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Adjustment disorder and risk of Parkinson's disease

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Abstract

Objective—It has been postulated that stress is part of the etiological process of Parkinson's disease (PD). We examined the risk of PD in a cohort of patients with adjustment disorders, a diagnosis made in the presence of a severe response to a stressful life event

Methods—Using Danish medical registries, we examined PD occurrence in a nationwide population-based cohort of patients with adjustment disorder diagnosed between 1995 and 2011. We calculated standardized incidence ratios of PD, as the ratio of observed to expected cases, stratified by time and potential risk factors, including depression and anxiety.

Results—Our adjustment disorder cohort (67,786 patients) was followed for a median of eight years (inter quartile range: 4, 12.6 years). During follow-up, 119 patients developed PD, versus 64 expected, corresponding to a standardized incidence ratio of 1.84 (95% confidence interval 1.53, 2.20). Consistent results were observed after stratification on potential risk factors, including depression and anxiety.

Conclusion—Adjustment disorder, a diagnosis made in the presence of severe response to stressful life events, was associated with an increased risk of PD.

Keywords

Parkinson's disease; Adjustment disorder; Psychological stress

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Authors' Roles:

All authors made substantial contributions to the design of the work, and interpretation of the data. Ms. Farkas and Dr. Svensson made significant contributions to the acquisition and analysis of data. Ms. Farkas had full access to the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors contributed to the drafting and revision of the current manuscript, provided final approval of this version, and agreed to be accountable for all aspects of the work.

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INTRODUCTION

The etiology of Parkinson's disease (PD) is multifactorial, but not well understood [1]. It has been postulated that stress is part of the etiological process [2], however two former studies did not observe an effect of specific stressful life events on risk of PD, while those examining stress syndromes or breakdown of stress response did [3-5]. Thus, we hypothesize that it is not only the experience of a stressful life event that is important in the etiology of PD, but instead a more severe chronic response to stressors from one or more major life events. On the other hand, as other psychological disorders, such as depression, are thought to be an early non-motor clinical symptom of PD [6,7], and as the non-motor preclinical phase of PD is perhaps 10-20 years [8], long-term follow-up may help to establish differences between risk factors or risk markers of disease. We examined the risk of PD in a cohort of patients with adjustment disorders [9], a diagnosis made in the presence of a severe response to a stressful life event [10,11].

METHODS

We conducted this nationwide population-based cohort study in Denmark using medical databases. Denmark has universal tax-supported health care, including free access to hospital care. All individuals are assigned a unique personal identification number, registered in the Danish Civil Registration System [12], permitting unambiguous linkage among all Danish registries.

Adjustment disorder

We used the Danish Psychiatric Central Research Registry (DPCRR) to create a cohort of all Danish residents with at least one incident *International Classification of Diseases* (ICD) -10 diagnosis of severe stress or adjustment disorder from January 1, 1995 to December 31, 2011 [9]. For the current study, adjustment disorder cases from this cohort, but also from the Danish National Patient Registry (DNPR), were included. Since 1969, the DPCRR has collected data on all inpatient psychiatric hospitalizations [13,14], while corresponding data from acute non-psychiatric hospitals are registered in the DNPR since 1977 [15]; for both, outpatient treatment is registered since 1995. Diagnoses were coded according to the ICD, 8th edition from 1977 to 1993 and 10th edition since 1994 (codes used in the current study are included in the Appendix)[16].

Parkinson's disease

PD was identified by an incident ICD-10 diagnosis in the DNPR, including only first-time in-or outpatient hospitalizations with PD. We excluded patients with a diagnosis of PD in the year following the date of adjustment diagnosis, to prevent reverse causation from undiagnosed PD affecting exposure.

Other covariates

We searched the literature to *a priori* determine potential confounders, in addition to age and sex, that are both associated with adjustment disorder and Parkinson's disease. As the

literature on adjustment disorders is sparse, we looked also for associations with mental disorders overall.

As depression is an early non-motor symptom of PD [6,7], and significant comorbidity is seen between adjustment disorder and depression and anxiety [17], we obtained information on diagnosis of depression and anxiety prior to index date from the DCPRR. Furthermore, smoking is associated with a protective effect of PD, while smoking is also associated with mental disorders [18]. As we did not have information on smoking, we used chronic pulmonary disease, registered in the DNPR, to determine if this correlate of heavy smoking would account for our observed associations. Inflammation is also associated with mental disorders [19] and PD [1], and again as we did not have information on inflammation, we included connective tissue disease, as a correlate of inflammation. We also included diabetes, even though the evidence is inconclusive on the association with PD [1], and mental disorders [20].

Statistical analyses

We calculated the expected number of incident cases of PD after adjustment disorder diagnoses using national incidence rates of PD diagnoses according to sex, 5-year age groups, and 5-year calendar periods. Multiplying person-years of follow-up by incidence rates yielded the number of PD cases that would be expected if persons with adjustment disorder had the same risk of PD as the general population. The cumulative base population consisted of Danish-born residents of Denmark from January 1, 1995 through December 31, 2011.

We calculated standardized incidence ratios (SIRs), as the ratio of observed to expected cases, to measure the association between adjustment disorder and PD [21]. Exact 95% CIs were used when the observed number was less than ten, otherwise Byar's approximation was used. When fewer than five cases of PD were identified among patients in a stratified analysis, the SIR was not reported.

We further restricted our analyses to adults, defined as being age 16 or older, as this defines end of compulsory education and admittance to adult wards in Denmark. Analyses were stratified by time interval between the first adjustment disorder diagnosis and the incident PD diagnosis (1 to <5 years, 5 to <10 years, 10 to <15 years, and 15+ years), sex, age at adjustment disorder diagnosis (16–39 years, 40–59 years, and 60+ years), and for the specific diseases.

All statistical analyses were conducted using SAS version 9.2.

The study was approved by the Danish Data Protection Agency (record no. 2012-41-0841) and by the Institutional Review Board at Boston University.

RESULTS

We identified 67,786 adults with a diagnosis of adjustment disorder (61% female) (92% DPCRR only, 5% from DNRP only, 3% were included in both). These patients were followed for an average of 8.4 years (median follow-up: 7.8 years; IQR: 4, 12.6 years). Age

at adjustment disorder diagnosis ranged from 16 years through 100 years (mean age: 39.7 years; median age: 37.4). In total, 16% had depression and 5% had anxiety disorder diagnoses. Additionally, 6% had chronic pulmonary disease, 2% had connective tissue disease, and 3% had diabetes at the time of their adjustment disorder diagnosis.

We observed 119 cases of PD during the follow-up period, while 64 were expected. The median age of PD diagnosis was 72 (IQR 64 – 77), and 11 patients got the diagnosis before age 50 years. An association was found between adjustment disorder and PD (SIR = 1.84, 95% confidence interval (CI) = 1.53, 2.20). Similar results were observed for the analyses stratified by gender, and across strata of potential confounders (Table 1), with poor statistical precision for several covariates. There were no substantial evidence for effect modification. Patients with follow-up time <5 years had a SIR of 2.20 (95% CI 1.67, 2.85). For follow-up time 5 to <10 years the SIR was 1.56 (95% CI 1.09, 2.17), and for follow-up time 10 to <15 years, the SIR was 1.28 (95% CI 0.74, 2.04). For patients followed up for 15 years, the SIR was 3.51 (95% CI 1.61, 6.66) (Table 1).

DISCUSSION

This nationwide cohort study showed that adjustment disorder, a diagnosis made in the presence of a severe and chronic response to a stressful life event, was associated with an increased risk of PD.

The results are consistent with the findings of Clark *et al*, who examined life events in the cohort of 9,955 participants in the Copenhagen Heart Study, with an average follow-up of 14 years [4]. They found that having a breakdown of the stress response, defined as vital exhaustion, was associated with a 2.5-fold higher risk of PD hospitalization (adjusted hazard ratio 2.50 (95% confidence interval 1.28-4.89) comparing highest vs lowest category). In a case-control study of 12,093 female PD patients, Latourelle *et al* examined a wide range of diagnoses, and found an association between neurotic, stress and somatoform syndromes and PD (Odds Ratio 2.16, adjusted P-value of 1.5E-07) [5]. We corroborate and extend these results, seeing similar results for men and for the stress disorders alone, and after stratification on a range of possible confounders, providing information about the impact of potential confounding in the restricted groups. This stratification also gives no indication of potential effect modification. Furthermore, we also provide information on early vs late onset PD. Of the 11 patients who developed young onset PD, most are captured in the group who were diagnosed with adjustment disorder between 16 and 39 years of age (n=7), with small differences in results. This indicates that early/late onset does not seem to make a difference for the association. Thus, our results support our hypothesis that a more severe chronic response to stressors from one or more major life events is associated with subsequent risk of PD.

As depression and anxiety are associated with risk of Parkinson's disease, possible as early non-motor symptoms of the disorder, is it important to rule out possible confounding by these factors. The observed association is unchanged in a sample restricted to those without depression at baseline. Unlike major depression, adjustment disorder is caused by an outside stressor and generally resolves once the individual is able to adapt to the situation. We

know, however, that a large proportion of patients with adjustment disorder are subsequently diagnosed with depression [17]. A prospective study, taking into account possible time-varying exposure of adjustment disorder and depression could be worthwhile to conduct, to try to disentangle the effects of the stress and depression.

Our results indicate an increased risk of PD in patients with adjustment disorder after 15 years of follow-up. As, however, these estimates over time are not directly comparable due to changing population structure, they might suffer from residual confounding [22], and our approach cannot disentangle the role of this disorder in the pathogenesis of PD. Shrag *et al* indicate that depression is possibly a non-motor symptom commencing up to five years prior to the motor symptoms of the disorder [7]. Further investigation is warranted to examine whether a psychiatric response to stress may be not only an early non-motor symptom of PD but may also be implicated in its early pathogenesis. As it is hypothesized that PD has an enteric origin [23, 24], where a neurotrophic pathogen, possibly an infection [25,26] may initiate the propagation of alpha-synuclein to the brain, the role of stress may be important, via the suppression of the immune system by chronic stress [27]. It is notable that only chronic stressors, not major life events, do impact the immune system [27].

Our study's nationwide population-based design and large population size reduced the potential for selection bias. In registry-based studies, validity of the registered diagnoses is essential, and has been found to be good for both adjustment disorder and PD [28, 29]. However, a limitation of registry based studies is the possibility that the disorder under investigation was not truly PD but other atypical syndromes. Wermuth *et al* investigated 857 patients with a primary discharge diagnosis of idiopathic PD from DNPR, and of these 80% were seen to have idiopathic PD after examination of their medical records [29]. In addition, it is possible that our study includes more severe cases of adjustment disorder and PD as we only included diagnoses made in Danish hospitals; these disorders are also treated by general practitioners and in private practices, information which would not be captured in the registries used in the current study. We did not have information on symptomatology or dopaminergic responsiveness of the PD patients.

Several other limitations must also be considered when interpreting our results. To prevent reverse causation, a one year lag period was included. We cannot rule out the possibility of surveillance bias, that patients with adjustment disorders are in contact with the health care system, and might therefore to a greater extent receive closer follow-up with respect to other diseases. However, we do not think that increased regular medical care among people with adjustment disorder would explain our observed associations because PD almost always will require some level of medical attention regardless of previous medical care.

To capture potential confounding, the analyses were standardized according to age, and we also performed several stratified analysis on comorbidities that may affect the risk of PD. However, some residual or unmeasured confounding may have biased our results, especially concerning smoking and inflammation, for which we were not able to adjust. We were able to adjust for severe diseases that are highly correlated with these covariates providing information about how robust the results are when adjusting for a close correlate, and these adjustments did not account for the observed associations. Regarding smoking, stress is

associated with an increased prevalence of smoking, which may protect against PD [1] (although it has recently been suggested that the apparent protective effect of smoking on PD may be explained by reverse causation [30]), so confounding by smoking would not be expected to create a bias in the direction of our observed association. We only had information on depression and anxiety starting 1995, introducing problems with left truncation. Finally, there may be some unmeasured confounding by socioeconomic position, which we did not have information on in the current register-linkage study.

Our results support our hypothesis that a more severe chronic response to stressors from one or more major life events is associated with subsequent risk of PD. Future research should aim to disentangle the effect of stress diagnoses and depression, and to further explore this in relation to the long preclinical phase of PD, to assess whether this severe chronic response to stress is a risk factor or risk marker of disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Standard Incidence Ratios (SIRs) for Parkinson's disease (PD) one or more years after diagnosis of an adjustment disorder.

		Observed	Expected	SIR
Overall		119	64	1.84 (1.53-2.20)
Sex				
	Female	66	36	1.84 (1.43, 2.35)
	Male	53	29	1.84 (1.38, 2.41)
Age at first adjustment disorder diagnosis, years				
	16 – 39	7	3	2.46 (0.98, 5.06)
	40 – 59	36	22	1.61 (1.13, 2.23)
	60+	76	39	1.93 (1.52, 2.41)
Depression				
	No	86	52	1.67(1.33, 2.06)
	Yes	33	12	2.55 (1.75, 3.58)
Anxiety				
	No	116	62	1.88 (1.55, 2.25)
Chronic pulmonary disease				
	No	113	60	1.89 (1.55, 2.27)
	Yes	6	5	1.28 (0.47, 2.78)
Connective tissue disease				
	No	114	63	1.81 (1.49, 2.18)
	Yes	5	2	3.00 (0.97, 6.98)
Diabetes				
	No	115	61	1.87 (1.54, 2.25)
Time from adjustment disorder diagnosis to PD diagnosis				
	1 to < 5 years	58	26	2.20 (1.67, 2.85)
	5 to < 10 years	35	22	1.56 (1.09, 2.17)
	10 to < 15 years	17	13	1.28 (0.74, 2.04)
	15 years	9	3	3.51 (1.61, 6.66)

Note: Results not presented when fewer than five incident PD cases were identified in subgroup stratification