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Non-motor symptoms in Parkinson's disease

Ronald F. Pfeiffer

Department of Neurology, Oregon Health & Science University, 3181 SW Sam Jackson Park Road, Portland, OR 97239-3098, USA

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ABSTRACT

With the growing awareness of the presence of non-motor symptoms in Parkinson's disease (PD) has come the realization that these non-motor features play a tremendously important, and sometimes dominant, role in the management and even the diagnosis of the disorder. Despite this, a reluctance to formally address and treat the non-motor symptoms of PD remains and quality of life for PD patients suffers. This review provides an overview of the impact non-motor symptoms have on persons with PD, along with a brief description of some of the more common non-motor features of PD.

1. Introduction

Over the past several decades much has been written about the "discovery" of non-motor dysfunction as a part of Parkinson's disease (PD). What often is not recognized is that in this instance the term "discovery" is actually a misnomer, because many of these aspects of PD were already recognized and described by none other than James Parkinson himself in his classic treatise on the disorder that now bears his name. Sleep disturbances, gastrointestinal dysfunction, bladder dysfunction, and even fatigue (extreme exhaustion) all are described by Dr. Parkinson. What has changed is the growing recognition of the prevalence and importance of non-motor dysfunction in both the diagnosis and management of PD. It is now widely accepted that PD is characterized not only by its motor aspects, but also by numerous non-motor symptoms (NMS) that encompass sensory abnormalities, behavioral changes, sleep disturbances, autonomic dysfunction, and some more difficult to categorize symptoms such as fatigue.

NMS are by all accounts very common in individuals with PD. In two recent studies, at least one NMS was reported by almost 100% of patients [1,2] and in yet another, NMS were present in 100% of PD subjects who were also experiencing motor fluctuations [3]. NMS also occur frequently in individuals without PD as a part of normal aging – studies suggest 68–88% of normal, comparably aged individuals will experience at least one NMS; this should impart caution in rushing to attribute all NMS described by PD patients to their PD [1,2]. However, individuals with PD tend to have a larger number of different NMS, compared with normal controls (mean 8.4 vs. 2.8 in one study), and the NMS in persons with PD tend to be more frequent and more severe [2,4].

NMS also may be the presenting clinical feature of PD in over 20% of individuals [5]. In such situations, PD diagnosis often is delayed and individuals are subjected to a variety of specialist referrals and inappropriate treatments [5]. Most prominently, pain is likely to be attributed to orthopedic or rheumatologic causes, and it is not uncommon for individuals eventually diagnosed with PD to have been treated with a variety of pain and anti-inflammatory medications and even to have received steroid injections for suspected bursitis and other diagnoses. Some NMS may actually appear years, and even decades, before the classic motor features of PD make their appearance.

As with parkinsonian motor abnormalities, NMS also may show a pattern of fluctuation [3,6]. Non-motor fluctuations tend to correlate with the motor fluctuations and tend to emerge during motor "off" periods; this is especially true of behavioral NMS [6]. For other NMS, this pattern is less robust, but it is rare for individuals to experience non-motor fluctuations exclusively [3,6]. For a significant percentage of individuals – 28% in one study - their non-motor fluctuations cause a greater degree of disability than their motor fluctuations [3].

This somewhat surprising fact has been reinforced by more recent studies that have demonstrated that NMS have a greater impact on health-related quality of life than do motor abnormalities, even early in the course of PD. Other studies have documented that NMS, specifically hallucinations, are the strongest predictor of nursing home placement for persons with PD. In the nursing home setting, NMS appear to be virtually universally present in patients with PD; individuals typically display multiple types of NMS, which occur with great frequency [7]. In persons with PD living at home,

E-mail address: pfeiffro@ohsu.edu.

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NMS in the form of neuropsychiatric symptoms also are important determinants of caregiver burden.

In light of the importance and impact that NMS hold for persons with PD and for their family, it is vitally important that physicians caring for them are familiar with and are attentive to diagnosing NMS when they occur. This can be difficult because patients themselves may not mention them to their physicians, either because they do not associate them with PD or, in some instances, out of embarrassment. Thus, it falls on the physician to query patients regarding NMS. Questionnaires have been developed to assist with this. Although recognition of NMS by physicians- neurologists and non-neurologists alike- has improved with the cornucopia of published reports that have been published on NMS in PD in recent years, prompt diagnosis still lags and assuring appropriate treatment looms as a potentially greater hurdle. In one recent report, specific treatment of NMS was found to be distressingly infrequent in routine clinical care of PD patients – only 28% of those with moderate to severe depression were being prescribed pharmacologic treatment, and only 2% of patients who screened positive for REM sleep behavior disorder, 13% of persons with significant urinary symptoms, 3% of men with erectile dysfunction, and 66% of individuals with moderate or greater constipation were receiving treatment for their NMS [8].

So, exactly what are the NMS of PD? Other presentations/contributions at this Congress and in these Proceedings will address individual manifestations in more detail, so just a brief summary will be delineated here and treatment issues will be mentioned only in passing.

2. Abnormalities of sensation

A variety of abnormalities of sensation have been described in the setting of PD. Impairment of olfaction is perhaps the most widely recognized, but a variety of problems with vision and patterns of pain are also prone to occur.

Olfactory impairment is present in up to 90% of persons with PD, often already at the time of diagnosis. However, over 70% of affected individuals may be unaware that their sense of smell is impaired [9]. Although some investigators report that impaired olfaction is independent of disease stage and duration [9], others report that olfactory impairment is associated with higher disease severity and faster progression and that severe hyposmia in PD patients may predict the development of PD dementia [10]. Olfactory testing has been suggested to be useful for screening for PD but can be time-consuming in the clinical setting. Of interest, in this regard, is the recent report that testing with only three odors (coffee, peppermint, anise) provided comparable results to testing with the entire odor panel [11]. Both same-day and longer term improvement in odor identification has been reported with olfactory training, but confirmation with additional studies is necessary [12].

In the clinic, it is very common for patients with PD to voice their frustration with vision problems and their frustration often is amplified by prior visits to their ophthalmologist in which they have been informed that no explanation for their visual symptoms can be found. However, with more detailed testing, a variety of abnormalities potentially affecting vision emerge in the setting of PD, including reduced contrast sensitivity, impaired color discrimination, convergence insufficiency, and dry eye syndrome; as a group, PD patients also have reduced distance and near best corrected visual acuity, compared with controls [13]. Abnormalities affecting structures around the eye, such as seborrheic blepharitis and meibomian gland disease also are more common in individuals with PD [13]. Stereopsis also is disturbed in PD. The basis for visual symptoms in PD may be multifactorial, but elegant work has demonstrated that thinning of the retinal nerve fiber layer and the inner retinal fovea are characteristic of PD and deposition of alpha-synuclein has been described in amacrine and ganglion cells within the inner retina [14].

In a recent report, pain was noted to be present in 76% of 100 individuals with PD [15]. Pain in PD has been classified into five categories: musculoskeletal pain, radicular or neuropathic pain, dystonia-related pain, primary or central parkinsonian pain, and akathitic discomfort. Of these, musculoskeletal pain is the most frequent, described in almost 50% of individuals experiencing pain, although this is also the category in which it likely is most difficult to separate pain directly related to PD from pain due to other causes. An alternative approach to classifying pain in PD divides pain into primary PD pain (e.g. pain related to dyskinesia, “off” period dystonia, central pain) and secondary PD pain (e.g. musculoskeletal pain, orofacial pain, limb and abdominal pain). Not surprisingly, pain can severely impact quality of life for individuals experiencing it. Management approaches to pain in the setting of PD depend upon the cause of the pain and may include oral pharmacological approaches, botulinum toxin injections, physical therapy, and pain management and other specialist consultations.

3. Behavioral changes

Depression is common in PD; one review and meta-analysis reported a prevalence of major depressive disorder in 17%, minor depression in 22% and dysthymia in 13% of individuals with PD [16]. Depression may occur at any time during the course of PD. It may precede the appearance of motor dysfunction and may be an early prodromal sign of PD. It often is attributed to serotonin deficiency, but a recent study documented reduced serotonin raphe transporter availability to correlate with tremor but not depression in individuals with PD [17]. Persons who develop depression early in the course of PD have an increased risk of greater impairment of motor function and increased disability over time. Antidepressant medications have been shown to be effective in treating parkinsonian depression; evidence of benefit of transcranial magnetic stimulation is also surfacing.

The reported prevalence of anxiety in PD is 25–40% [18]. Like depression, anxiety may appear at any time during the course of PD. It also may precede the appearance of the classic motor features of PD and persons with anxiety have an increased risk of developing PD. In PD anxiety most often takes the form of generalized anxiety disorder, panic disorder, or one of the phobic disorders. It may become quite strikingly evident as a wearing off phenomenon.

A recent meta-analysis suggests that the prevalence of apathy in PD is approximately 40% [19]. It can be difficult to separate apathy from depression and fatigue in PD patients, but what distinguishes apathy is the indifference of the affected person, which is especially frustrating for caregivers. An association between apathy and executive dysfunction, specifically difficulty with initiation, is apparent in PD [20].

Perhaps the complication, whether motor or non-motor, most feared by patients with PD and their family members is the development of dementia. Unfortunately, it is a complication that is eventually realized in over 80% of individuals with PD who survive for 20 years [21]. Although cognitive difficulties clearly become more frequent and prominent as PD progresses, mild cognitive impairment may already be present in almost 25% of PD patients in the early stages of the disorder [22]. The diagnostic division between PD dementia and dementia with Lewy bodies has been drawn rather arbitrarily, but the actual distinction can be more indistinct. Current treatment of cognitive impairment in PD is centered on cholinesterase inhibitors, but is suboptimal.

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