The Pain of Parkinson's Disease

Introduction

As Grandma listened to the rhythm she lifted her trembling hands and smiled. Since being diagnosed with Parkinson's Disease (PD) this previously energetic lady had slowed quite a bit, but as my violin played, even the doctors commented on its positive effects. Just as it was described in Oliver Sacks' book *Musicophilia, the* music was helping her "dance out of the frame of sickness[1]."

It had been six years since she was first diagnosed with PD, a chronic and progressive neurodegenerative disorder attributed to the gradual loss of striatal dopaminergic neurons in the substantia nigra and the ventral tegmental area of her brain. Her neurologist had described how she was in a high-risk age group and that PD is especially pronounced in adults like her over the age of 65. He also explained in detail that it had developed through the depleted production of dopamine, an amine that is part of the catecholamine and phenethylamine chemical families. At the outset of her diagnosis our family was overcome by a sense of despair, but eager for more knowledge, we quickly discovered that PD is becoming more common in the elder population, and is the second most common neurodegenerative disorder after Alzheimer's with 7 to 10 million people worldwide having been diagnosed with the disease[2]. Unfortunately, there currently is no cure, and the incidence is expected to increase dramatically as the world's population continues to age[3]. Grandmother had the classic motor symptoms: a 4-Hz to 6-Hz resting tremor, cog-wheel rigidity and bradykinesia, as well as several non-motor symptoms like nausea, constipation, insomnia, and depression[4].

Increasingly however, it was the pain, a lesser-known non-motor symptom of PD, that was having the greatest negative impact on her quality-of-life, and as one of her caregivers, I felt absolutely helpless one day when in her sweet trembling voice, she asked "what is causing my pain, and how do I manage it?" Her questions were not surprising as Grandma would often tell us that it was through knowledge that we find better solutions. While her doctors did their best to help her, as a medical student I also felt compelled to better understanding everything I could about her PD pain. So, with the objective of helping her, and thousands of people like Grandma, I embarked on writing about the nature of PD pain, the various types of pain, the pathophysiology, and the most common treatment methods currently available.

The Pain of PD

While most people with PD experience motor symptoms that result in stiffness, slowness of movement and poor mobility, during my investigation I also discovered that chronic pain is a leading non-motor symptom that is experienced by 60 percent of people with PD[5]. I witnessed through my daily interaction with my grandma how her pain became a catalyst for other quality-of-life issues including sleep disturbance, malnutrition, social withdrawal, physical and cognitive decline, depression, and impaired cognition. Her PD became maladaptive, widely impairing her outlook to everyday experiences and future expectations. Surprisingly, because of the close association with many other medical conditions, it is estimated that PD pain remains misunderstood and undeclared in 41 percent of patients[6]. Sadly, it is well down the list of treated symptoms. In the same vein, while there is extensive research confirming

that the origins of PD are related to oxidative stress and the formation of free radicals, the pathophysiology of PD pain is still not clear. The body of knowledge is limited, and even recent practice standards by the American Academy of Neurology fail to mention treatment guidelines for PD pain[7,8]. What is clear is that in its early stages, PD pain is rated as the most troublesome non-motor symptoms, and will often become pronounced by first affecting the side of the body that was initially afflicted by motor symptoms[9].

Types of PD Pain

Pain can be defined as an unpleasant sensory and emotional experience that is associated with actual or potential tissue damage. This is compounded further in older people with PD pain, as the symptoms become more severe as a result of age, severity, duration of the disease, and complications from other age-related ailments. For example, pain contributors could also be rooted in pre-existing co-morbid conditions such as osteoarthritis, postherpetic neuralgia, and peripheral neuropathy. To provide Grandma with a better understanding of her pain, I decided it would be useful to use an etiological classification, which also provides a useful framework for treatment[10,11]. On this basis, there are five different types of PD pain that can appear in isolation or concurrently at any time during the disease, and can also be present before diagnosis: (1) Musculoskeletal pain describes the most common pain that arises from muscular, joint, and postural etiologies. It is typically caused by rigidity and decreased movement, and can be compounded further if arthritis is also present. This pain, affects 45 to 75 percent of PD patients, and typically appears in the neck, arm, paraspinal and calf muscles. Joints also inflicted occurred most frequently in the shoulder, hip, knee, and ankles. In clinical studies, from a patient's perspective, musculocutaneous pain was complained about the most by both early and advanced PD patients, and early pain sensations reflected the structural changes that are taking place in the lower brainstem nuclei and peripheral nervous system, including the autonomic and enteric ganglia[12]. Like many other symptoms of PD, pain can be present for many years before the disease is ever properly diagnosed. (2) A second type of PD pain is dystonic pain, which is also common and occurs as dystonic spasms that are usually paroxysmal or triggered by movement or activity. This pain, affecting 8 to 50 percent of PD patients, involves frequent co-contraction of muscles and is described by patients as a pattern of two muscles fighting against each other. It can be spontaneous or triggered by specific movements, and is often observed in the extremities, the face, and the pharyngeal muscles. This pain can be very intense during medication deficiency, typically in the early mornings, but the intensity decreases after medication[13]. (3) Radicular-neuropathic pain is another type that manifests in the form of numbness or weakness due to nerve root lesion, but is also experienced as a sharp or tingly pain in 5 to 20 percent of PD patients. It may also be caused by postural abnormalities, dystonia developments, radiculopathy, or peripheral neuropathy that occurs during the disease[14]. (4) Central pain or primary pain is the least prevalent pain type and is typically insistent and disease specific. Often described as a vague pain, it manifests as neuropathic sensory events such as paresthesia or shooting pain, and patients usually experience it as a vague sensation on the side most affected by PD[15]. (5) While Grandma often complained about her musculoskeletal and dystonic pain, she also experienced akathitic

discomfort. Akathisia is the last type of pain and is often described as a restlessness. While some patients describe it as uncomfortable, others experience it as more of a painful impulse to move continuously. As PD develops, all pain types can be experienced simultaneously, however, it has also been observed that male and female patients do not complain of pain in the same locations, as women reported higher prevalence of neck and low back pain than men[16]. Unfortunately, as PD progresses, the symptoms become more pronounced, yet it is surprising to learn that there is no specific validated scale that is widely used to accurately quantify the pain[17]. Two pain scales that have been randomly used are the Pain-O-Meter and the King's PD Pain Scale. The Pain-O-Meter is a self-administered general pain assessment method that uses a white plastic scoring tool with movable parts that allows patients to rate their own pain. On the other hand, the King's PD Pain Scale has been specifically designed for people with PD and involves the investigator asking the patient 14 questions that score both severity and frequency of pain over the course of 15 minutes.

The Pathophysiology of PD Pain

Although there has been considerable advancement in the understanding of the various types of PD pain, the root causes are still poorly understood. While classifying PD pain by etiology provided a valuable understanding for me and grandmother, I still needed to drill deeper to understand the origins of her pain. It appeared that the pain sensations resulted from an extremely complex and collaborative series of mechanisms at all levels of the neuroaxis, from the periphery to higher cerebral structures including the basal ganglia. It quickly became apparent to me that to properly examine the pain mechanisms experienced by patients with PD, two distinct types of pain were worthy of review, nociceptive and neuropathic.

Nociceptive pain is manifested in different parts of the body and relates to actual or potential tissue damage. It implicates the millions of pain receptors in the skin, bones or surrounding tissues that are sensitive to pressure and vibration, and presents itself as an aching, sharp, and throbbing sensation. Musculoskeletal and dystonic pain types are nociceptive in nature, and are typically well-localized to the affected body part. Nociceptors can be myelinated or unmyelinated, and this determines the type of stimuli they respond to. For instance, myelinated nociceptors respond to mechanical and thermal stimuli, while unmyelinated nociceptors respond to mechanical, thermal, or chemical stimulation. In contrast, neuropathic pain relates to an injury of sensory fibres or damage to the peripheral and especially the central nervous system[18]. It presents itself as a burning, tingling feeling or even a sharp, shooting sensation. Radicular pain and central PD pain are neuropathic in nature. While less common than nociceptive pain, radicular pain can also include conditions not directly related to PD, including cancer pain, diabetic neuropathy, peripheral neuropathy and shingles. Although data suggests against currently accepted criteria for defining neuropathic pain given that the diagnosis requires a sensory deficit, many investigators support that this type of pain ascends directly from a dysfunction of the basal ganglia that alters sensory processing of nociceptive inputs[19]. In some cases, mixed pain syndrome can involve both nociceptive and neuropathic pain types.

Pathophysiologically, in both nociceptive and neuropathic pain, the dorsal horn within the spinal cord receive the stimuli from primary afferent fibres (PAFs), which are specialized free nerve endings connected to different types of receptors in the skin, muscles and internal organs. They provide direct input signals to the substantia gelatinosa, a collection of gelatinous neuroglia that performs a major role in the modulation of pain at the spinal cord[18]. There are three main types of PAFs classified based on their diameter, structure, and conduction velocity. From thin to thick, they are C, Að, Aß fibres, and each are responsible for conveying different pain sensations. For example, the C fibres are unmyelinated and conduct slowly and because of their slow impulse transmission they are responsible for sensing aching and burning pain sensations. In contrast, Að fibres are myelinated and of intermediate velocity and help to sense a prickling and stabbing pain. Both C and Að fibres are responsible for transmitting nociceptive information and need to be recruited over a period of time for pain to be experienced[18]. In accordance with the Gate Control Theory, proposed by Ronald Melzack and Patrick Wall, a neural "gate" exists in the spinal cord which when open allows the pain signal to go through and when closed reduces the experience of pain. In other words, this gating mechanism is influenced by the activity of the C and Að PAFs, and modulates the incoming pain signals before they reach the brain. For instance, when there is an increase in the activity of the pain fibres, then the neural gate opens and there is more pain. Gate control is also controlled by the amount of activity in other peripheral fibres, mainly Aß PAFs. For example, if there is mild stimulation, then the neural gate closes and there is less pain. Psychological factors also play a role in gate control. Messages descending from the brain such as effects of anxiety or excitement can also influence the opening and closing of the neural gate. While the Gate Control Theory explains why pain can be interpreted differently by people with PD, it also explains why pain is sometimes not experienced immediately, and suggests that a person with PD has some control over the experience[20].

Although there is not a wide body of knowledge to explain the exact pathogenesis for each individual type of PD pain, there is a broad understanding of pain pathways. In general**,** pain stimuli are transferred to higher center brain neurons and processed through two different pain systems: the medial and lateral pain systems. The medial system is involved in the affective or cognitive dimension of pain, pain memory, and autonomic responses, and links the physical sensation of pain to an emotional response and to memory. It is mainly constituted by the paleospinothalamic, spinomesenchephalic, spinoreticular, spinoparabrachial hypothalamic, and spinothalamic tract fibres. These fibres terminate in the parabrachial nucleus, locus caeruleus, peri-aqueductal gray substance, intra-laminar and medial thalamic nuclei, thalamic ventral caudal parvocellular nucleus and ventral caudal portae and the hippocampus. The lateral system involves the sensory-discriminative component of pain, providing information about pain location and duration, and is formed by the neospinothalamic, neotrigeminothalamic, the cervical bundle, and the beam of the dorsal horn. These fibres end in the lateral thalamus, primary and secondary somatosensory areas, parietal operculum, and the insula.

Serotonergic, noradrenergic, and dopaminergic descending networks originating in the brain stem are also important in the incorporation and variation of nociceptive information in the dorsal horn[21].

Nociceptive information reaches the basal ganglia through multiple pathways, including the sensory areas of the cortex, the amygdalae, and the cingulate cortex[22]. The basal ganglia is a converging point for PAF's in the organization of behavioral responses to stimuli[23,24]. Substantia nigra efferent pathways connect the amygdala, pre-frontal cortex and cingulate cortex areas involved in the motivational-affective pain dimension, while inflow from cortical and subcortical brain regions contributes to the network between the thalamus, cortex, and basal ganglia[25,26]. The two main dopaminergic pathways are also well recognized. The nigrostriatal dopamine system projects from the substantia nigra to dorsal striatal structures in the corpus striatum. This route has an established function in terms of sensorimotor integration and control. Subcortical structures, such as the amygdala, thalamus, and nucleus accumbens, are reached by neurons with an origin in the ventral tegmental area. Distinct projections from the ventral tegmental area also innervate specific cortical regions, such as the motor and prefrontal cortices. There have also been neuroimaging studies in humans that show pain modulation involves striatal dopamine D2 receptors[27].

The substantial overlap between the dopaminergic system and the basal ganglia suggests that PD related pain could be rooted in the dysfunction of the basal ganglia, the dopaminergic neurons themselves, the sensory pathways within the basal ganglia, and the thalamocortical-basal ganglia circuits. Evidence for this is the incidence of musculoskeletal pain, the relief patients feel after Levedopa therapy, and the increased pain threshold observed when the medication concentration is highest[28]. In addition, central pain is usually associated with lesions in the thalamus, and the intralaminar nuclei of this region of the brain. Both have major inputs on the basal ganglia. Interestingly, patients with several pain syndromes have abnormalities in brain dopamine metabolism[29]. For example, the burning mouth syndrome and facial pain syndrome are associated with low levels of homovanillic acid, a metabolite of dopamine, in the cerebrospinal fluid and deficient dopaminergic inhibition[30]. PET scan studies in patients with burning mouth syndrome, which sometimes co-exists with PD, revealed decreased uptake of 6-flurodopa in the putamen and higher D1 and D2 receptor binding in the striatum. The alleviation of the pain and dysesthesia on treatment with chronic pallidal deep brain stimulation in patients with PD of 70 to 90 percent also supports the interaction of the basal ganglia and pain system[31]. Furthermore, a study by Zambito and colleagues is especially revealing. Using electrical stimulation, they assessed tactile threshold, pain threshold, and pain tolerance in 106 PD patients, 66 of whom had chronic pain. They found that pain threshold and pain tolerance were significantly lower in PD patients than in control subjects, whereas tactile threshold values were comparable in both groups[32]. Surprisingly pain threshold and pain tolerance tend to lower as PD progresses, thus suggesting that as basal ganglia dysfunction worsens, nociceptive system involvement increases.

Treating PD Pain

While my attempts to understand the pathophysiology of pain were fascinating, it was stil too intricate for discussion with Grandma. Talking with her about the various treatment strategies available to manage her pain would have a greater positive impact on her health. During this process, I discovered that the early identification of pain symptoms is very important since a quick treatment regimen influences the disease course and improves the long-term outcomes. Although the pain symptoms of PD are under-recognized, under-reported, and detrimental to quality of life they are manageable once the pain type is clearly identified by the healthcare provider. Although there is no cure or treatment that reverses the gradual loss of dopaminergic neurons which causes PD, there are various physical and psychological methods to manage the pain towards improving the patient's overall quality-of-life[33]. Physical management methods are most commonly used and include both pharmacological and non-pharmacological treatments. Most pharmacological treatments are tailored to the pain type and are focused on reducing the severity of common motor symptoms. This is accomplished by replenishing dopamine with synthetically produced dopaminergic medications such as Levodopa, an aromatic amino acid, which is converted enzymatically to the neurotransmitter dopamine by a declining population of neurons in the substantia nigra. Because of the relationship between dopamine levels and pain intensity, dosage optimization is very important as levodopa can significantly alleviate a patient's symptoms and perception of pain. PD patients whose medication is at peak effectiveness are said to be in the "ON" Levodopa state, and during this time they generally report less pain than those in the "OFF" state. However, this is also dependent on timing and the progression of the disease. As illustrated in Figure 1, early PD patients generally respond well to their medication, feeling a smooth lasting response from the continuous level of dopamine without distinct "ON" and "OFF" periods throughout the day. In contrast, advanced PD patients experience motor fluctuations, which slowly emerge after 3 to 5 years of chronic Levodopa therapy. As shown in Figure 2, as the disease progresses it also takes longer for medications to take effect resulting in a different and often less effective experience for advanced PD patients[34]. There are longer "OFF" periods throughout the day, and once the dopamine level peaks, the "ON" state is heightened. This condition sometimes results in dyskinesia and dystonia[35].

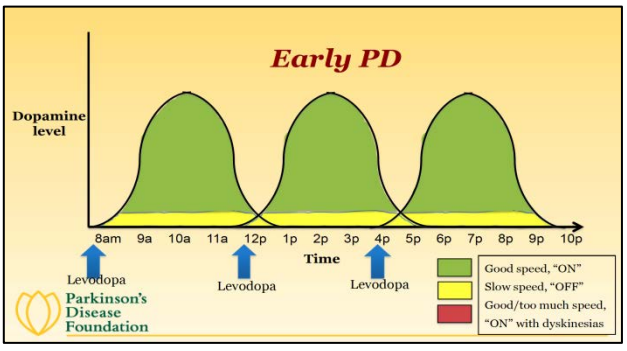

Figure 1 – Levodopa State in Early PD Patients

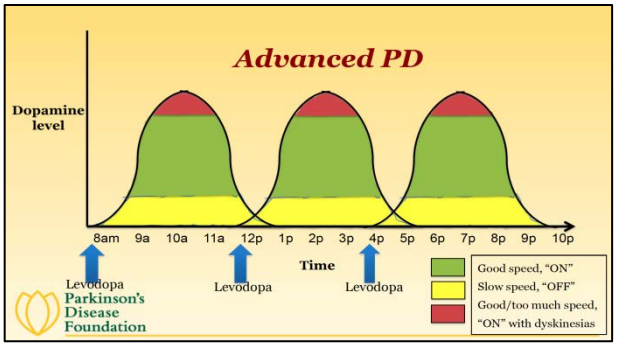

Figure 2 – Levodopa State in Advanced PD Patients

As the pain profile of each PD patient is unique, treatments are individualized and often require multiple strategies supported by the skills of a multidisciplinary team. Exercise and physical therapy are beneficial for maintaining range of motion, mobility, and preventing contractures, and when used in combination with dopaminergic therapy and other

medications, provide an effective treatment program to treat common musculoskeletal and dystonic pains. Dystonic, central pain, and even akathisia can be alleviated by optimizing the dopaminergic therapy dose and the frequency of doses to reduce dopamine pulsatility. The use of medications such as catechol-O-methyl transferase (COMT) inhibitors and monoamine oxidase B (MAOB) inhibitors like Entacapone and Rasagiline can also be used to extend the duration and effectiveness of dopaminergics[34]. Care should be exercised as certain dopaminergic therapy levels may cause the onset of dyskinesia. Other medications that have been found to be effective for dystonic pain are anticholinergics, and muscle relaxants such as Baclofen, and Amantadine for peak-dose dyskinesias[14].

Radicular-neuropathic pain, which is often caused by postural abnormalities and dystonia, may be amenable to an optimized dopaminergic therapy, and especially physical therapy and occupational therapy. Fortunately, postural anomalies often are not permanent. Low-dose tricyclic antidepressants like nortriptyline and selective serotonin-norepinephrine reuptake inhibitors like duloxetine can also be used to treat neuropathic pain. Antiepileptics like Gabapentin or Pregabalin have also been found to be very effective with some patients[34]. Rheumatologic or orthopedic issues can be addressed with nonsteroidal anti-inflammatory drugs such as ibuprofen or naproxen, or other analgesics. In severe cases, opioid analgesics like codeine and morphine can be used, but only after careful assessment of risks and benefits as they can cause confusion, lightheadedness, and nausea. In addition to exercise, patients can also benefit from other non-pharmacological treatments such as repetitive transcranial magnetic stimulation, and botulinum toxin injections for focal dystonia to treat striatal toes and dystonic fists. Deep brain stimulation of the sub-thalamic nucleus has been shown to improve dystonia and dystonic pain, and is commonly used to treat people with advanced phases of PD[36,37]. While central pain and associated paresthesia is more complex to treat, dopaminergic therapy is most often used to provide continuous stimulation.

Further complimentary therapies to treat PD include psychological methods that help patients change their behavior towards their PD-related pain. These include music therapy, biofeedback, relaxation and distraction, cognitive methods, behavior therapy, and hypnosis. Grandma especially liked listening to classical violin tunes as this genre invoked a strong emotional response and would make her want to dance. Remarkably when others also moved in-sync to the music, it seemed to create a sense of safety and social belonging that helped to reduce her anxiety. While music therapy can promote relaxation, biofeedback sessions can also encourage different thoughts and behaviors to better cope and influence physiological responses. It's quite magical how, over time, patients learn how to selectively let go of tension by changing their behavior[38]. Another alternative pain treatment could involve the use of medical marijuana. While current research suggests that cannabinoids are probably ineffective for both levodopa-induced dyskinesias and motor symptoms, further rigorous study of different dose formulations and target symptoms may reveal specific benefits[39].

Outside of the immediate management of PD pain, a preemptive approach to averting PD and the associated pain symptoms could be the early use of neuroprotective antioxidants that can help to prevent oxidative stress and the formation of Lewey bodies. A particularly powerful enzymatic antioxidant produced by the body is superoxide dismutase, which acts to catalyze and facilitate the conversion of superoxide molecules into inert chemicals that do not harm the body. Ingesting dietary plants with high levels of polyphenols can augment the presence of these beneficial enzymes. Because of the multiple hydroxyl groups present, polyphenols are also effective scavengers of reactive oxygen species, and examples of plants with these prophylactic properties are legumes such as beans, various fruits such as berries and apples, vegetables such as spinach, tea, and red wine[40].

Conclusion

PD has rapidly become the second most common neurodegenerative disorder after Alzheimer's and is especially pronounced in adults over the age of 65. As the world's population continues to age, the incidence of PD, and the associated symptoms of pain, is expected to increase dramatically and will impact thousands of elders. While pain symptoms are often under-recognized and not treated properly, there is hope through the growing understanding of the five basic pain types, and their origins, which involve a complex interconnected series of mechanisms at all levels of the neuroaxis. There is also good knowledge on the corresponding treatment methods to manage the pain towards improving the patient's overall quality of life. To that end, early recognition of the type of pain disorder is valuable in order to select the most appropriate treatment strategy. For example, dystonic and central pain is best managed with an optimized dopaminergic therapy and physical therapy program, which greatly influences the disease course and improves the long-term outcomes. While there is an increasing understanding of the role played by the neuro-axis and in particular the basal ganglia networks, the exact mechanism of most PD related pain syndromes remains unclear, and additional research is still needed to more clearly define the exact pathophysiological mechanism behind each type of PD pain. A better understanding would allow the planning of more efficient pharmacological trials that, in-turn, could translate to key advances and significant quality-of-life improvements for people with PD. In addition, there remain basic and fundamental questions relating to the connection between gender, age, and pain, including how the efficacy of pain management medication changes as the disease progresses to more advanced stages. The disentanglement of these connections, and the underlying mechanisms and pathophysiology by pain type would ultimately lead to treatment advances and better long-term outcomes for millions of elders like my grandma.

Word Count: 4090

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