A Descriptive Pilot Study of Emergency Department Usage in Progressive Supranuclear Palsy, and a Literature Review of the Pathophysiology and Epidemiology of the Disease

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Abstract

Progressive nuclear palsy (PSP) is a lethal neurodegenerative disease, characterized by the deposition of 4-repeat (4R)-Tau in the brain. Few therapeutic options exist. Public health efforts to reduce the morbidity and mortality of this disease are currently undermined by our limited understanding of the disease and its pathogenesis. While information on healthcare resource utilization and the economic impact of PSP is generally lacking, the sparse data that exists suggests that patients with PSP utilize the emergency department (ED) an inordinate amount. Anecdotal clinical experience suggests that falls and fall related injuries are likely responsible for the majority of ED utilization in PSP. However, the literature on ED utilization in PSP is limited and somewhat outdated. *The overall aim of this pilot study was to describe the usage of the ED by patients with PSP, to better characterize the impact of specific causes of morbidity in the disease.* Increased knowledge of how and why the ED is used in PSP could improve public health efforts targeted at reducing morbidity by highlighting where better preventative measures need to be developed. Our findings suggest that falls are indeed the most common and significant reason that PSP patients seek emergency medical care.

Table of Contents

List of Tables

List of Figures

1.0 Background Information and Literature Review

1.1 Epidemiology

1.1.1 Clinical Presentation, Diagnosis, and Natural History

PSP was originally identified in 1964, and was described as a syndrome of supranuclear ophthalmoplegia, pseudobulbar palsy, dysarthria, dystonic rigidity of the neck and upper trunk, dementia, as well as cerebellar and pyramidal symptoms [1]. Since then, the field has recognized that there are multiple different clinical presentations of PSP including the classic Richardson's syndrome (featuring falls, vertical gaze palsy, and dementia) and PSP-parkinsonism (in which parkinsonism is the predominant feature, and falls, vertical gaze palsy, and dementia occur much later, if at all) [2]. The classic NINDS-SPSP criteria for diagnosis of PSP emphasize frequent falls and the presence of vertical supranuclear gaze palsy or slowed vertical saccades [3]. This criteria is excellent at identifying cases of Richardson's syndrome, but misses many cases of PSP-Parkinsonism at least early in the course of the disease [4]. New criteria have recently been published seeking to address this issue by expanding criteria to include akinesia and cognitive dysfunction [4]. Still, accurate diagnosis of PSP is difficult, as it must be based entirely on clinical examination and patient history. No biomarkers, imaging, or genetic finding has the required specificity and sensitivity to distinguish PSP from other neurodegenerative diseases or healthy controls [4]. Imaging results (such as mid brain atrophy on MRI, or the patterning of Tau PET scans) can suggest or be consistent with a diagnosis of PSP, but have low sensitivity early in disease progression at the point of clinical presentation and are mainly used to exclude other

diseases [5]. Diagnosis remains dependent on recognition of the characteristic constellation of clinical symptoms and signs, many of which can be subtle or absent at initial presentation so that early detection is currently impossible. A definite diagnosis of PSP requires demonstration of characteristic patterns of cell loss and deposition of 4R-Tua in neurons and glia through post-mortem analysis of Tau in the brain.

PSP presents insidiously (Fig 1.). Fascinatingly, post-mortem analysis shows 4R-Tau accumulation reminiscent of PSP pathology in many individuals who are clinically normal [5]. Community autopsy studies suggest that up to 4.6% of elderly people have underlying PSP pathology, and it remains unclear why only a small percentage of these individuals progress from 'presymptomatic PSP' to clinical disease [6, 7]. Classically, patients present to the clinic in their sixth decade of life with postural instability and frequent falls. Patients also display slowed vertical saccades early on, which progress to the hallmark vertical gaze palsy over time. Patients quickly deteriorate, often developing dysarthria and dysphagia. Aspiration pneumonia is the most common cause of death in PSP, reflecting patient's impaired ability to swallow [8]. Patients with Richardson's syndrome have a mean survival of 7 years post diagnosis [2]. PSP-Parkinsonism patients have a longer mean survival time of approximately 10 years [2]. Treatment is supportive and aimed at preventing complications such as fractures or aspiration. There are no treatments that reliably mitigate symptoms, prevent disease progression or reverse pathology.

1.1.2 Demographics

PSP is a relatively uncommon disease. The prevalence of PSP is estimated to be between 1-17 cases per 100,000 people worldwide [9-13]. Estimates of prevalence seem to vary substantially across populations (e.g., 1 per 100,000 in the UK vs 17 per 100,000 in Japan).

Whether this reflects a true difference in the burden of disease, perhaps reflecting a distribution of environmental or genetic risk factors, or is merely a methodological artifact is somewhat uncertain. Earlier studies likely underestimate prevalence as PSP is a difficult disease to diagnose correctly due to high symptomatic overlap with other neurodegenerative diseases. Notably, most of the studies of the demographics of PSP have occurred in western European countries or Japan, with fewer studying the U.S. population. A recent analysis of a large insurance claims database found a prevalence of 2.95 cases per 100,000 people in the United States [14]. Another prospective study of a cohort located in a county of Minnesota observed an incidence of 2.6 cases per 100,000 person years [15].

PSP is a disease of the elderly. In fact, the mandatory inclusion criteria for diagnosis of PSP requires that a patient be at least 40 years of age at symptom onset as pathologically-confirmed cases with symptom onset before this age have not yet been described [4]. As demonstrated by the diagnostic criteria, patients can present clinically in their early 40s, although this is rare. Patients tend to present with symptoms in the sixth decade of life, with a mean age of onset of approximately 65 years [16, 17]. The incidence of PSP also increases drastically with age. One U.S. based study found that the incidence of PSP increased from 1.7 cases per 100,000 person years in people aged 50-59 to 14.7 for peopled aged between 80 and 99 years [18].

Many studies have attempted to examine other demographic risk factors of PSP but have met with little success. Cohort studies, the optimal study design for many of the questions researchers would like to ask, require large sample sizes which are frequently infeasible when studying a disease with low incidence, like PSP [19]. As such, case control studies recruiting from prevalent rather than incident cases are the norm. It is likely that biases (e.g. survival biases and misclassification of past exposures) complicate interpretation of the current available data [19]. A

common theme throughout these studies is that lower educational levels seem to be associated with PSP cases [20-23]. Living in rural areas and years spent drinking well water are also associated [22, 24]. It seems plausible that these associations could be due to environmental or occupational exposures that remain unidentified. The lack of apparent patterns (beyond age) in who develops PSP has made it difficult to identify specific etiological agents. Previous analytical epidemiologic studies of PSP have not had solid information on where and what they should be looking for.

1.1.3 Environmental Risk Factors

Geographical clustering of PSP cases is uncommon, with only one cluster in northern France reported recently in the literature [25]. The high amounts of industrial pollution in the affected town suggest that environmental toxicants could play a role in PSP pathogenesis. Ore processing, textile dyeing, and tanning were central to the economy of this region during the 20th century. A local physician observed that incidence of PSP in this community was 12 times higher than expected over a seven-year period extending from 2007-2012 [25]. Significant amounts of heavy metals (including chromium and nickel) were found both in the soil where local crops grew and in the canal that provided the primary source of drinking water for the town's inhabitants [26]. Genetic factors alone are unable to explain the cluster, as all the cases were unrelated and came from relatively diverse genetic backgrounds. However, no analytical study has been done to demonstrate the association between the environmental contaminants of the town and the outbreak of PSP. The local government has refused to approve any such study, likely due to issues related to liability and politics.

After the initial report describing this cluster of cases was published in 2015, the incidence of PSP in this population has declined drastically. No new patients have been diagnosed since 2016. Dr. Golbe, an author on the study, suggested in correspondence with us that this was likely due to behavioral changes in the populace sparked by the results of the study. The town closed its communal garden, and there has anecdotally been a decline in people willing to eat locally grown produce. The decrease in cases following these interventions suggests that an environmental toxicant in the soil was likely involved in the outbreak. Due to the drop off in cases, and the obstinance of the local government, an epidemiological investigation of this population is no longer feasible.

However, an in vitro study of the heavy metals found in northern France discovered that neuronal induced pluripotent stem cells expressing Tau were vulnerable to nickel and chromium exposure, which caused increased phosphor-Tau formation and eventual apoptosis [26]. The mechanisms behind these observations are currently unclear. These results suggest an obvious model for PSP pathogenesis, though the picture is far from clear (Fig 2.).

1.1.4 Economic Burden of PSP

The mean age of onset of PSP is roughly 65 years of age, with a life expectancy of 7 years. The WHO estimated the normal life expectancy of an individual aged 65 years living in the U.S. in 2018 to be 19.5 years. As such, PSP steals more than a decade of life expectancy and productivity from those affected by the disease, while also substantially reducing their quality of life and ability to live independently.

The economic impact of PSP is not limited to years of life lost, but also involves significant health costs. Although PSP is currently a rare disease with fewer than 200,000 affected patients in

the U.S., its impact on our health care system is likely to rise in the coming years as demographic trends indicate a shift towards an increasingly aged U.S. population. Studies of the economic cost of PSP in various European countries report that the mean six-month service costs of PSP are approximately 28,000 dollars, a burden equal to roughly 36% of the income for the patients in the study [27, 28]. These costs were reported to be higher than those found for cases of idiopathic Parkinson's disease in the same population, perhaps reflecting the fact that, as a rapidly progressing disease with no effective treatment, PSP can force individuals into early retirement.

Studies of the economic impact of PSP are more limited in the U.S, but some have utilized insurance claims databases to estimate costs related to the disease. One such estimate of the annual economic costs associated with PSP was $38,975 per patient, of which $1,671 was directly related to ED visits, and $13,001 was related to inpatient admissions, a common sequelae of ED usage [29]. Another estimate using similar methodology noted the annual cost to be $35,261 per patient, and concluded that the costs associated with ED visits and inpatient admissions were higher for PSP patients than age, sex, and geographically matched controls [30]. These studies highlight the economic importance of exploring the factors related to inpatient admission and ED usage in PSP.

1.2 Pathophysiology

1.2.1 Overview

PSP is a neurodegenerative disease. The hallmark histopathologic feature of PSP is the accumulation of the microtubule binding protein Tau in the brain [31]. Neuronal loss and hyper-phosphorylated Tau deposition are seen in the basal ganglia, the brainstem, the cerebral cortex, the

dentate nucleus, and the spinal cord. Tau mRNA undergoes alternative splicing, and it is specifically the family of protein isoforms with four repeated microtubule binding domains (4R-Tau) that aggregates in PSP [32]. In PSP, 4R-Tau is hyperphosphorylated, causing it to lose its affinity towards microtubules and aggregate in neurofibrillary tangles (neuronal pathology) and tufted astrocytes (astroglial pathology) [33, 34]. It remains to be determined whether neuronal and astroglial pathology develops simultaneously, or if one precedes the other.

The neuronal death associated with intra- and extra-cellular Tau accumulation causes altered neurotransmitter release in the numerous anatomical areas of the brain [35]. This disruption in neurotransmitter-dependent neuronal signaling may contribute to the symptoms seen in PSP. The specific regions of the brain affected can vary between patients, leading to the heterogeneity observed in clinical presentation (i.e., RS PSP vs P-PSP). The dopaminergic nigrostriatal pathway, various cholinergic pathways of the brain (including the primary motor and pre-motor areas of the cortex), and the GABAergic functions of the striatum, and globus pallidus interna/externa are commonly affected [35, 36]. This damage to the GABAergic pathways of the basal ganglia is thought to contribute to the motor deficits and Parkinsonism seen in some patients [37].

Neuronal death and Tau accumulation in brainstem structures are directly responsible for many of the 'hallmark' symptoms of classic RS PSP. Damage to the pedunculopontine nucleus, a midbrain structure, is thought to contribute to the postural instability and gait freezing seen in these patients [38-40]. The vertical gaze palsy after which PSP is named is the result of degeneration of the ventral midbrain structures that control vertical gaze, such as the substantia nigra pars reticula and its connections to the superior colliculus [35]. Because the deficits in voluntary vertical gaze arise from dysfunction occurring above the oculomotor nuclei present in the brainstem (as reflected

clinically by the preservation of oculocephalic reflexes despite the loss of voluntary eye movements), it is a ‘supranuclear’ palsy.

1.2.2 Etiology

Currently the cause of PSP is unknown. While the exact mechanisms remain unclear, genetic evidence seems to link disrupted Tau metabolism to PSP pathogenesis. Frontotemporal Dementia with Parkinsonism-17 (FTDP17) is an autosomal dominant Tauopathy in which inherited mutations within the Tau encoding gene, MAPT, cause accumulation of hyperphosphorylated Tau. There is a wide range of mutations and associated phenotypes, but mutations in exon 10 that alter the amino acid sequence specifically in the 4R isoform, or splice site mutations in intron 10 that cause over-production of 4R Tau can both cause a Parkinsonian movement disorder and cognitive-behavioral issues that phenocopy PSP [41]. As such, we know that overaccumulation of hyperphosphorylated Tau is sufficient to cause neuronal death and a symptomatic disease similar to PSP. Unlike FTDP17, PSP is a sporadic disease and most patients do not have pathogenic mutations in MAPT that cause 4R-Tau to accumulate. 10% of human chromosomes have an inversion polymorphism (the H2 haplotype) that includes MAPT and reduces the expression of 4R-Tau. This allele is strongly protective against PSP and underscores the importance of Tau in pathogenesis; less 4R-Tau means less disease risk [42, 43]. Genome wide association studies (GWAS) have also identified single nucleotide polymorphisms (SNPs) nearby MAPT that are strikingly associated with increased risk of PSP, even after correcting for the H2 haplotype, further implicating Tau in the proximate upstream mechanisms underlying the disease [44, 45]. Research indicates that these SNPs could mediate risk by altering expression or splicing of Tau [46-49].

The precise mechanisms and cause of pathologic Tau accumulation in PSP remains to be discovered, as does the link between disrupted Tau metabolism and neuronal pathology. Clarifying these questions is a priority for the field, as understanding these underlying mechanisms could yield insight into whether they can be targeted pharmacologically to prevent disease progression.

1.2.3 Genetic Risk Factors

PSP is a sporadic disease that rarely, if ever, clusters in families [50, 51]. Like many other sporadic diseases, it is believed that majority of PSP cases are caused by an interplay between genetic susceptibility and environmental exposures. Most of our current understanding of the genetic risk factors for PSP come from GWAS studies. In addition to MAPT, GWAS studies have associated other genetic loci with PSP risk. Specifically, SNPs nearby the genes STX6, EIF2AK3, MOBP, SLC25A38, SLCO1A2, DUSP10, and TRIM11 have been implicated [44, 45, 52]. One study suggests that the genetic variation at the TRIM11 may modulate clinical presentation of PSP (RS vs PSP-P), perhaps by somehow influencing which brain regions are susceptible to 4R-Tauopathy [52]. How genetic variability at this locus affects where Tau accumulates is currently unknown. As variation of TRIM11 does not account for all the variability observed in clinical presentation, it is likely that there are other factors in play that remain to be discovered.

The SNPs identified in the GWAS studies are primarily located in intronic regions of DNA, making it difficult to determine the functional consequences of these polymorphisms. It is possible that some of these SNPs are in linkage disequilibrium with variants that do in fact affect coding sequences. For example, the intronic rs7571971 polymorphism of EIF2AK3 associated with PSP has been revealed to be in linkage disequilibrium with other coding variants that cause amino acid substitutions. These amino acid substitutions resulted in significantly impaired protein

function when studied in vitro [53] and a loss of function mechanism seems likely as null alleles in this gene cause Wolcott-Rallison syndrome in which Tau hyperphosphorylation has been observed. Another possibility is that intronic variants might be occurring in enhancer or suppressor regions of intronic DNA, thereby altering the level of mRNA expression of the adjacent genes. If this were true, altered levels of mRNA expression could be responsible for cellular vulnerability to Tau accumulation. Postmortem gene expression analysis indicates that this might be true for the genes STX6, MOBP, and SLC25a38, as the risk SNPs for these genes seem to be associated with altered mRNA expression [44, 54, 55]. These studies are complicated by confounding changes in cell populations that occur postmortem, making it difficult to interpret the results of the cited studies. Currently the field is struggling with how to progress from the data generated by the GWAS studies to clinically relevant results. Determining what role, if any, these SNPs and genes play in disrupted Tau metabolism could yield insights into the pathogenic mechanisms underlying PSP.

1.3 Falls in Progressive Supranuclear Palsy

Falls are a major diagnostic criteria and hallmark of PSP, but the field remains limited in its understanding of them. The precise pathophysiological etiology and neuroanatomical regions responsible for falls in PSP is not conclusively proven, nor are the risk factors that contribute to falls and fall related injuries in the disease. We lack effective pharmacological and non-pharmacological interventions for fall prevention, and the research surrounding the strategies we do have is incomplete. The following section will provide a brief overview of what is known about falls in PSP.

1.3.1 Pathophysiology and Neuroanatomy of Falls

Current theories that explain the mechanism of falls and postural instability in PSP rely on the clinicopathological studies that detail areas of neuronal death and Tau accumulation to inform a pathophysiologic rationale that implicates neuroanatomical substrates known to be involved in movement. The distribution of hyperphosphorylated Tau discussed earlier identifies two such primary substrates; the pedunculopontine nucleus (PPN) and the indirect motor pathway [38].

The PPN, a midbrain structure located in the dorsolateral portion of the ponto-mesencephalic tegmentum with notable connections to basal ganglia, is thought to contribute to the regulation of motor control during locomotion [40]. Patients with PSP specifically demonstrate a high burden of hyperphosphorylated Tau in this brainstem region [39]. Moreover, post mortem analysis of brain tissue reveals degeneration of the PPM in multiple forms of Parkinsonism, including PSP [40]. Further support for PPN dysfunction comes from the reduced levels of choline acetyltransferase observed in this region in patients with PSP [56]. The combination of the PPN's role in motor control, and the evidence for its dysfunction in PSP, inform the hypothesis that it could be responsible for the falls seen in the disease.

The indirect motor pathway is a neural circuit composed of connections between the prefrontal cortex, the basal ganglia, the mesencephalic locomotor region (including the PPN itself and the cuneiform nuclei) and the thalamus [57, 58]. This pathway is thought to modulate ambulatory movements, such as turning. One imaging study identified dysfunction in the thalamus and precentral gyrus in patients with PSP, implicating parts of the indirect motor pathway beyond just the PPN [59]. This is supported by evidence of hyperphosphorylated Tau accumulation in the

subthalamic nucleus, the striatum, and the globus pallidus which are important parts of the indirect pathway [60, 61]. Phenotypically, patients with PSP tend to have trouble with turning and falling backwards, which further supports dysfunction of the indirect motor pathway in the disease [60].

1.3.2 Epidemiology of Falls in PSP

Falls and fall related injuries are a leading cause of death, morbidity, and hospital admissions in older community-dwelling adults, and are an even greater issue for those with gait disturbances [62, 63]. As such, falls represent a significant economic burden to our health care system and represent an important public health issue. Individuals with bradykinetic movement disorders such as PSP suffer fall-related fractures more often than those with other forms of neurological gait disturbances, highlighting the importance of understanding falls in these diseases [64].

There are far fewer epidemiological studies of falls and fall related injuries in PSP than in PD, even though falls occur more frequently and arguably contribute more to morbidity in PSP [38, 65]. This is explained by the comparative rarity of PSP to PD, which has not only made PSP less of a priority for clinical research, but actively makes PSP more challenging to study due to the difficulty in enrolling significant numbers of patients. As mentioned earlier, prospective studies are often not feasible in PSP. As such, many studies are retrospective and depend on patient recall or medical records, which are likely to underreport the true number of falls that a patient experiences. An additional barrier to understanding falls in PSP is that diagnosis cannot be proven clinically, and many studies have not had the luxury of being able to use only pathologically proven cases. Past studies also skew towards PSP-RS, and may not be representative of other phenotypes [38].

Individuals with PSP tend to fall backwards, and often have difficulties with turning [60]. The odds of falling are 2.33 times higher for individuals with PSP than PD [66]. One study of bradykinetic movement disorders (PD, PSP, Multiple Systems Atrophy, Dementia with Lewy Bodies, Corticobasilar Degeneration) found that PSP had the shortest median time to first fall, and that this time was significantly shorter in PSP-RS than PSP-P [65]. Patients with PSP almost invariably fall in the first year after a diagnosis [67]. One study of pathologically proven cases noted that 82% of patients suffered from frequent falls, which began roughly 4 years from the first sign of disease onset. Another prospective study of pathologically proven cases estimated that patients fell a median of 20 times in a 12 month period [68]. Taken together, these data strongly support the conclusion that falls occur early and frequently in PSP and highlight why falls are such an important clinical criterion for diagnosis.

The risk factors that are associated with earlier falls or frequent falls are not well characterized. There are also some conflicting results between studies. In general, falls in PSP may be associated with early cognitive dysfunction, early speech disturbance, axial rigidity, symmetrical disease onset, postural instability, and ocular dysfunction [65].

1.3.3 Fall Related Injuries

The research on fall related injuries in PSP focuses heavily on fractures. Individuals with PSP have a significantly higher 10-year probability of suffering a fall related fracture in comparison to similarly aged community dwelling adults [65, 66]. Patients with PSP also have the highest risk of developing a fracture out of all the parkinsonian movement disorders. 28.6% of Patients with PSP develop a fracture from falling, compared to 19.8% of patients with other forms of atypical parkinsonism, and 16.9% of patients with PD [65]. Patients also sustain multiple

fractures more commonly in PSP. The nature of the fractures themselves also differ across the bradykinetic movement disorders. Individuals with PSP are much more likely to suffer upper body injuries such as upper limb fractures, skull fractures, or truncal fractures than individuals with PD, but at lower risk of suffering hip fracture [65]. Specific risk factors for falling are also not well characterized, but female gender and older age are associated with greater odds of fracture [66]. This observation is thought to be explained by the increased risk of osteoporosis in older and female individuals. Other fall related injuries, such as traumatic brain injuries, spinal trauma, and soft tissue injuries have not been characterized.

1.3.4 Fall Prevention Strategies

The high frequency of falls and fractures in PSP creates a significant amount of suffering for patients. It is well established that frequent falls result in anxiety for patients and reduce quality of life [69-71] This emphasizes the importance of fall prevention strategies. Unfortunately, there is currently no evidence-based solution that has been shown to be effective in PSP.

Numerous clinical trials have been conducted, but a pharmacological agent effective at reducing falls in PDP has yet to be found [5]. Many patients try levodopa or dopamine agonist therapies, although few cases of PSP respond to this line of treatment and there is no evidence that either class of drug is useful for preventing falls [72, 73]. One study of coenzyme Q10 offered hope of clinical utility in PSP, but the effect was not replicated in a second, larger study of the drug [74, 75]. Trials of riluzole, davunetide, and tideglusib have similarly proved to be ineffective [76-78]. An evidence based pharmacologic therapy has yet to be found, though the hope remains that breakthroughs in our understanding of the pathophysiology and etiology of the disease could yield insight into new therapeutic targets.

Non-pharmacological approaches are also limited, and largely lack evidence. Most patients with PSP are eventually referred to physical therapy (PT), though there is no evidence that demonstrates PT is effective at reducing fall frequency or severity. Weak evidence of fall prevention exists for several non-standard treatment options, such as treadmill training, robot-assisted therapy, and deep brain stimulation [DBS] of the PPN [79-82]. However, many of these studies lacked an appropriate control group, and the benefits of deep brain stimulation were not repeated in subsequent studies. Moreover, many patients with PSP are not good candidates for DBS because of co-morbidities.

Best practices for minimizing fall risk include combating polypharmacy and trying to reduce the use of pharmacological agents known to increase fall risk in the elderly [38]. Environmental modifications are often employed, such as the installation of hand railings around the patient's house, though there is no evidence for its effectiveness specifically in PSP. Cognitive deficits and executive dysfunction are thought to contribute to falls in PSP. Many patients are unable to inhibit the urge to quickly stand up, forgetting or ignoring their postural stability. This classic phenomenon is termed the 'rocket sign', and efforts to combat it include wheelchair lap belts and repeated training to always count to 5 before standing up. Finally, it has been recommended by some to ensure that patients are properly evaluated for osteoporosis to minimize risk of unnecessary fractures [38].

1.3.5 Emergency Department Use in PSP

Surprisingly, there is no literature surrounding the usage of the ED in PSP. Clinical experience suggests that falls and fall related injuries are likely to be the most common chief complaint at presentation, but there is currently no evidence to support this claim. ED use and

subsequent inpatient admission contribute substantially to the economic burden caused by PSP, making it critical to determine the chief complaints responsible for health care utilization in the disease. [29, 30] Moreover, understanding the epidemiologic concepts of person, place, and time as they pertain to ED use in PSP could reveal patterns which shed light on key risk factors and inform the development of preventative measures.

2.0 Pilot Study of ED Usage in Progressive Supranuclear Palsy

2.1 Methods

2.1.1 Study Design

To describe the utilization of the ED by patients with PSP, a retrospective case series was performed. Observation began at the first symptom of PSP or Parkinsonism noted in the electronic medical records and continued forward until present day or death.

2.1.2 Patients

We studied patients seen by Dr. Burton at the University of Pittsburgh's Comprehensive Movement Disorders Clinic between 2015 and 2022. The inclusion criteria for this study were probable or possible clinical diagnosis of RS PSP using the NINDS-SPSP criteria, as this clinical phenotype has the highest predictive value for PSP pathology [83]. There were no exclusion criteria.

2.1.3 Data Collection

Data was extracted from the electronic medical records for each patient and stored on a REDCap database designed for this study. We carefully reviewed the case notes of primary physicians, neurologists, otolaryngologists, ophthalmologists, physical therapists, and speech and language therapists. We also examined, when available, ED admission notes, hospital notes,

inpatient consultations, and correspondence between the patient and medical professionals. From these sources we extracted the following demographic information: age (at death or present at time of data collection if alive), sex, race, and ethnicity. The following clinical information was collected to describe ED utilization by patients with PSP: age at symptom onset of PSP , age at diagnosis of PSP, age mobility aid usage began, age when cognitive symptoms developed, age at each ED visit, number of ED visits, chief complaint at each ED visit, whether and what kind of fall related injuries occurred, whether the patient was admitted from the ED and for how long, whether the patient was using a mobility aid at the time of the ED visit, and whether the patient received a referral from the ED to a PSP related department (neurology, PT, SLT, ENT).

2.1.4 Statistical Methods

Generation of descriptive statistics including means, standard deviation, medians, interquartile ranges and proportions was done using STATA. The limited analytical statistics reported in this paper, which include calculation of 95% confidence intervals, Mann-Whitney Tests, KS tests, Chi-Squared tests and Fisher Exact tests, were done using PRISM. An α of .05 was used as the cut off for determining statistical significance. KS tests were used to test for normality of quantitative data. Normal data is presented as the mean ± the standard deviation, while non-normal data is presented as the median and interquartile range. Categorical data is presented as proportion with 95% Wilson-Brown confidence interval. STATA was used to generate histograms, while PRISM was used to create all other graphs.

2.2 Results

2.2.1 Demographic information

We examined the medical records of 21 patients with a clinical diagnosis of PSP (Table 1) to describe their patterns of ED usage. Demographic information was collected to determine how representative our study sample was of the population with PSP. 11 (52%) were male, 21 (100%) of them were non-Hispanic white. The mean age at diagnosis of PSP was 68 years (Standard Deviation (STD) 5.9 years), while the mean age of symptom onset was 65.2 years (STD 6.14 years). 100% of patients had experienced a fall, with a mean age of first fall of 65.8 years (STD 6.4 years), and a mean time from first fall to diagnosis of 2.6 years (STD 2.1 years). 14 (66.7%) of the patients were deceased at the time of data collection, and they exhibited a mean disease duration time of 6.4 years (STD 2.59 years). The surviving patients had a mean disease duration of 5.3 years (STD 1.1 years).

20 (95%) patients made use of a mobility aid (defined as use of either cane, wheelchair, or walker) during the disease course. Mobility aid use began at a mean age of 68 years (STD 6.5 years). The mean time from symptom onset of PSP to use of a mobility aid was observed to be 2.5 years (STD 2.0 years), while the median time from diagnosis to mobility aid use was -.05 years, (interquartile range (IQR) of -1.6 -.26 years).

21 (100%) patients in this study displayed cognitive impairment, with a mean age of onset of 67.2 years (STD 6.1 years). The mean time from onset of PSP symptoms to development of cognitive symptoms was observed to be 2 years (STD 2.1 years), while the mean time from diagnosis of PSP to development of cognitive symptoms was -1.1 years (STD 1.5 years). The mean score of the most recent mini-mental status exam (MMSE) administered to patients was 23.7/30

(STD 3.1), while the mean frontal cognitive assessment battery score was 10.4/18 (STD 2.6), reflecting the predominant deficits in frontal-executive cognitive domains that characterize PSP.

2.2.2 Overview of Emergency Department Usage

The major focus of this study was to describe the use of the ED by patients with PSP. We observed a total of 113 ED visits in this population of 21 PSP patients. 19 patients (90.5% of patients, 95% Wilson Brown CI 71 to 98%) used the ED at least once (Table 1, Figure 3). The mean number of ED visits over the course of the disease was 5.6 visits (STD 4.3 visits) which was calculated by averaging the number of ED visits observed among deceased patients. The frequency of ED usage was found to be .95 (STD .8) ED visits per patient-year and was calculated by dividing the total number of ED visits observed by the total number of patient-years of observation.

This study also sought to describe when ED visits occurred during the natural history of PSP. The mean age ED visits occurred at was 68.2 years (STD 5.9 years). The median time between symptom onset and ED visit was 3.4 years (IQR 2.4 - 5.1 years) (Figure 4). The mean time from diagnosis of PSP to ED visit was .49 years (STD 2.3 years) (Figure 5).

To assess the severity and impact of the medical emergencies occurring in PSP, we sought to describe how often patients with PSP were admitted to the hospital from the ED. We observed that 32 (32.7%) ED visits lead to inpatient admission and observed a median inpatient treatment duration of 5 days (IQR 2 to 8 days) (table 1). Overall, ED visits were responsible for a total of 219 days of inpatient admission in this patient population (table 1).

We also sought to characterize whether patients with PSP were receiving relevant and proper referrals from the ED. Referrals to neurologists, physical therapists, otolaryngologists, and speech and language therapists were considered disease-relevant referrals. We observed that only

17 (19.1%) ED visits resulted in a relevant referral (Figure 6). Referrals to physical therapy represented the highest proportion of referrals (42%, 95% Wilson Brown CI 23.1 to 63.7%), followed by neurology (36.8%, 95% Wilson Brown CI 19.1% to 59.0%) (Figure 7). We also observed that ED visits which occurred before diagnosis of PSP had significantly greater odds of receiving a referral (odds ratio of 3.4, $p<.0451$ Fisher's exact test) (Figure 8).

2.2.3 Analysis of Chief Complaints

To better understand the causes of medical emergencies in PSP, we sought to characterize the chief complaints with which patients presented to the ED. Table 2 summarizes the relative frequencies of the chief complaints observed in this study. The chief complaints that we observed were sorted into those deemed attributable to PSP (falls, pneumonia, choking, and trouble speaking), and those which were not (all others). We found that 85% (95% Wilson Brown confidence interval 77.2 to 90.4%) of chief complaints were attributable to PSP (Figure 9).

We then noted the relative proportions of individual chief complaints (Table 2, Figure 10). Falls were overwhelmingly the most common chief complaint, representing 72% (95% Wilson Brown CI 64 to 79.9%) of all visits. Pneumonia was the second most common single cause, at 8.8% (95% Wilson Brown CI 4.9 to 15.5%).

We then examined which chief complaints resulted in inpatient admission (Table 3, figure 11). Falls were responsible for the greatest proportion of ED admissions (53.1%, 95% Wilson Brown CI of 36.4 to 69.1%), as well as 118 total days of inpatient admission, the most of all chief complaints (53.9% of inpatient days, Wilson Brown CI 47.3 to 60.4%) (figure 12). ED visits due to Pneumonia were the second most common cause of inpatient admission (18.8% of admissions,

95% CI of 8.9 to 35.3%), and resulted in 66 days of inpatient admission (30.1%, 95% Wilson Brown CI 24.4 to 36.5%).

We next described the relationship between the time from symptom onset of the ED visit and the chief complaints that occurred (figure 13). A Mann-Whitney test showed that ED visits due to falls (median time from symptom onset of 3.7 years, IQR 2.1- 5.1 years) had a significantly lower median time from symptom onset than those due to Pneumonia (median 5.2 years, IQR 4 - 6.01 years) ($p<.0095$) (Figure 14).

2.2.4 Falls and Fall Related Injuries

A major focus of this study was to characterize the natures of falls and fall related injuries as they pertain to ED use in PSP. Table 4 summarizes our results. We found that 18 patients (85.7%, 95% Wilson Brown CI 65.4 to 95%) had at least one ED visit attributable to a fall. The mean age at which fall related ED visits occurred was 67.8 years (STD 5.2 years). The median time in years from symptom onset to a fall related ED visit was 3.0 years (IQR 2.1 to 5.1 years) (figure 15). The mean time from diagnosis of PSP to a fall related ED visit was .2 years (STD 2.1 years) (figure 16).

Most falls (85.4%, 95% Wilson Brown CI of 76.1 to 91.4%) resulted in an injury (Figure 17). Most of the injuries sustained were soft tissue injuries (42.7%, 95% Wilson Brown CI 37.2 to 57.5%), but a relatively high proportion were fractures (27%, 95% Wilson Brown CI 18.8 to 37%) and traumatic brain injuries (25.8%, 95% Wilson Brown CI 17.9 to 35.8%) (Figure 18). 13 patients in this study experienced at least one fracture (61.9%, 95% Wilson Brown CI 40.9% to 79.2%) (Figure 19). Interestingly, fractures overwhelmingly occurred on the upper body (91%, 95% Wilson Brown CI 72.2 to 98.4%) (figure 20).

As mentioned earlier, falls were responsible for 53.1% of inpatient admission from the ED and caused the greatest total number of inpatient days of any chief complaint. A relatively high percentage of falls (33%, 95% Wilson Brown CI 11 to 25.8%) required inpatient admission (table 3). The median number of days admitted for fall related ED visits was 5 (IQR 2 – 9).

Only 5 falls (6.1% of falls), representing 20.8% of all fractures, were severe enough to require surgery (table 3). We sought to explore whether there was a pattern to which falls required surgery. We noted that falls which required surgery were significantly more likely to occur before diagnosis ($p<.019$, Fisher Exact Test, odds ratio infinity) (Figure 21). Falls requiring surgery also had much higher odds of occurring when canes were not used as a safety precaution (odds ratio.1202, Fisher Exact $p=.05$) (Figure 22).

2.2.5 Pneumonia

Table 5 summarizes our findings on pneumonia as a chief complaint. We observed 10 ED visits with pneumonia listed as the chief complaint. The average age at ED visits attributed to pneumonia was 69 years (STD 7.7). The median time from symptom onset was 5.2 (IQR 4 - 6.01 years). 6 visits (60%) resulted in inpatient admission. The median number of days admitted in ED visits attributed to Pneumonia was 7 (IQR 7 to 14 days).

2.3 Discussion

The results of this study emphasize that patients with PSP utilize the ED an inordinate amount. The overwhelming majority of patients used the ED (Figure 3) for causes that were

attributable to PSP (Figure 9). The ED was used roughly once per year (.95 visits per person year, SD .8) by patients with PSP, notably higher than the CDC's estimate of .43 visits per person year for adults aged 60 plus (table 1) [84]. The distribution of when ED visits occurred with respect to symptom onset in PSP demonstrated a positive skew, with a median of 3.4, and an interquartile range of 2.4 to 5.1 years. This suggests ED usage in PSP begins around symptom onset, reaches a peak in the first three years of disease progression, before starting to slowly taper off. Interestingly, the distribution of when ED visits occur with respect to the diagnosis of PSP is relatively symmetric, with a peak close to the time of diagnosis (mean time of .49 years after diagnosis, STD 2.1) (Figure 5). The reason why ED visits began to taper off after diagnosis, or roughly 3 years after symptom onset, is unclear. One potential explanation is that perhaps the medical interventions that occur post diagnosis are effective at reducing the need for ED use even if we do not have evidence that they are effective at reducing the frequency of falls. Another explanation is that perhaps patients with PSP seek emergency care less frequently later in the disease course when the symptoms of the disease have been normalized. It is also possible that the relative immobility which occurs later in the course of the disease results in less severe falls, causing patients to seek emergency medical care less often. Finally, it is possible that the drop in ED use is explained by patient death, as fewer patients survive past the first five years of the disease.

Our findings highlight the importance of falls as a source of morbidity in PSP. Falls were by far the most frequent reason for visiting the ED (Figure 10), were the most frequent cause of inpatient admission (Figure 11) and resulted in the largest total number of inpatient days (figure 12). ED visits due to falls occurred at much higher rates in PSP than in the CDC's estimate of the general U.S. cohort aged 60 and over [84]. Because inpatient admissions and ED use are critical components of the economic burden faced by patients with PSP [29, 30], this study supports the

hypothesis that frequent falls and fall related injuries contribute substantially to the economic burden of this disease. This underscores the need for the development of effective therapies to reduce falls and prevent fall related injuries.

It is interesting to note that while the vast majority of fall-related ED visits reported in this study resulted in injury, roughly 15 percent did not (Figure 17). One might ask why patients are presenting to the ED with a fall if a serious injury has not occurred. One explanation for this is that many patients experienced pain after serious falls and were likely seeking to determine whether a fracture or TBI was sustained.

Although our study is limited by the small sample size that is common in studies on rare diseases like PSP, the findings that falls requiring surgery seem to be occur before disease diagnosis and in patients who did not use canes, are intriguing (Figures 20 and 21). Taken together, these findings suggest that diagnosis of PSP and the subsequent fall prevention measures which are put in place may be effective at preventing fractures severe enough to warrant surgery. Anecdotally, many patients with PSP are reluctant to use mobility aids at the start of the disease, declining to do so until they are physically unable to ambulate without a walker or wheelchair. As such, these findings highlight the potential importance of early diagnosis and mobility aid usage in PSP. These results are worth exploring in a larger sample size that is better powered to answer this question. An alternative explanation for this observation is that perhaps surgeons are less willing to operate on patients once a diagnosis of a neurodegenerative disease has been established.

Given the potential importance of diagnosing PSP discussed above, it was particularly interesting to see that such a low proportion of ED visits resulted in referrals to PSP related specialties (Figures 6, 7). One explanation for this is that patients do not receive referrals once care has been established with a neurologist to oversee their treatment. This conclusion is supported by

our finding that patients are more likely to receive a referral from the ED before diagnosis of PSP than after (Figure 9). Still, a minority of ED visits before diagnosis received a referral to a neurologist or physical therapist. Perhaps efforts to improve this proportion of visits resulting in referrals could reduce the time to diagnosis and mitigate some of the early morbidity experienced by patients.

Interestingly, this study observed a much higher proportion of patients who experienced fractures than previously reported in the literature (Figure 19). Roughly 61.9% of our study population experienced a fracture, compared to the previously finding of 28.6%. [65] One potential explanation for this observation is that our study population had a higher proportion of women than the earlier study, and female gender is known to be a risk factor for fractures. Another potential explanation is that our study used only patients with PSP RS, who may have a substantially higher fracture risk than other PSP subtypes. Finally, it is possible that there are significant differences in the medical sequalae of PSP in the U.S. and the U.K., and that the higher proportion of patients who experience a fracture observed in our study reflects a true difference between the populations.

Our study also supports the previous finding that falls in PSP are more likely to cause fractures of the upper body than the lower body [65]. This suggests that the mechanisms of falls in PSP could be substantially different than those seen in PD, where hip fractures are relatively more common. One potential implication of this is that fall prevention strategies that are effective at reducing fall frequency and injury risk in PD may not in fact apply to PSP.

Finally, the finding that ED visits attributed to falls have an earlier median time from symptom onset than those attributed to pneumonia is a novel finding (Figure 14). This aligns with

what is known about the natural history of PSP, where aspiration pneumonias develop later in the disease course and are a frequent cause of death [8].

2.4 Limitations

This study has several limitations. Our sample of 21 patients is small and not powered for analytical statistics. Our study also relies on clinically diagnosed cases of PSP without pathological proof. As such, we cannot be sure that all our patients have PSP, although the predictive value of RS for PSP pathology is high.

Another potential issue is that our sample was overwhelmingly white and non-Hispanic. The patterns of ED use exhibited by white non-Hispanic patients is not necessarily representative of the behaviors of patients from other racial and ethnic backgrounds. Race and ethnicity are closely linked to socio-economic status, which significantly impacts the ways in which individuals are able to access and utilize medical care. As such it is hard to generalize the results of this study broadly to different populations. Given our small sample size, and the racial and ethnic makeup of the population in the at-risk age group for PSP in Pittsburgh and the surrounding areas of Allegheny County, it is likely that the distribution of race and ethnicity we observed happened by chance. However, the possibility of referral bias in who is referred to the movement disorders clinic at UPMC might be investigated in a larger study.

Another limitation of our study is our reliance on the EMR. The EMR is frequently full of mistakes and omissions and, given our small sample size, this bias could have impacted the results of our study. This is unlikely to have affected the neurology notes, which were from a specialist research clinic, and therefore complete and detailed. However, missing information from the ED

visits seems likely, as only half of the ED visits we found in the EMR occurred at a UPMC facility (table 1). We were able to find many scans of ED admission notes from other hospitals in the EMR and also supplemented this information with details on ED use contained in primary care notes, patient communications and other aspects of UPMC's EMR. Still, we are almost certainly missing information on a fair number of ED visits, especially those which might have occurred before patients established care at UPMC. As such, our study likely underestimates the true usage of the ED in PSP.

Because UPMC is a large medical center, it is also possible that patients are more likely to seek care here over their local ED for certain kinds of emergencies, potentially confounding our data. As such, our estimation of the relative frequencies of certain chief complaints could be wrong. Similarly, patients may be more likely to seek care at the UPMC ED over their local ED if they perceive the emergency to be more serious, potentially confounding our estimation of how serious the medical emergencies in PSP are. It is also possible that sicker patients were more frequently referred to the UPMC movement disorder clinic. This is perhaps supported by the fact that our median survival time of 5.7 years is on the lower end of the estimates reported for PSP RS [2]. An alternative explanation for this somewhat shorter survival is that we were often forced to rely on patient recall to determine when symptoms of PSP began, which is impacted by recall bias.

2.5 Public Health Significance

This thesis represents a significant contribution to the field of public health for several reasons. Foremost, it has expanded our knowledge about the usage of the ED in Progressive Supranuclear Palsy and contributes findings to the field that were previously unknown. Descriptive

studies help with hypothesis generation and are a crucial part of the scientific process that leads to the improvement of health care. For example, our novel findings that the odds of needing surgery from a fall might depend on cane use, or whether a diagnosis of PSP has been reached, warrants further exploration. Similarly, our finding that patients with PSP do not receive referrals from the ED could represent a gap in the medical system, which if addressed, could impact patient care. The study's confirmation of our hypothesis that falls and fall-related injuries lead to high rates of ED utilization and inpatient admission in PSP further highlights the importance of developing fall prevention strategies to reduce the economic burden and suffering experienced by patients.

2.6 Future work

We are currently working to validate our findings in a larger sample size by constructing a database of de-identified patient data from all UPMC facilities using a Health Records Research Request (R3) submitted to the Department of Biomedical Informatics. Using this methodology, we have identified a population of 273 patients with the ICD Code of PSP (G23.1) in their medical records. This approach is better powered for analytical statistics than our initial chart review was.

A multi-center study would also help to eliminate many of the potential confounders mentioned in the discussion section. Using the REDCap database forms we created for this study, it would be relatively simple to collaborate with other hospital systems to add more patients to the database via chart review. Ideally however, we would collaborate on a prospective study. A longitudinal collaboration involving multiple large hospital systems could result in sufficient incident cases of PSP to perform the cohort study best suited to determine how early diagnosis,

physician education, and simple interventions such as walking aids can reduce ED usage and morbidity in PSP.

3.0 Figures

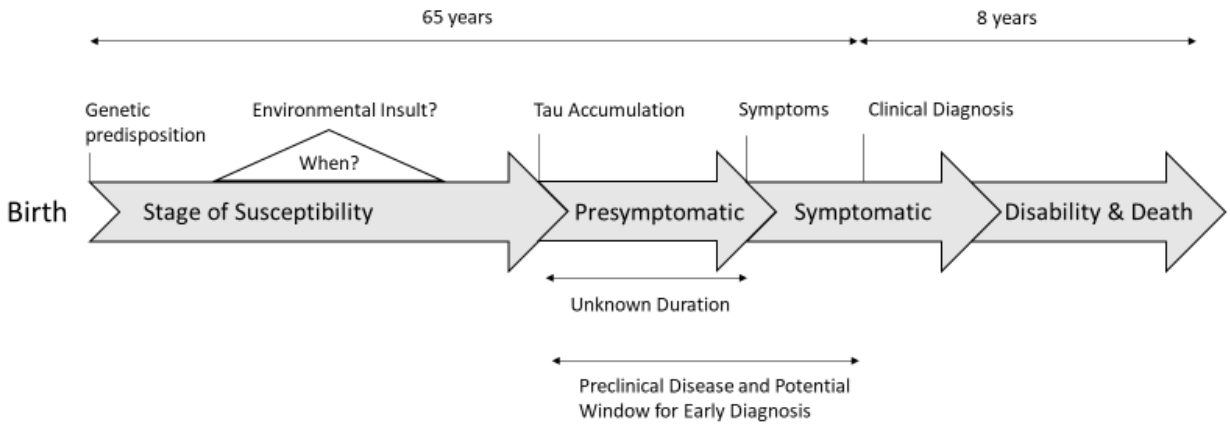

Figure 1: The Natural History of PSP

The Natural History of PSP. The etiology of PSP is unknown, but the prevailing theory is that susceptibility is determined by the interaction of genetic risk factors (tau haplotype, genome wide association study risk SNPs, etc.) and environmental insults (yet to be determined) that results in the accumulation of phosphorylated 4R-tau. It seems that there is a presymptomatic period, as evidenced by the existence of asymptomatic elderly adults who display pathological signs of tauopathy on autopsy. Symptoms tend appear in the 6th decade of life. There is often a significant latency to diagnosis because of high symptomatic overlap with other neurodegenerative diseases and the lack of conclusive diagnostic testing. PSP invariably and rapidly progresses to severe disability and death.

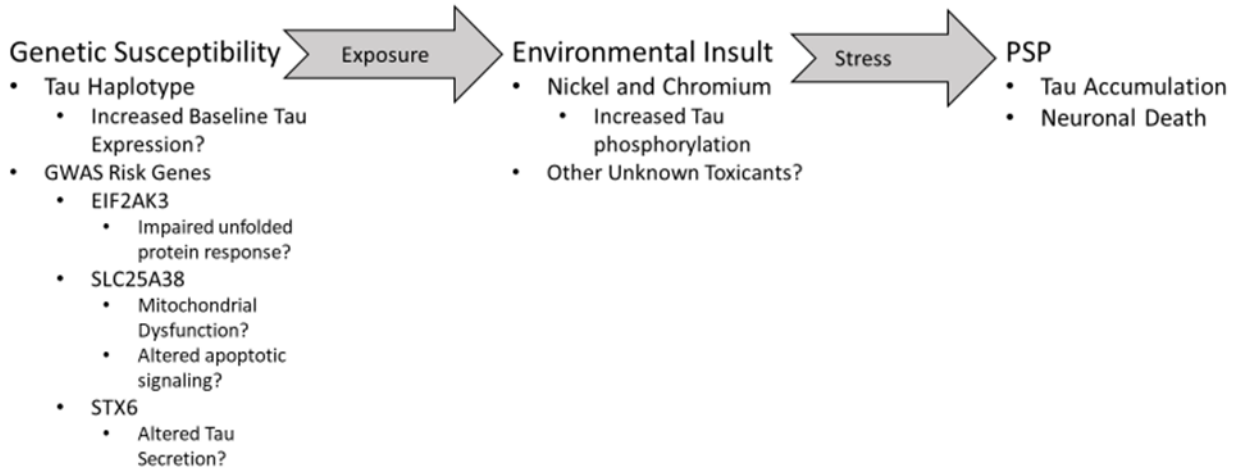

Figure 2: Biological Model of the Pathogenesis of PSP

A proposed biological model of PSP pathogenesis. This model theorizes that some individuals are genetically more susceptible to the accumulation of phosphorylated 4R-tau which is triggered by environmental insults. The susceptibility is mediated by tau haplotypes (perhaps determining the endogenous expression levels of tau), and GWAS risk genes. While the exact mechanisms by which the GWAS risk genes contribute to altered tau metabolism is unknown, the normal function of each gene suggests potential biological mechanisms. Variation in EIF2AK3, a protein kinase essential to the function of the unfolded protein response (UPR), might contribute to PSP pathogenesis by impairing the UPR and hindering the ability of neurons to handle the stress of phospho-tau accumulation. SLC25A38, a mitochondrial transporter protein, may play a role in regulating mitochondrial dependent apoptotic signaling and variation in this gene could alter the thresholds of stress needed to trigger programmed neuronal death. STX6 is a protein involved in vesicle transport and its variation could contribute to the development of tau accumulation through altered tau transport. Individuals with these genetic risk factors may only develop PSP when exposed to specific environmental insults. Recent epidemiological evidence seems to implicate the heavy metals nickel and chromium and in vitro experiments suggest these metals can increase tau phosphorylation in human cells. The interaction between genes and environment results in neuronal stress, and eventual neuronal death.

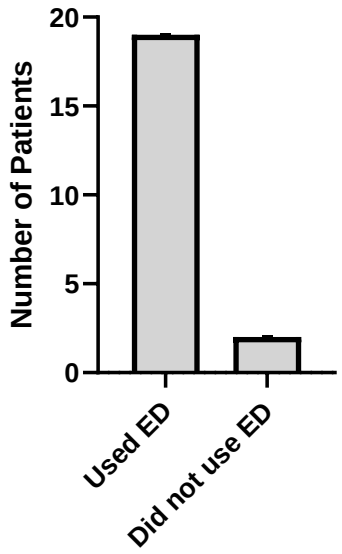

Figure 3: Proportion of Patients with PSP Who Used the ED

Most patients with PSP use the ED at least once after symptom onset. The EMR was reviewed for evidence of whether 21 patients with PSP had used the ED at any point after symptom onset. 19 patients had used the ED at least once (90.5%, 95% Wilson Brown CI 71.1 to 98.3%), while 2 had not (9.5%, %, 95% Wilson Brown CI 1.7 to 28.9%).

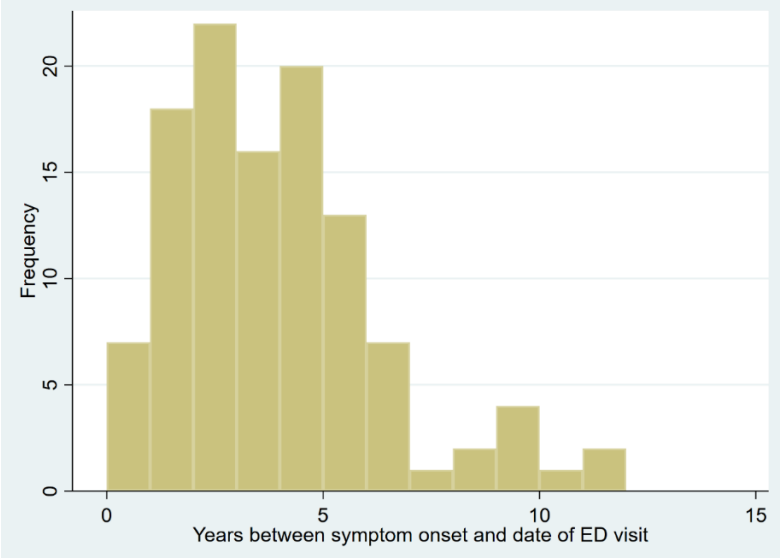

Figure 4: Time Between Symptom onset of PSP and Dates of ED Visit

ED visits in PSP peak quickly after symptom onset, with most occurring within 5 years of symptom onset. The EMR was reviewed to determine the date of symptom onset for each of the 21 patients and to determine the date at which each of the 113 ED observed in this study occurred. The difference between these dates is plotted on the x axis of this histogram, in one year time bins. The y axis represents the number of ED visits that fall within each time bin. The distribution showed a significant positive skew and had a median of 3.5 years with an interquartile range of 2.4 to 5.1 years.

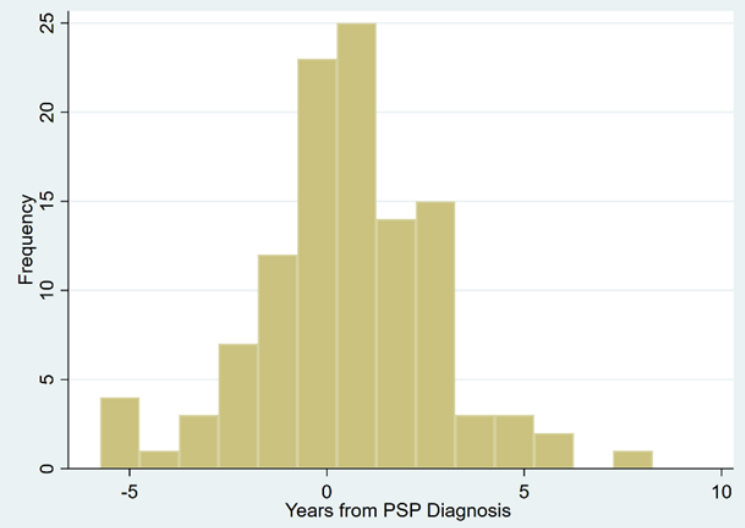

Figure 5: Time Between Diagnosis of PSP and Dates of ED Visit

ED visits in PSP peak and are symmetrically distributed around the point of diagnosis. The EMR was reviewed to determine the date of diagnosis for each of the 21 patients and to determine the date at which each of the 113 ED observed in this study occurred. The difference between these dates is plotted on the x axis of this histogram in one year time bins. The y axis represents the number of ED visits that fall within each time bin. The distribution was normal and symmetrical and exhibited a mean of .49 years with a standard deviation of 2.3 years.

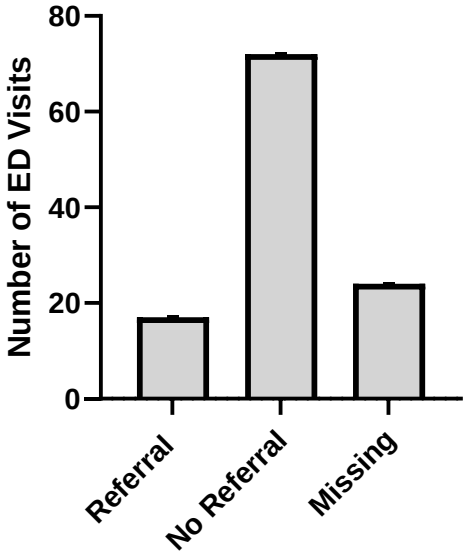

Figure 6: Proportion of Patients Who Received a Referral from the ED

Most patients with PSP do not receive a disease relevant referral after visiting the ED. The EMR was reviewed for documentation of the referrals patients with PSP received after visiting the ED. Disease relevant referrals were considered to be to neurologists, physical therapists, otolaryngologists, and speech and language therapists. Of the 113 visits, 24 (21.2%) lacked sufficient information to determine whether a referral occurred. 17 ED visits received at least one disease relevant referral (19.1% of ED visits with sufficient information, 95% Wilson Brown CI of 12.3 to 19.1%), while 72 did not (80.9 %, 95% Wilson Brown CI of 71.5 to 87.7%)

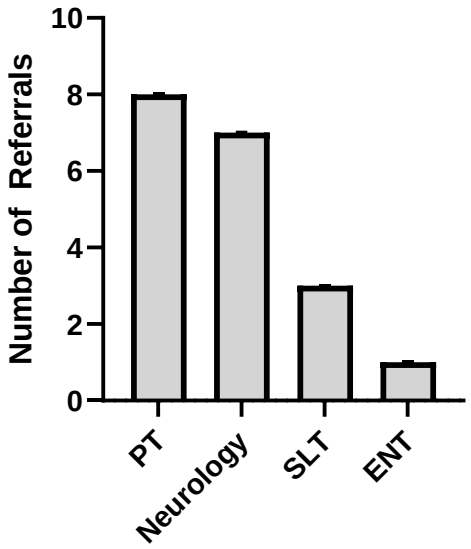

Figure 7: Relative Proportions of Disease Relevant Referrals from the ED

The most common disease relevant referral was to physical therapy, which was closely followed by referral to a neurologist. 8 patients received a referral to PT (42%, 95% Wilson Brown CI 23.1 to 63.7%), 7 received a referral to a neurologist (36.8%, 95% Wilson Brown CI 19.1 to 59.0%), 3 received a referral to a speech and language therapist (15.8%, 95% Wilson Brown CI 5.5% to 37.6%), and 1 received a referral to an otolaryngologist (ENT) (5.3 %, 95% Wilson Brown CI .3 to 24.6%).

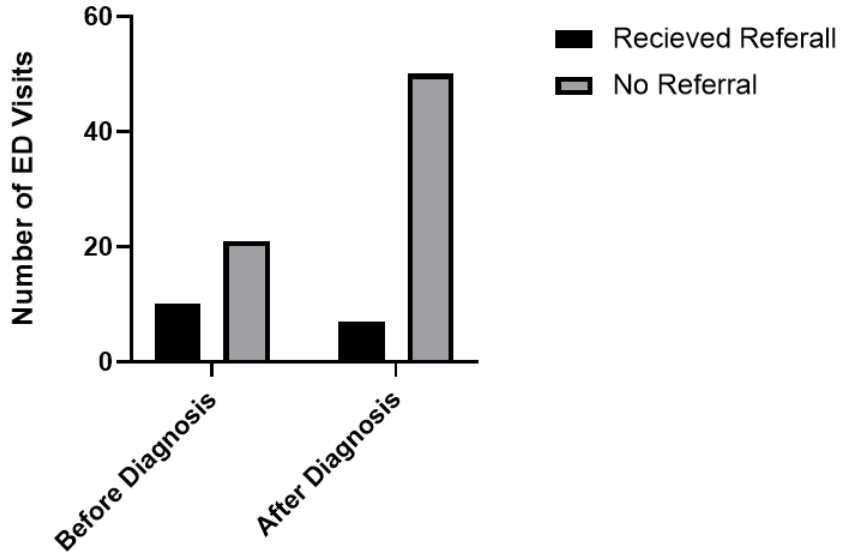

Figure 8: Diagnosis affects Odds of Referral in PSP

Patients with PSP had significantly greater odds of receiving a referral from the ED before diagnosis. The EMR was studied to determine when referrals from the ED occurred with respect to diagnosis of PSP. Before diagnosis, 10 ED visits (32%) received disease relevant referrals, while 21 (68%) did not. After diagnosis, 7 ED visits (12%) received disease relevant referrals, while 50 (88%) did not. The odds of an ED visit resulting in a disease relevant referral where 3.4 time greater before diagnosis of PSP and were determined to be significantly different by a Chi Squared test (p=.0234).

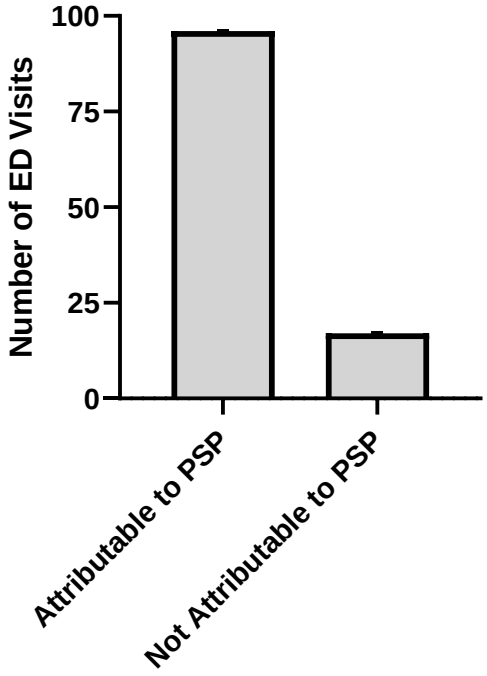

Figure 9: Proportion of Chief Complaints Attributable to PSP

Most chief complaints in the ED were attributable to PSP. The EMR was studied to determine the chief complaints for each of the 113 ED visits discovered in our chart review. For the purposes of this study the chief complaints attributable to PSP were considered to be falls, aspiration pneumonia, choking, trouble speaking, and cognitive impairment. 96 chief complaints (85%, 95% Wilson Brown CI of 77.2 to 90.4%) were attributable to PSP, while 17 (15%, 95% Wilson Brown CI 9.6 to 22.8%) were not.

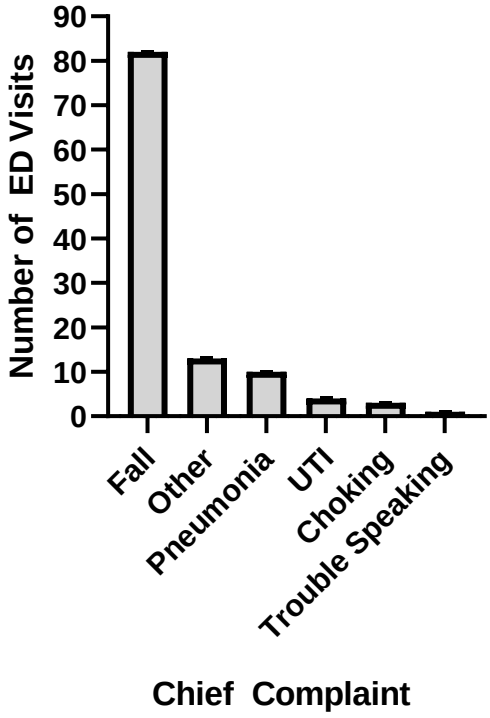

Figure 10: Relative Proportions of the Chief Complaints Underlying ED Use in PSP

Falls were the most common cause of ED use in PSP by a considerable margin. The EMR was studied to determine the chief complaints for each of the 113 ED visits discovered in our chart review. Falls were the chief complaint in 82 ED visits (72.6%, 95% Wilson Brown CI 63.7 to 79.9%). Other causes (which were determined to be unrelated to PSP and occurred so infrequently so as to not warrant separate consideration) accounted for 13 visits (11.5% 95% Wilson Brown CI 6.8% to 18.7%). Pneumonias were the second most common individual chief complaint, accounting for 10 visits (8.8%, 95% Wilson Brown CI 4.9% to 15.5%). Urinary Tract Infections, while unrelated to PSP pathogenesis, occurred in multiple patients and accounted for 4 ED visits (3.5%, 95% Wilson Brown CI 1.4% to 7.5%). Choking, related to the swallowing difficulties that develop in PSP, was the chief complaint in 3 visits (2.7%, 95% Wilson Brown CI .7 to 7.5%). Finally, trouble speaking was responsible for 1 ED visit (.9%, 95% Wilson Brown CI 0.005 to 4.8%).

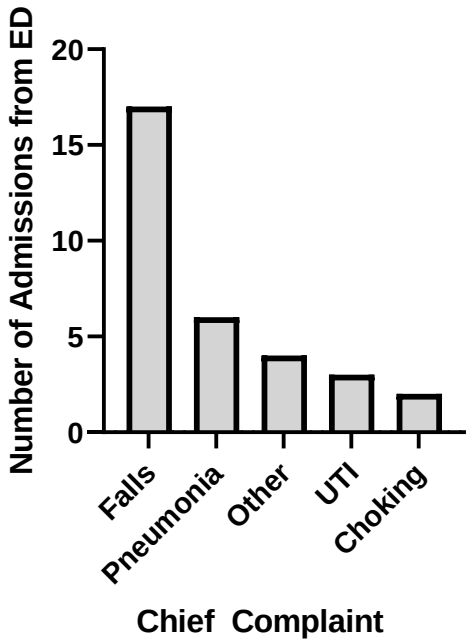

Figure 11: Chief Complaints Responsible for Inpatient Admission from the ED in PSP

Falls were the most common cause of inpatient admission from the ED in PSP. The EMR was studied to determine which ED visits resulted in inpatient admission. 32 ED visits (33%) resulted in inpatient admission. 17 falls (53.1% of inpatient admissions, 95% Wilson Brown CI 36.4 to 69.1%) resulted in admission, the most of any chief complaint. Pneumonia was the second most common cause of admission, with 6 admissions (18.8%, 95% Wilson Brown CI 8.9 to 35.3%). Other causes resulted in 4 admissions (12.5%, 95% Wilson Brown CI 5% to 28.1%), UTIs in 3 admissions (9.4%, 95% Wilson Brown CI 3.2 to 24.2%), and choking in 1 admission (6.3%, 95% Wilson Brown CI 1.1 to 20.1%). Lines drawn to indicate that confidence intervals do not overlap.

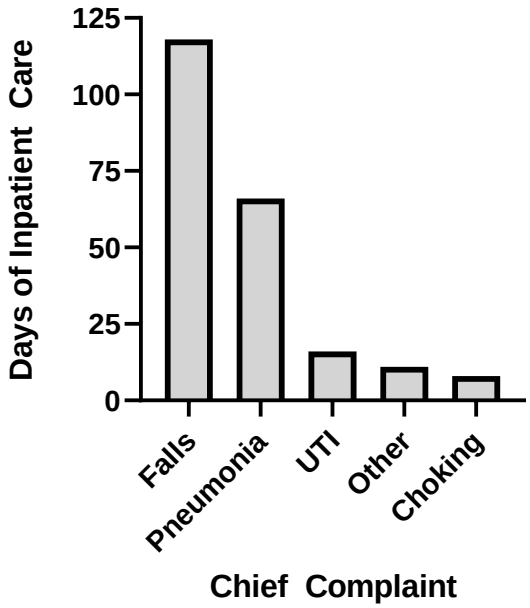

Figure 12: Proportion of Total Days of Inpatient Admission

Falls were responsible for most of the days of inpatient admission from the ED in patients with PSP. The EMR was studied to determine the total number of days of inpatient admission attributable to each chief complaint. The total number of days of inpatient admission from the ED across all chief complaints was 219. Falls were responsible for more days of inpatient admission than any other chief complaint, causing 118 days of inpatient admissions (53.9% of total days of inpatient admission, 95% Wilson Brown CI 47.4 to 60.4%). Pneumonia was the second greatest contributor to days of inpatient admission, resulting in 66 days (30.1%, 95% Wilson Brown CI 24.4 to 36.5%). UTIs caused 16 days of inpatient admission (7.3%, 95% Wilson Brown CI 4.5 to 11.5%), Other chief complaints caused 11 days (5%, 95% Wilson Brown CI 2.8 to 8.8%), and choking caused 8 days (3.7%, 95% Wilson Brown CI 1.9 to 7.0%).

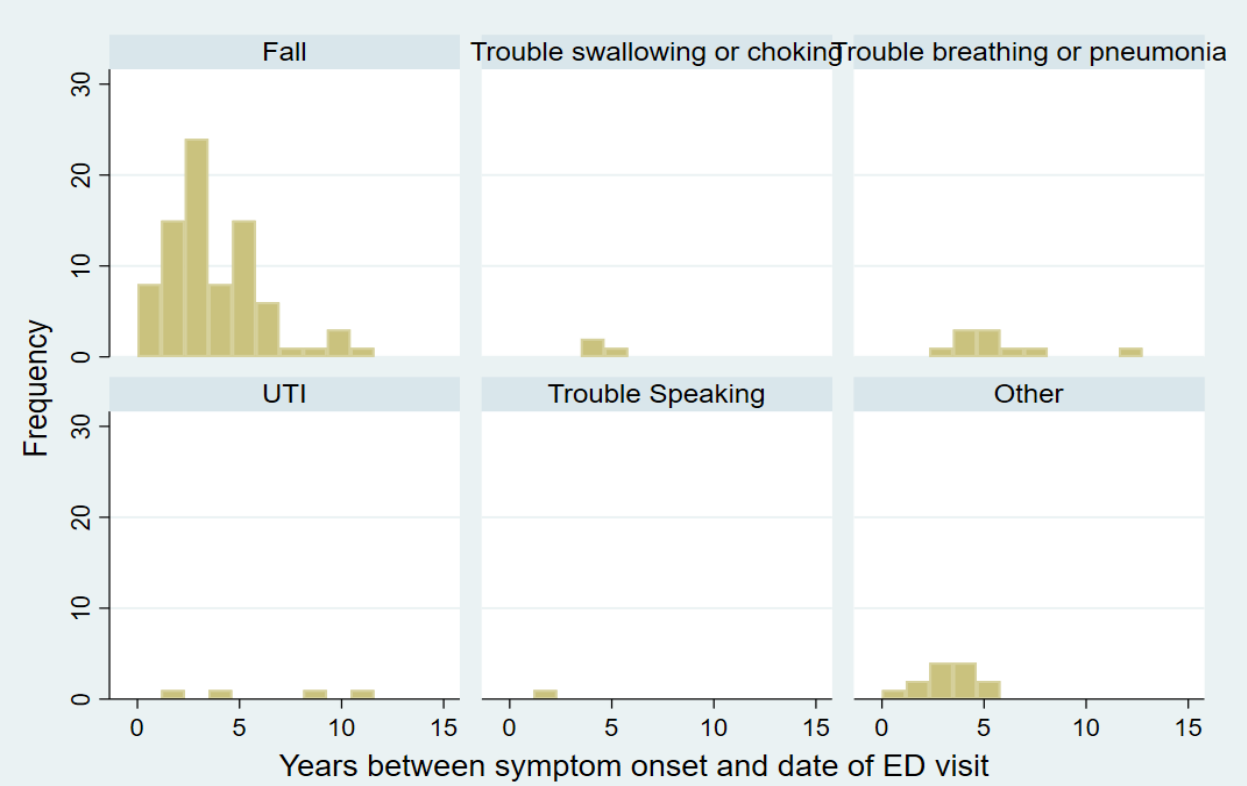

Figure 13: When Chief Complaints occur with Respect to Symptom Onset in PSP

Visualization of when chief complaints present to the ED relative to symptom onset in PSP. The EMR was studied to determine the time between symptom onset and the date of each ED visit. The results were sorted by chief complaint and plotted as histograms. The X axis represents years from symptom onset in one year time bins, while the Y axis depicts the number of ED visits in that time bin. The data for choking, UTI, and trouble speaking was too sparse to form noticeable patterns. ED visits due to falls demonstrated a positive skew, a median of 3.0 years and an interquartile range of 2.1 to 5.1 years. ED visits due to falls appear to begin rapidly after symptom onset, and peak within the first three years. The distribution of visits due to pneumonia also appears to have a positive skew, with a median of 5.2 years and an interquartile range of 4 to 6.1 years. Visits due to other causes had a median of 3.2 years and an interquartile range of 2.8 to 4.5 years.

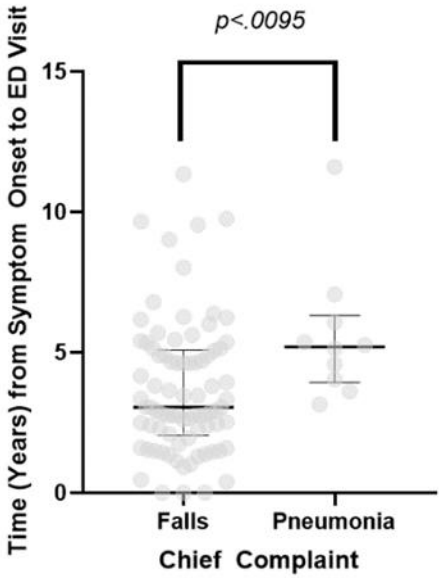

Figure 14: ED Visits due to Falls Occur Earlier than ED Visits due to Pneumonia

ED visits attributable to falls have a significantly shorter median time from symptom onset than those due to pneumonia. The median time from symptom onset for ED visits due to falls was f 3.0 years (IQR 2.1 to 5.1 years) compared to 5.2 years (IQR 4 to 6.1 years) for pneumonia (Mann Whitney test, p<.0095).

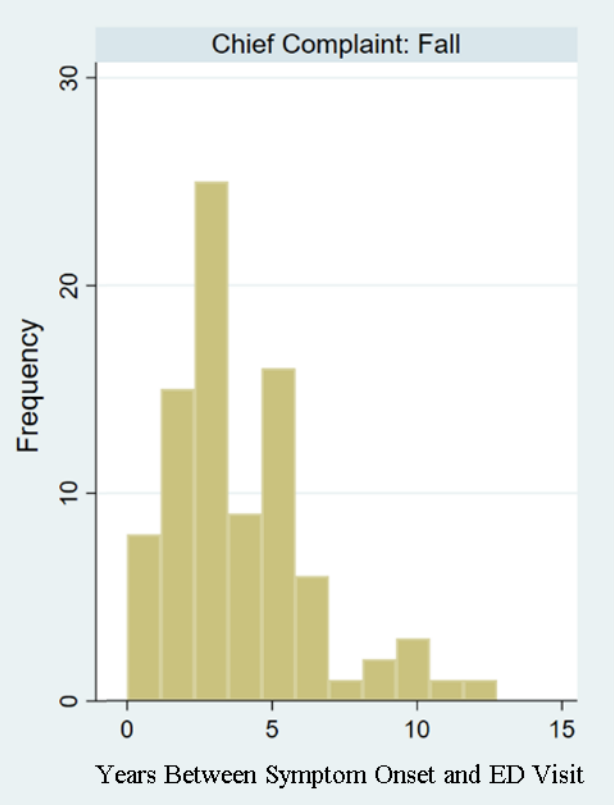

Figure 15: When ED Visits due to Falls Occur Relative to Symptom Onset in PSP

Visualization of when ED visits due to falls occur relative to symptom onset. The EMR was studied to determine the time between symptom onset and the date of each ED visit attributable to falls. The X axis represents years from symptom onset in one year time bins, while the Y axis depicts the number of ED visits in that time bin. ED visits due to falls demonstrated a positive skew, a median of 3.0 years and an interquartile range of 2.1 to 5.1 years.

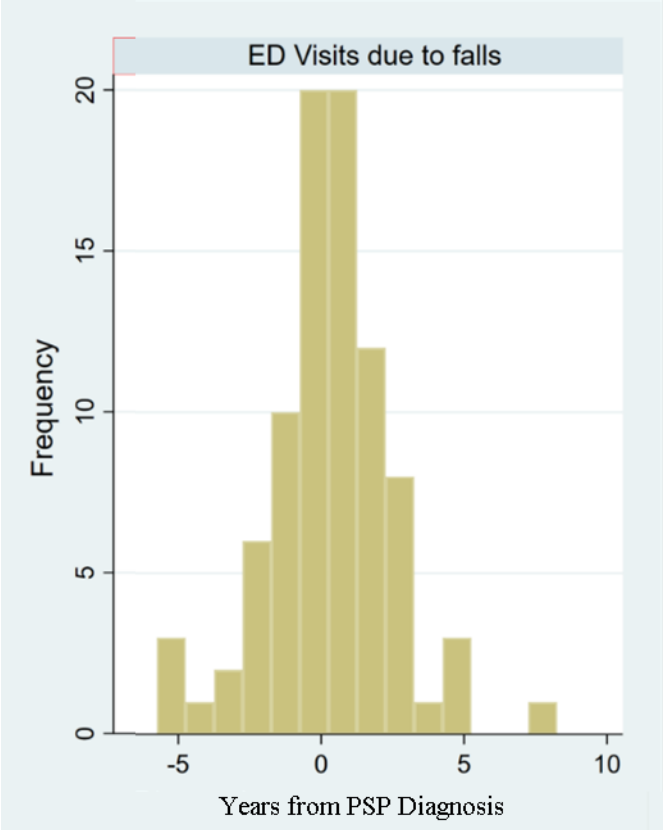

Figure 16: When ED Visits due to Falls Occur Relative to Diagnosis of PSP

Visualization of when ED visits due to falls occur relative to diagnosis of PSP. The EMR was studied to determine the time between diagnosis of PSP and the date of each ED visit attributable to falls. The X axis represents years from diagnosis in one year time bins, while the Y axis depicts the number of ED visits in that time bin. The data shows a symmetric distribution centered around the time of diagnosis with a mean of .16 years from diagnosis (STD 2.1 years).

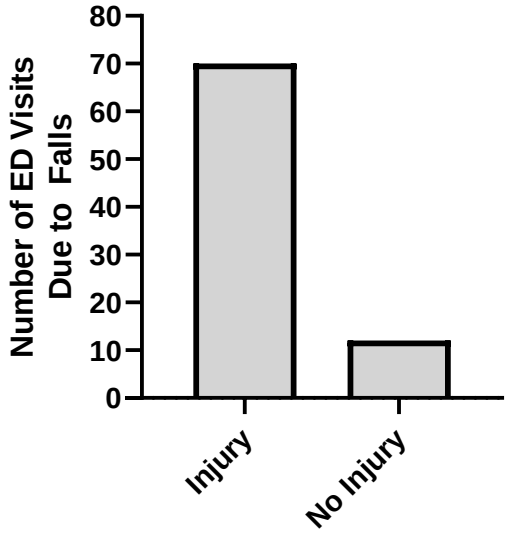

Figure 17: Proportion of ED Visits due to Falls that Result in Fall Related Injuries

The vast majority of ED visits due to falls resulted in fall related injuries. Of the 82 ED visits with a chief complaint of a 'fall', 70 of them caused a fall related injury (85.4%, 95% Wilson Brown CI 76.1 to 91.4%) and 12 did not (14.6% 95% Wilson Brown CI of 8.5 to 23.9%).

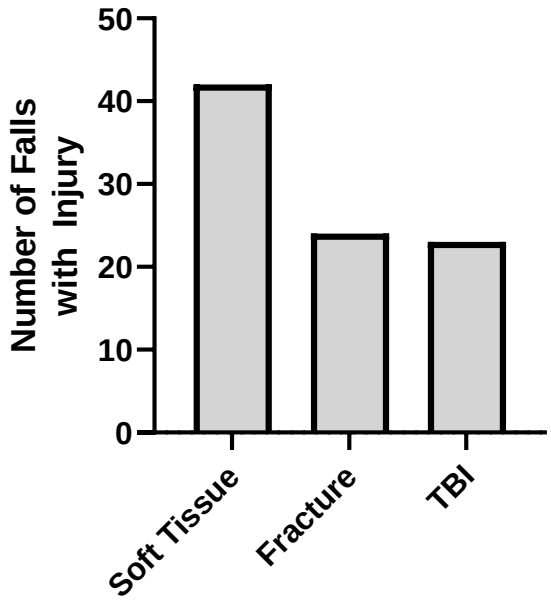

Figure 18: Types of Fall Related Injuries Sustained in PSP

Soft tissue injuries were the most common fall related injury, but a high number of fractures and traumatic brain injuries (TBIs) occurred as well. 42 of the ED visits attributable to falls resulted in a soft tissue injury (47.2% of all fall related injuries, 95% Wilson Brown CI 37.3 to 57.5%), while 24 resulted in fractures (27%, 95% Wilson Brown CI 18.8 to 37.0%) and 23 in TBIs (25.8%, 95% Wilson Brown CI 17.9 to 35.8%). Lines drawn to indicate that confidence intervals do not overlap.

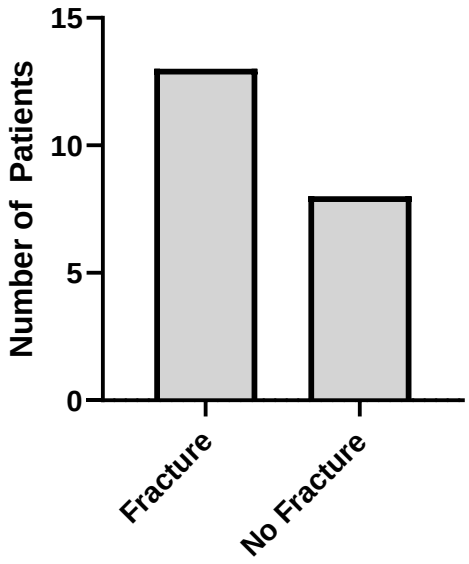

Figure 19: Proportion of Patients Who Experienced at Least One Fracture

The majority of the patients in the study experienced at least one fracture. The EMR indicated that 13 patients sustained a fracture after falling and seeking treatment in the ED (61.9% 95% Wilson Brown CI 40.9 to 79.2%), while 8 did not (38.1%, 95% Wilson Brown CI 20.8 to 59.1%).

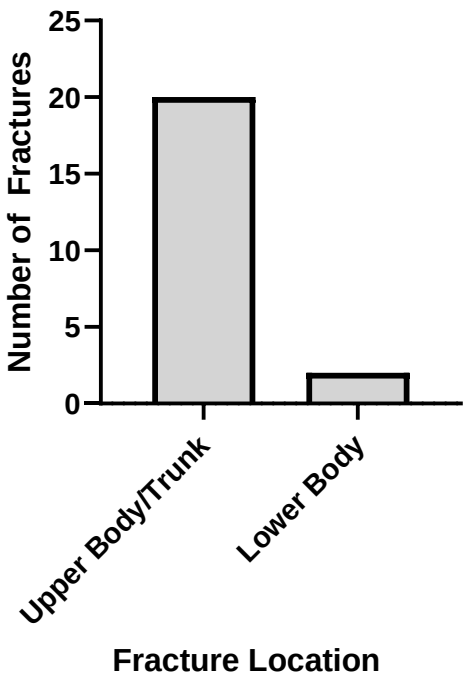

Figure 20: Location of Fractures in PSP

An overwhelming majority of the fractures sustained were to the upper body or trunk. 20 fractures were located on the upper body or trunk (90.9%, 95% Wilson Brown CI 72.2 to 98.4%) compared to only 2 on the lower body (9.1%, 95% Wilson Brown CI 1.6 to 27.8%). The location of a single fraction was not discernable from the EMR.

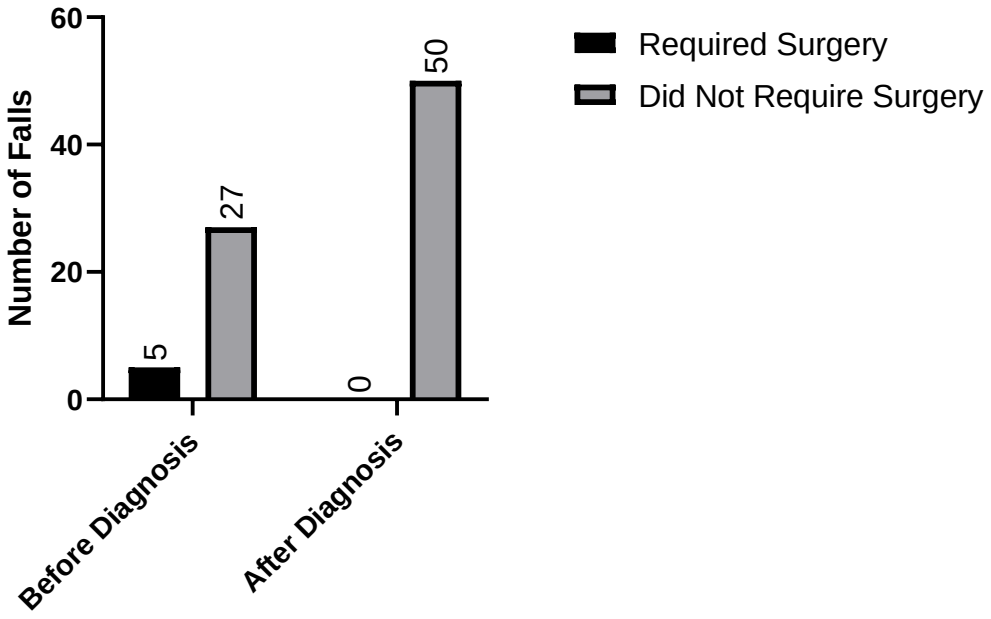

Figure 21: Diagnosis of PSP Affects Odds of Surgery

Falls that occurred before diagnosis of PSP had significantly elevated odds of requiring surgery. Each of the 5 falls which required surgery occurred before diagnosis of PSP, representing 15.6% of ED visits attributable to falls that occurred before diagnosis. None of the 50 falls that required use of the ED which occurred after diagnosis resulted in surgery (Odds ratio infinity, Fisher's Exact p=.0074).

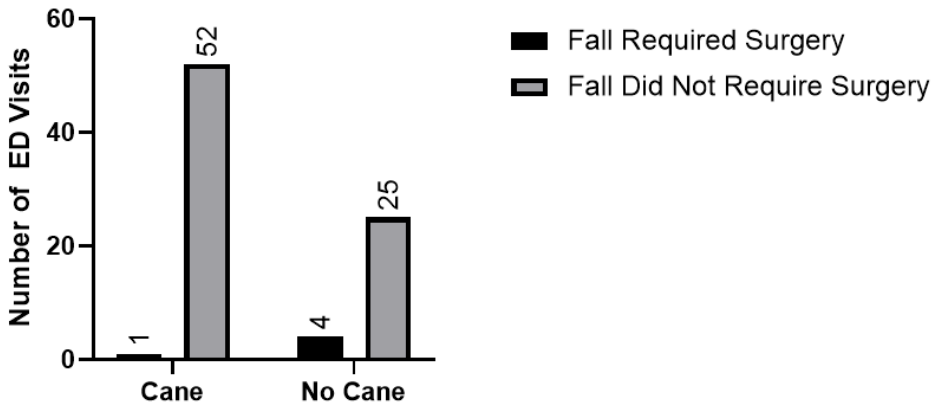

Figure 22: Using a Cane Reduces the Odds of having a Fall Requiring Surgery

Falls sustained by patients who did not use canes as a mobility aid had significantly elevated odds of requiring surgery. We examined the EMR to determine whether there was evidence to suggest that the patient used a cane as a mobility aid prior to ED visits attributed to a fall. Only 1 out of the 52 falls sustained by a patient using a cane to ambulate required surgery (1.89%), while 4 of the falls sustained by patients who did not use canes to ambulate required surgery (13.79%). The odds of a fall requiring surgery were .1202 times lower among those who used canes as a mobility aid compared to those who did not (Fisher's Exact p=.05).

4.0 Tables

Table 1

Demographic Information	
Number of patients	21
Male, n (%)	11 (52%)
White, n (%)	21 (100%)
Non-Hispanic, n (%)	21 (100%)
Number of deceased cases, n (%)	14 (66.7%)
Age of death, years (mean ± SD)	70.9 ± 6.5
Clinical Information	
Age of symptom onset, years (mean ± SD)	65.2± 6.14
Age of diagnosis, years (mean ± SD)	68± 5.9
Time from symptom onset to diagnosis, years (median, Interquartile)	2.5, 2-3.5
Total disease duration of deceased cases, years (mean ± SD)	6.4± 2.59
Total disease duration of living cases, years (mean ± SD)	5.3± 1.1
Age at first fall, years (mean ± SD)	65.8± 6.4
Time from first fall to diagnosis, years (mean ± SD)	2.6± 2.1
Mobility Aid Information	
Used mobility aids, n (%)	20, (95%)
Age mobility aid usage began, years (mean ± SD)	68± 6.5
Time from symptom onset to use of mobility aid, years (mean ± SD)	2.5± 2.0
Time from diagnosis to use of mobility aid, years (median, interquartile)	-.05, -1.6-.26
Cognitive Symptom Information	
Cognitive Symptoms, n (%)	21, (100%)
Age of onset for cognitive symptoms, years (mean ± SD)	67.2± 6.1
Time from symptom onset to onset of cognitive symptoms, years (mean ± SD)	2± 2.1
Time from diagnosis to onset of cognitive symptoms, years (mean ± SD)	-1.1± 1.5
Most recent MMSE score (mean ± SD)	23.7± 3.1
Most recent FCAB score (mean ± SD)	10.4± 2.6
ED Information	
Total number of ED visits observed	113
Used ED, n (%)	19 (90%)
Age at ED visit, (mean ± SD)	68.2 ± 5.9
Time from symptom onset, years (median, interquartile)	3.5, 2.4-5.1
Time from diagnosis, years (mean ± SD)	.49 ± 2.3
Visits at UPMC ED, n (%)	55 (50.5%)
ED visits in deceased cases (mean ± SD)	5.6, ± 4.3
ED visits per year of PSP (mean ± SD)	.95± .8
Visits that lead to inpatient admission, n (%)	32 (32.7%)
Days admitted, (median, interquartile)	5, 2-8
Total days of Inpatient Admission, n	219
Visits with prior mobility aid usage, n (%)	88 (79.3%)
Visits with cognitive symptoms present, n (%)	78 (70.9%)
Closest MMSE score to visit, (median, interquartile)	25, 23-27
Closest FCAB score to visit, (median, interquartile)	10, 9-11
Percentage of visits that received a referral, n (%)	17 (19.1%)

Table 2

Chief Complaint (n=113)	
Attributable to PSP, n (%)	96 (85%)
Falls, n (%)	82 (72%)
Other, n (%)	13 (11.5%)
Pneumonia, n (%)	10 (8.8%)
UTI, n (%)	4 (3.5%)
Choking, n (%)	3 (2.7%)
Trouble Speaking, n (%)	1 (.88%)

Table 3

ED Visits Leading to Inpatient Admission (n=32, 32.7% of all ED Visits)	
Admissions due to falls, n (%)	17 (53.1%)
Total inpatient days due to falls, n (%)	118 (53.9%)
Admissions due to pneumonia, n (%)	6 (18.8%)
Total inpatient days due to pneumonia, n (%)	66 (30.1%)
Admissions due to other n (%)	4 (12.5%)
Total inpatient days due to other, n (%)	11 (5%)
Admissions due to UTI, n (%)	3 (9.4%)
Total days admitted to UTI, n (%)	16 (7.3%)
Admissions due to choking, n (%)	2 (6.3%)
Total inpatient days due to choking, n (%)	8 (3.7%)

Table 4

Falls Related ED Visits	
Patients who visited ED because of a fall, n (%)	18, (85.7%)
Age at ED visit, years (mean ± SD)	67.8 ± 5.2
Time from symptom onset, years (median, interquartile)	3.7, 2.1-5.1
Time from Diagnosis, years (mean ± SD))	.2 ± 2.1
Fall with injuries, n (%)	70, (85.4)
Soft Tissue Injury, n (%)	42 (51.2%)
Falls with Fractures, n (%)	24 (29.3 %)
Patients who experienced a fracture, n (%)	13 (61.9%)
Upper Body Fracture, n (% of fractures)	20 (91%)
Lower Body Fracture, n (% of fractures)	2 (9%)
Falls Requiring Surgery, n (%)	5 (6.1%)
Fractures Requiring Surgery, n (%)	5 (20.8%)
Traumatic Brain Injuries, n (%)	23 (28%)
Inpatient admission, n (%)	17 (33%)
Days admitted (median, interquartile)	5, 2-9
Evidence of mobility aid use before fall, n (%)	63 (77.8%)

Table 5

Pneumonia Information (N=10)	
Age at ED visit, years (mean ± SD)	69± 7.7
Time from symptom onset, years (median, interquartile)	5.2, 4-6.01
Inpatient admission, n (%)	6 (60%)
Days admitted (median, interquartile)	7, 7-14

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