

## Anesthesia and Ehlers-Danlos Syndrome (EDS)

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*Ehlers-Danlos syndrome is not or poorly known to doctors, anesthetists and surgeons. This lack of knowledge exposes patients to therapeutic accidents that can be prevented. This inherited connective tissue disease, which combines tissue fragility with a major proprioception disorder, causes very paradoxical reactions with local anesthetics such as xylocaine. Very often, it is ineffective as anesthetic while it sometimes has a spectacular and immediate effect on chronic pain and proprioceptive disorders. Hemorrhagic risk in this disease is considerable and underestimated imposing caution in the way such patients are treated. Lack of protection of peripheral nerves and hypermobility increase risks in positional paralysis thus necessitating positioning precautions during anesthesia.*

**Keywords:** Ehlers-Danlos, Hemorrhages, Local Anesthesia, Surgery, Tissues Fragility, Lidocaine, Odontology, Obstetrical Accidents, Iatrogeny, Dysproprioception, Hereditary Disease.

**Introduction**

Ehlers-Danlos syndrome has had many avatars since its first descriptions by Tchernogoubov in Moscow in 1892 and Ehlers, Copenhagen, in 1900 [1,2].

Frequently, however, it is diagnosed very late, confused with other diseases or labeled as fibromyalgia, because of historical confusion that led rheumatologists to give this name to authentic Ehlers-Danlos syndromes for they did not know its symptomatology [3-5].

EDS is hereditary, but without effective genetic testing usable in daily practice. In most cases, it is transmitted, as we have seen in our clinical practice of more than 5000 patients, to all children of a parent who suffers from this illness. Its severity varies drastically, some patients may experience few or even no symptoms, at least in the beginning of life [6]. Histological support of the disease is a particular alteration of the connective tissue with a structural modification of the collagen tissue which has two consequences, explaining the physiopathology: a very great fragility of all tissues (including bone) and a generalized syndrome of dysproprioception. This dysproprioception has its origin in poor quality signals sent to the neurological centers of regulation of voluntary motor skills, automatic motricity and the neurovegetative system. Indeed, the excessive stretchability, the lower resistance to crushing, the

loss of elasticity of the connective tissues disrupt, in the sense of hypersensoriality, most often, but also hyposensoriality, sensors scattered in the whole body. The structural features of the connective tissue cause changes in the diffusion of molecules due to intestinal and vascular hyperpermeability but also their stagnation in distensible interstitial spaces, transported by little contractile microvessels. Tissue fragility affects all tissues of the human body causing hemorrhages which are difficult to control, tears, ischemia sometimes gangrenous, disorders of healing. These elements have an impact on local and general anesthesia and on the conduct of operative procedures and resuscitation. These tissue behaviors concern all Ehlers-Danlos syndromes and not only certain clinical forms of the disease, especially those which have been called "vascular".

The widespread ignorance of this pathology exposes patients suffering from EDS to significant risks during surgical procedures. Appropriate knowledge is required for relevant professionals in dentistry, obstetrics, surgery, including, ophthalmologists, ENT specialists, orthopedic surgeons, urologist surgeons, plastic surgeons and vascular surgeons.

**Screening and Clinical Diagnosis of Ehlers-Danlos Disease**

Diagnosis is easy and can be made by a simple clinical examination on the association of a grouping of suggestive clinical signs and, if we know the family context, of the demonstration of other familial cases, proof of the hereditary character. This screening should be systematic before any surgery and delivery (Figure 1).



“A mathematical modeling of the signs made it possible to establish that the presence of 5 signs, on a list of 9, makes it possible to pose the diagnosis with a sensitivity of 98,0% and a specificity of 99,6% [7]. These events are significantly more marked in women than in men [7].”

1. Joint and periarticular pain, across multiple locations, variously distributed (neck, shoulders, elbows, wrists, fingers, back, pelvis, hips, knees, ankles, feet), type “neuropathic” or, brief and very violent, variable in intensity (often very strong) according to the localization, usually evolving by crises on a continuous background, aggravated, with often a shift to the following day, by physical activity and may persist for a long time.
2. A significant feeling of fatigue, present at awakening, with impressions of heaviness of the body, exaggerated during unpredictable crises, with sometimes somnolence attacks. Fatigue is very often considered by patients as the symptom responsible for the largest number of disability situations.
3. Disorders of voluntary movement’s control, of proprioceptive origin, with blunders, clashes of obstacles (“sign of the door”), walking deviation and sometimes falls.
4. Particular instability responsible for pseudo sprains, joint blockages, subluxations (including joint crunches) or dislocations.
5. A thinned skin, pale, transparent, revealing the forearms, the breast and the back subcutaneous venous network, soft to the touch, not protecting against electrostatic discharges resulting in sensations of electric shock at contact with metal objects (car door, caddy, physical contact with another person).
6. Particular hypermobility, more or less diffuse, which is maximum in childhood (put one foot behind the head, make large facial gap) and may disappear later or be masked by pain and / or muscle contractures in some joints. Its absence does not exclude the diagnosis. Retractions (sural triceps, hamstrings) can be seen, especially in children.
7. Gastro esophageal reflux can occur early in life (breast or bottle feeding.) and cause bronchial irritation.
8. Early bruises, occurring for minimal trauma, often unnoticed, or purpura.
9. Hypersensoriality that results in vertigo, resulting in changes in position of the head, compromising the postural balance and / or hyperacusis with a very fine perception of sounds and an intolerance to noise.
10. Other frequent manifestations suggestive of dysproprioception or tissue fragility contribute to the diagnosis. They are important to know, because of their interferences with paraclinical

instigations or administered therapies by anesthetists and surgeons.

11. Neuro-vegetative disorders are very common: hypotension but also hypertension, thermoregulation disorders, bradycardia or brutal tachycardia, discomfort with consciousness suspension (usually very brief).
12. Dystonia is frequent and can be at the origin of sudden movements, more or less widespread tonic crises, especially at the time of falling asleep, dislocations or subluxations [8]. A treatment with L-Dopa or its precursors allows, most often, a control of these symptoms. If this treatment is on-going, it should not be interrupted. In case of absence of treatment, and important signs of dystonia, one should not hesitate to treat. Oxygen therapy has also been shown to be effective on dystonia manifestations.
13. Respiratory manifestations are very frequent: effort dyspnea, respiratory crises, often painful whose origin is thoraco-abdominal with xiphoidal and costal pains, abdominal bloating limiting diaphragmatic excursion and abdominal muscles function already not very effective because of the connective tissue involvement. The starting point is often the presence of xiphoidal and / or costal pains easily resolved by xylocaine local injection in the painful areas. Proprioception, distensibility of the bronchial mucous membranes and the weak efficiency of the bronchial muscle contractions are responsible for stasis and congestion. The use of pulsed air associated with oxygen has been particularly effective in such cases. Functional breathing tests are usually normal [9].
14. Digestive manifestations are dominated by gastro esophageal reflux, constipation with the risk of occlusion that can be aggravated by the prescription of opioids. Elsewhere are episodes of diarrhea associated with swallowing disorders, dysphagia, nausea, vomiting, especially when taking medication.
15. Sleep disorders are important, marked by considerable difficulty falling asleep. Melatonin is usually very efficient.
16. Anxiety is an important aspect of Ehlers-Danlos patient’s behavior, which Antonio Bulbena has very well studied [10, 11]. It can be accompanied by a depressive reaction that is rarely major in these patients who have will to action and considerable dynamism. Neuroleptics, antidepressants cause, most often, a worsening of their proprioceptive syndrome. Venlafaxine, at a low dose, can help them.
17. Association Ehlers-Danlos and mastocytosis is very common. The consequences in terms of skin allergies (intolerance to adhesives, eruptions, pruritus) are often observed. Digestive intolerances (food or medication), and some respiratory manifestations are, perhaps, related to this mechanism. Antihistamines may be beneficial if they are well tolerated (risk of drowsiness).

#### **Ehlers-Danlos and local anesthesia, Paradoxical effects**

One of the aspects of Ehlers-Danlos Syndrome is that local anesthetics are often ineffective. The relative or absolute ineffectiveness of Xylocaine is observed in local anesthesia, spinal anesthesia epidural anesthesia and dental care. Injection supplements can improve the situation but not always. Diffusion of the product at too great a speed in very soft and highly permeable tissues is a possible explanation. This argument is supported by the observation of improvements brought on by the association of adrenaline and Xylocaine.

Though often ineffective in local anesthesia, local injections of

xylocaine may help reduce pain dramatically. The injected areas are: muscular trigger zones, easily identified by palpation, proximity of the tendons (injections made parallel to the path of the painful tendon, avoiding injecting into the tendon). A few drops of the product are often sufficient. The injection sites are multiple and involve the entire musculotendinous system as well as the ligaments (fibula). Thorax (xiphoid or “pain point of Ehlers, ribs) is particularly concerned. The results obtained go beyond the ephemeral effects of local anesthesia, they are immediate and can last several days, weeks, months or more. Pain disappearance is accompanied by a sensation of “recovering one’s body”, “no longer feeling like being crushed in a vise”. This tends towards an action on proprioception whose neurophysiologic mechanism is to be found. These injections (which can be repeated as soon as the effect wears off) must use thin, low trauma, needles, (hematomas, ecchymosis risks) and be preceded by the application, if necessary, of anesthetic patches (“Emla<sup>®</sup>”) because of the frequent cutaneous hyperesthesia. These pain sensations can exist at the level of the gingival mucosa but also genitals (especially during sexual intercourse) and are relieved by “viscous xylocaine” gels which, because of the thinness of the skin penetrates subcutaneously and relieves musculotendinous and costal pain. Xylocaine (“Versatis<sup>®</sup>”) patches have identical effects. The existence of dysphagia with retrosternal burning sensation may benefit from the ingestion of a teaspoon of the same gel before taking a food. This will also be used when placing a gastric tube by coating the gel probe before introducing it. This technique makes it possible to obtain better tolerance of the nasal probe during oxygen therapy.

### Should epidurals be formally contraindicated in Ehlers-Danlos syndrome?

Among the possible accidents, related to the fragility of the tissues in EDS, is the risk of meningeal breccia. This risk has led some medical practitioners to give up epidurals during deliveries. Labor in EDS patients is often very painful (hypersensoriality) and very prolonged because of dysproprioception. Uterus contracts, cervix does not open. This phenomenon is poorly known by obstetricians and midwives. The solution is to facilitate cervical dilatation. The risk of hurting the dura should not make physicians give up epidural. On the other hand, it must be done with caution and, in the event of a breach, one should not wait for the classical 48 hours necessary for a spontaneous repair, unreliable in EDS, and the “blood patch” technique must be applied quicker.

### Hemorrhagic risk in Ehlers-Danlos syndrome

This is the major risk that can be life threatening, especially during a colonoscopy, anticoagulant or antiaggregant treatment, abdominal or postpartum intervention. The diagnosis of phlebitis is difficult in EDS. Calves are often painful and contracted, triceps are retracted, and their stretching is painful. Venous scans give improbable results because of the tissues plasticity with, sometimes, false images of thrombosis. The choice of anticoagulants, if decided, must take this risk into account. Venous fragility is at the origin of punctures and infusions difficulties with hematomas. Punctures of arterial blood can cause arterial wounds difficult to control. Mucous membranes frailty can also cause major hemorrhages during esophageal, bronchial or especially intestinal endoscopies, which make it necessary to limit this type of investigation to the strict minimum, knowing that blood in the stool after vomiting or coughing up is widespread in Ehlers-Danlos syndrome. The placement of an endotracheal cannula also involves risks.

### Tissue Fragility and Positional Syndromes

Peripheral nerves are poorly protected by weak muscle and stretchable skin. This is responsible for the compression or stretching suffering of specific nerves exposed to direct compression (ulnar, external popliteal sciatica) or stretching (brachial plexus in the thoracic outlet). Protection of these risk areas and the careful mobilization and positioning of the upper limbs during general anesthesia can prevent this type of accident. We can compare the risk of dislocations (shoulders, hips) during the operative installation or during childbirth. In dental surgery, it is the jaw that can be dislocated. To facilitate the reduction of these dislocations, injections of Xylocaine into the tensest periarticular muscles have often positive results. This tissue fragility may cause serious perioperative lesions, such as organ rupture by a retractor during an intervention, for example the gallbladder. Wound dehiscence is very common requiring the use of non-absorbable suture left longer than usual.

### General anesthesia and Ehlers-Danlos syndrome

Several patients report premature awakenings during general anesthesia. This encourages more careful monitoring and re-induction of anesthesia if necessary.

### Conclusion

Tissue fragility and dysproprioception observed in patients with Ehlers-Danlos syndrome induce particular reactions to anesthetics, and, more generally, surgery. Responses to local anesthetics are surprising, ranging from inefficiency to body proprioception restitution with disappearance of painful sensations [12]. This offers new therapeutic options for a disease which is particularly resistant to treatment. Tissue fragility can be responsible for serious per and postoperative accidents dominated by hemorrhagic risks and wound dehiscence. The observed accidents occur as anesthetists and surgeons are not informed of the risks of a disease that is generally not diagnosed before surgery. Systematic screening is possible by clinical examination alone and should be systematic, this disease is indeed not uncommon<sup>2</sup>, probably affecting 2% of the world population.

**Conflict of interest:** The authors declare that they do not have a conflict of interest with the subject.

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