Fallers Versus Non Fallers Undergoing “On Off” Levodopa Testing: A Sensory Deficit in Parkinson Disease?

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Abstract

Postural Instability (PI) is a disabling symptom in Parkinson Disease (PD). Falls a consequence of PI impairs patients’ quality of life. Postural instability is usually a late appearing symptom in PD. It’s usually regarded as a motor symptom but unlike most of the motor symptoms in PD, it usually does not respond to levodopa. Increasing evidence indicates the pathophysiology of PI includes deficits in proprioceptive and vestibular processing and integration, sensory, not motor symptoms. To better understand PI and falls and the effect, or non effect of levodopa, we studied 20 PD patients, all of whom were tested “off levodopa” for 16 hours and then “on levodopa.” Ten patients were frequent fallers. Their motor symptoms: rigidity, bradykinesia and tremor had improved on levodopa. Falls did not improve, decrease, on levodopa. Ten patients were non fallers. Their motor symptoms had improved on levodopa. We were particularly interested in the effect of levodopa on “bedside” tests of PI : the “pull test” part of the MDS-UPDRS motor examination, and the ability, or inability, of patients to stand on one leg for at least 3 seconds: “one legged stance. The one- legged stance is utilized by us to evaluate PI and fall risk. Mean age of fallers and non fallers were similar: 64.1 +/- 10.68 years versus 63.3 +/- 6.28. Fallers had PD significantly longer: 11.18 +/- years versus 5.1 +/- 1.29. The “pull test” was significantly improved with levodopa. The one- legged stance was not. This suggests the one- legged stance better reflects PI than the “pull test.” It also suggests that PI is more likely to reflect a sensory than a motor deficiency.

INTRODUCTION

Falls are a risk PD [1,2]. In a study of 761 hospital admissions for PD only 15% were for management of PD, while 39% were for falls [1]. PD patients who fall once may do so because of PD or because of factors such as poor eye-sight, leg weakness, and environmental hazards. However, some PD patients fall repeatedly [3,4]. Falls, if they appear early in the course of PD, and are not associated with atypical parkinson disorders, decrease with levodopa. Falls, when they appear later in the course of PD, the usual occurrence usually do not respond to levodopa [3].

There is variability in the reported prevalence of falls in PD: from 11% to 68% [3-14]. The variability depends on whether specific fall risk factors are excluded. These include visual loss, orthostatic hypotension resulting from anti- hypertensives or imbalance resulting from tranquilizers, sedatives, or alcohol. The variability also includes whether persons with evolving atypical Parkinson disorders such as Progressive Supranuclear Palsy (PSP) or Multiple System Atrophy (MSA) persons but with a high predilection to fall were excluded [6]

METHODS

We examined 10 PD patients who had fallen at least twice in the past year. There were 6 men and 4 women. Diagnosis of PD was made by standard criteria. We excluded patients with atypical Parkinson disorders. We excluded patients with PD and dementia, Mini- Mental Status Examinations, MMSE, < 27. We excluded patients who were legally blind. We excluded patients with orthostatic hypotension. Although orthostatic hypotension can be part of PD, it can also result from the use of anti-hypertensives, diuretics or dehydration [15]. As we often could not distinguish between them we excluded such patients. We excluded patients with neuropathy when it resulted in impaired proprioception or weakness [16]. We compared them with 10 PD patients who had not fallen. There were 6 men and 4 women.
The 10 patients who had fallen and the 10 who had not expressed an interest came under deep brain stimulation (DBS). As part of their evaluation for DBS all patients discontinued levodopa for 16 hours. Equal numbers of fallers and non fallers were on dopamine agonists (3 fallers, 3 non fallers) and/or amantadine (3 fallers, 3 non fallers). Patients were evaluated in an "off" state. Then they were given 150 % of their daily levodopa dose. They were then evaluated in their "on" state. Evaluation consisted of the Movement Disorder Society (MDS) - Unified Parkinson Disease Rating Scale (MDS-UPDRS), particular attention was paid to the Freezing of Gait (FOG) and "PT" pull test, subtests of the UPDRS [17]. Patients were also evaluated with the One-Legged Stance, ability to stand on one leg for at least 3 seconds, and step-length: measured by counting the number of steps the patient took to walking 10 meters, after adjusting for height (Table 1). The one-legged stance test is part of the BNI Balance Scale [18] and the Berg Balance Scale [19].

All patients were informed that the information collected could be used for research but that they personally could not be identified. Approval for the analysis was obtained by the St. Joseph’s Hospital institutional review board. No patients were compensated. As the evaluations were part of the patient’s routine care no special consent other than the standard signed consent obtained from all patients at the time their visit was obtained.

Continuous variables were analyzed using t-tests, categorical variables were analyzed using chi-square tests, and odds ratios were calculated.

RESULTS

Mean age of fallers and non fallers were similar: 64.1 +/- 10.68 years versus 63.3 +/- 9.18 years. fallers had PD significantly longer: 11.18 +/- years versus 5.1 +/- 1.29. The motor part of the UPDRS improved significantly, by 45%, in fallers from "off" to "on" (Table 1). The motor part of the UPDRS improved significantly, by 46%, in non fallers from "off" to "on." Step length, a motor symptom, improved, significantly, with levodopa from "off" to "on" in fallers and non fallers (Table 1). This has been previously noted by us [20]. FOG did not improve significantly in fallers or non fallers from "off" to "on": Seven fallers had FOG when "off" and 5 had FOG when "on." Freezing of gait, usually regarded as a motor symptom, has a major sensory component, it is improved with visual cues: walking over stripped lines, walking in cadence. This sensory component is not improved with levodopa. None of the non fallers had FOG in either "off" or "on." Six of 10 fallers and 5/10 non fallers had dyskinesias.

The "pull test" improved significantly in "on" versus "off" states in fallers and non fallers. This suggests, to us, that the "pull test" is mainly a motor symptom, one that is levodopa responsive. The ability to stand on one leg for at least 3 seconds did not improve in either fallers or non fallers. This suggests to us, that the ability to stand on one leg is not, mainly, a motor symptom: there is a major sensory component. When a person stands on one leg, in addition to requiring increased motor control, the person effectively removes 50% of their proprioceptive input. This may be the critical feature of the one-legged stance test.

DISCUSSION

In our study there were clear and significant differences between fallers and non fallers. Fallers had PD longer. Fallers had significantly higher (worse) UPDRS scores when "off" levodopa: 33.2 +/- 11.1 versus 19.7 +/- 6.6 p < 0.03 and when "on" levodopa: 23.0 +/- 5.4 versus 12.2 +/- 4.0 p < 0.03. As a motor part of the UPDRS consists of mainly motor symptoms: rigidity, bradykinesia and tremor, it's reasonable to regard PD as mainly a motor disorder of the extra pyramidal system.

Postural instability as reflected in the "pull test", a subtest of the UPDRS, improved significantly on levodopa. We know, however, these patients fall while on levodopa. This suggests the "pull test" is not the best reflection of PT. The "pull test" consists of two parts. In part one there's a backward displacement, a "pull." This is a sensory "input." In part two patients respond: they "right" themselves by quickly stepping backwards-- a motor "output." The way the "pull test" is done, the "pull" is variable, the integration of the "pull" with the extra pyramidal motor system is variable, and the motor "output" dominates. This may explain

| Table 1: Recurrent Fallers vs Non Fallers, "Off- On" Testing with Levodopa. |
|------------------|------------------|------------------|------------------|------------------|
| **Fallers Off** | **Fallers On** | **Non Faller Off** | **Non Faller On** |
| UPDRS            | 33.2 +/- 11.1   | 19.7 +/- 6.6     | 23 +/- 5.4       | 12.2 +/- 4       |
| p= 0.018         |                 |                  |                  |                  |
| FOG Off          | 7/10 FOG        | 5/5 FOG NS       | 0/10 FOG         | 0/10 FOG NS      |
| Post Stability   | 8/10 abnl       | 1/10 abnl OR 13.5 (2.4-74.87) | 4/10 abnl       |
| p= 0.0029        |                 | 1/10 abnl OR 13.4 (2.4-74.9) | 0.029 |
| Stand 1 Foot < 3 sec | 9/10 abnl | 8/10 abnl NS | 2/10 abnl NS | 2/10 abnl NS |
| p= 0.027         |                 |                  |                  |                  |
| Step Length      | 0.35 +/- 0.12   | 0.98 +/- 0.085   | 0.6 +/- 0.036    | 0.71 +/- 0.043   |
| p= 0.0096        |                 | 0.0096           | 0.027            |                  |
| Dyskinesia       | None            | 5/10 present     |                  | 5/10 present     |

**Abbreviations:** UPDRS: Motor Portion MDS Unified Parkinson Rating Scale; FOG: Freezing of Gait; Abnl: Abnormal

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why patients have “pull tests” that improve on levodopa, yet they continue to fall. The one-legged stance test does not improve on levodopa. And the one-legged stance test, in our experience, correlates best with recurrent fallers. The one-legged stance test has two parts. In part one upon attempting to stand on one leg the patients increases the extensor tone of his trunk and on the leg upon which he is standing. This is a motor phenomenon: it may or may not respond to levodopa. In part two, to continue standing, the patient needs proprioceptive, sensory, input from joint position sensors in the tendons, muscles, and peripheral nerves of his legs. However, by standing on one leg, he has “effectively” removed half of the proprioceptive input from his legs. The removal of this input, an input not corrected by levodopa, is we feel the main reason PD patients fall. Similar tests were made by others [12,21,22] who conducted “on” and “off” testing with levodopa. Nova evaluated 23 PD patients utilizing the UPDRS as well as the Berg Balance Scale [19]. The Berg Balance scale incorporates the one-legged stance. Nova like us noted the limitations of the UPDRS and the utility of the Berg Balance Scale. They wrote:

The results demonstrate that levodopa is an effective drug for the treatment of PD.....Most of the patients obtained higher (better) scores in the Berg (Balance) scale when comparing their “on” and “off” periods thus showing an improved functional balance. The Berg scale is a more far reaching (than the UPDRS for evaluating balance) and embodies various aspects of stance stability (including proprioceptive and vestibular information).

PD is viewed mainly a motor disorder. However, increasing the importance of sensory inputs and the integration of these inputs with the extrapyramidal motor is being recognized. In a seminal study 50 years ago, the great English neurologist, J Purdon –Martin evaluated 130 patients with post-encephalitic Parkinson [23]. He wrote:

In the upright position man stands on a base which is narrow and small relative to his height. A manikin or dummy figure is easily knocked over and man himself is stable only as long as his center of gravity remains within the vertical projection of his base..... Some physical instability is widespread among our patients and the more severely affected are remarkable in that they are unable to preserve their equilibrium not only when they are standing but also when they are sitting.

Purdon- Martin attributed his patient’s PI to a combination of proprioceptive and vestibular dysfunction. Traditional tests of proprioception: joint position sense, two point discrimination, graphesthesia and point localization were intact. This implied a deficit in integration of proprioceptive information in high centers including the basal ganglia, the thalamus, and parietal cortex. Purdon- Martin also attributed part of his patient’s PI, particularly their inability to compensate for tilting, to vestibular dysfunction. Presumably, it is an inability to integrate vestibular inputs from their otoliths and statoliths with their extrapyramidal motor systems.

Vaugoyeau and her group are among several that have recognized the importance of sensory information in PD, and especially its contribution to falls. They wrote [16]:

Impairment of postural control is a common consequence of Parkinson Disease PD. Increasing evidences demonstrate that the pathophysiology of postural disorders (PI) in PD includes deficits in proprioceptive processing and integration.

Another group Rinalduzzi and associates wrote [24]:

Postural control (and PI) in humans depends on information coming from visual, vestibular and somatosensory systems..... during postural (adjustments) and movements the somatosensory input is generated by muscle sensory organs, mainly spindles sensitive to changes in movement during postural adjustments, the somatosensory input is (also) generated by muscle sensory organs, mainly (a different set of spindles) spindles sensitive to changes in fasicle length and by Golgi tendon organs, sensitive to changes in muscle tension. Proprioceptive information is integrated with visual and vestibular information to interpret the complex sensory environment and to weigh the relative dependency of posture on each of these senses.

Horak and her group after studying pointing errors and abnormal multi-joint coordination in the arms of seated PD patients commented on the extent to which PD patients have problems with integrating proprioceptive information with motor control [25]. This had also been noted by Purdon Martin [23] and by us [26,27]. Horak and her group extended their studies to PI, and concluded on the importance of such information to PI [25].

The locomotor network interacts with a postural stability network that includes inputs from proprioceptors in the peripheral nerves, joints, and muscles as well as inputs from the vestibular nuclei and visual system. This network is not under dopaminergic control [28-31]. Lower extremity proprioceptive inputs are probably the most important input to the nervous system. These inputs interact with networks including the basal ganglia, the thalamus, the cerebellum and prefrontal peduncular nuclei [32]. A patient’s ability to compensate for the impaired postural stability is their ability to generate rapid, large-scale leg movements. When this is also impaired in PD, as manifested by the short step, patients who fall take [20] and by the development of FOG, the ultimate short step [33,34].

Falls, occurring early in the course of PD, when they are not part of an atypical Parkinson disorder, usually, but not always decrease with levodopa. We postulate PI associated with early falls consists of an impaired proprioceptive and/ or vestibular input and an impaired, or slowed, motor response. The impaired proprioceptive and/ or vestibular input is minor compared to the slowed motor response. Levodopa improves the motor response and this overcomes the impaired sensory inputs. Falls, occurring late in the course of PD, usually but not always decrease with levodopa. We postulate PI associated with late falls consists of an impaired sensory input and as lowered motor response. The impaired sensory input is major compared to the slowed motor response and cannot be overcome with levodopa.

AUTHOR CONTRIBUTIONS

A. Lieberman designed the studies, obtained the data, and wrote the manuscript. Both authors were involved in interpretation of the data, critical evaluation of the manuscript, and gave their final approval.
DISCLOSURES

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