

# Enhancement of quality of life in progressive supranuclear palsy: a review of clinical practice elements

LIANNE PICKETT<sup>1</sup> BSc (Hons) AND FIONA J. ROWE<sup>2</sup> PhD DBO

<sup>1</sup>Department of Orthoptics, Ayr Hospital, Ayr

<sup>2</sup>Directorate of Orthoptics and Vision Science, University of Liverpool, Liverpool

## Abstract

**Aim:** In the absence of a disease-modifying therapy, the aim of this review is to investigate how, and to what extent, progressive supranuclear palsy (PSP) affects patient quality of life (QoL) and thus establish a QoL-based approach to clinical practice.

**Method:** A literature review was conducted using the search engines PubMed, Ovid and Google Scholar. Study and review abstracts from the literature search were analysed and marked for inclusion if they contained the following terms in reference to PSP: 'prevalence', 'diagnosis', 'quality of life' and 'rehabilitation'. Only journals written in English and available to the University of Liverpool were included in this review.

**Results:** PSP has a negative bearing on patient QoL, affecting almost all aspects of the patient's daily living. However, a standard approach to clinical practice has not been established in the literature. Furthermore, studies fail to relate how current strategies of rehabilitation influence patient QoL.

**Conclusion:** Early diagnosis is particularly associated with enhanced QoL, and although a limited amount of success can be associated with current strategies of rehabilitation, the feasibility of such interventions is limited to a very select group of patients.

## Introduction

Progressive supranuclear palsy (PSP) is a disease of devastating consequences. It has an insidious onset; symptoms progress rapidly, and death is inevitable.

Common symptoms include unexpected falls, postural instability, axial rigidity, limitation of eye movements, and changes in personality.<sup>1,2</sup> Many of these early symptoms are also present in Parkinson's disease (PD), and as a result misdiagnosis is common.<sup>3</sup> Consequently, many patients with PSP do not receive adequate care or appropriate rehabilitation, resulting in a further reduction of what is essentially already a poor quality of life (QoL).<sup>3</sup>

The purpose of this review is to investigate how, why

and to what extent PSP affects patient QoL. Current strategies of rehabilitation will be systematically critiqued on the basis of their feasibility, and probability of enhancing patient QoL. Subsequently, this information may be utilised to establish clinically meaningful patient care in future research.

## Features

PSP was first described as a distinct clinical identity in 1963, with reported observations of 6 patients with a neurodegenerative disorder not yet defined by the literature.<sup>4</sup> The following common features were reported: ophthalmoplegia, dysarthria, rigidity of the neck with head retraction, and dementia. The disease was named accordingly, in reference to the progressive degeneration of the brain stem structures located rostral to the oculomotor nuclei.<sup>3</sup>

Today PSP is defined as a four-repeat tauopathy, by which deposition of insoluble protein results in massive neuronal loss in the brain stem, diencephalon, cerebellum, basal ganglia, and other cortical areas related to balance, movement, vision and speech.<sup>5–7</sup> This shift to an entirely neuropathological definition of the disease has led to the discovery of a number of clinical syndromes associated with PSP-tau pathology that differ significantly from Richardson's original clinical description.<sup>7</sup> It is currently recommended that the classic clinical presentation be named Richardson's disease (RD), and that the commonest clinical variant be termed PSP-parkinsonism (PSP-P); thus, redefining the notion of atypical PSP.<sup>7</sup>

Although a vast number of symptoms and signs are associated with the disease, few people suffer from them all, while severity and progression varies from patient to patient.<sup>6</sup> Generally, poor mobility is the presenting symptom of PSP, although bulbar, cognitive and visual problems, as well as tremor, may also present in a substantial number of cases.<sup>8</sup> The clinical picture of advanced PSP is, however, both striking and highly characteristic.<sup>1</sup> Typically, the patient has a fixed 'Mona Lisa' stare, with a decreased blink.<sup>1,9</sup> The head is retracted, and the voice is reduced to a slurred growl.<sup>1</sup> The walk is awkward and unsteady, and in the midst of other advancing gait disturbances, most patients end up wheelchair-bound within 4 to 7 years of disease onset.<sup>1,9</sup> Further disease progression leads to swallowing diffi-

Correspondence and offprint requests to: Dr Fiona Rowe, Directorate of Orthoptics and Vision Science, University of Liverpool, Thompson Yates Building, Brownlow Hill, Liverpool L69 3GB. e-mail: rowef@liverpool.ac.uk

**Table 1.** NINDS-SPSP clinical criteria for the diagnosis of PSP<sup>12</sup>

PSP	Mandatory inclusion criteria	Mandatory exclusion criteria	Supportive criteria
Possible	Gradually progressive disorder Onset at age 40 or later <i>Either</i> vertical (upward or downward gaze) supranuclear palsy <i>or</i> both slowing of vertical saccades and prominent postural instability with falls in the first year of disease onset No evidence of other diseases that could explain the foregoing features, as indicated by mandatory exclusion criteria	Recent history of encephalitis Alien limb syndrome, cortical sensory deficits, focal frontal or temporoparietal atrophy Hallucinations or delusions unrelated to dopaminergic therapy Cortical dementia of Alzheimer's type (severe amnesia and aphasia or agnosia, according to NINCDS-ADFD criteria) Prominent, early cerebellar symptoms or prominent, early unexplained dysautonomia (marked), hypotension and urinary disturbances	Symmetric akinesia or rigidity, proximal more than distal Abnormal neck posture, especially retrocollis Poor or absent response of parkinsonism to levodopa therapy Early dysphagia and dysarthria
Probable	Gradually progressive disorder Onset at age 40 or later Vertical (upward or downward gaze) supranuclear palsy <i>and</i> prominent postural instability with falls in the first year of disease onset No evidence of other diseases that could explain the foregoing features, as indicated by mandatory exclusion criteria	Severe, asymmetric parkinsonian signs (i.e., bradykinesia) Neuroradiological evidence of relevant structural abnormality (i.e., basal ganglia or brain stem infarcts, lobar atrophy) Whipple's disease, confirmed by polymerase chain reaction, if indicated	Early onset of cognitive impairment including at least two of the following: apathy, impairment in abstract thought, decreased verbal fluency, utilisation or imitation behaviour, or frontal release signs
Definite <sup>a</sup>	Clinically probable or possible PSP and histopathological evidence of typical PSP		

<sup>a</sup>Definite PSP is a clinicopathological diagnosis.

culties and urinary incontinence, while death usually occurs secondary to pneumonia, pulmonary embolus, and infection, generalised reduction in vitality and prolonged debilitation, or gait disturbances.<sup>10</sup>

The variable presentation and multitude of progressive symptoms associated with the disease means that PSP requires a multidisciplinary approach to diagnosis, symptom management and rehabilitation.<sup>10</sup> In the absence of disease-altering interventions, management of PSP should focus on relieving the symptoms of the disease and implementing rehabilitation strategies to counteract disability; thus, promoting patient QoL.<sup>6</sup> Like many neurological diseases, PSP is age related, with a mean age at disease onset between 60 and 65 years.<sup>1</sup>

### Prevalence

To date, only a few epidemiological studies have specifically addressed the prevalence of PSP, independent of PD or other parkinsonian disorders.<sup>3</sup> In 1988, Globe *et al.* estimated a minimum prevalence figure of 1.39 cases per 100 000 of the general population.<sup>11</sup> With the advent of strict diagnostic criteria devised by the National Institute of Neurological Disorders and Stroke and the Society for PSP (NINDS-SPSP) (Table 1),<sup>12</sup> Schrag and colleagues reported a much higher age-adjusted prevalence of 6.4 per 100 000.<sup>13</sup> This rate was later confirmed by Nath and colleagues' community-based study in the United Kingdom in 2001, which yielded a prevalence of 5.0 per 100 000.<sup>14</sup> Thus, PSP is essentially a common motor-neuron disease<sup>1</sup> and is the second most common form of degenerative parkinsonism after PD.<sup>13</sup> However, public awareness of the disease does not match its prevalence.

### Early diagnosis

Despite the existence of strict diagnostic criteria, vast difficulties associated with diagnosis remain.<sup>3</sup> Essentially, this is due to the broad phenotypic variability

associated with the disease.<sup>14</sup> As a result, misdiagnosis is common, especially in the earlier stages of the disease where PSP is more likely to mimic PD.<sup>3,8,14</sup> This is particularly true for the recently described 'PSP-parkinsonism' variant, which comprises a quarter of all PSP cases.<sup>15,16</sup> However, the progression of symptoms in PSP is much faster than that in PD.<sup>17</sup> Consequently, early and accurate diagnosis is crucial in order to provide patients and their families with a realistic prognosis, and enough time to prepare for the appropriate future management of disease-related symptoms.<sup>16</sup>

Previously, Globe and colleagues found that a mean delay of 4.7 years existed between symptom onset and the diagnosis.<sup>11</sup> However, a decade later, a somewhat smaller mean time lag was reported of  $2.81 \pm 2.46$  years for deceased and  $2.55 \pm 2.13$  years for living patients.<sup>18</sup> This variation may be attributed to the different diagnostic criterion used in the two studies. The later study, which yielded the lesser time lag, utilised diagnostic criteria devised by NINDS-SPSP. Preliminary findings suggest that this criterion exhibits high sensitivity and positive predictive value even in the first few years of illness;<sup>12,19</sup> thus, early diagnostic accuracy may be associated with its use.

In addition to the clinical application of standard diagnostic criteria, it has been proposed that precise measurements of saccadic eye movements may provide a means of differentially diagnosing PSP from other parkinsonian disorders.<sup>20</sup> Limitation of voluntary vertical saccades is a hallmark of PSP, and its presence is of paramount importance in the diagnosis of 'possible', 'probable' and 'definite' PSP.<sup>12</sup> However, the diagnostic value of restricted vertical gaze alone is not sufficient as, not only has it been reported in diffuse Lewy body disease,<sup>21</sup> but typically it does not develop for 3 years after the onset of other characteristic symptoms.<sup>22</sup>

Consequently, in 2000, Rivaud-Péchoix and colleagues investigated whether comparisons of eye-movement recordings made at different points during the

disease course can result in earlier and more reliable diagnosis.<sup>23</sup> Preliminary findings showed that an early decrease in horizontal saccadic velocity, the presence of square-wave jerks and preservation of saccade latency strongly favoured a diagnosis of PSP. However, as this study only compared the eye movements of PSP patients with those of corticobasal degeneration (CBD) and atypical CBD, other overlapping disorders can not yet be excluded in the differential diagnosis of PSP.

Overall, it is clear that a standardised clinical approach to the diagnosis of PSP is lacking. With the exception of some limited progress in the area of MRI diagnosis,<sup>24</sup> the pathological detection of PSP is not yet a reality in clinical practice.<sup>3</sup> Very recently, though, the existence of an evidently reliable biomarker has been reported in the literature.<sup>25</sup> However, future diagnostic strategies which rely solely on the detection of pathological hallmarks may be equally flawed; by pathological definition alone PSP becomes an umbrella term for a number of its clinical variants.<sup>7,26</sup> Diagnostic emphasis must continue to be placed on clinical features and syndromes in order to correctly manage the individual symptoms of each clinical variant.<sup>7</sup> Furthermore, epidemiological studies highlight that further follow-up and regular assessment of patients with suspected atypical parkinsonism may result in earlier detection and improved diagnostic accuracy.<sup>14,27</sup> Subsequent early diagnosis will greatly benefit both the patient and his or her family, as a more informed prognosis is possible, in addition to appropriate counselling.<sup>14,27</sup> Furthermore, these studies also highlight the extent of undiagnosed patients within a given community,<sup>13</sup> an alarming fact which has an extremely negative bearing on the QoL of the people in these populations.

### Impairment of daily living

From the reported neurological abnormalities alone, it is evident that the disease has a negative, disabling effect on patients' lives. However, only one study to date has explored how PSP affects life from the patient's own point of view.<sup>28</sup> In 2003, Schrag *et al.* identified that reduced mobility and impairment of daily living activities had the most severe impact on patient QoL. Although this study assessed a variety of clinical aspects of the disease and its impact on PSP patients, no disease-specific QoL instrument existed at this time and, as a result, may be termed less sensitive.

In 2006 a new instrument which assessed health-related QoL specific to PSP was developed.<sup>29</sup> However, it became apparent that patients in the more advanced stages of the disease, and in particular those with cognitive impairment, were unable to respond accurately on their own to the postal surveys and were therefore 'underrepresented'.<sup>29</sup> Although it had previously been shown that there is considerable agreement between PSP patients and their carers, the same study highlighted that carers did in fact consistently rate frontal lobe impairment higher than did their patients.<sup>28</sup> Consequently these QoL issues may have been falsely overestimated by the carers of the patients who fell into this group.

Due to the rapidly progressive nature of PSP<sup>11,19</sup> it would be of great benefit if, were rehabilitation to be

feasible, one could predict the key impairments and their time of onset within the disease. Such data may provide clinicians with an invaluable time-scale to facilitate patients with the most relevant and effective form of rehabilitation, possibly before the disability has even occurred. For instance, it has been recommended that gait should be defined as the first key motor impairment, with a median onset time of 48 months from initial diagnosis of probable PSP.<sup>18,19</sup> Studies have also shown that gait, in particular, plays a key role in patient prognosis and survival time.<sup>8,18,19</sup>

What the study by Goetz *et al.*<sup>19</sup> failed to include was the systematic decline of cognitive function and visual-spatial dysfunction, factors which would most likely reduce the effectiveness of intervention at any stage of the disease. It is evident from the literature that the inability to execute downward saccades plays a major role in balance and gait defects in PSP.<sup>30</sup> With hindsight, it would have been appropriate to assess the progression of the vertical gaze paresis alongside deteriorating postural stability; thus postulating whether rehabilitation should involve some form of eye movement training, in addition to balance and gait training.<sup>3</sup> Moreover, it has been confirmed that an association between severity of eye movements and deficits in sustained and divided attention exists.<sup>31</sup> Thus, attention abnormalities may in fact be central to the occurrence of the other cognitive deficits such as memory and specifically retrieval of information, which if present will again affect the feasibility of any rehabilitation programme.<sup>31</sup>

A complication is whether or not personality changes reduce patient QoL. Because of frontal lobe dysfunction, such symptoms may have more bearing on their carers than on the patients themselves.<sup>28</sup> This trend highlights a particular concern among carers who mistake apathy for depression, and consequently reduce patient QoL by striving to engage patients in activities which prove more challenging than beneficial.<sup>28</sup> Conversely, subjective symptoms such as double vision and blepharospasm may actually be under-reported among PSP patients.<sup>8,18,32</sup> This concept of patients' versus carers' perception of disease progression and severity is of great importance to the future design of any rehabilitation programme which aims to assist rather than reduce patient QoL.

### QoL-based rehabilitation

Currently, there is no known medication or surgical procedure to cure or delay symptoms in PSP.<sup>3</sup> The aim of this review is to critically evaluate the effectiveness of current rehabilitation strategies and, in turn, to assess the feasibility of such interventions among this patient population, with the intention of improving patient QoL.

Although it is currently unknown how often people with PSP seek or are referred for rehabilitation, with increased awareness of the disease comes an increased demand for rehabilitation.<sup>3</sup> Gait disturbances, postural instability and falls are among the most common disease complications that cause patients and their families to seek rehabilitation.<sup>5</sup> Moreover, falls are one of the leading causes of secondary disease complications,<sup>6</sup> and a further substantial cause of mortality.<sup>33</sup>

## Review of the literature

Unfortunately, evidence-based approaches to rehabilitation in PSP are lacking<sup>3</sup> and, historically, research has been limited to qualitative case reports of one or two patients.<sup>34,35</sup> Furthermore, the diagnostic criteria used were not in-keeping with the current NINDS-SPSP recommendations, therefore detracting from the overall specificity and reliability of any reported findings.

In 2002, Suteerawattananon *et al.* were first to report fall reduction, improved gait and improved balance following an intensive body-weight-support training programme for a person with PSP.<sup>5</sup> Quantitative improvements were seen in the areas of gait and balance; however, there is no evidence as to whether or not the tests selected to evaluate and improve these areas had PSP-specific validity. Fall incidence was monitored before, during, and for a 2-week period after treatment had ceased. Although an overall fall reduction was reported, the reliability of these findings may be weakened by the fact that the information relied solely on the observation skills of the patient's wife. Furthermore, due to the relatively short follow-up period (2 weeks), the long-term value of this particular intervention strategy remains unknown.<sup>5</sup>

Although the above study did not directly address patient QoL, it is possible that continued training and support may have relieved the patient from the fear of falling,<sup>5</sup> which is reportedly present in 89% of PSP patients versus 59% of PD patients,<sup>32</sup> and would thus have enhanced patient QoL. Use of the current PSP-QoL instrument<sup>29</sup> is subsequently advocated as a means of assessing patient QoL before and after any future rehabilitation strategy. Only by these means can rehabilitation designed specifically to enhance patients' well-being be realised.

## The role of vision

Interestingly, even though evidence has shown that gaze limitations are strongly linked to impaired mobility, none of the above-mentioned case studies investigated this relationship.<sup>36</sup> Vertical gaze palsy is characteristic of PSP and therefore may explain the additional balance and mobility problems associated with the disease compared with PD and other neurological disorders.<sup>3</sup> For the purpose of rehabilitation, greater emphasis must be placed on how gaze limitation affects the clinical picture of PSP as a whole and, specifically, the role of gaze control in balance, gait, and mobility deficits.<sup>3</sup> As a result, current research is focused on evaluating the effects of eye movement training in patients with PSP, in the hope of addressing and potentially improving the mobility impairments specifically experienced by these patients.<sup>36</sup>

It is universally accepted that vision plays a critical role in guiding locomotion in everyday life. Studies have shown that anticipatory saccadic eye movements are an important part of reorientation during locomotion, while down saccades in particular are consistently detected prior to step initiation and obstacle avoidance in healthy young and elderly people.<sup>37,38</sup> Moreover, previous research has shown that older people with a high fall

risk generate fewer saccades than those with a low risk of falling,<sup>39</sup> while the National Service Framework for Older People<sup>40</sup> recognises that visual impairment alone is a fundamental factor in falls for elderly individuals.

In the case of PSP, the input provided by vision is limited because these patients have difficulty executing down saccades.<sup>3</sup> A recent study has investigated the relationship between these visual limitations and the balance and gait deficits associated with PSP.<sup>36</sup> Patients with severe oculomotor deficits had on average reduced accuracy during stair climbing and/or obstacle avoidance compared with those with mild oculomotor deficits.<sup>36</sup>

The preliminary findings of a recent study support the use of eye movement exercises as a 'complementary therapy' for balance training in PSP.<sup>36</sup> In this study, a two-group pre-test/post-test design was used to compare the benefits of balance and eye movement training (treatment group) against balance training alone (comparison group) in the rehabilitation of gait in people with PSP. Exercises specific to the treatment group included: visual awareness training, by which participants were encouraged to scan an area for a hidden object (e.g., a tennis ball) which had been previously presented; biofeedback training; computer training; and platform limb cue training. Although the improvements scored by the treatment group were not statistically greater than those seen in the comparison group, a within-group analysis revealed a greater number of statistically significant pre-test/post-test improvements in the treatment group. Furthermore, when effect size was formulated to express the clinical significance of the data, on average a larger effect size was associated with the treatment group. Although the study investigators felt that these results alone were sufficient to support the use of eye movement exercises, when contextualised within current communication and applied to patient QoL, the significance of these results may be weakened. It is possible that the complicated techniques associated with the eye movement exercises presented more unwanted challenge for the treatment group. Interestingly, this study showed no significant improvement in swing time (amount of time that the foot was in contact with the ground) or step length (distance from the heel strike of one foot to the heel strike of the other foot in the forward direction) in the treatment group.<sup>36</sup> As the same investigators had recently shown that defects in gaze control in PSP resulted in foot lift asymmetry, and in particular lower lag-foot elevation relative to lead-foot elevation, improvement specifically in swing time and step length should signify the true effectiveness of eye movement training in the rehabilitation of gait in people with PSP. As this was not the case, it remains unproven as to whether or not the eye movement and visual awareness training received by the treatment group of this study actually specifically addressed and/or enhanced the particular component of oculomotor performance which leads to gait instability in PSP.

## Overt versus covert visual orientation in PSP

Although the above studies<sup>30,36</sup> have shown that gaze limitation alone has a negative bearing on locomotion, these findings only account for the eye-movement

component of a more global dysfunction of visually guided behaviour in PSP patients.<sup>3,41</sup> In PSP visual exploration or reorientation has historically been associated with overt movements of the head, eyes and body.<sup>41</sup> However, normally covert, internal orientation of a peripheral target is elicited prior to eye movement.<sup>42</sup> This mechanism facilitates advanced knowledge of the location of an approaching target, even when eye movements are not allowed.<sup>43</sup> Unfortunately, in the case of PSP, studies have shown that the mesencephalic visuomotor centres, which are extensively affected in PSP, are important not only in the control of ocular motility but also in the covert orientation of visual attention in the vertical plane.<sup>41,43</sup> This is disputed by others, who claim that outside the inputs to the oculomotor nuclei, other cortical inputs may exist that could facilitate saccades and gaze control despite disease progression.<sup>44</sup>

It has been shown that visual search exercises, including auditory biofeedback, can enhance the extent of gaze shifts and consequently attention capacity in people with PSP.<sup>44</sup> More recently the same investigators have postulated that, specifically, the pedunculopontine nucleus (PPN) and its projections may be responsive to balance and eye movement training.<sup>36</sup> Essentially, the PPN is known to integrate the systems controlling eye movements and locomotion,<sup>45</sup> whereas its projections to the frontal eye fields, basal ganglia and spinal cord contribute to combined roles in attention, posture and gait, and cognition, respectively.<sup>36,46</sup> For these reasons, and because the PPN is not completely degenerated in the presence of the disease, it has been speculated that function may be recruited with stimulation of these areas via balance and eye movement training.<sup>36</sup> Furthermore, it may indicate that some degree of plasticity remains, even in a progressively degenerative disease such as PSP.<sup>44</sup> Subsequently, this may in turn affect and shape the design of future potential drug therapies.

In all, preliminary findings suggest that some form of rehabilitation strategy is feasible among PSP patients. However, these approaches appear confined to PSP patients with mild cognitive impairment and those who are still ambulatory.<sup>5,36</sup> Little is known about the best possible way of managing patients in the more advanced stages of the disease.

Although somewhat outside the scope of this review, a continued multidisciplinary approach to therapeutic intervention is also encouraged to cater for the vast needs and symptoms of PSP patients.<sup>10</sup> Alarming reports suggest that subjective symptoms such as diplopia and blepharospasm are largely underreported in patients' records,<sup>8</sup> even though they have been found to be a common and treatable cause of falls in PSP.<sup>32,47</sup>

## Conclusion

PSP is a difficult and challenging disorder. Consequently, it is of paramount importance that all involved in the evaluation and management of PSP patients continue to apply the most up-to-date research-led advances to their practice.

Future studies must fulfil the growing need for a larger sample size in order to prove or disprove the efficacy of

balance and eye movement exercises.<sup>36</sup> The hope for the future is that patient-led, rather than scientifically driven, research will prevail. Amidst advancing technologies it must be highlighted that apathy is prevalent and often severe in PSP.<sup>48</sup> This level of diminished motivation may be a contraindication to intense and challenging rehabilitation strategies. Furthermore, it is important not to mistake apathy for depression among PSP sufferers. Distinguishing these two syndromes may lead to a more patient-specific form of rehabilitation or, conversely, palliative intervention.<sup>48</sup> Only by assessment of these functions, combined with an enhanced understanding of patient QoL, can the most appropriate forms of rehabilitation be formulated.

Falls cause much avoidable suffering in PSP patients. For this reason alone it is essential to establish the merits of current rehabilitation strategies in this area. Finally, although this review has established that a certain degree of feasibility and effectiveness can be associated with current strategies of rehabilitation, these are appropriate for only a select number of patients. PSP patients in the advanced stages of the disease are grossly under-represented throughout the literature; further research is therefore needed to establish the most suitable way of caring for them.

## References

- Burn DJ, Lee AJ. Progressive supranuclear palsy: Where are we now? *Lancet Neurol* 2002; **1**: 359–369.
- Litvan I, Bhatnagar KP, Burn DJ, Goetz CG, Lang AE, McKeith I, et al. Movement Disorders Society Scientific Issues Committee report: SIC Task Force appraisal of clinical diagnostic criteria for parkinsonian disorders. *Mov Disord* 2003; **18**: 467–486.
- Zampieri C, Di Fabio R.P. Progressive supranuclear palsy: disease profile and rehabilitation strategies. *Phys Ther* 2006; **86**: 870–880.
- Richardson JC, Steele JC, Olszewski J. Supranuclear ophthalmoplegia, pseudobulbar palsy, nuchal dystonia and dementia. *Trans Am Neurol Assoc* 1963; **8**: 25–29.
- Suteerawattananon M, MacNeill B, Protas EJ. Supported treadmill training for gait and balance in a patient with progressive supranuclear palsy. *Phys Ther* 2002; **82**: 485–495.
- Wilson A. Progressive supranuclear palsy. *Practice Nurse* 2008; **35**(12): 27–30.
- Williams DR, Lees AJ, Wherrett JR, Steele JC. J. Clifford Richardson and 50 years of progressive supranuclear palsy. *Neurology* 2008; **70**: 566–573.
- Nath U, Ben-Shlomo Y, Thomson RG, Lees AJ, Burn DJ. Clinical features and natural history of progressive supranuclear palsy: a clinical cohort study. *Neurology* 2003; **60**: 910–916.
- Lubarsky M, Juncos JL. Progressive supranuclear palsy: a current review. *The Neurologist* 2008; **14**(2): 79–88.
- Ward C. Characteristic and symptom management of progressive supranuclear palsy: a multidisciplinary approach. *J Neurosci Nursing* 2006; **38**: 242–247.
- Globe LI, Davis PH, Schoenberg BS, Duvoisin RC. Prevalence and natural history of progressive supranuclear palsy. *Neurology* 1988; **38**: 1031–1034.
- Litvan I, Agid Y, Calne D, Campell G, Dubois B, Duvoisin RC, et al. Clinical research criteria for the diagnosis for progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome): report of the NINDS-SPSP international workshop [review]. *Neurology* 1996; **47**: 1–9.
- Schrag A, Ben-Shlomo Y, Quinn NP. Prevalence of progressive supranuclear palsy and multiple system atrophy: a cross-sectional study. *Lancet* 1999; **354**: 1771–1775.
- Nath U, Ben-Shlomo Y, Thomson RG, Morris HR, Wood NW, et al. The prevalence of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome) in the UK. *Brain* 2001; **124**: 1438–1449.
- Williams DR, de Silva R, Paviour DC, et al. Characteristics of two distinct clinical phenotypes in pathological proven progressive supranuclear palsy: Richardson's syndrome and PSP-parkinsonism. *Brain* 2005; **128**: 1247–1258.
- Globe LI. Early diagnosis of progressive supranuclear palsy: bucking the odds. *Neurology* 2008; **71**: 1754–1755.

17. Litvan I. Diagnosis and management of progressive supranuclear palsy. *Semin Neurol* 2001; **21**: 41–48.
18. Santacruz P, Uttl B, Litvan I, Grafman J. Progressive supranuclear palsy: a survey of the disease course. *Neurology* 1998; **50**: 1637–1647.
19. Goetz CG, Leurgans S, Lang AE, Litvan I. Progression of gait, speech and swallowing deficits in progressive supranuclear palsy. *Neurology* 2003; **60**: 917–922.
20. Averbuch-Heller L, Paulson GW, Daroff RB, Leigh RJ. Whipple's disease mimicking progressive supranuclear palsy: diagnostic value of eye movement recordings. *J Neurol Neurosurg Psychiatry* 1999; **66**: 532–535.
21. De Bruin VM, Lees AJ, Daniel SE. Diffuse Lewy body disease presenting with supranuclear palsy, parkinsonism and dementia: a case report. *Mov Disord* 1992; **7**: 335–358.
22. Litvan I. Update on progressive supranuclear palsy. *Curr Neurol Neurosci Rep* 2004; **4**: 296–302.
23. Rivaud-Péchoux S, Vidailhet M, Gallouedec G, et al. Longitudinal ocular motor study in corticobasal degeneration and progressive supranuclear palsy. *Neurology* 2000; **54**: 1029–1032.
24. Oba H, Yagishita A, Terada H, et al. New and reliable MRI diagnosis for progressive supranuclear palsy. *Neurology* 2005; **64**: 2005–2055.
25. Borroni M, Malinverno F, Gardoni F, et al. Tau forms in CSF as a reliable biomarker for progressive supranuclear palsy. *Neurology* 2008; **71**: 1796–1803.
26. Williams DR, Lees AJ. Progressive supranuclear palsy: clinico-pathological concepts and diagnostic challenges. *Lancet Neurol* 2009; **8**: 270–279.
27. Kawashima M, Miyake M, Kusumi M, Adachi Y, Nakashima K. Prevalence of progressive supranuclear palsy in Yonago, Japan. *Mov Disord* 2004; **19**: 1239–1258.
28. Schrag A, Selia C, Davis J, et al. Health-related quality of life in patients with progressive supranuclear palsy. *Mov Disord* 2003; **18**: 1464–1469.
29. Schrag A, Selia C, Quinn N, et al. Measuring quality of life in PSP: the PSP-QoL. *Neurology* 2006; **67**: 39–44.
30. Di Fabio R.P, Zampieri C, Tuite P. Gaze control and foot kinematics during stair climbing: characteristics leading to fall risk in progressive supranuclear palsy. *Phys Ther* 2008; **88**: 240–251.
31. Esmonde T, Giles E, Gibson M, Hodges JR. Neuropsychological performance, disease severity, and depression in progressive supranuclear palsy. *J Neurol* 1996; **248**: 638–643.
32. Bloem DR. Falls and fall-related injuries in patients with PSP. 2004. Available from: [http://www.pspeur.org/research/funded/projects/completed\\_bloem/](http://www.pspeur.org/research/funded/projects/completed_bloem/) [accessed 2 Feb 2009].
33. Williams DR, Watt HC, Lees AJ. Predictors of falls and fractures in bradykinetic rigid syndromes: a retrospective study. *J Neurol Neurosurg Psychiatry* 2006; **77**: 468–473.
34. Izzo K, DiLorenzo P, Roth A. Rehabilitation in progressive supranuclear palsy: case report. *Arch Phys Med Rehabil* 1986; **67**: 473–476.
35. Sosner J, Wall, GC, Snzajder J. Progressive supranuclear palsy: clinical presentation and rehabilitation of two patients. *Arch Phys Med Rehabil* 1993; **74**: 537–539.
36. Zampieri C, Di Fabio RP. Balance and eye movement training to improve gait in people with progressive supranuclear palsy: quasi-randomized clinical trial. *Am Phys Ther Assoc* 2008; **88**: 1460–1473.
37. Hollands M, Patla A, Vickers J. 'Look where you're going!': gaze behaviour associated with maintaining and changing the direction of locomotion. *Exp Brain Res* 2002; **143**: 221–230.
38. Di Fabio RP, Zampieri C, Greany JF. Aging and saccade-stepping interactions in humans. *Neurosci Lett* 2003; **339**: 179–182.
39. Di Fabio RP, Zampieri C, Henke J, et al. Influence of elderly executive cognitive function on attention in the lower visual field during step initiation. *Gerontology* 2005; **51**: 94–107.
40. *National Service Framework for Older People*. London: Department of Health, 2001.
41. Rafal RD, Posner MI, Friedman JH, et al. Orientating of visual attention in progressive supranuclear palsy. *Brain* 1988; **111**: 267–280.
42. Posner MI. Orientating of attention. *Q J Exp Psychol* 1980; **32**: 3–25.
43. Rafal RD, Grimm RJ. Progressive supranuclear palsy: functional analysis of the response to merthysuride and antiparkinsonian agents. *Neurology* 1981; **31**: 1507–1518.
44. Di Fabio RP, Zampieri C, Tuite P, et al. Vertical gaze enhanced with biofeedback for patients with progressive supranuclear palsy: evidence for movement plasticity in a chronic progressive neurological disorder [abstract]. *Mov Disord* 2004; **16**: 1124.
45. Mena-Segovia J, Bolam JP, Magill PJ. Pedunculopontine nucleus and basal ganglia: distant relatives or part of the same family? *Trends Neurosci* 2004; **27**: 585–588.
46. Pahapill PA, Lorenzo AM. The pedunculopontine nucleus and Parkinson's disease. *Brain* 2000; **123**: 1767–1783.
47. Piccione F, Macini E, Tonin P, et al. Botulinum toxin treatment of apraxia of eyelid opening in progressive supranuclear palsy: report of two cases. *Arch Phys Med Rehabil* 1997; **78**: 525–529.
48. Levy ML, Cummings JL, Fairbanks LA. Apathy is not depression. *J Neuropsychiatry Clin Neurosci* 1998; **10**: 314–319.