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Orthostatic Hypotension

Orthostatic hypotension is a common cardiovascular disorder, whether it has or does not have underlying neurodegenerative disease. One must have a systolic blood pressure drop of 20 mmHg and a diastolic of 10 mmHg or more upon standing. It can also be diagnosed with a tilt test, which is passive and not active as standing is. Orthostatic hypotension is 5 percent in patients under 50 years of age to 30 percent in those greater than 70 years of age. Orthostatic hypotension can complicate treatment of hypertension, heart failure, and coronary artery disease, and can cause disabling symptoms and traumatic injuries, and reduce quality of life. The presence of orthostatic hypotension independently increases mortality and the incidence of myocardial infarction, stroke, heart failure, and atrial fibrillation.

Lewy bodies or glial inclusions containing alpha-synuclein are found in the brain and peripheral autonomic nerves of people affected with these disorders. These include:

1. Parkinson's disease.
2. Dementia with Lewy bodies.
3. Multiple system atrophy (MSA)
4. Pure autonomic failure (PAF).

I. Parkinson's Disease.

Parkinson's presents with motor abnormalities and autonomic failure. Between 20 – 60 percent of people with Parkinson's will develop neurogenic orthostatic hypotension, which increases with age. The main autonomic manifestations of Parkinson's disease include orthostatic hypotension, gastrointestinal symptoms, including decreased motility disorders, bladder dysfunction, and sweating or pseudomotor dysfunction.

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Parkinson's is a disorder with widespread alpha-synuclein pathology and a loss of dopamine neurons of a part of the brain known as a substantia nigra. Alpha- synuclein accumulates in the Lewy bodies and fibrils of alpha-synuclein can cause Lewy neuritis in the axons of nerves. These deposits of alpha-synuclein are present in the brain, the cerebral cortex, the brain limbic system, the brain nucleus basalis, and the dorsal motor nucleus of the vagus nerve. They are also present in the sympathetic ganglia, and the intestinal mesenteric and mucosal plexus of the digestive tract. Therefore, these abnormal accumulations, or deposits in fibrils of alpha-synuclein in Parkinson's can be found in many parts of the body. Interestingly, when Parkinson's patients develop autonomic neuropathy with drops in blood pressure, GI symptoms, urinary symptoms, and sweating abnormalities, it is usually the peripheral nervous system and not the central system that is involved, predominantly. Some patients with Parkinson's can develop orthostatic hypotension early in the disease prior to the manifestations of the motor symptoms of Parkinson's, which can include bradykinesia, or slow movement, along with tremors and abnormal gait. Some patients are asymptomatic with orthostatic hypotension with Parkinson's, and it is our policy with all patients with Parkinson's to measure their blood pressure sitting and standing within a three-minute period of time. However, oftentimes they will get aggravated symptoms if they become hypotensive or dehydrated, and they can start having disabling falls. Also, sometimes just after eating, patients with Parkinson's get the so-called postprandial hypotension. We find that a good majority of patients with Parkinson's disease who develop orthostatic hypotension also have supine hypertension, and this increases the risk of cardiovascular disease. In fact, any orthostatic hypotension syndrome, which commonly is associated with supine hypertension, can increase the risk of cardiovascular diseases, and, therefore, not only treating the blood pressure drops of the patient is important, but also concomitantly treating the supine hypertension is important. This is a delicate balance and at times becomes almost impossible to manage as patients progress no matter how aggressive and meticulous one's pharmacological therapy is, as the condition is resistant to normalizing blood pressure in a small range and controlling blood pressure drops. This is extremely frustrating. While it is difficult with Parkinson's disease, it is particularly difficult with primary autonomic failure and multiple system atrophy, which we will discuss later. In Parkinson's disease, as the disease progresses, orthostatic hypotension can contribute to cognitive decline and decrease in memory, executive function, and visual spatial function when one is standing. With Parkinson's disease, constipation is the most relevant symptom and can be reported in 80-90 percent

of patients, and can occur several years before motor manifestations also. Drug treatment with anticholinergic drugs and dopamine agonists, which are used in Parkinson's disease, may actually aggravate the constipation. We have seen megacolon and intestinal pseudo-obstruction occur in patients with Parkinson's disease. Also, dysphagia could be a late progression in Parkinson's disease. Aspiration of liquids can occur, and this is a common cause of pneumonia and can often lead to morbidity and death, and sepsis. Drooling of saliva occurs in many patients with Parkinson's disease and is associated with dysphagia and dysarthria. Patients also, however, complain of dry mouth with Parkinson's with reduced salivary production. Upper GI symptoms include nausea, vomiting, early satiety, and weight loss caused by gastroparesis, which could be diagnosed with a gastric emptying study that shows delayed gastric emptying. A big advantage of gastroparesis in Parkinson's disease is that it may delay the absorption of levodopa through the intestines to alleviate the motor symptoms.

A good number of patients with Parkinson's disease will complain of nocturia, urgency of urination, increased urinary frequency during the day, and incontinence associated with urgency due to autonomic dysfunction. These individuals will show detrusor overactivity and abnormal external sphincter relaxation on urodynamic testing by a urologist. Erectile dysfunction is common in Parkinson's patients. Sweating can vary from diminished sweating to hyperhidrosis or increased sweating, and tests that can quantify sweating, such as QSART and sudomotor testing can be useful to monitor this in patients with Parkinson's. However, lack of sweating, although it occurs in Parkinson's, is lower in that which occurs in multiple system atrophy that we will discuss below.

Autonomic testing can show abnormalities in parasympathetic and sympathetic testing in patients with Parkinson’s. However, they cannot differentiate between the other types of synucleinopathies. In general, there are low supine plasma norepinephrine levels, supporting that this is a peripheral abnormality of the nervous system. If one performs a cardiac MIBG study, which is a radiotracer study that is extremely difficult to obtain in clinical practice, one can see the uptake in the heart is reduced 80-90 percent, and this supports the fact that this is a peripheral orthostatic hypotension disorder, unlike multiple system atrophy (MSA), which will show excellent uptake in the heart with an MIBG study.

Cardiac sympathetic nervous system is also present in Lewy body dementia and primary autonomic failure and has been found in some patients with multiple system atrophy, however. Unfortunately, orthostatic hypotension is a significant prognostic factor for cognitive decline and mortality in Parkinson's disease, as it is with multiple system atrophy, Lewy body dementia, and primary autonomic failure. All of these disorders are quite serious and need treatment by cardiologists and neurologists experienced in this area.

In regard to Parkinson's disease, it is an adult-onset neurodegenerative disorder. It arises after the age of 60. It has been described as Shaking Palsy over 20 years ago by Dr. James Parkinson. Its hallmark features are tremor, rigidity, and bradykinesia. It is traditionally considered a motor system disorder, but, as noted above, can affect the autonomic nervous system.

Occasionally, hyposmia/olfactory dysfunction is seen with Parkinson's. Depression, anxiety, and color vision impairment can occur along with neurocognitive dysfunction. Postural instability is often accompanying the tremor, bradykinesia, and rigidity.

The diagnosis of Parkinson's disease is a clinical diagnosis because no diagnostic tests have been developed. Recently, DaTscans, which involve dopamine and nuclear testing, have become commonly employed. A strong beneficial response to dopaminergic therapy is important in supporting the diagnosis. And if one does not have a response to high-dose levodopa therapy (that is greater than 1000 mg a day), the diagnosis of Parkinson's disease is unlikely. Also, postural instability occurs later in the course of Parkinson's disease. If a person presents early with it, one should look for another neurodegenerative disorder that is causing this. Alpha-synuclein testing by cerebrospinal fluid analysis or skin biopsies is commercially available but not really routinely used in clinical diagnosis, although it is performed at specialty university centers.

It is best to have a person with suspected Parkinson's disease be seen at an expert movement center for a comprehensive assessment and diagnosis.

While MRI is often done of the brain to rule out other structural abnormalities and special MRI sequences may show neurodegenerative changes in Parkinson's disease and multiple system atrophy. The DaTscan, which is a striatal dopamine transporter imaging test using a special tracer, can allow for the detection of a decrease in the number of the dopaminergic neurons in the part of the brain known as the striatum. A positive DaTscan, which will

show reduced size of the isotope in the striatum part of the brain, will be seen in patients with Parkinson's disease, MSA, and Lewy bodies, but is also seen in corticobasal degenerative disorders, and will not be seen in controls in people who have essential tremors. Basically, the DaTscan has a high sensitivity for diagnosing the so-called presynaptic dopaminergic parkinsonian syndromes, including Parkinson's disease. It will not differentiate Parkinson's disease from multiple system atrophy or Lewy body dementia, but will be negative in primary autonomic failure. It is often recommended that the DaTscan be used for people when the diagnosis is unclear or do not respond to levodopa but have features of Parkinson's clinically. Also, patients suspected of having drug-induced Parkinson's will have normal uptake in the striata, unlike Parkinson's disease, and it may be indicated to differentiate that. Also, before attempting to consider deep brain stimulation, a DaTscan may be useful as a negative study might steer one more toward essential tremor and avoid an invasive neurosurgical procedure. Again, we emphasize that a movement specialist should be involved in the diagnosis and care of patients with Parkinson's disease.

Recent research has shown that a FDG-PET may discriminate Parkinson's disease from atypical Parkinson's syndrome, but this is not in general clinical use.

We have found that olfactory testing may be important in differentiating Parkinson's disease from other parkinsonian disorders such as MSA. Olfactory dysfunction is common in Parkinson's disease but is rarely, if ever, seen with MSA. In our Delaware Valley area, the University of Pennsylvania Smell Identification Test and Sniffin' Sticks are commercially available.

In diagnosing Parkinson's disease, red flags are important to document. These often will argue against a diagnosis of Parkinson's disease and point one to look for an alternate diagnosis. These include rapid progression of gait impairment requiring regular use of a wheelchair within five years of onset, a complete absence of progression of motor symptoms over five years or more unless these symptoms are stable with treatment, bulbar dysfunction, inspiratory respiratory dysfunction, frequent inspiratory sigh, and severe autonomic failure in the first five years, which includes orthostatic hypotension and severe urinary retention, and in males, erectile dysfunction. Also, recurrent falls because of impaired balance within three years of onset should also be considered a red flag.

Bilateral symmetrical parkinsonism syndrome is also a red flag, since Parkinson's usually presents more unilaterally.

II: Multiple system atrophy (MSA):

This disorder affects the central nervous system but predominantly spares peripheral autonomic neurons. There are two types. Type A, which is parkinsonian, and Type B, which is cerebellar. Both have significant autonomic failure. Patients with multiple system atrophy can present more with a rapid deterioration of motor and autonomic function. This can include the presence of incomplete bladder emptying, that evolves over a short period of time, to severe urinary retention and disabling symptoms of orthostatic intolerance, which favors multiple system atrophy. Usually, there are normal values of supine norepinephrine without an increase on standing, and there is a preserved peripheral cardiac imaging sympathetic innervation on MIBG imaging. This is compatible with central sympathetic denervation. Also, respiratory signs, including nocturnal stridor, which is due to laryngeal dystonia and involuntary inspiratory gasps are seen and are rare in Parkinson's disease. A polysomnography can confirm the presence of sleep apnea and laryngeal stridor. Also, cold hands are often seen as a problem with the microcirculation. The most frequent type is the type A with associated Parkinsonian-type abnormalities with rigidity, bradykinesia and tremor. The cerebellar ataxia Type B is more often seen in Japan. In multiple system atrophy, there are deposits of protein alpha-synuclein primarily in oligodendrocytes (glial cytoplasmic inclusions) with the presence of neuronal loss in the striatum, substantia nigra, pontine nuclei, inferior olivary nuclei, cerebellum and premotor and autonomic nuclei. Clinical manifestations include severe orthostatic hypotension. Patients with multiple system atrophy who can present with an initial phenotype of pure autonomic failure (PAF to be discussed later) may evolve into multiple system atrophy phenotype over years. An MSA orthostatic hypotension is usually associated with supine hypertension. Orthostatic hypotension contributes to cognitive dysfunction, visual problems, and executive dysfunction. MSA is due to predominantly central denervation. Urinary dysfunction is more common and severe in Parkinson's disease and occurs early. Urge incontinence, nocturia, difficulty voiding, and incomplete bladder emptying are seen. Urodynamic studies are important. Erectile dysfunction occurs in almost all males with

multiple system atrophy and may be an early manifestation. Interestingly, erectile dysfunction may precede the onset of urinary symptoms in males. If a male has preserved erectile dysfunction, this argues against him having multiple system atrophy. Pseudomotor dysfunction is common with loss of sweating and intolerance to heat. It is usually a global pattern of anhidrosis. Sweat tests may be useful in diagnosing this. Usually, pseudomotor acts on reflex as normal, and thermoregulatory sweat tests (TSA) are abnormal, confirming a central cause of sweating abnormality. However, it is not unusual at a very late stage for postganglionic pseudomotor dysfunction to develop.

Dysphagia in the oropharynx may interfere with nutrition and eating with MSA. Tracheal aspiration can occur. Patients may have gastroparesis, and this may be a result of dorsal motor nucleus involvement of the vagus nerve centrally. This affects gastrointestinal motility. Constipation is frequent and occurs very early, and may be severe, and fecal impaction can occur.

Sympathetic and parasympathetic reflex testing is useful to follow the course of the disease and to assess the level of severity of autonomic dysfunction. There are certain MRI findings in the Type A MSA parkinsonian-type patient with a hyperintense rim in the posterior putamen and putamen atrophy. In the cerebellar Type B, there was abnormal signaling in the base of the pontine, associated with cerebellar atrophy. PET scanning may show decreased metabolism in the putamen. Cardiac imaging with MIBG does show preserved peripheral sympathetic innervation and normal uptake of the heart. Polysomnography is a useful tool to detect the presence of nocturnal laryngeal stridor.

The median survival from symptoms of onset of multiple system atrophy is 8 to 10 years, but the spectrum ranges from 4 to 15 years. Older age and earlier presence of autonomic dysfunction are poor prognostic factors. Early need for urinary catheterization in the presence of stridor is linked to decreased survival.

In summary, the diagnosis of MSA is based primarily on clinical, motor, autonomic, and respiratory features. Urinary dysfunction is common, and urinary retention characteristic. Polysomnography should be performed to detect laryngeal stridor and sleep apnea.

Early Therapy for symptoms associated with urinary dysfunction, laryngeal stridor, and dysphagia can improve survival in multiple system atrophy patients.

III. Pure Autonomic Failure:

Pure autonomic failure, like multiple system atrophy, Parkinson's disease, and dementia with Lewy bodies, may present with early autonomic failure for several years before the complete phenotype of synucleinopathy develops. Patients with primary autonomic failure usually develop the illness between 50 and 70 years of age. Autonomic symptoms can come on insidiously and slowly in the early stages, but slowly progress, and orthostatic intolerance can become severe with severe orthostatic hypotension and repeated syncope. Diminished sweating is often seen in intolerance to hot environments. Moderate symptoms of urgency and frequency with urination may be seen. Urinary incontinence is less frequent. Males may get erectile dysfunction. Constipation may occur in these patients and may be a late manifestation. Usually, primary autonomic failure is an initial presumptive clinical diagnosis. Norepinephrine levels are generally low when tested, and there are low circulating norepinephrines without an increase on standing, indicating that the patient has a disease that compromises the postganglionic autonomic neurons, qualifying it as a peripheral autonomic neuropathy. If a patient is followed up for many years and does not convert to MSA, Parkinson's disease, or Lewy body dementia, this more supports a diagnosis of primary autonomic failure. Long-term follow-up is needed in these patients as they can often with exacerbation, transition to a multiple system atrophy disorder. In this disorder, accumulation of alpha-synuclein and Lewy bodies with sympathetic ganglia and Lewy neurites is seen with sympathetic axons in the heart, bladder, adrenal tissue, colon, and skin. Primary autonomic failure is a peripheral autonomic neuron disorder, but patients may convert to a central nervous system disorder. The disease has no specific treatment. Management of orthostatic hypotension,

constipation, and urinary dysfunction is important. In primary autonomic failure, there is a slowly progressive deterioration of autonomic failure, and patients can survive for many decades, but once autonomic dysfunction becomes accelerated, the prognosis is guarded, and life expectancy is abbreviated. This is especially true if they are in the process of transforming into a multiple system atrophy stage also. Patients may develop severe drops in blood pressure and sometimes up to 100 mmHg, which are almost impossible to control, despite multiple vasoactive agents, and falls are common and difficult to prevent, and we recommend that caretakers be continuously with these patients as the disease progresses. As the orthostatic hypotension worsens, patients will invariably have hypertension. This needs to be treated with nocturnal antihypertensive agents concomitantly, when vasoactive agents to try to limit the orthostatic blood pressure drops are given. Management of primary autonomic failure is particularly challenging when it coexists with supine hypertension. There are a few physicians who will attempt to treat this disorder, as it is extremely complex and difficult to improve. Many patients we have seen come in on stretchers and wheelchairs and can no longer ambulate because of such severe blood pressure drops. Pharmacological interventions for orthostatic hypotension to be used in conjunction with non-pharmacological approaches, include elevating the head of the bed, compression stockings and waistbands, fluids during the day, and decreasing fluid and salt intake is recommended at bedtime to alleviate supine hypertension. Low-dose antihypertensives should be given often at night. Transdermal agents like nitroglycerine, clonidine, Captopril, nifedipine, losartan, and short-acting beta-blockers can be prescribed to control blood pressure. Pharmacological interventions for orthostatic hypotension should be used in conjunction with non-pharmacologic approaches. Midodrine, droxidopa, pyridostigmine, fludrocortisone, are Food and Drug Administration-approved for treating orthostatic hypotension and should be used while attempting to lower nocturnal hypertension with the measures that we have described. Patients who become more disabled will need combinations of these medications, and midodrine with droxidopa has been used with pyridostigmine, all in series successfully in limiting blood pressure drops in some patients. Fludrocortisone may cause fluid retention and usually has to be limited in dosing. It can also cause hypokalemia. The prognosis for controlling symptoms is poor, and orthostatic hypotension is thought of as a disorder, like other disorders, portends a higher risk of cardiovascular events the longer the patient survives. Blood pressure management and a multidisciplinary approach, including remote monitoring of blood pressure, consideration for cardiorespiratory rehabilitation, and

psychological support may improve quality of life in some patients, but not necessarily affect life expectancy.

As mentioned, primary autonomic failure is a predominantly peripheral autonomic dysfunction, but there is increasing awareness that patients may progress to other synucleinopathies characterized by central nervous system involvement, such as multiple system atrophy, Parkinson's disease, or dementia with Lewy body.

Patients do get insomnia, and it has been estimated that up to 80 percent will have defects on olfactory testing. Rapid eye movement disorders are present in nearly three-quarters of people with this disorder. Cognitive dysfunction can be affected. Long-term hypertension in these patients leads to the development of hypertensive heart disease and increased arterial stiffness. It is hoped that the evaluation of skin biopsy for alpha-synuclein will be validated in the future for diagnostic purposes.

The median survival of patients with primary autonomic failure has been reported to be 12.5 years, with a range of 5.1 to 15.9 years. However, if they begin to evolve into a synucleinopathy with significant CNS involvement, the prognosis becomes poor, especially when acceleration of autonomic dysfunction occurs.

In contrast, MSA patients with primary autonomic failure do not develop respiratory symptoms of stridor, and sleep apnea is uncommon.

Patients who have orthostatic hypotension become severe and may be restricted in mobility because of large drops in blood pressure. In addition, rapid or severe fluctuation in blood pressure may lead to end-organ damage, and sudden death is also reported in patients with primary autonomic failure. Monitoring for end-organ damage is important in the long-term care of these patients. There is no cure for primary autonomic failure, although patients may improve clinically with non-pharmacological and pharmacological

measures that control blood pressure fluctuations. We have seen very high blood pressure fluctuations in patients with this disorder. The goal in treatment is to reduce syncope and other measures to improve symptomatic management rather than normalization of standing blood pressure.

IV. Dementia with Lewy Body Disease:

Patients with dementia with Lewy body disease present with fluctuating cognitive decline, parkinsonian features, and autonomic failure. Cognitive dysfunction occurs within the first year of motor symptoms and is often accompanied by visual hallucinations in these patients. The patients usually have orthostatic hypotension, incontinence, and constipation. They do not respond to levodopa. There are low values of supine norepinephrine and plasma, supporting the presence of peripheral sympathetic denervation. Cardiac imaging with MIBG shows evidence of cardiac sympathetic denervation similar to Parkinson's disease and other peripheral autonomic disorders. Patients can respond with their motor symptoms to levodopa. Orthostatic hypotension should be treated with vasoactive agents. The patients have slowly progressive asymmetric Parkinson's symptoms often, and moderate autonomic dysfunction, which can include urinary dysfunction.

Dementia with Lewy body is one of the most common types of degenerative dementia, second to Alzheimer's disease. Dementia is a common feature, along with visual hallucinations, Parkinsonian-type features, cognitive fluctuations, rapid eye movement abnormalities, sleep behavior disorders, dysautonomia, orthostatic hypotension, and neuroleptic sensitivity. Lewy bodies, which showed the presence of intracytoplasmic inclusions that contain alpha-synuclein, are typically seen in the deep cortical layers of the brain. Dementia is more progressive in Lewy body dementia than it is in regular Parkinson's disease. Dementia in Parkinson's disease usually occurs more than ten years after the onset of the disease, whereas Lewy body dementia occurs much earlier. Lewy body dementia carries a poor prognosis of Parkinson's disease, with an average disease duration of five to eight years from symptom onset. Dementia is progressive with cognitive decline.

There are deficits in attention. Visual hallucinations are seen in most patients with Lewy body dementia, whereas they are rare in Alzheimer's disease. They are usually very detailed. People will see children, small animals, bugs on the wall, and abstract shapes in colors. Bradykinesia, rest tremor, gait disorders, and rigidity are seen in a majority of patients with Lewy body dementia. Tremors are usually less common in Parkinson's disease. Sensitivity to antipsychotic drugs is common. Frequent falls occur commonly early in the course of Lewy body dementia. Episodes of syncope can occur due to orthostatic hypotension. They occur in more than half the people with Lewy body dementia. Urinary incontinence or retention may occur along with erectile dysfunction, constipation, and GI symptoms, such as gastroparesis and colonic hypomotility and constipation. In fact, the autonomic symptoms are more prevalent and severe in Lewy body dementia than in Parkinson's disease, but not as severe as multiple system atrophy autonomic dysfunction symptoms. Therefore, there appears to be a spectrum of severity of autonomic dysfunction in these alpha-synuclein disorders. Decreased olfactory function is common in these patients, along with hypersomnia or excessive daytime sleepiness. We have seen patients who also have auditory hallucinations with Lewy body dementia, where they hear children singing in choirs, for example. They can also get olfactory hallucinations and tactile hallucinations. Depression is also a common feature. MRI may show volume losses, more pronounced cortical atrophy than in Parkinson's disease. There is atrophy of the putamen. However, hippocampal atrophy in Lewy body dementia is not as prominent as seen in Alzheimer's disease. Alpha-synuclein can be detected peripherally with abnormal deposits in the GI tract, heart, sympathetic nerve fibers, and skin on biopsy. Studies have shown on skin biopsy that a high percentage of patients with Lewy body dementia have pathological deposition of alpha-synuclein and skin nerve fiber biopsies. It appears to be higher than in Parkinson's disease and multiple system atrophy, and pure autonomic failure, and more abundant in Lewy body dementia.

Orthostatic hypotension disorders are treated similarly as is supine hypertension in these alpha-synuclein disorders. However, if one is taking vasopressors such as midodrine or droxidopa, one should not lie down within four hours of a dose. Sleeping at a 30-degree angle is also beneficial while taking antihypertensive short-acting drugs in the nighttime. Volume expansion with fludrocortisone and sometimes desmopressin can be used, but electrolytes need to be followed. Another medication that is useful is pyridostigmine,

which is a peripheral acetylcholinesterase inhibitor that acts to increase acetylcholine concentrations in the autonomic ganglia. It is usually taken 60 mg three times a day and can modestly reduce the fall and standing blood pressure, but does not increase supine blood pressure, which is an advantage. Pyridostigmine also increases abdominal motility and is useful in patients with chronic constipation, which is often associated with these disorders.

Other drugs that may be used selectively include Yohimbine, alpha-2-adrenergic receptor antagonist, norepinephrine reuptake transporter inhibitors, such as atomoxetine (it can significantly increase blood pressure in patients with MSA), Cafergot caffeine, and ergotamine, which causes vasoconstriction through a non-sympathetic mechanism, and octreotide, an injectable peptide that works on splanchnic vasoconstriction, which shunts blood into the central circulation.

We have found that doing 50 leg raises before arising from bed while in bed are very valuable, and bolus water therapy, 12-16 ounces of water before even standing in the morning, and taken within four to five minutes, is helpful in invoking a sympathetic response to limit orthostatic hypotension. Of course, electrolytes and salt need to be taken cautiously in people with supine

hypertension. Individual management of that is made on a case-to-case basis with people with orthostatic hypotension.

On another note, peripheral denervation upgrades receptor super sensitivity to midodrine and droxidopa. Peripheral autonomic disorders that cause orthostatic hypotension are more responsive to these agents. These include Parkinson's, Lewy body dementia, and primary autonomic failure. Central autonomic dysfunction disorders, which cause orthostatic hypotension, include multiple system atrophy and autoimmune gangliopathy. In these disorders, atomoxetine may be more effective, and Yohimbine may be more effective if one is not getting an adequate response to conventional vasoactive agents such as midodrine, droxidopa, pyridostigmine, and volume expanders such as desmopressin

and fludrocortisone. However, one must be careful in using Yohimbine and not worsening supine hypertension. This drug works best if you have an intact peripheral noradrenergic innervation, as is present in MSA and autoimmune ganglionopathy

A quick note on autoimmune autonomic ganglionopathy (AAG). While this is not an alpha-synuclein disorder, it is worth noting that it usually comes on acutely or subacutely and can present with pure generalized autonomic failure. It can present with orthostatic hypotension. It can be associated with paraneoplastic syndromes. Paraneoplastic syndromes can cause both sensory and motor abnormalities. Orthostatic intolerance is common, as are GI complaints with nausea, vomiting, early satiety, bloating, and constipation. Patients may get achalasia and actually paralytic ileus. Pseudomotor dysfunction is noted in the majority of patients. Pupillary dysfunction presents with bilateral mydriasis reflecting parasympathetic denervation and is a prominent sign in AAG. This is known as an Adie's pupil. Therefore, this disorder is an autoimmune disorder often testing with positive autoantibodies. In 50 percent of patients, there are antibodies to the ganglionic AChR receptor, and antibody titers can correlate with the severity of autonomic dysfunction. In this disorder, immunomodulation and immunosuppressive drugs are used, such as intravenous immunoglobulins. Spontaneous recovery may occur, and immunotherapy may produce a complete or partial recovery. There is also a chronic form of AAG with persistent autonomic symptoms that persist through life.

In response to autoantibodies and orthostatic disorders, there has been some data suggesting that postural orthostatic tachycardia is associated with some autoimmune antibodies, although we have not found this to be the case. Lambert-Eaton syndrome, and some cases of postural orthostatic tachycardia do show positive antibodies to AChR, as do other paraneoplastic AAG syndromes. Therefore, if one sees a patient with newly diagnosed or presenting autonomic dysfunction features that come on within a three-month period of time, associated with GI symptoms, dry eyes, dry mouth, severe upper gastrointestinal dysautonomia, orthostatic hypotension, and large pupils that react poorly to light and accommodation along with a neurogenic bladder, AAG should be strongly suspected. Testing positive for nicotinic acetylcholine receptors (nAChR), autoantibodies are usually associated with the subacute, less than three-month dysautonomia. Usually, one likes to see antibody titers higher than 0.2 nmol/L.

Other causes of orthostatic hypotension include severe acute sensory and autonomic neuropathy, which is a rare disorder, presumed to be autoimmune, but no antibodies have been identified.

Paraneoplastic autonomic neuropathy can occur in association with anti-Hu antibodies and ANNA-1, most often in patients with small lung cell cancers, but other malignancies. Also, antibodies to Type 2 PCA-2 and antibodies to protein-CRMP-5 are seen with paraneoplastic syndromes. Sometimes the nAChR antibodies are seen with paraneoplastic autonomic neuropathy. Patients present with orthostatic hypotension, pseudomotor, tubal abnormalities, intestinal abnormalities, bladder dysfunction, and constipation with these disorders.

Familial dysautonomia, the so-called Riley-Day syndrome, is a very rare hereditary sensory and autonomic neuropathy (SHSAN type 3) caused by the mutation in the ELPI gene and is autosomal recessive and is expressed at birth with impaired pain, temperature, and abnormal baroreflex failure. We do not see these types of patients in our clinical practice.

Hereditary forms of amyloid, including transthyretin (TTR) mutations are associated with orthostatic hypotension, fainting, cardiomyopathy, gastroparesis, and a length-dependent peripheral neuropathy.

Familial autonomic ganglionopathy due to a pathological variant in the CHRNA#3 gene leads to low norepinephrine levels in the peripheral nervous system causing peripheral autonomic neuropathy associated with orthostatic hypotension. Small pupils, myosis, and constipation and rarely seen. Other genetic rare diseases include beta-hydroxylase deficiency.

One must keep in mind that as one ages, decreased baroreceptor sensitivity and milder forms of orthostatic hypotension due to sympathetic withdrawal in older adults can be noted. This can be tested for using HRV coupled with respiratory techniques in the laboratory.

Before diagnosing neurogenic orthostatic hypotension, make sure that there is not a volume depletion state, make sure that the patient is off diuretics, and there has not been GI bleeding, vomiting, or profuse sweating. Exclude drugs that may cause orthostatic hypotension. An increase of less than 0.5 beats per minute for every 1 mm drop in systolic blood pressure during a tilt test or active standing test is very useful in diagnosing neurogenic orthostatic hypotension. Values above 0.5 beats per minute can be seen with neurogenic orthostatic hypotension but are more commonly seen with low volume states, such as dehydration, hypovolemia, GI bleed, and drug effects. In these cases, the heart rate is disproportionately high, indicating an intact sympathetic nervous system.

When one sees an increase in heart rate greater than 30 beats per minute without a drop in blood pressure, this is suggestive of a postural orthostatic tachycardia response, which is the subject of another discussion.

Cardiovascular diseases are more common in individuals with orthostatic hypotension, and, in fact, orthostatic hypotension is a risk factor for cardiovascular events and increased mortality usually due to the underlying disease and other associated diseases. Therefore, we consider neurogenic orthostatic hypotension a marker of increased cardiac risk.

Small fiber neuropathies can affect the postganglionic autonomic nerves and cause autonomic dysfunction. This is more commonly seen with diabetes. They can develop alongside of distal neuropathies and sensory neuropathies with pain or sensory loss. Diabetes mellitus is the most common type of autonomic neuropathy. Also, acquired and hereditary amyloidosis are occasionally seen and need to be tested for. As mentioned,

autoimmune diseases, such as Sjögren's and Lupus, can also cause peripheral neuropathies with orthostatic hypotension as can B vitamin deficiencies, kidney failure, toxins, and infections. Sarcoidosis is a rare cause of orthostatic hypotension as is porphyria.

Patients with acute Guillain-Barre syndrome, often hospitalized, will show evidence of orthostatic hypotension, and their blood pressure should be taken lying, sitting, and standing. With chronic inflammatory demyelinating polyneuropathy with CIDP, autonomic dysfunction is not usually seen.

If one has orthostatic hypotension, especially if symptomatic, and volume and medicine causes are excluded, significant testing with a neurologist, cardiologist, and perhaps even an endocrinologist is indicated.