EUROMEDITERRANEAN BIOMEDICAL JOURNAL
2023,18 (2) 10-14
(*FORMERLY: CAPSULA EBURNEA*)

Original article

PARKINSON'S DISEASE AND OCCUPATIONAL EXPOSURE: A CASE-CONTROL STUDY CONDUCTED IN SOUSSE (TUNISIA)

Imène Kacem [1,2], Imène Jemmali [2], Wafa Hmila [1,3], Manel Ben Halima [1,3], Chaima Sridi [1,2], Mariem Hafsia [1,2], Maher Maoua [1,2], Houda Kalboussi [1,2], Hanene Jrah [4], Chakib Zedini [1,4], Sana Ben Amor [1,3], Nejib Mrizak [1,2]

1. Faculty of Medicine of Sousse Ibn Al Jazzar, Sousse (Tunisia)
2. Department of occupational medicine, Farhat Hached University Hospital-Sousse (Tunisia)
3. Department of Neurology, Sahloul University Hospital-Sousse (Tunisia)
4. Institute of Nursing Sciences of Sousse (Tunisia)

ARTICLE INFO

Article history:
Received 12 Nov 2022
Accepted 23 Jan 2023
Published 04 Feb 2023

Keywords:
Parkinson's disease, Risk factors, Occupational exposure.

ABSTRACT

To study the relationship between exposure to the risk factors highlighted in the literature and Parkinson's disease. This is a case-control study. The cases were patients with Parkinson's disease and who were treated at the Neurology Department of the Sahloul Teaching Hospital of Sousse (Tunisia). The controls were matched and recruited among the patients of the hospital and were free from neurological pathologies. We recruited 92 cases of Parkinson's disease during the study period. The mean age was 65.16 ± 10.98 years for the study group and 65.02 ± 11.09 years for the control group. The factors independently associated with risk of Parkinson's disease at the end of the multivariate analysis were: the construction and public works sector (p= 0,004; ORa= 8.15; IC95% [4.13-146.1]),occupational exposure to pesticides ($p = 10^{-3}$, OR = 19.6 [4.23-90.70]), personal history of head trauma (p = 0.04, OR = 7.98 [1.09-58.22]), well water consumption (p = 0.05, OR = 7.28 [1.81-29, 19] and stress ($p = 10^{-3}$, OR = 19.87 [3.48-71.97]). The etiology of Parkinson's disease is complex and involves genetic and environmental factors. Studying these risk factors will further understanding of the underlying mechanisms of the disease.

1. Introduction

Parkinson's disease (PD) represents the most common neurodegenerative disease after Alzheimer's disease [1, 2]. This pathology affects about 10 million people around the world [3], with a rate from 1% to 3% among people over 60 years [4, 5]. The motor and non-motor features of PD lead to functional difficulties which affect daily life and can increase mortality and morbidity related to this disease. In fact, individuals suffering from PD require social and medical care resulting in a potentially large economic burden for them, their families, and their care partners [6].

There are multiple genetic and environmental factors implicated in the development of PD and the complicated interaction between these factors could contribute to its diversity [7].

The classic clinical picture associates, to varying degrees, a rest tremor, muscle rigidity also called plastic, a slowness or loss of movement and postural instability [8].

These symptoms are caused by a progressive loss of dopaminergic neurons that are located in a specific zone of the brain called the subtantianigra or the black substance [9, 10]. Its etiopathogenesis probably complex and multi-factorial involving numerous genetic, environmental and infectious or toxic factors [6, 11, 12]. The discovery of a link between the pesticide 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and the appearance of symptoms of PD in humans has allowed for the implication of certain environmental agents in the genesis of this disease [12].

Subsequently, multiple studies have been conducted in order to evaluate the association between pesticides and PD [12, 13]. Occupational exposure to other substances such as heavy metals, solvents and magnetic fields has also been associated with an increased risk of PD [14]. An increased risk of PD has even been reported in certain occupational groups [15, 16]. However, results regarding the association between these factors and the occurrence of PD remain far from conclusive.

* Corresponding author: Imène Kacem, kacem.imane@live.fr
DOI: 10.3269/1970-5492.2023.18.2
 ISSN: 2279-7165 - Available on-line at www.embj.org

The aim of this study was to identify potential occupational factors associated with PD in the Tunisian population.

2. Material and methods

This case-control study was carried out in the department of neurology at the Sahloul Teaching Hospital and in the Department of Occupational Medicine in Farhat Hached Teaching Hospital over a period of six months from December 1st 2018 to May 31st 2019.

The cases were made up of patients with PD being treated in the outpatient clinics and/or in the Department of Neurology of the Sahloul Teaching Hospital during the study period. The inclusion criteria were patients diagnosed with PD according to criteria defined by the "Movement Disorder Society" (MDS 2015) and who had been employed for at least one year, before or at the time of onset of the first clinical symptoms. Patients diagnosed with PD who had worked for a period of less than one year and individuals who did not consent to be part of the study were excluded.

The control group consisted of patients who were not suffering from PD or any other neurological condition and who had worked for at least one year and were randomly recruited during the same period among consultants in the Department of Occupational Medicine in Farhat Hached Teaching Hospital, Sousse. Participants who had a family history of PD or any other neurological disease and who did not consent to participate in the study were excluded. The two groups had the same number of participants and were matched for age and gender.

Data were collected by the same investigator from medical records and direct interviews with patients who attended the outpatient neurology clinics.

Data included socio-demographic characteristics, medical history and family history, lifestyle habits and nutritional habits. The frequency of consumption of firbre (fruits and vegetables) and of red meat and fat were considered low if the weekly consumption was ≤1, medium if the consumption was between 2 and 3 and frequent if it wasabove4 times a week. Coffee consumption was considered zero if the daily consumption was zero and frequent if the daily consumption was≥ 3[17].Physical activity was classified into 3 categories: absent, light, and intense. Stress was assessed using a question of two levels« Do you consider your job to be stressful? »[18].

Socioeconomic level was assessed on the basis of the monthly salary of the participants, low if the salary was below 320 dinars/month, medium if the salary was between 320 and 1000 dinars/month and high if it was superior to 1000 dinars/month [18].

A semi quantitative estimate (self-reported) of the exposure to occupational factors implicated in the occurrence of PD according to literature was made taking into account the frequency if the daily exposure (H), the duration of the exposure in term of years (D) and the level of exposure (N).

The level of exposure was ranked from 0 to 3; it was classified as 0 if the exposure was normal, 1 if the exposure was mild, 2 if the exposure was moderate with direct contact with the product and 3 if there was a close handling of the product. An exposure index (I) was calculated for each product to evaluate the approximate intensity of exposure.

This index (I) was calculated according to the following formula: I = H x D x N [13]. The list of products investigated included pesticides, organic solvents, detergents, polycyclic aromatic hydrocarbons (PAH) metal dusts, cement dust, textile dust, ionizing radiations and magnetic fields.

Medical data was organized according to the age at onset of symptoms of PD, and thus into 4 categories: juvenile (<20 years), early onset (between 20 and 40 years), the common form (between 41 years and 70 years), and late onset (>70 years).Other parameters were considered, such as the duration of the disease, the received medications, evolution under treatment and professional impact. The clinical form was characterized according to the predominant symptom: the tremulous form, akine to-rigid, akinetic and mixed form.

Data was input and analyzed using SPSS 20.0 software. For the comparison of means, Student's t test was used if the variable followed anormal distribution; otherwise, the Mann-Whitney U test was used. Comparison of frequencies was done using the Pearson Chi-Square test. Regarding the multivariate analysis, a multiple binary logistic regression was performed. For all the statistical tests, the level of significance was set at $p \leq 0.05$.

3. Results

In total, 92 patients with PD and 92 controls were recruited during the period of the study. The mean age was 65.11 ± 10.9 years for the cases, versus 65.0 ± 11.1 years for the controls without any statistically significant difference (p=0.93).The sex ratio was 1.42 for both groups.

The risk of developing of PD was higher in subjects who did not have any children (p=0.04, OR IC95%= 3.61[0.96-13.6]), who were illiterate ($p<10^{-3}$, OR=4.68 ; IC 95% [2.08-10.56]),those who had a low socio-economic level ($p<10^{-3}$, OR IC 95%=33.95[4.48-256]),those who were living in an Arabic-style house p=0.001; OR IC 95%= 2.78 [1.53-5.06]) and those who had a medical history of head trauma (p=0.001 ; OR= 6.70 IC95% [1.89-23.83]) (Table 1).

The risk was also increased by low consumption of fruits and vegetables ($p<10^{-3}$; OR=18.69 IC95% [4.29-81.40]), the consumption of well water ($p<10^{-3}$; OR= 5.27 IC95% [2.42-11.48]), stress ($p<10^{-3}$; OR= 6.80 IC95% [3.56-12.97]) and chronic alcohol consumption (p=0.02; OR IC95% =3.01 [1.12-8.10]). Smoking was more frequent in controls than cases (p=0.001 ; OR=0.27 IC95% [0.12-0.62]).

Variables	Cases		Controls		P	OR (IC 95%)
	N	%	N	%		
1/ Marital status						
Single	5	5.4	3	3.3	0.71	1.7 ;[0.39-7.35]
Married	**79**	**85.9**	**79**	**85.9**	**1**	**1 ; [0.43-2.29]**
Divorced	1	1.1	4	4.3	0.36	0.24 ; [0.02-2.2]
Widowed	7	7.6	6	6.5	0.77	1.18 ; [0.38-3.65]
2/Level of education						
Illeterate	31	33.7	9	9.8	**10^{-3}**	4.68 [2.08-10.56]
Primary school	38	41.3	30	32.6	0.22	1.45 [0.79-2.65]
Secondary school	20	21.7	35	38	0.016	0.45 [0.23-0.86]
University	3	3.3	18	19.6	0.001	0.13 [0.03-0.48]
3/Number of children						
Without children	10	10.9	3	3.3	**0.04**	3.61 [0.96-13.6]
1	2	2.2	2	2.2	1	1 [0.13-7.25]
2	5	5.4	10	10.9	0.17	0.47 [0.15-1.43]
3	21	22.8	41	44.6	0.002	0.36 [0.19-0.69]
≥ 4	54	58.7	36	39.1	0.08	2.21 [1.22-3.98]
4/Socio economic level						
Low	25	27.2	1	1.1	**$<10^{-3}$**	33.95 [4.48-256]
Medium	61	66.3	70	76.1	0.14	0.61 [0.32-1.17]
High	6	6.5	20	21.7	0.003	0.25 [0.09-0.65]
5/Housing						
Villa	24	26.1	41	44.6	0.009	0.43 [0.23-0.81]
Arabic house	60	65.2	37	40.2	0.001	2.78 [1.53-5.06]
Appartment	8	8.7	14	15.2	0.17	0.53 [0.21-1.33]
6/Medical history						
Diabetes	6	6.5	13	14.1	0.09	0.42 [0.15-1.16]
HTA	23	25.0	34	37.0	0.07	0.56 [0.30-1.07]
Head trauma	17	18.5	3	3.3	**0.001**	6.7 [1.89-23.83]
Psychiatric history	7	7.6	3	3.3	0.19	2.44 [0.61-9.75]

Table 1. Demographic characteristics of Parkinson disease cases and controls in Tunisia.

A statistically significant decrease of the risk of PD has been associated with regular physical activity (OR=0.29 IC95% [0.15-0.54], $p<10^{-3}$); average daily coffee consumption (OR IC95%= 0.39[0.21-0.72] ; p= 0.003), average consumption of fruits and vegetables (OR=0.45 IC95% [0.24-0.81]) and of fat (OR= 0.49 IC95% [0.27-0.88], p=0.018).The long-term consumption of non-steroidal anti-inflammatory drugs NSAIDs seems to be a protective factor for PD (OR= 0.22 ; IC 95% [0.06-0.082] and p= 0.01).

The different sectors to which our participants were assigned during their professional activity are illustrated in table 2.

The majority of cases had worked in the agriculture sector (40.2%) while the majority of controls worked in the health sector (25%).The risk of developing PD was significantly higher in the agriculture sector ($p<10^{-3}$; OR=8.16 IC95% [3.40-19.61]),electronics industry sector (p= 0.01) and construction and public works sector (p=0.005, OR=5.32 IC 95% [1.47 – 19.21]). Farmers and masons had a significantly higher risk of PD ($p<10^{-3}$; OR= 9.21 IC95% [3.64-23.29] et p=0.01 ; OR= 6.11 IC95% [1.31-28.39] respectively). A significant risk of developing PD was noted in individuals who had more than one job ($p<10^{-3}$; OR= 9.13 IC95% [3.04-27.39]).

Activity sector	Cases		Controls		p-value	OR (IC95%)
	N	%	N	%		
1/Agriculture	37	40.2	7	7.6	**10^{-3}**	8.16 [3.40-19.61]
2/Education	3	3.3	13	14.1	**0.009**	0.2 [0.05-0.74]
3/Health	3	3.3	23	25	**10^{-3}**	0.10 [0.02-0.35]
4/Transport	3	3.3	3	3.3	1	1
5/Communication	0	0	2	2.2	0.15	-
6/Métallurgy	3	3.3	0	0	0.08	-
7/Electronics industry	6	6.5	0	0	0.01	-
8/Buildings and public works	14	15.2	3	3.3	**0.005**	5.32 [1.47-19.21]
9/Textile	6	6.5	12	13	0.13	0.46 [0.16-1.29]
10/Automotive industry	2	2.2	0	0	0.15	-
11/Administration	6	6.5	19	20.7	**0.005**	0.26 [0.10-0.70]
12/Carpentry	0	0	2	2.2	0.15	-

Table 2. The distribution of cases and controls according to the sector of activity

In terms of occupational exposure to the implicated products as detailed above, factors significantly associated with PD were exposure to pesticides ($p<10^{-3}$ et OR= 14.6 IC95% [5.42-9.34]),exposure to organic solvents (p=0.003 et OR= 3.98 IC95% [1.51-10.44]),exposure to metal dusts of iron (p= 0.001 et OR= 9.47 IC95% [2.11-42.51]) and exposure to cement p = 0.005 et OR=3.73 IC95% [1.41-9.83]) (Table 3).

Exposition professionnelle		Cases	Controls	P	OR IC95%
Pesticides	n (%)	42 (55.7)	5 (5.4)	**10^{-3}**	14.6 [5.42-9.34]
	EI : M ± SD	235.34±355.39	9.26±45.65	**10^{-3}**	
Organic solvents	n (%)	20 (21.7)	6 (6.5)	0.003	3.98 [1.51-10.44]
	EI: M ± SD	110.87±250.30	30.24±146.72	0.008	
Detergents	n (%)	18 (19.6)	14 (15.2)	0.43	1.35[0.62-2.91]
	EI :M ± SD	56,92±161,8	41,52±120,53	0.46	
Lead	n (%)	7 (7.6)	2 (2.2)	0.08	3.70[0.74-8.34]
	EI : M ± SD	37.17±156.67	3.59±31.39	0.045	
Copper	n (%)	7 (7.6)	0	0.02	-
	EI : M ± SD	27.74±105.71	0	**0.013**	-
Iron	n (%)	16 (17.4)	2 (2.2)	0.001	9.47(2.11-42.51]
	EI : M ± SD	80.08±213.63	14.46±97.64	**0.008**	
Mercury	n (%)	1 (1.1)	0	0.31	-
	EI : M ± SD	1.13±10.83	0	0.31	-
Cement	n (%)	19 (20.7)	6 (6.5)	0.005	3.73 [1.41-9.83]
	EI : M ± SD	89.38±218.95	26.09±115.21	**0.015**	
Magnetic fields	n (%)	2 (2.2)	0	0.15	-
	EI:M ± SD	6.78±45.8	0	0.15	-

Table 3. The frequency and intensity of occupational exposures of cases and controls (M ± SD : Mean ± Standard deviation ; IE : Exposure index)

After the multivariate analysis, the factors independently associated with PD were the construction and public works sector (p= 0,004; ORa= 8.15; IC95% [4.13-146.1]),exposure to pesticides ($p = 10^{-3}$, ORa = 19.6 [4.23-90.70]), a personal history of head trauma (p = 0.04, ORa = 7.98 [1.09-58.22]), well water consumption (p = 0.05, OR = 7.28 [1.81-29, 19] and stress ($p = 10^{-3}$, ORa = 19.87 [3.48-71.97]) (Table 4).

	Cases N (%)	Controls N (%)	p-value	ORb IC 95%	p-value	ORa IC 95%
Stress	66(71.7)	25(27.2)	10^{-3}	6.8 [3.56-12.97]	10^{-3}	19.87 [3.48-71.97]
Well water consumption	36 (39.1)	10 (10.9)	10^{-3}	5.27 [2.42-11.48]	0.05	7.28 [1.81-29.19]
Building and public works sector	14 (15.2)	3 (3.3)	0.005	5.32 [1.47-19.21]	0.004	8.15 [4.13-146.1]
Exposure to pesticides	42 (45.7)	5 (5.4)	10^{-3}	14,61 [5,42-39,34]	10^{-3}	19.6 [4.23-90.7]
Medical history of head trauma	17 (18.5)	3 (3.3)	0.001	6.72 [1,89-23,83]	0.04	7.98 [1.09-58.22]

Table 4. Factors independently associated with the risk of developing PD after binary logistic regression

4. Discussion

This study has highlighted the role of certain risk factors related to lifestyle and occupational exposures in the genesis of PD. These risk factors are: a medical history of head trauma, stress, the consumption of well-water and occupational exposure to pesticides.

As this is a rare disease, as is the case for most neurodegenerative pathologies, the use of the case-control approach made it possible to study many risk factors at the same time [19, 20] and to assess occupational exposures for the cases and controls in the same way, particularly taking into consideration previous exposures at the expense of a risk of a recall bias. For all the cases included, the diagnosis was made by experts from an academic center which results in a low risk of selection bias at the expense of a relatively limited size of the sample.

In this study, rural life was associated -in univariate analysis- with an increased risk of PD ($p= 10^{-3}$; OR= 4.52 IC95% [2.39 – 8.5]).Similar results were found in a French ecological study showing a higher incidence of PD in rural areas and in areas with agricultural activity [21]. According to some studies, pesticides used in agriculture could contaminate the environment (soil, air, well water) and consequently become a source of exposure to inhabitants who live near the agricultural areas of even within a certain distance [22]. These findings could explain, therefore, the association between well water consumption and PD, as groundwater may become contaminated by pesticides, especially in rural areas. In this context, Jane and al [23] have investigated the link between PD and underground pesticide levels and concluded that for each 0.01 mg/l of pesticides in ground water, the risk of PD would increase by 3% (OR=1.03 IC 95% [1.02-1.04]).

The risk would be also increase among males, since PD has a male predominance as shown by the sex ratio of 1.42 in our study and of 1.37 to 3.7 in the majority if epidemiological studies [6, 24, 25]. These data could be explained by the role of sexual dimorphism in the development of the nigrostriatal pathway and the presence of genes related to chromosome Y, in particular the gene SRY, which can have an influence on the occurrence of PD [26].

In a meta-analysis carried out by Bellou et al [27], a significant association was noted between other neuro-psychiatric disorders (anxiety, depression) and the risk of PD. This could also be the case for neurological traumatic damage since subjects who had a medical history of head trauma had a higher risk of PD ($p = 0.04$, OR = 7.98 [1.09-58.22]). Similar findings were reported by Gao and Hong [28] whoidentifiedan increased incidence of abnormal parkinsonian movements in boxers.

Regarding the role of stress in the development of PD, in a large prospective cohort study, authors have reported positive associations between stress indicators and the risk of PD [29] which is consistent with our results where stress was independently associated with PD ($p = 10^{-3}$, OR = 19.87 [3.48-71.97]).This could be explained by the fact that chronic stress can trigger an alteration and a degeneration of dopaminergic neurons, accompanied by an increase in abnormal alpha syncleine inclusions and an activation of a pro-inflammatory response [30] as well as an increase in catecholamines (including dopamine) and glucocorticoids that are responsible for auto-oxidation which could induce the neuro-degeneration[31].

However, certain factors related to lifestyle maybe associated with a decreased risk of PD, such as the practice of physical activity on a regular basis (OR=0.29 IC95% [0.15-0.54], $p<10^{-3}$). According to a study conducted by Paul and al. [17] that measured physical activity by calculating the metabolic equivalent (MET/hours/weeks/year),intense physical activity is associated with the reduction of the risk of PD.Similarly,a study performed in 2016 in central California noted a negative association between the risk of PD and moderate or vigorous physical activity over the course of life as well as the participation in competitive sports at an early age [32].

As for the impact of nutrition on the occurrence of PD,in this study, reduced risk of PD was noted among coffee consumers which is consistent with the majority of studies in literature [33]. This neuroprotective effect could be explained by the fact that caffeine is an antagonist of A2a receptor of adenosine [34]. In addition, caffeine can change the composition of intestinal microbiota in order to alleviate intestinal inflammation which can reduce the folding of the alpha synecleine protein decreasing the risk of PD by minimizing the propagation of protein aggregates to the central nervous system [35]. Correlations between the consumption of fruit and vegetables and PD have been assessed in many studies with results suggesting a protective effect. In fact, in a cross-sectional study carried out by Mischeley and al [36] among 1053 individuals with self-declared idiopathic PD, authors have concluded that fresh fruits and vegetables were associated with statistically significantly lower rates of disease progression.

The analysis of the effect of occupational exposures on the development of PD has made it possible to suggest a role form any products, in particular, pesticides, solvents and metals [37, 38]. According to a meta-analysis including 104 studies, results have shown a significant association between pesticides, solvents and PD [39]. Several types of pesticides have been implicated, mainly organophosphates and organochlorines the principle being dichlorodiphenyltrichloroethane (or DDT). The latter, which has a half-life superior to 60 years, was widely used as an insecticide in developed countries until the 1960s and it is currently banned in most western countries. Nevertheless, it continues to be used in developing countries notably Tunisia [40].

The potential role of organic solvents in the etiopathogenesis of PD has been investigated since the 1980s [41, 42]. Since then, several epidemiological studies have aimed to highlight the link between PD and organic solvents, the most studied of which were trichloroethylene (TCE), toluene and methanol [43, 44].

5. Conclusions

The risk of developing PD is increased by factors related to lifestyle and the work environment. Improving methods of evaluating exposure risks could provide more data in order to develop a professional theory with which to identify the main risk factors for PD and implement effective preventive strategies.

References

1- Reich SG, Savitt JM. Parkinson's Disease. Medical Clinics of North America 2019;103:337–50.

2-Toro R, Downward GS, van der Mark M, Brouwer M, Huss A, Peters S, et al. Parkinson's disease and long-term exposure to outdoor air pollution: A matched case-control study in the Netherlands. Environment International 2019;129:28–34.

3-James SL, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet 2018;392:1789–858.

4-Shalash AS, Hamid E, Elrassas HH, Bedair AS, Abushouk AI, Khamis M, et al. Non-Motor Symptoms as Predictors of Quality of Life in Egyptian Patients With Parkinson's Disease: A Cross-Sectional Study Using a Culturally Adapted 39-Item Parkinson's Disease Questionnaire. Front Neurol 2018;9:357.

5- Scorza FA, do Carmo AC, Fiorini AC, Nejm MB, Scorza CA, Finsterer J, et al. Sudden unexpected death in Parkinson's disease (SUDPAR): a review of publications since the decade of the brain. Clinics (Sao Paulo) 2017;72:649–51.

6- Rosemary Martino,HamiltonCandundo,Pascal van Lieshou, Sabina Shin. Onset and Progression Factors in Parkinson's Disease: A Systematic Review.Neurotoxicology 2016

7- EfthaliaAngelopouloua, Maria Bozia, Athina-Maria Simitsi, Christos Koros.The relationship between environmental factors and different Parkinson's disease subtypes in Greece: Data analysis of the Hellenic Biobank of Parkinson's disease. Parkinsonism and RelatedDisorders.AUGUST 2019

8- Ball N, Teo W-P, Chandra S, Chapman J. Parkinson's Disease and the Environment. Front Neurol 2019;10:218.

9-Wu T, Hallett M. The cerebellum in Parkinson's disease. Brain 2013;136:696–709.

10-Stoessl AJ, Lehericy S, Strafella AP. Imaging insights into basal ganglia function, Parkinson's disease, and dystonia. The Lancet 2014;384:532–44.

11-Nabli F, Ben Sassi S, Amouri R, Duda JE, Farrer MJ, Hentati F. Motor phenotype of LRRK2-associated Parkinson's disease: a Tunisian longitudinal study. MovDisord 2015;30:253–8.

12-Defebvre L. Maladie de Parkinson : rôle des facteurs génétiques et environnementaux. Implication en pratique clinique quotidienne. Revue Neurologique 2010;166:764–9.

13-Narayan S, Liew Z, Bronstein JM, Ritz B. Occupational pesticide use and Parkinson's disease in the Parkinson Environment Gene (PEG) study. Environment International 2017;107:266–73.

14-Tanaka K, Miyake Y, Fukushima W, Sasaki S, Kiyohara C, Tsuboi Y, et al. Occupational risk factors for Parkinson's disease: a case-control study in Japan. BMC Neurol 2011;11:83.

15-Vlaar T, Kab S, Schwaab Y, Fréry N, Elbaz A, Moisan F. Association of Parkinson's disease with industry sectors: a French nationwide incidence study. Eur J Epidemiol 2018;33:1101–11.

16-Eleonar lingor, Lingor P. Insights on the interaction of alpha-synuclein and metals in the pathophysiology of Parkinson's disease. Metallomics 2015;7:395–404.

17- Paul KC, Chuang Y-H, Shih I-F, Keener A, Bordelon Y, Bronstein JM, et al. The association between lifestyle factors and Parkinson's disease progression and mortality: Lifestyle and Parkinson's disease progression. Mov Disord 2019;34:58–66.

18- M Hafsia, K Imen, N Mrizak, O El Maalel.Impact du stress professionnel sur la séverité de l'Eczema des mains 2018.

19- McGuire V, Nelson LM, Koepsell TD, Checkoway H, Longstreth WT. Assessment of Occupational Exposures in Community-Based Case-Control Studies. Annual Review of Public Health 1998;19:35–53.

20- BOUYER. Epidémiologie. Librairie Lavoisier 2019.

21- Kab S, Spinosi J, Chaperon L, Dugravot A, Singh-Manoux A, Moisan F, et al.Agricultural activities and the incidence of Parkinson's disease in the general French population. European Journal of Epidemiology 2017;32:203–16.

22- Mamane A. Effets sanitaires aigus de l'exposition aux pesticides en milieu rural: étude dans un pays du nord: étude PhytoRiv: étude dans un pays du sud: PhytoNiger 2015.

23-James KA, Hall DA. Groundwater Pesticide Levels and the Association With Parkinson Disease. Int J Toxicol 2015;34:266–73.

24- Labarere DJ. Interprétation d'une enquête épidémiologique : type d'enquête, notion de biais, causalité (72) n.d.:7.

25- Gillies GE, Pienaar IS, Vohra S, Qamhawi Z. Sex differences in Parkinson's disease. Front Neuroendocrinol 2014;35:370–84.

26-Jurado-Coronel JC, Cabezas R, Ávila Rodríguez MF, Echeverria V, García-Segura LM, Barreto GE. Sex differences in Parkinson's disease: Features on clinical symptoms, treatment outcome, sexual hormones and genetics. Frontiers in Neuroendocrinology 2018;50:18–30.

27- Bellou V, Belbasis L, Tzoulaki I, Evangelou E, Ioannidis JPA. Environmental risk factors and Parkinson's disease: An umbrella review of meta-analyses. Parkinsonism & Related Disorders 2016;23:1–9.

28- Gao H-M, Hong J. Gene–environment interactions: key to unraveling the mystery of Parkinson's disease. Prog Neurobiol 2011;94:1–19.

29- Sieurin J, Andel R, Tillander A, Valdes EG, Pedersen NL, Wirdefeldt K. Occupational stress and risk for Parkinson's disease: A nationwide cohort study: Stress and Risk of PD. Mov Disord 2018;33:1456–64.

30- Wu Q, Yang X, Zhang Y, Zhang L, Feng L. Chronic mild stress accelerates the progression of Parkinson's disease in A53T α-synuclein transgenic mice. Experimental Neurology 2016;285:61–71.

31- Wassouf Z, Schulze- Hentrich JM. Alpha- synuclein at the nexus of genes and environment: the impact of environmental enrichment and stress on brain health and disease. J Neurochem 2019:jnc.14787.

32-Shih I-F, Liew Z, Krause N, Ritz B. Lifetime Occupational and Leisure Time Physical Activity and Risk of Parkinson's Disease. Parkinsonism RelatDisord 2016;28:112–7.

33- Sääksjärvi K, Knekt P, Männistö S, Lyytinen J, Jääskeläinen T, Kanerva N, et al. Reduced risk of Parkinson's disease associated with lower body mass index and heavy leisure-time physical activity. Eur J Epidemiol 2014;29:285–92.

34-Chuang Y-H, Lill CM, Lee P-C, Hansen J, Lassen CF, Bertram L, et al. Gene-environment interaction in Parkinson's disease: coffee, ADORA2A, and CYP1A2. Neuroepidemiology 2016;47:192–200.

35-Derkinderen P, Shannon KM, Brundin P. Gut feelings about smoking and coffee in Parkinson's disease. Mov Disord 2014;29:976–9.

36-Mischley LK, Lau RC, Bennett RD. Role of Diet and Nutritional Supplements in Parkinson's Disease Progression. Oxid Med Cell Longev 2017;2017.

37-Goldman SM. Environmental Toxins and Parkinson's Disease. Annual Review of Pharmacology and Toxicology 2014;54:141–64.

38-Caudle WM, Guillot TS, Lazo CR, Miller GW. Industrial toxicants and Parkinson's disease. Neurotoxicology 2012;33:178–88.

39-Pezzoli G, Cereda E. Exposure to pesticides or solvents and risk of Parkinson disease. Neurology 2013;80:2035–41.

40- Ennaceur S. Etude des Résidus des Pesticides Organochlorés & des BiphénylesPolychlorés (PCB) dans le Lait Maternel et le Sang d'Adulte en Tunisie: Niveau de Contamination & Génotoxicité dans les Lymphocytes Humains. ResearchGate 2019.

41-Ohlson CG, Hogstedt C. Parkinson's disease and occupational exposure to organic solvents, agricultural chemicals and mercury--a case-referent study. Scand J Work Environ Health 1981;7:252–6.

42-Reis J, Benbrick E, Bonneterre V, Spencer PS. Parkinson's disease and solvents: Is there a causal link? Revue Neurologique 2016;172:761–5.

43- Lock EA, Zhang J, Checkoway H. Solvents and Parkinson disease: A systematic review of toxicological and epidemiological evidence. Toxicol Appl Pharmacol 2013;266:345–55.

44- Liu M, Shin E-J, Dang D-K, Jin C-H, Lee PH, Jeong JH, et al. Trichloroethylene and Parkinson's Disease: Risk Assessment. Mol Neurobiol 2018;55:6201–14.