

Ehlers-Danlos Syndrome (EDS) a Diagnostic Trap for the Neurologist, an Iatrogenic Risk for the Patient

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Abstract

Ehlers-Danlos syndrome is a frequent systemic, hereditary connective tissue disease with multiple and deceptive clinical expressions, leading to numerous diagnostic errors, notably in neurology. The successive descriptions of its signs by Dermatologists (Tschernogobow, Moscow 1892, Ehlers Copenhagen, 1900), Rheumatologists (Bywaters, 1967), and Geneticists (Beighton, Cape-town, 1969). Medical practice today, centered on organ pathologies, is unlikely to recognize a disease which, through the connective tissue, affects them all. This was compounded, at the time of triumphant biomedicine, by the absence of biological marker in the most common forms of this syndrome. The diagnosis is clinical and is based on the association of pain, fatigue, proprioceptive disorders, joint hypermobility, knee flexor retractions in children, thinness and fragility of the skin, vasomotor disorders, hemorrhagic syndrome, hypersensitivity including hearing, olfaction and vestibular responses, digestive disorders, combined with other familial cases. Diagnostic confusion most commonly encountered in neurology is with multiple sclerosis, stroke, muscular dystrophy, neurological consequences of disc disease, neurological bladder, seizures with spectacular manifestation of dystonia which is frequent in this syndrome. Confusion with a mental pathology (depression, bipolar syndrome, anorexia nervosa, somatization) leads to hospitalizations and is frequent. They are favored by the presence of cognitive disorders, coexisting with high-performance intellectual capacities. The peak symptoms in adolescence, their more intense expression in women (80% of consultants) is probably an incentive to attribute a psychosomatic character to the encountered symptoms. A link with autism exists. The possibilities of cerebral arterial aneurysms accidents, possible in all forms of the syndrome and Arnold-Chiari syndrome must also be known to the neurologists.

Keywords: Ehlers-Danlos; Joint Hypermobility Syndrome; Iatrogeny; Neurology; Psychiatry; Multiple Sclerosis; Proprioceptive Disorders; Chronic Pains; Cognitive Disorders; Asthenia; Fibromyalgia; Dystonia; Autism; History of Medicine

Introduction

Ehlers-Danlos syndrome has undergone a major overhaul of its semiology over the last 10 years and the diagnostic criteria have evolved considerably [1-8]. This development explains that EDS symptomatology, very diversified, confusing and deceptive for the doctor who does not know it can lead to misdiagnosis of neurological or psychiatric illnesses with serious iatrogenic consequences for invasive explorations such as lumbar puncture, or medical or surgical treatment at risk for these patients with particularly fragile tissues.

A brief 124-year reconstruction of the chaotic history of Ehlers-Danlos syndrome

If we trace this disease's description history [9,10] through the successive interests of dermatologists, rheumatologists (articular hypermobility), geneticists (research of collagens mutations and genetic classification), we better understand why such a frequent pathology is never diagnosed or with an average delay of more than 20 years [11] after the onset of the first signs.

The most apparent manifestations, those of the skin, first attracted the doctors' attention. Dermatologist Nicolai Alexandrovich Chernogubow described two cases at the Society of Dermatology and Syphiligraphy of Moscow in 1882 [14]. The Russians would give his name to the disease. In Copenhagen in 1900 [15], Edvard Ehlers presented the case of a law student to the Society of Dermatology and Syphiligraphy, Copenhagen. In this description, there are already three key signs for the diagnosis: skin's frailty, joint instability and hemorrhages, the hereditary side is also evoked. Unfortunately, these descriptions have been forgotten or, perhaps, never been read. Then Danlos' error occurred: He described, in 1908, to the French Society of Dermatology and Syphiligraphy a case of elastic pseudo xanthoma [16] with a very important cutaneous stretch, unusual in the syndrome of Ehlers-Danlos [17]. Unfortunately, this sign described as "extraordinary" by Danlos is still, wrongly, retained as a necessary criterion for the diagnosis by some doctors. Beginning in the 1950s, two other emerging specialties became involved in this disease: Rheumatology and Genetics.

On the Rheumatologists' side, there was a growing idea that it was not a disease but a curiosity of nature, another way of being "normal" [18], Both "monstrous" and "amusing", which leads to a career in circuses or in freak shows [19]. They retained the name of benign articular hypermobility [20]. This notion of benignity is still very often attached to this pathology, the many other associated manifestations being systematically "tilted" into psychopathology. Or, they are labeled fibromyalgia. Indeed, due to a "casting" error, French and American rheumatologists, ignorant of the Ehlers-Danlos syndrome, chose several signs of EDS (rebellious pain, fatigue, sleep disorders, multiple painful points, female predominance), to "create" a new pathology.

As for geneticists, the hereditary character was recognized as early as 1949 [21]. He very quickly led to classification trials in types that linked a collagen mutation to a clinical picture. Initially three forms were identified by Barrabas [22], then 11 in Berlin [23], 6 in Villefranche [24] and 13 in New York [25]. The clinical differences between the types described are slim and their resemblance is evident. Genetic tests, identified for a few forms, considered rare or very rare, are inaccessible in routine clinical practice. Moreover, their reliability is not absolute. They are absent [23-25] in the type that covers almost all the cases encountered. The proof of the hereditary character is, on the other hand, very naturally highlighted by finding other cases in the concerned families. The transmission exceeds very clearly the forecasts of the Mendel's laws. In our personal experience, the presence of clinical signs of connective tissue disease, suggestive of Ehlers-Danlos syndrome, is present in more than 4000 people diagnosed in 22 years in all children whose at least one parent is affected.

Ehlers-Danlos diagnosis today, only rests on clinical arguments that are sufficient

Several clinicians, Rheumatologists such as Rodney Grahame (London, 3, 4) and Bravo (Santiago de Chile, 5), Algologist like Pradeep Chopra (USA, 6), Psychiatrist like Antonio Bulbena (Barcelona, 7) or Physical Medicine and Rehabilitation Specialist (8, 9, 10) completely renovated the description of this pathology, starting from a new look at the description of the symptoms by patients and their families. In a recent study (10) of 636 patients from a cohort of 2677 patients (80% women), we showed the following signs: multiple stubborn pain (93%), severe fatigue (95%), sleep disturbances (85%), hamstrings retractions (54.2%), motor proprioceptive disorders (87%), dystonia (66%), joint hypermobility (96%), skin frailty (69%), enhanced skin stretchiness (73%), neurovegetative disorders (76%), bleeding tendency (83%), respiratory manifestations (79%), hypersensitive skin (69%), hearing (89%), inner ear vestibule (89%), binocular vision disorders (80%), major digestive disorders (70%), important oral conditions (70%), vesico-sphincter disorders (59%), dyspareunia (66%), obstetric problems (66%), cognitive disorders (68%), contrasting with clearly developed intelligence, emotional and behavioral problems, some of whom are related to the autistic spectrum disorders [26,27]. Twelve of these criteria were selected as particularly significant: joint pain, fatigue, proprioceptive motor control disorders with joint instability, thin, transparent, fragile skin that does not protect against electrostatics, joint hypermobility, retractions of knee flexor muscles in children, extremities vasomotor disorders wrong-

ly suggesting Raynaud's syndrome, cutaneous and subcutaneous hemorrhages (bruises), hyperacusis, constipation, gastroesophageal reflux. The presence of five of them is sufficient to confirm the diagnosis of Ehlers-Danlos syndrome (specificity: 99.10%, sensitivity: 98.63%). The absence of a criterion (including hypermobility) cannot eliminate this diagnosis. On the other hand, identification of the hereditary character with the discovery of other family cases (in the father or the mother (or both), the children, the collaterals in direct family connection with the person in whom the diagnosis is evoked) is a very important argument.

Diagnostic pitfalls for the neurologist

Because of the importance of pain and motor impairment, neurological diseases are among the most frequently encountered diagnoses in Ehlers-Danlos patients. The suspicion of non-organicity in front of a multiplicity of subjective symptoms, association with cognitive disorders and affectivity often orientate towards a psychiatric pathology, especially on the part of neurologists, due to the negativity of clinical and paraclinical neurological investigations.

Some pathophysiological elements for a better interpretation of the symptoms

The observed signs have two origins: tissue frailty (bleeding, healing disorders) and diffuse proprioception disorders. These proprioceptive disorders are related to the interoceptive and exteroceptive sensors message perturbations. These sensors are in a tissue which has a specific reactivity to the stimulations. This is true for skin that may show hyperesthesia or, conversely, does not transmit a burning sensation. This is also true for the bladder, which is very flexible and allows itself to be distended and does not send to the medullary centers the information on its repletion accompanied by the need to urinate. This may result in a chronic bladder retention condition. The proprioceptive disorder is generalized and concerns both conscious voluntary muscles and automatic motor function, neurovegetative control as well as binocular vision. Thus, people with Ehlers-Danlos syndrome have a very peculiar perception of their body since birth, which can complicate the diagnosis because they consider that "it is normal".

Multiple sclerosis

Multiple sclerosis is often evoked, due to motor, bladder-sphincter, swallowing, and vision disorders, pseudo-paralysis of proprioceptive origin and symptoms variability. The confusion is aggravated by the presence of signs (28) at the cerebral MRI (Figure 1) which are the result of EDS.

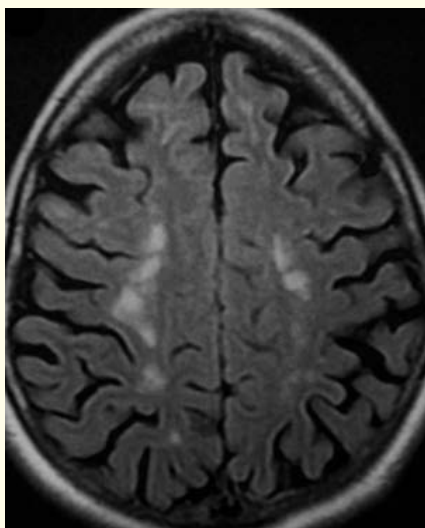


Figure 1: *Leucoaraiosis of the supra-ventricular region typically occurring in small rounded bilateral and symmetrical opacities in centro-semi-oval rosaries in Ehlers-Danlos syndrome.*

Lumbar puncture, which can cause a meningeal breach, is a dangerous gesture. The other dangerous gesture is the prescription of multiple sclerosis treatments, including cortisone which is contraindicated in this disease where there already is osteopenia.

Guillain-Barré polyradiculoneuritis is evoked in front of a clinical picture of diffuse motor deficits associated with paresthesia. Here again the danger is the lumbar puncture.

Stroke is often diagnosed in front of dysautonomic discomfort with a brief loss of consciousness which may be accompanied by a transient motor deficit. There are no signs of stroke in cerebral imaging. The danger here is the implementation of an anti-aggregation platelet therapy with a hemorrhagic risk.

The neurological consequences of vertebral lesions are often discussed. Disc squeezing, a consequence of tissue compaction due to Ehlers-Danlos syndrome, combined with pain in the lower limbs, often suggests root compression. The diagnosis can be discarded on the non-radicular topography of the pains, a normal Achilles' reflex, the absence of pain on the path of sciatica nerve in the Lassègue's maneuver. Surgery should be avoided because of its effects on pain and, more generally, on the symptomatology of the disease.

Elsewhere, it is very painful vertebral displacements which lead to a surgical solution of arthrodesis. The possible presence of Arnold-Chiari syndrome poses identical questions. In all these cases, surgery is difficult (bleeding, scarring and bone consolidation in case of graft).

Mitochondrial myasthenia in front of muscular fatigability and pain.

Bladder-sphincter dysfunction, of proprioceptive origin, is often confused with a neurological bladder and can lead to surgical gestures whose outcome, on such terrain, is uncertain.

Entrapment neuropathies and scaleni pass syndrome: Because of the tissues stretchability and their low resistance to compression, the ulnar nerve at the elbow, the median at the carpal tunnel, and the brachial plexus in the scaleni pass may be compressed or stretched. The solution is not surgical but orthotic: elbow pads, wrist orthotics, proprioceptive shoulder orthosis.

Muscular dystrophies are a common error of diagnosis, due to the diffuse nature of the pathology but also to the frequent presence of the lower limbs' posterior muscle contractions.

Small fibers neuropathies are evoked in front of the "neuropathic" character of the pains encountered in the SED.

Dizziness leads to poorly supported medication.

Dystonia is frequent [8], manifested by myoclonus or abrupt involuntary movements, leading to joint dislocations and joint blockages, tremors, a writer's cramp syndrome, and sometimes generalized contracture cramps, evoking historical descriptions Of Charcot. In this context, the question arises of the connection of hysteria with the symptomatology of the Ehlers-Danlos syndrome in which hypnosis is very effective. Dystonia may also be the cause of a diagnosis of Parkinson's disease as we have observed. Interpretation, again, is dysproprioception. It is important to recognize the organicity of the symptom because L-Dopa, with a low dosage, is sometimes remarkably effective [29]. In some cases, hypertonia is such that botulinum toxin injections are not enough. The use of functional surgery becomes necessary.

Epilepsy is sometimes evoked in the presence of large tonic seizures with pseudo absences, in the form of brief suspensions of knowledge, usual in EDS and poorly explained, of probable neurovegetative origin (POTS, voltage drop). The normality of the Electroencephalogram is a decisive argument.

Headaches can lead to difficult diagnostic discussions due to the diversity of their origins: migraines with aura and especially mixed headaches between headaches of cervical origin, algo-dysfunctional syndrome of the temporo-mandibular joint (ASTMJ), hypotension headache, cephalgia by spontaneous hypotension of the cerebrospinal fluid, POTS-related headache [30].

The question of pseudo-paralysis arises regularly in this pathology. This can be difficulty to perform a gesture such as taking an object or getting up from a seat. Patients describe the impossibility of realizing it despite their will to act. Otherwise, it is the sensation of an “absent”, “untraceable” superior member, as if he were “detached from the body”. In this case, an attempt movement creates pain and the “lost” limb is found but painfully perceived. In another case, it is a total motor and sensitive paraplegia during several years with a complete bladder retention, osteotendinous reflexes present and a normal medullary MRI. Some of our patients suffered several years from hemiplegia or paraplegia with an abrupt onset. The role of proprioceptive disorders appears as the probable explanation, but the physiopathological explanation remains to be found. These difficulties in perceiving one’s body are responsible for the sensations experienced by many of our patients who describe their bodies as “Alien to themselves”, as “the body of another” that they perceive as “detached from themselves.” These sensations disappear with the wearing of proprioceptive clothing specially studied for these patients to improve proprioception by compressing the tissues and improving their capacities to react to the mechanical changes. There is a great future for research in the field of the interactions between the body and the person.

Cerebral arterial aneurysms are one possible expression of tissue fragility in Ehlers-Danlos syndrome. They can be observed in all cases of Ehlers-Danlos disease and not only in the “vascular” forms for which a mutation of collagen C320L3A1 can be found. The discovery of an aneurysm or the notion of a brutal stroke in a young subject in the family leads to the search systematically by a cerebral MRI.

The diagnosis of mental illness with corresponding therapies is very common in our experience. The diagnosis of depression is one of the most usual. It is paradoxical for these people who, on the contrary, behave very “combatively” in the face of the encountered difficulties. The negative results of the Beck depression test, systematically applied in our consultation, confirm this point of view. The variation of the symptoms over time, the presence of phases of hyperactivity, lead to evoke a bipolar syndrome. Otherwise the diagnosis of schizophrenia is proposed. The importance of work memory disorders orients towards a clinical picture of Alzheimer’s disease that we never have encountered in our extensive experience. Difficulties in palatability and difficulty in swallowing, esophageal and stomach pain lead to dietary restrictions and weight loss, which are often referred to as anorexia nervosa and lead to hospitalizations in psychiatry.

The most common diagnosis presented in front of the usual clinical picture of asthenia and pain, increased or revealed at the time of adolescence in a female population (80% of the consultants), is “psychosomatic disorder” expressed by this formula, very often reported by our patients: “It’s in the head”. The diagnosis of substitution of fibromyalgia, in fact, implies a similar opinion on the part of the doctor who poses it. The occurrence of spectacular seizures of dystonia invariably leads to revive the Hippocratic view of hysteria.

The special case of autism deserves special attention [26]. A child psychiatrist, Vincent Guinchat, had the idea to use proprioceptive compressive clothing that our team developed for people with EDS [27]. Examination of several of these patients revealed signs of EDS: fragility of the skin, hemorrhagic tendency, joint hyperlaxity, constipation. The examination of the family also revealed cases of Ehlers-Danlos without autism among parents and siblings. These findings are related to behaviors that we observe in some children of parents with Ehlers-Danlos syndrome that lead to diagnosis of Asperger’s syndrome.

Difficulties in learning, dysorthographia, dyslexia, dyspraxia and cognitive disorders of Ehlers-Danlos syndrome: Cognitive disorders have long and are still rarely mentioned by authors who write about this syndrome. They are very real and are present in 68% of our patients [10]. They are responsible for academic difficulties [31] and later for work exclusion. Their presence justifies the search for signs in favor of the Ehlers-Danlos syndrome for a better therapeutic and pedagogical orientation. They contrast with an intelligence evaluated very much above the average for the age group.

Conclusions

Ehlers-Danlos syndrome appears today as a frequent pathology with multiple and misleading clinical expressions, resulting in numerous diagnostic errors, notably in neurology. This diagnostic hypothesis must be evoked by the neurologists and discussed in particular in the following cases: suspicion of multiple sclerosis, dystonia, severe proprioceptive disorders, intense and polymorphic pain syndrome,

severe dysuria, arterial cerebral aneurysm, Arnold Chiari syndrome, joint hypermobility, flexor muscle contraction in a child, carpal tunnel syndrome, cognitive impairment, anorexia nervosa, autism.

Diagnosis remains clinical, in the vast majority of cases, in the absence of biological marker. It is based on a significant grouping of seemingly disparate signs which have a common unity: expression of a structural peculiarity of the connective tissue. This alteration of the connective tissue is hereditary transmitted to all children whose parents are affected. It is therefore not only beneficial to avoid dangerous treatments, but also to inform people with the disease that they are transmitting the disease.

Conflicts of Interest

Authors declare no conflicts of interest.

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