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Parkinson's Disease and Peripheral Neuropathy

Peter Podgorny and Cory Toth

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1. Introduction

Idiopathic Parkinson's disease (IPD), an age-dependent neurodegenerative disorder without known cause, is well known to manifest with rest tremor, rigidity, bradykinesia and gait instability on examination [1, 2]. However, other ancillary manifestations have become accepted over the years, including cognitive decline, depression, and autonomic dysfunction [3]. All of these clinically presenting features have long been known to result from disease within the central nervous system, where IPD is pathologically associated with degeneration of the substantia nigra [4].

The possibility of peripheral nervous system functional or pathological involvement in IPD has only recently been considered. One form of peripheral nervous system disease is a peripheral neuropathy, a distal-predominant process affecting the feet and legs, and in more severe cases, the hands and torso [5]. Peripheral neuropathy can manifest as a disease of the axons or the myelin, or both, within nerve fibers. In addition, sensory nerve fibers carrying information for touch, pain and temperature sensations (small nerve fibers termed Aδ and C fibers) as well as for vibration detection and proprioception (large nerve fibers termed Aα and Aβ fibers) can be selectively affected. In most cases, sensory dysfunction appears first, followed by further disease of large nerve fibers leading to loss of reflexes and the possible development of weakness. Symptoms of a peripheral neuropathy may include the early onset of numbness, tingling or prickling sensations, followed by the later onset of incoordination, weakness and pain [6]. The presence of such symptoms in patients should lead to a detailed neurological examination of the peripheral nervous system. Physical examination findings in a patient with peripheral neuropathy will often include abnormal responses to touch, pinprick, temperature, vibration and proprioception, as well as abnormal reflexes, weakness and ataxia. These features will typically display a stocking-glove pattern of distribution due to the distal predominance of peripheral neuropathy with the feet being implicated first.

Recently, an association of peripheral neuropathy with IPD has been demonstrated [7-10]. The importance of this finding has been the new appreciation of peripheral nervous system presentations in patients with IPD. However, for patients with IPD already suffering mobility issues [11], a concurrent peripheral neuropathy may contribute to immobility, risk of falling and autonomic dysfunction. In addition, a peripheral neuropathy may contribute to development of new symptoms including sensory phenomena, distal limb weakness, and pain. This chapter will examine the occurrence of peripheral neuropathy and IPD, its potential causes, progression, and its management.

2. Peripheral neuropathy

2.1. General assessment of peripheral neuropathy

Peripheral neuropathy, as compared with IPD, can be due to hundreds of different etiologies [12], and is associated with a variety of pathological changes within a peripheral nerve. The most common causes of peripheral neuropathy are metabolic or endocrine disorders such as with diabetes mellitus, uremia, or thyroid disease, infections such as with human immuno-deficiency virus or leprosy, toxic effects as with chemotherapy or alcohol excess, genetic disorders such as with Charcot-Marie-Tooth disease, amongst other causes. Another potentially underdiagnosed cause of peripheral neuropathy is a nutritional deficiency such as with insufficient vitamin B1, vitamin B6, vitamin B12, folate or thiamine [13, 14]. Many other causes of peripheral neuropathy occur, but between 40-50% of patients with peripheral neuropathy have no determined cause for their peripheral neuropathy, leading to its designation as an idiopathic peripheral neuropathy [15]. Typically, idiopathic peripheral neuropathy occurs in older patients and has a slow progression over many years, but its overall clinical presentation and course of progression is similar when compared with other forms of peripheral neuropathy. There are likely a number of causes of idiopathic peripheral neuropathy, many of which may be due to neurodegenerative conditions which have not yet been determined.

The diagnosis of peripheral neuropathy, unlike that of IPD, does not depend upon clinical criteria. Instead, the diagnosis can be supported by electrophysiological testing of peripheral nerves using nerve conduction studies and electromyography. Pathological investigations include nerve biopsy and skin biopsies for the identification of epidermal nerve fibers [16, 17]. Peripheral neuropathy will often develop from an asymptomatic (mild signs, no symptoms) or subclinical (no signs or symptoms) peripheral neuropathy [18] in which neurological changes have already begun but can only be detected electrophysiologically, pathologically or through quantitative sensory testing. Because peripheral nerves have some regenerative capacity, early recognition of the peripheral neuropathy could reduce morbidity. Although there is no gold standard diagnostic test for peripheral neuropathy, nerve conduction studies are considered a well established method of diagnosis, classification and quantification of peripheral neuropathy [19]. However, nerve conduction studies and electromyography cannot detect all forms of peripheral neuropathy, such as with a small fiber dominant neuropathy [20], where clinical assessment and skin biopsy findings may be abnormal. In other forms of

peripheral neuropathy, such as with remitted immune-mediated peripheral neuropathies, only electrophysiological testing may be abnormal. Therefore, the diagnosis of peripheral neuropathy is subject to the overall impression of the assessing neurologist. In order to assist the clinician, clinical scoring systems have been validated for the assessment of peripheral neuropathy, particularly with diabetic polyneuropathy. The Toronto Clinical Scoring System [21] and the Utah Early Neuropathy Scale [22] have been developed to assist with quantification of peripheral neuropathy, specifically for clinical trials. Overall, the clinician must examine a number of aspects when assessing for a peripheral neuropathy, including clinical presentation and examination findings, electrophysiological results, and pathological investigations. In some cases, a subclinical peripheral neuropathy may only be captured by a combination of physical examination, electrophysiology and pathological investigations.

2.2. Peripheral neuropathy in idiopathic Parkinson's disease

A number of non-motor features have been reported to occur in IPD (Table 1). These may range from cognitive dysfunction and neuropsychiatric presentations to dysautonomia and sleep disorders. Sensory manifestations, such as may occur with a peripheral neuropathy were first recognized in 1976 [23]. Nearly half of IPD patients were described to have sensory manifestations with normal clinical examination; less than 10% of these patients had sensory manifestations initiate before motor symptoms onset. Due to patient reports of sensory manifestations being more likely to be present when IPD patients were in an "off" medication state rather than in the "on" medication state, the possibility of sensory symptoms emanating from the central nervous system arose [24-26]. Furthermore, earlier electrophysiological studies for peripheral and central-peripheral sensory conduction failed to determine any abnormalities, leading to a belief that all sensory manifestations occurring in IPD patients occur without the involvement of the somatosensory pathways [27]. The possibility of sensory manifestations in IPD patients occurring due to an "off" medication state previously led to beliefs of a dopamine-mediated origin for all sensory phenomena in IPD patients. Furthermore, hypotheses had arisen regarding the dysfunction of the basal ganglia and pathways involving the striatum in particular [28]. Some older papers have reported sensory symptoms to occur in 40-70% of IPD patients, often consisting of pain, paresthesias, itching and burning sensations [29]; many of these symptoms are often unreported [30]. In particular, it was felt that pain was most often related to the presence of concurrent dystonia [31]. The beliefs that sensory features in IPD patients were only related to medication (dopamine) and the "off" state and/or abnormalities in the basal ganglia likely contributed to decades of a relative absence of studies to better determine the nature of sensory symptoms in IPD patients. However, work in the most recent years has re-examined the potential for peripheral nervous system involvement in patients with IPD.

Any consideraton for involvement of the peripheral nervous system in IPD patients must first begin with consideration of concurrent conditions in the same patient. The most well established estimation for the prevalence of peripheral neuropathy in the general population is 2.4% overall, but this may rise to as high as 8% in older populations, with diabetic and idiopathic forms being the most common cause [32]. Certainly, this high prevalence needs to be consid-

Cognitive dysfunction
Executive impairment
Inattention
Impaired visuomotor processing
Mild Cognitive Impairment
Dementia
Neuropsychiatric manifestations
Mood and anxiety disorders
Anhedonia and apathy
Psychosis and hallucinosis
Autonomic dysfunction
Arrhythmias and other cardiovascular manifestations
Orthostatic hypotension
Urinary urgency, incontinence or nocturia
Gastrointestinal manifestations including constipation
Thermoregulatory dysfunction including change in sweating function
Sleep disorders
REM behavioral disorder (RBD)
Periodic limb movements/restless legs syndrome
Excessive daytime somnolence
Insomnia
Sensory symptoms
Numbness, tingling, pain
Other
Fatigue
Dysphagia
Olfactory dysfunction
Visual disturbances including lack of accommodation
Seborrhoeic dermatitis

Table 1. Non-motor manifestations in Idiopathic Parkinson's Disease

ered in any population, particular an older population of IPD patients. The estimated preva-lance of IPD is 0.1-0.2% of the general population, but this also rises to 1% of those above 60 years of age [33]. Thus, a small percentage of the general population may have concurrent and unrelated Parkinsonism and peripheral neuropathy which may be estimated to be less than 0.01% of those above 60 years of age if based upon chance alone.

Genetic considerations have been considered as well for the concurrence of IPD and peripheral neuropathy. In one study of IPD patients with a parkin gene mutation, a genetic mutation related to younger onset of IPD, one out of 24 patients had a sensory and autonomic peripheral

neuropathy based upon nerve conduction studies and nerve biopsy [34]. Another single case report identified a patient with IPD and peripheral neuropathy using similar methods [35]. In both of these cases, the peripheral neuropathy appeared axonal in nature. The potential role of parkin is interesting, as parkin mRNA is present within human peripheral nerve [36]. In IPD patients with parkin mutations and presence of a sensory dominant axonal peripheral neuropathy [37], two fragments of the parkin gene product could be identified [36]. In addition, abnormal electrophysiological findings in patients with PARK2 mutations suggest there are pre-symptomatic neurodegenerative processes occuring in the periphery [38] and may be indicative of a sensory neuropathy [39].

Concurrent peripheral neuropathy may occur in conditions related to Parkinson's Disease, such as multiple system atrophy (MSA). Patients with MSA may have peripheral neuropathy present in as many as 40% of cases when the peripheral nervous system is specifically examined [40-42]. Another clue may be the co-occurrence of peripheral neuropathy and Parkinsonism in patients with mitochondrial disorders while Parkinsonism may be seen with mitochondrial disorders [43, 44]. However, these disorders have important differences from Parkinson's disease, including the presence of peripheral nervous system pathology. For example, patients with MSA have pathological changes within autonomic ganglia, where α-synuclein accumulation occurs within neurons of the sympathetic ganglia. Many forms of mitochondrial diseases have axonal atrophy and loss in the peripheral nerves along with concurrent development of ragged red fibers and myopathic changes. Finally, even patients with IPD can have presence of α-synuclein accumulation in sympathetic ganglia and in the enteric nervous system [45] as well as in some sensory nerves innervating the pharynx [46]. Despite this knowledge, there has been no literature reports investigating the prevalence of peripheral neuropathy within a large population of IPD patients until recently.

Our group began to identify patients with IPD and concurrent peripheral neuropathy beginning in 2002 [7]. Patients identified in a tertiary care Movement Disorders Clinic were assessed prospectively for presence of peripheral neuropathy and potential causative relationships. All patients with IPD and potential peripheral neuropathy were assessed for other potential causes of peripheral neuropathy and had documentation for other comorbid conditions, treatment for IPD, and the nature of peripheral neuropathy present. Each patient was assessed clinically with a Toronto Clinical Scoring System (TCSS) calculated for each patient and electrophysiological assessment using nerve conduction studies of the upper and lower limbs. Following assessment of routine blood work investigations obtained for determination for other related causes of peripheral neuropathy, patients were reassessed for causation of identified peripheral neuropathies. Studies included assessment of fasting methylmalonic acid, which is recommended for investigation of undetermined peripheral neuropathy [47].

Interestingly, and somewhat unexpectedly, we identified a total of 40 IPD patients with both clinical and electrophysiological evidence of a concurrent peripheral neuropathy [7]. Of these 40 patients, 30% had another etiology for peripheral neuropathy – diabetes mellitus was determined in 13% of patients, a monoclonal gammopathy of uncertain significance with possible relationship to peripheral neuropathy was determined in 10% of patients, and possible

or probable chronic inflammatory demyelinating peripheral neuropathy was discovered in 7% of patients. However, the remaining 70% of IPD patients had no defined cause for peripheral neuropathy, a much higher anticipated prevalence than would be anticipated in the general population (up to 40%). Clinical and electrophysiological abnormalities of peripheral neuropathy in the remaining population suggested an axonal form of peripheral neuropathy. In this remaining population, fasting methylmalonic acid elevation was seen in 93% of patients, considerably higher than in patients with IPD without peripheral neuropathy and than in patients without IPD with otherwise idiopathic peripheral neuropathy. The reasons for the elevated fasting methylmalonic acid were not immediately understood, nor the importance. The levels of cobalamin, or vitamin B12, were not significantly abnormal in the majority of patients; cobalamin deficiency is the most well reported cause of methylmalonic acid elevations. However, examination of the severity of peripheral neuropathy using the Toronto Clinical Scoring System revealed a strong positive association with lifetime consumption of levodopa, the mainstay of therapy for IPD. The daily levodopa equivalence dose, particularly when administered as an intestinal gel infusion, also appeared to correlate with neuropathic impairment [48]. Although this could be explained by longer duration and worse severity of illness in IPD patients with concurrent peripheral neuropathy, another relationship also emerged. Severity of peripheral neuropathy also correlated positively with the degree of elevation of fasting methylmalonic acid.

Although cobalamin deficiency is most classically associated with subacute combined degeneration manifesting as a myelopathy in combination with peripheral neuropathy, an exclusive presentation with peripheral neuropathy can also occur [49] as an axonal form of peripheral neuropathy [50]. Typically, cobalamin deficiency has been identified as a cause of peripheral neuropathy in 8% of patients with cryptogenic peripheral neuropathy [51]. Making the diagnosis of cobalamin deficiency-associated peripheral neuropathy can be problematic, since a significant proportion of up to 50% of cobalamin deficient patients will have normal serum cobalamin levels [13, 52]. However, measurement of the serum metabolite methylmalonic acid improves diagnostic specificity and sensitivity [53] and is now recommended [5].

A mainstay of PD therapy for several decades has been levodopa [54]. Although arguably the most effective long-term therapeutic option in IPD patients, several long-term complications have emerged from the use of long-term levodopa. These have included dyskinesias, dopamine dysregulation syndrome, addiction, impulse control disorders, punding, and compulsive medication use [55, 56, 57]. In addition to these adverse effects, levodopa's catabolism is associated with elevation of serum homocysteine and methylmalonic acid [58]. This occurs via levodopa exerting its influence upon methyltetrahydrofolate (methyl-THF) pathways during folate metabolism (Figure 1). One-carbon fragments are stepwise reduced to methyl groups in cobalamin-dependent reactions from methyl-THF to homocysteine, forming methionine. Adenosylation of methionine then follows, leading to S-adenosylmethionine (SAM) formation - this serves as the methyl group donor in several transmethylation reactions, some of which are catalyzed by catechol-O-methyltransferase (COMT). Whereas demethylation of SAM leads to formation of S-adenosylhomocysteine (SAH), this is immediately cleaved to form homocysteine. During these transmethylations, homocysteine may be remethylated by methyl-THF

and cobalamin to form methionine and SAM. Upon introduction of levodopa, the process of its methylation likely leads to the depletion of SAM and subsequently leads to elevated plasma homocysteine. Cobalamin is an essential cofactor in the conversion of homocysteine to methionine and SAM, and is likely depleted as SAM levels return to normal. Further downstream in the pathway, cobalamin serves as a cofactor for the isomerisation of succinyl-CoA; hence, a cobalamin deficiency may lead to methylmalonic acid accumulation [59]. Systemic aromatic L-amino acid decarboxylase inhibitors (such as carbidopa) given to IPD patients also direct the systemic metabolism of levodopa to occur through COMT to 3-O-methyldopa (3-OMD); this reaction also involves methylation by SAM, further contributing to increasing homocysteine and methylmalonic acid formation. The methylation potential within an individual can be measured by the SAM/SAH ratio and appeared to be an important factor for neurodegeneration, in one study [60]. The B complex vitamins including cobalamin are important in the control of one-carbon metabolism (Figure 1), it is possible for plasma concentrations of cobalamin to decline in IPD patients due to increasing methylation demands of daily levodopa consumption. As a result of these biochemical implications, it can be speculated that levodopa's interaction with these methylation pathways precipitates elevations in both homocysteine and methylmalonic acid in IPD patients.

It was previously shown that homocysteine was elevated amongst IPD patients when compared to control subjects [61-63], with greatest elevation noted in those with levodopa usage [64-66]. In IPD patients initiating levodopa therapy, homocysteine levels elevate and cobalamin levels fall at about 3 months after levodopa initiation. Similar elevations in homocysteine and depression in cobalamin occur in IPD patients who double their daily levodopa intake [67]. As well, IPD patients treated with levodopa for at least a year have significantly lower cobalamin levels than matched controls [68]. Although it could be speculated that the use of a COMT inhibitor could prevent these changes, this may or may not be the case [67, 69, 70]. Patients with IPD and concurrent homocysteine elevation may also be subject to a genetic alteration – approximately 1/3 of IPD patients with homocysteine elevation have a more inefficient (thermolabile) form of methylenetetrahydrofolate reductase (MTHFR), the key enzyme for the remethylation of homocysteine to methionine [71]. This may indicate that specific IPD patients are genetically susceptible to the development of homocysteine and methylmalonic acid elevation due to levodopa therapy. However, it is not known if IPD individuals are more susceptible to MTHFR polymorphisms, as they occur in healthy individuals as well [72]. This may also explain why only a proportion of patients we have studied with IPD and levodopa use were identified to have peripheral neuropathy.

The identification of a series of patients with IPD, levodopa usage, and elevations in homocysteine and methylmalonic acid led to a further prospective cohort investigation to attempt to identify if the association with IPD and peripheral neuropathy was more than chance [8]. We selected IPD patients randomly from a comprehensive database at a tertiary clinic and compared these patients to control subjects without IPD or levodopa usage. This study format was used to determine the relationship of levodopa use with serum levels of cobalamin, methylmalonic acid and homocysteine. We also explored the association between presence and severity of peripheral neuropathy and age, duration of IPD, cumulative levodopa dosing,
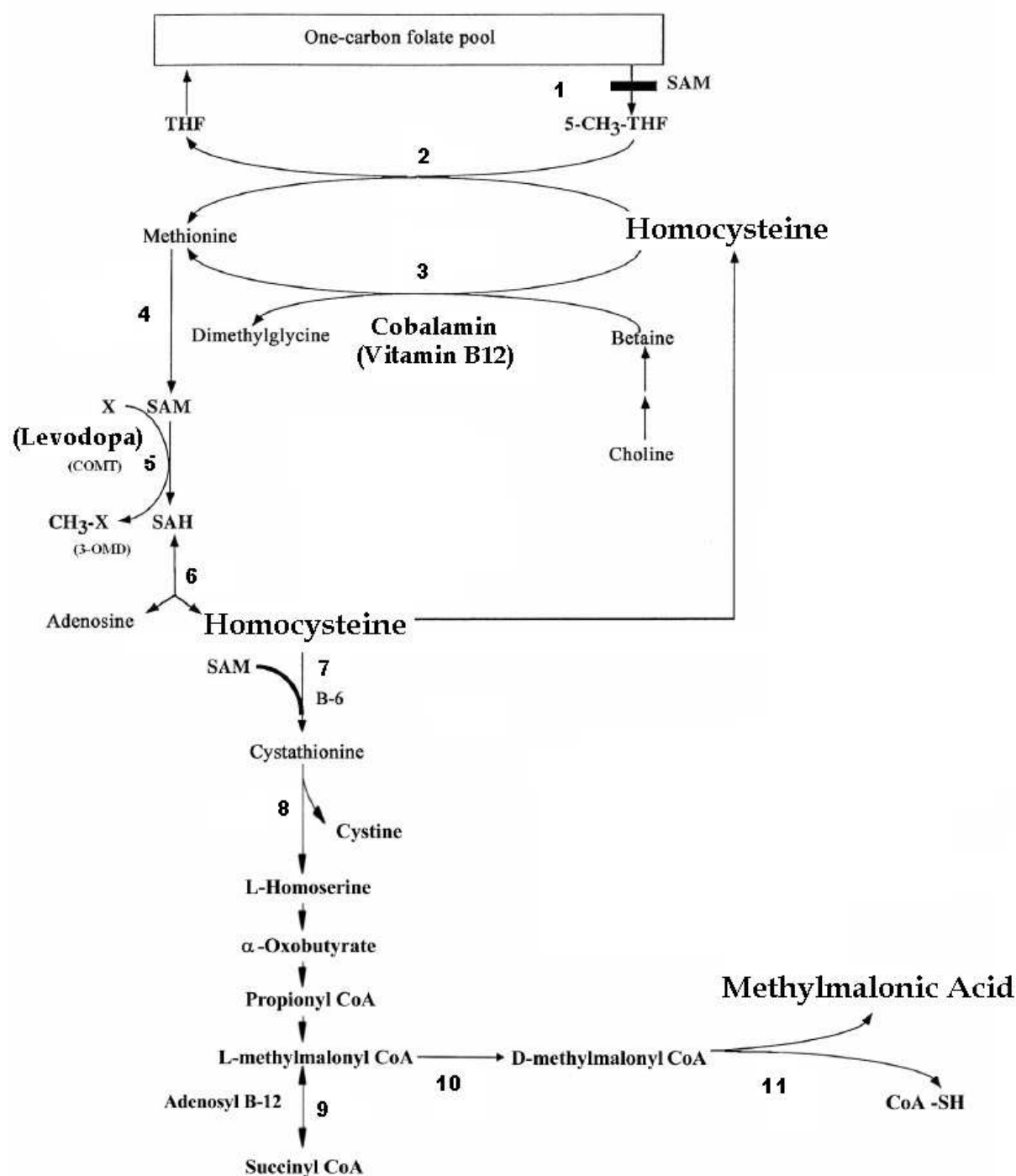
Figure 1. Folate and methyl group metabolism related to levodopa, methylmalonic acid and homocysteine. The numbers refer to the enzymes as listed: 1, methylenetetrahydrofolate (THF) reductase; 2, 5-methyltetrahydrofolate–homocysteine S-methyltransferase; 3, methionine synthase; 4, methionine adenosyltransferase; 5, a variety of methyltransferase reactions including catechol-O-methyltransferase (COMT); 6, adenosylhomocysteinase; 7, cystathionine-ß-synthase; 8, cystathionine lyase; 9, L-methylmalonyl CoA mutase; 10, D,L-methylmalonyl CoA racemase; 11, D-methylmalonyl CoA hydrolase. The heavy bar in reaction 1 denotes an allosteric inhibition by S-adenosylmethionine (SAM). The heavy arrow in reaction 7 denotes activation by SAM. SAH is S-adenosylhomocysteine. Note that levodopa acts in the methylation of SAH in enzymatic reaction 6, while cobalamin is an important factor in enzymatic reaction 3.

cobalamin, methylmalonic acid, and homocysteine levels. The majority (86%) of the 58 IPD patients assessed were taking levodopa at time of assessment. A blinded and unblinded Neurologist assessed the clinical and electrophysiological presentations for all patients and control subjects. A total of 58% of IPD patients assessed had clinical and electrophysiological features of peripheral neuropathy - 75% of these patients had symptomatic peripheral neuropathy, while 25% of these IPD patients had subclinical neuropathy. This was contrasted by only 9% of age- and sex-matched control subjects receiving a diagnosis of peripheral neuropathy.

Although the duration of IPD was similar between IPD patients with or without peripheral neuropathy, the severity of IPD, based upon the Unified Parkinson's Disease Rating Scale, was greater in IPD patients with peripheral neuropathy. This indicated that peripheral neuropathy was not likely to be present near the time of diagnosis of IPD, but appeared to occur later. Likewise, greater severities of disease would tend to indicate higher cumulative intakes of levodopa for disease management, which was the case for IPD patients with peripheral neuropathy. Interestingly, cobalamin levels were similar between IPD patients with and without peripheral neuropathy; however, both fasting homocysteine and methylmalonic acid levels were higher in those IPD patients with peripheral neuropathy than in IPD patients without peripheral neuropathy. An odds ratio of 12.4 emerged for levodopa exposure contributing to peripheral neuropathy. Cumulative levodopa exposure was significantly and positively associated with the severity of peripheral neuropathy using the Toronto Clinical Scoring System for all IPD patients studied. In addition, fasting methylmalonic acid levels were also positively associated with severity of peripheral neuropathy amongst all IPD patients. Finally, cumulative levodopa exposure was also directly associated with fasting methylmalonic acid levels in all IPD patients.

Although this may appear as though methylmalonic acid elevations are clearly responsible, it must be considered that a higher severity and longer duration of disease with IPD will lead to greater cumulative use of levodopa. Indeed, greater severity of disease in IPD was also positively associated with greater severity of peripheral neuropathy. At this time, it is not possible to separate the prospect of peripheral neuropathy developing based upon the severity of central nervous system disease occurring in IPD patients. There were no associations of peripheral neuropathy severity with advancing age such as is expected in the general population. Despite the association with levodopa usage that appeared, there was also no relationship to the use of COMT-inhibitors, dopamine agonists, anticholinergic agents, amantidine, or surgical interventions used for IPD. In particular, the use of a COMT-inhibitor did not appear to be protective against the occurrence of homocysteine or methylmalonic acid elevation in IPD patients.

These studies have been followed by case series, including two patients with IPD being treated with high dose levodopa (duodopa) developing subacute axonal peripheral neuropathy with associated cobalamin and vitamin B6 deficiency [73]; another case series suggests there may be an additional demyelinating component in some patients [74]. Another small case series identified clinical and electrophysiological changes of peripheral neuropathy in patients with IPD; these patients had concurrent cobalamin deficiencies in most cases, but also identified

other potential causes for peripheral neuropathy as well [75]. Similar observations were made in another population treated with duodopa [76].

2.3. Potential pathogenic mechanisms of peripheral neuropathy in idiopathic Parkinson's disease patients

The studies to date have been descriptive and associative in nature only. The precise pathogenic mechanisms for the development of peripheral neuropathy in IPD patients remain speculative. Before considering the mechanisms by which methylmalonic acid and/or homocysteine may be pathogenic, other considerations require discussion.

As mentioned, considerations for genetic influences are important. The potential implications of parkin mutations given the expression of parkin mRNA in peripheral nerve [36] may be of importance, but only a small percentage of IPD patients with parkin mutations appear to have an axonal form of peripheral neuropathy [34, 35]. The relationship of concurrent peripheral neuropathy to the so called Parkinson's Plus forms of disease, such as with multiple system atrophy must also be considered; patients with multiple system atrophy frequently (40%) have an axonal peripheral neuropathy present [40-42]. Associations such as this may suggest a neurodegenerative pathogenesis for peripheral neuropathy rather than a deficiency. Indeed, patients with greater severity and longer duration of IPD were more susceptible to development of peripheral neuropathy in our studies as well [8]. Further studies will be required to determine if the peripheral neuropathy present in IPD patients develops in an analagous fashion to the central nervous system neurodegeneration in IPD.

It is possible that alpha-synuclein protein deposits in IPD may exhibit neurotoxic properties in peripheral nerves leading to a neuropathy [77]. This is consistent with recent studies demonstrating the presence of alpha-synuclein deposits in the periphery, but in autonomic nerves, not somatic sensory nerves [78]. One study has also demonstrated impaired CNS axonal transport, especially where alpha-synuclein deposits were present, leading to neuronal degeneration in both experimental and human forms of IPD; whether this may also be the case in peripheral neurons has yet to be investigated [79].

The mechanisms by which homocysteine and/or methylmalonic acid may contribute to development of peripheral neuropathy are not as clear. Homocysteine may increase susceptibility to mitochondrial toxins, contribute to free radical formation, exert glutaminergic-associated neurotoxicity, and impair DNA repair mechanisms [62, 80]. Elevated levels of homocyteine may also increase systemic oxidative stress [81]. Thus, homocysteine may exert toxic effects in multiple ways, although which of these may be relevant at the level of the peripheral nerve is not established as of yet. Another nutritional deficiency was detected in a separate population of patients with peripheral neuropathy and IPD: pyridoxine (vitamin B6) [82]; relevance of this finding remains uncertain.

Methylmalonic acid elevations can be detected within both tissues and blood. *In vitro*, methylmalonic acid plays a role in lipid and protein oxidative damage and affects the production of reactive species in cerebral synaptosomes [83]. *In vivo*, MMA can induce preventable

or modifiable lipid peroxidation and protein oxidative damage, as well as inhibition of glutathione peroxidase, suggesting that reactive oxygen species generation may be a main product of methylmalonic acid excess [84]. Further work is needed to determine the susceptibility of the dorsal root ganglia sensory neurons to excessive levels of methylmalonic acid and subsequent mechanisms of toxicity.

In IPD patients that we have assessed, it is probable that methylmalonic acid accumulation or relative cobalamin deficiency is the cause of peripheral neuropathy for a number of reasons. In all cases in our prospective cohort study, symptoms of a peripheral neuropathy started years after the onset of IPD and the initiation of levodopa therapy. Second, higher severity levels of peripheral neuropathy were positively correlated with levodopa cumulative use over time, suggesting a treatment-related effect. Third, no other reason could be identified in the majority of cases of peripheral neuropathy identified in a randomly selected IPD population. Finally, treatment of the peripheral neuropathy, described below, appeared to stabilize progression of peripheral neuropathy.

2.4. Treatment options for peripheral neuropathy in idiopathic Parkinson's disease patients

In our initial case series with IPD patients identified to have peripheral neuropathy [7], all patients identified to have one of cobalamin deficiency, methylmalonic acid elevation, or elevated homocystine levels were prescribed monthly intramuscular injections of 1000 µg of cobalamin (vitamin B12). This was provided via intramuscular injections and not oral therapy due to concerns of potential inadequate absorption from the gastrointestinal tract. All patients initialized on therapy were subjected to repeated clinical examinations using the Toronto Clinical Scoring System and electrophysiological evaluations at 6, 12, and 24 months after diagnosis of the peripheral neuropathy when cobalamin therapy was initiated. Repeated blood tests for cobalamin, fasting methylmalonic acid and fasting homocysteine were concurrently performed.

Beginning at 6 months after monthly cobalamin injections were initiated, significant improvements in each of cobalamin, fasting methylmalonic acid and fasting homocysteine were noted all measurements were noted, with cobalamin returning to normal levels in all patients and with fasting homocysteine and fasting methylmalonic acid levels improving to normal levels in approximately 2/3 of cases. Interestingly, clinical assessments and electrophysiological measurements essentially stabilized over follow-up at 12 and 24 months after initiation of intramuscular cobalamin treatment. When compared to a cohort of patients without IPD but with idiopathic peripheral neuropathy identified to have isolated methylmalonic acid elevation, differences in clinical course could be identified; this patient population continued to exhibit mild clinical and electrophysiological decline over the 12 and 24 months follow-up as compared to the IPD patient population receiving cobalamin injections. This initial data is supportive of management of the identified elevated methylmalonic academia, but further studies are required before definitive suggestions can be applied.

3. Conclusion

Peripheral neuropathy developing concurrently in patients with established IPD can be problematic and should be investigated. A further contribution to disability and mobility may certainly develop in an already compromised patient population. Fortunately, we are starting to learn some of the relationships and the potential iatrogenic effect of levodopa therapy. Future studies should examine the potential mechanisms by which methylmalonic acid may exert its toxic effects, and the prospective options for management of concurrent peripheral neuropathy in IPD patients. Therapeutic intervention studies are required to establish whether cobalamin replacement may be viable. Further genetic susceptibility testing may determine the heterogenous development of peripheral neuropathy in IPD patients. Finally, the possibility of prophylactic interventions at the time of diagnosis of IPD or at the time of levodopa initiation for the prevention of peripheral neuropathy may be a future endeavour. We do not yet know the role of dopamine antagonists and COMT inhibitors, amongst other IPD interventions, but future studies may assist in our understanding. Our knowledge of the development of peripheral neuropathy in IPD patients has developed over a short duration of time, but is certain to expand over the coming generations.

Acknowledgements

Author details

Peter Podgorny and Cory Toth

University of Calgary, Canada

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