PSP: Some Answers

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What is Progressive Supranuclear Palsy (PSP)?

Of the approximately 30,000 to 40,000 people in the United States with progressive supranuclear palsy (PSP), few, if any, had ever heard of the disease before their diagnosis. In fact, most patients with PSP report that their family doctors knew nothing about it until a neurologist made the diagnosis. As of now, three of every four people with a diagnosis of PSP could have been diagnosed earlier if their doctors had suspected it and performed the appropriate examination. However, there is evidence that doctors are becoming more familiar with PSP. This pamphlet should help patients and their families do the same.

Why has no one heard of PSP?

PSP is rare. No one even realized it existed until 1963, when eight patients were first described at a national neurology research convention and the disease was given its name. In retrospect, at least 12 cases of PSP had appeared in the medical literature between 1909 and 1962, but because of its resemblance to Parkinson’s disease, it wasn’t recognized as a distinct disease.

PSP is slightly more common than the better known amyotrophic lateral sclerosis (called ALS, or Lou Gehrig disease in the U.S. and motor neuron disease elsewhere). ALS is easier to diagnose than PSP and often affects much younger people.

At any one time, 10 to 12 people per 100,000 are living with the disease. This figure was thought to be half this large until the past few years, when neurologists have come to recognize that PSP can have several different forms, most of which were not previously recognized as having the same underlying brain abnormalities as the classic form.

One of CurePSP’s most important goals is to improve awareness of PSP among the public and medical profession. A correct diagnosis for everyone with PSP would provide access to expert medical management that avoids unnecessary diagnostic testing and futile treatment and would allow patients to enroll in clinical trials and support groups. Just as important, full and accurate identification of those with PSP would stimulate interest among researchers, philanthropists, funding agencies and pharmaceutical companies to find the cause and cure of the unique and puzzling illness.
What are the common types of PSP and their early symptoms?

PSP is occasionally referred to as Steele-Richardson-Olszewski syndrome after the three physicians who first described the disease in 1963. The most common form is Richardson’s syndrome after Dr. J. C. Richardson, the leader of the project.

About half of those with PSP have the Richardson’s syndrome type. The most common first symptom is loss of balance while walking and occurs, on average, at age 63. This may take the form of unexplained falls or of a stiffness and awkwardness in a person’s gait that can resemble Parkinson’s disease. Sometimes the falls are described by patients as attacks of dizziness. This often prompts the doctor to suspect an inner ear problem, hardening of the arteries of the brain, or a heart problem.

The second most common form of PSP, accounting for about a quarter of cases, is called PSP-parkinsonism. Its early stages more closely resemble those of Parkinson’s disease, with less emphasis on balance problems and behavior changes and more on tremor. These typically have a better early response to antiparkinson drugs than is typical for PSP.

Other, less common PSP types are characterized by predominance of progressive gait freezing (PSP-PGF), postural instability (PSP-PI), speech and language difficulty (PSP-SL), corticobasal syndrome (PSP-CBS), ocular motor difficulties (PSP-OM), behavioral-variant frontotemporal dementia (PSP-bvFTD), nonfluent-agrammatic-variant of primary progressive aphasia (PSP-nfaPPA), cerebellar deficits (PSP-C), and primary lateral sclerosis (PSP-PLS).

What are the most common early symptoms of PSP?

In the most common type of PSP, PSP-Richardson’s syndrome, balance difficulty, usually with falls, is the first symptom for the majority of people. Other common early symptoms can be misinterpreted as depression or even as senility. These include forgetfulness and personality changes, such as loss of interest in ordinary pleasurable activities or increased irritability.

Less common early symptoms are trouble with eyesight, slurred speech, mild shaking of the hands, and difficulty driving a car. Freezing of gait can be a first and only symptom for several years and difficulty finding words, or aphasia, can be a first and most prominent issue.

What happens next?

The name of the disease includes the word “progressive” because, unfortunately, the early symptoms get worse and new symptoms develop over time. After five or six years, on average, the imbalance and stiffness worsen to make walking very difficult or impossible. Trouble with eyesight eventually develops in almost all cases and can sometimes be as disabling as the movement difficulty. Difficulty with eye movements, speech, and swallowing are additional important features of PSP that eventually occur in most patients.

What does the name “supranuclear palsy” mean?

In general, palsy is a weakness or paralysis of a part of the body. The term “supranuclear” refers to the nature of the eye problem in PSP. Although some patients with PSP describe their symptom as blurring, the actual problem is an inability to aim the eyes properly because of weakness or paralysis (palsy) of the muscles that move the eyeballs. These muscles are controlled by nerve cells residing in clusters or nuclei near the base of the brain, in the brainstem. Most other brain problems that affect the eye movements originate in those nuclei, but in PSP, the problem originates in parts of the brain that control those eye-movement nuclei. These “higher” control areas are what the prefix “supra” in “supranuclear” refers to.
Is the visual problem the most important part of PSP?

In most cases, the visual problem is at least as important as the walking difficulty, though it does not typically appear until a few years later. Because aiming the eyes properly is the main difficulty, reading often becomes challenging. The patient finds it hard to automatically shift down from line to line. This is very different from just needing reading glasses. An eye doctor unfamiliar with PSP may be baffled by the patient’s complaint of being unable to read a newspaper despite normal ability to read the individual letters on an eye chart. Some patients have their mild cataracts extracted in a vain effort to relieve such a visual problem.

Another common visual problem is an inability to maintain eye contact during conversation. This can give the mistaken impression that the patient is senile, hostile, or uninterested. The same eye movement problem can create the symptom of tunnel vision and interfere with driving a car.

The most common and characteristic eye movement problem in PSP is an impaired ability to move the eyes up or down. This impairment can interfere with eating or with descending a flight of stairs, among other things. This problem is not usually as vexing for the patient and family as the inability to maintain eye contact or to coordinate eye movements while reading, but it is much easier for the doctor to detect. Slowing of vertical eye movement is usually the first clue that the diagnosis is PSP, often followed by restriction of the range of eye movement up or down or both. Although other conditions, particularly Parkinson’s disease and normal aging, can sometimes cause difficulty moving the eyes up, PSP is nearly unique in also causing problems moving the eyes down. This problem often takes the form of eye movement apraxia, where the patient can move the eyes up or down only after several requests or with a delay after initiating the effort.

In most people with PSP, the difficulty in downward eye movement starts out as a slowing of that movement. This difficulty can also interfere with vision but can be very difficult for a physician to detect. Another eye movement problem that starts early in the illness is square wave jerks—rapid, involuntary, right-left movements that interfere with the ability to precisely aim the eyes at a target. Yet another is that large eye movements become jerky rather than smooth.

Yet another eye problem in PSP can be abnormal eyelid movement. One such problem is called blepharospasm, which can take the form either of forceful involuntary closing of the eyes for a few seconds or minutes at a time, or of difficulty opening the eyes, even though the lids seem to be relaxed. The person may try to use the muscles of the forehead, or even the fingers, in an effort to open the eyelids (“apraxia of lid opening”). About 20% of patients with PSP eventually develop one of these problems.

Others, on the contrary, have trouble closing the eyes and blink very little. While about 15 to 25 blinks per minute are normal, people with PSP blink, on average, only about three or four times per minute. This can allow the eyes to become irritated and to react by producing extra tears, which in itself can become annoying. This irritation often causes painful sensitivity to light called photophobia.

What sort of speech problems occur?

The same general area of the brain that controls eye movement also controls movements of the mouth, tongue, and throat, and these movements also weaken in PSP. Speech becomes slurred in most patients after three or four years, on average, although it is the first symptom in a few patients. In Parkinson’s disease, the speech problem is characterized by soft volume and rapid succession of words. In PSP, however, the speech may have an irregular, explosive, or rubber-band quality (called spastic speech) or a drunken quality (ataxic speech) or the same softening of speech as in Parkinson’s disease. Most commonly, there is a combination of at least two of these three features in the speech of patients with PSP.

The speech difficulty of PSP, in combination with the forgetfulness, slow mental responses, personality change, apathy, and poor eye contact during conversation can create an erroneous impression of senility or dementia. True dementia of a sort does occur in many people with PSP, however, and is discussed below.
What about the swallowing problems?
Swallowing problems are the source of the most important and dangerous long-term complications of PSP. Swallowing tough foods or thin liquids can become difficult because of throat muscle weakness or incoordination. These problems tend to occur later than the walking, visual, and speech problems, but they can become very troublesome if the patient tends to choke on food or if food goes into the breathing passages. Usually, problems managing thin liquids precedes difficulty with solid food because the swallowing muscles have difficulty creating a watertight seal that separates the path to the stomach from the path to the lungs. This is true with many neurological diseases. For non-neurologic conditions such as stricture of the esophagus, the difficulties start with solid foods.
Repeated, minor, often unnoticed episodes of small amounts of food and drink dripping into the lungs can cause pneumonia. Often, it is not apparent to the physician or family that the PSP patient’s pneumonia is in fact the result of subtle aspiration. But aspiration pneumonia is the most common cause of death in PSP.
The risk of aspiration is aggravated by the tendency to overload the mouth or to take big gulps of beverages because of a loss of inhibition or a reckless impulsiveness that can be partly involuntary.

Does PSP lead to dementia as in Alzheimer’s disease?
Most patients do eventually develop some degree of mental impairment during the course of the disease. Some, however, are mislabeled as having Alzheimer’s disease. A similar situation exists in Parkinson’s disease.
Dementia in PSP, if it does occur, does not feature the memory problem that is so apparent in Alzheimer’s disease. In PSP, the dementia typically features slowed thought, difficulty resisting impulses, and difficulty synthesizing several different ideas into a new idea or plan. These mental functions are performed mostly by the front part of the brain (the frontal lobes). In Alzheimer’s disease, on the other hand, the problem is mostly in the part of the brain just above the ears (the temporal lobes) where memory functions are concentrated. Another important cognitive function of Alzheimer’s disease is either difficulty with language (such as trouble recalling correct names of common objects) or difficulty finding one’s way around a previously familiar environment, or both. Fortunately, these symptoms almost never occur in PSP. Personality changes in the form of social withdrawal or irritability are common in PSP. While these changes do not affect thinking ability, they nevertheless can cause some degree of disability.
Slowing of thought can cause major problems for people with PSP by making it difficult to partake in conversation. A question may be answered with great accuracy and detail but with a delay of several seconds to minutes. Another important part of PSP dementia is apathy. People with PSP seem to lose interest in their surroundings, creating the impression of lost thinking ability and interfering with family interactions.

How is PSP different from Parkinson’s disease?
Both PSP and Parkinson’s disease cause parkinsonism (with a small “p”)—a combination of stiffness, slowness, and clumsiness. This is why PSP may be difficult to distinguish from Parkinson’s disease early on. However, shaking (tremor), while prominent in about 70% of people with Parkinson’s disease, occurs in only about 10% of people with PSP. A more common type of tremor occurring in PSP is irregular, mild, and present only when the hands are in use, not at rest as in Parkinson’s disease.
Patients with PSP usually stand up straight or occasionally even tilt the head backward and tend to fall backward, while those with Parkinson’s disease usually are bent forward, with their falls forward or to the side. The problems with vision, speech, and swallowing are much more common and severe in PSP than in Parkinson’s disease. Parkinson’s disease causes more difficulty using the hands and more stiffness in the limbs than does PSP. Finally, and perhaps most important, the medications that are so effective for Parkinson’s disease offer much less benefit in PSP.
The PSP-parkinsonism variant of PSP is more likely than typical PSP to have a tremor, to involve one side of the body more than the other, to have less of a problem with vision and swallowing, and to respond better to drugs for Parkinson’s disease.
Most drugs for Parkinson's disease enhance, replace, or mimic a brain chemical called dopamine. Parkinson's disease responds better to such drugs than does PSP because dopamine deficiency is by far the most important abnormality in Parkinson's disease. In PSP, deficiencies of several other brain chemicals are at least as severe as the dopamine deficiency, and no good way exists to replace those brain chemicals. Also in PSP, there is damage to the brain cells that receive the dopamine-encoded messages, while these cells remain largely intact in Parkinson's disease.

**What about treatment with medication?**

Several prescription medications can help patients with PSP, at least in some cases.

Levodopa and carbidopa are the almost universally prescribed generic form of the brand name Sinemet. Levodopa is the component that helps the disease symptoms; carbidopa simply helps prevent the nausea that levodopa can cause. When levodopa came along in the late 1960s, it was a revolutionary treatment for Parkinson's disease, but it is of only modest benefit in PSP. It can help the slowness and stiffness of PSP to a degree but usually not the mental, speech, visual, swallowing, or balance difficulties. About 50% of those with PSP-parkinsonism respond to levodopa/carbidopa, while the figure is only 14% for Richardson's syndrome. The drug typically loses its benefit after two or three years, but a few patients, especially those with PSP-parkinsonism, continue to respond.

Some patients with PSP require large dosages to see an improvement—up to 1,200 milligrams of levodopa (with carbidopa) per day—so the dosage should generally be raised to at least that level under the close supervision of a physician, unless a benefit or intolerable side effects occur sooner. The most common side effects of this drug in PSP are confusion, hallucinations, and dizziness. These side effects typically disappear after the drug is stopped. The most common side effect in patients with Parkinson's disease—involuntary writhing movements (chorea or dyskinesias)—occur very rarely in PSP, even at high dosages.

Patients with PSP should generally receive the standard Sinemet or generic immediate-release carbidopa/levodopa preparation rather than any of the controlled-release or extended-release forms such as Sinemet CR, generic carbidopa/levodopa ER, and Rytary. These long-acting formulations are absorbed from the intestine into the blood slowly and can be useful for people with Parkinson's disease who respond well to carbidopa/levodopa but need to prolong the number of hours of benefit from each dose. In PSP, however, such response fluctuations almost never occur. Because the CR or ER is sometimes absorbed very little or erratically, a poor response in a patient with PSP might be incorrectly blamed on the fact that the disease is usually unresponsive to the drug. Such a patient might actually respond to the standard form, which reaches the brain in a more predictable way. For people with PSP who cannot swallow pills safely, a solution is to crush a regular carbidopa/levodopa tablet into a food or beverage that is easily swallowed. The drug dissolves best in acidic beverages such as juices or sodas.

Another formulation of carbidopa/levodopa combines those two drugs with a third drug, entacapone, in the same tablet called Stalevo. Entacapone slows the rate at which dopamine is broken down. It is useful for patients with Parkinson's disease—but rarely, if ever, in PSP.

There are three dopamine receptor agonists drugs on the market for Parkinson's disease—Mirapex (pramipexole), Requip (ropinirole), and Neupro (rotigotine, which comes only as a skin patch). For PSP, these drugs rarely give any benefit beyond that provided by carbidopa/levodopa and may cause hallucinations and confusion, excessive involuntary movements, dizziness, and nausea.

Another class of drugs for Parkinson's disease is the monoamine oxidase type B inhibitors, including Azilect (rasagiline); Deprenyl, Eldepryl, Emsam, Zelapar (selegiline); and Xadago (safinamide). These drugs have not been shown to help PSP and can cause important side effects such as blood pressure changes and agitation. Another anti-Parkinson's drug, Nourianz (istrydelfylline), works by a different mechanism and has not been formally tested in PSP, but the experience of PSP experts recommends against its use.
Antidepressants have also had some modest success in PSP, sometimes relieving the depression that can be part of the disease. There are many antidepressants and none has been shown to be clearly superior to any others. The older, tricyclic antidepressants seem to be no less effective in PSP than the newer reuptake blocker antidepressants. However, their blocking of the brain chemical acetylcholine aggravates the cognitive problems of PSP and can cause urinary retention. In addition, the most commonly used of the older antidepressants, Elavil (amitriptyline), may aggravate the balance problem in PSP. For these reasons, when depression in PSP requires medication, a reuptake blocker such as Zoloft (sertraline) or Lexapro (escitalopram) are the usual first choices. One should be careful, however, not to mistake apathy for depression. Apathy is much more common in PSP.

Amantadine has been used for Parkinson’s disease since the 1960s. It can be effective against the “freezing” component of the PSP gait disorder even if Sinemet is not, possibly because it affects more than just the dopamine system. It may also have a general activating or energizing effect. Its benefit generally lasts only a few months, however. Its principal potential side effects are dry mouth, constipation, confusion, swelling of the ankles, and a pink skin discoloration in a lacy pattern called livedo reticularis. In people with PSP, the dosage should be kept low, generally no more than 200 mg per day, because of the potential for confusion or agitation.

Drugs for dementia, including Aricept (donepezil), Reminyl (galantamine), and Exelon (rivastigmine), enhance the activity of the brain chemical acetylcholine and are modestly useful against the dementia of Alzheimer’s disease. They can also be somewhat useful in Parkinson’s disease and other forms of dementia. Donepezil has been found to be modestly helpful in PSP. It is probably worth trying that or one of the other three for a period of two months, and then to discontinue it if improvement is not seen. A fourth anti-Alzheimer drug, Namenda (memantine), acts on a different brain chemical, glutamate. It has not been shown to work well for PSP, where it can cause confusion and agitation.

What about other experimental drugs?

Fortunately for PSP sufferers, drug companies have started to act on the realization that a prevention or disease-slowing treatment for PSP, where the market is tiny, could also work in Alzheimer’s disease, where the market is huge. A number of promising novel neuroprotective approaches will enter trials for PSP in 2021 or soon thereafter. These include RT001, which addresses a lipid-related chemical imbalance in brain cells in PSP; UCB0107, a monoclonal antibody that protects against the tau protein; ASN120290, an O-GlcNAcase inhibitor, which prevents the tau protein from misfolding and clumping up; AZP2006, which reduces tau production; MP201, which addresses the energy production problem in the mitochondria in PSP; tolfenamic acid and its analogs, which are nonsteroidal anti-inflammatory drugs that, unlike other NSAIDs, reduce tau production; and several antisense oligonucleotides, which are small stretches of RNA injected directly into the spinal fluid to reduce tau production. A drug trial for PSP typically takes three years to complete.
**Is tube feeding advisable for advanced patients?**

For extreme cases of poor swallowing where choking is a definite risk, the placement of a tube through the abdomen into the stomach (called gastrostomy or percutaneous endoscopic gastrostomy or PEG) may be advised. PEG feeding may allow patients to regain lost weight, avoid hunger, and receive the nourishment they need to fight off other potential complications of PSP. A patient receiving the necessary nutrients and fluids is much happier and stronger overall and will probably find general movement, speech, and thinking easier.

PEG placement may be considered when any of the following occur: a first episode of aspiration pneumonia, small amounts of aspiration with each swallow, significant weight loss from insufficient feeding, or when the prolonged time required for a meal disrupts the operation of the household.

The PEG tube can be inserted with the patient awake but sedated, often as an outpatient procedure. The tube is clamped shut and hidden under the clothes when not in use. The feeding can be managed easily at home by pureeing the family's regular food in a blender and injecting it into the tube with what looks like a basting syringe. The skin site where the tube enters requires only a little care that can be provided easily by a family member or even by the patient in some cases.

If the need for tube feeding abates (as through a new medication, for example), normal oral feeding can be resumed and the tube can be kept as a backup or removed.

An important potential downside of tube feedings for some patients is a loss of feeling “whole” or of feeling fully human. Just as important, the effect of the feeding tube on the quality of life must be considered carefully by the family, physician, and if possible, the patient, sometimes with ethical or spiritual advisors. In my experience, most patients in the advanced stages of PSP feel that their quality of life is so poor that prolonging that life with a feeding tube is not what they want.

It’s important to note that some nursing homes will advise PEG placement because it reduces the personnel time needed to feed the patients and because third-party payers often will pay an additional fee for tube feeding but not for the time-consuming task of hand feeding a patient by mouth.

**Do any of the new brain operations for Parkinson’s disease work for PSP?**

Not so far, unfortunately. The operations for Parkinson’s disease fall into two categories. One is based on the theory that the basal ganglia (the group of nuclei that control movement) are overactive compared to the rest of the brain. At present, the most common operation to dampen this overactivity is subthalamic nucleus stimulation. The previous approach, pallidotomy, is rarely performed now. In PSP, however, the output area of the basal ganglia is damaged, so its activity is already dampened. The operation would only make things worse. Focused ultrasound is gaining popularity as a noninvasive way to destroy tiny, malfunctioning areas of the brain circuitry to treat Parkinson’s disease or essential tremor. This treatment has not been tested for PSP but is unlikely to work for the same reasons that pallidotomy would not work.

There have been attempts to test stimulation of the area of the brain that serves balance, the pedunculopontine nucleus (PPN). The PPN is in the brainstem, which is an area tightly packed with critical circuitry. The procedure seems to be acceptably safe and does seem to help the balance problem in some patients with Parkinson’s disease. However the overall improvement in patients with Parkinson’s disease is still undetermined, and the procedure has barely been attempted in PSP.

Stem cell implants are offered in some countries as treatment for Parkinson’s disease and many other brain disorders. The benefit and safety of this procedure are unproven and for many reasons unlikely to be adequate. However, stem cells may have a role in the future as permanent vehicles for delivery of drugs into the brain without the need for intravenous infusions. First, an effective and safe drug has to be found. Then stem cells programmed genetically to produce that drug could be implanted into the fluid-filled space around the brain. This, as indicated, is still years away. Stem cells infused throughout the brain can stimulate the brain’s own repair mechanisms. This approach is presently being tested in other neurodegenerative diseases and may hold promise for PSP in the future. The best advice right now for someone with PSP is to join such a trial if the opportunity exists and to avoid stem cell treatments outside of formal trials at reputable research institutions.
What about other non-drug treatment?
Formal physical therapy is worth a trial in PSP, especially with the goal of teaching the patient to use gait-assistive devices such as a walker. Certain exercises done in the home by oneself on a regular schedule can keep the joints limber. Exercise also has a clear psychological benefit that improves a sense of well-being for anyone with a chronic illness. There is evidence that a program of retraining eye movements in patients with PSP can actually help their balance and gait. For specific exercises, consult one of the books for patients with Parkinson's disease or the pamphlets distributed by the national organizations for Parkinson's disease.

The special balance problems in PSP dictate caution in performing any exercises while standing. Many useful exercises can be performed seated in a chair or lying on a mat. Using a stationary bicycle is usually feasible as long as there is help in mounting and dismounting safely. The best strategy is to have an evaluation and treatment plan from a physical therapist or physiatrist (a physician specializing in rehabilitation of chronic conditions).

Probably the most important part of dealing with PSP is for the patient's family to understand that the problems with visual inattention and personality changes are part of the illness. The patient is not lacking willpower nor faking. Furthermore, many of the problems in PSP are intermittent and can be aggravated by the patient's mental or emotional state. For example, walking, writing, and eating may be poor one hour and better the next. The family should understand that these fluctuations are not under the patient's control and that nagging and shouting usually just make matters worse. A wise policy is to be prepared to take advantage of the good periods to have an outing, a relaxing shower, or some other activity that would be more difficult at another time.

Walking aids are often important for patients with PSP. Because of the tendency to fall backward, if a walker is required, it should be weighted in front with sandbags over the lower rung. A better but more expensive solution is a large, heavy walker resembling a small shopping cart with three or four fat, soft rubber wheels and a hand brake. The tendency to fall backward can also be countered by the use of built-up heels. Leg braces are not helpful because the problems in PSP are coordination and balance rather than actual muscle weakness.

Shoes with smooth soles are often better than rubber-soled athletic shoes. In many people with PSP, the gait disorder includes some element of “freezing,” a phenomenon that makes it difficult to lift a foot from the ground to initiate gait. People with such symptoms can fall if they move their body forward before the foot moves. In these cases, smooth soles could make it easier to slide the first foot forward.

Handrails installed in the home, especially in the bathroom, may also be helpful. The difficulty looking down dictates that low objects such as throw rugs and low coffee tables be removed from the patient's living space.

To remedy the difficulty of looking down, bifocals or special prism glasses are sometimes prescribed for people with PSP. These visual treatment options are worth trying but can be of limited value because there is not only a problem moving the eyes in PSP but also a problem directing the person's attention (the "mind's eye") to objects located below the eyes.

What is the cause of PSP?
The symptoms of PSP are caused by a gradual deterioration of brain cells in a few tiny but important places in the base of the brain. The most important such place, the substantia nigra (sub-STAN-cha NYE-gra), is also affected in Parkinson's disease; damage to it accounts for the symptoms that PSP and Parkinson's disease have in common. However, several important areas that are affected in PSP are normal in Parkinson's disease, and vice versa. And, under the microscope, the appearance of the damaged brain cells in PSP is quite different from those in Parkinson's disease and instead resembles the degeneration in Alzheimer's disease. In addition, the location of the damaged cells is quite different in PSP compared with Alzheimer's disease, and PSP lacks amyloid plaques, which are deposits of waxy protein that are a hallmark of Alzheimer's disease.
**But what causes the brain cells to degenerate in the first place?**

No one knows yet, but we have some clues. In the brain cells that are degenerating in PSP, there is an abnormal accumulation of the normal protein tau. These clumps of tau, once they reach a size that can be seen through a microscope, are called neurofibrillary tangles. One normal function of tau is to help support the microtubules, which have two important jobs: one is to form the internal “skeleton” of the brain cells and the other is to serve as a “monorail” system, transporting nutrients around the cell. There are several plausible explanations for what causes the tau to misbehave in the first place, each with its supporting evidence. The tau may be defective from the time of its manufacture or it may be damaged later by a toxin or indirectly by the action of a toxin on some other molecules in the cell. Its behavior may be affected by inappropriate attachment of smaller molecules such as phosphate, causing the tau to misfold.

Regardless of the cause of tau's misbehavior, the first thing that tau does wrong is to misfold. Ordinarily, tau protein that's not attached to microtubules floats around without fixed shape in the cell's fluid, similar to a strand of overcooked spaghetti in boiling water. But when it misfolds, it assumes a more rigid structure, similar to a strand of dried-out spaghetti. Like spaghetti, it's sticky and forms clumps with other misfolded tau molecules.

Other possible explanations for the misbehavior of tau protein in PSP may be simply that it is produced in excess. Or the proportions of the different types of tau may be wrong. Finally, the brain cell's mechanism for disposing of worn-out, defective, or excess tau may be malfunctioning. The last of these possibilities is now emerging as the most important, but the final answer will probably be some combination of these problems.

In the past few years, evidence has been discovered that a single strand of misfolded tau can cause normal, free-floating copies of tau protein to misfold in the same way. This phenomenon is called a templating process. The newly misfolded copies then cause other copies to misfold and so on, in a chain reaction. Then the misfolded tau molecules start to clump. The clumps are toxic to the cell, which eventually dies. Even before the cell dies, it releases misfolded, clumped tau protein into the fluid surrounding the cells. That tau is then taken up by neighboring healthy cells that undergo the same damaging chain reaction of tau misfolding, templating, and clumping. In this way, the process of brain cell malfunction and death spreads slowly through the brain. A similar process is thought to occur in most of the neurodegenerative diseases but with different kinds of proteins in different diseases. This insight raises the tantalizing possibility that a drug that prevents the misfolding templating process could prevent all neurodegenerative diseases.

Since the 1980s, it's been known that one type of normal protein in the cell, called prion protein (pronounced PREE-on) does in fact misfold, template itself, and form toxic clumps to cause certain neurodegenerative diseases such as mad cow disease and Creutzfeldt-Jakob disease. Those diseases progress very rapidly and can be transmitted from one individual to another via exposure to diseased tissue. But misfolded prion protein behaves very differently from misfolded tau protein. Furthermore, PSP, Parkinson's disease, Alzheimer's disease, and the other neurodegenerative diseases progress far more slowly and are not transmissible between people. They should not be lumped with the true prion diseases. What the true prion diseases and PSP (and Parkinson's disease, Alzheimer's disease, etc.) have in common is the spread of a misfolding and aggregating protein from one brain cell to the next. However—and this is critical—we don't yet know whether the prion-like process involving tau in PSP is the most important explanation for the spread of the disease through the brain.

**Is PSP genetic?**

PSP very rarely runs in families. Fewer than one in 20 people with PSP knows of even one other family member with PSP, and detailed neurological exams of relatives of patients with PSP show no more definite abnormalities than exams of relatives of healthy people. However, two different variants in the gene on chromosome 17 that encodes the tau protein are more common in PSP than in the rest of the population. One of the variants is called the H1 haplotype. About 95% of people with PSP have this variant on both of their copies of chromosome 17, while this is true for only about 60% of people without PSP. So clearly, the H1 haplotype is (nearly) necessary but far from sufficient to cause the disease.
We’re still not quite sure how the H1 haplotype increases PSP risk. One possibility is that it simply increases the amount of tau produced, which causes that protein to stick together, even if it’s not misfolded. Another possibility is that it causes too many methyl groups to stick to the tau gene, which alters its function. A methyl group is simply a carbon atom with three hydrogen atoms attached. These small units can bind to large molecules, including our DNA, a process called methylation. This is a normal way for the cell to regulate the function of DNA. In other words, methylation affects the function of genes without actually changing the content of the genetic code as ordinary mutations do.

Over the past two decades, a handful of other gene variants not on chromosome 17 have been found to be more common in people with PSP than in people without PSP. These genes help control a variety of critical processes such as disposal of damaged proteins, inflammatory mechanisms, operation of synapses, and integrity of the brain cells’ insulating sheaths. More research is needed to identify how these insights can translate into possible PSP prevention.

**Could PSP be caused by toxins?**

There is evidence that chemicals in the environment or diet may contribute to the cause of PSP. Surveys of PSP patients have shown, on average, lesser educational attainment in people with PSP. This suggests that part of the cause of PSP may be certain occupational factors exposing people to different chemicals than are encountered by people with more sedentary or office-bound occupations. Another possibility is that people with less education tend to live in areas closer to industrial sites, some of which may generate toxins.

One important clue to a possible dietary factor in the cause of PSP comes from the island of Guadeloupe in the Caribbean. People there are far more likely to develop PSP and other atypical parkinsonisms than people elsewhere. A questionnaire survey on Guadeloupe revealed that people there with PSP-like illnesses were more likely than others to have consumed two native fruits called sweetsop and soursop. These fruits have since been shown to harbor toxins that, when given to laboratory rats, cause damage to the brain very similar to human PSP. We don’t yet know what foods in the Western diet, if any, may contain similar toxins. Research on that question is underway.

Another intriguing geographical cluster of PSP exists in a group of suburban towns in northern France. The area was the site of metal-related industry that contaminated the soil in that area over much of the 20th century. Subsequent laboratory research showed that when brain cells growing in a dish are given chromium and nickel, two of the metals contaminating that small area in France, they develop abnormalities similar to those of PSP. Clearly, more research is needed in this promising scientific lead.

**How can I help research?**

CurePSP welcomes donations to its research grants program. Since its inception in 1997, the program has provided over $20 million to institutions and senior researchers with excellent track records of productivity and to junior scientists with original ideas and first-rate training. CurePSP favors projects with the potential to produce preliminary findings that would support an application to a government agency for a much larger grant in the future. It does not restrict its grants to any country or continent.

The various national organizations that sponsor research in Parkinson’s disease sometimes sponsor deserving PSP research. Their support of research in Parkinson’s disease adds to our knowledge of PSP.

Another way to help research and yourself is to participate in studies of PSP if so requested by a researcher. This may take the form of answering questionnaires, having medical examinations or tests, or taking experimental medication. There are so few people with PSP in any one geographical area that each can make a very important contribution. Joining the mailing list at CurePSP will allow PSP researchers to contact you regarding participation in new research studies.
Should I make arrangements to donate my brain after death?
Another very important way to help PSP research is to make arrangements to donate your brain after death. CurePSP supports the Eloise H. Troxel Memorial Brain Bank, located at the Mayo Clinic in Jacksonville, Florida. Brains donated there are stored and used only for research in PSP by legitimate researchers who request it. Donating to a brain bank does not interfere with funeral arrangements and costs several hundred dollars for expenses of brain removal and transportation, which may be reimbursed by CurePSP. The family will receive, at no charge, a full diagnostic report from the Mayo Clinic pathologist, Dennis W. Dickson, MD, who is one of the world’s foremost authorities on PSP and related disorders. Further information is available from CurePSP or by calling the Brain Bank at 904-953-2439. There are several other brain banks throughout the country, generally located at major university hospitals. It is important to make formal brain donation arrangements in advance of death. This allows the identification of a local pathologist or technician who can remove, prepare, and ship the brain properly. It also allows the family, which may be in a stressed state immediately before and after the event, to be sure of the patient’s own wishes. It is important to note that completing the forms from CurePSP in advance is only a convenience and is not legally binding. Official consent for an autopsy can come only after death, and only from the next of kin.

Should I join a support group?
There can be great value in joining a group of other people with the same problem. You can exchange helpful tips on ways to cope physically and psychologically with the limitations of the illness, and you can learn more about the problem and its treatment from guest speakers. Many large medical centers have a Parkinson’s disease support group that welcomes members with PSP. While there are far fewer people with PSP than Parkinson’s disease in one geographical area, several dozen successful PSP support groups have been organized in the U.S., usually in more densely populated areas. All it takes is one organizer with some time and energy. Contact CurePSP for help.