Effect of Phlebotomy on Motor UPDRS Score, Pain and Medication Dosage in a Patient with Parkinson's Disease and Hemochromatosis

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ABSTRACT

Parkinson's disease (PD) is a slowly progressive neurodegenerative disorder associated with loss of dopaminergic neurons in the substantia nigra, some theories regarding the causes of PD include: environmental factors, genetic factors and oxidative stress induced by iron, copper, lipids, and proteins. We present a 43-year-old man with a past medical history of hemochromatosis, hypothyroidism and Parkinson's disease with a modest improvement over a course of two years under maximum doses of parkinsonism medications. After the patient initiated phlebotomy to treat hemochromatosis, significant improvement was noted in movement, gait, pain as well as a decrease in Motor UPDRS score and medication dosage. Phlebotomy may reduce motor impairment, pain and decrease medication dosage in a patient with PD and hemochromatosis.

Key words: Parkinson's disease, hemochromatosis, phlebotomy, UPDRS.

INTRODUCTION

Parkinson's disease (PD) is a slowly progressive neurodegenerative disorder associated with loss of dopaminergic neurons in the substantia nigra. It begins at a mean age of 50-60. The cause of this cell impairment is still unknown, but some theories regarding the causes of PD include: environmental factors, MPTP, genetic factors, and oxidative stress induced by iron, copper, lipids and proteins.[1,2] Clinically, PD is characterized by resting tremor, muscular rigidity, bradykinesia, loss of postural reflexes, flexed posture, and freezing (motor blocks). A combination of these signs is used to clinically define definite, probable, and possible Parkinsonism.[3]

Although a variety of neurophysiologic and computer-based methods have been proposed to quantitate the severity of the various parkinsonian symptoms and signs, most studies rely on clinical rating scales like the UPDRS (Unified Parkinson's Disease Rating Scale). The UPDRS rating scale is used to follow the longitudinal course of Parkinson's disease. It is made up of four sections: mentation, behavior, and mood; activities of daily living; motor; and complications of therapy. The motor section, in which a lower score denotes less disability, particularly indicates the progression of a person's Parkinson's disease.[4]

Bradykinesia is manifested by slowness in activities of daily living and slow movement and reaction times. Other manifestations of bradykinesia include drooling due to failure to swallow saliva; monotonic and hypophonic dysarthria; loss of facial expression (hypomania); reduced arm swing when walking (loss of autonomic movement); and micrographia.[3,5,6] Resting tremor is most prominent in the distal part of an extremity and typically has a frequency between 4 and 6 Hz. In the hand, the tremor has been called a "pill-rolling tremor". In the head region, tremor is most prominent in the lips, chin and jaw. Rigidity, tested by passive flexing, extending, and rotating the body part, is manifested by increased resistance throughout the range of movement known as "cog wheeling rigidity". Loss of postural reflexes usually occurs in more advanced stages of disease, along with freezing of gait. While most descriptions of PD focus on motor manifestations, some nonmotor symptoms like anxiety, drenching sweats, slowness of thinking, fatigue, depression, dementia, and others have been found to be more disabling than motor.[7]

Case presentation

A 43-year-old man presents with complaints of pain and impaired mobility for the last 9 years. He has had a number of progressive neurological symptoms. His mobility has been impaired over the last year and he has progressed from using a cane to a wheelchair. He can stand up and walk independently but if he walks more than 30 or 40 feet his legs feel heavy, his gait is unstable and he drags his feet. He has pain in the back and neck most severely at night which interferes with his sleep. During the day, he experiences discomfort at the calves exacerbated by activity. He has poor coordination in the hands and fingers. Swelling occurs in the hands, fingers, forearms and occasionally the lower legs. He has failed treatment for pain with Duragestic patch, Oxycontin, Neurontin and Prednisone.

His past medical history includes Parkinson's disease, hemochromatosis and hypothyroidism. Current medications include: Synthroid, Ultracet and Lexapro. He has an allergy to morphine derivatives and a family history of stroke and

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aneurysm. On review of systems he admits to headache, focal weakness, numbness, speech change, gait change and back pain. On physical exam, vital signs are within normal limits. General appearance is normal except masked facies and bradykinesia are present with resting tremor in both hands.

On neurological exam, cranial nerves II to XII are grossly intact. Muscle strength is 5/5 in upper/lower extremities and there is increase tone in all four extremities (cogwheeling) but no spasticity or atrophy. Deep tendon reflexes are 2+ throughout with down going plantar responses. Sensory exam is intact to all modalities. Cerebellar exam shows intact finger-to-nose and heel-to-shin testing but severely decreased rapid alternating movement, mild retropulsion, and a moderate shuffling gait with decreased bilateral arm swing. He requires a walker to ambulate. Mental status exam is normal.

MRI of the brain was normal and there were no evidence of iron deposition within the brain and basal ganglia. Laboratory results were normal except for a total Iron: 193, Iron Saturation: 75%, Ferritin: 11. He was preliminarily diagnosed with idiopathic Parkinson's disease with Motor UPDRS score of 78 (range 0-108). We started treatment for Parkinson's disease, with the following medications: Carbidopa/Levodopa 25/100 mg 1 tab QID (100/400 mg total daily), Pramipexole 0.25 mg 1 tab TID (0.75mg total daily), Selegilline 5mg 1 tab BID (10mg total daily). In the follow up visit, little improvement of the symptoms was initially noted. We gradually increased dosages to the most efficacious and maximum tolerated during the subsequent two years to the following dosages with significant clinical improvement but residual disability due to motor symptoms: Carbidopa/Levodopa 25/100 mg 4 tabs QID (400/1600 mg total daily), Pramipexole 0.5 mg/ 0.25 mg/ 0.25 mg/ 0.25 mg QID (1.25mg total daily), Selegilline 5mg 1 tab BID (10mg total daily), Entacapone 200mg 1 tab QID (800mg total daily).

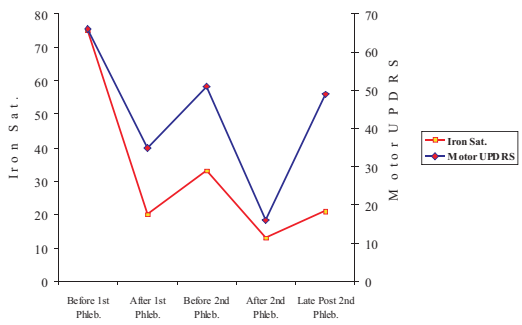
During the course of two years and treatment of PD with maximum medication dosage, we noted gradual worsening of his gait and pain. His hereditary hemochromatosis was being monitored but not treated by hematology during this time (i.e. no regular phlebotomy). In the second phase of our treatment, we decided to treat with a standard round of phlebotomy (removal of 600ml of blood x 2-3 with goal of ferritin < 10) per hematology to decrease his iron overload and evaluate the progression of his symptoms. Review of his labs and chart prior to phlebotomy showed: iron sat = 75%, ferritin = 12, and Motor UPDRS score = 66.

In the follow up visit 3 weeks after phlebotomy (iron sat = 20%, ferritin = 6), significant improvement was noted in the patient's mobility and pain. On-time and gait freezing improved, off-time symptoms decreased, movements were more fluid, and muscle pains decreased dramatically (pain intensity decreased from 10/10 to 3/10). Motor UPDRS score dropped to 35. These improvements were fairly rapid over the 3 weeks and associated with a change in tolerability of his medications but also improved function of the meds at lower doses. The patient self-titrated down on his meds due to both his new found motor improvement and a new inability to tolerate the higher doses he was on: Carbidopa/Levodopa 25/100 mg 2 tabs TID (150/600 mg total daily), Pramipexole 0.5 mg/0.25 mg/ 0.25 mg (1mg total daily), Selegilline 5mg 1 tab BID (10mg total daily), Entacapone 200mg 1 tab TID (600mg total daily).

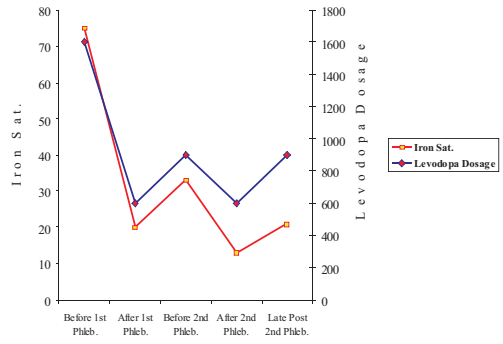
In the follow up visit after 4 months, as the ferritin increased to 16 and iron sat to 33%, the patient symptoms again worsened. He began having pain on back of the neck and felt of choking as well as contraction and pulling of his neck. Pain intensity increased to 7/10 and more freezing occurred but not as bad as before the first phlebotomy. The Motor UPDRS score increased to 51 so we decided to increase the dosage of levodopa to 900mg to compensate and we ordered a second phlebotomy. In the follow up visit 3 weeks after the second phlebotomy (iron sat = 13%, ferritin = 7), we again noted significant improvement in his gait and freezing. Pain completely resolved (0/10 in intensity), the Motor UPDRS score improved to 16, and we were able to decrease the levodopa to 600 mg again.

Three months after the second phlebotomy (i.e. late post 2nd phlebotomy on the graph) with iron sat = 21% and ferritin = 10, we noticed worsening of both the Motor UPDRS (49) and increased pain intensity (5/10) involving burning/cramping in the legs and back. We increased Levodopa to 900 mg to alleviate these symptoms with good effect.

Correlation between Iron Saturation and Motor UPDRS



Correlation between Iron Saturation and Levodopa Dosage



Discussion

Coexistence of Parkinson's disease and hereditary hemochromatosis is very rare. Some studies report that the presence of common variants in HFE gene (C282Y) which cause hereditary hemochromatosis may be a risk factor for PD as well. Dysregulation of the iron pool may participate in the degenerative process affecting dopaminergic neurons in PD. It means iron overload as well as deficiency can cause neurodegenerative disorders. A high intake of iron, especially in combination with high manganese intake, may be related to risk for PD. Iron acts to promote neurodegeneration via formation of oxidative stress.[8,9]

Intranigral iron injection into rats in some studies progressively reduce striatal dopamine metabolism and promote behavioral and biochemical Parkinsonism.[10,11] Higher iron levels especially in males may contribute to higher risk for younger-onset neurodegenerative diseases such as PD.[12] In 2000 Pierre hospital in France reported 3 patients with Hereditary Hemochromatosis. The first had disabling cerebellar syndrome, action tremor, and myoclonus. The second presented with cerebellar syndrome, head/arm tremor, and cervical dystonia. The third possessed disabling parkinsonian syndrome unresponsive to levodopa. Phlebotomy and symptomatic therapy in these patients did not change the course of their disease.[13]

In 2003, Florida State University reported that iron chelation may prevent the reduction in dopamine and motor disturbance associated with PD.[14] Other studies have shown in animal models that reduction in reactive iron by either genetic or pharmacological means results in protection against the toxin. This suggests that iron chelation may be an effective therapy for prevention and treatment of the PD.[15-18]

To the best of our knowledge, some studies have found a relationship between PD and hemochromatosis and they suggest chelation therapy for prevention and treatment. However, we did not find any specific report in effectiveness of phlebotomy in PD symptoms in patients with hemochromatosis. What we describe here is a patient with a rare case of PD with hereditary hemochromatosis. After the patient responded suboptimally to the maximum tolerated dose of medication and his pain and movement disturbance did not improve, we considered phlebotomy therapy as an additional option. Fortunately, after each phlebotomy the patient responded with dramatic improvements in his motor UPDRS score, gait, freezing, rigidity, and pain. His medication burden was also significantly lessened between phlebotomy sessions until his iron levels began to rise again at 3-4 months and additional medication was then needed. This study has found a correlation between iron saturation/ferritin and PD symptoms. Future studies could be considered examining the threshold for iron saturation and ferritin at which this patient's symptoms are exacerbated. Phlebotomy may reduce motor impairment, pain, and medication dosage in a patient with PD and hemochromatosis.

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