Progressive Supranuclear Palsy

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

Progressive supranuclear palsy (PSP) is a rare brain disorder that causes problems with movement, walking and balance, and eye movement. It results from damage to nerve cells in the brain that control thinking and body movement. 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)* that control eye movements.

PSP is different than Parkinson's disease—another movement disorder—although they share some symptoms (see section, "How is PSP different from Parkinson's Disease?"). Currently there is no effective treatment for PSP, but some symptoms can be managed with medication or other interventions.

What are the symptoms?

PSP affects movement, control of walking (gait) and balance, speech, swallowing, eye movements and vision, mood and behavior, and thinking. 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 abrupt and unexplained falls without loss of consciousness, a stiff and awkward gait, or slow movement.

As the disease progresses, most people will begin to develop **a blurring of vision and problems controlling eye movement**. These symptoms may include:

- Slow eye movements.
- Trouble voluntarily shifting gaze vertically (i.e., downward and/or upward).
- Trouble controlling eyelids.
- Tendency to move the head to look in different directions.
- Involuntary closing of the eyes.
- Prolonged or infrequent blinking.
- Difficulty in opening the eyes.
- Inability to maintain eye contact during a conversation.

People with PSP often show **alterations of mood and behavior**. These symptoms may include:

- Depression.
- Apathy.

- Changes in judgment, insight, and problem solving.
- Difficulty finding words.
- Loss of interest in ordinary pleasurable activities.
- Increased irritability and forgetfulness.
- Sudden laughing or crying or displaying angry outbursts for no apparent reason.
- Personality changes.

Other symptoms may include:

- Slowness of thought.
- Memory problems.
- Slowed, slurred, or monotone speech.
- Difficulty swallowing solid foods or liquids.
- Mask-like facial expressions.

How is PSP different from Parkinson's disease?

PSP is often misdiagnosed as Parkinson's disease, especially early in the disorder, as they share many symptoms, including stiffness, movement difficulties, clumsiness, bradykinesia (slow movement), and rigidity of muscles. The onset of both diseases is in late middle age. However, PSP progresses more rapidly than Parkinson's disease.

- People with PSP usually stand exceptionally straight or occasionally 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 disease.
- Eye movements are abnormal in PSP but close to normal in Parkinson's disease.
- Tremor is rare in PSP but very common in individuals with Parkinson's disease.

Although individuals with Parkinson's disease markedly benefit from the drug levodopa, people with PSP respond minimally and only briefly to this drug.

People with PSP show accumulation of the protein *tau* in affected brain cells, whereas people with Parkinson's disease show accumulation of a different protein called *alpha-synuclein*.

What causes PSP?

The exact cause of PSP is unknown, but research suggests that it involves a gradual deterioration of brain cells in a few specific areas in the brain, mainly in brain stem. The death of brain cells in one of these areas, the substantia nigra, accounts in part for the motor symptoms that PSP and Parkinson's have in common.

The hallmark of PSP is the accumulation of abnormal deposits of the protein tau in nerve cells in the brain. These deposits cause the cells to malfunction and die, which stops the flow of information to other nerve cells. The accumulation of tau puts PSP in

the group of disorders called the *tauopathies,* which includes Alzheimer's disease, corticobasal degeneration, and some forms of frontotemporal degeneration.

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

Several theories suggest that PSP might be caused by:

- The abnormal buildup of the protein tau in a cell causes the buildup in a connected cell, which then spreads through the nervous system.
- An unconventional infectious agent that takes years or decades to start producing visible effects (as is seen in disorders like Creutzfeldt-Jakob Disease).
- Random genetic mutations—the kind that occur in individuals all the time—happen to occur in particular cells or certain genes, in a specific combination that injures these cells.
- Exposure to some unknown chemical in food, air, or water, which slowly damages certain vulnerable areas of the brain, mimicking a neurological disorder found on the Pacific island of Guam and on a few neighboring islands.

- 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.

How is PSP diagnosed?

Currently there are no tests or brain imaging techniques to definitively diagnose PSP. An initial diagnosis is based on the person's medical history and a physical and neurological exam. Identifying early gait problems, problems moving the eyes, speech and swallowing abnormalities, as well as ruling out other similar disorders is important. Diagnostic imaging may show shrinkage at the top of the brain stem and look at brain activity in known areas of degeneration.

Is there any treatment?

There is currently no effective treatment for PSP and symptoms usually do not respond to medications.

- **Parkinson's disease medications**, such as ropinirole, rarely provide additional benefit. In some individuals, other antiparkinsonian medications, such as levodopa, can treat the slowness, stiffness, and balance problems associated with PSP, but the effect is usually minimal and short-lasting.

- **Botulinum toxin**, which can be injected into muscles around the eyes, can treat excessive eye closing.
- **Some antidepressant drugs** may offer some benefits beyond treating depression, such as pain relief and decreasing drooling.

Non-drug treatment for PSP can take many forms.

- **Weighted walking aids** can help individuals avoid falling 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** (which involves placing 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 surgically implanted electrodes and a pacemaker-like medical device to deliver electrical stimulation to specific areas in the brain to block signals that cause the motor symptoms of several neurological disorders—and other surgical procedures commonly used in individuals with Parkinson's disease have *not* been proven effective in PSP.

What is the prognosis?

PSP gets progressively worse, with people becoming severely disabled within three to five years of onset. Affected individuals are predisposed to serious medical complications such as pneumonia, choking, head injury, and fractures. The most common cause of death in those with PSP 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 disease appears.

What research is being done?

The National Institute of Neurological Disorders and Stroke (NINDS), a component of the National Institutes of Health, is the primary funder of research on the brain and nervous system. NIH is the leading funder of biomedical research in the world.

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 is aimed at discovering ways to identify individuals at risk for developing Parkinson's disease and related disorders, and to track the progression of these diseases. NINDS also supports clinical research studies to develop brain imaging that may allow for earlier and more accurate diagnosis of PSP.

Genetic studies of PSP may identify underlying genetic causes. Previous studies have linked regions of chromosomes containing multiple genes, including the gene for the **tau protein** (*MAPT*), with PSP.

Researchers hope to identify specific disease-causing mutation and are also studying how genetics and environment interaction may work together to contribute to disease susceptibility.

Scientists hope to understand the mechanisms involving tau that lead to PSP and its symptoms. Tau can exist in multiple shapes, or conformations, and research has shown that some of these conformations are harmful, leading to the buildup of toxic clumps and disruption of normal molecular signaling pathways inside cells. NINDS supports a number of studies that aim to characterize and distinguish the different conformations of tau, to identify the location of tau depositions in individuals with PSP, to clear the abnormally accumulated tau protein in the brain, and to understand their role in disease. Other studies are exploring ways to improve how to image or visualize tau in the brain. Because the symptoms of individuals with PSP progress more rapidly than in other tau-related disorders, some investigators believe that an anti-tau therapy will show benefit rather quickly in PSP clinical trials. Many of these anti-tau therapies make use of treatments that help the immune system fight infections and other diseases.

Animal models of PSP and other tau-related disorders, including fruit fly and zebrafish models, may identify basic disease mechanisms and lead to 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, which may also yield insights into disease mechanisms and treatments.

Other research focuses on therapies that aim to **treat the symptoms of PSP**, rather than the underlying disorder itself. These studies have examined the effects of numerous drugs and therapies, including non-steroidal anti-inflammatory drugs (NSAIDs), transcranial magnetic stimulation, and blood plasma transfers from young, healthy individuals on the symptoms of PSP.

The **Rare Diseases Clinical Research Network**, which is led by NIH's National Center for Advancing Translational Sciences (NCATS), is designed to facilitate 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** (https://reporter.nih.gov), a searchable database of current and past research projects supported by NIH and other federal agencies. NIH 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
http://www.ninds.nih.gov

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

CurePSP
1216 Broadway, 2nd Floor
New York, NY 10001
347-294-2873; toll-free 800-457-4777
https://www.psp.org

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

U.S. National Library of Medicine
National Institutes of Health/DHHS
8600 Rockville Pike
Bethesda, MD 20894
301-594-5983; toll-free 888-346-3656
https://medlineplus.gov

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