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UNLOCKING THE SECRETS OF BRAIN DISEASE®

PSP: Some Answers

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What is Progressive Supranuclear Palsy (PSP)?

Of the approximately 15,000-20,000 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 doctor had suspected it and performed the appropriate examination. However, it is appearing in medical journals more and more often, which will help doctors become 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 several 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, it wasn't recognized as a distinct disease. The brain under the microscope is almost identical to that of "post-encephalitic parkinsonism," a common condition in the early 20th century but now nearly extinct, which also made for erroneous diagnoses during that era.

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

Each year an average of 1.1 people per 100,000 are newly diagnosed with PSP; five or six people per 100,000 are living with the disease. These figures are nearly identical wherever they have been carefully measured, which is in only three countries—the U.K., the U.S., and Japan.

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, who only recently retired from a career in neurology research.

About half of everyone with PSP has the Richardson's syndrome type. The most common first symptom, which occurs, on average, when a person is in her or his 60s, is loss of balance while walking. 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 or hardening of the arteries supplying the brain.

The second most common form of PSP 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. PSP-parkinsonism comprises about a quarter of all PSP.

What are the most common early symptoms of PSP?

Balance difficulty, usually with falls, is the first symptom in a 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.

Are there other, rare types of PSP?

Another type, called *corticobasal syndrome*, affects limbs on one side of the body far earlier and more severely than on the other side. It is a rare type that was described only a few years ago, mostly in Japan, and starts with ataxia, which is specific type of coordination problem arising from the cerebellum and resembling drunkenness. Most people with these minority phenotypes eventually do develop the more classic signs and symptoms of PSP.

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 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 three to five years after. 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 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 is much easier for the doctor to detect. Reduced vertical eye movement is usually the first clue that the diagnosis is PSP. 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 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 eye problem in PSP can be abnormal eyelid movement—either too much or too little—called *blepharospasm*. A few patients experience forceful involuntary closing of the eyes for a few seconds or minutes at a time, while others have difficulty opening the eyes, even though the lids seem to be relaxed. They 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 percent 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 react by producing extra tears, which in itself can become annoying.

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 may have the same softening of speech as 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?

This is 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. This tends to occur later than the walking, visual, and speech problems, but 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 nonneurologic 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 due a loss of inhibition or a reckless impulsiveness that can be partly involuntary.

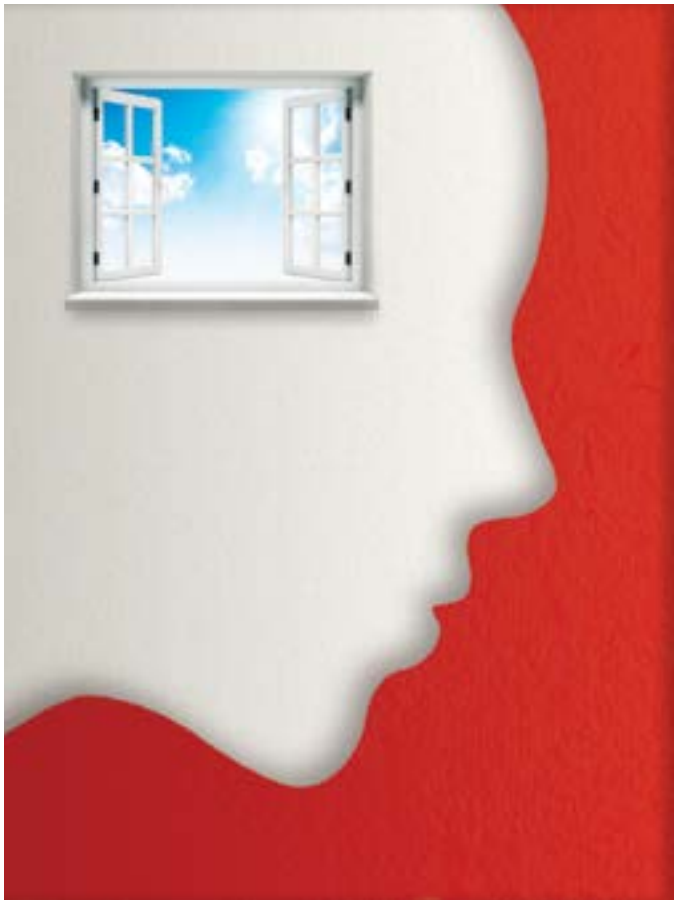
Does PSP lead to dementia as in Alzheimer's disease?

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. This is not unlike the situation 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. Rather, the dementia of PSP is characterized by 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, 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.

Alzheimer's disease also includes either difficulty with language (such as trouble recalling correct names of common objects) or difficulty finding one's way around a previously familiar environment. Fortunately, these symptoms almost never occur in PSP. Nevertheless, these problems can interfere to a major degree with the ability to function independently and the patient's irritability in some cases can make it difficult for caregivers to help.

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. Probably the most important aspect 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 percent of people with Parkinson's disease, occurs in only about 10 percent 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 backwards and tend to fall backwards, while those with Parkinson's usually are bent forwards. The problems with vision, speech, and swallowing are much more common and severe in PSP than in Parkinson's. Parkinson's causes more difficulty using the hands and more stiffness in the limbs than does PSP. Finally, 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.

Most drugs for Parkinson's disease enhance, replace, or mimic a brain chemical called *dopamine*. Parkinson's responds better to such drugs than does PSP because dopamine deficiency is by far Parkinson's most important abnormality. 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. Also, in PSP, there is damage to the brain cells that receive the dopamine-encoded messages, while these remain intact in Parkinson's.

What about treatment with medication?

Several prescription medications can help patients with PSP, 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 but it is of only modest benefit in PSP. It can help the slowness, stiffness, and balance problems of PSP to a degree, but usually not the mental, speech, visual, or swallowing difficulties. About 50 percent of those with PSP-parkinsonism respond to levodopa/carbidopa, while the figure is only 14 percent for Richardson's syndrome. The drug typically loses its benefit after two or three years, but a few patients with PSP 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 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 carbidopa/levodopa preparation rather than the controlled-release (Sinemet CR or generic carbidopa/levodopa ER) form. The CR or ER form is 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 levodopa-carbidopa 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 levodopa-carbidopa combines those two drugs with a third drug, *entacapone*, in the same tablet called Stalevo. The entacapone slows the rate at which dopamine is broken down. It is useful for patients with Parkinson's but rarely, if ever, in PSP.

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

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 superior to any others. The older, tricyclic antidepressants seem to be no less effective in PSP than the newer reuptake blocker antidepressants.

Amantadine has been used for Parkinson's since the 1960s. It can be effective against the PSP gait disorder even if Sinemet is not, possibly because it affects more than just the dopamine system. 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. None of them has been found helpful in PSP, but rivastigmine is probably worth trying. A fourth anti-Alzheimer drug, Namenda (memantine), acts on a different brain chemical, glutamate. It works no better for PSP than the others and can cause confusion and agitation in those patients.

One possible success story is the dietary supplement *Coenzyme Q-10* (CoQ10), is which is available without a prescription, although the jury is still out. It helps the body's cells produce energy from sugar and oxygen and is a normal constituent of the mitochondria, the tiny compartments in our cells where that chemical process occurs. One small study gave modestly favorable results. Another gave similar benefit, but was too small to be sure that its outcome was not just the result of chance. The required dosage of the standard formulation of CoQ10 is probably at least 1200 mg per day and perhaps as high as 2400 mg. The newer *liposomal* form probably gives the same benefit at 300 mg per day. As a nonprescription item, CoQ10 is not covered by drug insurance and costs $50 to $100 month. Therefore, people with PSP should carefully consider the meager evidence to date for the benefit of CoQ10 before taking that long-term financial plunge. Their neurologists should do a careful exam upon starting the drug and repeat it two months later to determine whether the treatment is working, and if not, discontinue it.

Botox or *Myobloc*, two types of botulinum toxin, are a different sort of drug that can be useful for people whose PSP is complicated by blepharospasm. A very dilute solution of the toxin, which is produced by certain bacteria that can contaminate food, can be carefully injected by a neurologist into the eyelid muscles as a temporary remedy for abnormal involuntary eyelid closure. Botox can also be used for involuntary turning or bending of the head that occurs in PSP, but injecting it into the neck muscles can sometimes cause slight weakness of the nearby swallowing muscles. In PSP, where swallowing is already impaired in many patients, caution should be used when considering use of Botox in neck muscles.

What about other experimental drugs?

In the past 20 years, many drugs have been tested in patients with PSP. Some of these are intended to actually slow the long-term brain cell loss; i.e., slow progression of the disease. Unfortunately, none has helped. The most promising were *riluzole*, which modestly helps amyotrophic lateral sclerosis; *davunetide*, which is a fragment of a protein that helps maintain brain cells' internal skeletons; and *tideglusib*, which prevents the abnormal attachment of phosphate to the tau protein, preventing it from clumping up in the brain cells. The last drug did show a glimmer of promise; MRI scans showed less loss of brain mass in the patients on tideglusib than in those on placebo. This may justify further study of the drug, but it is doubtful that any drug company will want to pursue it after it failed to slow progression of the actual symptoms of the disease.

Two other approaches to slowing the progression of PSP have just entered clinical trials. One gives antibodies designed to attack the abnormal tau protein as if it were an invading virus or bacterium. There are two such trials, sponsored by the companies Bristol-Myers Squibb and AbbVie, respectively. Another uses a version of the cancer drug *Taxol* to help maintain the brain cells' inner skeletons, which break down in PSP.

Two current, small, preliminary trials use existing drugs that are marketed for other diseases. One uses *Salsalate,* a nonsteroidal anti-inflammatory drug, which may prevent the tau protein from aggregating via a mechanism unrelated to its anti-inflammatory effect. Another tests the drug methylene blue or LMT-X in Alzheimer's disease, hoping that it will also be useful in PSP.

Two drugs that reduce the tendency of tau protein to aggregate by altering the ability of phosphate molecules to attach to it will enter trials in the next year or two. The two drug companies involved are Asceneuron and Merck.

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.

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 easily be managed 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 easily be provided 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.

One potential downside of tube feedings for some patients is a loss of feeling "whole" or part of humanity. The issue of how a feeding tube will affect a patient's quality of life must be considered carefully by the family, physician, and, if possible, the patient and sometimes ethical or spiritual advisors. Some patients in the advanced stages of PSP may feel that their quality of life is so poor that prolonging that life by having a PEG installed 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 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. The most common operation to dampen down this overactivity at present 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.

There are, however, trials now in progress in people with PSP to test stimulation of the area of the brain that serves balance, the *pedunculo-pontine* 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, but the overall improvement in patients is still undetermined.

In patients with Parkinson's, there is also an operation that attempts to replace the lost dopamine-producing brain cells. This is unlikely to work for PSP because, while in Parkinson's, most of the movement problem is caused by loss of the main dopamine-producing nucleus, the *substantia nigra*, the movement problems in PSP are caused by the loss of many additional nuclei. Many of those other nuclei receive their input from the substantia nigra, so replacing only the first link in the chain would not help much and, at this point, it would cause too much trauma to the brain to replace cells in all of the nuclei involved in PSP.

An exciting experiment in progress in Milan, Italy, but one that has only a slim chance of success, is the injection of stem cells directly into the arteries feeding the brain. This project is still in the very early phases designed to test its safety. If it succeeds, then a large project will test for benefit. The intent is not to replace lost cells, as the injections land in random spots, but to stimulate the brain to produce its own growth factors to repair the damage of PSP.

What about other nondrug 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. For specific exercises, consult one of the books for patients with Parkinson's disease or the pamphlets distributed by the national Parkinson organizations.

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 will power 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 backwards, 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 backwards can also be countered by the use of built-up heels. Leg braces are not helpful because the problem in PSP is 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 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 and damage to it accounts for the symptoms that PSP and Parkinson's have in common. However, several important areas that are affected in PSP are normal in Parkinson's, and vice versa. And, under the microscope, the appearance of the damaged brain cells in PSP is quite different from those in Parkinson's and instead resembles the degeneration in Alzheimer's disease. In addition, the location of the damaged cells is quite different in PSP and Alzheimer's and PSP lacks amyloid plaques, which are deposits of waxy protein that are a hallmark of Alzheimer's.

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*. The 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. We don't know whether the problem is that the tau is defective from the time of its manufacture, or if it is damaged later, or even if it remains normal but is produced in excess. If it is damaged, the nature of that damage could be the excessive attachment of phosphate (see the section on PSP preventive drugs). Or, the excessive phosphates on the tau molecules could simply be how the brain minimizes the effects of tau protein that is misbehaving for some other reason.

Regardless of its origin, the excessive phosphate on the tau protein molecules causes the tau to misfold. Ordinarily, tau protein that's not attached to microtubules floats around without fixed shape in the cell's fluid, like a strand of overcooked spaghetti in boiling water. But when it misfolds, it assumes a more rigid structure, like the strand of dried-out spaghetti. Like spaghetti, it's sticky and it forms clumps with other misfolded tau molecules.

In the past few years, evidence has been discovered that a single strand of misfolded tau can cause normal, freely floating copies of tau protein to misfold in the same way. This 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 that templating process could prevent all neurodegenerative diseases.

Since the 1980s, it's been known that one type of 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, and PSP, Parkinson's, Alzheimer's, 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.

Is PSP genetic?

PSP only 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 percent of people with PSP have this variant on both of their copies of chromosome 17, while this is true for only about 60 percent of the rest of us. 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, discovered only this year, 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 hydrogens that can attach to large molecules including DNA. *Methylation* is a normal way for the cell to regulate the function of DNA, thereby affecting the function of genes without actually changing the content of the genetic code like ordinary mutations do. This is exciting because certain molecules that can be developed into drugs alter DNA methylation.

Insights into the other PSP-related variant in the tau gene were published in 2011 by a group of scientists working in the Charles D. Peebler, Jr. Genetics Program, sponsored by CurePSP. The approximate location of this defect in the tau gene is known, but its relationship to the brain cell loss of PSP is not yet. This has been the subject of intense research since 2010.

CurePSP's Peebler Genetics Program has also discovered several other genetic variants that are more common in people with PSP than in those without PSP. One, called *EIF2AK3*, makes an enzyme that helps control the brain's system for disposing of misfolded proteins. This could explain why the clumps of tau protein form. Another gene newly implicated in PSP, called *STX6*, helps direct the movement of packets of important chemicals within brain cells. Transporting such packets is one of the functions of the microtubules, the internal skeleton or monorail system that the tau protein maintains. A third, *MOBP*, is the blueprint for the manufacture of a protein in brain cells' myelin sheath, which serves as a layer of electrical insulation on the wires connecting brain cells together. Still others help control the body's immune system, the relation of which to PSP remains unknown.

In 2016, CurePSP, in conjunction with the Tau Consortium, formed the PSP Genetics Consortium, an international team of investigators. Unlike the 2010 study, which was only able to find the approximate location of genes, this effort will work out the genetic code of all genes that make proteins in a group of people with PSP and in a similar group without PSP. This will not only discover additional genes, it will also show exactly what those "typos" in the genetic code are.

The next step will be to figure out how those errors damage the normal function of brain cells. Those insights, in turn, will provide new ideas for drug targets. In other words, once scientists work out which steps in the brain cells' normal function become disordered as a result of these PSP-related gene variations, they will know where new drugs could be directed to prevent the process from proceeding further. Coupled with a test to detect PSP in its earliest stages, before it actually causes any disability, such a drug treatment would amount to a PSP prevention. This multistep process is the basis of CurePSP's "Research Roadmap" to a cure.

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 are people elsewhere. A questionnaire survey on Guadeloupe revealed that people with PSP-like illnesses there 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. Investigations are now underway to narrow the long list of toxins that could explain this cluster and then to assess the role of such toxins in PSP elsewhere.

How can I help research?

CurePSP welcomes donations to its research grants program. Since its inception in 1997, the program it has provided over $10 million to institutions and senior researchers with excellent track records of productivity and to junior people 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, and/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 participating 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, FL. 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 a few 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 directly at 904-953-2439. There are several other brain banks throughout the country, generally located at major university hospitals.

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 can learn more about the problem and its treatment from guest speakers. Many large medical centers have a Parkinson support group that welcomes members with PSP. While there are far fewer people with PSP than Parkinson's 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.

A major goal of CurePSP is to increase awareness of PSP among the public and the medical profession in order allow its correct diagnosis. If, as we suspect, PSP proves to be much more common than has been assumed, improved diagnosis may allow local support groups to flourish. This in turn will foster the growth of CurePSP and will draw the attention of more researchers to finding the cause and cure of this unique and puzzling illness.

curePSP®
UNLOCKING THE SECRETS OF BRAIN DISEASE®

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