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Environmental toxic factors and clinical pattern of Parkinson's disease

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Abstract

Background: Parkinson's disease (PD) – the most common neuro-degenerative movement disorder – is considered a result of a multifactorial pathogenic process modulated by cumulative and interactive effects of genes and exposures. An environmental exposure could enhance or create dopaminergic neurons vulnerability and increase PD risk. The purpose of the study was to find if excessive exposure to toxic environmental factors may influence clinical pattern of PD.
Material and methods: The study was conducted on 111 patients diagnosed with PD, study group being defined as PD exposed to toxins (33 patients), control group including PD patients without toxin exposure (78 patients). General epidemiological data and clinical data were recorded.
Results: Toxin exposure was found in 33 patients (29.73%), more of them – men and rural residents. Toxin exposed PD patients had an insignificantly younger age. The most common disease phenotype in the study group was the akinetic-rigid phenotype (64.7%, p = 0.040), bradykinesia being the most common sign at the disease onset (57.6%, p = 0.008). Levodopa equivalent daily dose also was higher in the study group (659.02 ± 232.46, p = 0.042).
Conclusions: Excessive exposure to toxic environmental factors may influence the clinical pattern of PD. In this study the akinetic-rigid type was the predominant disease phenotype associated with toxin exposure. Doses needed for treatment were higher in PD patients exposed to toxins, as an indicator of a more severe motor impairment in this group.
Key words: Parkinson's disease, toxic environmental factors.

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Introduction

Parkinson's disease is the most common neuro-degenerative movement disorder with a prevalence of about 2% in the population over the age of 65 years [1].

PD has no known cause. The exposure of the human population to environmental contaminants is recognized as a significant contributing factor for the development of Parkinson's disease and other forms of parkinsonism. Evidence exists to suggest that age and gender and some environmental factors (pesticide exposure, occupation) are associated with the development of PD. Instead, tobacco use, and caffeine consumption are believed to be inversely associated to the development of PD, tobacco and black tea having a protective effect on age at onset in genetic PD – LRRK2 [2, 3].

PD varies in age of symptom onset, rate of progression, severity of motor and non- motor symptoms, extent of central and peripheral inflammation, maybe, because genetic and environmental factors act synergistically in PD pathogenesis.

A lot of recent research has focused particularly on genetic causes of PD. Although several genes have been implicated as monogenic causes of the disease, these genetic mutations are only responsible for approximately 10% of cases, indicating that the majority of PD is the result of a multifactorial pathogenic process [4] and environmental causes also may play a role in developing the disease. Rare (causative) and common (risk) variants associated with PD have been identified, including SNCA and LRRK2.

Some authors propose that environmental factors (pesticides and infections) increase the risk for PD via the immune system [5], because several of the genes associated with PD risk, function in the immune system. Peripheral immune activation and neuroinflammation in the brain contribute to neuropathology and neurodegeneration [6]. An environmental exposure that increases α-synuclein expression and/or inflammatory cytokine secretion could create a state in which dopaminergic neurons are vulnerable to immune-driven stress [5]. Increased kinase activity associated with the G2019S LRRK2 mutation may contribute to shifts in immune cell population frequencies and function [7]. In response to an exposure or experience, physiological and epigenetic regulation can occur, and the resulting cell-signaling cascades could influence disease pathogenesis [8]. The immune system's response to exposure may depend on the genetic variations or mutations of SNCA, LRRK2,

PINK1, and MHCII. There is a gene-by-environment-by-immune- system triangle in PD pathogenesis [5].

So, PD risk can be modulated by cumulative and interactive effects of genes and exposures [4]. One study showed that gene-environmental interactions increased the OR for PD from about 1.6 at the individual level up to OR 12.6 for some combinations [4].

Environmental factors such as drinking well water, rural living, farming, exposure to agricultural chemicals, farm and industrial compounds, exposure to different metals and industrial compounds as manganese, lead, copper, iron, zinc, aluminium or amalgam have been reported to be associated with the risk of developing PD [9-11].

So far, is known that toxin exposure can promote PD by several mechanisms: oxidative stress, dopamine homeostasis, calcium homeostasis, alpha-synuclein fibrillization, mitochondrial dysfunction neuroinflammation [12].

As toxic exposures to these compounds can result in a spectrum of PD and related disorders, it is imperative to identify, not only their mechanisms of action, but also shared clinical patterns to further delineate the resultant disorders for improving diagnosis, preventive strategies and therapeutic interventions [12].

Material and methods

These are preliminary data of a cohort study of Moldovan patients with incident of Parkinson's disease. Diagnosis of PD was based on widely acknowledged criteria [13]. Structured interview on medical and drug history, family history of neurological and psychiatric diseases, years of education, all previous and current occupations, previous and current lifestyle habits, details regarding exposure to pesticides, and other toxins were recorded and a general neurological and medical examination conducted. Severity of parkinsonism and disability were assessed by the Modified Unified Parkinson's Disease Rating Scale (MDS-UPDRS) [14]. Patients were subclassified at baseline into three groups according to Jankovic method: tremor dominant (TD), akinetic-rigid (AR) or intermediate (IND) [15]. The groups were defined as: (1) Toxic substances contact present (*ToxSC+*) – study group; and (2) absent (*ToxSC-*) – control group. The data analysis was performed via statistical program StatDirect, using descriptive, variation, and correlational analysis. Student's t tests or Mann-Whitney tests were used as appropriate. P values less than 0.05 were considered statistically significant.

Results and discussion

These are preliminary data of a cohort study of Moldovan patients with incident Parkinson's Disease (PD). The study group consisted of 111 consecutive PD patients. The mean age in the cohort was 64.87 ± 7.69 years. By sexes, PD patients, were distributed as follows: 48 were women (43.2%) and 63 were men (56.8%)).

Contact with toxic substances (*ToxSC)*, was recorded by history taking about previous and current occupations, previous and current lifestyle habits, exposure to pesticides, and other toxins; and was found in 33 patients (29.73%). In this study, excessive exposure to toxic environmental factors was more common in men and rural residents. Among *ToxSC+* patients, 30 patients (90.9%) were men and 3 (9.1%) patients were women (p=0.000). Nineteen of the toxin exposed patients (57.6%, p=0.000) were rural residents. Similarly, in a meta-analysis of PD risk, RR was statistically significant for: rural living (RR = 1.43; 95% CI = 1.22–1.69), farming (RR = 1.24; 95% CI = 1.12–1.37) and well-water consumption (RR = 1.30; 95% CI = 1.12–1.51); the association between pesticide use and PD was statistically significant for all studies combined (RR = 1.22; 95% Cl = 1.18–1.27); and use of herbicides (RR = 1.20; 95% CI = 1.06–1.36) or insecticides (RR = 1.32; 95% CI = 1.14–1.52) was associated with statistically significantly increased PD risk [8]. Also, in Norwegian ParkWest study, agricultural work was associated with a higher risk of PD (OR 1.75 (1.03–3.0) P 5 0.009): PD patients were more often agricultural workers than controls (23% PD vs 14.4% of controls, P 5 0.026 [$\chi 2$ test], odds ratio [OR] 1.75 [1.03–3.0]); whether patients or controls were born and raised on a farm did not affect the risk of PD [9].

Different toxic exposure was found in the study group: petrol intake (10 patients (9%)), diesel intake (4 patients (3.6%)), petrol + diesel intake (6 patients (5.4%)), exposure to pesticides (7 patients (6.3%)), to solvents – 3 patients (2.7%), to reinforced concrete (polystyrene) – 1 patient (0.9%), to welding gas – 1 patient (0.9%), to freon – 1 patient (0.9%).

In a study, prevalence of parkinsonism among active male welders age 40 to 69 statewide was 977 to 1336 cases/100000 population. The prevalence of Parkinsonism was higher among welders vs age-standardized data for the general population (prevalence ratio – 10.19, 95% CI 4.43 to 23.43). The authors concluded that the estimated prevalence of parkinsonism was higher within a sample of male welders vs the general population of males [16]. By contrast, the results of Danish Cohort Study (5867 Danish welders and 1735 non- welding metal workers exposed to welding fume from general Danish population in 1987–2008) do not support the hypothesis that welders are at increased risk for Parkinson's disease [17]. It was established that parkinsonism can occur after chronic exposure to high levels of manganese, usually above the permissible exposure limit ceiling at 5 mg/m3 total dust set by the Occupational Safety and Health Administration [18].

In the present study was found that in *ToxSC+* patients, the disease began at an insignificantly younger age than in *ToxSC-* patients (59.24 ± 6.93 vs 60.95 ± 8.86 years, p <0.005). By history taking, was established, that bradykinesia was the most often PD onset symptom in *ToxSC+* patients (57.6%, p = 0.008). Applying the Jankovic method of defining PD motor phenotype, the more frequent PD phenotype in *ToxSC+* patients was the akinetic-rigid one (64.7%, p = 0.040).

There are interesting clinical differences between subgroups of PD patients (tremor dominant (TD) vs postural

instability gait difficulties PIGD), provided by literature. In a study, a protective association of alcohol and smoking was only seen in postural instability gait difficulties (PIGD) – akinetic-rigid PD and not in tremor dominant (TD) PD [9], may be because the underlying pathogenic mechanisms are heterogeneous, including environmental exposure.

Levodopa equivalent daily dose needed to compensate motor impairment in *ToxSC+* patients was significantly higher than in the control group (659.02 ± 232.46 vs 483.77 ± 355.41, p = 0.042), as an indicator of a more severe motor disability in PD patients exposed to environmental toxic factors.

Overall, studies suggest that environmental insults may play an important role in the appearance and progression of PD pathology [19], PD onset and its clinical presentation may be due to a combination of external aggressors and individual genetic susceptibility to this aggression; and low incidence of PD suggests that gene-environment interactions play an important role in the process. According to our results excessive exposure to toxic environmental factors was more common associated with the akinetic-rigid type of Parkinson's disease – a phenotype with more severe motor impairment. And *ToxSC+* patients needed higher doses of dopaminergic drugs – an indicator of a more motor impairment in this category.

Conclusions

Environmental factors may play an important role in the appearance, progression and clinical presentation of Parkinson's disease. This study, replicated that excessive exposure to toxic environmental factors is more commonly found in men and rural residents. According to the received results, toxin exposure was more frequently associated with the akinetic-rigid type of Parkinson's disease and with higher doses of dopaminergic drugs needed for motor symptoms control, indicating a higher severity of motor impairment in toxin exposed PD patients.

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