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House Calls

FALL 2022

Neurology Issue

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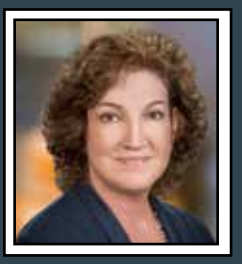
Peripheral Neuropathy: A Frequently Misdiagnosed Neurological Disorder



Jackie Owens, Executive Vice President

The nervous system regulates and coordinates body activities and has two major divisions:

- The Central nervous system (CNS): the brain and spinal cord; and
- The Peripheral nervous system (PNS): all other neural elements, such as eyes, ears, skin, and other "sensory receptors"[1]

Peripheral neuropathy (PN) results when the peripheral nerves are damaged, typically causing weakness, numbness and pain, usually in the hands and feet. It can also affect other areas and body functions including digestion, urination and circulation.

Polyneuropathy results when multiple nerves are damaged; Mononeuropathy results when a single nerve or nerve group is damaged, usually by trauma, injury, local compression, prolonged pressure, or inflammation.[2]

Symptoms can range from mild to disabling and are rarely life-threatening. The symptoms depend on the type of nerve fibers affected (motor nerve, sensory nerve or autonomic nerve) and the type and severity of damage. In some cases, the symptoms improve on their own and may not require advanced care. Unlike nerve cells in the central nervous system, peripheral nerve cells continue to grow throughout life.[3]

Motor nerve damage is most commonly associated with muscle movement. Other symptoms include painful cramps, fasciculations (uncontrolled muscle twitching visible under the skin) and muscle shrinking.

Sensory nerve damage causes various symptoms because sensory nerves have a broad range of functions.

- Damage to large sensory fibers harms the ability to feel vibrations and touch, especially in the hands and feet. This damage may contribute to the loss of reflexes (as can motor nerve damage). Loss of position sense often makes people unable to coordinate complex movements like walking or fastening buttons or maintaining their balance when a their eyes are closed.
- The "small fibers" without myelin sheaths (protective coating, like insulation that normally surrounds a wire) include fiber extensions called axons that transmit pain and temperature sensations. Small-fiber polyneuropathy can interfere with the ability to feel pain or changes in temperature. This is often difficult for medical caregivers to control, which can seriously affect a patient's emotional well-being and overall quality of life.

Autonomic nerve damage affects the axons in small-fiber neuropathies which control blood pressure, perspiration, heart rate, digestion, sexual function, and bladder function. Common symptoms include excess sweating, heat intolerance, inability to expand and contract the small blood vessels that regulate blood pressure, and gastrointestinal symptoms. Although rare, some people develop problems eating or swallowing if the nerves that control the esophagus are affected.[3]

Neuropathy is often misdiagnosed due to its complex array of symptoms. More than 20 million people in the United States are estimated to have some form of peripheral neuropathy. The actual figure may be significantly higher, however, as not all people with symptoms of neuropathy are tested for the disease and tests currently don't look for all forms of neuropathy. Diagnosis of PN typically includes the patient's medical history, physical and neurological exams, body fluid tests, genetic tests, nerve conduction velocity, electromyography, nerve biopsy, neurodiagnostic skin biopsy, and QSART tests. MRIs of the spine can reveal nerve compression and a CT scan can show herniated disks, spinal stenosis, tumors, bone and vascular irregularities that may affect nerves.[3]

Causes of PN include:

- Autoimmune diseases (rheumatoid arthritis, lupus, Guillain-Barre syndrome)
- Diabetes
- Vascular and blood problems (high blood pressure, atherosclerosis, vasculitis)
- Infections (Lyme disease, shingles, Epstein-Barr virus, hepatitis B and C and HIV)

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- Inherited disorders (Charcot-Marie-Tooth disease, family history of neuropathy)
- Certain Cancers and Benign Tumors
- Chemotherapy drugs
- Bone marrow disorders
- Diseases (kidney, liver, connective tissue disorders and underactive thyroid)
- Alcoholism
- Exposure to toxins
- Medications (especially chemotherapy, radiation therapy)
- Physical Injury, Trauma or pressure on the nerve
- Vitamin deficiencies and Hormonal imbalances
- Repetitive motion (carpal tunnel syndrome)

(Source: National Institute of Neurological Disorders & Stroke; https://www.ninds.nih.gov)

Treatment and Prevention:

Treatments depend entirely on the type of nerve damage, symptoms, and location. Definitive treatment can permit functional recovery over time, as long as the nerve cell itself has not died. Inflammatory and autoimmune conditions leading to neuropathy can be controlled using immunosuppressive drugs such as prednisone, cyclosporine, or azathioprine. Plasmapheresis can help reduce inflammation or suppress immune system activity. Agents such as rituximab that target specific inflammatory cells, large intravenously administered doses of immunoglobulins, and antibodies that alter the immune system, also can suppress abnormal immune system activity.[3,4]

Medications recommended for chronic neuropathic pain are also used for other medical conditions. Among the most effective are a class of drugs first marketed to treat depression. Nortriptyline and newer serotonin-norepinephrine reuptake inhibitors such as duloxetine hydrochloride modulate pain by increasing the brain's ability to inhibit incoming pain signals. Another class of medications that quiets nerve cell electrical signaling is also used for epilepsy. Common drugs include gabapentin, pregabalin, and less often topiramate and lamotrigine. Carbamazepine and oxcarbazepine are particularly effective for trigeminal neuralgia, a focal neuropathy of the face.[4]

Narcotics (opioids) can be used for pain that doesn't respond to other pain-control medications and if disease-improving treatments aren't fully effective. Because pain relievers that contain opioids can lead to dependence and addiction, their use must be closely monitored. A more recent drug approved for treating diabetic neuropathy is tapentadol, which has both opioid activity and the norepinephrine-reuptake inhibition activity of an antidepressant.

Surgery is the recommended treatment for some types of neuropathies. Protruding disks ("pinched nerves") are commonly treated surgically to free the affected nerve root and allow it to heal. Trigeminal neuralgia on the face is also often treated with neurosurgical decompression. Injuries to a single nerve caused by compression, entrapment, tumors or infections may require surgery to release the nerve compression. Neuropathies that involve more diffuse nerve damage, such as diabetic neuropathy, are not helped by surgical intervention.

Less damaging procedures such as electrically stimulating remaining peripheral nerve fibers or pain-processing areas of the spinal cord or brain have largely replaced interventional procedures involving cutting or injuring nerves. Transcutaneous electrical nerve stimulation (TENS) is a noninvasive intervention used for pain relief in a range of conditions.

One of the most effective ways to prevent PN is to manage medical conditions that put the patient at risk (diabetes, rheumatoid arthritis). A healthy diet, regular exercise, and avoidance of toxic chemicals, smoking and excessive alcohol intake are also recommended. Ensure that patients are vaccinated against viruses that cause PN (Lyme disease, shingles, Epstein-Barr virus, hepatitis B and C and HIV). The current vaccine against shingles prevents more than 95 percent of cases and is widely recommended for people over 50, including those who have had previous shingles or vaccination with the older, less effective vaccine.[4]

Further Research

Clinical studies are being conducted on genetics and genetic mutations, and on the natural history of hereditary neuropathies. Discoveries of new causes and treatments and the biological mechanisms responsible for chronic neuropathic pain are ongoing. Researchers are also exploring the use of tissue engineered from the cells of humans with peripheral neuropathy as models to identify specific defects in the transport of cellular components along axons and the interactions of nerves with muscles. Additional studies involve the immune system and blocking components that cause nerve damage.[4]

References available upon request.

An Overview of Multiple Sclerosis

By: Kraiyuth Vongxaiburana, MD, SIMEDHealth Neurology

Multiple sclerosis (MS) is an autoimmune/inflammatory disease that attacks the central nervous system including the brain and spinal cord. Patients with MS have a near normal life expectancy and most live a relatively normal life. Left untreated approximately 30% of patients with MS will develop significant physical disability within 25 years of onset. Therefore, it is important to correctly diagnosis and treat patients in order to slow disability progression and to improve quality of life.

Epidemiology and Risk Factors: MS affects females more than males and tends to occur in relatively young individuals. The average age at diagnosis is 30 years old. Approximately 2.3 million people are living with MS worldwide, including approximately 400,000 people in the United States. Both environmental and genetic factors are thought to increase the risk for developing MS. There are over 200 single-nucleotide polymorphisms associated with increased risk for developing MS. The environmental risk factors of prior Epstein-Barr Virus exposure, low levels of vitamin D, smoking, obesity, and decreased exposure to ultraviolet light all confer increased risk for developing MS (Nourbakhsh and Mowry, 2019, p.596). These environmental and genetic factors affect the immune system ultimately causing neuroinflammation, and importantly, with MS it is not a one-time neuroinflammatory event.

For the diagnosis of MS, clinical presentation and neurologic exam are important but modern diagnostic tools have helped to allow for a more accurate and earlier diagnosis. MRI of the brain and spine is appropriate to look for CNS lesions that might be typical for MS. MRI of the brain often shows periventricular demyelinating lesions that are perpendicular to the ventricles. An MRI of the spine might show a partial myelitis spanning only a short segment of the spinal cord. Lumbar puncture should be considered in patients with atypical presentations and in patients who have other potential causes for abnormal MRI findings. For instance, consider lumbar puncture in patients with vascular risk factors, possible migraine-associated white matter changes, or in patients with possible functional presentations. CSF-specific oligoclonal bands (OCBs) would point towards the possibility of MS. Approximately 90% of patients with MS will have CSF-specific OCBs.

Multiple sclerosis has three main phenotypes: relapsing remitting multiple sclerosis, secondary progressive multiple sclerosis, and primary progressive multiple sclerosis.

Relapsing remitting multiple sclerosis (RRMS) is the most common presentation at disease onset. The MS attacks/relapses are typically separated by months to years. With each MS attack patients typically have some clinical recovery, but it's not always complete recovery and with time neurologic disabilities often accumulate. Some typical MS attacks include optic neuritis, partial transverse myelitis, and brain stem syndromes (such as bilateral intranuclear ophthalmoplegia, sixth cranial nerve palsy, or trigeminal neuralgia) and hemiparesis or hemi-body sensory symptoms. To diagnose MS, a patient would have to have more than one MS attack separated in time and space. For instance, if a patient developed a partial transverse myelitis and then several months later developed right-sided hemisensory symptoms from a left hemispheric lesion, then this would meet criteria for two separate attacks disseminated in time and in space (i.e. the 1st attack affected the spinal cord and the second attack affected the brain/left hemisphere). In recent years, the MS diagnosis often can be made earlier by applying the more recent McDonald criteria, which allow MRI findings to meet criteria to qualify as two separate MS attacks separated in time and space. For example, applying the McDonald criteria for a patient having had only one clinical attack of an acute/subacute partial transverse myelitis and their MRIs show an acute/subacute demyelinating/inflammatory lesion in the spinal cord with gadolinium enhancement (qualifies as a recent attack in the spinal cord). Their MRI of the brain also shows several asymptomatic

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periventricular non-enhancing demyelinating lesions (this would qualify as past attack in a different location) then this patient would meet the criteria to diagnose multiple sclerosis by having separate attacks disseminated in time and space diagnosed by MRI findings. To diagnosis MS there should also be no better explanation for the patient's clinical presentation. For instance, if an elderly patient with vascular risk factors has white matter lesions present on MRI of the brain, then a potential vascular etiology for the patient's findings should be considered. McDonald criteria also allows for the presence of CSF-specific oligoclonal bands (OCB) to suffice for dissemination in time (Solomon, 2019, p. 614). Approximately 90% of MS patients will have CSF-specific oligoclonal bands found when lumbar puncture is performed.

For most patients it's important to initiate disease modifying drugs (DMDs) early in the course of the disease process, when still in the relapsing remitting phase of the disease and before neurologic disability accumulates. DMDs work by suppressing CNS inflammation, and this CNS inflammation is most prominent early in the disease course.

Within 25 years of symptom onset over 80% of patients with relapsing remitting multiple sclerosis will develop secondary progressive multiple sclerosis (SPMS). Typically with SPMS, the relapsing remitting phase of the disease is overshadowed by a gradual progression of neurologic disability. Often SPMS presents with gradual onset of myelopathy. The progressive phase of MS on average begins in the mid-5th decade of life (Kantarci, 2019, p. 644). Typically, secondary progressive MS is associated with less CNS inflammation, so SPMS doesn't respond as well to disease modifying drugs as relapsing remitting MS. Progressive neurologic decline in SPMS can be explained not just by CNS inflammation but may also be due to axonal degeneration, microglial activation, mitochondrial injury, oxidative stress and glutamate excitoxicity (Ontaneda, p. 737). The stage for secondary progressive MS has been set in motion long before the diagnoses of this progressive form of MS can officially be made. Limited recovery from early relapses accelerates the progression to SPMS (Kantarci, 2019, p. 645). Therefore, it's important to diagnose MS early and get the patient on the appropriate treatment to help lessen potential future disability. Some patients with SPMS still have active inflammation evidenced by continued relapses (on top of their progressive disease course) or as evidenced by continued accumulation of new inflammatory brain or spinal cord MRI lesions. This type of SPMS with ongoing inflammation is known as active SPMS, and DMDs should be considered to suppress the inflammation in these patients. It's unclear if patients with long-standing SPMS without evidence of active inflammation would benefit from initiating DMDs.

Only around 10-15% of MS patients present with the phenotype of primary progressive multiple sclerosis (PPMS) (Solomon, 2019, p. 623). These patients present with a progressive course from initial onset and are typically free of well-defined relapses. Patients with PPMS still have the typical MRI findings seen in the other MS phenotypes. Ocrelizumab, a humanized anti-CD20 monoclonal antibody, is the only DMD approved for treatment of PPMS. However, it's thought to be most effective in those PPMS patients with a more active inflammatory component as evidenced by CSF-specific OCBs and ongoing accumulation of MS-related MRI inflammatory lesions (Ontaneda, 2019, 746). It seems unlikely that DMDs would help a patient with PPMS who is older and whose MRI's have shown no active inflammatory disease for many years. It's prudent to choose the appropriate patient when initiating DMDs for progressive forms of MS to avoid unnecessary, potentially harmful, and costly treatments.

With regards to treatment with DMDs, over the last 10-15 years more DMDs have come to fruition that have substantially improved the outlook for treating MS. The oldest DMDs, with the longest safe track record would include the immune modulator beta interferon drugs and glatiramer. However, these medications are given by injection and they're not the most effective at suppressing CNS inflammation. Over the last decade oral DMDs started coming to the market. Fingolimod, teriflunomide, and dimethyl fumarate are among the most widely used oral DMDs to treat MS. Teriflunomide is not as strong an immunosuppressant, and while deemed safer than the others, it is similar to glatiramer or interferon in that it's less effective at treating MS. Dimethyl Fumarate and Fingolimod are somewhere between the weaker MS drugs and the more powerful infusion medications. Though in my personal experience

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treating MS patients, Fingolimod appears more effective than dimethyl fumarate. Natalizumab and Ocrelizumab infusions are among the most effective DMDs at suppressing CNS inflammation though they come at the expense of increased risk for secondary infections. Natalizumab carries increased risk for developing progressive multifocal leukoencephalopathy, a potentially fatal CNS infection caused by the JC virus.

There are 3 main treatment paradigms guiding physicians on what DMDs to recommend to our patients. The escalation paradigm starts with a DMD that's weaker at suppressing CNS inflammation, but is safer with regards to potential adverse reactions. If MS remains active with one of the weaker DMDs then escalation to a more consistently effective treatment, with potentially more risk for adverse reaction is made (Gross and Corboy, 2019, p. 717). Countering the escalation paradigm is that CNS inflammation, MRI changes, and MS relapses are most active early in the disease course. The induction paradigm begins with a very potent immunosuppressing therapy that is then followed by a less effective albeit safer DMD (Gross and Corboy, 2019, p. 719). Another common treatment approach is to use a more powerful second generation DMD as a 1st line treatment, and then maintain this ongoing treatment with the appropriate monitoring for potential adverse reactions (Gross and Corboy, 2019, p. 720). Patient presentation at onset (i.e. how aggressive the disease is when initially diagnosed) along with potential comorbidities dictate what approach is optimal. For example, if a patient presents with a severe brainstem relapse and has many enhancing lesions on MRI, then a more aggressive DMD would be indicated from onset.

In summary, multiple sclerosis is an autoimmune/inflammatory disease affecting the central nervous system with potential for significant neurologic disability. Over the last 10-15 years there have been many more effective treatments that have come to market allowing for slowing of disability progression. Compared to 30 years ago the outlook for MS patients is brighter.

References available upon request.

Dystonia: Causes, Clinical Features, and Treatment

Aparna Wagle Shukla, MD
UF Health Neurology

Dystonia is the third most common type of movement disorder. Dystonia occurs due to abnormal firing of brain signals leading to excessive muscle contractions. These excessive muscle contractions clinically lead to abnormal jerking movements and twisting postures. Dystonia can affect muscles in one or more body regions, including the eyelids, face, jaws, neck, vocal cords, torso, limbs, hands, and feet. In some patients, rapid jerking movements and slow twisting posture affect the entire body. The abnormal posturing could be mild and intermittent initially, but they can evolve into fixed postures and joint deformities as the severity increases. Dystonic movements are typically patterned and may be tremulous. Dystonia is often initiated or worsened by voluntary action and is associated with overflow muscle activation.

The clinical approach to dystonia focuses on specific historical elements and physical examination features. In addition to the body region affected, it is important to consider age at the onset because subtypes that emerge in infancy are most commonly due to inherited metabolic disorders. Those that arise in later childhood or adolescence are more often inherited genetic dystonia, and those that arise in later adulthood are most often idiopathic. Early-onset cases often start in one body region and progress to broader distributions over months or years. In contrast, late-onset cases tend to have a slower and more limited progression. Another important consideration is a temporal feature that refers to a variation of symptoms over time. Dystonia symptoms can emerge over a short period and remain relatively static. They can also progress rapidly over a few hours or days; they can progress more slowly over many years or sometimes progress in a stepwise fashion. A small percentage of patients can experience remission. Dystonia can occur in isolation or co-occur with tremors, parkinsonism, or ataxia. It can be accompanied by other neurologic problems, such as neuropathy or retinopathy, or systemic issues like liver or kidney disease.

In some cases, dystonia emerges when performing specific motor tasks only. For example, patients with writer's cramp may have cramping of hand muscles and posturing of fingers, wrists, elbow, or shoulder when writing, but have no difficulty using the same hand for eating with forks and knives, drinking, and dressing. Patients with musician's dystonia may report abnormal movements and posture when playing one specific instrument and not another.

More than a century ago, Brissaud, a French neurologist, described a clinical phenomenon known as the sensory trick or the geste antagoniste. Along with many other neurologists, he considered that dystonia might have an underlying psychological origin. He noted that patients with cervical dystonia could reverse the neck movement by a minor voluntary action. The psychological theory was later proved to be incorrect. Sensory tricks are various maneuvers that can ameliorate dystonia. In cervical dystonia, the most common form of focal dystonia, where there is recurrent turning or tilting of the neck, touching specific skin areas of the face, cheek, chin, or back of the neck can relieve the posturing. The light touch application is sufficient even when the force is weak and ordinarily may not have counteracted the dystonic contractions simply by overpowering them. In blepharospasm involving recurrent involuntary closure of the eyes, a device inserted in glasses to mimic touching the lateral eyelid has been found to potentially alleviate the symptoms. In patients with recurrent opening or closing of the jaw, a toothpick placed in the mouth, holding an object clenched between the teeth, and using a dental splint can relieve the symptoms.

How is dystonia diagnosed and managed?

Dystonia is a clinical diagnosis. Diagnostic testing is usually unrevealing in cervical dystonia or

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blepharospasm, the more common focal forms as most cases are idiopathic with no apparent cause. For laryngeal dystonia, laryngoscopy is recommended to rule out structural defects of the vocal apparatus. The yield of diagnostic testing is higher when dystonia manifests early in life.

In general, focal dystonia symptoms are usually controlled with oral medications and/or botulinum toxin injection treatments. However, when dystonia is generalized, most patients require additional surgical treatments such as deep brain stimulation. Recently, dystonia has been found to affect patients' mood, sleep, cognition, and balance, referred to as nonmotor symptoms. Therefore, many patients require multidisciplinary care to successfully treat the numerous aspects of dystonia symptomatology.

Oral medications should be initiated at low doses and titrated up slowly to avoid off-target side effects, especially in older patients. Sometimes, peak benefits are observed only weeks after maintaining constant doses for certain medications like anticholinergic drugs. If the peak benefits are inadequate or short-lasting, a further buildup of doses is recommended. If dose-limiting side effects develop with further escalation, an additional line of therapy is needed to achieve the best possible symptom control. Oral medications for dystonia modulate the functions of brain chemicals such as acetylcholine, gamma-aminobutyric acid (GABA), glutamate, and dopamine that are usually involved in the signaling process. Animal models have shown that acetylcholine signaling in the basal ganglia neurons is abnormal in dystonia. Anticholinergic medications have been among the oldest treatments available in clinical practice. Trihexyphenidyl (Artane) and benztropine (Cogentin) are commonly prescribed anticholinergic medications; however, these drugs non-selectively block all types of muscarinic receptors in the brain (M1, M2, M3, M4, and M5). Thus, side effects of off-target stimulation such as confusional behavior, visual blurriness, and constipation are major limiting factors. Researchers have found that selectively blocking M4 receptors, highly concentrated in the basal ganglia neurons, will likely result in better clinical outcomes. These selective drugs, with potentially greater benefits and fewer side effects, are currently in the development phase. Drugs targeting GABAergic receptors, including benzodiazepines (clonazepam, diazepam, and lorazepam) and baclofen, are other commonly used agents for treating dystonia. GABA is an inhibitory neurotransmitter. An increase in GABA signaling leads to the alleviation of excessive muscle contractions. In some individuals with dystonia, a specific cause can be identified. For example, when dystonia occurs due to a deficiency of enzymes needed to synthesize dopamine, dopamine replacement is found to alleviate symptoms (dopa-responsive dystonia). Sometimes dystonia is related to abnormalities in protein or lipid metabolism or deposition of heavy metals in the brain (e.g., copper, iron). Once the diagnosis is confirmed, appropriate specific therapies can be initiated in these circumstances.

Botulinum toxin is a powerful muscle relaxant effective in controlling abnormal muscle contractions of dystonia. A recent survey involving more than 2000 dystonia patients found botulinum toxin injections were most frequently employed for treating focal dystonia. Botulinum toxin injections block signals sent from the nerve cells to the muscles, preventing the release of the neurotransmitter called acetylcholine. When this release is blocked, the muscle contraction is blocked as well. The muscles can relax and consequently reduces the effects of dystonia. Botulinum toxin effectively relieves symptoms of focal dystonia such as blepharospasm, cervical dystonia, jaw dystonia, and limb dystonia. The benefits of injections start within a few days and last about 10-14 weeks. These injections are therefore repeated every 3 to 4 months. Botulinum toxin is available as BOTOX, XEOMIN, DYSPORT, and MYOBLOC.

DBS is a surgical therapy that involves implanting stimulating electrodes into select brain targets forming an abnormal network. Although the exact mechanism is unclear, DBS is thought to interrupt faulty communication between brain regions participating in these networks. DBS therapy relieves symptoms through reorganization since the brain can adapt to its plastic nature.

Exercises, transcutaneous electrical nerve stimulation, massage therapy, and biofeedback are other promising treatments, although more research is needed.

References available upon request.

Update on Parkinson's Disease

By: Justin Yancey, MD, SIMEDHealth Neurology

Parkinson's disease was first described in 1817 by James Parkinson in his "An Essay on the Shaking Palsy." Parkinson described six patients with the characteristic resting tremor, slowness, and shuffling gait. Today, after Alzheimer's disease, Parkinson's disease (PD) is the second most common neurodegenerative disorder, affecting about 1 million people in the United States and 10 million people worldwide. Approximately 60,000 Americans are diagnosed with Parkinson's disease each year and the incidence increases with age. The average age at the time of diagnosis of Parkinson's disease is 60. Men are slightly more likely than women to develop the disease.

The etiology of Parkinson's disease is not known but it appears to be a combination of genetic and environmental factors. The risk of PD development is increased by several environmental factors, including exposure to certain pesticides, industrial agents, and solvents. Lifestyle factors also seem to play a part with a higher incidence of Parkinson's disease seen in people who live in rural areas, on farms, and drink well water. Interestingly enough, tobacco smoking has been shown in multiple studies to be protective against PD, but obviously is not recommended. Monogenic forms of PD are rare and likely account for less than 10% of cases.

The four cardinal symptoms of Parkinson's disease are resting tremor, rigidity, bradykinesia, and gait instability. The classic unilateral resting tremor of Parkinson's disease is often the first recognized symptom, and what brings patients to medical attention. Tremor is seen in about 90% of patients at some point in the course of their disease. The tremor is typically unilateral but becomes bilateral as disease progresses. Rigidity refers to the stiffness of a limb when passively flexed and is often called cogwheeling. Bradykinesia is slowness to movement. Postural instability, imbalance, and falls often occur later in the course of disease and may correlate with disease severity. Falls are often a major cause of morbidity and mortality in PD patients, causing fractures, loss of independence, and nursing home placement.

Nonmotor symptoms of Parkinson's disease are often overlooked but may cause an even bigger impact on a patient's quality of life than motor symptoms. Some of the nonmotor symptoms of PD include gastrointestinal issues such as constipation, dysphagia and sialorrhea. Sleep issues are often seen and include restless legs, REM sleep behavior disorder, vivid dreams, and excessive daytime sleepiness. Neuropsychiatric symptoms include higher rates of depression, anxiety, apathy, hallucinations, psychosis, and impulse control disorders. Treatment includes antidepressant medications and cognitive behavioral therapy. A close review of a patient's medications may also show possible contributors to these symptoms, and offending medications should be reduced or eliminated if possible. If treatment is needed for bothersome or dangerous hallucinations, the best options include Nuplazid (pimavanserin), Seroquel (quetiapine), or Clozaril (clozapine). These agents are less likely to worsen Parkinson symptoms. Dementia may occur as disease progresses and patients often complain of difficulty with memory retrieval, executive dysfunction, and visuospatial misperception. This is in contrast to the dementia of Alzheimer's disease which includes more aphasia and apraxia. Cholinesterase inhibitors are often used but data is mostly inconsistent.

The gold standard treatment for Parkinson's disease remains levodopa replacement. Levodopa is paired with carbidopa to help prevent nausea and help more dopamine get to the brain. The initiation of treatment early in disease often has an excellent response, but over time the majority of patients will develop motor complications including medication effect wearing off and dyskinesia. Levodopa comes in various forms including immediate release tablet (Sinemet IR), controlled release tablet (Sinemet CR), oral dissolving tablet (Parcopa), easily breakable tablet (Dhivy), dual release capsule (Rytary), continuous intestinal gel infusion (Duopa), and oral inhalation (Inbrija). Sinemet IR is often the most recommended for patients initially due to better tolerance, cost, and pharmacokinetics. Patients are often started at one 25/100 oral tablet three times daily, spaced about every 4 hours from the first morning dose. A dose at bedtime is often not

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needed in early PD. Nausea is the most common side effect with levodopa. It may be taken with food initially while avoiding protein as it seems to prevent some absorption. A catechol-O-methyl transferase (COMT) inhibitor can be added to levodopa-carbidopa to help prevent breakdown of levodopa. These include Comtan (entacapone) and Ongentys (opicapone). The COMT inhibitor Tasmar (tolcapone) should generally not be used due to concern for hepatotoxicity. Care should be used when prescribing these medications due to higher risk of dyskinesia, but in the correct patient these can be beneficial.

Dopamine agonists have also been found to help alleviate symptoms of Parkinson's disease. These most commonly include Mirapex (pramipexole), Requip (ropinirole) and Neupro patch (rotigotine). Mirapex and Requip also include extended-release forms. Dopamine agonists act directly on dopamine receptors and mimic dopamine's effect. Adverse effects to dopamine agonists are similar to dopamine and includes nausea, orthostasis and hallucinations. A worrisome side effect to dopamine agonists include impulse control disorders (ICDs). ICDs are a class effect and likely affects 50% of patients with long-term use. ICDs commonly include pathologic gambling, impulsive sexual behavioral, and excessive spending. These should be carefully screened for at every visit for patients on these medications, including for patients treated for restless legs syndrome with dopamine agonists.

Monoamine oxidase-B (MAO-B) inhibitors are another class of medication commonly used to treat Parkinson's disease. MAO-B inhibitors act to help prevent the breakdown of dopamine in the brain. These include Zelapar (selegiline), Azilect (rasagiline) and Xadago (safinamide). Studies have shown these drugs to have a modest effect on PD symptoms, but are generally well-tolerated with nausea and headache occasionally occurring. These selective MAO-B inhibitors also lack the tyramine effect seen with MAO-A inhibitors when used at recommended doses. Other medications including amantadine, anticholinergics (Artane, Cogentin), and an adenosine receptor antagonist (Nourianz) are also used to augment dopamine but are beyond the scope of this article.

For patients who experience continued motor symptoms despite medication management, surgical and procedural options are also available as therapies. Deep brain stimulation (DBS) is a common surgical procedure used in Parkinson's disease. It was approved in 2002 by the FDA as adjunctive therapy for reducing complications of advanced PD. It may also be beneficial early in the course of PD for patients with refractory tremor, dyskinesia, and/or intolerance to levodopa. In DBS surgery electrodes are placed in one or both sides of the brain in the areas affecting movement. These electrodes are then connected to a battery pack located in the chest, similar to a cardiac pacemaker. The device provides continuous electrical stimulation to these specific brain areas to help ameliorate symptoms of PD. Adjustments can be made to the DBS settings over time and if symptoms change. Often DBS allows patients to reduce, but not completely eliminate, oral medications for PD. Focused ultrasound is another procedure for PD that involves lesioning areas in the brain involved with Parkinson's disease. It was first FDA approved in 2018 for Parkinson's tremor and then expanded in 2021 for rigidity, bradykinesia, and dyskinesia. Focused ultrasound is marketed as "noninvasive" as it is not a surgical procedure - however brain tissue is destroyed and results are irreversible. Focused ultrasound can only be performed on one side of the brain so it is not suitable for patients with bilateral symptoms. It is likely best reserved for patients who are not interested in DBS, cannot undergo invasive surgery, or do not want to manage logistics of DBS programming and battery replacement.

As Parkinson's disease progresses the symptoms will become worse and have more impact on a patient's quality of life. Progression is variable and no particular sign, symptom, or test can accurately determine the future course of the disease. There are currently no medications shown to slow progression of PD. Most studies suggest mortality is only modestly increased for PD patients compared with age-matched controls. Physicians and other members of the healthcare team should closely monitor PD patients for fall risk and dysphagia. Coordinated care and close follow-up with a multidisciplinary team consisting of the patient's primary care physician, neurologist, mental health specialist, dietician, and physical, occupational, and speech therapists help improve the patient's functionality and quality of life. Much ongoing research is occurring in Parkinson's disease and with time, I believe we will have a cure.

References available upon request.

ACMS HAPPENINGS

2022 FMA Meeting

Hyatt Regency Grande Cypress , Orlando FL

August 5-7, 2022

L to R:Angeli Akey, MD; Carl Dragstedt, DO, ACMS President; Jean Cibula, MD; and Steven Reid, MD at the Friday night gathering.

Steven Reid, MD addressing the House of Delegates.

L to R: Steven Reid, MD; Angeli Akey, MD; Brittany Bruggeman, MD, ACMS Secretary/Treasurer; Christoppher Bray, MD; and Carl Dragstedt, DO, ACMS President at the House of Delegates Meeting.

L to R: (first row) Brittany Bruggeman, MD, ACMS Secretary/ Treasurer; Carl Dragstedt, DO, ACMS President; (second row) Steven Reid, MD; Joseph Thornton, MD and Angeli Akey, MD at the House of Delegated Meeting.

Thanks to all our Delegates for representing the ACMS and Alachua County at the statewide FMA meeting this year!

ACMS Board Highlights

Alachua County Medical Society - Board of Directors Meeting Minutes, April 5, 2022

Pursuant to notice, the Board of Directors of the Alachua County Medical Society met on Tuesday, April 5, 2022, virtually on Zoom.com.

Secretary's Report: Dr. Bruggeman welcomed and introduced Christina Sedaros, the UF COM Medical Student Representative.

Treasurer's Report:

Alachua County Medical Society, Inc. – a 501(c)6: Membership dues collected from August 2021 to March 2022 totaled $67.7K for the seven months of operations, a $24K increase over this time last year, showing an upward trend in Membership Dues Income overall. Publication and Activities Income totaled $27K, compared to $12K in the prior year, returning to pre-covid levels. This resulted in a Gross Profit of $96.7K for the period. Event expenses increased to $7.7K as the ACMS is hosting in-person events again in outdoor venues. Publication expenses continue to decline as we have converted much of our readership to electronic versions, resulting in a Net Income of $13.7K for the period under review.

Alachua County Medical Society Foundation, Inc. - a 501(c)3: The Foundation disbursed $17.2K in grants during the period – going to FIT Kits for the We Care Clinic and Salaries for We Care Clinic support staff. Grant Income was $23.7K. Total Assets are $166K, with $0 liabilities. Dr. Bruggeman motioned acceptance of the Treasurer's Report, seconded by Dr. Riggs, and carried by the Board.

President's Report: The Board voted on the candidates for the UF COM Resident Board Representative with Varsha Kurup, MD and Brandon Lucke-Wold, MD, PhD receiving the most votes. Their appointment was unanimously approved by the Board.

EVP Report: Ms. Owens discussed upcoming ACMS meetings for April and May, announcing that the April meeting would be an in-person Vendor Show and Poker Run at Celebration Pointe.

Alachua County Medical Society - Board of Directors Meeting Minutes, May 24, 2022

Pursuant to notice, the Board of Directors of the Alachua County Medical Society met on Tuesday, May 24, 2022, virtually on Zoom.com.

Secretary's Report: Dr. Bruggeman welcomed Brandon Lucke-Wold, MD and Varsha Kurup, MD, the UF COM Resident Representatives.

Treasurer's Report:
Alachua County Medical Society, Inc. – a 501(c)6:
Membership dues, Publication Income and Activities Income have improved with a total of $96K in 2022 compared to $59.7K in 2021. Event expense has increased due to the resumption of in-person meetings and is approximately equal to the Events Income (sponsorships for those events). Publication Expense continues to decline as more members are converting to electronic copies of our publications. Net Income for the eight month period in 2022 is $4.9K.

Alachua County Medical Society Foundation, Inc. - a 501(c)3: The Foundation disbursed $54.5K in grants during the eight months under review – going to FIT Kits for the We Care Clinic and Salaries for We Care Clinic support staff. Grant Income was $68.9K. Total Assets are $165K, with $0 liabilities. Dr. Riggs motioned acceptance of the Treasurer's Report, seconded by Dr. Balamucki, and carried by the Board.

President's Report: Dr. Dragstedt discussed a letter from Desmond Schatz, MD (UF Health Interim Chair, Pediatrics) regarding statements issued by the Florida Surgeon General and the Florida Department of Health on the treatment of gender dysphoria for children and adolescents. The Board asked that the EVP circulate this letter to ACMS members and allow them to decide individually if they wish to add their signature to a letter to the FDOH from Dr. Schatz.

The Board discussed the ACMS position on COVID-19 vaccine recommendations for children and stated that we will continue to provide scientifically based medical advice to the public in recommending that children should receive the vaccine.

EVP Report: Ms. Owens discussed a request from FMA President-Elect Jason Goldman, MD, for endorsement as FMA President. Dr. Riggs volunteered to talk with Dr. Goldman to find out his stance on medical issues and report back to the Board. After receiving Dr. Riggs summary and circulating it to the Board, the EVP will poll the Board Members to determine if an endorsement is approved, and if so, issue said endorsement to Dr. Goldman.

PSP and MSA: Rare but Devastating

By Scott Medley, MD

For this Neurology Issue of House Calls, I decided to write about two rare but devastating Neurologic diseases – Progressive Supranuclear Palsy (PSP), and Multisystem Atrophy (MSA). This will not be an exhaustive review of either disease, but rather a brief overview of both. These diseases are similar in some ways. And in some cases, especially in the early stages, it may be difficult to distinguish between them. They are both sometimes referred to as "Parkinson-plus" syndromes. Unfortunately, neither syndrome has a cure, and it just so happens that each of these diseases has occurred recently in individuals who are my good friends. Both of these friends were in previous good health and they had both just retired from impressive, productive occupations. Thus, I have a bit of a closer interest and insight into these devastating conditions.

Unfortunately, neither syndrome has a cure, and it just so happens that each of these diseases has occurred recently in individuals who are my good friends. Both of these friends were in previous good health and they had both just retired from impressive, productive occupations. Thus, I have a bit of a closer interest and insight into these devastating conditions.

PSP

The onset is often insidious, presenting with a number of neurologic symptoms – vague fatigue, headaches, arthralgias, dizziness, depression, personality changes, memory problems and others. Two hallmarks of the disease are postural instability leading to falls, and ophthalmologic problems such as vertical and downward gaze abnormalities. In fact, "supra-nuclear" refers to a lesion that is situated above the oculomotor nuclei. This is almost always a gradually progressive disorder, leading to multiple neurologic disabilities. Cognitive dysfunction is common, but usually not as severe as that found in Alzheimer's disease and other forms of dementia.[1]

The diagnosis of PSP is usually a clinical one. There may be tau forms in the cerebral spinal fluid. An MRI is usually of little help in the diagnosis except in advanced cases. The MRI may be helpful, however, in eliminating other diseases. A PET scan may be helpful also.

No medication is generally effective, including Parkinson's medications. Care is mostly supportive. Consults with ophthalmology, rehab medicine, physical therapy and speech therapy may be helpful. Swallowing difficulties with bronchoaspiration may occur, prompting the need for a feeding gastrostomy. The prognosis until death is usually a few years, but may be much longer with excellent supportive care.

MSA

Like PSP, MSA is a rare condition of the nervous system that causes gradually progressive damage. And, like PSP, MSA is an idiopathic process that causes a wide array of neurologic symptoms. Hallmarks include balance

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problems, movement disorders, Parkinson-like features and autonomic nervous system failure, eventually leading to problems with breathing, digestion, and bladder control.[2] Symptoms include dizziness, syncope, and falls. There is now recognized a cluster of conditions – some with rather exotic names - olivopontocerebellar atrophy (OPCA); striatronized degeneration (SND); and Shy-Drager syndrome (SDS), which are now considered variants of MSA. As mentioned earlier, MSA may have predominantly Parkinson-like symptoms (MSA-P) or prominent cerebellar dysfunction (MSA-C). This disease usually progresses more rapidly than Parkinson's disease. Fifty percent of patients are wheelchair-bound in 5-6 years. Dementia is less frequent than in PSP.

Pathologic features include glial cytoplasmic inclusions and neuronal multisystem degeneration. This disease is sporadic, usually not familial. Unfortunately, there is no way to slow its progress, and no cure. Parkinson's drugs like levodopa may be tried, but are usually not helpful. [3]

Life expectancy may be about six years from onset of disease, but varies widely. Death usually occurs from autonomic failure, aspiration pneumonia, or pulmonary emboli (see Table 1).

References available upon request.

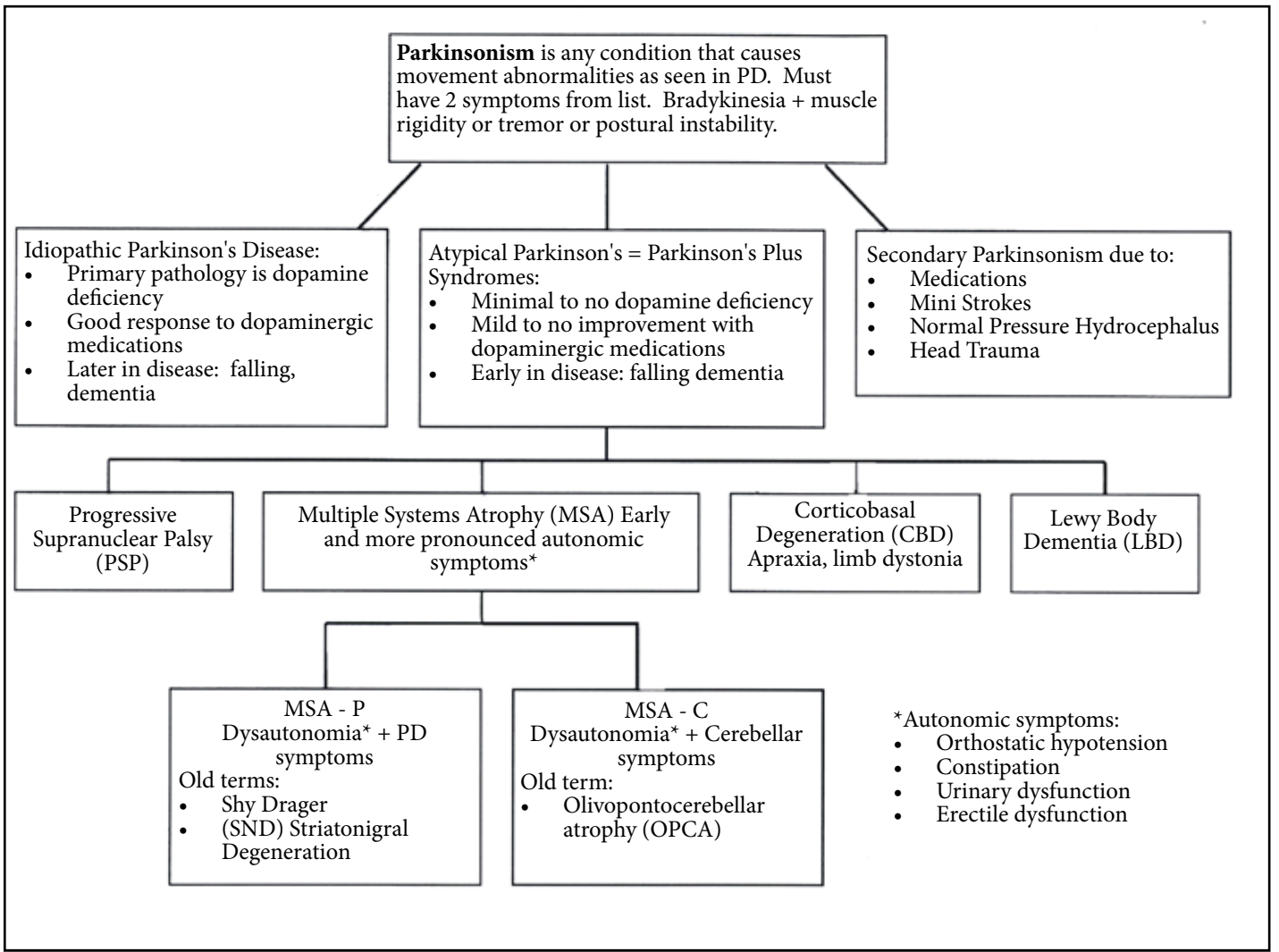

Table 1: Source: Science of Parkinsonism

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