FAMILY HISTORY BASED APPROACH IN RISK PREDICTION FOR PARKINSON’S DISEASE: ADDITIONAL CONTRIBUTION OF FAMILIAL ASSOCIATED DISORDERS

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The aim of our study was to examine the contribution of family history of Parkinson’s disease and its associated disorders in the assessment of predictive capacity of risk models for Parkinson’s disease. In a population of 192 patients with Parkinson’s disease and 1659 healthy individuals we investigated the impact of environmental factors and the effects of family history on Parkinson’s disease risk. Pesticides exposure, positive family history of Parkinson’s disease and a positive family history of dementia and melanoma were associated to an increased risk for Parkinson’s disease, with results regarding family history of depression near to statistical significance. Smoking and caffeine intake were associated to a decreased risk for Parkinson’s disease. Three risk prediction models were assessed using the area under the curve approach: first model was based on known environmental risk factors, in the second model we added family history of Parkinson’s disease and in the third model we additionally included family history of dementia, melanoma and depression. We showed that inclusion of data on family history of associated disorders (AUC 0.76) improves predictive capacity of risk model for Parkinson’s disease in
comparison with the first (AUC 0.62) and the second model (AUC 0.71). We concluded that family history of associated disorders: dementia, depression and melanoma improves predictive capacity of risk models for Parkinson’s disease.

Key words: Parkinson’s disease, family history, risk prediction

INTRODUCTION

Parkinson’s disease (PD) is the second most common neurodegenerative disease in the world. The pathogenesis leading to neurodegeneration has not yet been fully explained, but several risk factors, including a positive family history of PD, environmental and genetic risk factors have been established (DICK et al., 2007; GORELL et al., 2004; MAVER and PETERLIN, 2011; PALADA et al., 2012; TAYLOR et al., 1999). Combining these factors in risk prediction models could lead to identification of healthy individuals at risk for developing idiopathic PD and allow for implementation of preventive strategies for PD.

Previous PD risk screening approaches included anamnestic (family history of PD, presence of environmental risk factors and early non-motor symptoms, i.e. decreased olfaction, autonomic symptoms, sleepiness and insomnia, depression and personality changes), and clinical risk factors (subtle motor impairment, hyposmia, autonomic testing, dopaminergic functional imaging, genetic studies and neuroimaging techniques, e.g. enlarged substantia nigra hyperechogenicity) (BERG et al., 2013; HALL et al., 2013; POSTUMA and MONTPLAISIR, 2009; STERN and SIDEROWF, 2010). These studies demonstrated that PD prediction models, though not yet ideal, could be useful for PD risk prediction.

Next to conventional parameters, previously included in PD risk models and screening batteries, it is known that PD is associated with several other PD co-occurring disorders in the family. Alzheimer’s disease and PD have been shown to aggregate in families with positive family history of both neurodegenerative diseases (ROSEN et al., 2007). Moreover, a study on familial aggregation of depression, dementia and PD found the risk of bipolar depression might be increased for those with relatives with PD (FAHIM et al., 1998). Additionally, a family history of melanoma in a first degree relative has been associated with a higher risk of PD, independently of environmental risk factors (GAO et al., 2009).

We hypothesized that aggregation of PD associated disorders occurring within families could be used as a new risk factor in determining individuals who may be at risk for PD. To test the hypothesis we performed a study to assess familial co-occurrence of selected associated disorders in patients with PD and to further develop the related risk prediction model.

MATERIALS AND METHODS

Study design and settings

This study was designed as a part of a larger cross-sectional observational study Family history – genetic tool for preventive medicine taking place in Slovenia from November 2010 to May 2013.

Ethical statement

The study received ethical approval from the National Medical Ethics Committee of the Republic of Slovenia (No.98/12/10). All participants gave informed written consent to
participate in the study. A doctor or a trained nurse was present to assess each patient’s capacity to consent.

Study population

The study population consisted of 192 consecutive PD patients of “The Centre for Extrapyramidal Disorders” (in collaboration with the Department for Neurology University Medical Center Ljubljana). All patients met UK PD Society Brain Bank diagnostic criteria as determined by a neurologist. Simultaneously, data from healthy individuals were collected from consecutive individuals who came for their regular preventive check-up in occupational health practices from November 2010 to June 2012 (KLEMENC-KETIS and PETERLIN, 2013). Data were collected by means of a self-developed questionnaire. The questionnaire consisted of demographic questions and questions on family history of PD and other chronic diseases. The respondents selected the chronic diseases from a list (PD, dementia, depression, melanoma) and were also given a chance to add other diseases not included in the questionnaire. We also acquired data on the presence of known PD risk factors (regular caffeine intake, smoking – ever vs. never, prolonged pesticide and well water exposure).

Statistical analysis

Family history was considered positive when at least one first-degree or second-degree relative was affected.

Descriptive statistics were computed with SPSS 17.0 package (SPSS Inc., Chicago, IL). Odds ratios (OR) and their respective 95% confidence intervals (CI) were calculated. Associations were regarded as significant when they reached the P-value equal to or less than 0.05.

We constructed three risk prediction models using the machine learning algorithms by incrementally introducing collected variables in the model (KRUPPA et al., 2012). Model 1 was based on known environmental risk factors for PD, smoking, coffee consumption and pesticide exposure. In model 2 we used parameters from model 1 and added family history of PD. In model 3 we used parameters from model 2 and added family history of dementia, depression and melanoma. For each model we evaluated predictive accuracy measured by the area under the ROC (receiver operating characteristics) curve (AUC).

Performance of each model was independently estimated by performing cross-validation by dividing the complete study population on subsets of training and test samples. The cross-validation method utilized for this purpose consisted of 5-fold cross-validation scheme, where estimations for each fold were re-calculated in 10 iterations. The learning sets and test sets were selected to retain the case-control ratios comparable to that of the whole study group. Performance of the models was estimated by determining the area under curve (AUC) metric, which captures the relationship profile between specificity and sensitivity. We regarded differences in AUC significant when a model generated consistently and significantly higher AUC values across several iterations of cross-validation procedure (P<0.01). The AUC values from separate iterations of cross-validation procedure were averaged and presented as mean AUC value with 95% interval of confidence calculated based on the t-distribution.
The subjects with incomplete data and missing values were excluded from prediction model generation and cross-validation.

RESULTS

The final sample consisted of 192 patients with Parkinson’s disease and 1659 healthy control participants. Of 192 PD patients 115 (59.9%) were male. The mean age of our patients was 67.1 ± 9.2 years. Healthy control group consisted of 1,659 respondents, of which 1007 (60.7%) were male. The mean age of control group was 40.8 ±10.2 years. 36 (18.8%) PD patients reported at least one family member affected with PD (Table 1). Of known environmental risk factors for PD, exposure to pesticides was associated with higher risk for PD and smoking and coffee consumption were associated with lower risk for PD (Table 1). Exposure to well water was not significantly associated with PD.

In families of patients we found significantly higher prevalence of dementia and melanoma as well as a trend for depression (Table 1).

| Table 1. Demographic characteristics, risk factors exposure and family history data |
|---------------------------------|-----------------|-----------------|-----------------|
|                                 | Study group N=194 (%) | Control group N=1671 (%) | OR (95% CI)     | P value         |
| Smoking                         | 10 (5.2)          | 447 (26.8)       | 0.15 (0.08-0.28) | p < 0.0001     |
| Caffeine intake                 | 107 (55.2)        | 1148 (68.7)      | 0.56 (0.42-0.76) | p = 0.0002     |
| Pesticide exposure              | 20 (10.3)         | 97 (5.8)         | 1.87 (1.12-3.09) | p = 0.0158     |
| Family history of PD            | 36 (18.6)         | 20 (1.2)         | 18.81 (10.63-33.27) | p < 0.0001     |
| Family history of dementia      | 29 (14.9)         | 61 (3.7)         | 4.64 (2.90-7.42)  | p < 0.0001     |
| Family history of depression    | 9 (4.6)           | 38 (2.3)         | 2.09 (1.00-4.39)  | p = 0.0515     |
| Family history of melanoma      | 6 (3.1)           | 11 (0.7)         | 4.82 (1.76-13.17) | p = 0.0022     |

Legend: Family history applies to first and second-degree relatives; more distant relatives are not included. PD = Parkinson’s disease, OR=odds ratio, CI= confidence interval.

By using the cross-validation approach (KRUPTA et al., 2012) we constructed three risk prediction models for PD. The first model with environmental risk factors achieved discriminatory capacity of 0.62 (AUC) (95% CI: 0.619-0.621). Adding family history for PD in the second model significantly increased discriminatory capacity to 0.71 (AUC) (95% CI: 0.709-0.711). In the third model we added family history for dementia, depression and melanoma and achieved highest discriminatory capacity of 0.76 (95% CI: 0.757-0.763). Comparison of prediction efficiency in repeated cross-validation iterations showed that the AUC differences between the models were significant (P<0.001). The receiver operating characteristic curves for all three models are shown in Figure 1. With our third model we achieved 94.1% positive predictive value, 99.5% specificity and 74.5% sensitivity.
DISCUSSION

We constructed risk prediction model for PD and showed that family history of PD associated disorders (dementia, melanoma, depression) improves its predictive capacity. In our baseline model we included environmental risk factors that were previously most consistently linked to PD. The most commonly reported environmental risk factors in other studies include exposure to pesticides and herbicides and well-water consumption (Dick et al., 2007; Taylor et al., 1999). Neuroprotection was associated with tobacco use, caffeine consumption and possibly by estrogen in women (Kieburzt and Wunderle, 2013; Wooten, 2004). In concordance with previous reports our study confirmed the protective effect of prolonged caffeine and tobacco use while pesticide exposure was associated with higher risk of PD. Consumption of well water was
included in the questionnaire but was not significantly connected to PD in our set of patients and was therefore not included in our risk model. By adding family history of PD to basic risk factors in our second model, the discriminatory capacity increased from 0.62 (baseline model) to 0.71 (second model). A combination of family history of PD and basic risk factors yielded similar results to previous study by Hall, whose study achieved predictive ability of 0.71 (HALL et al., 2013). Evidence for familial aggregation of PD is strong as demonstrated by in 2008 published meta-analysis with clearly elevated risks for having a first-degree relative with PD based on 29 identified published studies on familial aggregation of PD (THACKER and ASCHERIO, 2008).

The main focus of our study was to evaluate if adding family history of other associated disorders improves the predictive ability of PD risk models. The existence of common genetic and/or environmental factors has been suggested also for PD and Alzheimer’s disease in a family history study on possible common etiology of both disorders (ROSEN et al., 2007) and the possibility of shared neurodegenerative pathogenesis (mitochondrial dysfunction, endoplasmatic reticulum dysfunction) has been investigated (COSKUN et al., 2012; ROUSSEL et al., 2013). Familial aggregation of depression and PD has been studied with inconclusive results (FAHIM et al., 1998). Common genetic components of melanoma and PD have been previously proposed and a family history of melanoma in a first-degree relative was associated with a higher risk of PD (GAO et al., 2009). Our data confirmed higher prevalence of melanoma and dementia and a trend for depression in Slovenian families with PD. Adding PD associated disorders as an additional parameter improved prediction, resulting in highest discriminatory power in our set (AUC 0.76).

We acknowledge that self-reported family history could be subject to recall bias. As recall bias has been previously reported in PD studies (PERERA et al., 2010; PRESSLEY et al., 2005; RUGBJERG et al., 2011), we have to take into consideration that self-reported family history could also be subjected to misreporting of actual incidence of PD (and possibly that of PD associated disorders) in family relatives. We considered family history positive when the subjects reported the diagnosis of PD was made by a medical doctor. We also acknowledge the possible limiting influence age difference might present for our study.

In conclusion, our study showed that family history of PD associated disorders (dementia, depression and melanoma) improves predictive capacity of risk models for Parkinson’s disease.

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DOPRINOS PORODIČNE ISTORIJE U PREDIKCIJI RIZIKA PARKINSONOVE BOLESTI: DODATNI DOPRINOS POVEZANIH POREMEĆAJA

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Izvod

Cilj našega istraživanja bilo je ispitivanje doprinosa porodične istorije Parkinsonove bolesti i sa njom povezanih poremećaja u proceni prediktivnog kapaciteta modela rizika za Parkinsonovu bolest. U populaciji od 192 pacijenta sa Parkinsonovom bolesti i 1659 zdravih pojedinaca ispitivali smo uticaj faktora okoline i efekte porodične istorije na rizik Parkinsonove bolesti. Izloženost pesticidima, pozitivna porodična istorija Parkinsonove bolesti i pozitivna porodična istorija demencije i melanoma su povezani sa povećanim rizikom za Parkinsonovu bolest, sa rezultatima u vezi porodične istorije depresije blizu statističke značajnosti. Pušenje i unos kofeina su povezani sa smanjenim rizikom za Parkinsonovu bolest. Korišćenjem metode površine ispod krivulje merena su tri modela predviđanja rizika. Prvi model zasnovan je na poznatim faktorima rizika okoline, u drugom modelu data je porodična istorija Parkinsonove bolesti i u trećem modelu dodatno smo uključili porodičnu istoriju demencije, melanoma i depresije. Pokazali smo da uključivanje podataka s porodičnom istorijom povezanih poremećaja (AUC 0.76) poboljšava prediktivni kapacitet modela rizika za Parkinsonovu bolest u poređenju sa prvim (AUC 0.62) i drugim (AUC 0.71) modelom. Zaključili smo da porodična istorija povezanih poremećaja: demencije, depresije i melanoma poboljšava prediktivni kapacitet modela rizika za Parkinsonovu bolest.

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