



Foundation for PSP | CBD and Related Brain Diseases

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PSP: Some Answers

What is progressive supranuclear palsy?

PSP is a brain disease in the category of “neurodegenerative” diseases. Alzheimer’s, Parkinson’s and Lou Gehrig diseases are in the same category – where brain cells cumulatively break down for unclear reasons. PSP affects cells that control walking, balance, mobility, vision, speech, swallowing and behavior. Five to six people per 100,000 have PSP, a number similar to that of Lou Gehrig disease, but only about a third of these have received the correct diagnosis. Symptoms begin, on average, when an individual is in the early 60’s, but may start as early as in the 40’s. It is slightly more common in men than women, but PSP has no known geographical, occupational or racial preference.

Why has no one heard of PSP?

PSP is rare - only about one percent as common as Parkinson's disease - and because even when it does occur, it is often misdiagnosed. This is gradually changing. As more doctors become familiar with PSP, it will be diagnosed more readily. No one even realized it existed until 1964, when several patients were first described at a national neurology research convention and the disease received its name. In retrospect, at least 12 cases of PSP had appeared in the medical literature since 1909, but because of its resemblance to Parkinson's disease, no one had recognized it as a distinct disease until the 1960's.

The rarity of PSP is not the only reason it is not widely known. PSP is a bit more common than the very well-known disease amyotrophic lateral sclerosis (ALS; called Lou Gehrig disease in the US and motor neuron disease elsewhere). But ALS is easier to diagnose than PSP and affects much younger people in the prime of life.

It is unlikely that any of the approximately 4,500 people in the United States who have been diagnosed as having progressive supranuclear palsy had ever heard of the disease before. In fact, many patients with PSP report that their family doctors knew nothing about PSP until a neurologist made the diagnosis. Moreover, the neurologist probably thought the diagnosis was Parkinson's disease until several years into the illness. For every person with a diagnosis of PSP, there are three with PSP that could be diagnosed if their doctor suspected it and performed the appropriate examination. Recently, more and more has appeared in medical journals to help doctors remedy their unfamiliarity with PSP.

What does the name "supranuclear palsy" mean?

In general, a "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 themselves. These "higher" control areas are what the prefix "supra" in "supranuclear" refers to.

Sometimes complicated disease names are avoided by the use of the name of the physician who discovered the disease. However, for PSP, there were three such physicians and the string of names - Steele, Richardson, and Olszewski (ol-SHEF-skee) - was even less convenient than the descriptive name. "Steele-Richardson-Olszewski syndrome" is rarely used these days as a synonym for PSP.

Incidentally, although Drs. Richardson and Olszewski are deceased, Dr. John C. Steele, who was a neurology resident (i.e., a trainee) when he collaborated in the original description of PSP, still does neurological research and serves as Honorary Chairman of CurePSP.

What are the common early symptoms of PSP?

The most common first symptom, occurring, on average, in the 60's, is loss of balance while walking. This may take the form of unexplained falls or of a stiffness and awkwardness in the walk that can resemble Parkinson's disease. Sometimes the falls are described by the person experiencing them as attacks of "dizziness." This often prompts the doctor to suspect an inner ear problem or hardening of the arteries supplying the brain.

Other common early symptoms are forgetfulness and changes in personality. The latter can take the form of a loss of interest in ordinary pleasurable activities or increased irritability. These mental changes are misinterpreted as depression or even as senility. Less common early symptoms are trouble with eyesight, slurring of speech, and mild shaking of the hands. Difficulty driving a car with several accidents or near misses is common early in the course of PSP. The exact reason for this problem is not clear.

There is a form of PSP, called "PSP-parkinsonism," in which the early stages more closely resemble those of Parkinson's disease, with less emphasis on balance problems and behavior changes and more on tremor, with a better early response to antiparkinson drugs than is typical for PSP. PSP-parkinsonism comprises about a third of all PSP.

What happens next?

The term "progressive" was included in the name of the disease because, unfortunately, the early symptoms get worse and new symptoms develop sooner or later. After 5 to 6 years, on average, the imbalance and stiffness worsen to make walking very difficult or impossible. If trouble with eyesight was not present early on, it 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 occur eventually in most patients.

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 appear, on average, until 3 to 5 years after the walking problem. Because the main difficulty with the eyes is in aiming them properly, reading often becomes difficult. The patient finds it hard to shift down to the beginning of the next line automatically after reaching the end of the first 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 can interfere with driving a car.

The most common 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. This reduction in vertical eye movement is usually the first clue to the doctor that the diagnosis of the difficulty is PSP. Other conditions, particularly Parkinson's disease and normal aging, can sometimes cause difficulty moving the eyes up. However, PSP is nearly unique in also causing problems moving the eyes down.

In most people with PSP, the difficulty in downward eye movement starts out not as a restriction of the degree of downward movement, but as a slowing of that movement. This can interfere with vision also, but can be very difficult for a physician to detect. Another eye movement problem that starts early in the illness is "square wave jerks." These rapid, involuntary, right-left movements interfere with precisely aiming the eyes at a target.

Yet another eye problem in PSP can be abnormal eyelid movement -- either too much or too little. A few patients experience forceful involuntary closing of the eyes for a few seconds or minutes at a time, called "blepharospasm." Others have difficulty opening the eyes, even though the lids seem to be relaxed, and will 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 3 or 4 times per minute. This can allow the eyes to become irritated. They often 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 3 or 4 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 features of speech in Parkinson's disease. Most commonly, there is a combination of at least two of these three features in the speech of PSP.

The speech difficulty of PSP, in combination with the forgetfulness, slow (albeit accurate) 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 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. Unlike the other difficulties in PSP, this one can sometimes pose a danger for the patient - the danger of food going down the wrong pipe into the breathing passages, termed "aspiration." Usually, difficulty managing thin liquids precedes difficulty with solid food. This is because in PSP, the swallowing muscles have difficulty creating a watertight seal separating the path to the stomach from the path to the lungs. The same is true for the swallowing difficulty of many neurological diseases. For non-neurologic conditions such as stricture of the esophagus, however, 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," in fact, 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. In many people with PSP, there is a loss of inhibition or an impulsiveness that the ill person recognizes and promises to resist, but these risky behaviors can be partly involuntary.

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

Although mental confusion in patients with PSP is more apparent than real, most patients do eventually develop some degree of mental impairment. Some are mislabeled as having Alzheimer's disease. This is not very different from the situation in Parkinson's disease.

In PSP, the dementia, 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 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 previous familiar environment. Fortunately, these symptoms almost never occur in PSP. Nevertheless, the "frontal" problems of PSP 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 minutes. Probably the most important aspect of the dementia of PSP is apathy. People with PSP seem to lose interest in their surroundings, again creating the impression of loss of thinking ability and interfering with family interactions.

How is PSP different from Parkinson's disease?

Both PSP and Parkinson's disease cause stiffness, slowness, and clumsiness, a combination called "parkinsonism" (with a small p). This is why early on, PSP may be difficult to distinguish from Parkinson's disease. However, shaking ("tremor"), while prominent in about two-thirds of people with Parkinson's disease, occurs in only about one in twenty people with PSP. A more common type of tremor occurring in PSP is irregular, mild, and present only when the hand is 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 of 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 problem with vision and swallowing and to respond better to drugs for Parkinson's.

The mainstays of drugs for Parkinson's disease are those that enhance replace or mimic a brain chemical called dopamine. Parkinson's responds better to such drugs than does PSP because in PD, deficiency of dopamine is by far the most important abnormality, while 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 medications, all available only by prescription, can help PSP in some cases.

Sinemet - this is the brand name for a combination of levodopa and carbidopa. Levodopa is the component that helps the disease symptoms. Carbidopa simply helps prevent the nausea that levodopa alone can cause. When levodopa came along in the late 1960's, it was a revolutionary advance for Parkinson's but, unfortunately, 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. It usually loses its benefit after two or three years, but a few patients with PSP never fully lose their responsiveness to Sinemet.

Some patients with PSP require large dosages, up to 1,500 milligrams of levodopa (with carbidopa) per day, to see an improvement, 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 Sinemet in patients with 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 Sinemet dosages.

Patients with PSP should generally receive the standard Sinemet (or generic levodopa/carbidopa) preparation rather than the controlled-release (Sinemet CR or generic levodopa/carbidopa ER) form. The CR form is absorbed from the intestine into the blood slowly and can be useful for people with Parkinson's disease who respond well to Sinemet but need to prolong the number of hours of benefit from each dose. In PSP, however, such response fluctuations almost never occur. Because Sinemet CR is sometimes absorbed very little or

erratically, a poor CR 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.

A new formulation of levodopa-carbidopa is Parcopa, which dissolves under the tongue. For people with PSP who cannot swallow medication safely, this could be useful. Another approach for such patients 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 new formulation of levodopa-carbidopa combines those two drugs with a third drug, entacapone, in the same tablet. This is called Stalevo. The entacapone slows the rate at which dopamine is broken down. It is useful for patients with Parkinson's whose levodopa-carbidopa works well but only for a few hours per dose. This situation rarely, if ever, occurs in PSP.

Dopamine receptor agonists - there are three such drugs on the market for Parkinson's - Parlodel (generic name, bromocriptine), Permax (pergolide), Mirapex (pramipexole) and Requip (ropinirole). A fifth drug in this class, rotigotine, will soon be available in the US as a skin patch called Neupro (it is already available in Europe). For PSP, these rarely give any benefit beyond that provided by carbidopa/levodopa. One careful trial of Mirapex showed no benefit at all in PSP.

The main possible side effects of the dopamine receptor agonists are hallucinations and confusion, which can be more troublesome for PSP than for Parkinson's. They can also cause excessive involuntary movements, dizziness and nausea.

Antidepressants - another group of drugs that has been of some modest success in PSP are the antidepressant drugs. The anti-PSP benefit of these drugs is not related to their ability to relieve depression. The best antidepressant drug for the movement problems of PSP is probably amitriptyline (brand name, Elavil). It has been used against depression since the early 1960's. The dosage should start at 10 mg once daily, preferably at bedtime. It can be increased slowly and taken divided into at least two doses per day. Past 40 mg per day, the likelihood of side effects increases to an unacceptable level for most patients. Amitriptyline is also a good sleep medication for some elderly people and may provide this benefit in PSP if taken at bedtime. One important side effect in some people is constipation. Others are dry mouth, confusion and difficulty urinating (in men). Unfortunately, some patients with PSP find that their balance difficulty worsens on amitriptyline.

Symmetrel - this drug (generic name, amantadine) has been used for Parkinson's since the 1960s. Because it affects more than just the dopamine system, it can be effective in PSP even if Sinemet is not. It seems to help the gait disorder more than anything else. 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."

Drugs for dementia - Cognex (tacrine), Aricept (donepezil), Reminyl (galantamine) and Exelon (rivastigmine) are drugs that 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. But they do not help the mental difficulties of PSP. A fourth anti-Alzheimer drug, Namenda (memantine) acts on a different brain chemical, glutamate. It works no better for PSP than the others and in addition can cause confusion and agitation in those patients.

Botox - a different sort of drug that can be useful for people whose PSP is complicated by blepharospasm is Botox or Myobloc (two types of botulinum toxin). This substance is produced

by certain bacteria that can contaminate food. Its poisonous action occurs because it weakens muscles. A very dilute solution of the toxin 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 injection of Botox into the neck muscles can sometimes cause slight weakness of the swallowing muscles, which are nearby. In PSP, where swallowing is already impaired in many patients, caution should be used when considering use of Botox in neck muscles.

Experimental drugs - in the past 20 years, many drugs have been tested by researchers in patients with PSP. Some of these are intended to actually slow the long-term brain cell loss and therefore slow the progression of the disease. Perhaps the largest trial was of the drug riluzole, which helps amyotrophic lateral sclerosis modestly but was found not to help PSP.

One possible success story, though the jury is still out, is the dietary supplement coenzyme Q-10. That drug is available without a prescription and helps the body's cells produce energy from sugar and oxygen. It is a normal constituent of the mitochondria, the tiny compartments in our cells where that chemical process occurs. In one small, brief study in Germany, it was found to improve the signs of PSP, both by neurological examination and by a high-tech measure of energy production by the brain. Two other trials of coenzyme Q-10 in PSP and one large trial in Parkinson's are in progress. The dosage of this supplement needed to give benefit is probably at least 1200 mg per day and perhaps as high as 2400 mg. Even the lower amount costs \$200 per month and is not covered by prescription insurance. Therefore, people with PSP should carefully consider the meager evidence to date for the benefit of coenzyme Q-10 before taking that long-term financial plunge.

Another experimental approach to slowing of disease progression in PSP attempts to prevent the abnormal attachment of phosphate groups to the tau protein. We are still unsure why phosphate groups become abnormally attached to tau in PSP. But in animal "models" such as mice genetically engineered to develop tau tangles in the brain, such drugs do slow that process. These drugs inhibit an enzyme called GSK3-beta.

One such GSK3-beta inhibitor, lithium, has been used in psychiatry for bipolar disorder for many years for reasons unrelated to its action on tau. Unfortunately, patients with PSP were unable to tolerate it because of a variety of side effects such as nausea and dizziness.

Another, called tideglusib (brand name, Zentylor; formerly called Nypta) has completed enrollment and is expected to announce results in early 2012. It appears to be better tolerated than lithium, at least so far. If this trial demonstrates successful slowing of PSP progression, Zentylor will probably be approved by the FDA for commercial sale.

A different approach to slowing the progression of PSP is to enhance the growth and maintenance of the microtubules, ordinarily the job of the tau protein. The drug davunetide, which is taken as a nasal spray, does this. It is being tested at present in 44 sites in Europe and North America and will continue to recruit new patients into the second half of 2011.

Fortunately for PSP sufferers, drug companies have started to act on the realization that a prevention for PSP, where the market is tiny, could work also in Alzheimer's disease, where the market is huge.

Is tube feeding advisable for advanced patients?

An operation that may be advised for extreme cases of poor swallowing where choking is a definite risk is the placement of a tube through the skin of the abdomen into the stomach ("gastrostomy" or "percutaneous endoscopic gastrostomy" or "PEG") for feeding purposes. 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 who is 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: aspiration pneumonia; small amounts of aspiration with each swallow; significant weight loss from insufficient feeding; or when a meal requires so much time that the functioning of the household is disrupted.

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 the feeling of "wholeness" or humanity. The issue of how much additional quality will be introduced into the patient's life must be considered carefully. The family, physician and if possible, the patient must all voice their opinions. Another downside is that some patients who are 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 may be useful 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 payors 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 output of the basal ganglia (the group of nuclei that control movement) to the rest of the brain is overactive in Parkinson's. The operations dampen down this overactivity. The main operations for this purpose are pallidotomy, which is rarely performed nowadays, and subthalamic nucleus stimulation, which is the most common Parkinson's operation at present. In PSP, the area of the basal ganglia from which the output comes is itself damaged, so its activity is already dampened down. The operations would only make things worse.

However, there are trials now in progress to test stimulation of an area of the brain serving balance, the "pedunculo-pontine nucleus" (PPN), in people with PSP. The PPN is in the brainstem, which is an area tightly packed with critical circuitry. The procedure seems to be acceptably safe, but the overall improvement in the patients is still undetermined. The procedure does seem to help the balance problem in some patients with Parkinson's disease.

The other category of operation for Parkinson's attempts is to replace the lost dopamine-producing brain cells. The reason this is unlikely to work for PSP is that while in Parkinson's,

most of the movement problem is caused by loss of the main dopamine-producing nucleus, the substantia nigra, while in PSP, the movement problems are caused by loss of many other nuclei in addition. Many of those other nuclei receive their input from the substantia nigra, so replacing only the first "link in the chain" will not help much. It would be impractical to replace cells in all of the nuclei involved in PSP – it would require too much trauma to the brain.

What about other non-drug treatment?

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 conscious 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 during the "bad" times.

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. Such people can fall if they move their body forward before the foot moves. In these cases, a smooth sole 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 in 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 glasses called prisms are sometimes prescribed for people with PSP. These are sometimes worth trying, but are usually 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. If this additional problem exists, special glasses would not help.

Formal physical therapy is of no proven benefit in PSP, but 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 the sense of well-being of 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.

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", 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 are affected in PSP that are normal in Parkinson's (and vice-versa). Moreover, under the microscope, the appearance of the damaged brain cells in PSP is quite different from those in Parkinson's and resembles, rather, the degeneration in Alzheimer's disease. However, the location of the damaged cells is quite different in PSP and Alzheimer's. Furthermore, in PSP there are no amyloid plaques, 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 a normal protein called "tau." These clumps of tau are called "neurofibrillary tangles." The normal function of tau is to help support the internal "skeleton" of the brain cells whose long extensions make contact with other brain cells. 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 produced in excess. If it is damaged, the nature of that damage could be the excessive attachment of phosphate (see above). Or, the excessive phosphates observed could simply be the brain's normal response to minimize the effects of tau protein that is misbehaving for some other reason.

A clue to what is going wrong with tau protein is that most of the tau protein in the neurofibrillary tangles of PSP is of one type called "four-repeat" tau. In the normal brain cells, there are equal amounts of four-repeat and three-repeat tau. The "repeat" number refers to the number of copies of the part of the protein that binds it to another component of the cell's internal skeleton, the microtubules. So in PSP, the problem may be that too much four-repeat tau is made, or that too little three-repeat tau is made, the result being clumps of four-repeat tau.

It is looking more likely that at least one important part of the cause of the misbehavior of the tau protein is some sort of genetic defect in or near the tau protein's gene on chromosome 17. But the nature of that defect remains elusive.

Is PSP genetic?

PSP only very rarely runs in families. Fewer than 1 in 100 people with PSP know of even one other family member with PSP. 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 the rest of us. So clearly, the H1 haplotype is (nearly) necessary but far from sufficient to cause the disease. There is evidence that what this variant is doing wrong is directing the brain cells to produce too much tau protein. The evidence suggests the tau starts to aggregate into clumps and that the damage is caused by an early stage of these that is still too small to be seen through the microscope. The larger, mature neurofibrillary tangles may simply be the result of the cell's attempts to pack the small, toxic, clumps of tau into a harmless mass that cannot interact with normal cell constituents.

The other PSP-related variant in the tau gene was discovered in 2010 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. This will be the subject of intense research over the next few years.

The same Peebler Genetics Program of CurePSP has discovered several other genetic variants that are more common in people with PSP than in those without PSP. Those genes make enzymes that help control the brain's system for disposing of mis-folded proteins. This could explain why the clumps of tau protein form. Other genes newly implicated in PSP help 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.

The insights from this new genetic study 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.

Could PSP be caused by toxins?

There is also evidence that chemicals in the environment or diet may contribute to the cause of PSP. Surveys of PSP patients have hinted at a predilection for rural living and, on average, lesser educational attainment in people with PSP. This suggests that part of the cause of PSP is certain occupational factors exposing people to different chemicals than are encountered by non-rural people or those with more sedentary, office-bound occupations.

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, if any, foods in the Western diet may contain similar toxins. Research on that question is under way.

What research is being done?

Research is proceeding in the areas of genetics, epidemiology, treatment trials, and molecular studies. CurePSP’s genetics program has searched the entire genome for genes related to PSP and corticobasal degeneration (CBD). The results, which showed at least four genes not previously suspected of a relation to these diseases, will be published in 2011. In addition to working with researchers at the University of Louisville to study environmental, occupational, and genetic risk factors associated with PSP, CurePSP and other funding agencies are presently sponsoring exciting and promising research into many aspects of PSP, including ways to prevent the brain cells from dying and treatment of the symptoms with drugs, magnetic stimulation, and deep-brain electrical stimulation. Two drug companies are presently running large, formal trials of new medications designed to slow progression of PSP.

How can I help research?

Of course, CurePSP welcomes donations to its research grants program. Since its inception in 1997, it has provided over \$9 million to researchers’ institutions to support their work. Some of the support has gone to senior researchers with excellent track records of productivity and some

has gone to junior scientists with original ideas and first-rate training. CurePSP does not restrict its grants to any country or continent. It 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.

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, too.

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 in this way. 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 sponsors 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 after their proposals are examined and approved by the CurePSP Scientific Advisory Board. Donating to a brain bank does not interfere with funeral arrangements and costs the family a few hundred dollars for expenses of brain removal and transportation. 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 the CurePSP. There are many other brain banks throughout the country, generally located at major university hospitals.

Should I join some sort of support group?

The value of membership in a group of other people with the same problem is tremendous. 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 PD 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, 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.

This information provided by:

Lawrence I. Golbe, MD
Director of Research and Clinical Affairs, CurePSP
Professor of Neurology, University of Medicine and Dentistry of New Jersey,
Robert Wood Johnson Medical School
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