

Risk of Parkinson's disease after hospital contact for head injury: population based case-control study

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ABSTRACT

Objective To determine whether a hospital contact for a head injury increases the risk of subsequently developing Parkinson's disease.

Design Population based case-control study.

Setting Denmark.

Participants 13 695 patients with a primary diagnosis of Parkinson's disease in the Danish national hospital register during 1986-2006, each matched on age and sex to five population controls selected at random from inhabitants in Denmark alive at the date of the patient's diagnosis (n=68 445).

Main outcome measures Hospital contacts for head injuries ascertained from hospital register; frequency of history of head injury.

Results An overall 50% increase in prevalence of hospital contacts for head injury was seen before the first registration of Parkinson's disease in this population (odds ratio 1.5, 95% confidence interval 1.4 to 1.7). The observed association was, however, due almost entirely to injuries that occurred during the three months before the first record of Parkinson's disease (odds ratio 8.0, 5.6 to 11.6), and no association was found between the two events when they occurred 10 or more years apart (1.1, 0.9 to 1.3).

Conclusions The steeply increased frequency of hospital contacts for a head injury during the months preceding the date at which Parkinson's disease was first recorded is a consequence of the evolving movement disorder rather than its cause.

INTRODUCTION

Parkinson's disease is a movement disorder characterised mainly by rigidity, bradykinesia, postural instability, and tremor.^{1,2} It has an insidious onset, usually in the second half of life. The symptoms are related to a relative deficiency of the neurotransmitter dopamine, causing imbalances in the related neural circuitry following the accelerated death of dopaminergic neurones in the substantia nigra of the brain.³ Apart from a few patients with genetically caused parkinsonism, the reason for the degeneration is unknown, although several non-genetic risk factors have been examined. One such risk factor is previous injury to the head, a hypothesis first put forward by

James Parkinson in 1817.⁴ Early case reports published in the 1920s and 1930s speculated on the association, and a relatively large number of case-control studies have been published in the past 20 years presenting odds ratios for Parkinson's disease subsequent to a head injury ranging from 0.6 to 6.2.⁵⁻²¹ All but three studies suggested a positive association with a previous head injury,^{11 12 14} and the association reported reached traditional statistical significance in eight studies.^{5 7-9 15 16 20 22} All but one of these studies,⁵ however, were based on self reported instances of head injury. This raised the possibility of recall bias differential by case status, such that patients were motivated to recall and report events more frequently than were control subjects. However, the hypothesis gained further strength from the positive results of a small case-control study done in the Mayo Clinic population in Olmsted County, MN, USA, which was able to ascertain information and confirm diagnoses of head injuries through a review of the medical records for both Parkinson's disease patients and population controls.⁵

Here, we report the results of the largest population based case-control study of Parkinson's disease subsequent to hospital contact for a head injury. We obtained information on diagnosis of head injury at the time of hospital contact independently of case or control status by linking patients and population controls to the files of the Danish national hospital register that has been operating for more than 30 years.

METHODS

Danish hospital register

The Danish national hospital register was instituted on 1 January 1977 and contains individual information on all admissions for medical conditions other than psychiatric diseases to hospitals in Denmark.²³ Information on outpatient visits, including visits to emergency rooms, was added to the register on 1 January 1994. Any contact of a Danish resident with the hospital system generates a record in the hospital register, which includes the personal identification number of the patient, the dates of admission and discharge (inpatient registration), the dates of first and last contact (outpatient registrations), the identity of the

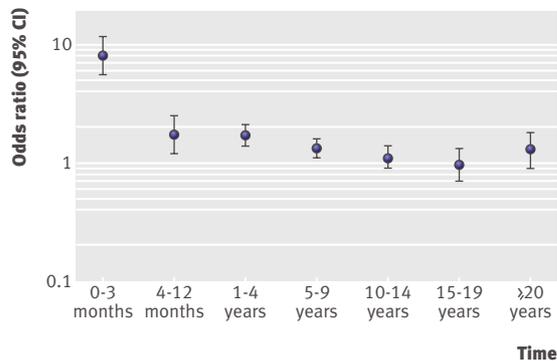


Fig 1 Risk of Parkinson's disease after hospital admission for head injury, by time between head injury and first hospital contact for Parkinson's disease

department, a code for the main diagnosis from the hospital contact, and codes for up to 19 supplementary diagnoses. The personal identification number, which is unique to every Danish citizen, incorporates sex and date of birth and permits accurate linkage between registers and the assembly of various records linked to the same person. The diagnoses, taken at discharge from hospital, were coded according to the Danish version of the ICD-8 (international classification of diseases, 8th revision) until the end of 1993 and the 10th revision thereafter.

Study populations

We identified 13 739 patients with a first time diagnosis of Parkinson's disease (ICD-8 code 342; ICD-10 code G20) in the files of the hospital register during the period 1986-2006; we chose 1986 in order to eliminate prevalent cases of Parkinson's disease included in the hospital register in the first years of registration. After exclusion of patients who were citizens of Greenland (n=1) and patients who were younger than 35 years at the time of first hospital admission for Parkinson's disease (n=43), we were left with a case group of 13 695 patients: 7423 men and 6272 women (table 1).

Among the patients included in this study, 6134 (45%) received their first diagnosis of Parkinson's disease in a specialised neurological treatment centre. In the risk analysis, we regarded the date of first hospital contact (the index date) as the date of diagnosis of Parkinson's disease. For each patient, we chose five control subjects at random from the Danish central population register from among all inhabitants of the same sex and year of birth who were alive at the index date of their respective case (incidence density sampling). Although we aimed to recruit five control subjects for each case, 26 cases were matched with either two, three, or four controls, yielding a total of 68 445 controls (table 1).

Register information on head injuries

We re-linked cases and linked controls to the files of the Danish hospital register to ascertain hospital contacts for head injury that occurred before the index dates and after 1 January 1977. We reviewed records for the

occurrence of concussion (ICD-8 850; ICD-10 S06.0), fractured skull (800, 801, 803; S02.0, S02.1, S02.7-S02.9), traumatic intracranial haemorrhage (852, 853; S06.4, S06.5, S06.6), and cerebral contusion (851, 854; S06.1-S06.3, S06.7-S06.9, S07.0, S07.1). As a measure of severity, we ranked head injuries in the following order: concussion < fractured skull < intracranial haemorrhage/cerebral contusion. We included both primary and supplementary diagnoses of head injuries. However, using inpatient and outpatient information to verify cases of head injury also implies that the study is unable to evaluate the consequences of mild and perhaps repeated trauma to the head as these do not usually lead to a hospital contact.

Analyses

We compared the frequency of a history of a previous head injury in Parkinson's disease patients with that of their population controls. We expressed the association as an odds ratio derived from a conditional logistic regression analysis for matched sets. We counted study subjects who were registered with more than one head injury only once, counting the date of the first injury as the primary exposure date for lagged analyses. In injury specific analyses, we included people with head injury diagnoses in more than one category only when appropriate—that is, with their first head injury in each category. We estimated risks for various intervals between the hospital contact for a head injury and the first registration of a diagnosis of Parkinson's disease (0-3 months, 4-12 months, 1-4 years, 5-9 years, 10-14 years, 15-19 years, ≥20 years). For the subgroup of people for whom a head injury was mentioned as the primary diagnosis, we combined the information on type of injury with length of hospital stay (visit to the emergency room only and admission to hospital for

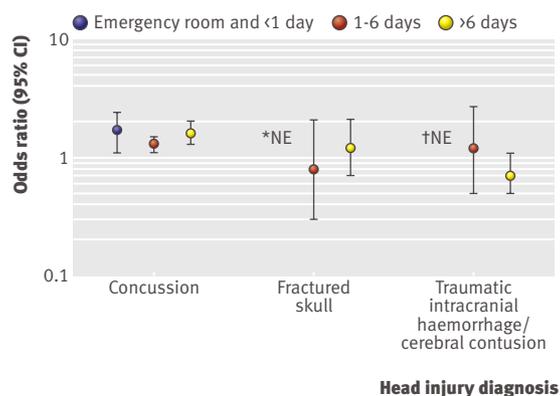


Fig 2 Risk of Parkinson's disease after hospital contact for head injury, by type of injury and length of admission (first year before Parkinson's disease diagnosis excluded). *No estimate owing to small numbers; category "Emergency room and <1 day" included one case and three controls with fractured skull—three with unspecific diagnoses and one with specific diagnosis. †No estimate owing to small numbers; category "Emergency room and <1 day" included two cases and five controls with traumatic intracranial haemorrhage/cerebral contusion—five with unspecific diagnoses and two with specific diagnoses

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less than one day < one to six days < more than six days) to evaluate not only whether Parkinson's disease is related to a previous head injury but also whether the association is restricted to particular characteristics of the injury, including the degree of severity. For this, we evaluated linear trends with a χ^2 test. We used SAS software version 9.1 for all analyses.

Validation of the diagnosis of Parkinson's disease

To validate the diagnosis of Parkinson's disease listed in the hospital register, we used a continuously updated national prescription database started on 1 January 1995, which covers all prescribed drugs dispensed at any pharmacy in the country.²⁴ We thus established a full prescription history since 1995 for 2572 (19%) patients whose first hospital contact for Parkinson's disease was in the period 2002-6. We found that treatment for Parkinson's disease (ATC code N04B: L-dopa, dopamine agonists, COMT, and MAO-B inhibitors) had been prescribed for 2353 (91%) patients

and that for 1929 (75%) of them the drug treatments were established through the general practitioner before the first hospital contact. Patients started treatment on average three years before the contact.

RESULTS

The average age of patients at their first hospital contact for Parkinson's disease was 73.0 years (72.5 for men and 73.6 for women). More than 90% were born before 1940 (table 1). Of the patients, 566 (4.1%) were reported as having had at least one hospital contact for a head injury before the index date. For the 68 445 population controls (37 101 men and 31 344 women), the corresponding figure was 1904 (2.8%) (table 1). Thus, a head injury of any type was significantly more prevalent among people in whom Parkinson's disease was subsequently diagnosed than among population controls (odds ratio 1.5, 95% confidence interval 1.4 to 1.7).

As indicated in figure 1, which shows the estimated relative risks for Parkinson's disease by time between the two medical events, the increased overall risk of Parkinson's disease seemed to be due almost entirely to head injuries that occurred during the three months before a first hospital contact for the disease (odds ratio 8.0, 5.6 to 11.6). Head injuries that had occurred within four months to nine years before were associated with only a modestly increased risk of Parkinson's disease (1.5, 1.3 to 1.7), and those occurring even more distantly in time showed no association (≥ 10 years: 1.1, 0.9 to 1.3). Similar analyses done separately for each of the three sub-entities of head injuries (concussion of the brain, fractured skull, and traumatic intracranial haemorrhage/cerebral contusion) showed a risk pattern comparable to the one for all types of head injuries combined (table 2). The estimated risk for concussion, representing the mildest forms of head injury, showed some increase in all time windows from zero to nine years before diagnosis of Parkinson's disease, but we found a clear negative trend with increasing time between the two events ($P < 0.0001$) (table 2).

For the subset of people for whom the head injury was the main diagnosis and the primary reason for the hospital contact, we combined type of injury and length of stay in hospital as a proxy measure for severity. In this analysis, we excluded head injuries registered within one year of a first record of Parkinson's disease, as we considered that such injuries might have been a result of the evolving movement disorder rather than a risk factor. We found no indication of an increased risk of Parkinson's disease after an accident that resulted in a fractured skull or intracranial haemorrhage/cerebral contusion, irrespective of length of stay in hospital for the injury (fig 2). Moreover, this analysis substantiated the finding in the overall analysis of a moderately increased risk of Parkinson's disease after concussion, but with no clear trend in risk with increasing length of hospital stay ($P = 0.52$). In a further analysis, when we excluded head injuries registered in the five year period before first contact for Parkinson's disease, we found

Table 1 Characteristics of patients with Parkinson's disease and population controls. Values are numbers (percentages)

Characteristic	Patients with Parkinson's disease (n=13 695)	Population controls (n=68 445)
No of controls per case		
5	13 669	68 345
4	23	92
3	2	6
2	1	2
Sex:		
Male	7 423 (54.2)	37 101 (54.2)
Female	6 272 (45.8)	31 344 (45.8)
Age at index date (years)*		
35-44	149 (1.1)	725 (1.1)
45-54	506 (3.7)	2 535 (3.7)
55-64	1 658 (12.1)	8 265 (12.1)
65-74	4 575 (33.4)	22 882 (33.4)
75-84	5 723 (41.8)	28 547 (41.7)
85-94	1 070 (7.8)	5 429 (7.9)
95-99	14 (0.1)	62 (0.1)
Year of birth		
Before 1900	54 (0.4)	270 (0.4)
1900-9	1 406 (10.3)	7 030 (10.3)
1910-9	4 749 (34.7)	23 741 (34.7)
1920-9	4 379 (32.0)	21 887 (32.0)
1930-9	2 044 (14.9)	10 218 (14.9)
1940-9	819 (6.0)	4 089 (6.0)
1950-9	194 (1.4)	965 (1.4)
1960-9	50 (0.4)	245 (0.4)
Head injury†		
No	13 129 (95.9)	66 541 (97.2)
Yes:		
Concussion	566 (4.1)	1 904 (2.8)
Fractured skull	501 (3.7)	1 653 (2.4)
Traumatic intracranial haemorrhage/cerebral contusion	43 (0.3)	170 (0.2)
	68 (0.5)	267 (0.4)

*Date of first hospital contact for patients with Parkinson's disease and equivalent index date for controls.

†Study subjects with head injury can belong to more than one subcategory.

Table 2 Risk of Parkinson's disease after hospital contact for head injury by type of head injury and time between medical events

Type of head injury	No of cases/controls (n=13 695/68 445)	Odds ratio (95% CI)
Concussion		
Latency:		
0-3 months	54/41	6.6 (4.4 to 9.9)
4-12 months	38/99	1.9 (1.3 to 2.8)
1-4 years	106/298	1.8 (1.4 to 2.2)
5-9 years	133/480	1.4 (1.1 to 1.7)
10-14 years	76/320	1.2 (0.98 to 1.5)
15-19 years	53/254	1.0 (0.8 to 1.4)
≥20 years	41/161	1.3 (0.9 to 1.8)
Total	501/1653	1.5 (1.4 to 1.7)
Fractured skull		
Latency:		
0-3 months	6/3	10.0 (2.5 to 40)
4-12 months	2/3	3.4 (0.6 to 20)
1-4 years	6/27	1.1 (0.5 to 2.7)
5-9 years	11/53	1.0 (0.5 to 2.0)
10-14 years	10/47	1.1 (0.5 to 2.1)
15-19 years	4/22	0.9 (0.3 to 2.6)
≥20 years	4/15	1.3 (0.4 to 4.0)
Total	43/170	1.3 (0.9 to 1.8)
Traumatic intracranial haemorrhage/cerebral contusion		
Latency:		
0-3 months	19/7	13.6 (5.7 to 32)
4-12 months	6/27	1.1 (0.4 to 2.4)
1-4 years	12/64	0.9 (0.5 to 1.7)
5-9 years	14/86	0.8 (0.5 to 1.4)
10-14 years	10/45	1.1 (0.6 to 2.2)
15-19 years	3/28	0.5 (0.2 to 1.8)
≥20 years	4/10	2.0 (0.6 to 6.4)
Total	68/267	1.3 (0.98 to 1.7)

odds ratios of 1.4 (0.9 to 2.3) for concussion that led to a hospital stay of less than one day, 1.3 (1.1 to 1.6) for one to six days, and 1.3 (0.95 to 1.7) for stays of more than six days (*P* for trend=0.7) (data not shown). When we stratified by age at onset of Parkinson's disease, we found no difference in risk subsequent to a head injury (odds ratios 1.6, 1.3 to 2.0 for <65 years and 1.5, 1.3 to 1.7 for ≥65 years).

DISCUSSION

In this population based case-control study of more than 13 000 patients with a primary diagnosis of Parkinson's disease recorded in the national hospital register in Denmark, a previous, medically confirmed diagnosis of a head injury treated at a hospital or clinic increased the risk of Parkinson's disease by 50% compared with age and sex matched population controls. This association was, however, due entirely to head injuries that had occurred less than 10 years before the first hospital contact for Parkinson's disease, particularly injuries occurring during the three months preceding the first hospital contact for Parkinson's disease. After exclusion of this three month period from the analysis, the results were compatible with no

association for the most serious forms of head injuries (fractured skull, traumatic intracranial haemorrhage/cerebral contusion) and a modestly increased risk, if any, associated with a previous concussion. For concussions, furthermore, the risk decreased with increasing time between the two medical events and was not linked to the degree of severity of the concussion, as judged by the length of the hospital stay. If our finding of an overall association between a head injury and Parkinson's disease represented a true causal relation, we would have to hypothesise that the biological mechanism linking the injury to the disease must be rapid—that is, immediately inducing extensive cell death, preferentially in the substantia nigra of the brain. This seems to be an unlikely explanation. An often proposed mechanism for the purported link is that head injuries damage the blood-brain barrier, exposing the brain to inflammatory factors, toxins, and antigens.^{8,22} According to McGeer and colleagues, this process, if uncontrolled, can result in chronic inflammation and activated microglia, leading to Parkinson's disease over a decade or two.²⁵ This hypothesised pathogenic process is clearly in conflict with the findings of our study.

Interpretation of the results

We find it more reasonable to conclude that our findings of a positive association between head injuries and a hospital contact for Parkinson's disease can be explained by reverse causality—that is, that the frequency of head injuries before the first hospital contact for Parkinson's disease strongly increases as a consequence of the movement disorder developing rather than being its cause; thus, head injury does not seem to be causally associated with risk of Parkinson's disease. Recent findings suggesting that poor balance is an early sign of Parkinson's disease support this interpretation.²⁶ This conclusion is further supported by the lack of an association with injuries that occurred 10 or more years before the first hospital contact for Parkinson's disease. It is also in accordance with the observation that in most patients for whom prescription data existed, the date of the first prescription for anti-parkinsonian drugs was before the date of the first hospital contact for the disease, suggesting that the diagnosis had already been made by a physician in the primary healthcare system. Finally, we argue that the apparent absence of a relation between the severity of the head injury and the risk of Parkinson's disease further supports the interpretation of reverse causation between the two medical events.

Comparison with earlier studies

Our results contrast with the findings of several of the earlier interview based case-control studies,^{7-9 15 16 20 22} as well as a previous medical record review study in the Mayo Clinic system.⁵ Two studies found that the association was enhanced when the researchers included only more severe head injuries,^{5,9} and in one study the risk of Parkinson's disease remained high even after exclusion of head injuries that had occurred

WHAT IS ALREADY KNOWN ON THIS TOPIC

Parkinson's disease is characterised by an insidious onset, with imbalance as an early sign
 Parkinson's disease has been associated in several case-control studies with a self reported head injury event that occurred before the diagnosis of Parkinson's disease

WHAT THIS STUDY ADDS

A positive association was found between Parkinson's disease and a head injury before the diagnosis

However, the overall associations were due almost exclusively to injuries occurring months to a few years before hospital contact for Parkinson's disease

The statistical association between the two medical events reported in the literature probably has no causal basis and might be due to differential recall bias or inaccurate timing of events

in the 10 year period before the diagnosis.⁹ These interview based case-control studies may, however, be influenced by recall bias, as the information on head injuries was collected from patients with prevalent Parkinson's disease and controls with no movement disorder. As patients with Parkinson's disease have an increasing number of accidental falls as the disease progresses, they might tend to recall and report head injuries more frequently when asked. This would falsely elevate the relative risk estimates for Parkinson's disease and head injury. We could not confirm the hypothesis that head injury causes the onset of Parkinson's disease at younger ages, as suggested by Maher and colleagues, who found that head injury was associated with a 3.3 year younger age at onset ($P=0.03$).²⁷

Strengths and limitations

The strengths of our study include identification of patients from a national hospital register, unbiased selection of population controls through linkage to a population registry, unbiased ascertainment and validation of head injuries among patients and controls through (re)linkage to the hospital register, and an unprecedented large number of patients. Furthermore, in this study we were able to examine the temporal relation between a diagnosis of head injury and a diagnosis of Parkinson's disease. The limitations of our study are lack of information on diagnostic details for patients with Parkinson's disease and lack of information on the date of first symptoms of Parkinson's disease or the date of first treatment with anti-parkinsonian drugs for the entire study group. Our linkage of a subgroup of patients to the files of a national prescription database revealed that 9% of cases never received treatment with anti-parkinsonian drugs, indicating some diagnostic misclassification. If this disease misclassification is non-differential with respect to exposure, it would tend to dilute—but not remove—a truly positive or negative association between a head injury and Parkinson's disease, leading to an underestimate of the risk.

Milder single and repeated head injuries were not included, as we assessed only those that resulted in at least an emergency room visit, if not a hospital visit.

This limitation applies, however, to the same extent to our controls and thus should not affect our risk estimates. If Parkinson's disease is selectively caused by mild or repeated injuries to the head, this linkage study would not be able to detect such an association.

Contributors: JHO and BR designed and planned the study and developed the protocol. KR and NM did the statistical analyses. KR and JHO interpreted the final data analyses and wrote the manuscript. All authors read and critically commented on the paper. KR is the guarantor.

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