Interaction Between ABCB1 and Professional Exposure to Organochlorine Insecticides in Parkinson Disease

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Objective: To study the association between Parkinson disease (PD) and 2 polymorphisms in ABCB1 among subjects enrolled in the French health system for agricultural workers (Mutualité Sociale Agricole), as well as the interaction between ABCB1 and organochlorine insecticides.

Design: Case-control study.

Setting: Mutualité Sociale Agricole.

Participants: Patients with PD were examined by a neurologist and were matched to a maximum of 3 controls. Participants were classified as never users, users for gardening, and professional users of pesticides. Detailed information on pesticides lifelong use was obtained for professional users by occupational health physicians.

Main Outcome Measures: DNA was obtained and 2 ABCB1 polymorphisms (exon 21: G2677[A,T]; exon 26: C3435T) associated with altered P-glycoprotein function were genotyped.

Results: Among 207 cases and 482 matched controls, ABCB1 polymorphisms were not associated with PD (C3435T, \( P = .43 \); G2677[A,T], \( P = .97 \)). Among 101 male cases and 234 matched controls, the odds ratio for organochlorines was 3.5 (95% confidence interval, 0.9-14.5) times higher among homozygous carriers of variant G2677 (A,T) alleles than noncarriers. Among cases only, we found an association between carrying 2 variant G2677(A,T) alleles and organochlorines (odds ratio, 5.4, 95% confidence interval, 1.1-27.5) as well as with the number of cumulative lifetime number of hours of exposure (\( P = .005 \); analyses restricted to subjects exposed to organochlorines, \( P = .03 \)).

Conclusions: Our findings suggest that the ABCB1 gene and exposure to organochlorine insecticides interact to increase PD risk: in subjects professionally exposed to organochlorines, polymorphisms associated with a decreased ability of ABCB1 to clear xenobiotics from the brain increased the risk of PD. These findings support the hypothesis of gene x pesticides interactions in PD.

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In most cases, the etiology of Parkinson disease (PD) is likely to be multifactorial, and environmental factors as well as their interaction with susceptibility genes are considered to contribute to the disease.\(^1\) Humans exposed to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) develop parkinsonism via inhibition of mitochondrial function in dopaminergic neurons.\(^2\) To be active, MPTP is metabolized into 1-methyl-4-pyridinium (MPP\(^+\)) that has a chemical structure similar to that of the herbicide paraquat. Epidemiologic studies show a consistent association between pesticide exposure and PD.\(^3\) We recently showed that organochlorine insecticides may be more particularly involved in this association.\(^4\) If environmental chemicals can increase PD risk, host factors that contribute to variability in their uptake, metabolism, and distribution in the body may modulate individual risk. Genetic polymorphisms of xenobiotic metabolizing enzymes may act as such susceptibility factors. The P-glycoprotein (P-gp) is a member of the superfamily of adenosine triphosphate–binding cassette (ABC) transporters and is encoded by the multidrug resistance protein 1 gene (MDR1 or ABCB1) on chromosome 7. This 170-kDa glycoprotein is a transmembrane transporter acting as an active efflux pump for a wide range of endogenous molecules and xenobiotics. P-glycoprotein is found on the luminal surface of blood capillaries in the blood-brain barrier and regulates intracerebral penetration of these compounds. Several pesticides, including organochlorines, are P-gp substrates and/or inhibitors.\(^6,7\) Previous studies on the relation between ABCB1 and PD yielded inconsis-
ent findings. Only 2 of them, using a case-only design, assessed the joint effects of ABCB1 and pesticides and suggested that ABCB1 may interact with pesticides in PD.

We studied the association between PD and 2 ABCB1 polymorphisms known to alter P-gp function (C3435T, rs 1045642; G2677[A,T], rs 2032582) in a community-based case-control study conducted in a population characterized by a high prevalence of pesticide exposure. We also investigated the interaction between ABCB1 polymorphisms and professional exposure to organochlorine insecticides.

**METHODS**

**SUBJECTS**

This study was conducted among subjects enrolled in Mutualité Sociale Agricole, the organization responsible for the reimbursement of health-related expenses to workers in the agricultural area. The detailed study protocol is described elsewhere.4

In France, PD is part of a list of 30 diseases for which complete and free health coverage can be obtained. Patients applying for free coverage for the first time (February 1998 to August 1999) and aged 18 to 75 years were included. A neurologist examined them; if impossible, the patient’s treating neurologist filled out a clinical questionnaire. Parkinsonism was defined as the presence of at least 2 cardinal signs (rest tremor, bradykinesia, rigidity, impaired postural reflexes); PD was defined as the presence of parkinsonism after exclusion of other causes of parkinsonism.14

In France, affiliates of health insurance organizations have to make a request to be reimbursed for a number of health expenses. Controls were recruited among all the Mutualité Sociale Agricole affiliates who made such requests (February 1998 to February 2000). A maximum of 3 controls were matched to each case on age (±2 years), sex, and region of residency.

**ASSESSMENT OF PESTICIDE EXPOSURE**

The methods used to assess pesticide exposure are described elsewhere.4 Briefly, participants completed self-administered questionnaires including detailed occupational history and information on pesticide use for work or gardening. Professional pesticide users were interviewed at home by occupational health physicians to confirm professional exposure and obtain detailed data on pesticide use: description of farms, pesticide type and use, spraying frequency (per year), number of hours of spraying (per year), calendar period, and spraying method. The questionnaires were reviewed by a panel of experts (agricultural engineer, epidemiologist, occupational health physician), blinded to the case or control status, to confirm exposure and check for consistency. Following this 2-stage procedure, participants were classified as never users of pesticides, users for gardening only, or professional users.4

We constructed an “exposure history” data set consisting of multiple observations per subject, each corresponding to an instance of pesticide use. Pesticides were coded using a pesticide dictionary and were grouped into (1) 50 families based on chemical similarities: 12 insecticides (eg, organochlorines), 21 herbicides (eg, triazines), and 17 fungicides (eg, carbamates) and (2) 3 pesticide categories: insecticides, fungicides, and herbicides. Four generic “unknown” codes were used when a subject did not remember the specific pesticide used (unknown insecticide, fungicide, herbicide, and pesticide). Fifty-three indicators were computed (50 families, 3 categories).

**GENETIC ANALYSES**

Single-nucleotide polymorphisms in exon 21 (G2677[A, T]) and 26 (C3435T) were detected using a 5’ nucleic acid discrimination assay (ABI PRISM 7900 Sequence Detection System; Applied Biosystems, Foster City, California). For exon 21 amplification, we used the forward 5’- GAGCATAGTACAGTAGGAGAAACA-3’ and reverse 3’- GGACACGACGTGAA GATAAAAGA-3’ primers and for exon 26, the forward 5’- ATGTATGTGCGCTCTCTTGCT-3’ and reverse 5’- AACAGCAGGTTGTTGCTC-3’ primers. Specific probes for each allele were labeled with fluorescence reporter dyes FAM (2677G) and VIC (2677A and T) at their 5’ extremities.

**STATISTICAL ANALYSIS**

Analyses are based on subjects with both parents born in Europe, of whom the large majority were born in France. We used conditional logistic regression (PROC PHREG, SAS version 9.1; SAS Institute Inc, Cary, North Carolina) for matched sets to compute odds ratios (ORs). All analyses were adjusted for Mini-Mental State Examination (MMSE) level (categorical variable with 3 levels defined according to tertiles of the MMSE score distribution: ≤26, 27-28, and ≥29) and smoking (categorical variable with 3 levels: never smoker, ever smoker ≤17 [median] pack-years, ever smoker >17 pack-years).

Analyses of the association between PD and the polymorphisms were performed overall (men and women combined). Analyses of the interaction between the polymorphisms and organochlorine insecticides were restricted to men because professional exposure to pesticides is considerably more frequent among men than women.4 We assessed interactions by estimating ORs for individual and joint effects and introducing multiplicative terms in the models. For these analyses, an indicator variable for “gardening-only” pesticide use was included in the models to exclude from the reference group subjects exposed exclusively through gardening; therefore, we are evaluating interactions between the genetic polymorphisms and professional exposures.

Two types of interaction analyses were performed. First, we based our analyses on subjects with definite exposure to organochlorines (yes/no); subjects with missing values were excluded from the analyses. Second, we imputed missing values for organochlorines in the pesticide history exposure data set using a method described elsewhere based on the strongest predictors of exposure (sex, age, period, crop, MMSE score) and case/control status. The substituted exposure summary data set was used to compute ORs (PROC MI (SAS version 9.1); each data set was generated using PROC MI (SAS version 9.1)); each of these was reduced to an exposure summary data set. Imputed exposure summary data sets were analyzed as complete data; the 10 sets of results were pooled using PROC MI (SAS version 9.1).

We also followed a case-only approach using the imputed data set by investigating the association between ABCB1 polymorphisms and exposure to organochlorines (ever/never; cumulative lifetime number of hours of exposure) among cases. We used logistic regression and analysis of covariance and...
checked that organochlorines and ABCB1 polymorphisms were independent among controls. In a previous article, we showed an interaction between CYP2D6 poor metabolizers and pesticide exposure; to rule out that the interaction between ABCB1 polymorphisms and organochlorines was not confounded by CYP2D6 poor metabolizers and that our findings were confirmed among persons who were not poor metabolizers, we performed sensitivity analyses by excluding or adjusting for CYP2D6 poor metabolizers.

RESULTS

DNA was obtained for 207 cases and 482 matched controls (Figure). Among male participants, detailed pesticide information was obtained for 101 cases and 234 matched controls. Table 1 shows the characteristics of the participants and the distribution of the G2677(A,T) and C3435T polymorphisms, overall and in men with pesticide data.

Both polymorphisms were in Hardy-Weinberg equilibrium among controls (G2677[A,T], P = .37; C3435T, P = .36). Their allelic frequencies among controls were similar to those previously reported among white individuals (G2677[A,T]: G = 0.56, T = 0.43, A = 0.01; C3435T: C = 0.49, T = 0.51). Overall, there was no difference in the distributions of both polymorphisms in cases and controls (Table 1). Similar results were observed in strata defined by age at onset and sex (data not shown).

In men, the OR for organochlorines was 2.2 (95% confidence interval [CI], 1.1-4.5; P = .02) in subjects with definite exposure (Table 1) and 2.1 (95% CI, 1.1-4.1; P = .03) in the imputed data set. Our interaction analyses are shown in Table 2. Among men with definite exposure, we found that the association between organochlorines and PD was significantly stronger for carriers of 2 variant alleles than in noncarriers, for both polymorphisms; moreover, homozygous mutant carriers exposed to organochlorines were at the highest risk of PD. Using multiple imputation, the interaction P value remained of borderline significance for the G2677(A,T) polymorphism, while it considerably decreased for C3435T. The interaction between organochlorines and G2677 was not statistically different in men with PD onset before and after median age 65 years (P = .90).

In case-only analyses, we found an association between carrying 2 variant alleles and organochlorines (G2677[A,T], OR, 5.4; 95% CI, 1.1-27.5; P = .04; C3435T, OR, 4.1; 95% CI, 1.0-17.0; P = .05). In addition, carrying 2 variant alleles was associated with the number of cumulative lifetime number of hours of exposure for the G2677(A,T) polymorphism (overall, P = .005; in analyses restricted to subjects exposed to organochlorines, P = .03) but not for the C3435T polymorphism (overall, P = .08; in analyses restricted to subjects exposed to organochlorines, P = .23). There was no association between both polymorphisms and organochlorines among controls (G2677[A,T], P = .44; C3435T, P = .21).

Both in case-control and case-only analyses among men, excluding or adjusting for CYP2D6 poor metabolizers (6 cases, 12 controls) from the analyses and adjusting for exposure to organophosphate insecticides led to similar results (data not shown).

COMMENT

In this study, we found that 2 polymorphisms in ABCB1 were not associated with PD overall. However, our find-
ings are in favor of an interaction between the G2677 (A,T) polymorphism and organochlorines: the relation between organochlorines and PD was approximately 3.5 times stronger among male carriers of 2 variant alleles than among noncarriers, and among cases, we found an association between the polymorphism and organochlorines using 2 different measures of exposure.

Previous studies of ABCB1 in PD suggested that this gene plays a minor role.8,10,11,17 However, most of these studies did not assess pesticide exposure and there is already some evidence of gene × pesticides interactions in PD.16,18-20 Two studies, using a case-only design, showed an association between pesticides and the C3435T polymorphism with ORs of 4.99 and 4.7.12 The crucial assumption underlying the case-only design is that the environmental exposure and the genetic polymorphism are independent among controls;15 however, data presented in both studies did not allow checking whether this assumption held. In both studies, men and women, who have very different exposure profiles, were not distinguished and exposure to pesticides was considered overall, without investigating specific pesticide families.

Using a detailed exposure assessment method, we showed that the G2677(A,T) polymorphism modified the association between organochlorines and PD. We3 and others21-23 have shown an association between PD and exposure to organochlorines. In addition, it was recently reported that β-hexachlorocyclohexane was more frequently detected in the sera of patients with PD, and at higher levels, compared with controls.24,25 Organochlorines tend to accumulate in lipid-rich organs, such as the brain.26 and postmortem studies found increased levels of dieldrin and γ-hexachlorocyclohexane in PD brains compared with controls.27 Several organochlorines, including DDT and cyclodiene (eg, heptachlor, endosulfan, and dieldrin), exert selective effects on striatal dopaminergic neurons.28 Dieldrin is more toxic to dopaminergic cells than nondopaminergic cells, and depletes brain dopamine levels by increasing the expression of the dopamine and the vesicular monoamine transporters in presynaptic terminals of dopaminergic neurons.

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Table 1. General Characteristics and ABCB1 Genotype Distributions in Cases and Controls

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All Subjects</th>
<th>Male Subjects With Pesticide Data Available</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%)</td>
<td>No. (%)</td>
</tr>
<tr>
<td></td>
<td>(n = 207)</td>
<td>(n = 101)</td>
</tr>
<tr>
<td></td>
<td>(n = 482)</td>
<td>(n = 234)</td>
</tr>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td></td>
<td>P Value</td>
<td>P Value</td>
</tr>
<tr>
<td>Male</td>
<td>118 (57)</td>
<td>101 (100)</td>
</tr>
<tr>
<td></td>
<td>286 (59)</td>
<td>234 (100)</td>
</tr>
<tr>
<td>Age at onset, y, median (IQR)</td>
<td>65 (10)</td>
<td>65 (9)</td>
</tr>
<tr>
<td>Age at study, y, median (IQR)</td>
<td>69 (9)</td>
<td>69 (9)</td>
</tr>
<tr>
<td>MMSE score, median (IQR)</td>
<td>27 (5)</td>
<td>26 (4)</td>
</tr>
<tr>
<td></td>
<td>28 (3)</td>
<td>28 (3)</td>
</tr>
<tr>
<td>Family history of PD</td>
<td>18 (9)</td>
<td>9 (9)</td>
</tr>
<tr>
<td>Ever smoking</td>
<td>52 (25)</td>
<td>40 (40)</td>
</tr>
<tr>
<td>Professional</td>
<td>158 (33)</td>
<td>122 (53)</td>
</tr>
<tr>
<td>Professional</td>
<td>0.6 (0.4-0.9)</td>
<td>0.6 (0.4-0.9)</td>
</tr>
<tr>
<td>Pesticide exposure</td>
<td>56 (27)</td>
<td>8 (8)</td>
</tr>
<tr>
<td>Gardening</td>
<td>41 (20)</td>
<td>14 (14)</td>
</tr>
<tr>
<td>Professional</td>
<td>207 (43)</td>
<td>169 (72)</td>
</tr>
<tr>
<td>Professional</td>
<td>1.8 (1.1-3.3)</td>
<td>1.9 (0.8-4.1)</td>
</tr>
<tr>
<td>ABBB1 C3435T</td>
<td>45 (22)</td>
<td>25 (25)</td>
</tr>
<tr>
<td>GG</td>
<td>122 (54)</td>
<td>52 (51)</td>
</tr>
<tr>
<td>CC</td>
<td>112 (54)</td>
<td>118 (50)</td>
</tr>
<tr>
<td>TT</td>
<td>20 (10)</td>
<td>60 (26)</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>1.0 (0.6-1.6)</td>
<td>0.9 (0.5-1.8)</td>
</tr>
<tr>
<td>P Value</td>
<td>0.39</td>
<td>0.82</td>
</tr>
<tr>
<td>ABBB1 G2677(A,T)</td>
<td>3 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>TA</td>
<td>65 (31)</td>
<td>34 (34)</td>
</tr>
<tr>
<td>GT</td>
<td>99 (48)</td>
<td>47 (47)</td>
</tr>
<tr>
<td>AA</td>
<td>50 (24)</td>
<td>24 (24)</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>1.0 (0.6-1.6)</td>
<td>0.9 (0.5-1.8)</td>
</tr>
<tr>
<td>P Value</td>
<td>0.95</td>
<td>0.91</td>
</tr>
<tr>
<td>ABBB1 G2677(A,T)</td>
<td>39 (19)</td>
<td>20 (20)</td>
</tr>
<tr>
<td>GG</td>
<td>65 (31)</td>
<td>34 (34)</td>
</tr>
<tr>
<td>GT, TA</td>
<td>102 (50)</td>
<td>47 (46)</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>1.0 (0.6-1.6)</td>
<td>0.9 (0.5-1.9)</td>
</tr>
<tr>
<td>P Value</td>
<td>0.98</td>
<td>0.91</td>
</tr>
<tr>
<td>Organochlorine insecticide exposurec</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>35 (35)</td>
<td>109 (47)</td>
</tr>
<tr>
<td>Yes</td>
<td>42 (41)</td>
<td>71 (30)</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>1.0 (0.6-1.6)</td>
<td>2.2 (1.1-4.5)</td>
</tr>
<tr>
<td>P Value</td>
<td>0.83</td>
<td>0.02</td>
</tr>
<tr>
<td>Missing</td>
<td>24 (24)</td>
<td>54 (23)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; IQR, interquartile range; MMSE, Mini-Mental State Examination; OR, odds ratio; PD, Parkinson disease.

a We used conditional logistic regression for matched sets with a varying number of controls to compute ORs (95% CI). Mini-Mental State Examination score was categorized according to the tertiles of its pooled distribution to perform a trend test.

b P values for the global comparison of the distributions of genotypes in cases and controls.

c Subjects exposed for gardening exclusively are treated as their own exposure group and are not included in the “No” exposure group for the computation of ORs. There were 14 male cases and 31 male controls who were exposed through gardening exclusively.

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in the striatum of mice.\textsuperscript{30,31} In addition, dieldrin induces apoptotic cell death, mitochondrial dysfunction, and protein aggregation\textsuperscript{32} and induces oxidative damage in the mouse nigrostriatal dopamine system.\textsuperscript{33}

Several pesticides, including organochlorines, have been shown to be P-gp substrates and/or to inhibit human P-gp.\textsuperscript{4} P-glycoprotein substrates have common characteristics: molecular mass of 300 Da or more, lipophilicity, and amphipathic properties.\textsuperscript{6} Therefore, this pump may be important for the clearance of polycyclic aromatic hydrocarbons and pesticides.\textsuperscript{6,34,35} A study of the interaction between P-gp and 4 insecticides, including an organochlorine (endosulfan), suggested that these compounds interact with P-gp with high affinity and that they may be transported by the protein; moreover, these insecticides block its transport activity at low concentrations, suggesting that they are P-gp inhibitors.\textsuperscript{7} DDT has also been shown to be a P-gp inhibitor.\textsuperscript{36} Therefore, the ability of P-gp to clear xenobiotics from the body may be compromised by the presence of pesticides, leading to a higher risk of toxic effects. This hypothesis is consistent with the observation that mice lacking a functional \textit{mdr1a} gene accumulate higher levels of many drugs in several tissues, especially the brain, when compared with wild-type mice.\textsuperscript{37}

Among several \textit{ABCB1} single-nucleotide polymorphisms, those located in exon 21 (\textit{G2677[A,T]}) and exon 26 (\textit{C3435T}) have been shown to be of particular interest. \textit{C3435T} and \textit{G2677[A,T]} are in strong linkage disequilibrium; \textit{G2677[A,T]} leads to a missense mutation and can explain, at least partly, the impact of \textit{C3435T} on P-gp function, although there is evidence that the silent \textit{C3435T} variant can also contribute to change substrate specificity.\textsuperscript{38} In a study of the effect of different \textit{ABCB1} polymorphisms on P-gp functionality, the \textit{G2677[A,T]-TT}, and to a lesser extent \textit{C3435T-TT} genotypes, decreased P-gp activity in vitro.\textsuperscript{39}

Two case-only studies on the association between pesticides and \textit{ABCB1} in PD found an association with the \textit{C3435T} polymorphism,\textsuperscript{9,12} whereas our findings were more robust for the \textit{G2677[A,T]} polymorphism; similarly, \textit{G2677[A,T]-TT} is considered as a positive predictor of tacrolimus-induced neurotoxicity.\textsuperscript{40} In 1 study, only \textit{C3435T} was genotyped,\textsuperscript{9} and in another study, both polymorphisms were genotyped but only the association between \textit{C3435T} and pesticides was reported.\textsuperscript{12}

An important strength of our study is the use of a detailed pesticide exposure assessment method in a population characterized by a high exposure level. It is however possible that farmers did not declare some products (eg, rarely used ones). Because cognitive impairment is more frequent in PD, recall may be differential. We therefore adjusted all our analyses for Mini-Mental State Examination score and cigarette smoking (in pack-years). The main limit of this study is the difficulty in accounting for multiple correlated exposures in the analyses. We therefore focused on organochlorines because (1) they were found to display the most robust association with PD and a dose-effect trend in previous analy-
ses based on the same subjects,\(^4\) (2) there are laboratory data in favor of dopaminergic toxicity of these compounds, and (3) there is evidence that they interact with P-gp. Because organochlorines were one of the pesticide families with the highest frequency of use, it is possible that the lack of association with other less frequently used families may be due to insufficient power. Similarly, it is also possible that other pesticides interact with \(ABC\) in PD. For instance, the organophosphate insecticides diazinon and chlorpyrifos\(^{12,43}\) affect P-gp function. Including organophosphate insecticides in the model did not modify the interaction between \(G2677\) (\(A,T\)) and organochlorines, thus suggesting that the interaction was not explained by organophosphates; however, we were not able to include in the same model both an interaction term for organochlorines and organophosphates because of the size of the study and larger studies would be needed to disentangle their respective role. Despite the high frequency of pesticide exposure in this sample, our interaction analyses are based on small numbers and larger studies of subjects exposed to pesticides will be necessary to confirm these findings. Finally, the multiple imputation method that we used did not allow us to study the association with \(ABC\) haplotypes.

Based on this laboratory hypothesis, we show that organochlorine insecticides may interact with \(ABC\) in determining the risk of PD. These findings support the hypothesis of gene\(\times\)pesticide interactions in PD. A better understanding of the relation between P-gp and pesticides, in particular organochlorines, and of the functionality of \(ABC\) polymorphisms is therefore needed.

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