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Environmental and Occupational Risk Factors for Progressive Supranuclear Palsy: Case-Control Study

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Abstract

Background—The cause of progressive supranuclear palsy (PSP) is largely unknown. Based on evidence for impaired mitochondrial activity in PSP, we hypothesized that the disease may be related to exposure to environmental toxins, some of which are mitochondrial inhibitors.

Methods—This multicenter case-control study included 284 incident PSP cases out of 350 cases and 284 age-, sex- and race-matched controls primarily from the same geographical areas. All subjects were administered standardized interviews to obtain data on demographics, residential history and lifetime occupational history. An industrial hygienist and a toxicologist unaware of case status assessed occupational histories to estimate past exposure to metals, pesticides, organic solvents and other chemicals.

Findings—Cases and controls were similar on demographic factors. In unadjusted analyses, PSP was associated with lower education, lower income, more smoking pack-years, more years of drinking well water, more years living on a farm, more years living one mile from an agricultural region, more transportation jobs, and more jobs with exposure to metals in general. However, in adjusted models, only more years of drinking well water was significantly associated with PSP. There was an inverse association with having a college degree.

Interpretation—We did not find evidence for a specific causative chemical exposure; higher number of years of drinking well water is a risk factor for PSP. This result remained significant after adjusting for income, smoking, education and occupational exposures. This is the first case-control study to demonstrate PSP is associated with environmental factors.

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Keywords

Keywords: Progressive supranuclear palsy; case-control study; epidemiology; risk factors; Parkinsonism

Introduction

Progressive supranuclear palsy (PSP) is the most common atypical parkinsonian disorder.[1, 2] It classically presents in middle-to-late age with postural instability and falls, levodopa unresponsiveness, frontal cognitive disturbances, supranuclear vertical gaze palsy and/or slowing of vertical saccades and early dysarthria and dysphagia.[3] The incidence in persons over age 50 years is estimated to be 5.3 cases per 100,000 person-years and it increases with age.[1, 4] The median survival time for the classic PSP (Richardson) phenotype is approximately 5-6 years after symptom onset.[4]

It is hypothesized that both environmental and genetic factors may be critical to the etiology of PSP, a primary tauopathy.[5, 6] Previous PSP case-control studies reported several potential

risk factors but the results remain controversial.[7-9] The weaknesses of these prior studies include small sample size, lack of rigorous case selection, and non-validated questionnaires.

We designed ENGENE (Environmental Genetic)–PSP, a multicenter case-control study, to examine the association between PSP and environmental and genetic factors. Because of previous data pointing to abnormalities of mitochondrial function in PSP,[5, 6] we focused the search on occupational exposures to classes of chemicals known to inhibit mitochondrial enzyme activity. Metals, organic solvents, and pesticides, were identified as potential exposures of particular interest. This is the largest PSP case-control study to date.

Design

a. Study Population

Two hundred eighty-four out of 350 incident PSP cases were age-, sex- and race-matched to 284 out of 300 healthy controls recruited primarily from the same geographical areas by 15 sites throughout North America between 10/01/2006 and 02/01/2013. Sixty-six cases were excluded because they lacked a matched control (Figure). Comparison between the included and excluded cases showed that both had similar age, disease duration and education, but there were more males ($p<0.01$) and non-whites of European descent ($p<0.0001$, data not shown) in the excluded cases. The sampling framework was defined as the catchment area of the clinical centers participating in the study, which comprised all individuals who would normally attend the participating clinics if they had symptoms of PSP. In addition, referrals from other clinics around the country were forwarded to the closest of the 15 screening sites. The IRBs approved the use of human subjects in this study. Every participant signed a written informed consent.

b. Inclusion/Exclusion Criteria

PSP was defined using NINDS-SPSP criteria for probable PSP.[3] Case eligibility criteria included incident cases defined as being diagnosed with PSP within the past year by the screening site principal investigator and absence of other central nervous system pathology. A Mini-Mental State Examination (MMSE) score ≥ 24 was required to exclude dementia or cognitive impairment that could have interfered with recall of life events.

Each case identified an age- (±5 years) and sex-matched, non-blood relative (i.e., in-laws, but not spouses) or when not possible a friend, to serve as a control. To be eligible, controls had to screen negative for both parkinsonism and dementia. Because each case-control pair was usually recruited from the same site, geographic distribution was largely similar for cases and controls.

c. Neurological and Neuropsychological Evaluation

Movement disorder specialists followed a detailed protocol to collect neurological data on cases in a standardized manner using validated instruments (i.e., PSP Rating Scale (PSP-RS) and the Unified Parkinson Disease Rating Scale (UPDRS)). A battery of neuropsychological tests, including the Mini-Mental Status Examination and California Verbal Learning Test,[10] were administered and used to assess global cognition and memory. Controls received a

short screening interview to exclude dementia and parkinsonism using the validated Telephone Interview of Cognitive Status (TICS-M, score ≥ 28)[11] and the Telephone Questionnaire for PD.[12]

d. Occupational Exposures

At the time of enrollment, the research coordinator administered an occupational questionnaire to all subjects, which captured information about all jobs held since age 16, including information on the name of the company, job sector, position held, years employed, job duties, any tools or equipment used, and chemicals used or encountered. Occupational history data were reviewed at the central site and any queries were resolved upon follow-up interview. Self-reported chemical exposures were recorded. In addition, jobs and data associated with each job were reviewed independently by an industrial hygienist and a toxicologist to assess and assign potential exposure (i.e., chemicals in general, metals, pesticides and organic solvents) independent of the self-report. Because the occupational histories were self-reported and spanned the subjects' entire work career, it was not feasible, in most instances, to obtain detailed information regarding specific chemical use or exposure. Therefore, exposure assessment was based on job title, job duties, location, era within which the work was performed and related information. Each job was assessed individually and was accordingly assigned a potential for exposure to chemicals from the following: metals (i.e., lead, mercury, tin, zinc, aluminum, manganese, etc.); pesticides (rotenone, 2,4-D, paraquat, etc.); organic solvents (acetone, benzene, carbon tetrachloride, xylene, etc.); and other chemicals (ammonia, oils, water based cleaners, etc.). Because of the nature of the data collection (self-reported, retrospective), it was not possible to quantify exposure precisely. The experts assessing exposure were blinded to case-versus-control status. For statistical analyses, job histories and associated exposures were truncated, i.e., lagged, at the reference date (10 years before case symptom onset).

e. Environmental/Lifestyle/Medical exposures

A modified telephone questionnaire from Stewart and colleagues [13] was administered by the central site to both cases and controls that captured information regarding: demographics (i.e., marital and socioeconomic status); residential history (including all places of residence since birth, well water exposure, rural vs. urban setting); hobbies; medication history (including prescribed and over-the-counter medications used for more than six months since the age of 30, specific data on chemotherapeutic agents, mitochondrial disruptors and anti-oxidants); family history of related neurodegenerative disorders; military service (dates and locations of service, and exposure to potential hazards); and gardening or lawn-care habits (home pesticide and fertilizer usage). The Stewart telephone questionnaire was previously validated in PSP patients in a pilot study comparing patients' responses to medical records (data not shown).

f. Analyses

Descriptive statistics related to subject characteristics and exposures were tabulated. The frequency of categorical variables between case and control groups was compared using conditional logistic regression. Persons with missing data were dropped from analyses

requiring those data. As can be seen in the tables, this was a rare occurrence for most variables.

For the primary analysis, we used standard methods for matched case-control studies. [14, 15] Conditional logistic regression models were used to calculate odds ratios (OR) and 95% confidence intervals (CI) for the association between exposure and disease. Exposures were entered into models as categorical variables (yes/no exposure**;** and no exposure, less than 10 years of exposure, and greater than or equal to 10 years). Environment-related demographics were also entered into models as continuous variables (years of exposure). The OR's and CI's for these continuous variables were calculated based on a 10 year increase in exposure instead of a one year increase. Job group data were available for 553 of the 568 subjects, including 271 matched case-control pairs, 5 unmatched cases, and 6 unmatched controls. In addition to common job categories, the following more general job categories were also constructed by combining selected individual job groups: (1) Construction and Trades consist of Construction, Miscellaneous Trades, and Trades; (2) Office 1 consist of General Office, and Other Office-Based; (3) Office 2 consist of General Office, Other Office-Based, Teaching, Professional, and Supervisory. Job groups not included in these more general categories above were compared individually.

The association of specific job groups/categories (ever versus never) with case-control status was compared and tested using conditional logistic regression. [15] To adjust for multiple testing we used Holms multiple test procedure.[16]

Only complete data were used in summing up job group work years for an individual. If a specific job group was included in the work history for a subject, but the number of years could not be determined due to missing information (for example missing data in beginning or ending years of work for a job), then the years for a specified job group for a subject was treated as missing. This resulted in no more than 8 additional missing subjects for any of the job groupings. If a specific job group was completely absent from the work history of a subject, then that subject was assigned zero years for that job group.

To adjust for possible confounding variables and interaction effects, we first conducted a univariate analysis and then included in the multivariate conditional logistic regression analysis only the variables with p-values <0.05 in the univariate analysis. In variables expected to be highly associated with each other, such as ever drinking well water and years of drinking well water, only the variable with the lower p-value was included. Variables in the multivariate logistic regression model with p-values <0.05 were then evaluated two at a time, for possible two-way interaction effects. Multivariate conditional logistic regression including both main effects and interaction was used for this purpose. A significance level of $p<0.05$ was used for interaction effects.

With 284 matched case and control pairs, and using a two-sided test with significance level $\alpha=0.05$, 80% power to detect an OR of 1.83 is attained assuming an exposure prevalence of 15%. Statistical analyses were performed using SAS. [17] Quanto 1.2.4 software was used for power calculations.[18]

Results

Demographics

Cases and controls were similar on most demographic characteristics consistent with the matched study design (Table 1). Cases mean±SD age at interview was 68.8±7.0 years and controls 69.0±7.4 years. Overall, 97.5% of the study population identified themselves as Caucasians. Mean PSP symptom duration was 3.7±1.8 at the interview.

PSP characteristics

To assure accuracy of PSP patients reporting we evaluated their memory. The large majority of the PSP patients in this sample did not present memory retrieval deficits (cases mean CVLT-2 Total Recall z-score = -0.83 and CVLT-2 Long Delay Recall z-score = -0.28), although approximately 8% had mild impairment. In addition, performance in a memory recognition format was above the mean in relation to age- and sex-matched peers (CVLT Recognition Discrimination z-score = 0.55) and only less than 3% of the sample exhibited mild impairment.

Unadjusted Univariate Analyses

Educational attainment differed between cases and controls, with cases less likely to have earned a college degree (Odds Ratio, OR: 0.42; 95% CI: 0.27, 0.64, p<0.001) than controls. They also had a lower income (<$50,000 vs. >$80,000, OR: 0.54; 95% CI: 0.32-0.90, p=0.02) than controls. PSP cases also smoked more pack-years (OR 1.15; 95% CI: 1.05, 1.27, p=0.002) than controls.

PSP cases were more likely to report more years drinking well water (OR 1.29; 95% CI: 1.13, 1.50, p<0.001), more years living within one mile of an agricultural area (OR 1.22, 95% CI: 1.06, 1.41, p=0.004) and more years living on a farm or ranch (OR 1.26, 95% CI: 1.09, 1.49, p=0.002) compared to controls (Table 2). In addition, PSP cases were more likely to have worked in transportation (OR 1.46; 95% CI: 1.06, 2.06, p=0.02, Table 1S). As seen in Table 2S, there were more cases than controls self-reporting exposure to pesticides (OR 1.44; 95% CI: 1.00, 2.13, p=0.05) and organic solvents (OR 1.35; 95% CI: 1.07, 1.72, p=0.009). Table 3 shows that PSP cases were more likely to be assigned to occupational metal exposure (OR 1.30; 95% CI: 1.00, 1.70, p=0.05). There was also a tendency for them to be exposed to chemicals (OR 1.20; 95% CI: 0.99, 1.45, p=0.06).

Adjusted Analyses

Multivariate conditional logistic regression analysis (Table 4) showed that only having a college degree and years drinking well water were significantly associated with disease status (p<0.05). When these two factors were included in a model together (Table 4S), the interaction was not significant (p=0.66). Self-reported exposures (i.e., organic solvents were not included in the adjusted analyses.

Discussion

We used a case-control design to examine the role of environmental factors in the etiology of PSP. We hypothesized that occupational and environmental exposures to chemicals, particularly those known to inhibit mitochondrial enzymes or alter oxidative state such as pesticides, organic solvents, and metals, would be associated with PSP.[5, 6, 19] Our hypothesis was based on several lines of evidence: (1) oxidative injury may induce tau hyperphosphorylation in PSP and in neuronal cultures, [20] (2) oxidative injury is observed in PSP brain regions with well established tau pathology, [21, 22] (3) there is impaired mitochondrial complex I activity in PSP patients' muscle and blood cells [23, 24] and experimentally, (4) a mitochondrial inhibitor has been shown to induce an animal model resembling clinical and pathological aspects of PSP.[25]

In the univariate analysis we found that PSP cases were more likely than controls to: (1) have lived within one mile from an agricultural area; (2) have lived on a ranch or a farm; (3) have drank well water; (4) have worked in transportation; (5) have been exposed to metals; (6) have lower income and (7) have smoked more pack-years.

Living more years on a ranch or a farm, living near an agricultural area and drinking well water might indicate an exposure to pesticides, which, in addition to organic solvent exposure, were both significant exposures reported by the cases. However, neither pesticides nor organic solvents were identified as occupational exposures significantly associated with PSP by the industrial hygienist and toxicologist who performed an assessment unaware of case status. Since cases may under- or over-report certain exposures, we chose a priori the more objective assignment of exposures by expert analysis. These associations found in PSP are similar to those initially found in Parkinson disease (PD), a related neurodegenerative disease in which mitochondrial dysfunction plays a role in its etiopathogenesis. [26] In PD, recent studies in large populations have revealed links between the occurrence of PD and occupational exposure to specific pesticides, [27, 28] and thereby strengthened the evidence that pesticides may account for the effect of well water on PD risk. [29, 30] Larger studies will be needed to determine whether the same is true in PSP.

As observed in other studies, PSP cases had lower levels of academic achievement than controls. [8, 9] This could be a marker of working in occupations where there is greater likelihood of exposure to chemicals, which also tended to be more likely in cases than in controls. We recruited controls from friends and unrelated family, which suggests that simple referral bias is a less likely explanation.

The expert-inferred exposures analysis showed that cases were more likely than controls to work in the transportation industry (mostly truck drivers). Cases were also more often assigned to metal occupational exposures by case-status-blinded experts. In addition, expert-inferred exposures analysis showed that PSP patients had greater but not significantly different exposures to manufacturing and mining jobs than controls (not shown). However, it is possible that statistical differences were not found due to the overall low frequency of these jobs in our cohort. In fact, a recent report of a cluster of PSP patients in France in a

geographical area with severe environmental contamination by industrial metals supports our findings.[31]

On the other hand, the study also showed that PSP cases smoked more pack-years than controls, although while significant, overall the between-group differences were not large. Prior PSP case-control studies[9, 32] did not show an association between smoking and PSP. This finding is in contrast to what is found in PD [33] in which cases smoke fewer pack-years than controls.

Only years of drinking well water remained significant after multivariate adjusting for possible confounders (college degree, income and smoking pack-years). This does not exclude the possibility that other exposures may play a role because, despite being the largest PSP case-control study to date, this study had limited statistical power to detect associations with rare exposures. Limited statistical power restricted our ability to rule these out as significant associations and the suggestive findings could form the basis of future hypothesis-driven studies.

Rather than a causative factor, low income may be the result of employment in industries that involve exposure to environmental chemicals. Examples are: agriculture, transportation and metal industries. The same is true for a college education. The results suggesting that education is an independent predictor of a higher incidence of PSP may also be a function of the types of jobs that are less likely to require a college degree.

Strengths and Limitations

Exposure assessment may be limited by recall. We did assess cognitive function to determine whether the effects of PSP itself might impair recall; we found only a limited number of cases (3%) exhibiting borderline to mild retrieval deficit. Thus, a distortion of the measure of association is unlikely to have had a major effect on the outcomes. Moreover, assessment of occupational exposures by expert consensus unaware of case status, as done in this study, is generally considered a better method of retrospective exposure assessment in the absence of prospective exposure measures or biological markers of exposure.[34] On the other hand, because of this exclusion the study may not fully represent patients who develop prominent early cognitive problems.

In view of the low prevalence of PSP, ENGENE was, of necessity, a multicenter study. In order to minimize inter-center variability; specific training in eligibility criteria, case ascertainment, data collection, and use of standardized scales occurred before initiation and during the study. [35] The geographical diversity among study sites increased the probability that our results may be representative of the PSP population at large. In fact, cases and controls were distributed across 46 states of the United States as well as Canada. However, the study may not be representative of severely affected PSP patients, as they would have been ineligible due to cognitive impairment, and less able to travel to study sites.

There are at present no reliable diagnostic biomarkers for PSP. Therefore we cannot be certain that patients with corticobasal degeneration presenting with a PSP phenotype were not included. However, we are quite confident that a high percentage of our cases had PSP

since site investigators were experienced, had training prior to the study initiation and used the NINDS-SPSP diagnostic criteria that have a high specificity and positive predictive value to diagnose patients presenting with the classical PSP phenotype. [36] In order to maintain the highest possible level of diagnostic certainty we excluded other, less specific PSP phenotypes such as PSP-parkinsonism and thus our study does not reflect the full spectrum of PSP.

Another important limitation was the inability to recruit enough controls, which did not allow the inclusion of all the cases recruited. In fact, analyses including 300 cases and 300 controls matched by age and sex but not by race, not only showed the same results reported, but some exposures with a tendency of being significant became significant. For example, the p-values for assigned chemical exposures and having ever worked in agriculture for the cohort of 568 subjects reported here were non significant (p=0.06), but became significant (p= 0.03) for the case-control cohort of 600. Despite our attempt to exclude differences in socioeconomic levels between cases and controls by choosing in-laws or friends as controls, the cases had a lower socioeconomic and educational level than the controls.

To exclude the impact of recent exposures and changes in behaviors that could be irrelevant to disease causation, exposures up to 10 years prior to symptoms-onset were censored (lagged). This assumes a relatively long pre-symptomatic period of disease development after the critical initiator(s).

Conclusions

The case-control design used for ENGENE-PSP made it possible to overcome many of the limitations of previous investigations by: (1) including the largest sample of well-defined cases and well-selected controls to date; (2) using up-to-date instruments and proven methodology to investigate potential exposures; (3) using *a priori*-defined hypotheses that allowed us to anticipate and control for potential confounders (i.e., socioeconomic status); (4) using exposure lagging to exclude recent exposures that have no bearing on causation; (5) including incident cases to decrease bias associated with over-representation of long disease duration cases that could lead to identification of factors associated with disease duration rather than with causation; and (6) using well-trained interviewers to administer the modified Stewart questionnaire.

We obtained evidence for a potential role of the environment in the etiology of PSP, particularly drinking well water and living in, or near, agricultural regions, and other evidence that suggests pesticide, metal and transportation industries exposure. These results are consistent with similar studies on PD, lending credence to the PSP results. Understanding the etiology of PSP may also help explain the causes of cell death in other neurodegenerative tauopathies, such as Alzheimer disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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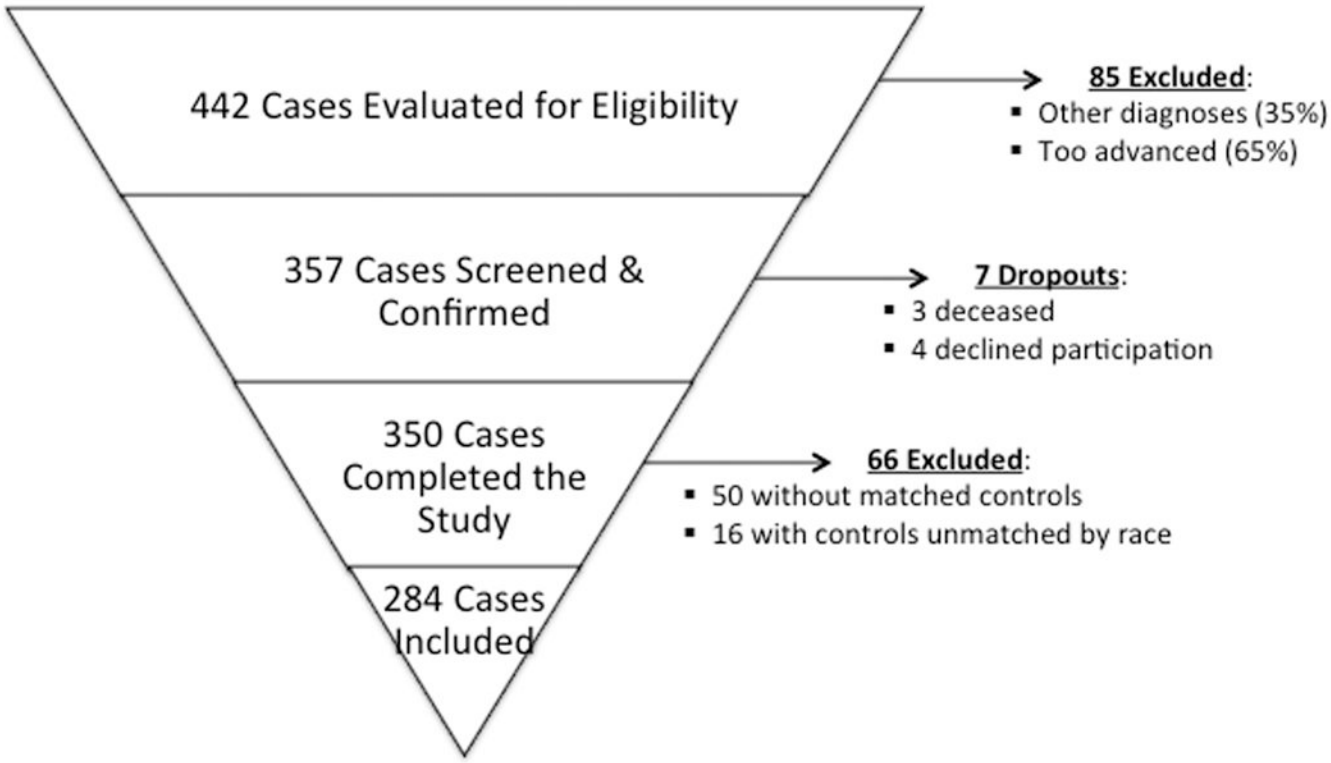

Figure.

Table 1
Distribution of demographic characteristics by case-control status

		Group		
Variables	**Total N =568**	**Case N =284**	**Control N =284**	**p-value**
Sex				1.00
Female (%)	286 (50.4)	143 (50.4)	143 (50.4)	
Male (%)	282 (49.6)	141 (49.6)	141 (49.6)	
Race				1.00
White (%)	554 (97.5)	277 (97.5)	277 (97.5)	
Other (%)	14 (2.5)	7 (2.5))	7 (2.5)	
Age at interview				0.65
41-60 (%)	66 (11.6)	30 (10.6)	36 (12.7)	
61-70 (%)	275 (48.4)	142 (50.0)	133 (46.8)	
71-90 (%)	226 (39.8)	112 (39.4)	114 (40.1)	
Symptom duration (years)		3.7 ± 1.8	NA	
Total Mini Mental Status Examination		27.3 ± 2.0	NA	
Total PSP-Rating Scale		36.4 ± 11.2	NA	
PSP-Rating Scale Bulbar		2.6 ± 1.3	NA	
PSP-Rating Scale Ocular		9.0 ± 4.2	NA	
PSP-Rating Scale Gait		9.7 ± 4.3	NA	
Total Unified Parkinson Disease Rating Scale		51.7 ± 17.8	NA	

NA, not applicable.

Table 2
Environment-related demographics by case-control stat

Variables	Total N=568	Case N=284	Control N=284	p-value
College degree				**<0.001**
No (%)	198 (34.9)	122 (43.0)	76 (26.8)	
Yes (%)	370 (65.1)	162 (57.0)	208 (73.2)	
Income 10 yrs prior to onset				**0.04**
<50K (%)	157 (27.6)	86 (30.3)	71 (25.0)	
50K-80K (%)	140 (24.6)	64 (22.5)	76 (26.8)	
>80K (%)	202 (35.6)	86 (30.3)	116 (40.8)	
Ever drank well water				0.08
Yes (%)	260 (45.8)	141 (49.6)	119 (41.9)	
No (%)	308 (54.2)	143 (50.4)	165 (58.1)	
Years of drinking well water				**<0.001**
Mean (95%CI)	9.5 (8.3 - 10.8)	11.7 (9.7 - 13.7)	7.4 (5.9 - 8.8)	
Median (min - max)	0.0 (0.0 - 65.0)	0.0 (0.0 - 65.0)	0.0 (0.0 - 60.0)	
Ever lived within 1 mile of agriculture				**0.010**
Yes (%)	155 (27.3)	90 (31.7)	65 (22.9)	
No (%)	413 (72.7)	194 (68.3)	219 (77.1)	
Years lived within one mile of agriculture				**0.004**
Mean (95%CI)	7.0 (5.8 - 8.2)	8.6 (6.7 - 10.4)	5.4 (3.9 - 6.9)	
Median (min - max)	0.0 (0.0 - 65.0)	0.0 (0.0 - 65.0)	0.0 (0.0 - 65.0)	
Ever lived on a farm or ranch				0.05
Yes (%)	126 (22.2)	73 (25.7)	53 (18.7)	
No (%)	442 (77.8)	211 (74.3)	231 (81.3)	
Years lived on a farm or ranch				**0.002**
Mean (95%CI)	5.1 (4.1 - 6.2)	6.6 (5.0 - 8.3)	3.6 (2.4 - 4.9)	
Median (min - max)	0.0 (0.0 - 65.0)	0.0 (0.0 - 64.0)	0.0 (0.0 - 65.0)	
Family history neurodegenerative diseases				0.25
Yes (%)	137 (24.1)	62 (21.8)	75 (26.4)	
No (%)	431 (75.9)	222 (78.2)	209 (73.6)	
Ever Smoked				0.16
Yes (%)	271 (47.7)	144 (50.7)	127 (44.7)	
No (%)	297 (52.3)	140 (49.3)	157 (55.3)	
Smoking pack-years				**0.002**
Mean (95%CI)	13.2 (11.3 - 15.0)	15.8 (12.8 - 18.7)	10.6 (8.3 - 12.8)	
Median (min - max)	0.0 (0.0 - 172.0)	0.2 (0.0 - 172.0)	0.0 (0.0 - 114.0)	

P-values from exact conditional logistic regression

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Table 3

Distribution of Assigned Occupational Exposures

Variables	Total (N=568)	Case (N=284)	Control (N=284)	OR (95% CI)	P Value
Assigned Chemical exposure					0.06
No (%)	344 (60.6)	161 (56.7)	183 (64.4)	1	
Yes (%)	224 (39.4)	123 (43.3)	101 (35.6)	1.20(0.99-1.45)	
Assigned Metal exposure					**0.05**
No (%)	469 (82.6)	226 (79.6)	243 (85.6)	1	
Yes (%)	99 (17.4)	58 (20.4)	41 (14.4)	1.30(1.00-1.70)	
Assigned Pesticide exposure					0.82
No (%)	542 (95.4)	272 (95.8)	270 (95.1)	1	
Yes (%)	26 (4.6)	12 (4.2)	14 (4.9)	0.89(0.52-1.50)	
Assigned Organic Solvent exposure					0.38
No (%)	435 (76.6)	213 (75.0)	222 (78.2)	1	
Yes (%)	133 (23.4)	71 (25.0)	62 (21.8)	1.12(0.89-1.41)	
Assigned Other exposures					0.17
No (%)	384 (67.6)	184 (64.8)	200 (70.4)	1	
Yes (%)	184 (32.4)	100 (35.2)	84 (29.6)	1.14(0.95-1.38)	

Abbreviations: OR - Odds Ratio. CI – Confidence Interval. P-values and confidence intervals from exact conditional logistic regression. *Metal exposures is non-significant (p=0.25) after using Holm's multiple testing procedure.[16]

Table 4

Multivariate Analysis

Factor	OR	95% CI		P-Value
Ever College Diploma	0.59	0.35	0.99	**0.05**
Income 50K-80K vs <50K	0.81	0.45	1.42	0.45
Income >80K vs <50K	0.73	0.41	1.29	0.28
Years of drinking well water	1.23	1.02	1.46	**0.03**
Years of living one mile from agricultural area	1.15	0.95	1.39	0.15
Years of living on farm or ranch	0.96	0.75	1.22	0.69
Smoke pack-years	1.10	0.99	1.22	0.08
Ever Transportation job	1.69	0.78	3.66	0.19
Ever Assigned Metal exposure	0.96	0.53	1.74	0.89

Abbreviations: OR - Odds Ratio. CI – Confidence Interval. P-values and confidence intervals from conditional logistic regression. OR's for continuous variables are for 10 years