Anemia or low hemoglobin levels preceding Parkinson disease

A case-control study

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ABSTRACT

Objective: It has been suggested that anemia may be a risk factor for dementia, for restless legs syndrome, and for Parkinson disease (PD). Thus, we investigated the association of anemia with the subsequent risk of PD using a case-control study design.

Methods: We used the medical records–linkage system of the Rochester Epidemiology Project to identify 196 subjects who developed PD in Olmsted County, Minnesota, from 1976 through 1995. Each incident case was matched by age (±1 year) and sex to a general population control. We reviewed the complete medical records of cases and controls in the system to detect anemia defined using the World Health Organization criteria.

Results: Anemia was more common in the history of cases than of controls (odds ratio 2.00, 95% confidence interval 1.31–3.06, $p = 0.001$). The association remained significant after adjustment for cigarette smoking, exposure to pesticides, or hysterectomy (in women). The association was not significantly different between men and women, or between PD patients with or without rest tremor. Analyses stratified by time of onset of anemia showed a greater association for anemia that started 20 to 29 years before the onset of PD. Hemoglobin levels were slightly but consistently lower in cases than in controls across all ages.

Conclusions: Our results support an association between anemia experienced early in life and the later development of Parkinson disease. The interpretation of this association remains uncertain.

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GLOSSARY

AD = Alzheimer disease; **CI** = confidence interval; **OR** = odds ratio; **PD** = Parkinson disease; **RLS** = restless legs syndrome; **WHO** = World Health Organization.

A recent case-control study documented an increased risk of Parkinson disease (PD) among men who reported a higher number of blood donations proximate to the onset of PD. Because regular blood donors have reduced levels of hemoglobin and reduced levels of systemic iron stores, this finding suggests that anemia may be a risk factor for PD.[1] Similarly, anemia has been associated with an increased risk of Alzheimer disease (AD)[2-5] and of restless legs syndrome (RLS).[6,7] In turn, both AD and RLS are associated with PD.[8,9] Therefore, we conducted a population-based case-control study to investigate the putative association between anemia at any time in life and the long-term risk of PD.

METHODS

Cases. We used the medical records–linkage system of the Rochester Epidemiology Project to identify all subjects residing in Olmsted County, Minnesota, who developed PD from 1976 through 1995. Details about the study population and the identification of incident cases were reported elsewhere.[10,11] Our diagnostic criteria included 2 steps: the definition of parkinsonism as a syndrome and the definition of PD within the syndrome. Parkinsonism was defined as the presence of at least 2 of 4 cardinal signs: rest tremor, bradykinesia, rigidity, and impaired postural reflexes. PD was defined as the presence of parkinsonism with all 3 of the following criteria: 1) no other cause (e.g., repeated stroke with stepwise progression, repeated head injury, history of encephalitis, neuroleptic treatment within 6 months before onset, hydrocephalus, brain tumor); 2) no documentation of unresponsiveness to levodopa at doses of at least 1 g/day in combination with

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carbidopa (applicable only to patients who were treated); and 3) no prominent or early (within 1 year of onset) signs of more extensive nervous system involvement (e.g., dementia, dysautonomia) not explained otherwise.[11] Our clinical classification of patients with PD through medical records review was found to be valid compared with a direct examination by a movement disorders specialist, as reported elsewhere.[12] Onset of PD was defined as the year in which a cardinal sign of PD was first noted by the patient, by family members, or by a care provider (as recorded in the medical record).

Controls. Each case was individually matched by age (±1 year) and sex to a general population control residing in Olmsted County and free of PD, other parkinsonism, or tremor of any type in the index year (year of onset of PD in the matched case). The list of all county residents from which potential controls were randomly drawn was provided by the records-linkage system.[10] This list has been shown to be complete by comparison with a random digit–dialing telephone sample and with the census.[10] Records of potential controls were reviewed by a neurologist (D.M.M.) to exclude the presence of PD, other types of parkinsonism, or tremor of any type before or during the index year. The presence of dementia or other neurologic diseases was not an exclusion criterion. Our exclusion of parkinsonism in controls through medical record review was found to be valid compared with a direct examination by a movement disorders specialist, as reported elsewhere.[12]

Ascertainment of anemia. The complete medical records of cases and controls, which are routinely linked and stored in the records-linkage system of the Rochester Epidemiology Project,[10] were reviewed and abstracted by a physician (R.S.) to document anemia. Anemia was defined using the following 2 criteria: 1) a diagnosis of anemia ever mentioned in medical records; or 2) a hemoglobin level <13.0 g/dL in men or <12.0 g/dL in women, according to the World Health Organization (WHO) criteria.[13] Hemoglobin levels measured within 6 weeks of a hemorrhage due to trauma or surgery were not considered (exclusion of acute anemia). However, low hemoglobin levels persisting outside of the 6-week window were considered evidence of anemia.

We abstracted data about anemia in chronological order starting from the first available record through the onset of PD or the index year. For those subjects who had a large number of hemoglobin measures over their full life spans, we anchored the data collection to the decade birthdays (e.g., hemoglobin levels nearest to age 20, 30, 40 years, etc.). Subjects without a diagnosis of anemia and without any hemoglobin levels recorded in the medical records were considered free of anemia.

For subjects who received a diagnosis of anemia, we abstracted the diagnosis of clinical subtype of anemia that was historically assigned by the care giving physician. Unfortunately, because of the historic nature of the records, measures of mean corpuscular volume or blood levels of iron, ferritin, vitamin B_{12}, or folate were not routinely available even when anemia was diagnosed. Almost all of the cases and controls in the study who received a historic diagnosis of anemia had at least 1 low hemoglobin level documented in their records (34 of 36 subjects). The remaining 2 subjects were diagnosed on the basis of blood tests performed outside of the records-linkage system. We defined severe anemia as a hemoglobin level lower than 7 g/dL.[14] In addition, we collected information on blood transfusions and other treatments (iron, folate, or B_{12}) as possible indirect markers of the severity of anemia. Only diagnoses of anemia or hemoglobin levels that were documented in the medical record before the index year were accepted as exposure.

To validate our abstracting procedure for anemia, a second physician (M.I.), who was kept unaware of the case or control status of subjects, reabstracted the complete medical records for a random sample of 20 study subjects (approximately 5% of all cases and controls). The interrater agreement on presence or absence of anemia or low hemoglobin level was 90.0% (positive agreement for 8 pairs and negative agreement for 10 pairs), with a κ value of 0.80 (95% confidence interval [CI] 0.53–1.00). This small study suggests that our abstracting procedure was reliable.

Data analysis. Consistent with our design, matched-pairs analyses were performed, and the odds ratio (OR) was used to estimate the relative risk. For each variable, we calculated an OR, a 95% CI, and a p value (2-tailed test, $\alpha = 0.05$) using conditional logistic regression. We also conducted analyses stratified by sex and by clinical characteristics of PD (early vs late onset, and with vs without rest tremor). To explore the effect of anemia experienced in early life, midlife, or proximate to the index year, we also conducted analyses stratified by lag time between onset of anemia and index year, and by age at first diagnosis or age at first low hemoglobin level. Finally, we conducted analyses adjusted for cigarette smoking, for exposure to pesticides, or for hysterectomy in women (possible confounding variables).

To avoid the possible shortcomings of defining anemia using predefined hemoglobin cutoffs,[13,15,16] we also conducted a set of sensitivity analyses dividing the group of controls into quartiles based on the lowest value of hemoglobin recorded for each subject (men and women separately). These sex-specific quartile cutoff values were then used to define anemia in both cases and controls, and the lowest quartile was compared with the remaining 3 quartiles pooled together.

In addition, we graphically displayed the distribution of all available hemoglobin levels in cases and controls by age. Finally, we used linear mixed models to compare the trajectory of hemoglobin values across age in cases and controls for men and women separately. These models accounted for the correlation of equally spaced repeated hemoglobin measures within each individual and allowed for separate intercepts for each trajectory line. In particular, we used a heterogeneous compound symmetry correlation structure selected using the Akaike information criterion.[17] In addition, we accounted for correlations within matched pairs by including a block random effect in the model. All analyses were performed using SAS® version 9 (SAS Institute, Cary, NC).

Standard protocol approvals, registrations, and patient consent. The study was approved by the institutional review boards of the Mayo Clinic and of Olmsted Medical Center. Written informed consent was not required for passive medical record review.

RESULTS We identified 202 patients who developed PD from 1976 through 1995 (incident cases). These patients were matched by age and sex with 202 controls. However, 6 individuals (5 cases and 1 control) did not authorize the use of their medical records for research, and the corresponding pairs could not be studied. Therefore, we included 196 case-control pairs for a total of 392 individuals. Among the cases, 121 (61.7%) were men and 75 (38.3%) were women; the median age at onset of PD was 71 years (range 41–97 years). The distribution by age and sex was similar in controls because of the matched design. The median duration of enrollment in the records-linkage system preceding the index

Table 1 Association between Parkinson disease and preceding anemia (196 cases and 196 controls)

Definitions of anemia and strata	Exposure frequency		Discordant case/control pairs*		Concordant case/control pairs*			
	Cases no. (%)	Controls no. (%)	+/−	−/+	+/+	−/−	Odds ratio (95% CI)	*p* Value
Anemia or low hemoglobin†	86 (43.9)	54 (27.6)	64	32	22	78	2.00 (1.31–3.06)‡	0.001
Diagnosis of anemia§	20 (10.2)	16 (8.2)	20	16	0	160	1.25 (0.65–2.41)	0.51
Treated anemia‖	16 (8.2)	15 (7.7)	16	15	0	165	1.07 (0.53–2.16)	0.86
Low hemoglobin (≥1)¶	85 (43.4)	53 (27.0)	64	32	21	79	2.00 (1.31–3.06)#	0.001
Low hemoglobin (≥2)¶	41 (20.9)	21 (10.7)	38	18	3	137	2.11 (1.21–3.70)	0.009
Stratified analyses**								
Men	38 (31.4)	27 (22.3)	32	21	6	62	1.52 (0.88–2.64)	0.13
Women	48 (64.0)	27 (36.0)	32	11	16	16	2.91 (1.47–5.77)††	0.002
Early onset of PD (≤71 y)	35 (36.1)	22 (22.7)	25	12	10	50	2.08 (1.05–4.15)	0.04
Late onset of PD (>71 y)	51 (51.5)	32 (32.3)	39	20	12	28	1.95 (1.14–3.34)	0.02
PD with rest tremor	66 (44.3)	47 (31.5)	47	28	19	55	1.68 (1.05–2.68)	0.03
PD without rest tremor	14 (37.8)	3 (8.1)	14	3	0	20	4.67 (1.34–16.24)	0.02

*+/− = matched pair with case exposed and control unexposed; −/+ = matched pair with case unexposed and control exposed; +/+ = matched pair with both case and control exposed; −/− = matched pair with both case and control unexposed.
†The analyses reported below (indented) refer to subsets of the overall analysis.
‡Analyses adjusted for cigarette smoking (ever vs never) yielded an odds ratio (OR) of 2.17 (95% confidence interval [CI] 1.40–3.37, $p = 0.0006$); analyses adjusted for exposure to pesticides (ever vs never) yielded an OR of 1.74 (95% CI 1.02–2.97, $p = 0.04$).
§Only cases or controls who received a diagnosis of anemia recorded historically in a medical record.
‖Anemia that required treatment. This was considered a possible indirect marker of severity.
¶Subjects with hemoglobin levels below the World Health Organization cutoff (regardless of a diagnosis of anemia). ≥1, at least 1 low hemoglobin value; ≥2, at least 2 low hemoglobin values.
#A sensitivity analysis defining exposure by using the lowest quartile of the empirical distribution of hemoglobin levels among controls yielded consistent results (OR 1.47, 95% CI 0.98–2.23, $p = 0.07$; the cutoff was ≤13.0 g/dL for men and ≤11.5 g/dL for women).
**None of the stratified analyses yielded a significant test for interaction (p for sex = 0.15, p for age at onset of Parkinson disease [PD] = 0.88, p for rest tremor = 0.13).
††In a sensitivity analysis including hysterectomy (ever vs never) in the model, the OR for anemia was 3.53 (95% CI 1.59–7.06, $p = 0.001$).

year was 38 years (range 2–73 years) for cases and 38 years (range <1–73 years) for controls (Wilcoxon signed rank test, $p = 0.35$).

Table 1 shows the results of our case-control analyses. Anemia or lower hemoglobin levels were found in 86 cases (43.9%) and 54 controls (27.6%), yielding an OR of 2.00 (95% CI 1.31–3.06, $p = 0.001$). Findings remained significant after adjustment for cigarette smoking, for exposure to pesticides, or for hysterectomy in the stratum of women. Analyses restricted to anemia diagnosed in medical records or to anemia that required treatment were not significant. Only 20 cases and 16 controls ever received a diagnosis of anemia. Among the 20 cases, 3 were diagnosed as iron deficient (15.0%), 5 were diagnosed as pernicious (25.0%), and 12 remained unclassified (60.0%). Among the 16 controls, 3 were diagnosed as iron deficient (18.8%), 3 were diagnosed as pernicious (18.8%), 3 were diagnosed as hemolytic (18.8%), and 7 remained unclassified (43.8%). Only 2 of the subjects ever had a hemoglobin level lower than 7 g/dL (definition of severe anemia; both controls, 1 man and 1 woman).

The association was significant for subjects who had at least 1 low hemoglobin value and for subjects with 2 or more low hemoglobin values (regardless of a diagnosis of anemia). A sensitivity analysis using quartiles of the empirical distribution of hemoglobin levels among controls yielded consistent findings (table 1, footnote #). No significant differences were observed between strata by sex, age at onset of PD (≤71 vs >71 years), and PD with or without rest tremor.

Table 2 shows the results of our case-control analyses stratified by lag time between PD and preceding anemia (first diagnosis or first low hemoglobin level). We observed a greater association for anemia experienced 20 to 29 years before the onset of PD (OR 4.26, 95% CI 1.55–11.69, $p = 0.005$). Results were similar for men and women (data not shown). In addition, results were similar throughout life when we stratified analyses on age at the onset of anemia (table 2).

Table 2 Association between Parkinson disease and preceding anemia stratified by time between onset of anemia and index year and by age at onset of anemia (196 cases and 196 controls)

Strata by time of anemia	Exposure frequency		Odds ratio (95% CI)	*p* Value
	Cases no. (%)	Controls no. (%)		
Time between onset of anemia and index year*				
No anemia	110 (56.1)	142 (72.5)	1.00 (reference)	—
0–9 y before index	19 (9.7)	17 (8.7)	1.28 (0.62–2.66)	0.51
10–19 y before index	11 (5.6)	8 (4.1)	1.87 (0.69–5.11)	0.22
20–29 y before index	21 (10.7)	8 (4.1)	4.26 (1.55–11.69)	0.005
≥30 y before index	35 (17.9)	21 (10.7)	2.14 (1.16–3.95)	0.02
Age at onset of anemia*				
No anemia	110 (56.1)	142 (72.5)	1.00 (reference)	—
Age 0–29 y	13 (6.6)	8 (4.1)	2.06 (0.79–5.35)	0.14
Age 30–49 y	37 (18.9)	22 (11.2)	2.26 (1.22–4.17)	0.009
Age 50–69 y	26 (13.3)	14 (7.1)	2.34 (1.15–4.77)	0.02
Age ≥ 70 y	10 (5.1)	10 (5.1)	1.18 (0.48–2.87)	0.72

*Onset of anemia was defined as the time of first diagnosis or of first low hemoglobin level reported in medical records.
CI = confidence interval.

Figure 1 shows the distribution of hemoglobin levels by age in cases and controls (men and women separately). The plot includes 114 men with PD and the corresponding 400 hemoglobin values, 110 men without PD and the corresponding 372 values, 73 women with PD and the corresponding 299 values, and 73 women without PD and the corresponding 260 hemoglobin values. The median number of hemoglobin values was 5 (range 0–9) for cases and 4 (range 0–7) for controls (Wilcoxon signed rank test, $p = 0.04$). Only 9 cases and 13 controls did not have any hemoglobin values. At all ages, the distribution of hemoglobin values was slightly but consistently lower in cases than in controls. However, the differences between cases and controls were not significant using linear mixed models for men (the mean hemoglobin level was 0.12 g/dL lower in cases than in controls at median age, $p = 0.33$) or for women (the mean hemoglobin level was 0.25 g/dL lower in cases than in controls at median age, $p = 0.09$).

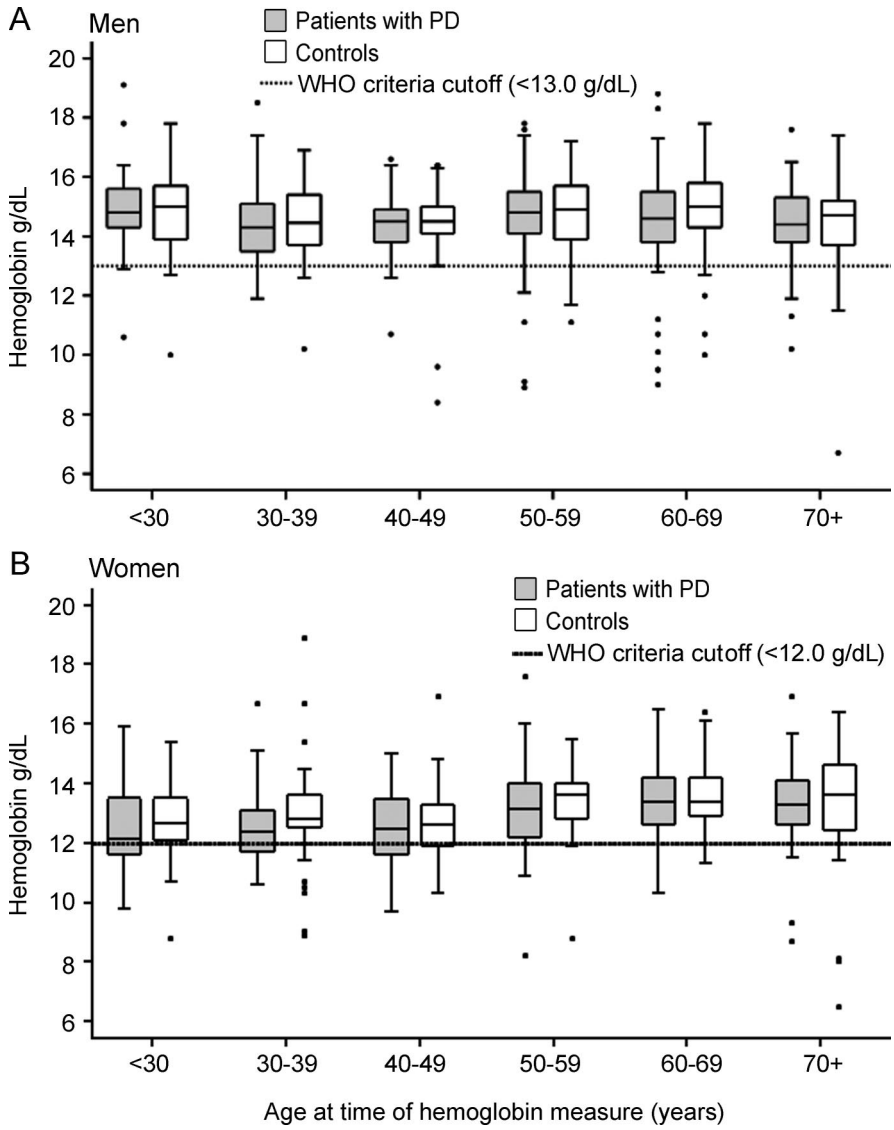
DISCUSSION Our study suggests that anemia defined by WHO criteria is associated with PD and may precede the onset of motor symptoms by 20 or more years. Subjects who later developed PD had a small but consistent downward shift of hemoglobin levels compared with controls that was evident as early as 20 or more years before the onset of motor symptoms (figure 1).

Similarly, several authors have reported a possible association between anemia (defined by WHO criteria) and AD.[2-5] Although the mechanism underlying the association of anemia with AD remains unknown, 2 hypotheses have been raised. First, AD could result from brain hypoxia caused by a chronic anemic state.[5] Second, AD could be a late-life sequela of epigenetic changes occurring during development.[18,19] Indeed, rats that experienced neonatal iron deficiency showed a persistently altered expression of several AD-related genes, possibly through a histone modification mechanism.[20] RLS is another neurodegenerative disease that has been related to anemia, iron deficiency,[6] and possibly frequent blood donations.[7] In turn, RLS has been associated with PD.[8]

We propose 3 hypothetical mechanisms linking anemia with increased risk of PD (figure 2). First, the association could be due to a cause-effect inversion if anemia was an early manifestation of the pathogenetic process underlying PD (figure 2). Thus, we hypothesize that PD may have a systemic onset and that the bone marrow is impaired early in life resulting in anemia and abnormalities in white blood cells and platelets. Some abnormalities in the oxidative phosphorylation of white blood cells and platelets have been reported in PD, and the abnormalities were not due to drugs used to treat PD.[21-23] In addition, genetic variability in the *SNCA* gene was correlated with α-synuclein levels in the peripheral blood.[24] The long interval from documented anemia to the onset of PD is consistent with increasing evidence that the premotor phase of PD may be quite long. Earlier studies suggested a preclinical period of 4.6 years estimated from neuropathology[25] and of 6 years extrapolated from imaging studies.[26] However, constipation and REM sleep behavior disorder may precede typical PD by a decade or more, whereas anxiety disorders may predate PD by at least 20 years.[27-29] Thus, our findings may add to the growing body of evidence in support of a more pervasive process in PD with involvement of tissues and organs outside the nervous system.

Second, anemia could be a surrogate marker of iron deficiency, folate deficiency, or another deficiency.[30] Iron is a crucial cofactor for the enzyme L-tyrosine hydroxylase,[31] plays a role in dopaminergic neurodevelopment, and is involved in the synthesis of monoamine neurotransmitters.[32] Thus, rats fed an iron-restricted diet develop a marked reduction of striatal dopamine and a reduced dopaminergic activity.[33] In addition, a recent case-control study suggested that the risk of PD was increased in men who reported multiple recent blood donations and thus experienced decreased body iron stores.[1] Finally, a prospective study showed that infants who experienced iron deficiency in the second year of life had a reduced dopaminergic function 10 years later (assessed indirectly by measuring serum prolactin levels in response to stress).[34] Thus, low iron could have early-life effects (epigenetic

Figure 1 Distribution of hemoglobin levels over age in men and women



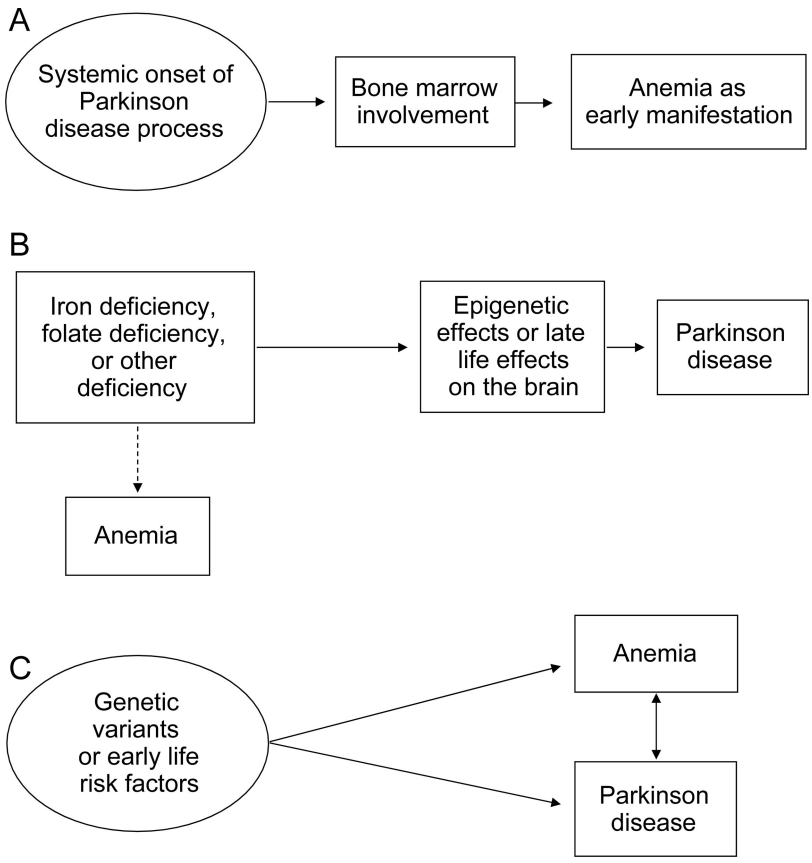
The grey boxes for patients with Parkinson disease (PD) are slightly but consistently lower than the white boxes for controls across all ages for both men (A) and women (B). The plot includes 114 men with PD and the corresponding 400 hemoglobin values, 110 men without PD and the corresponding 372 values, 73 women with PD and the corresponding 299 values, and 73 women without PD and the corresponding 260 hemoglobin values. The distribution by age at index year in cases and controls who had 1 or more hemoglobin values was similar to the distribution in cases and controls without any hemoglobin value (Wilcoxon rank sum test, $p = 0.10$).

changes during development) or late-life effects (alteration of enzymes or receptor activity).

Third, the association of anemia with PD could be due to confounding if some genetic variants or early life risk factors were responsible for an increased risk of anemia, and, independently, for an increased risk of PD. For example, some studies have investigated iron-related gene polymorphisms and PD; however, the results are inconclusive.[35,36] Similarly, association studies of genetic variants in iron-related genes and anemia are inconclusive.[37] We also considered hysterectomy as a potential confounder because hysterectomy was found to be associated with an increased risk of PD,[38] and the 2 most common indications for hysterectomy, fibroids and menorrhagia, are often a cause of anemia.[39] However, anemia remained associated with PD after adjustment for hysterectomy in analyses restricted to women (table 1, footnote ††).

Our study has a number of strengths. First, it was based on a series of incident PD cases and on well-defined general population controls, thus reducing referral bias and incidence-prevalence bias. Second, we were able to avoid recall bias by considering diagnoses of anemia or low hemoglobin levels that were historically documented in medical records before the onset of PD (or the index year). Third, our study

Figure 2 Three hypothetical mechanisms linking anemia with increased risk of Parkinson disease



(A) The Parkinson disease (PD) process may be systemic, and anemia may be an early manifestation of the involvement of the bone marrow (cause-effect inversion). (B) Anemia may be a surrogate marker of iron deficiency, folate deficiency, or another deficiency that caused early life effects (epigenetic changes during development) or late life effects (alteration of enzymes or receptors). (C) Genetic variants or early life risk factors may increase the risk of anemia earlier in life and, independently, may increase the risk of PD later in life (association due to confounding).

included both men and women, thus providing the opportunity to explore differences between the sexes. Fourth, the use of historic medical records in the records-linkage system facilitated the study of episodes of anemia that occurred several decades before the motor onset of PD, and we were able to collect several hemoglobin levels for most individuals. Fifth, analyses were adjusted for cigarette smoking, for pesticide use, or for hysterectomy in the stratum of women to explore possible confounding effects.

On the other hand, the study has several limitations. First, our sample size was limited for some of the stratified analyses as shown by the wide CIs. In addition, some of the findings may be due to multiple comparisons. Second, it is possible that some subjects were treated for anemia at a medical facility outside of the records-linkage system, and thus were not documented in the system. In addition, because hemoglobin levels were abstracted only nearest to decade birthdays, patients may have been anemic for several years in between 2 decade points and yet we may have failed to capture them. However, the prevalence of anemia in the adult US population is 32.5% in women and 11% in men using the WHO criteria.[40] These percentages are consistent with the frequency of anemia observed in our control group (36.0% in women and 22.3% in men).

Third, the WHO sex-specific cutoffs for hemoglobin that we used to define anemia were introduced in 1968 but have been subsequently criticized.[15,16] However, sensitivity analyses using quartiles of the empirical distribution of hemoglobin levels among controls yielded consistent findings. Fourth, our case-control series was recruited over a 20-year period, and secular trends in the diagnosis or treatment of anemia may have occurred. However, sensitivity analyses that stratified the sample into two 10-year strata (1976–1985 and 1986–1995) showed similar ORs (data not shown). Finally, the population of Olmsted County is primarily white of European ancestry, and the findings may not apply to other ethnic groups.

AUTHOR CONTRIBUTIONS

Statistical analyses were conducted by B.R. Grossardt, MS, and J.M. Carlin, BA, of the Division of Biomedical Statistics and Informatics, Department of Health Sciences Research, College of Medicine, Mayo Clinic, Rochester, MN.

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DISCLOSURE

Dr. Savica conducted this study while on leave from the Department of Neurosciences, Psychiatry, and Anesthesiology, University of Messina, Italy. Mr. Grossardt, Mr. Carlin, and Dr. Icen report no disclosures. Dr. Bower has served as a consultant to Allergan, Inc. Dr. Ahlskog received the American Parkinson's Disease Society Fred Springer Award; receives royalties from publishing *The Parkinson's Disease Treatment Book* (Oxford University Press, 2005), *Parkinson's Disease Treatment Guide for Physicians* (Oxford University Press, 2009), *Parkinson's Disease and Movement Disorders* (Humana Press, 2000), and *Surgical Treatment of Parkinson's Disease and other Movement Disorders* (Humana Press, 2003); and receives research support from the NIH/NINDS [P50 NS 40256-R (Coinvestigator)]. Dr. Maraganore may accrue revenue from pending patent applications related to the prediction of Parkinson disease and the treatment of neurodegenerative disease; has received license fee payments and royalty payments from Alnylam Pharmaceuticals (method to treat Parkinson disease); and receives research support from the NIH [ES10751 (PI)]. Dr. Steensma receives institutional research support from Eisai Inc., Genzyme Corporation, Amgen, Johnson & Johnson, and Celgene and research support from the NIH [K12 CA90628 (Coinvestigator)]. Dr. Rocca receives research support from the NIH [AR030582 (PI), AG006786 (Coinvestigator), and ES010751 (Coinvestigator)].

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