Parkinson's Evil Twin

A Researched Science Essay for the General Public

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21W.031 – Fall 2012

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Have you ever witnessed a computer with a virus? Most likely it was a Windows PC, not an Apple, but aside from the matter, you try installing antivirus software to cure this malicious content within the computer’s inner workings. Ultimately, the virus is uncontrollable and the hard drive becomes corrupt, meaning you just lost all your information and have no other option but to purchase a new one for a couple hundred dollars. In this case, the “dead” hard drive only cost you some hard-earned money and stress. However, the case is not the same with a human brain: there is no such thing as a replaceable brain or even more so, a replacement for all the memories and experiences one gathers in a lifetime. This phenomenon is the basic process behind neurodegenerative diseases, an array of malicious illnesses which corrupt brain cells, causing them to break down and alter the lives of those you most care for.

A neurodegenerative disease is defined as: a disease in which the nervous system progressively and irreversibly deteriorates (11). A large number of illnesses fall under this category, some of which are well-known (e.g. Alzheimer’s disease, Parkinson’s disease) and others that are relatively rare amongst the human population, such as Huntington’s disease, Lou Gehrig’s disease (also known as “motor neuron disease”), and Progressive Supranuclear Palsy (PSP). Although these illnesses are diverse in character, they all share a common host, the human brain.

The Brain: The Human Hard Drive

Have you ever wondered how your computer’s hard drive works? Why it fails or why sometimes it takes an immense amount of time to load information? By understanding these concepts, it may surprise you how closely the process of analyzing and transmitting data in a computer resembles that of our brain.
The human brain is comprised of millions of brain cells known as neurons. Each neuron is alive in the sense that it transmits information from one neuron to the next through a network system operated by dendrites. However, neurons, unlike many other cells in the human body, are not regenerated once they are damaged or die (13).

Communication between adjacent neurons occurs over a synapse, where information is transferred and transmitted to the rest of the body (see Figures 2 & 3). Certain signals, or “messages,” are relayed to specific neurons which control unique muscles in the body (i.e. motor neurons, sensory neurons) and allow for smooth, coordinated muscle movement. Neurons propagate these signals in the form of action potentials, or impulses, at a speed of anywhere from 1 to 120 meters per second (see Figure 2). An action potential occurs as a result of a membrane potential along the axon where two ions, sodium (Na+) and potassium (K+), are actively exchanged in and out of the neuron, causing a change in the neuron’s membrane potential across the synaptic gap.
out of the axon. This method is commonly referred to as the sodium-potassium pump. While most impulses make it across the synaptic gap without interruption, some are stopped short due to a deficiency in neurotransmitters, a chemical substance that aids the transmission of nerve impulses across the synapse. In order for impulses to travel across the synaptic gap (approximately 20 nm in width), neurotransmitters are responsible for unlocking the receptor sites on the adjacent neuron, crossing into the subsequent neuron and therefore generating a new action potential. (9)

Neurodegenerative diseases are commonly associated with the deficiency of neurotransmitters, such as dopamine and acetylcholine which help coordinate movement and balance throughout the body. Many of the symptoms associated with Parkinson’s disease and PSP, for example, show the gradual death of neurons in a specific area of the brain where production of neurotransmitters takes place. The “substantia nigra” is the part of the brain which is responsible for producing neurotransmitters known as dopamine (see Figure 4); death of neurons in this part of the brain therefore leads to a significant reduction in dopamine. Such reduction disables the neurons from sending smooth, coordinated muscle movements to the rest of the body, causing a common symptom associated with Parkinson’s, bodily tremors.

A similar interpretation can be described with the analogy of a computer hard disk drive, where data from the hard drive is processed by the computer over a gap known as the flying height, or floating height. Information is transferred over a gap of approximately three nanometers to a reader head which reads the data magnetically from the platter.
and sent to the respective program you are running. The reader head and the spinning head are never meant to touch; however, the distance between them is so miniscule, any type of debris (e.g. dust/smoke particle) can interrupt the flow of information and make your hard drive “crash” (see Figure 6).

Parkinson’s disease and PSP therefore share a common characteristic as inhibitors of neurotransmitters in the brain; however, this aspect only begins to scratch the surface behind the inner workings of PSP which makes it incredibly distinct and unique among the elite leaders of neurodegenerative diseases.

**The Evil Twin**

Parkinson’s disease is considered perhaps the most widely known “neurodegenerative” disease among elders 60 years of age and older across the entire globe. Although unlike Parkinson’s disease, progressive supranuclear palsy is a neurodegenerative disease with no current known cause, treatment, or cure, and has about 1% the prevalence of Parkinson's. Many of the early stages associated with both Parkinson’s disease and progressive supranuclear palsy are strikingly similar, which is a common factor leading to misdiagnosis among patients. My father is one of the five to six people per 100,000 who have been diagnosed with PSP, after being misdiagnosed with Parkinson’s in 2007. (4, 8)

**What does the name “Progressive Supranuclear Palsy” mean?**

Progressive Supranuclear Palsy (PSP) occurs as a result of the loss of neurons and glial cells (specialized cells that surround neurons, providing mechanical and physical support and electrical insulation between neurons) in the brain including areas of the cerebral cortex,
particularly the frontal and motor areas (1). Scientists developed the name, identifying each term with a characteristic unique to the disease:

- “Progressive” simply stands for the tendency of the illness to get radically worse as time goes on, continually degenerating cells in the brain, ultimately leading to death. Life expectancy for someone who has been diagnosed with PSP is estimated to be 6-8 years after diagnosis, a number significantly smaller than patients with Parkinson’s. (5)

- “Supranuclear” refers to the specific area of the brain where the death of neurons occurs (mainly in the brain stem and basal ganglia). This is the area, above the nuclei (hence supranuclear), which controls balance, movement, vision (particularly upgaze and downgaze), speech and ability to swallow. (5)

- “Palsy” alludes to muscle stiffness and weakness often found in patients with PSP. This feature is also the main cause for falls and uncontrollable balance when walking or standing. (5)

**What symptoms are commonly associated with PSP?**

PSP is generally first diagnosed in age groups ranging from 40 to 60 years or older. The fact that many early stage symptoms are so similar to Parkinson’s disease prolongs the diagnosis of PSP even by expert neurologists, who have trouble differentiating the two. In other words, PSP does a fine job of mimicking the early subtle symptoms of Parkinson’s until late into the final stages of the disease. For example, my father on the onstage of the illness noticed slight tremors while driving, eating, and writing when he was approximately 75 years old. He went to see his neurologist, and after a couple of sessions, the neurologist gathered several of his colleagues and had him walk across the hallway outside his office several times to note any
significant changes in his walking. It was reported that the shaking in his hand might be the result of Parkinson's and so the doctor prescribed him with the first of many medications, Carbidopa-Levodopa. This medication is a common treatment for Parkinson's patients meant to increase levels of dopamine in the brain and effectively help reduce tremors.

As the disease progresses, other common symptoms including loss of balance and coordination while walking and frequent falls become more prominent in patients with PSP. My father soon thereafter was referred for an otoscopy (ear examination) to determine what was the leading cause of his falls and loss of balance. Potential causes suggested by the neurologist lay in the inner ear or hardening of the arteries supplying the brain; fortunately, the results checked back normal. However, there was still the concern about him falling and getting injured. In light of the situation, it was recommended for him to use crutches or a cane for support measures and to reduce the chances of him falling. At the age of 77, my father was still working; this brought concern over his job, but a hard-worker at heart, he kept working despite his condition, which unfortunately took a turn for the worse in the years ahead.

**What is the cause of PSP?**

PSP, like other neurodegenerative diseases, is similar in affecting a distinct area of the brain; however, “several important areas are affected in PSP that are normal in Parkinson's (and vice-versa).” More recent, groundbreaking research in PSP has led to the investigation of protein accumulation or “neurofibrillary tangles” in parts of the brain associated with the transferring of signals across neurons. In normal brain cells this protein, known as “tau,” is found in the axon region of a neuron, stabilizing structure critical to the cell’s internal transport system (see Figure 7). To understand
the function of the tau protein, imagine the structure of a typical railroad track. The railroad tracks represent the microtubules in the axon and the tau protein “ties” the tracks together, allowing nutrients and other cellular “cargo” to travel along the length of the neuron. Neurofibrillary tangles occur when abnormal tau protein separates from the microtubules, forming tangles and disabling the transport system, ultimately destroying the cell (see Figures 8 & 9). As a result of this occurrence, neurons break down causing memory loss and brain shrinkage, a common characteristic also found in Alzheimer’s disease (see Figure 10). Unfortunately, researchers “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.” The latest medication to help prevent the accumulation of tau in brain cells is known as “davunetide” and is expected to be available late 2012 into early 2013. (2, 3, 5)

Figure 8

Figure 9

What happens next?

The term “progressive” in PSP is justified in the sense that degeneration is quite rapid and new symptoms start to appear 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.” (5)

A couple of years down the road, it was confirmed that my father’s condition was steadily worsening. He was falling repeatedly and one fall left him with severe internal bleeding and broken ribs, leading him to the hospital. It was not until this incident that more immediate attention to his condition led to a change in neurologist who knew more about the symptoms he was experiencing. It was after three years following his misdiagnosis of Parkinson's disease that my father was told the reality behind his illness.

**Behind PSP**

With groundbreaking knowledge and information that my father had PSP, it was soon confirmed that the medication he was taking for Parkinson's had almost no effect on the disease. The resemblance of PSP to Parkinson's disease is explained by the fact that both disorders feature important involvement in dopamine produced by the substantia nigra. However, unlike Parkinson's disease, PSP patients also experience the degeneration of dopamine receptors inside the brain, essentially negating the positive effects of the medication. (5)

As time progresses, PSP manifests itself by impairing the ability to speak, write, see, walk, or recall thoughts properly, causing great distress for the individual. My father was exhibiting a spastic speech pattern (spastic dysarthria), characterized by way of grouped syllables and unclear words, sometimes appearing to sound “drunk” on the phone. Furthermore, muscles throughout the digestive system become stiff and hard to move, causing the person to drool and making it impossible to swallow large pieces of food (dysphagia), which may in turn cause further complications such as aspiration, pneumonia, or even the extreme case of tube-feeding the patient. As a result of bradykinesia, or abnormal slowness of movement, my father’s ability
to walk was drastically limited, to the point where he required a wheelchair to move around the house to avoid suffering from a fall. When he attempts to walk, his feet appear to be glued to the floor, making him unable to move without a support system. This all correlates with the fact that the degeneration of neurons in his brain causes the inability to control muscle movement throughout his entire body. (5)

My father, once a scrupulous and strong man, was deprived of his ability to live a normal life. One day he told me, “This thing has robbed me of my self-being and of who I was in this world; it has taken all purpose away from me.” This disability strips one’s independence and freedom as an individual. It offers no remorse, and towards the final stages, forces the need for a caregiver to provide for the patient who at this point is unable to achieve anything on their own. This in turn introduces other common symptoms of PSP, such as changes in personality, signs of depression, and dementia.

Many PSP patients exhibit mental confusion which is often misattributed to 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 [commonly associated with] 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….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.” (5)

Furthermore, research has shown that many of the problems associated with PSP are intermittent and can be directly influenced by a patient’s current mental or emotional state. For example, walking, writing, and eating may be poor one hour and better the next. On a good day,
my father is able to go out in the morning for a bicycle ride or fresh air; however, on a bad day he will be stuck in bed with the terrible fear of getting up and falling, potentially jeopardizing his life. PSP has taken a hold of him in a way that he will never be able to regain his old life. At one point during this time he became desperate for answers, to the extent that he began attending weekly church services in hopes of attaining a life with purpose, something which seemed he no longer had. As the person’s abilities to speak, write, and walk gradually deteriorate, mental impairment eventually becomes a key concern leading to slowing of thought and apathy. As medical expert Lawrence Golbe observed, “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.” (5)

**Pseudo-Treatments**

The term “Pseudo-Treatments” refers to the fact that although there exists a number of prescription drugs which have proved to alleviate symptoms of PSP in some patients (symptomatic treatment), there is yet to be discovered a medication which targets the progressive movement of the disease and provides a complete cure for patients. For a rather long time, doctors who have diagnosed individuals with PSP have prescribed medication very much similar to those given to Parkinson’s patients. While some patients with PSP exhibited a decrease in symptoms, it is important to note that PSP’s most unique characteristic is that of degeneration of brain receptors necessary to process the ingredients found in today’s drugs.

One commonly used prescription drug is Sinemet. These pills, often taken orally, consist of two components which help increase levels of dopamine in the brain. These components, levodopa and carbidopa, work together by helping alleviate disease symptoms and reducing the likelihood of side effects such as nausea, confusion, and dizziness commonly associated with
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PSP. With the introduction of levodopa in the 1960s, the research was described as “a revolutionary advance for Parkinson's but, unfortunately, 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.” Patients with PSP generally need to take a large dosage of levodopa (up to 1,500 milligrams) to notice any improvement, thereby increasing their susceptibility to a wider number of side-effects. (5)

Following the same combination of levodopa and carbidopa, another type of medication combines a third additive known as entacapone. This medication helps reduce the rate at which the dopamine is broken down inside the brain, leading to a more long-lasting effect in some patients. Other common tested drugs include antidepressants, drugs for dementia, and the dietary supplement coenzyme Q-10. Coenzyme Q-10, also known as CQ10 and often found without a prescription, has revealed positive signs for patients with high blood pressure, heart failure, excess weight, and even Parkinson’s disease. Patients considering this approach, however, are often shocked to find that the dosage required to achieve benefit is at least 1,200 mg per day and perhaps as high as 2,400 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 [CQ10] before taking that long-term financial plunge.” (5)

A range of non-drug treatments have been found to provide a somewhat more practical approach to the treatment of PSP, most commonly in the form of exercising and physical therapy. Lawrence Golbe, MD. suggests that, “[While] formal physical therapy is of no proven benefit in PSP…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.” (5) Therefore, by engaging in physical activities,
patients can avoid other disorders often associated with inactive muscle movement such as muscle stiffness and atrophy.

There is also evidence that suggests 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 education attainment in people with PSP.” Two studies, both with the same result, have shown individuals who did not complete high school are more likely to have PSP, suggesting that a job in the field of industry increases the likelihood of exposure to toxic chemicals unlike those individuals with more sedentary, office-bound occupations. With this in mind, recent medical research has also raised concern over the use of levodopa medications (such as Sinemet) in Parkinson’s patients, since it has now been demonstrated that levodopa significantly enhances the production of “brain damaging free radicals.” The concern over free radical production by levodopa is compounded by a report in a prestigious medical journal, The Lancet, showing that levodopa increases levels of homocysteine, an amino acid directly linked to increased risk of stroke and marcodiocal infarction. (5, 6, 7, 10, 12)

Research in the 1980s uncovered a brain chemical deficiency in Parkinson’s disease known as glutathione. Glutathione is a brain protecting antioxidant which normally exists and is produced inside the human body. According to scientists, all other antioxidants like Vitamin C, A, E, and so forth depend on the presence of glutathione to function properly, making glutathione the master antioxidant. Its main purpose in the human body is to maintain cells healthy, especially in the central nervous system. Glutathione’s role is to act as a “buffer” in the human brain, protecting brain cells from oxidation stress as a result of free radicals. Scientists infer low levels of glutathione in the body correlate with most chronic diseases (such as diabetes, cancer, etc.) which are known for depleting levels of glutathione in the body. However, the main
concern lies behind how to increase levels of glutathione inside the body. Oral supplements have shown great magnitudes of inefficiency absorbing into the body’s blood stream, making intravenous (IV) and intramuscular injections the most effective. While discovered in the 1980s and evidence suggesting dramatic improvements in Parkinson’s patients by leading doctors in the field such as David Perlmutter, MD., the use of glutathione to treat neurodegenerative diseases still remains modest. (See Recommended Readings/Videos)

**Living with PSP**

While research is still coming up with answers on a more effective treatment of PSP, it is important for patients and families to take appropriate steps towards providing safety to the lives of those surrounding them. As I have personally experienced, having a loved one diagnosed with this disease has changed the course of our entire family’s future, requiring certain measures and special arrangements to allow my father to live as comfortably as possible.

One such measure takes into account the patient’s lifestyle and way of living. “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.” In the case of my father, such characteristics result in his body moving forward while his feet remain “stuck” to the floor, potentially leading to a fall. Having shoes with smooth soles instead of rubber-soled athletic shoes would therefore significantly reduce the likelihood of a fall. “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.” Furthermore, the introduction of electric or manual wheelchairs and walkers as a walking aid may require general rearrangement or offering for sale of furniture to accommodate these devices in the household. (5)
Is PSP genetic?

A great deal of concern lies behind whether or not PSP is a genetic disorder. Investigative research of the tau protein has shown that at least one important part of neurofibrillary tangles is some sort of genetic defect in or near chromosome 17. However, “PSP only very rarely runs in families. Fewer than 1 in 100 people with PSP know of even one other family member with PSP.” Leading evidence suggests that H1 haplotype, one of two different variants in the gene on chromosome 17 that encodes the tau protein, is “directing the brain cells to produce too much tau protein.” Moreover, “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.” Additional and more recent PSP-related variants in the tau gene are being investigated and will be the leading subject of research over the next few years. (5)

Conclusion and Future Study

From the point of view of a son whose father has been diagnosed with PSP, I find that it must be the most incredibly frustrating thing in the world to be aware of the fact that you have something like this and there is nothing anybody can do about it. Unlike any other neurodegenerative brain disease, PSP still remains a mysterious disease which few have heard of and which science is only beginning to uncover. Its distinct attributes and characteristics set it apart from any other neurological disease, stealthily propagating and eating away at the brain and its function.

As of today, there is no effective treatment and no cure for this disease, though there is an increasing amount of ongoing research supporting patients with PSP. The only thing to rely on is hope that more people become aware of this disease and for a new scientific breakthrough that will unlock an answer to the neurological war against the twins of evil.
References


Figure 7: Healthy Neuron Showing the Normal Tau Protein. 2012. Retrieved November 9, 2012, from: http://www.ahaf.org/alzheimers/newsupdates/study-shows-alzheimers.html


Figure 9: Comparison of a healthy neuron with a deformed neuron that is usually seen in Alzheimer's disease. 2012. Retrieved November 9, 2012, from: https://wiki.engr.illinois.edu/display/BIOE414/Alzheimer's+Disease+and+EEG+Diagnosis


Recommended Readings/Videos:

- CurePSP: Foundation for PSP | CBD and Related Brain Diseases
  - http://www.psp.org/
  - http://www.psp.org/mission/education/
- The PSP Association
  - http://www.pspassociation.org.uk/
- Lawrence I. Golbe, MD.: PSP Causes and Treatments – 2011 East Coast Conference
  - http://www.youtube.com/watch?v=thnoNj50J_A&feature=relmfu
- Glutathione Therapy for Parkinson’s Part 1 from David Perlmutter, MD.
  - http://www.drperlmutter.com/
  - http://www.youtube.com/watch?v=wxno30sQkyU
- Doctors opinion of Glutathione & Parkinson’s Disease
  - https://www.youtube.com/watch?v=AugPcD2ho5M