My Ideas that may not be well explained in my studies, videos or books, or that I want to highlight, due to its importance.

Importance of making the Ehlers-Danlos diagnosis.

Joint Hypermobility without symptoms is a good condition and not a disease. When there are also symptoms, it becomes the disease called Joint Hypermobility Syndrome, now called Hypermobile Ehlers-Danlos Syndrome (hEDS). This is very common and affects 40% of the population. These people may have a lot, little, or no joint hypermobility. It causes significant joint and extra-articular problems, which affect the quality of life of patients. It is not arthritis (there is no inflammation) and it is not an immune problem. It is a hereditary disease and as such, it can manifest itself from childhood. - By making an accurate diagnosis, the patient's pilgrimage from doctor to doctor is avoided, avoiding countless unnecessary laboratory tests and interconsultations. - It gives peace of mind to the patient, who finally has a definitive diagnosis, which explains his multiple problems. - It allows the specialist to differentiate Hypermobile Ehlers-Danlos, which is the most frequent, from Vascular EDS, which is the most serious and sometimes fatal. This can cause aneurysms and/or arterial and organ ruptures (rupture of the lung or gravid uterus). The diagnosis of hEDS is clinical and is confirmed by the Brighton Criterion. Since the causative gene is not known, it is useless to do a genetic study. 80% of the SEDh have Dysautonomia. Early diagnosis allows it to be treated and avoid further loss of memory and concentration, due to the fact that little oxygen reaches the brain, due to low blood pressure. Not being hyperlax does not rule out dysautonomia. 50% of dysautonomia's are hyperlax, the others are not. Remember that some are not very hypermobile and hardly notice it. The diagnosis of EDS and Dysautonomia should be suspected in a person with chronic pain, a history of sports injuries, sprains and sprained ankles, with chronic fatigue, drowsiness, headaches, fainting or near fainting and that many doctors have seen, without reaching an accurate diagnosis.

Cracking joints and arthralgias: It is common for patients with Ehlers-Danlos to have cracking joints. This does not harm anything and allows us to suspect that the patient has an Ehlers-Danlos (EDS). The noise would be due to ruptures of nitrogen bubbles in the joint.

Joint pain or arthralgias are frequent and sometimes the pain is severe and disabling. It is important to note that there is no inflammation, the joint is not red or hot. These patients do not have arthritis, nor do they have any immunological ones. They may have osteoarthritis, and even joint fluid, but not of an inflammatory nature. Osteoarthritis in these patients is early, erosive and more aggressive and generalized. What's more, if a

hypermobile person has a red and hot joint, he has two diseases, in addition to Ehlers-Danlos he has Gout, Lupus or Rheumatoid Arthritis, etc.

Fibromyalgia (FM). FM causes diffuse musculoskeletal pain, chronic joint pain, or muscle pain, difficult to pin down, frequently associated with depression or anxiety. Pain is described by the patients with words, such as burning, heartbreaking, with an important emotional charge. "Trigger points" have been described, but they have become less important, because they depend on the pressure that the researcher imprints on them. There is no inflammatory process and blood tests are negative. There is no marker for the disease. I made the diagnosis of FM every day when I was a professor of Rheumatology in the USA, for 30 years and I did not know about EDS. Now, since I have been back in Chile, 25 years ago and I work on EDS and Dysautonomia, I no longer make the diagnosis of FM, since in reality I think that all of them have Ehlers-Danlos and many also have Dysautonomia. They have the same symptoms and when studying the families, a dominant inheritance is noticed, in many cases. I give them the Brighton Criterion, which when positive confirms the diagnosis of hEDS. And I treat them as such. Some have joint crackles and may or may not have dysautonomia. It is common for my patients with EDS and/or Dysautonomia to tell me that their mother or aunt has FM, I tell them that they probably do not have FM, but EDS and Dysautonomia. I look at them and give them the Brighton Criterion and it is positive.

Many authors think that the association of FM and hypermobility is frequent, but I go further and think that they are the same disease.

Cervical and lumbar disc disease. In young people, they should make you think of EDS, since the discs are made of collagen. It is interesting to think that EDS patients have diseases of old age, at a younger age, due to failure of the collagen of all their tissues. This is why they may have early osteoarthritis, early bunions, osteopenia or early osteoporosis, umbilical hernias, inguinal hernias, hiatal hernias, varicose veins, etc. Crises of disc disease or hernias of the nucleus are repeated, sometimes an operation helps to get out of the acute problem, but the discomfort persists and the problem worsens over time. Bone pieces, osteophytes, appear that narrow the space occupied by the spinal column and Spinal Stenosis appears. This is characterized by severe low back pain when standing or walking and decreases or disappears when leaning on a tree, car or wall. The operation for spinal stenosis is beneficial, as it decompresses the pressure on the spinal cord.

Making an early diagnosis of EDS helps prevent disease. The person must admit that he has weak tissues and that he must protect and fortify them with exercises. For example, do not gain weight due to the danger of osteoarthritis of the knees and hips, especially if you have Genu Recurvatum (knees that go backwards when standing, misaligned). These patients are like a truck with a lot of weight and with misaligned wheels and poor-quality tires, due to

the collagen problem. Taking collagen does not work, but taking Folic Acid for life does seem to help.

Osteopenia and Early Osteoporosis, **in the EDS.** In our studies, these exist in just under 10% of patients, under 30 years of age. The interesting thing is that we have not seen fractures in them. This indicates that in the elderly, in addition to the decrease in bone density, there are other important factors such as vision failure, failure of reflexes, muscle weakness, loss of balance, etc. We suggest doing a densitometry from the age of 20. If it is done before, it is necessary to do a Volumetric Densitometry. Which is done at the Hospital of the Catholic University, in Santiago, Chile. If the diagnosis of Osteopenia or Osteoporosis and treatment are not made in time, you will reach adulthood with fractures.

All women of childbearing age, even if they are healthy, **should take folic acid (FA**) daily. This is in order to prevent open spina bifida that causes paralysis for life, in children if the mother becomes pregnant and is not taking PA, from 3 months before pregnancy. Because of this, wheat flour was fortified with FA, but it was of help only to the few women who eat a lot of bread. FA is part of the DNA of cells and hence its importance. The mechanism of helping collagen could be similar to its effect in preventing malformations in the children of women who become pregnant and are not taking FA.

The easiest thing to do is to buy the 1 mg FA at the pharmacy and take one tablet a day, for life. It has no side effects, since it is a vitamin B-9, which does not accumulate, does not require a prescription and has no side effects.

Respiratory and allergic problems. It is known that Ehlers-Danlos, hypermobile or not, are generally allergic and suffer from Asthma or allergic rhinitis. Others have Mast Cell Syndrome. Hypermobile people who smoke often end their days with COPD. This is why they are advised to quit smoking. A higher frequency of Long Covid has been described in EDS.

Digestive problems. These patients frequently present gastritis, reflux, irritable bowel and constipation. They have a slow bowel, which is called Gastroparesis, they can have severe constipation and, in some cases, even Megacolon.

Urinary problems. There may be incontinence, cystitis, recurrent infections, and irritative bladder. The latter benefits from pelvic floor kinesitherapy.

Failure of recent memory, failure of concentration and attention deficit. Hyperactive children usually have attention deficit, which should be treated as dysautonomia and not only with medications such as Ritalin, Concerta, etc. With hyperactivity, their blood pressure rises and they feel better. The parents of these children usually have dysautonomia. In adults with a late or poorly done treatment of Dysautonomia, brain damage would occur due to poor cerebral oxygenation, due to low blood pressure. This apparent brain damage is quite

resistant to treatment and is sometimes irreversible. Hence, it is advisable to start the treatment of Dysautonomia in young people and as early as possible and it must be well done and for life.

Joint hypermobility and dysautonomia. How are they related? Collagen deficiency in these patients extends to all tissues, and hence can cause many symptoms. But the most serious, I believe, is that the collagen deficiency in the venous wall produces low blood pressure, which decreases cerebral oxygenation and the appearance of dysautonomia symptoms, such as chronic fatigue, headaches, dizziness, and sometimes fainting and near-fainting. Ehlers-Danlos is the name given to the hereditary hypermobility disorder. Some people may be very hypermobility, such as contortionists, slightly hypermobility, or even non-hypermobility. In my study of 2,300 patients with dysautonomia, 51% were not hypermobility. So, not being hypermobility does not rule out dysautonomia. Now, if a person is hypermobile, they most likely have or will have dysautonomia, as it occurs in 80% of hypermobile individuals. Dysautonomia requires Ehlers-Danlos syndrome, with or without hypermobility. A lack of collagen in the veins is necessary to cause low blood pressure and poor cerebral oxygenation.

How to combat orthostatic hypertrophy (a tendency to faint)

• Positions to combat the symptoms of low blood pressure

- While standing, cross your legs.
- Squat.
- While sitting, bend over and put your head between your legs.
- While standing, put your foot on a chair.

• If you are experiencing near-fainting (presyncope)

- Lie on your back and raise your legs.
- Drink a glass of water with one or two teaspoons of salt.
- Take 1 tablet of Gutron (5 mg Midodrine).
- Remain lying down for 10 to 15 minutes.

Note: Syncope and presyncope are prevented by proper treatment of dysautonomia.

Autism spectrum disorder. It is common to find autistic individuals among those with EDS.

Depression and anxiety are common in these patients. The lack of an accurate diagnosis, the need to go from doctor to doctor, and multiple tests, which are usually negative, lead to frustration, anxiety, and depression. The help of psychiatrists and psychologists is recommended.

High frequency of these patients in all specialties. Since the frequency in the general population is so high (around 40%), it is easy to imagine that, in the waiting room of any

specialist, there will be at least 50% EDS. This is because the collagen problem affects all tissues, resulting in a myriad of symptoms. This problem exists in most countries, with a similar frequency. The downside is that there are no specialists interested in these patients. Therefore, through telemedicine, I have seen about 150 foreign patients from 23 countries since the pandemic began four or five years ago. I recommend that specialists review my suggestions in my book "Hypermobile Ehlers-Danlos, Dysautonomia, and Fibromyalgia." It can be purchased at my office and on Amazon. See www.reumatologia-dr-bravo.cl.

Eye conditions. Strabismus is common. Keratoconus is occasionally seen. It is little known that Ehlers-Danlos can also cause dry eyes (xerophthalmia) and dry mouth (xerostomia), as can Sjögren's, which is an immunological arthritis. Because Ehlers-Danlos is underdiagnosed, many patients are misdiagnosed as Sjögren's who actually have Ehlers-Danlos. Light blue sclerae aid in diagnosis simply by looking at the patient. Droopy eyelids are also characteristic of this condition. Fluodrocortisone is contraindicated in patients with glaucoma.

Temporomandibular Dysfunction and Bruxism. Temporomandibular joint involvement is common in these patients. It causes pain, subluxations, grinding, and functional impairment. It can lead to TMJ osteoarthritis and require surgery. Treatment is required by a maxillofacial specialist in treating patients with EDS, such as Professor Mariano Rocabado, in Santiago, Chile.

Skin Changes. The skin may be pale, smooth, velvety, and youthful, giving the person a younger appearance than their biological age. It can also be very lax, as in Classic Ehlers-Danlos, and may bruise easily and frequently and have severe scarring, such as keloids or papyrus scars. Lenticular moles, like lentils, may be present, which help guide the diagnosis.

Marfanoid habitus. 15% of EDS patients are tall, with long limbs and large feet. They sometimes have excavated (sunken) pectus, pectus carinatum (chicken keel chest), square shoulders, and prominent ribs. They are called Marfanoid because they resemble Marfan's patients. These are tall hypermobile people, due to an alteration in the fibrillin gene, who can be more serious, as they may have arterial problems and/or spontaneous lung rupture.

Scoliosis in Adolescents: Hypermobile. Ehlers-Danlos patients, whether hypermobile or not, can develop dorsal scoliosis.

Prof. Jaime F. Bravo, MD
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