

**Parkinson's Disease Center
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Progressive Supranuclear Palsy

Diagnosis

Progressive supranuclear palsy (PSP) is a rare neurodegenerative condition that is a form of atypical parkinsonism, meaning that it shares some features with Parkinson's disease. These include stiffness of neck and trunk muscles (rigidity), slowness of movement (bradykinesia), and impaired balance. Unlike classic Parkinson's disease, tremor is rarely a prominent part of PSP. The most common symptoms are reduced eye movements, recurrent falls (frequently backwards), reduced balance and mobility, speech and swallowing difficulties, and cognitive decline. PSP was first described in 1964 by Drs. Steele, Richardson, and Olszewski. It occurs more often in men, and the age at onset is typically in the 60's, roughly ten years later than the usual onset of classic Parkinson's disease. Up to 6 in 100,000 people develop PSP.

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Gait instability with falls is the most disabling symptom and is often one of the earliest manifestations of PSP. Gait instability and falls are caused by a combination of problems, including loss of postural (adjustment) reflexes, difficulty lifting one's feet ("freezing") particularly when turning, stiffness of neck and trunk muscles, slowness of movement, and inability to look down at the floor. The average period from onset of symptoms to the first fall in PSP is 16.8 months, as compared to 108 months in Parkinson's disease. After an average of 5-8 years, worsening balance usually makes walking (ambulation) very difficult, if not

impossible. A common early feature of PSP is motor recklessness (moving without thinking or caution). Patients may demonstrate the “rocket sign” where he or she stands straight up and falls back forcefully into a chair when sitting and standing.

The most specific diagnostic feature is the supranuclear vertical gaze palsy (inability to look up and down). Difficulty moving one's eyes in the downward direction is particularly suggestive of the disorder. Many PSP patients become messy eaters because they are unable to look down at their plate. Patients usually do not complain of abnormal eye movements, although they may notice blurring of vision and problems reading. As the disease progresses, horizontal eye movements may also become affected. PSP patients may also develop involuntary, intermittent forceful eyelid closure (blepharospasm) or difficulty opening the eyelids at will (apraxia of eyelid opening).

Obvious facial signs may be present with examples including decreased blink rate and a “startled” facial expression, which results from rigid facial muscles, but these signs may not be present in the early stages of the disease.

PSP patients may develop slurred and monotonous speech and trouble swallowing. Mealtimes may become increasingly time consuming and effortful because of issues related to PSP. In most cases, support with eating and drinking will become necessary. Impulsivity can lead to food cramming and rapid drinking. This, in conjunction with weakened throat muscles, increases the risk for aspiration of food, which may lead to pneumonia. A patient with PSP may lack any awareness of these swallowing difficulties. If swallowing issues are identified, such as coughing or choking on food or liquids, it is advisable to undergo evaluation with a speech-language pathologist, who can help advise on dietary modifications to aid in safe swallowing.

Most patients retain relatively normal thinking and memory function until the more advanced stages of the disease. Cognitive problems are associated with memory, language, executive function (set of mental skills that help planning and getting things done), and flexibility of thought. PSP patients may have difficulty with word finding, learning new tasks, insight, multi-tasking, and impulsivity. Signs of depression need to be monitored for and support from counseling, psychology services and mental health services may be appropriate.

There are several variants of PSP that may present in a somewhat different manner from the “Classic” PSP described above.

- PSP-parkinsonism affects about 30% of people with PSP and features include asymmetric limb rigidity, tremor, and a moderate response to initial trials of levodopa therapy.
- Pure akinesia with gait freezing involves early gait problems, small handwriting, poor speech volume, and freezing of gait.
- PSP-corticobasal syndrome mimics cortico-basal degeneration (CBD), another atypical parkinsonism disorder, characterized by unilateral or asymmetric limb apraxia, dystonia and rigidity, and a variety of other motor and cognitive/behavioral symptoms.
- PSP-progressive non-fluent aphasia may present with spontaneous non-fluent speech, meaning there is a loss of the natural, coherent production of speech, although comprehension of speech remains intact.

Most patients with PSP are initially diagnosed with Parkinson's disease, but when the atypical features, particularly early falls and abnormal eye movements, emerge, the correct diagnosis becomes apparent. CurePSP suggested the use of the FIGS acronym to aid in differentiation of PSP from Parkinson's disease:

- **F**- Frequent sudden falls (generally backwards, occurring early in the disease)
- **I**- Ineffective medication (medications for Parkinson's disease generally do not work)
- **G**- Gaze palsy (difficulty moving the eyes vertically)

- **S-** Speech and swallow changes.

There is no definitive diagnostic test for PSP, therefore, the diagnosis is based on a detailed history, interpretation of physical examination signs and symptoms, and investigations to rule out other possible causes of symptoms. Neuroimaging with MRI (a brain scan) is useful to exclude strokes and other brain abnormalities that may present similarly to PSP. MRI of the brain often shows characteristic atrophy (shrinkage) of the brain, especially prominent in the midbrain, the uppermost segment of the brainstem, known as the “hummingbird sign.” Testing may be useful to document sleep disturbances and changes in other physiological parameters, but these are not yet suited to aid in diagnosis.

Cause

PSP is generally a sporadic condition, meaning that is not usually an inherited condition. The cause of PSP is still not fully understood, but pathological changes noted on autopsy examination have provided insights into the mechanisms of brain cell loss (neurodegeneration). Like many other neurodegenerative diseases, patients with PSP accumulate an abnormal amount of protein called tau. Recent studies have focused on mishandling of tau, a protein that normally acts to stabilize the cellular skeleton of nerve cells. Faulty processing of tau may impair mitochondria, the compartment of cells responsible for energy production, and thus lead to brain cell death. In PSP, cells within the basal ganglia and some brainstem structures are most severely affected.

Treatment

There are no approved drugs for the treatment of PSP, thus, treatment focuses on symptom management. In the early stages of PSP, levodopa and drugs that act directly on dopamine receptors (dopamine agonists) may partially improve parkinsonian symptoms, such as slowness of movement, but these drugs rarely provide any meaningful improvement in balance, eye, speech and swallowing problems.

Botulinum toxin injections into the eyelids and eyebrows can be effective for treating patients with blepharospasm and apraxia of eyelid opening.

Selective serotonin re-uptake inhibitors (SSRIs) may be beneficial in the treatment of depression in PSP patients. Antidepressant medications and Nuedexta™, dextromethorphan/quinidine (DM/Q) are sometimes useful, particularly in controlling emotional lability (also known as pseudobulbar affect).

Non-drug treatments of PSP include physical therapy and stretching exercises designed to improve rigidity and to prevent contractures and deformities as well as to maintain good strength and condition of muscles. Devices that make walking safer, such as a walker that is weighted in the front, can be helpful to prevent falls. Shoes with built-up heels can also help decrease falling backwards. Since patients have difficulty looking down, low objects like coffee tables and throw rugs are best avoided.

Because of swallowing problems some patients require placement of a feeding tube directly into the stomach in order to maintain adequate nutrition and prevent aspiration pneumonia. If general health and nutrition can be maintained, some PSP patients can live for 10 years or longer after the onset of symptoms, although their quality of life in the advanced stages of the disease is usually significantly impaired.

At present, there are no therapies that can reverse or even slow the progression of PSP. Furthermore, since PSP is quite rare, clinical drug trials are sometimes not available for affected patients. Nonetheless, there is reason for hope. Because the biology of PSP may be related to other neurodegenerative diseases, it is possible that therapies designed for other conditions will also prove helpful for patients with

PSP. Information about ongoing clinical trials that may present opportunities for patient participation can be found at clinicaltrials.gov and curepsp.org.

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