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Review Article

Falling Risk on Parkinson Disease: From its Causes to its Treatments

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Abstract

Parkinson's disease (PD) is a clinical syndrome that consists on four main features and they are: resting tremor, rigidity, bradykinesia, and postural instability. However gait, postural and balance disturbances are extremely important to the disease, once that those symptoms predict the falling risk in a PD patient. This kind of clinical manifestation responds poorly to dopaminergic medication. The DBS capacity to improve the gait and balance still little known. Low frequency DBS of the PPN is probably the best surgical approach to control the gait disturbances. However the PPN is a technically very difficult target to locate. Cholinergic therapies, using a cholinesterase inhibitor showed benefits for frequently falling PD patients.

Keywords: *Parkinson; PPN; Falling; Risk and DBS*

Introduction

Parkinson's disease (PD) is a clinical syndrome that consists on four main features and they are: resting tremor, rigidity, bradykinesia, and postural instability. Despite not being considered as one of the most important symptoms at the presentation of the disease, the inability to initiate movements (akinesia) or sustain movements (clinically perceived as sudden freezes) is a valuable feature to be analyzed at the patient.

The motor manifestations, such as the postural control impairments, at the PD patients are a result of the loss of striatal dopamine, due to the degeneration of dopaminergic neurons at the substantia nigra pars compacta (Basal Ganglia), mainly. The severity of the parkinsonian symptoms is directly connected to the loss level of dopaminergic neurons; bradykinesia is the most easily noticed. The progression of the disease varies a lot among PD patients [1,2]. Patients with PD that start the clinical manifestations with tremor-like symptoms, tend to present a slower progress than patients that onset with postural instability and gait disturbances (PIGD). So the akinesia and movement sustentation are important even to predict the PD prognosis and evolution.

Methods

We performed a literature review using PUBMED. We used Parkinson, PPN, Falling, Risk and DBS as our key words. The search was limited to the studies published in English, from 2001 to 2018. We raised a total of 60 articles, but only 20 had the data that interested

us. We observed the factors that were involved in the falling risk in PD patients. The articles used to evaluate the motor condition of the patient the UPDRS scale. The cognition were assessed by the MMSE, PDQ and by others specific tasks, like the ability to talk and walk. The disease evolution were measured by the Hoehn and Yahr scale. Due to retrospective design of this literature review, we did not apply for ethics committee approval.

Fall – An important concern on PD patients

The locomotion at the PD patients, presents some particular patterns, such as a slow gait and reduced angular excursion of joints. Stooped posture, short steps, and shuffling, mark the progression of the disease. Due to this gait and posture instability the falling risk is high on PD patients [1,3]. Most of the falls in PD occur during routine activities, such as walking, stopping, turning, and standing up or bending down. Fall risk in PD is a marker to the disease severity, because its consequences can be a catastrophe to PD patients. The falls lead to higher risks of mortality and morbidity in PD patients. Femoral neck fracture is one of the worst complications of the fall in those patients [1,4].

The patients that present important parkinsonian symptoms, but still able to walk with no huge difficulties, presents the higher fall risk (Hoehn and Yahr stage 3). The onset of postural instability remarks an increased risk for severe disability to those patients [1,2]. Around 40% of PD patients presenting postural instability suffers multiple falls, what can lead to serious repercussions. The resistance to dopaminergic treatment is responsible for most of the falls related to postural control and gait impairments [1,2,5]. The gait present some parameters that are usually improved with the dopaminergic treatment, such as including stride length, gait velocity, and movement amplitudes, the "kinematics data" about the gait. Temporal, kinetic and structure parameters related to the gait, like the cadence, swing and stance duration are often treatment resistant [1,2,5].

There are some scales that aims to evaluate the gait and balance disturbance, such as the Berg Balance Scale, the Tinetti Gait and Balance assessment, the Timed up and Go test and the postural instability and gait disability (PIGD). The problem with this scales is the low sensitivity and specificity to identifies the risk of falling for PD patients, specially when the patient presents mild to moderate disease severity, once that these scales considers few items and only related to specific motor impairment, what is not an exclusive condition of PD [6]. Therefore the construction of a score aiming to predict the falling risk for PD patients, based on factors that most affects these cohort should be a concern in the present moment.

Wearable sensors have been emerging as a way to assess the standing balance or walking in PD patients [3,6,7]. It has been showing good results at these features analysis, being particularly efficient for acceleration-based measures calculated while using the device [3,6].

Hubble., *et al*. [6] reported after realizing a systematic review that outcomes derived from these wearable sensors are effective in the differentiation of standing balance between patients at high risk of developing PD, PD patients and controls. Besides that the device is able to recognize a less rhythmic walking patterns for fallers PD patients when compared to non-fallers [6].

Weiss., *et al.* [3] also reported great results in the patient classification based on the sensors results. Their most valuable founds were that fallers and non-fallers PD patients presented different measures between them. Besides that the Wearable sensors are able predict when the first fall will happen among the cohort who reported no falls in the year before the baseline testing, whereas traditional measures and scales are not able [3]. So probably the device can be used to classify PD patients falling risk [3,6].

The characterization of the PD patients is very important once that the PD can present various clinical manifestations. The faller patient is different from the non-faller. Wood., *et al.* [4] analyzed 101 patients with PD and divided them according to their fall records, and falling occurred in 68,3% of the cohort. The fallers presented a longer disease duration, corroborating that falling-related symptoms mark a higher grade of destruction of nucleus related to movement, showing a higher disease severity [1,2,4,8,9]. Fallers presented worst presentation of general motor functions when compared to non-fallers, verified by higher UPDRS scores. Cognition was also more impaired

on fallers [2,4] verified by mini-mental state examination (MMSE), PDQ-8, short form Parkinson's disease questionnaire and geriatric depression scale-short form. There are some data that were highlighted as the most important to predict the falling risk to Wood., *et al.* [4] and they were falling in the previous year, loss of at least one arm swing, dementia [4,10] and longer disease duration [4].

After analyzing 63 PD patients Ashburn., *et al.* [8] reported that 64% of them presented a fall episode in the last year. They also identified that fallers took more steps to complete a mobility test. They also presented a worse equilibrium while completing a multi-task exercise than non-fallers.

Kotagal [2] reported that older individuals diagnosed with PD are prone to have much more axial motor disturbances, what increase the fall risk.

Gait – Anatomical and Physiological Disturbances in PD

Supraspinal locomotion centers in the brainstem, cerebellum, and forebrain have to be working appropriately to organize the spinal stimulus, to generate a correct gait. The most important regions to create the gait and balance are the cerebellar locomotor region, the mesencephalic locomotor region (MLR), composed by the cuneiform nucleus and the pedunculopontine nucleus (PPN) and the subthalamic locomotor region. However these zones cannot modulate and create all gait related-stimulus, the basal ganglia, represented by the striatum, pallidum, subthalamic nucleus, and substantia nigra, are involved in many different circuits. One of the most important functions of the basal ganglia is the learning and selection of the appropriate motor manifestation for each circumstance, such as the automatic selection of postural reactions due to a motor and/or sensory perturbations; regulation of muscle tone and integration of cognitive factors on balance and gait, like attention and multi-tasking. Other important function related with dopaminergic circuits is the establishment, selection, and sequencing of routine patterns of movements and positions. Both functions quoted are extremely important to the gait and posture [1,5].

PD affects all the gait process, like the initiation, braking, and turning. This action requires the execution of coordinated movements, to maintain the equilibrium and achieve the desired action. The impairment of the basal ganglia function, due to degeneration of dopaminergic neurons, leads PD patients to present a deficit in the gait process, resulting in freezing of gait, postural instability, and falls. So stopping and turning, particularly when in confined spaces are challenges to PD patients. The freezing of gait is usually manifested as an abrupt cessation of leg movement during walking, resulting in an elevated fall risk [1,9].

The loss of dopamine in PD patients starts mainly in the posterior putamen. Over time this lost evolves to the caudate nucleus, which is involved at the striatocortical circuit playing an important role in cognitive functions. Striatofrontal pathways work to compensate the control of the gait in patients presenting PD. However the manifestation of freezing of gait in patients with PD suggests a failure of the compensatory striatofrontal pathway functions. Gait in PD during a freezing episode can be improved by sensorial remarks, what shows the impairment of the dopamine pathways on the basal ganglia, that plays an important role on the maintenance of the gait according to the environment changes [1,9].

Cognition and Gait

The cognitive function is related to gait disturbances, because the cognition influences on secondary gait features, like the multi-tasking, represented as the capability to walk and talk simultaneously. Therefore PD patients that are not able to walk and talk presents higher risk for falling [1,8,11]. The difficulty can be verified once that PD patients that present freezing of gait present an increased number of steps to walk while performing a verbal fluency exercise. The data suggests that the multi-tasking causes impairment on gait functions, increasing the gait variability and makes the falling risk higher in PD patients [1,8]. This clinical manifestation gives the physiological evidence that a cortical dysfunction is in course [1,9]. Therefore not only the dopaminergic pathways are damaged, other circuits are also important to the pathogenesis of the PD.

Far Beyond Dopamine

The monoaminergic and cholinergic neurotransmitter circuits are probably impaired in the PD. The cholinergic pathways are probably affected because they are related to mobility functions, once that they are responsible for the attention in the cortex but they are also damaged in the PPN, a brainstem locomotor center, which is affected in PD and it's connected to subcortical, brainstem, spinal cord, basal ganglia and limbic regions what probably leads to impairment of initiation, acceleration, deceleration, and termination of gait. The PPN is formed by cholinergic and non-cholinergic pathways. Therefore cholinergic neuron death is associated with a greater risk to fall in PD patients [1,5,12]. This is corroborated by Karachi., *et al.* [5] with the postmortem analysis of PD patients brain, that found a severe PPN cholinergic lesion in PD patients that presented symptoms like the occurrence of falls and freezing of gait, not improved by dopaminergic treatment. The cholinergic denervation is heterogeneous between PD patients, what leads to the differences in the clinical manifestations [1,5]. Therefore the treatment with a cholinesterase inhibitor should promote the relief of symptoms [1,9,13,14]. Chung., *et al.* [13] confirmed this hypothesis after administering donepezil for 6 weeks, they observed a decrease on the frequency of falls. PD patients on use of it suffered half of their usual falls, but only in patients that fall more than 2 times per week [1,13]. The most improved patients were those who presented highest rate of falls. The medication is expected to produce an improvement on attention and/or executive functions (cortical action) or improved PPN pathways function [1,13,14]. The medication is also secure for the parkinsonian symptoms, resulting in no extra deficit, verified by the UPDRS, after the drug administration [13,14].

Deep Brain Stimulation and Its Effects on Gait Disturbances

The Deep Brain Stimulation (DBS) is a surgical procedure accomplished in PD patients that are resistant to the pharmacological treatment. A stimulating electrode is implanted to generate impulses to specific brain areas. The region that responds better to the stimulus is the subthalamic nucleus (STN). The DBS improves a lot 3 of the main symptoms of PD (rest tremor, bradykinesia, and rigidity). However the gait appears to be unchanged after the procedure, but the patient feels better after it and usually starts to do activities that they were incapable to realize, so the fall risk immediately-after the procedure is actually higher than before it. The long-term result appears to depend on the site stimulated. The globus pallidus interna (GPi) and the STN lead to different evolutions on the gait. The stimulation of the GPi probably plays a role on the improvement of the gait, once that the gait shows no deterioration after 2 years, whereas the STN stimulation is related to a worsening on gait disturbances on the long term, maybe because the STN stimulation causes greater impairment on cognition functions, verified by a decrease in phonemic and semantic verbal fluency for example [1,9,15]. These results are possibly related to the dopaminergic medication dosage after the procedure that is usually lower in the STN Group. The stimulation of other areas like the PPN is being discussed, once this site plays an important role in gait dysfunctions in PD. A low frequency PPN-DBS has been showing controversial results in the improvement of the gait, once that the number of falls and freezing of gait are reduced [9,16,17-19] in some studies and presents no effects in others [15], specially when it comes to the gait parameters [15], Besides that the PPN is a technically very difficult target to locate [5].

Stefani., *et al.* [16] analyzed 6 PD patients that underwent bilateral implantation of DBS of the STN and PPN. They related positive outcomes in those patients related to gait and posture [16].

Huang., *et al.* [9] concluded that DBS of PPN with low frequencies proves effective for freezing of gait symptoms [17], one of the most important symptoms to predict the fall risk [9,17]. They highlighted that particularly those patients with a long disease course and poorly responsive to dopaminergic medication were benefited from the procedure [9].

Khan., *et al.* [18] after analyzing 4 PD patients that underwent a DBS of the STN and PPN, reported functional changes in motor areas that are associated with an improvement of PD symptoms. The improvement of UPDRS scores was greater when the DBS were on STN and PPN when compared to only STN stimulation. The stimulation of those centers lead to an improvement of the blood flow to the cortical and subcortical regions, mainly in the prefrontal areas [18], what probably plays an important role in the conservation of the residual

cognitive functions and pathways. The patients presented gait and postural improvements in a low frequency stimulation, whereas high or lower than 60 Hz voltages presented postural instability [18].

Goetz., *et al.* [19] analyzed 9 patients that underwent a DBS of the PPN. Among them 2 patients presented bad responses to the treatment, 1 mild responses and 6 good responses. The treatment of the freezing of gait was the goal and was greatly achieved in 66,6% of the cases presented [19]. However the group highlighted the importance of a precise anatomical localization of the MLR [19].

Yousif., *et al.* [20] studied 4 patients and reinforced the idea that PPN DBS improves postural control in PD patients by improving their sensorial functions. They found in those patients an improvement of the vestibular perceptual limits. Therefore The PPN DBS probably makes easier to generate a postural sway, what will lead to a better control of the gait, posture and balance. That is probably due to an enhanced somatosensorial signalization. Their patients presented a concomitantly stimulation of the STN suggesting a synergistic action [20].

Discussion

The gait disturbance and postural instability marks the evolution of the PD for a severe disability and both increases the falling risk in PD patients [1,3]. Those patients that still able to walk present a greater risk to fall [1,2]. The postural instability, resistance to dopaminergic treatment are features that increases the falling risk on PD patients [1,2,5]. No existent score is able to predict the fall risk specifically in a PD cohort [6]. So the construction of a score aiming to predict the falling risk for PD patients, based on factors that most affects these cohort should be a concern in the present moment. As an alternative for the assessment of gait in PD patients to predict more precisely the fall risk the wearable sensors have been used in studies and is showing some encouraging results, once the gadget can differentiate the gait features of faller non-faller PD patients [3,6,7]. The faller patient presents some particular characteristics, such as a longer disease duration [4], higher UPDRS scores [4], falling in the previous year [4], loss of at least one arm swing [4], cognition impairment [4,10], more steps to complete a mobility test [8], worse equilibrium while completing a multi-task exercise (like walk and talk) [1,8,11], resistance to dopaminergic treatment [1,2,5], older aged [2] and freezing of gait [1,8,9].

Many sites in the central nervous system are extremely important to create and modulate the gait and posture, such as the MLR, basal ganglia, spinal cord, motor cortex, sensorial cortex and the prefrontal cortical and subcortical areas. One of the most important functions of the basal ganglia is the learning and selection of the appropriate motor manifestation for each situation and integration of cognitive factors on balance and gait, like attention and multi-tasking [1,5]. The degeneration of dopaminergic neurons leads to an impairment execution of coordinated movements and an impaired equilibrium maintenance. In PD dopamine pathways mainly those related to the basal ganglia are damaged, resulting in characteristics features like the freezing of gait [1,9].

The cognition functions are very important for the movement construction. An evidence of this is the importance of the multi-tasking when one of the actions is walk. Therefore the evaluation of the patient's capacity to walk and talk is an important risk predictor to fall episodes [1,8,11].

Not only the dopaminergic pathways are impaired in PD, there are others important circuits involved, particularly in the generation of symptoms related to the gait and posture disturbance. One important structure to the axial and cognitive PD manifestations is the PPN, that is composed by cholinergic and non-cholinergic pathways. However the cholinergic dysfunction generates symptoms related to the fall risk [1,5,12]. Based on this analysis the treatment with cholinesterase inhibitors is showing great results, leading to an diminished falls frequency [1,9,13,14].

The Deep Brain Stimulation (DBS) is a surgical procedure accomplished in PD patients that are resistant to the pharmacological treatment [1,9,15]. The faller patients are usually resistance to dopaminergic medication, so the procedures outcomes should aim the

improvement of gait, postural and balance disorders [1,2,5]. The STN is the target most of the times, because the DBS-STN promotes an improvement of the classic of PD: rest tremor, bradykinesia, and rigidity. However the gait appears to be unchanged after the procedure but the patient feels better after it and usually starts to do activities that they were incapable to realize, so the fall risk immediately-after the procedure is actually higher than before it [1,9,15]. The stimulation of the PPN is being considered as the greatest chance to improve gait disturbances, once this site plays an important role in gait dysfunctions in PD. A low frequency PPN-DBS stimulation has been showing great results in the improvement of the gait in most of the articles, once that the number of falls and freezing of gait are reduced [9,16,17,18,19]. However some studies presents no effects after the procedure [15], specially when it comes to the gait parameters [15], maybe because the PPN is a technically very difficult target to locate [5].

The literature still lacks information about this theme. More studies are requested mainly to determine the effects of PPN-DBS and the outcome of cholinesterase inhibitors usage.

Conclusion

Gait disorders and postural instability are important symptoms of the PD and are markers for bad prognosis and evolution for the disease. There are some scales that aims to evaluate these features, but considers few items and only related to specific motor impairment, what is not an exclusive condition of PD. Therefore the construction of a score aiming to predict the falling risk for PD patients, based on factors that most affects these cohort should be a concern in the present moment. Wearable sensors have been emerging as a way to assess the standing balance or walking in PD patients. The device can be used to classify PD patients falling risk. Therefore these sensors may become an important method to analyze the fall risk in PD patients. This kind of clinical manifestation responds poorly to dopaminergic medication. The pathogenesis involved in the generation of the gait and balance impairments in PD are probably due to degeneration in various pathways in different location. The degeneration on dopaminergic, cholinergic and noradrenergic pathways are important for the symptoms onset and nucleus in the cortex, brainstem, spinal cord and basal ganglia are important to generate the movement. The PPN is a special site for the integration of the information coming from various sites to generate the gait. This manifestations leads to a higher fall risk for the PD patients. The DBS in PD patients showed great results for the control of motor symptoms. However its capacity to improve the gait and balance still reduced, specially when the stimulation is focused to the GPi and STN. Low frequency DBS of the PPN is probably the best surgical approach to control the gait disturbances. However the PPN is a technically very difficult target to locate. Cholinergic therapies, using a cholinesterase inhibitor showed benefits for frequently falling PD patients.

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