

Health-Related Quality of Life (HR-QoL) in PSP

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(on behalf of the PSP-QoL research group)

Health-related Quality of Life (HR-QoL) instruments allow us to measure an individual's physical, emotional and social well-being. Data from HR-QoL measures help us to evaluate the benefit of treatments and help inform health policy decisions by providing important information from the patient's point of view.

We conducted semi-structured interviews with 27 patients with PSP and their carers, and asked participants to complete existing measures of HR-QoL and depression. Although existing HR-QoL measures were somewhat useful, they did not capture all aspects of importance to patients with PSP such as visual disturbances, dysarthria, dysphagia, muddled thinking, confusion and apathy.

We found no association of HR-QoL with age or gender. HR-QoL deteriorated with increasing disease duration and severity, and with greater cognitive impairment, and was associated with worse depression scores.

We used the data generated from the exploratory semi-structured interviews to develop the first draft of a new scale to measure HR-QoL in patients with PSP. The draft scale was further tested, in several stages, and found to be reliable and valid. The PSP-QoL may be a helpful patient-completed scale for studies in PSP.

What is the role of brain scanning in the diagnosis and assessment of PSP?

Luke Massey

Since the original description of PSP in 1963 it has become increasingly apparent that there are different forms of the disease; post mortem studies have shown that during life up to a quarter of patients may not be correctly diagnosed. Clinical diagnosis alone may not correctly identify all cases. MRI to date has proven a useful tool in helping with making a diagnosis in many, but not all, cases.

Recently advances in MRI technology and techniques have opened new avenues: by measuring the volume of regions of the brain affected in PSP it had been possible to find significant differences between PSP and other conditions; measuring the reduction in volume of these structures over time may enable us to monitor the progression of the disease. By measuring the freedom of movement of water molecules (so-called *Diffusion Weighted Imaging*) it has been possible in MSA, a similar condition to PSP, to show changes in specific regions of the brain giving some insight into the severity of the disease. Studies of this technique in PSP are not as advanced but early work shows promise. Diffusion weighted imaging enables the mapping of brain connections and early work shows some differences between PSP and other conditions.

There are other techniques currently under study (including magnetization transfer imaging, segmented inversion recovery imaging). Using high field MRI (increasing the strength of the magnet used in the MR machine) has enabled us to see structures in the brain with much more clarity. It is hoped that the combination of high field MRI and advanced techniques such as Diffusion Weighted Imaging will improve the ability of MRI to distinguish between these conditions. Also, by comparing MR imaging over time, the development of a method of measuring the progression of the disease may be possible. This would be very useful, for example, in showing how any new medical treatments alter the course of this illness in clinical trials.

Behavioural and Psychiatric Features of Progressive Supranuclear Palsy

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A range of behavioural and psychiatric symptoms (BPS) such as depression, anxiety, apathy, disinhibition, hallucinations, delusions, obsessive compulsive behaviours, agitation, irritability, euphoria, addictive behaviours, hypersexuality, REM sleep behaviour disorder occur in neurodegenerative disorders such as Parkinson's disease, Alzheimer's disease, multiple system atrophy, and progressive supranuclear palsy (PSP).

In people with PSP, apathy, depression, disinhibition and agitation are the most common BPS. In contrast, euphoria, hallucinations, delusions, and REM sleep behaviour disorder are rare in PSP.

Behavioural and Psychiatric Symptoms increase the level of disability and handicap and have a negative impact on the quality of life of people with PSP. BPS are also associated with increased carer stress and burden, and can influence decisions for nursing home placement. BPS require direct medical management. In addition, educating and supporting the carers and family, and provision of day and respite care may be useful in the management of BPS in PSP.

Visual difficulties experienced in PSP

Niall Quinn

Visual difficulties have long been associated with PSP, for example, increasing difficulty with upward and downward gaze, opening or closing the eyelids, slow or 'round the houses' eye movements, and sometimes blurring or even double vision. Sensitivity to light can also be a problem for some. While patients do not usually have all these symptoms they may have several at once.

This can cause problems such as dryness of eyes, or clipping the kerb while driving, bumping into doorframes, difficulty moving from one line to the next when reading or lifting food to one's mouth without spilling (or, conversely, 'ignoring' food on the near half of the plate); tying shoelaces or adjusting to bifocals.

Various ways can be used to help manage these challenges, including:

Prismatic spectacles to counter the inability to look up or down

Artificial tears for eye dryness

Tinted wraparound glasses for light sensitivity

'Ptosis props' – botulinum toxin, to strengthen eye muscles

Education and awareness of the patient, family and friends

Treatment Options for Progressive Supranuclear Palsy

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The Multidisciplinary Approach

A multidisciplinary approach is essential in the management of Progressive Supranuclear Palsy (PSP). Speech and language therapists and dieticians can help to improve swallowing and communication difficulties experienced by patients. The latter, compounded by cognitive and neurobehavioural problems, can be a source of great frustration to the patient and their carers. Severe swallowing difficulties may warrant insertion of a percutaneous gastrostomy feeding system or 'PEG', and although initially a frightening thought to many, this can considerably improve nutrition and quality of life.

Early occupational therapist input is essential as the inertia in the health care system means that adaptations around the home may be "playing catch up" with the patient's deteriorating physical state. Mirror-prism spectacles can make it possible for those with severe limitation of eye movements (particularly down-gaze) to read and feed themselves. Eyelid crutches, sometimes combined with botulinum toxin therapy, may be useful for eyelid opening problems (which can be severe enough to render a PSP patient functionally blind). Physiotherapists can advise on walking aids, such as weighted walkers and exercises, although there is a dearth of evidence-based advice in this area. Severe postural instability, coupled with the inability of the patient to recognise their balance problem because of "reckless" behavioural changes, may mean that a wheelchair is the safest option when falling becomes a regular occurrence. Depression affects around one third people with PSP and may be under-recognised. Antidepressant drugs may be useful in improving the mood disorder but good quality trial data is again lacking. The PSP (Europe) Association can provide important advice with regard to future care planning, legal options of Power of Attorney, trusteeship, advance directives and consideration for brain donation.

Neurotransmitter Replacement Strategies

There is only a weak evidence base for drug treatment; most studies have been small and therefore underpowered. Pragmatically, a trial of levodopa is worthwhile; increasing the dose to at least 1g per day before deciding it is of no benefit. Forty to fifty per cent of people with PSP can show some improvement with levodopa, although it is often short lived.

Adverse effects include visual hallucinations and, uncommonly, involuntary facial movements. Amantadine may produce modest benefit 15% of patients, although this is anecdotal and modern-day, high quality research is required to clarify this.

Dopamine agonists, monoamine oxidase inhibitors, and catechol-O-methyl transferase inhibitors, used in the treatment of Parkinson's Disease are, frustratingly, of no proven benefit in PSP.

Future Treatment Approaches

Simple neurotransmitter replacement strategies (analogous to "topping up the oil in a leaking engine") are unlikely to be of significant benefit in the treatment of PSP so new approaches are required. The consumption of tropical plants and herbal teas has been linked with an abnormally high frequency of a form of parkinsonism, clinically and pathologically resembling PSP, in Guadeloupe (French West Indies). Striking and sustained improvement in some symptoms occurred after cessation of consumption of these fruits and infusions. A short-term approach to disease modification in PSP might therefore emerge from studying dietary or occupational toxin exposure. The logistics of conducting such a study, which would require a large number of participants to give a meaningful answer, is however daunting.

More radical breakthroughs in PSP therapeutics will come from a greater understanding of the cause of the condition and the development of animal models in which to test new disease-modifying treatments. Regarding the latter, transgenic mice, *Drosophila* and zebrafish models have biological similarities with a number of "tauopathies" (diseases where abnormal tau protein accumulates in excess), including PSP. One example of the use of such models comes from a report of the inhibition of glycogen synthase kinase (GSK-3 β), an enzyme important in tau phosphorylation, which led to functional improvement in transgenic *Drosophila*. Lithium is an inhibitor of GSK-3 β and tolerability trials are planned for PSP in the UK and US. Sodium valproate, which started out life as an anti-epilepsy drug, may also inhibit GSK-3 β and a trial of this agent in PSP is underway in France.

Other approaches to disease modification in PSP could involve manipulating the genetic system that switches between production of two tau protein types. This could be achieved, for example, by the use of RNA interference. Inhibiting other enzymes that are involved in the aggregation of tau may also offer therapeutic hope – glycation and transglutamination have been principally implicated.

Oxidative stress within the cell may lead to abnormal tau processing, so a small pilot study in Germany is examining whether a mitochondrial enhancing drug (mitochondria produce energy within all cells of the body) called co-enzyme Q10 can alter the disease course in PSP. Anti-inflammatory agents could be considered, although from trials of these drugs in Alzheimer's disease and the size of effect, the feasibility of similar studies for PSP must be questionable.

Finally, the use of trophic factors (naturally occurring compounds that help nerve cells to sprout and grow, rather like fertilizer on the lawn) could be a promising therapeutic approach for PSP. Amongst other considerations, there would be considerable technical issues to overcome, not least the effective delivery of the growth factor to relevant areas of the brain.

Conclusion

No one can doubt that PSP is a brutal and aggressive disease, but this should not be accompanied by therapeutic nihilism. Although we are sadly falling short of the mark for drugs and other treatments that can improve symptoms of disease, there is still much to be gained by a rigorous and systematic multidisciplinary approach. Even relatively small interventions can improve quality of life for both the person with PSP and their carers.

In the medical profession, we also continue to learn from our patients by the ingenious ways they can sometimes find to overcome adversity. Disease-modifying treatments undoubtedly represent the "golden fleece" for slowing down the course of PSP. Real progress has been made in developing such treatments as our knowledge of the underlying cause of PSP continues to expand.

Balance and falls in PSP: impact for patients, carers and therapists

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Development of balance problems and recurrent falls early in the course of the disease are an important and frequently incapacitating feature of progressive supranuclear palsy (PSP). In fact, recurrent falls within the first year of disease onset are required to formally establish a diagnosis of "probable PSP". Falls are very common, and daily falls are present in most patients who are still mobile (1). Falls occur most often in a backward direction. A striking feature in PSP patients is the frequent occurrence of sudden and seemingly spontaneous falls, often in a backward direction. Unfortunately, injuries are also very common and occur in up to 90% of PSP patients (1;2). Many injuries are serious, including fractures (mainly of the arms and hips) or head injuries. "Minor" soft tissue injuries such as bruises or skin lacerations are even more common in PSP. Fear of falls is also commonly present, and this can be incapacitating in its own right.

There are multiple causes for these frequent and devastating falls. Contributing factors include the poor balance and the walking difficulties, in particular the sudden "gluing" of the feet to the floor ("freezing"). Other factors include the abnormal position of the neck (often extended backward – termed retrocollis – thereby hampering vision of the feet and walking trajectory) and the problems with moving the eyes up or down (e.g. causing falls while descending the stairs). A form of "recklessness" (lack of insight and impulsive behaviour) may partially explain the unusually high injury rate in PSP. Finally, sudden and involuntary eye closure (termed "blepharospasm") can contribute to falls in up to a quarter of PSP patients.

Treatment of falls in PSP is rarely gratifying, but several approaches are worth considering (3). Walking aids and provision of external support by the carer can help to reduce falls. Patients with recklessness often require continuous supervision of their activities. Medication is rarely very effective, but all patients deserve a trial of adequately dosed levodopa and, if that fails, a judicious trial of amantadine and amytriptiline. Retrocollis can sometimes be treated using botulinum toxin, and vertical gaze problems using prism glasses. Anecdotal reports suggest a possible therapeutic effect of physiotherapy, but this needs to be studied in more detail.

Physiotherapists can now use recently developed evidence-based Dutch guidelines with recommendations for clinical practice (4). Although these were developed originally for Parkinson patients, the guidelines also contain useful information for therapists involved in the management of patients with PSP. An English version is available via the web (www.kngf.nl).

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The Role of Palliative Care in PSP

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Specialist palliative care formed in response to the needs of cancer patients but there has always been involvement with non-cancer conditions and potential for greater involvement with longer-term neuro conditions.

Many people who have PSP will have multiple care needs over a relatively long period as their disease progresses. This will require multiple input from specialist services such as:

Neurologist, Ophthalmologist, Psychiatrist, Urologist, Nursing, Physiotherapy, Occupational therapy, SALT, Respiratory specialist, Dietician, Social care, Spiritual care, Support groups, and Palliative care (Ward, 2006).

However, much work still needs to be done to ensure a co-ordinated approach between services, particularly neurology, rehabilitation and palliative care, to support patients as they near their end of life.

The Role of Speech & Language Therapists in PSP

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People with PSP frequently present with dysarthria (speech difficulty) and dysphagia (swallowing difficulties). The speech and language therapist will assess the person's speech and swallowing and make recommendations regarding how best to communicate and also whether the person needs to modify their food and drink to make it safer or easier for them to swallow. Direct therapy may be offered with the aim being to maximise the person's communication. Therapy may be offered on a one to one basis or in groups and will often involve the carers as communication is central to any relationship.

Therapy may not be appropriate or of benefit to many people with PSP especially as the disease progresses and cognitive/behavioural difficulties begin to develop. Speech and language therapists may also contribute to the discussions regarding the need for non-oral feeding.