged in age from 5 to 77 years with a high prevalence of adults: 54 of them (61%) were over 30 years old. Fifty patients (56, 8%) have clear signs of dystonia. These figures are close to those of our previous publications (1), especially if we include forms with discrete manifestations, mainly nocturnal.

Pathophysiology and mechanism of symptoms

The common trait in all these patients is connective tissue damage and changes in its biomechanical characteristics responsible for excessive brittleness but also, stretchability, increased possibility of crushing with a decreased elasticity. Proprioceptive syndrome is omnipresent in Ehlers-Danlos syndrome. It was already implicitly described by Ehlers in 1900 [11]: ("Gait is somewhat ataxic", "Patient often suffers from spontaneous knee dislocations which must be corrected while walking." We believe that connective tissue damage is responsible for all the symptoms complained of by patients with EDS including pain, fatigue, changes in head and trunk, digestive tract or bladder's motor skills, and in a general way, hypersensoriality. However, it is necessary to agree on the meaning of the proprioception. This term, designating the "proper feeling of one's own body", is usually used in neurology in the narrow sense of the semiological expression of an involvement of the medullary pathways of the so-called "deep" sensibility (sense of position of the body). This concept has been broadened, particularly under the influence of Alain Berthoz, a neurophysiologist [19]. Proprioceptive syndrome appears as a global proprioception disorder of the sense of movement that Berthoz [19] calls the sixth sense. In the context of EDS, this notion of proprioception takes on a wider dimension, that of "self-perception", "to exist", "well-being" or " uneasy feeling " through the distorted sensations of his internal body, his exteriorized body, the body's interfaces with his environment, luminous, sonorous, fragrant, spatial and social. this includes musculotendinous, cutaneous, olfactory, vestibular hypersensoriality. This concept, generalized to all manifestations of Ehlers-Danlos syndrome, has the immense advantage of allowing a simple physiopathological conception, understandable by patients, that guides the choice of treatments and therapeutic education. In the case of dystonia, the poor quality of the information provided to the basal ganglia by all the sensors necessary for a good regulation of motor control (accompaniment of the voluntary movement) and the treatment of sensorimotor information, including oculomotricity, is responsible for an anarchic regulation of which one aspect is the occurrence of motor activities in times of inaction. Another possible consequence of dystonia is the exacerbation of fatigue, due to the many anarchic muscular contractions which are inefficient but consume energy, but also to a misleading distortion of the sensations of a body perceived as tired and incapable of exertion.

Dystonia treatment in Ehlers-Danlos syndrome: the positive role of L-Dopa

In EDS, treatment aims to prevent complications related to tissue fragility and improve proprioception. Various symptomatic treatments (pain, sleep, bladder instability, gastro-oesophageal reflux ...). An additional contribution: Oxygen, has been shown to be very effective on several symptoms, including dystonia, raising

the hypothesis of the role of inadequate cell oxygenation through poor diffusion of oxygen through interstitial tissues and small vessels.

Dystonia benefits from a specific treatment using antiparkinsonians. At first, encouraged by Pierre Cesaro, neurologist [6], we chose the Amantadine [6] successfully. The temporary shutdown of its commercial distribution in France has led us to use Levodopa, the effects of which have been more frequent and more lasting. The chosen dosage is very low: 62.5 mg three times a day. In recent months, to simplify drug intake, we prescribe 125 mg, extended-release in the morning and 62.5 mg in the evening. One to two intakes per day at 62.5mg are sometimes sufficient to achieve effectiveness. This dosage can be increased and even doubled during dystonia attacks. Efficiency is fast - a few days.

A prospective, questionnaire-based study of 50 people with Ehlers-Danlos Syndrome comparing their symptoms before treatment and after one month of treatment. 25 people answered the questionnaire. 22 questionnaires were usable. Three people stopped treatment because of the side effects. Positive responses to treatment appear after a delay of 5 to 20 days. The effects on dystonia are the most marked (82% improvement, 59% significantly). The most obvious sign of effectiveness is reduction of involuntary contractions ("bursts"), tremors, especially during voluntary movements or the maintenance of a position (mainly the upper limb).

Rapidly, within a few weeks, there are other positive effects, on muscular and articular pains, on the ease and fluidity of voluntary movements and proprioception. At the same time, inconsistent but frequent effects appear on fatigue, sleep quality, cognitive disorders, autonomic dysfunction and constipation. All these beneficial effects are more durable with L-Dopa than with Amantadine, with which we had observed relapses notwithstanding treatment. Patients are observant about their treatment; its stopping provoking very quickly relapse of the symptoms. It is remarkable, as is common in this disease, to observe a positive result with low drug dosages. Side effects are rare (gastric pain, diarrhea, insomnia, diffuse feeling of discomfort) and usually transient, but they can deter and often stop treatment.

Role of oxygen therapy appears to be positive as we have seen during a generalized crisis in the waiting room of our consultation. Intensity and permanence of contractures (triceps in particular) can lead to intramuscular injections of botulinum toxin and even, if unsuccessful, to functional surgery, as we have observed.

Self-observation of a 28-year-old patient on L-Dopa treatment for 28 months. Answers to a questionnaire

- - What dosage? 62.5 mg morning and evening.
- Have you had positive results? Yes, and immediately. At the first dose, my pain (bone, muscle, cutaneous) decreased by half. That was more effective than any analgesic tablet I had already tested: Paracetamol, codeine, opiates.
- On involuntary movements? Yes, positive effect on the bursts during the first phases of sleep (arms, legs). I even had bursts of the body, which woke me up and hurt me. These are much rarer and less strong. Decrease in involuntary movements of hands (hands that open on their own and let go of objects, muscular starts) and legs (restless leg syndrome, even awake). I also had very strong arm and leg tremors for no apparent reason. They disappeared with Modopar. "
- On muscle contractures? "Yes: Before Modopar, my hands and legs were sometimes blocked in certain positions, under the effect of muscle contractures impossible to remove, sometimes resulting in subluxations or dislocations. My hands sometimes remained closed and I could not do anything about it. Or my leg was contracted. I notice a decrease in muscle stiffness. "
- On the pains? "Yes, Modopar has more effect than an analgesic, and I cannot stop it. If I miss a dose, pains come back and are overwhelming and untenable. "Back and spine pains are improved too."
- On Fatigue? Yes, there is a decrease in fatigue throughout the day.
- On dislocation and subluxation? "There is better recovery of joint function after dislocation or subluxation"
- What effects on sleep? "I have better sleep"
- Other effects? "I regularly feel electric shocks and peaks of pain in the limbs and body as if I was plunging a needle into the muscles. Modopar has reduced the intensity of these pains and they have become rather rare."
- Are these effects lasting? "Yes, since the day I took the Modopar more than two years ago."
- Have you observed adverse effects? "Yes, at the beginning of the treatment, I had a week of sleeplessness, sleeping only three hours a night with deadly nightmares". I was psychologically tense, hyperactive"
- Comments. "I have been able to suppress many medications in recent years, but Modopar is the one I cannot live without."

Discussion

Some mechanisms of action of L-Dopa in EDS are directly related to the motor regulation improvement which is done through less tension and braking to muscular displacements, therefore with less triggering of painful sensations and energy saving [20].

It can also have a direct effect on fatigue: it is known that when L-Dopa is prescribed to patients in coma, some of them regain a higher degree of vigilance [21]. Other studies have been done in patients with narcolepsy [22] suggesting a role of dopamine on alertness. Dysautonomia is also improved (59%), and again, a role is possible on fatigue [23].

Conclusion

Use of anti-Parkinson's drugs in Ehlers-Danlos syndrome is often misunderstood by doctors because of their lack of knowledge about Ehlers-Danlos disease and its physiopathological mechanisms. The published descriptions remain limited, most often to cutaneous-articular historical events [2-4] and neglect

many elements of the clinical picture of this multi-systemic disease and therefore multi symptomatic. Thus, as for dystonia, cognitive, vesico-bladder-sphincter, psycho-affective disorders (in connection with autism and Asperger's disease) are not mentioned. The fact that this disease is frequent, instead of facilitating diagnosis, seems to hinder it. Clinicians who know how to recognize EDS are even accused of over-diagnosis. Psychiatrization remains, unfortunately frequent [24].

Identification of dystonia is an additional contribution to this disease's organicity if it is not confused with "hysterical" manifestations. The undeniable effect of the DOPA constitutes a strong argument in favor of these manifestations' organicity.

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