

ANOTHER FACE OF PARKINSON'S DISEASE: PERIPHERAL INVOLVEMENT

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Abstract

BACKGROUND AND AIM: Parkinson's disease (PD) was initially seen as a neurodegenerative process of the basal ganglia but clinical and pathological evidence revealed its strong systemic as well as peripheral nervous system involvement. The current review aims to present the recent data in the association of polyneuropathy (PN) and PD.

METHODS: We performed a systematic literature search in the most important international databases. We report the results of most recent studies in a narrative way.

RESULTS: Several recent studies have shown the presence of PN as a small fiber disease in the early

stages of PD. Also there seems to be a link between acquired axonal neuropathy and chronic Levo-Dopa intake. We present the possible pathogenesis of this association, also a summary of the evaluation of PN in PD patients and the main management approaches.

CONCLUSION: The association of PN in PD patients is an important phenomenon that significantly decreases their quality of life, underlining the value of clinical and paraclinical assessment the all stages of the disease

KEY WORDS: Parkinson's disease, polyneuropathy, Levo-Dopa, skin biopsy, corneal confocal microscopy.

O ALTĂ FAȚETĂ A BOLII PARKINSON: AFECTAREA PERIFERICĂ

Rezumat

OBIECTIVE: Boala Parkinson a fost inițial privită ca o boală neurodegenerativă, ce afectează ganglionii bazali dar datele clinice și anatomopatologice au evidențiat o afectare extinsă a sistemului nervos central și periferic. Scopul lucrării de față este de a prezenta datele curente în ceea ce privește asocierea dintre polineuropatie (PN) și boala Parkinson.

METODE: S-a realizat o căutare sistematică în literatură în cele mai importante baze de date

internaționale. Raportăm rezultatele celor mai recente studii identificate.

REZULTATE: Câteva studii recente au arătat că încă din stadiile incipiente de boală poate fi prezentă o PN de fibre mici. De asemenea, pare să fie o asociere între utilizarea cronică de Levo-Dopa și un grad de neuropatie axonală câștigată. Lucrarea sumarizează datele morfopatologice ce stau la baza acestei

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asocieri, de asemenea modalitatea de evaluare a PN la acești pacienți și posibilitățile terapeutice existente.

CONCLUZIE: Asocierea PN la pacienții cu boală Parkinson este un fenomen important ce contribuie semnificativ la scăderea calității vieții, de unde

derivă importanța evaluării clinice și paraclinice în toate stadiile de boală.

CUVINTE CHEIE: **Boala Parkinson, polineuropatie, Levo-Dopa, biopsie cutanată, microscopia corneană confocală.**

Introduction

During recent years the clinical and pathological evidence of a systemic involvement in PD overthrows the traditional concept of it being only a basal ganglia disorder. It seems that Lewy bodies can be detected before the diagnosis in the enteric, pelvic and cardiac ganglia, also in the olfactory cortex and brainstem nuclei [1].

In the last decade there was an abundance of studies that have shown a peripheral involvement in PD. This can be in the form of a small fiber neuropathy that tends to be considered an intrinsic feature of the disease, or in the form of a large fiber neuropathy that occurs in patients with long term with Levo-Dopa exposure [2].

For PD patients, who have already impaired mobility, concomitant PN may add to immobility, risk of falls and autonomic dysfunction. This will overall lower the quality of life of these patients.

Epidemiology

The frequency of the peripheral involvement in PD patients treated with Levo-Dopa varies in different studies, from 4.8% to 55% with no differences between the sexes⁽¹⁾. This wide range is caused by the differences in the studies population (age, disease duration, type of treatment, and diagnostic tools for neuropathy). More importantly it seems that up to 20% of the patients that receive Levo-Dopa develop neuropathy after only 3 years of treatment [2, 3].

On the other hand the small fiber PN seems to be more frequent, as it can be detected in about 57 % of patients (with a range from 37% to 91%) [4].

Etiopathogenesis

Involvement of the peripheral nervous system, even from the early stages of the disease, was proven by the finding of Lewy bodies in the small nervous

fibers in skin biopsy. Studies also found a decreased number of non-myelinated and myelinated fibers in skin biopsies, and alpha-synuclein deposits can be found in the sensory and autonomic nerve endings in patients with PD [5, 6, 7].

On the other hand, the large fiber PN seems to be caused by the way Levo-Dopa is metabolized, since it influences the homocysteine, vitamin B12 and methylmalonic acid levels. The conversion of Levo-Dopa to dopamine leads to homocysteine formation. The re-methylation of homocysteine requires either vitamin B12 or, by using another path, methyltetrahydrofolate and vitamin B6. As a result, in chronic Levo-Dopa intake one may find high homocysteine levels, vitamin B12, B6 and folate deficiency, with a positive correlation between the cumulative dose of Levo-Dopa and the presence of PN [1,8]. Studies have shown that the duration of the exposure to Levo-Dopa, combined with the age are the main risk factors for the development of PN. The duration of the disease and its severity alone do not increase the risk of PN [9].

During the recent years several cases of acute or subacute PN have been reported in patients treated with enteral Levo-Dopa. This may be caused by the increased bioavailability of the drug that increases the adverse reactions. Inflammation may also be involved, since enteral Levo-Dopa causes changes in the intestinal microenvironment [10].

Clinical aspects

The small fiber PN occurs at the early stages of PD, it is distal and symmetrical. The symptoms are predominantly sensory (paresthesia, impairment of the pain perception, impairment of the light touch response) or dysautonomic (urinary symptoms, altered intestinal transit, sudomotor disturbances). The clinical testing reveals an altered quantitative sensory testing [6].

The chronic large fiber PN occurs in patients receiving Levo-Dopa, it is slowly progressive, slight, symmetrical and distal. The patients may experience distal numbness, tingling or pain, and even mild weakness in the extremities. The clinical testing may show a decreased vibration sense, decreased deep tendon reflexes, a mild reduction of the muscular strength and possibly and impaired gait and postural instability [10].

The acute form of large fiber involvement is rare, more severe, and appears in patients that are treated with enteral Levo-Dopa. Patients experience a moderate to severe weakness in the lower extremities, with an ascending pattern. On clinical examination the deep tendon reflexes and the vibration sense are absent, and there is a severe weakness both proximally and distally with inability to walk [11].

The assessment of neuropathy in PD

In all cases of peripheral involvement in patients with PD the assessment should begin with the testing of other possible etiologies (eg: diabetes, thyroid dysfunction, neoplasm, chronic hepatitis or other infectious diseases, toxic exposure, monoclonal gammopathy, etc).

The further assessment should start with electrophysiological testing. It should evaluate the nerve conduction in the sural and radial nerves and at least one motor study, commonly the tibial nerve. This may show a predominantly sensory, axonal or demyelinating PN in the chronic large fiber form; however it will be normal in the small fiber PN [4].

For the small fiber PN different methods can be used, starting with autonomic testing. The autonomic questionnaires COMPASS, SCOPAAUT, or the Toronto Clinical Scoring System can be used^(7, 11). For a more objective evaluation, the skin biopsy should be considered. It can reveal a decrease of non-myelinated nerve fiber density, a reduction of Meissner corpuscles and the presence of cutaneous deposits of alpha-synuclein [12]. Some studies have shown that the alpha-synuclein deposits in the skin nerve fibers may help differentiate PD from other atypical parkinsonism syndromes [13]. Another helpful test is the skin wrinkling test. This can be used as a bedside diagnostic tool that is inexpensive and non-invasive⁽⁷⁾. Lastly recent studies showed that the corneal confocal microscopy can be used as an alternative to

demonstrate small nerve fiber damage in PD. This allows a non-invasive assessment of the corneal nerves and their density. In PD patients studies have shown a decreased corneal nerve fiber density with an increase of the branch density of the remaining fibers [12].

Management

In all patients with PD that are receiving Levo-Dopa treatment the screening for homocysteine and vitamin B12 levels, also a clinical and neurophysiological evaluation for neuropathy is advisable^(3,6).

The usage of vitamin supplementation (B12, B6) as a preventive treatment is debatable. Some studies suggested a clinical improvement after B12 supplementation for patients that have a borderline serum B12 value and are symptomatic [6, 1].

Prevention using the administration of Catechol-O-methyltransferase inhibitors (COMT) could be considered. It does indeed reduce homocysteine levels and it preserves the levels of folate and vitamin B12. However the risk/benefits ratio should be carefully assessed [14, 15].

In patients that are using enteral Levo-Dopa it is essential to perform a screening for a pre-existing neuropathy, also one should consider the serum level of vitamin B12, folate, homocysteine and the nutritional status of the patient before and during the treatment [16].

In the acute or subacute form the management consists in the discontinuation of enteral Levo-Dopa (oral Levo-Dopa should be given, in the lowest doses acceptable), the supplementation of vitamin B12 and folate. Some case reports consider the usage of intravenous immunoglobulin since the pathogenesis could be immune [16].

Conclusion

Peripheral neuropathy is more common in PD patients and it tends to correlate with older age and more advanced disease. When considering neuropathy in PD it is important to underline that both large and small fiber pathology can appear with different pathogenesis. It is also important to consider that additional etiological risk factors for neuropathy may be responsible for the peripheral involvement in some patients with PD.

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