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Chapter Five

Chronic Fatigue in Joint Hypermobility syndrome

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1

Introduction

Chronic fatigue (CF) is a frequent and disturbing symptom that affects significantly the quality of life of patients and can be seen in many conditions such as, chronic diseases, Depression, Chronic Fatigue syndrome (CFS) and Fibromyalgia (FM), between others. CF is also seen frequently in Joint Hypermobility syndrome (JHS), usually in young adults, especially in adolescent girls.

While referring to CF in the JHS, we will consider CF as a symptom and not as a syndrome, like in CFS. The CF in JHS is usually associated to Autonomic Nervous System (ANS) dysfunction. Considerations about CFS will be discussed in the differential diagnosis of CF.

When a physician sees JHS patients, they usually have had a long history of recurrent aches and pains and fatigue, which by then has become chronic. Since frequently they have seen many physicians and have undergone many tests, with normal results, and no clear diagnosis has been given and treatment has been ineffective, they usually also present some degree of fear, anger, chronic fatigue as well as depression. Since tissues are fragile due to the hereditary collagen alteration, JHS patients can have musculoskeletal as well as non-musculoskeletal symptoms. Collagen is the protein that forms the matrix of most tissues and gives resilience to tissues and organs. Multiple problems can arise depending of what happens to the collagen. If there is dilation of a tissue, the patient can have cysts, if it affects an artery it can develop an aneurysm, if a vein dilates it could give rise to varicose veins, if it affects the capillaries it will give capillary fragility and hematomas. Collagen wear and tear

will give tendinitis, tendon ruptures, muscular tears, hernias (abdominal, hiatal, herniated nucleus pulpous), early Osteoarthritis and early Osteoporosis. Symptoms from the locomotor system include recurrent sprains, arthralgias, tendinitis, bursitis, joint subluxations and back pain, between others. Symptoms derived from the involvement of other organs include, fragile skin with poor cicatrisation and abnormal scarring, uterine and rectal prolapse, mitral valve prolapse (MVP), myopia and even spontaneous pneumothorax, colon or gravid uterus rupture (these last two are not seen in JHS, but can be seen in Vascular Ehlers-Danlos syndrome, formerly called EDS type IV).

JHS patients frequently have symptoms due to Autonomic Nervous System dysfunction (Dysautonomia), characterized by: palpitations, lightheadedness, tiredness, dizziness, somnolence, poor thermostat regulation (usually with severe cold intolerance), chronic fatigue and

pre-syncope or syncope. In the past, palpitations and atypical chest pain in hypermobile patients were thought primarily to be caused by mitral valve prolapse (MVP).[1,2] Lately studies have raised doubts about the importance of this association.[3] Gazit in 2003 confirmed these symptoms studying 27 JHS patients with Dysautonomia (Dys) compared with 21 controls. Symptoms related to the ANS such as syncope and presyncope, palpitations, chest discomfort, fatigue, and heat intolerance, were significantly more common among patients. Orthostatic hypotension, postural orthostatic tachycardia syndrome (POTS), and uncategorized orthostatic intolerance were found in 78% (21/27) of patients compared with 10% (2/21) in controls.[4]

JHS patients may have CF due to the following causes:

- Chronic pain. JHS can cause severe recurrent pain and occasionally incapacity. Rheumatologists need to know that JHS is probably the principal cause of pain in their clinics.[5] Chronic pain can alter quality of life, sleep, sexual functions, social and working relations, physical activities and recreation.
- Years of suffering.
- Poor physical conditioning (muscle deconditioning).
- Associated diseases: Hypothyroidism, chronic Anemia, Asthma, Alcoholism and chronic illnesses, such as Diabetes, RA and SLE.
- Depression (endogenous or secondary to their poor quality of life).

- Dysautonomia. It is our impression that DYS is the main cause of CF in these patients.

We have seen chronic arthritis, such as RA, SLE or others, associated to JHS in 15% of cases.[6] In the above discussion we have not included FM as a cause of CF, since we agree with other authors that FM is frequently associated with Hypermobility. Gedalia in Israel noted that 81% of school children with FM had Joint Hypermobility (JH).[7] Ofluoglu, in Turkey, noted JH in 64% of adults with FM.[8] Karaaslan, also in Turkey, noted that from the patients that did not meet the criteria for FM 31% had JH.[9] Sendur discussed JH and its relation to clinical findings of FM [10] Nijs suggested that JH was an issue in FM and CFS.[11] Mary Ann Fitzcharles in Canada, states, "that a sub group of patients with FM have JH".[12]

It is our theory that FM is probably part of JHS. Our contention stands in that all the FM symptoms can be seen in JHS and we concur with Martinez-Lavin that the

multiple features of FM can be explained by a disruption of the ANS,[13] exactly as seen in JHS, where it is very prevalent. The ANS causes orthostatic intolerance, which is expressed as DYS or POTS. We agree with Acasuso-Diaz that CFS, FM and JHS are similar diseases or could be the same disease.[14] In our study of 1226 JHS patients, we found a very high prevalence of Dysautonomia (orthostatic intolerance, orthostatic hypotension), specially in adolescent girls and in JHS patients younger than 30 years old DYS was present in 72% of females and 44% of males.[15]

One sign of CF in JHS patients is that they usually hold their head with the hand when sitting in front of a table. We described this sign in 2006, called the " Hand holding the head sign", that is frequently noted in these patients.[16] (Fig.5.1). While observing this, one can see the joint hypermobility as noted by the extreme flexion or extension of the wrists and MCP joints. This not well

known sign, helps to suspect that the person probably has JHS.

JHS patients usually get secondary depression due to years of pain and suffering, plus the fact that they feel that their relatives and physicians do not understand their problems.. Gratacos and Bulbena have suggested that these patients also may have endogenous depression. They reported that JHS patients have susceptibility for panic crisis and phobias, due to a polymorphic genomic duplication on human chromosome 15, for JHS and panic crisis and phobias.[17] Unfortunately this study has not been reproduced.

If a person gets dizzy or fatigued when standing for a period of time, it is necessary to consider an orthostatic disorder, especially after ruling out other causes that can produce orthostatic tolerance failure, such as anemia, hypovolemia, decreased cardiac output and drugs that can

produce hypotension.[18] The orthostatic intolerance in most cases is due to inadequate perfusion of blood to the brain.

1 Prevalence and importance

The prevalence of these conditions is difficult to asses. The frequency of secondary CF would depend on the causal condition. In CFS the CF is 100%, since it is part of the definition. It is thought that CFS affects 0.4% of the USA population.[19] CF is frequent in FM and this condition affects about 8-10 of the people.[20] JH is said to exist in about 10 to 15% of the population worldwide, using the Beighton score. JHS is usually not diagnosed, but in places where the Brighton criteria is used routinely for the diagnosis of JHS, such as London [5] and Santiago, Chile [6,16] the frequency is of 45 to 50% of the patients attending a rheumatological clinic. We have reported 39% in a Chilean population.[16] In our study of 1226 JHS patients, 39% had DYS, but in the group younger than 30

years old it was present in 72% of females and in 44% of males.[15] So probably the most frequent cause of CF is JHS, albeit not diagnosed.

It is easy to realize that CF in general is the cause of a tremendous loss of working hours, but most important than that, is the poor quality of life that these patients have. This is very noticeable in JHS, in which since the diagnosis is usually not done, patients who have Dysautonomia have chronic fatigue, lightheadedness, dizziness and occasional syncope and suffer in silence developing anger and frustration.

1 Pathophyhsiology

It is our opinion that the main cause of tiredness in JHS is DYS, caused by a failure of the orthostatic tolerance. In these patients the problem could be attributed to the abnormal connective tissue present in the dependent blood vessels, which permit the veins to

distend excessively in response to normal hydrostatic pressures leading to a marked increase in venous pooling,[4,21] which is in accordance with the frequent occurrence of acrocyanosis in these patients. This can also be exacerbated by deconditioning due to muscle disuse, secondary to pain and fear of pain. Reinforcing the above notion of venous pooling is the fact that the use of elastic support hoses and abdominal bands can help prevent symptoms.[21] Some patients respond to the orthostatic intolerance (OIT) with tachycardia (≥ 30 beats/min or ≥ 120 beats/min within 10 min of standing or upright tilt), which is known as postural orthostatic tachycardia syndrome. Emerging evidence by Rowe has revealed that JHS is an important cause of secondary POTS,[21] as corroborated by Gazit, et al.[4] In other occasions when the autonomic failure is more significant it can lead to episodes of pre-syncope or syncope.

1 Clinical features

The CF in JHS is a very particular one, and in most cases it has been present in a mild form for years, so much so that the patient thinks that it is normal for him. All of a sudden, usually without an apparent cause, the weakness and fatigue becomes worse, at times presenting with pre-syncope or syncope, which prompts getting medical advise. They may have palpitations, chest pain and difficulty to breath. The patient complains of light-headiness, dizziness, getting tired easily (weakness) especially after standing on a line for a while, standing in a social event or while in church, after periods of inactivity or after slow walking, usually suffered by patients when at the supermarket or Malls. Also it is of note that this discomfort may not appear when the patient is happily doing his work, hobby or sport, but rather at the end of it or the next day. Frequently it appears before midday or in the evening, when the

person is ready for a lunch break or when going home, at that time they develop somnolence, yawning and tiredness. Some may have poor memory, lack of concentration or slight disorientation, especially when studying sitting for a long period of time, this can improve if studying while lying down, all due to cerebral hypoperfusion. These patients usually have significant cold intolerance and sometimes also heat intolerance (in general poor thermal regulation). On occasions there are other signs of ANS dysfunction not related to orthostatic tolerance, such as diaphoresis, gastrointestinal complaints, including nausea, abdominal pain, vomiting, constipation or diarrhea, bladder dysfunction, or mild xerophthalmia and xerostomia. Frequently dysautonomic patients complain also of headaches and sleep disturbances.

The CF and weakness sensation make this people look like they are lazy and anti-social, due to the fact that

they do not have energy to participate in social activities. Frequently they carry the mistaken diagnosis of Depression, Fibromyalgia, CFS, Hypothyroidism or Hypoglycemia. Many of our patients, have come to see us after seeing many different specialists and have had many blood tests and other exams including MRI, CAT scans, EEG, etc. The reason for this is that JHS and Dysautonomia are not well known and are not usually included in the differential diagnosis.

These patients may feel weak and tired after a hot bath or in hot weather. There is another important aspect of this type of fatigue and is that the person feels that he is loosing energy, like his "batteries are running out". This sensation can be so intense, that the person may feel that he has a very serious illness and may fear for his life.

Since JHS is a genetic condition, dysautonomic symptoms may appear in children. They may tire easily,

be a little clumsy, may not like to exercise and may have lack of concentration [22,23]. As in adults, Dysautonomia is usually not diagnosed in children either. Because of this, it is important that pediatricians be on the alert for this problem.

The following factors tend to precipitate or aggravate the orthostatic intolerance in JHS, thus increasing the CF symptoms:

- Dehydration (Poor water and salt intake, excessive heat, fever, vomiting, diarrhea, diuretics).
- Hot environment: Prolong hot baths (including saunas and Jacuzzi). Hot weather. Bikram Yoga (done at 42°C).
- High altitude.
- Anxiety, stress and depression.
- Acute and chronic anemia.

- Standing for a long period, without moving, slow walking or sitting at a computer for hours.
- Physical deconditioning, at times secondary to prolonged bed rest due to a concurrent illness.
- Medications that can produce orthostatic hypotension (Diuretics, vasodilators, tricycle antidepressants, etc.).
- A big meal (specially rich in carbohydrates).
- Alcohol.
- Menstrual periods.
- Pregnancy.

3 Case presentation

A 30 year-old, Caucasian woman, lawyer, was a late walker, and was always tired and had multiple and recurrent sprains since childhood. At a young age she was agile and able to do body contortions, and "party tricks" with the fingers. Her life was a struggle, because of

constant fatigue, arthralgias, myalgias, tendinitis, cervical and lumbar problems and varicose veins since childhood. She also had occasional sub-luxations of the elbows. Had syncopal episodes occasionally since she was an adolescent and on one occasion she fell from a horse due to one of these episodes. Was known to have cold and heat intolerance and had tendency to bruise. Would tire easily especially standing on a line or when walking slowly. Had depression, anxiety, panic crisis and phobias. Was seen by many physicians and was diagnosed as having Fibromyalgia and Chronic fatigue syndrome. Has had anemia since childhood and frequent headaches. Also has had acrocianosis, queloids, reflux, irritable bowel syndrome and hemorrhoids. She stated that her health problems made getting the lawyer degree very difficult.

The general physical examination was negative except: that her skin was pale and tran parented the veins. BP 10/6. She had joint hypermobility and the

Beighton score was positive (7 of a maximum of 9). The Brighton criterion was positive (1 mayor and 5 minor criterions) confirming the diagnosis of JHS.

Routine laboratory test were normal except for Hct/Hb of 34.6/11.4. She had palpitations, but a Holter monitor for arrhythmias was negative. The Tilt test was positive.

On a second visit, she was feeling better, but not well while on midodrine 2.5 mg twice a day and following the general measures for the treatment of Dysautonomia (fluid and salt supplementation, elastic hoses, avoiding inactivity, etc.). On that visit, two hours after taking midodrine 2.5 mg, her BP was low (11/7) indicating that the dose was insufficient. The anemia was an aggravating factor.

This patient represents a case of severe orthostatic intolerance, including severe fatigue, with marked JHS

manifestations, which affected the patient's quality of life. In many cases the main problem is chronic fatigue without syncope or with only one or two episodes.

1 Diagnosis

To confirm the diagnosis of JHS the Brighton Criteria needs to be positive in the absence of contraindications.[24] DYS can be diagnosed clinically and confirmed with a Tilt-table test [25] (Fig. 5.2). This test permits to evaluate the ANS function under a gravitational stress. After a period of stabilization in dorsal decubitus the patient in a stretcher is inclined generally up to 60-70°, for a period of time, that varies for the different protocols (20-40 min). Symptoms and BP are monitored constantly. The test is positive if it provokes a hypotensive episode that reproduces the patient's symptoms. Finally the test may end with a phase of isuprel or nitroglycerine provocation.

1 Differential diagnosis of CF in JHS

The vague nature of symptoms in CF makes the differential diagnosis difficult and the following conditions need to be considered:

2 CF from chronic illnesses

Deconditioning, usually secondary to chronic, debilitating diseases, including malignant diseases and prolonged bed rest or lack of exercise needs to be considered in the differential diagnosis of CF. Chronic anemia, dehydration, alcohol, recurrent use of medications (diuretics, hypotensors, nitrates, hypnotics, sedatives and muscle relaxants, between others), as well as the chronic use of illicit drugs, should be easy to rule out with a good medical history and a complete physical exam, including a complete neurological examination. It is necessary to rule out hypoglycemic crisis and hypothyroidism. Due to frequent headaches and

migraines, pre-syncope or syncope, at times with clonic movements that may simulate an epileptic crisis (from severe orthostatic intolerance) a neurological cause needs to be excluded.

2 Depression

Depression by itself gives lack of energy and tiredness that can last months and become chronic, but also depression can be associated to chronic illnesses, CFS and FM. Anxiety and panic attacks in JHS can contribute to CF.

2 Chronic Fatigue Syndrome (CFS)

CF is part and parcel of CFS. This is a complex and controversial condition that has been known for many years with different names and has been associated to many causes. The extreme fatigue in CFS does not improved with bed rest and usually gets worse with

physical or mental activity. Initially it was called Febricula or little fever, later was called DaCosta´s syndrome or soldier's heart. In 1869 Beard gave this psycho-pathological condition the name of Neurasthenia, comprising fatigue, anxiety, headaches, impotence, neuralgia and depressed mood.[26] Interesting name since it means lassitude and irritability. It was considered the result of exhaustion of the central nervous system energy reserves, due to stress. Already in those days, Sir William Osler noted the disparity between the complaints by the patients and the medical findings. After the outbreak of Myalgic Encephalitis in Los Angeles, CA in 1934, CFS has been known also with that name.[27] A similar outbreak was also reported in Iceland. Since immunologic causes have also been implicated, it has received also the name of "chronic fatigue and immune dysfunction syndrome".[28] Possible infectious etiologies have been discussed, chronic infections such as Mononucleosis,[29] Candidiasis [30] and

Ebstein Barr virus,[31,32] and the Multiple chemical sensitivity syndrome,[33] but none of these hypothesis has been scientifically approved.

Barron and Rowe noted that joint hypermobility was present in 60% of CFS patients compared to 24% in controls, so it was 3.5 times more frequent.[23] This study could be in favor of CFS being part of the CF in JHS, the problem being that CFS, FM and JHS may share many common symptoms and at times is difficult to differentiate them.

Rowe and associates first reported Dysautonomia in CFS, after noting that 60% of CFS patients had a positive head-up tilt test.[3,34] It is of interest that similar ANS response has been seen in JHS [4] and FM,[34] so the differential diagnosis of CF should include this three conditions. A positive Tilt test may confirm the diagnosis of DYS.

3

CFS is defined by the presence of:

(Using the revised criteria.[18])

1.- Clinically evaluated, unexplained, persistent or relapsing fatigue that is of new or definite onset; is not the result of ongoing exertion; is not alleviated by rest; and results in substantial reduction in previous levels of occupational, educational, social, or personal activities.

2.- Four or more of the following symptoms that persist or recur during six or more consecutive months of illness and that do not predate the fatigue:

- Self-reported impairment in short term memory or concentration.
- Sore throat.
- Tender cervical or axillary nodes.
- Muscle pain.

- Multi-joint pain without redness or swelling.
- Headaches of a new pattern or severity.
- Unrefreshing sleep.
- Post-exertional malaise lasting 24 hours.

Requiring fatigue to be "unexplained" despite clinical evaluation should exclude most patients with well-recognized diseases.

Since only sore throat and tender cervical or axillary nodes are symptoms not encountered in the FM or the JHS criteria, these conditions can be easily confused. Many people that have unexplained chronic fatigue and do not fit the case criteria for CFS are defined as having idiopathic chronic fatigue, but they could well have DYS, in a patient with undiagnosed JHS.

2 Fibromyalgia

In FM the CF is related to stress, sleep disturbances and ANS dysfunction. It is our impression that the alteration of the ANS (DYS) is also the cause of CF in CFS and JHS, all three conditions having overlapping symptoms due to the same pathogenesis. What is interesting is that DYS not only produces symptoms due to orthostatic intolerance but many others, such as gastrointestinal symptoms (irritable bowel syndrome and reflux), thermo regulatory abnormalities (cold and heat intolerance and diaphoresis) and urinary symptoms.

We agree with Crofford that the 1990 Criteria for the Classification of FM is very vague and incomplete, since it deals only with pain and does not consider depression, CF, stress and sleep and memory disturbances.[35,36] The general population also may have tenderness in the trigger point areas, and FM patients also have increased sensitivity to pain throughout the body. Clauw states that

this criteria is unspecific, since it is positive in 25% of patients with inflammatory disorders like RA, SLE, etc. and that more than half of the patients diagnosed clinically as FM do not fulfill the ACR criteria.[37]

2

Joint Hypermobility syndrome (JHS)

We concur with Rowe that in CF and in syndromes with orthostatic intolerance, it is necessary to look for JHS and other types of Ehlers-Danlos carefully, since it is frequently associated to them. He found association of CFS, orthostatic hypotension and Ehlers-Danlos Syndrome (EDS I-II and EDS-III (JHS). He also found acrocyanosis frequently associated to EDS.[21] In these cases acrocyanosis is reflecting excessive venous pooling.

It is important to consider, when talking about CF in JHS, that the diagnosis of JHS can be difficult, since the patient may not be hypermobile. JHS patients can have a few hypermobile joints, one or none and still may have JHS (if the Brighton criteria is positive, in spite of a

Beighton score of cero). It appears that in these patients, a better name for the condition would be EDS type III, rather than JHS.

1 Treatment of CF in JHS

The treatment will vary in different patients depending on the cause of the CF. In many cases just with a definite diagnosis and explanation of the problem, the patient with JHS will feel relieved and the fatigue will tend to subside. Avoiding constant pain with analgesics and improving the physical condition will help. If a JHS patient has an associated chronic illness, like RA or SLE, the treatment of the chronic condition will contribute to reduce the fatigue. The same happens in case of anemia, which causes tiredness by itself and by aggravating the DYS.

In our experience the main treatment of CF in JHS is the treatment of the underlying OIT. Unfortunately the optimal treatment is uncertain and many medications are being tested. It is necessary to educate the patient about his/her condition, the need to avoid precipitating or aggravating factors and to reassure them that the treatment if well done, will improve significantly their quality of life. They need to be instructed to lie down at the onset of any prodromal symptoms of syncope. Usually there is no single effective therapeutic approach and it is necessary to explain to the patient that the general measures are very important and that medications usually are necessary. The treatment is more complicated in cases in which the patient has tendency to hypertension, or frank hypertension, in which case the patient should be referred to a cardiologist for a more specialized treatment.

When treating a patient, depending on the severity of the condition, we need to consider non-pharmacological as well as pharmacological measures.

3

A.- Non-pharmacological measures

1.- Volume expansion and salt supplement.[38,39]

a)- Fluid intake: 2-2.5 liters a day. Usually with this measure, the urine should become colorless and the frequency of urination should be twice in AM and twice in PM. Drinking a liter rapidly should increase BP 20-30 mm Hg at 3 min and for 1 hour.[40,41]

b)- Salt supplementation: Salt should be increased to 3- 5 g a day. Patients usually gain 1 to 2 kg in weight if they are doing these measures well. Patients need to be reassured that increasing the

salt is not dangerous and that it is essential to increase their BP to relieve their symptoms. Isotonic solutions as taken by athletes are recommended. [42,43]

2.- Exercise program.

a).- Gradual physical reconditioning program. The plan is to get to 30 min of aerobic activity 3 times per week.[44] Moderate aerobic exercise is useful, since it raises the venous return to the heart by action of the muscles.

b).- Exercises especially of the abdomen, thighs and calves. Exercising the abdominal muscles help to counteract the splanic venous pool.

c).- Nocturnal rest with elevated head of bed (about 10° or 20-25 cm). The reason for this is

that it creates renal hypoperfusion, which activates the renin-angiotensin aldosterone axis, and that it increases the extra cellular volume of the lower extremities (edema), with reduction of the venous pool.[45] This maneuver reduces dizziness when getting out of bed in AM.

d).- Tilt training (exercises trying to stand against the wall for increasing periods of time), to accomplish this, the patient needs to be well motivated. Exercises twice a day for 8-12 weeks, followed by maintenance therapy 3-4 times weekly. Initially for 5 min. increasing gradually up to 40 min. [46-48]

e).- Isometric muscle contractions (gripping of the hands and pressing the legs, increases BP

and in many cases it helps to prevent an impending syncope. [38,46,49-51]

f).- Elastic support: Elastic hoses.
Abdominal band.

The use of elastic garments was proven by Sheps to be useful as early as 1976. He recommended elastic support hoses (panties if possible), with a pressure at the ankle of at least 20 mm of Hg, to minimize the degree of venous pooling in the lower extremities. [51]

When there is significant splanic venous pool besides exercises of the abdominal muscles it is useful to do abdominal compression, with a band like corset.

3.- Other measures

a).- Avoid high environmental temperatures,[53] because they produce vasodilatation and tendency to hypotension.

- No saunas or Jacuzzi.
- Prolonged hot baths or showers.
- Hot weather in summer.

b).- Avoid postprandial hypotension:[53]

- Avoid big meals, especially rich in carbohydrates and alcohol, because they tend to increase the splanic venous pool. It is recommended to have 4-6 small meals a day, low in carbohydrates.
- Postprandial rest is helpful.
- Coffee is OK.

c).- Avoid standing without moving for too long, because it aggravates the venous pooling

in the extremities. It is recommended not to stand for prolonged periods of time. If this can not be avoided, there are several movements that can help, such as crossing the legs; standing on tip toes and releasing; placing one foot in front of the other and alternating the position of the feet; bending forward, like if going to tie the shoe laces; squatting and/or placing a foot over a chair, with the knee extended.

Do not to walk slowly in Malls or supermarkets, and do not spend more than an hour in that activity, and less if at all possible.

d).- When sitting in a bus or an airplane, it is necessary to move the knees and ankles frequently and to get up and walk, to

improve blood circulation. Occasionally adopting the position of hyper flexion of the chest to knees or head between the knees.

3

B. - Pharmacological measures.

When non-pharmacological treatments are ineffective and symptoms persist, drugs are indicated. The most important of these drugs are:

a).- Fludrocortisone. [44,53] for some time it has been the drug of first choice in the treatment of the patient with orthostatic symptoms due to autonomic failure. It's a potent synthetic mineralocorticoid with minimal glucocorticoid effect. It has several potentially beneficial pharmacological effects like:

- Expansion of the intra vascular and extra vascular body fluids.

- Sensitization of vascular receptors to pressor amines.
- An increase in fluid content of vessel walls that makes them more resistant to stretching.

Usually the treatment is begun with a dose of 0.1 mg once a day, and is effective for about 12 hours. It can be increased by 0.1 mg up to 0.3 mg daily during a 1-2 week period, if needed. The pressor action is not immediate and takes some days to manifest. The full benefit requires a high dietary salt intake. A weight gain of 2-3 kg is a reasonably good clue for adequate volume expansion. Side effects are primarily accounted for its expected pharmacological action. Mild dependent edema can be expected. Patients may develop hypokalemia within 2 weeks, and foods high in potassium should be advised. Occasionally potassium supplements

may be needed and for this reason it is recommended to check the electrolytes during the first month. Headache is another possible side effect.

b).- Midodrine. [44,53] After absorption midodrine is converted to its active metabolite desglymidodrine. It acts as an alpha-adrenoreceptor agonist acting on constriction of both arterial resistance and venous capacitance vessels, with the predominant effect being on the venous side. It does not cross the blood brain barrier and consequently it has little in the way of undesirable central stimulant effects. Tablets are 2.5 and 5 mg. Midodrine is administered in doses of 2.5-10 mg 3-4 times daily. If the patient has symptoms in AM it is recommended to take their first dose about 20 minutes before getting out of bed. [44] The full effect is obtained in 30 minutes and lasts 4 hours. It has been approved in the United States for

the treatment of recurrent neurocardiogenic syncope.[54] There are no drugs approved for the treatment of POTS. [44] In a double blind study Ward using 5 mg three times a day, showed improvement in quality of life, when compared with placebo.[55] In a six month randomized trial, comparing midodrine with increased salt and fluid therapy showed significant difference in resolution of symptoms (81 vs. 13%).[56] Supine hypertension is a common, but not an often serious side effect. Scalp tingling is a very frequent side effect. Midodrine may be of particular value in patients with severe postural hypotension and in those with peripheral neurological lesions, as in pure autonomic failure. Midodrine may also aggravate urinary retention.

c).- Anti-depressants: Antidepressants and ansyolitics help since they reduce pain and improve sleep. In some cases Grubb would advise to add a

selective serotonin-reuptake inhibitor or norepinephrine reuptake inhibitor.[57]

Recently Thieben et al. after studying 152 POTS patients, that constituted the Mayo Clinic experience of 11 years, found no differences in the symptomatic response to the different medications such as beta-blockers, fludrocortisone, midodrine and selective serotonin reuptake inhibitors, all providing partial relief of symptoms in 40 to 60% of patients. [58]

d).- More specialized medications.[44,59] If the combination of fludrocortisone and sympathetic vasoconstrictor drugs does not produce the desired effect, selective targeting is then needed, depending on the pathophysiologic abnormalities. These patients need to be referred to a specialized unit with experience in intervention with medicines such as:

- Desmopressin [60] that may be of value in a patient with nocturnal polyuria.
- Octeotride [61] my benefit patients with post prandial hypotension.
- Erythropoietin [62] appears not only to augment intravascular volumen via its increase in red cell mass, but also appears to have a direct vasoconstrictive effect. The drawbacks of this treatment are its extreme expense and the fact that it must be administered by subcutaneous injection and red cell counts need to be monitored closely.

In some cases the lack of response to the DYS therapy is due to the fact that the general measures have not been well done. It is difficult to get the patients to add enough salt, since they have heard from us for years, that salt intake can be dangerous.

1 Further reading

Bravo JF. www.reumatologia-dr-bravo.cl

Grubb BP, Calkins H, Rowe PC. Postural tachycardia, orthostatic intolerance, and the chronic fatigue syndrome. In: Grubb BP, Olshansky B, eds. Syncope. Mechanisms and Management, 2nd edn. Massachusetts: Blackwell Futura; 2005: 225-244.

Keer R, Grahame R. Hypermobility syndrome recognition and management for physiotherapists. New York Butterworth Heinemann Health; 2003.

1 References

1.- Grahame R, Edwards JC, Pitcher D, et al. A clinical and echocardiographic study of patients with the hypermobility syndrome. Am Rheum Dis. 1981; 40:541-546.

2.- Coghlan C. Autonomic Dysfunction in the Mitral Valve Prolapse Syndrome: The brain-heart connection and interaction. In: Boudulas H, Wooley CF, eds. Mitral valve prolapse and the mitral valve prolapse syndrome. Mount Kisco, NY:Futura Publising Co;1988:389-426.

3.- Rowe PC, Bou-Holaigah I, Kan JS, et al. Is neurally mediated hypotension an unrecognized cause of chronic fatigue? Lancet 1995; 345:623-624.

4.- Gazit Y, Nahir AM, Grahame R, et al. Dysautonomia in the joint hypermobility syndrome. Am J med 2003; 115(1):33-40.

5.- Grahame R, Hakim AJ. High prevalence of joint hypermobility syndrome in clinic referrals to a north London community hospital (abstract) Rheumatology Oxford 2004; 43 suppl 2:91.

6.- Bravo JF, Wolff C. Clinical study of 1124 cases of Ehlers-Danlos (classic EDS, JHS and vascular EDS). (abstract). Arthritis Rheum 2007; 56(9) suppl: 1163.

7.- Gedalia A, Press J, Klein M, et al. Joint Hypermobility and Fibromyalgia in schoolchildren. Ann Rheum Dis 1993; 52:494-496.

8.- Ofluoglu D, Gunduz OH, Kul-Panza E, et al. Hypermobility in women with Fibromyalgia syndrome. Clin Rheumatol 2005; 16:1-3.

9.- Karaaslan Y, Haznedaroglu S, Ozturk M. Joint hypermobility and primary Fibromyalgia a clinical enigma. J Rheumatol 2000; 27:1774-1776.

10.- Sendur OF, Gurer G, Bozbas GT. The frequency of hypermobility and its relationship with clinical findings of Fibromyalgia. Clin Rheumatol 2007; 26:485-487.

11.- Nijs JO. Generalized joint hypermobility: An issue in Fibromyalgia and Chronic Fatigue syndrome ? J Body Work and movement therapies. 2005; 9:310-317.

12.- Fitzcharles MA, Esdaile JM. Hypermobility in Fibromyalgia syndrome (abstract) J Rheumatol 1996; 23:1462.

13.- Martinez-Lavin M, Hermosillo AG. Autonomic Nervous System may explain the multisystem features of Fibromyalgia. Sem Arthritis Rheum 2000; 29:197-199.

14.- Acasuso-Diaz M, Collantes-Estevez E. Joint hypermobility in patients with Fibromyalgia syndrome. Arthritis Rheum 1997; 11:39-42.

15.- Bravo JF, Wolff C. Clinical study of Dysautonomia in 1226 patients with Joint Hypermobility syndrome (abstract). J Clin Rheumatol 2008; 14(4) suppl S33.

16.- Bravo JF, Wolff C. Clinical study of hereditary disorders of connective tissues in a Chilean population. Joint hypermobility syndrome and vascular Ehlers-Danlos syndrome. Arthritis Rheum 2006; 54(2):515-523.

17.- Gratacos M, Nadal M, Martin-Santos R, et al. A polymorphic genomic duplication on human chromosome 15 is a susceptibility factor for panic and phobic disorders. Cell. 2001 Aug 10; 106(3): 367-369.

18.- Fukuda K, Straus SE, Hickie I, et al. The chronic fatigue syndrome: A comprehensive approach to its definition and study. International Chronic Fatigue syndrome study group. Ann Intern Med 1994; 121:953-959.

19.- Low P, Schondorf R, Novak V, et al. Postural tachycardia syndrome. In: Low P, ed. Clinical Autonomic Disorders. 2nd edn. Philadelphia, PA: Lippincott Raven; 1997: 681-697.

20.- Jason LA, Richman JA, Rademaker AW, et al. A community-based study of chronic fatigue syndrome. Arch Intern Med 1999; 159(18):2129-2137.

21.- Rowe PC, Barron DF, Calkins H, et al. Orthostatic intolerance and chronic fatigue syndrome associated with Ehlers-Danlos syndrome. J Pediatr 1999; 135 (4):494-499.

22.- Grahame R. [Editorial] Time to take hypermobility seriously (in adults and children). Rheumatology 2001; 40:485-491.

23.- Barron DF, Cohen BA, Geraghty MT, et al. Joint hypermobility is more common in children with chronic fatigue syndrome than in healthy controls. J Pediatr 2002; 141:421-425.

24.- Grahame R, Bird HA, Child A. The revised (Brighton 1998) criteria for the diagnosis of benign joint hypermobility syndrome (BJHS). J Rheumatol 2000; 27:1777-1779.

25.- Grubb BP, Kosinski D, Tilt table testing: concepts and limitations. Pacing Clin Electrophysiol 1997; 20:781-787.

26.- Beard G. Neurasthenia, or nervous exhaustion. The Boston Medical and Surgical Journal 1869; 217-221.

27.- Aronowitz RA. From myalgic encephalitis to yuppie flu: A history of chronic fatigue syndromes. In: Framing Disease, Rosenberg CE, Golden J (eds), Rutgers University Press. New Brunswick. NJ. 1992.

28.- Landay, AL, Jessop, C, Lennette, ET, et al. Chronic fatigue syndrome: Clinical condition associated with immune activation. Lancet 1991; 338:707.

29.- Straus, SE. The chronic mononucleosis syndrome. J Infect Dis 1988; 157:405-412.

30.- Renfro L, Feder HM, Lane TJ, et al. Yeast connection among 100 patients with chronic fatigue. Am J Med 1989; 86:165-168.

31.- Straus SE, Tosato G, Armstrong G, et al. Persisting illness and fatigue in adults and evidence of Epstein-Barr virus infection. Ann Intern Med 1985; 102:7.

32.- Jones JF, Ray CF, Minnich LL, et al. Evidence for active Epstein-Barr virus infection in patients with persistent, unexplained illnesses: Elevated anti-early antigen antibodies. Ann Intern Med 1985; 102:1-16.

33.- Simon GE, Daniell W, Stockbridge H, et al. Immunologic, psychological, and neuropsychological factors in multiple chemical sensitivity. Ann Intern Med 1993; 119:97-103.

34.- Bou-Holaigah I, Rowe PC, Kan J, et al. The relationship between neurally mediated hypotension and chronic fatigue syndrome. JAMA 1995; 274:961-967.

35.- Wolfe F, Smythe HA, Yunus MB, et al. The American College of Rheumatology 1990 criteria for the classification of Fibromyalgia. Arthritis Rheum 1990; 33:160-172.

36.- Crofford LJ, Clauw DJ. Fibromyalgia: Where are we a decade after the American College of Rheumatology classification criteria were developed? Arthritis Rheum 2000; 46(5):1136-1138.

37.- Clauw DJ, Paul P. The overlap between Fibromyalgia and inflammatory rheumatic diseases: when and how does it occur? J Clin Rheumatol 1995; 1:335-341.

38.- Wieling W, Colman N, Krediet CT, et al. Nonpharmacological treatment of reflex syncope. Clin Auton Res. 2004; 12(suppl 1):1/62-1/76.

39.- Wieling W, van Lieshout JJ, Hainsworth R. Extracelular fluid volumen expansion in patients with posturally related syncope. Clin Auton Res. 2002; 12:243–249.

40.- Yunoszai AK, Franklin WH, Chan DP, et al. Oral fluid therapy: a promising treatment for vasodepressor syncope. Arch Pediatr Adolesc Med 1998; 152:165-168.

41.- Jordan J, Shannon JR, Black BK, et al. The pressor response to water drinking in humans: a sympathetic reflex? *Circulation*. *2000*; *101:504-509*.

42.- El-Sayed H, Hainsworth R. Salt supplement increases plasma volume and orthostatic tolerance in patients with unexplained syncope. Heart 1996; 75:134-140.

43.- Claydon VE, Hainsworth R. Salt supplementation improves orthostatic cerebral and peripheral vascular control in patients with syncope. Hypertension 2004; 43:809-813.

44- Grubb BP, Calkins H, Rowe PC. Postural tachycardia, orthostatic intolerance, and the chronic fatigue syndrome. In: Grubb BP, Olshansky B, eds. Syncope. Mechanisms and Management, 2nd edn. Massachusetts: Blackwell Futura; 2005: 225-244.

45.- Omboni, Smit AA, van Lieshout JJ, et al. Mechanisms underlying the impairment in orthostatic intolerance after nocturnal recumbency in patients with autonomic failure. Clin Sci 2001; 101:609-618.

46.- Ector H, Reybrouck T. Improving tolerance to upright posture: current status of tilt- training and other physical maneuvers. In: Benditt DG, Brignole M, Raviele A, Wieling W, eds. Syncope and Transient Loss of Consciousness. Massachusetts: Blackwell; 2007: 72-75.

47.- Gajek J, Zysko D, Halawa B, et al. Influence of tilt training on activation of the autonomic nervous system in patients with vasovagal syncope. Acta Cardiol 2006; 61:123-128.

48.- Reybrouck T, Heidb chel H, Van Der Werf F, et al. Long- term follow-up results of tilt training therapy in patients with recurrent neurocardiogenic syncope. Pacing Clin Electrophysiol 2002; 25:144-146.

49.- Krediet CT, van Dijk N, Linzer M, et al. Management of vasovagal syncope controlling or aborting faints by leg crossing and muscle tensing. Circulation 2002; 106:1684-1689.

50.- Wieling W, van Lieshout JJ, van Leeuwen AM. Physical maneuvers that reduce postural hypotension in autonomic failure. Clin Auton Res. 1993; 3:57–65.

51.- Brignole M, Croci F, Menozzi C, et al. Isometric arm counter-pressure maneuvers to abort impending vasovagal syncope. J Am Coll Cardiol 2002; 40: 2053-2059.

52.- Sheps SG. Use of an elastic garment in the treatment of orthostatic hypotension. Cardiology 1976; 61(suppl 1):271-279.

53.- Mathias C. Intolerance to upright posture in autonomic failure and the postural tachycardia syndrome : assessment and treatment strategies. In: Benditt DG, Brignole M, Raviele A, Wieling W, eds. Syncope and transient loss of consciousness. Massachusetts: Blackwell; 2007: 67-71.

54.- Parry SW, Kenny RA. The management of vasovagal syncope. QJM 1999; 92:697-705.

55.- Ward CR, Gray JC, Gilroy JJ, et al. Midodrine: a role in the manage of neurocardiogenic syncope. Heart 1998; 79:45-49.

56.- Perez-Lugones A, Schweikert R, Pavia S, et al. Usefulness of midodrine in patients with severe symptomatic neurocardiogenic syncope: a randomized control study. J Cardiovasc Electrophysiol 2001; 12:935-938.

57.- Grubb BP. Postural tachycardia syndrome. Circulation 2008; 17:2814-2817.

58.- Thieben MJ, Sandroni P, Sletten DM, et al. Postural orthostatic tachycardia syndrome: The Mayo clinic experience. Mayo Clin Proc 2007; 82(3):308-313.

59.- Moya A, Wieling W. Orthostatic Syncope. In: Benditt DG, Blanc JJ, Brignole M, Sutton R, eds. The evaluation and treatment of syncope, 2nd edn. Massachusetts: Blackwell; 2006: 170-184.

60.- Mathias CJ, Fosbraey P, de Costa DS, et al. Desmopressin reduces nocturnal polyuria, reverses overnight weight loss, and improves morning postural hypotension in autonomic failure. BMJ 1986; 293:353-354.

61.- Hoeldtke RD, Davis KM. The orthostatic tachycardia syndrome: evaluation of autonomic function and treatment with octreotide and ergot alkaloids. J Clin Endocrinol Metab 1991; 73:132-139.

62.- Grubb BP, Karas B. Preliminary observation on the use of erythropoietin in the treatment refractory postural tachycardia syndrome. Clin Auton Res 1999; 9(4):228.

Figure 1.

Tiredness and fatigue as expressed by the

"Hand holding the head sign" in JHS.

Figure 2

The response to orthostatic changes is studied with the Tilt-test exam.