Progressive Supranuclear Palsy

U.S. DEPARTMENT OF HEALTH
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What is progressive supranuclear palsy?

Progressive supranuclear palsy (PSP) is an uncommon brain disorder that affects movement, control of walking (gait) and balance, speech, swallowing, vision, mood and behavior, and thinking. The disease results from damage to nerve cells in the brain. The disorder's long name indicates that the disease worsens (*progressive*) and causes weakness (*palsy*) by damaging certain parts of the brain above nerve cell clusters called nuclei (*supranuclear).* These nuclei particularly control eye movements. One of the classic signs of the disease is an inability to aim and move the eyes properly, which individuals may experience as blurring of vision.

Estimates vary, but only about three to six in every 100,000 people worldwide, or approximately 20,000 Americans, have PSP—making it much less common than Parkinson's disease (another movement disorder in which an estimated 50,000 Americans are diagnosed each year). Symptoms of PSP begin on average after age 60, but may occur earlier. Men are affected more often than women.

PSP was first described as a distinct disorder in 1964, when three scientists published a paper that distinguished the condition from Parkinson's disease. It was sometimes referred to as Steele-Richardson-Olszewski syndrome, reflecting the combined names of the scientists who defined the disorder.

Currently there is no effective treatment for PSP, but some symptoms can be managed with medication or other interventions.

What are the symptoms?

The pattern of signs and symptoms can be quite different from person to person. The most frequent first symptom of PSP is a loss of balance while walking. Individuals may have unexplained falls or a stiffness and awkwardness in gait.

As the disease progresses, most people will begin to develop a blurring of vision and problems controlling eye movement. In fact, eye problems, in particular slowness of eye movements, usually offer the first definitive clue that PSP is the proper diagnosis. Individuals affected by PSP especially have trouble voluntarily shifting their gaze vertically (i.e., downward and/or upward) and also can have trouble controlling their eyelids. This can lead to a need to move the head to look in different directions, involuntary closing of the eyes, prolonged or infrequent blinking, or difficulty in opening the eyes. Another common visual problem is an inability to maintain eye contact during a conversation. This can give the mistaken impression that the person is hostile or uninterested.

People with PSP often show alterations of mood and behavior, including depression and apathy. Some show changes in judgment, insight, and problem solving, and may have difficulty finding words. They may lose interest in ordinary pleasurable activities or show increased irritability and forgetfulness. Individuals may suddenly laugh or cry for no apparent reason, they may be apathetic, or they may have occasional angry outbursts, also for no apparent reason. Speech usually becomes slower and slurred and swallowing solid foods or liquids can be difficult. Other symptoms include slowed movement, monotone speech, and a mask-like facial expression. Since many symptoms of PSP are also seen in individuals with Parkinson's disease, particularly early in the disorder, PSP is often misdiagnosed as Parkinson's disease.

How is PSP different from Parkinson's disease?

Both PSP and Parkinson's disease cause stiffness, movement difficulties, and clumsiness, but PSP is more rapidly progressive as compared to Parkinson's disease. People with PSP usually stand exceptionally straight or occasionally even tilt their heads backward (and tend to fall backward). This is termed "axial rigidity." Those with Parkinson's disease usually bend forward. Problems with speech and swallowing are much more common and severe in PSP than in Parkinson's disease, and tend to show up earlier in the course of the disease. Eye movements are abnormal in PSP but close to normal in Parkinson's disease. Both diseases share other features: onset in late middle age, bradykinesia (slow

movement), and rigidity of muscles. Tremor, very common in individuals with Parkinson's disease, is rare in PSP. Although individuals with Parkinson's disease markedly benefit from the drug levodopa, people with PSP respond minimally and only briefly to this drug. Also, people with PSP show accumulation of the protein *tau* in affected brain cells, while people with Parkinson's disease show accumulation of a different protein, called *alpha-synuclein*.

What causes PSP?

The exact cause of PSP is unknown. The symptoms of PSP are caused by a gradual deterioration of brain cells in a few specific areas in the brain, mainly in the region called the brain stem. One of these areas, the substantia nigra, is also affected in Parkinson's disease, and damage to this region of the brain accounts in part for the motor symptoms that PSP and Parkinson's have in common.

The hallmark of the disease is the accumulation of abnormal deposits of the protein tau in nerve cells in the brain, so that the cells do not work properly and die. The protein tau is associated with microtubules – structures that support a nerve cell's long processes, or axons, that transmit information to other nerve cells. The accumulation of tau puts PSP in the group of disorders called the *tauopathies,* which also includes other disorders such as Alzheimer's disease, corticobasal degeneration, and some forms of frontotemporal degeneration. Scientists are looking at ways to prevent the harmful clumping of tau in treating each of these disorders.

PSP is usually sporadic, meaning that occurs infrequently and without known cause; in very few cases the disease results from mutations in the *MAPT* gene, which then provides faulty instructions for making tau to the nerve cell. Genetic factors have not been implicated in most individuals.

There are several theories about PSP's cause. A central hypothesis in many neurodegenerative diseases is that once the abnormal aggregates of proteins like tau form in a cell, they can affect a connected cell to also form the protein clumps. In this way the toxic protein aggregates spreads through the nervous system. How this process is triggered remains unknown. One possibility is that an unconventional infectious agent takes years or decades to start producing visible effects (as is seen in disorders like Creutzfeldt-Jakob Disease). Another possibility is that random genetic mutations, of the kind that occur in all of us all the time, happen to occur in particular cells or certain genes, in just the right combination to injure these cells. A third possibility is that there is exposure to some unknown chemical in the food, air, or water which slowly damages certain vulnerable areas of the brain. This theory stems from a clue found on the Pacific island of Guam, where a common neurological disease occurring only there and on a few neighboring islands shares some of the characteristics of PSP, Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis. Its cause is thought to be a dietary factor or toxic substance found only in that area.

Another possible cause of PSP is cellular damage caused by free radicals, which are reactive molecules produced continuously by all cells during normal metabolism. Although the body has built-in mechanisms for clearing free radicals from the system, scientists suspect that, under certain circumstances, free radicals can react with and damage other molecules. A great deal of research is directed at understanding the role of free radical damage in human diseases.

How is PSP diagnosed?

No specific laboratory tests or imaging approaches currently exist to definitively diagnose PSP. The disease is often difficult to diagnose because its symptoms can be very much like those of other movement disorders, and because some of the most characteristic symptoms may develop late or not at all. Initial complaints in PSP are typically vague and fall into these categories: 1) symptoms of disequilibrium, such as unsteady walking or abrupt and unexplained falls without loss of consciousness; 2) visual complaints, including blurred vision, difficulties in looking up or down, double vision, light sensitivity, burning eyes, or other eye trouble; 3) slurred speech; and 4) various mental complaints such as slowness of thought, impaired memory, personality changes, and changes in mood. An initial diagnosis is based on the person's medical history and a physical and neurological exam. Diagnostic scans such as magnetic resonance imaging may show shrinkage at the top of the brain stem. Other imaging tests can look at brain activity in known areas of degeneration.

PSP is often misdiagnosed because it is relatively rare and some of its symptoms are very much like those of Parkinson's disease. Memory problems and personality changes may also lead a physician to mistake PSP for depression, or even attribute symptoms to some form of dementia. The key to diagnosing PSP is identifying early gait instability and difficulty moving the eyes, speech and swallow abnormalities, as well as ruling out other similar disorders, some of which are treatable.

Is there any treatment?

There is currently no effective treatment for PSP, although scientists are searching for better ways to manage the disease. PSP symptoms usually do not respond to medications. Drugs prescribed to treat Parkinson's disease, such as ropinirole, rarely provide additional benefit. In some individuals the slowness, stiffness, and balance problems of PSP may respond to some degree to antiparkinsonian agents such as levodopa, but the effect is usually minimal and short-lasting. Excessive eye closing can be treated with botulinum injections. Some antidepressant drugs may provide benefit beyond treating depression, such as pain relief and decreasing drooling.

Recent approaches to therapeutic development for PSP have focused primarily on the clearance of abnormally accumulated tau in the brain. One ongoing clinical trial will determine the safety and tolerability of a compound that prevents accumulation of tau in preclinical models. Other studies are exploring improved tau imaging agents that will be used to assess disease progression and improvement in response to treatment.

Non-drug treatment for PSP can take many forms. Individuals frequently use weighted walking aids because of their tendency to fall backward. Bifocals or special glasses called prisms are sometimes prescribed for people with PSP to remedy the difficulty of looking down. Formal physical therapy is of no proven benefit in PSP, but certain exercises can be done to keep the joints limber.

A gastrostomy (a minimally invasive surgical procedure that involves the placement of a tube through the skin of the abdomen into the stomach for feeding purposes) may be necessary when there are swallowing disturbances or the definite risk of severe choking. Deep brain stimulation (which uses a surgically implanted electrode and pulse generator to stimulate the brain in a way that helps to block signals that cause many of the motor symptoms) and other surgical procedures used in individuals with Parkinson's disease have not been proven effective in PSP.

What is the prognosis?

The disease gets progressively worse, with people becoming severely disabled within three to five years of onset. Affected individuals are predisposed to serious complications such as pneumonia, choking, head injury, and fractures. The most common cause of death is pneumonia. With good attention to medical and nutritional needs, it is possible for individuals with PSP to live a decade or more after the first symptoms of the disease.

What research is being done?

The mission of the National Institute of Neurological Disorders and Stroke (NINDS) is to seek fundamental knowledge about the brain and nervous system and to use that knowledge to reduce the burden of neurological disease. The NINDS is a component of the National Institutes of Health (NIH), the leading funder of biomedical research in the world.

Previous studies have linked regions of chromosomes containing multiple genes, including the gene for tau (MAPT), with PSP. Researchers are now using methods to more finely map these regions and identify specific disease-causing mutations, which could point to additional targets for future therapy development.

PSP is one of the diseases being studied as part of the NINDS Parkinson's Disease Biomarkers Program (*http://pdbp.ninds.nih.gov/*). This major NINDS initiative aimed at discovering ways to identify individuals at risk for developing Parkinson's disease and related disorders, and to track the progression of the disease. NINDS also supports clinical research studies to develop brain imaging that may allow for earlier and more accurate diagnosis of PSP, and that may be used to predict or monitor disease progression. Such imaging markers could be important tools in clinical care to help distinguish PSP from other related disorders, as well as for research to test potential treatments that may not work equally well for outwardly similar disorders.

Researchers are looking for genes that might increase a person's risk of developing PSP. Scientists are studying gene-environment interaction – in which environmental factors and genetics may contribute to disease susceptibility for many diseases in which there may be genetic influences that differ among families or even in a single family. Investigators are integrating research tools involved with human genetics and disease epidemiology to better understand the joint risk factors that may contribute to the cause of PSP.

Although the protein tau has been linked to PSP and other related disorders, scientists do not yet understand the mechanisms that lead to disease and symptoms. Tau can exist in multiple shapes, or conformations, and research has shown that some of these conformations are harmful, leading to toxic clumps and disruption of signal pathways inside cells. NINDS supports a number of studies to characterize and distinguish the different conformations of tau and to understand their role in disease. Investigators are also developing animal models of PSP and other tau-related disorders, including fruit fly and zebrafish models, for research on disease mechanisms and preclinical testing of potential drugs. Other studies in animal models focus on brain circuits affected by PSP, such as those involved in motor control and sleep regulation, which may also yield insights into disease mechanisms and treatments.

Because the symptoms of individuals with PSP progress more rapidly than in other tauopathies, some investigators believe that an anti-tau therapy will show benefit more quickly in PSP clinical trials.

The Rare Diseases Clinical Research Network, which is led by NIH's National Center for Advancing Translational Sciences (NCATS), is designed to advance medical research on rare diseases by facilitating research collaboration, study enrollment, and data sharing among rare diseases researchers. A research consortium funded under this project studies neurological disorders, including PSP. For more information about the Rare Diseases Clinical Research Network, see *http://www.ncats.nih.gov/research/rare-diseases/ordr/rdcrn/rdcrn.html*.

Ongoing research supported across the NIH on related and more common diseases with shared features, such as Parkinson's and Alzheimer's diseases, will likely yield insights into PSP, just as studying PSP may help shed light on Parkinson's and Alzheimer's diseases. Research on these diseases and other disorders can be found using NIH RePORTER (*http://projectreporter.nih.gov*), a searchable database of current and past research projects supported by NIH and other federal agencies. RePORTER also includes links to publications and patents citing support from these projects.

Where can I get more information?

For more information on neurological disorders or research programs funded by the National Institute of Neurological Disorders and Stroke, contact the Institute's Brain Resources and Information Network (BRAIN) at:

BRAIN
P.O. Box 5801
Bethesda, MD 20824
800-352-9424
www.ninds.nih.gov

Information on progressive supranuclear palsy also is available from the following organizations:

CurePSP (Foundation for PSP|CBD and Related Brain Diseases)
30 E. Padonia Road, Suite 201
Timonium, MD 21093
410-785-7004
800-457-4777
www.curepsp.org

National Organization for Rare Disorders
55 Kenosia Avenue
Danbury, CT 06810
203-774-0100
www.rarediseases.org

U.S. National Library of Medicine
National Institutes of Health/DHHS
8600 Rockville Pike
Bethesda, MD 20894
301-594-5983
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