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Short communication

Anti-inflammatory drug use and progressive supranuclear palsy

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ABSTRACT

Background: Anti-inflammatory drug use, particularly ibuprofen, has been associated with a lower risk of Parkinson's disease. Microglial activation and inflammatory cytokine expression have been shown to be pathological features of progressive supranuclear palsy. We examined the association between NSAID use and risk of PSP, disease severity and age at onset.

Methods: The ENGINE-PSP multicenter case-control study recruited incident PSP cases who met the NINDS-PSP Society diagnostic criteria and age-, sex- and race-matched controls primarily from the same geographical areas. All subjects underwent standardized interviews to obtain data on demographics, residential history, medication history and lifetime occupational history. NSAID use was specifically queried by telephone interview using a standardized questionnaire.

Results: Information was obtained on anti-inflammatory drug exposure in 276 cases and 278 controls. No association was found between NSAID exposure and risk of PSP, age at onset or rate of change of UPDRS motor subscale, PSP Rating Scale or Mattis Dementia Rating Scale scores. This lack of association persisted when NSAID exposure was measured considering any NSAIDs, ibuprofen only, ASA only or non-ibuprofen, non-aspirin NSAIDs.

Conclusions: These results do not suggest an important association between NSAID use and PSP occurrence or expression. Despite the large size of our study, confidence intervals were wide. To rule out small associations, very large sample sizes will be required.

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1. Introduction

Progressive supranuclear palsy (PSP) is the second most common cause of neurodegenerative parkinsonism, after Parkinson's

disease. Its etiology is unknown but inflammation may play a role in its pathophysiology based on in vivo and pathological studies revealing microglial activation to a greater extent than in controls [1], and greater inflammatory cytokine expression (IL-1beta) in the subthalamic nucleus and substantia nigra [2]. Neuroinflammation is also a pathological feature of Parkinson's disease [3], and case-control studies have suggested an inverse association between prior intake of the non-steroid anti-inflammatory drug ibuprofen

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and the risk of Parkinson's disease [4]. Only one study, to our knowledge, has investigated the association between PSP occurrence and anti-inflammatory use and did not find an association in a sample of 79 cases and controls [5], but the confidence intervals were broad. We undertook a larger case-control study of risk factors for PSP and hypothesized that non-aspirin non-steroidal anti-inflammatories (NSAIDs), particularly ibuprofen, would be associated with a reduced risk of PSP as well as slower symptom progression in established PSP.

2. Methods

The methods have been described in detail elsewhere [6]. Briefly, patients with PSP and healthy controls were recruited at 15 movement disorders centers across North America between 10/01/2006 and 02/01/2013. PSP was defined using NINDS-SPSP criteria for probable PSP [7]. Eligible cases had been diagnosed with PSP within the past year by the screening site principal investigator. 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 (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. Controls received a short screening interview to exclude dementia and parkinsonism using the validated Telephone Interview of Cognitive Status (TICS-M, score ≥ 28) [8] and the Telephone Questionnaire for PD [9]. From a total of 280 cases with PSP and 280 controls matched for age, sex and race we had information on anti-inflammatory drug exposure in 276 cases and 278 controls. Regular anti-inflammatory exposure was assessed in two ways: 1. From a telephone interview asking about many lifestyle factors and environmental exposures including: "Prior to reference year (10 years prior to symptom onset), had you ever taken any NSAIDs such as Advil or Naproxen at least 2 times a week for a period of 6 months or longer?" and 2. From an in-person visit collecting a list of all medications taken for 6 months or more since the age of 30. For both methods the specific drug, duration of use and age at time of use was ascertained. The study was approved by the local research ethics board at all participating centers and written informed consent was obtained from all participants.

2.1. Statistical analysis

Exposure to NSAIDs was expressed/analyzed separately as ever/never and years of exposure. We also considered, separately, any NSAID, any non-aspirin, non-ibuprofen NSAID and ibuprofen use. The two methods of ascertainment described above were also considered separately. All exposure measurements considered only the period of life up to 10 years prior to symptom onset in the case and the same age in the matched control. To assess the relationship between PSP occurrence (yes/no) and anti-inflammatory drug use, we fit conditional logistic regression models with stratum defined by case/control pairs and case status as the outcome; with exposure and the potential confounders of age, sex, ethnicity, years of education, smoking (pack-years) and living 1 mile from an agricultural area as independent variables. To assess the relationship between age at onset of PSP and anti-inflammatory drug use we fit linear regression models including age at first symptom of PSP as the outcome, and the same potential confounders as covariates. A linear regression was also fit to assess the relationship between anti-inflammatory drug use and a more benign PSP phenotype. Separate analyses including one of three outcomes were conducted: 1. The motor subscale of

the Unified Parkinson's Disease Rating Scale, 2. the PSP Rating Scale and 3. the Mattis Dementia Rating Scale. These models included as independent variables anti-inflammatory drug use, symptom duration, exposure and symptom duration interaction, and the same potential confounders. A significant p-value for the interaction term was considered evidence of an association between symptom progression and exposure. All test statistics are two-sided, with significance level $\alpha = 0.05$ unless otherwise directed. The analysis was conducted in R version 3.2.2.

3. Results

Table 1 shows the demographic and clinical characteristics of the cases and controls and exposure frequencies. Among 280 cases, mean age was 69 (± 7) and mean symptom duration was 3.7 (± 1.8) years. Cases had on average one less year of education than controls, had a higher number of pack-years of smoking and were more likely to have lived within a mile of an agricultural area.

3.1. Associations with PSP

No measures of NSAID use were significantly associated with PSP (Table 2). Odds ratio estimates were generally close to 1, however confidence intervals were wide.

3.2. Associations with age at first symptom of PSP

All coefficients with the exception of that for ever having been regularly exposed to non-aspirin, non-ibuprofen NSAIDs were negative, indicating a lower age at onset in those exposed or more exposed (Table 2). However, no measures of NSAID use were significantly associated with age at first symptom of PSP (Table 2).

3.3. Associations with Unified Parkinson's disease Rating Scale motor scores, PSP Rating Scale and Mattis dementia Rating Scale scores

No measures of NSAID use were significantly associated with a difference in the rate of change of these measures of disease severity over the symptomatic period (Supplementary Tables 1–3). All parameter estimates for the time-exposure interaction term were negative, indicating a point estimate of a slower accumulation of points on these scales in those exposed or more exposed.

4. Discussion

Based on evidence of a possible role of neuroinflammation in the pathophysiology or etiology of PSP, this study examined the relationship between prior use of NSAIDs and PSP. We found no difference in the use of NSAIDs between patients with PSP and controls suggesting that NSAIDs do not have a neuroprotective effect for PSP. Similarly, the extent of NSAID use was not associated with age at onset of PSP or rate of progression. In addition to the lack of statistical significance, the point estimates do not suggest any protective effect of NSAIDs. However, the confidence intervals are broad. In addition, examination of the other outcomes of interest, age at onset of PSP and the rate of change of UPDRS, PSPRS and Mattis DRS scores did not suggest a beneficial effect. Unfortunately, despite the large size of this case-control study (the largest yet conducted), the precision of our estimates is still low, due to the relatively small numbers of individuals exposed. Given the exposure frequency of ibuprofen and total NSAID exposure that we observed, with a total of 280 case-control pairs, we had 80% power at the two sided 0.05 level to detect odds ratios of 0.33 and 0.45, respectively. Thus we are unable to definitively rule out associations of lower magnitude. Due to the low frequency of PSP in the population, large studies of

Table 1

Demographic and clinical characteristics of cases and controls at the time of evaluation.

	Cases (n = 280)	Controls (n = 280)	p-value
Age, mean	68.80 (6.95)	68.98 (7.41)	0.336
Gender			1.000
Female n (%)	142 (50.7%)	143 (51.1%)	
Male n (%)	138 (49.3%)	137 (48.9%)	
Symptom duration	3.69 (1.76)	—	—
Years of schooling	14.83 (2.91)	15.93 (3.42)	<0.0001
Tobacco use (years)	15.71 (25.00)	10.89 (20.05)	0.003
Income			0.009
<50,000 per year	87 (37.3%)	70 (27.0%)	
50–80,000 per year	61 (26.2%)	77 (29.7%)	
>80,000 per year	85 (36.5%)	112 (43.2%)	
Years living within 1 mile of an agricultural area	10.97 (17.17)	6.69 (14.15)	<0.001
UPDRS motor score	30.05 (12.07)	—	—
PSP Rating Scale	36.48 (11.17)	—	—
Mattis Dementia Rating Scale	126.74 (10.64)	—	—
NSAID exposure			
Ever regular use			
Direct questioning ^a	19 (6.8%)	19 (6.8%)	1.000
Medication history ^b	36 (13.0%)	36 (12.9%)	1.000
Mean years	1.05 (3.73)	1.14 (4.52)	0.924
Ibuprofen exposure			
Ever regular use			
Direct questioning ^a	9 (3.2%)	12 (4.3%)	0.66
Medication history ^b	12 (4.3%)	14 (5.0%)	0.85
Mean years	0.22 (1.43)	0.44 (3.07)	0.46
Non-ASA, non-ibuprofen NSAID exposure			
Ever regular use			
Direct questioning ^a	9 (3.2%)	6 (2.1%)	0.61
Medication history ^b	14 (5.1%)	9 (3.2%)	0.66
Mean years	0.47 (2.62)	0.08 (0.54)	0.03
ASA			
Ever regular use			
Direct questioning ^a	Not available	Not available	—
Medication history ^b	11 (3.9%)	14 (5.0%)	0.68
Mean years	0.39 (2.42)	0.62 (3.37)	0.40

^a Telephone interview.^b medication history all medications taken for 6 months or more, UPDRS=Unified Parkinson's disease Rating Scale.**Table 2**

Associations between case status and anti-inflammatory exposure.

Odds ratios for cases vs controls (conditional logistic regression)		
		95% CI
NSAID exposure		
Ever regular use ^a	0.958	(0.486, 1.891)
Years	1.008	(0.963, 1.054)
Ibuprofen exposure		
Ever regular use ^a	0.732	(0.296, 1.814)
Years	0.966	(0.882, 1.057)
Non-ASA, non-ibuprofen NSAID exposure		
Ever regular use ^a	1.296	(0.427, 3.931)
Years	1.202	(0.978, 1.478)
ASA		
Ever regular use ^a	Not available	Not available
Years	0.993	(0.927, 1.064)
Parameter estimates for age at first symptom (linear regression)		
NSAID exposure		
Ever regular use ^a	−0.702	(−3.965, 2.560)
Years	−0.148	(−0.364, 0.068)
Ibuprofen exposure		
Ever regular use ^a	−2.181	(−6.849, 2.487)
Years	−0.523	(−1.095, 0.048)
Non-ASA, non-ibuprofen NSAID exposure		
Ever regular use ^a	0.779	(−3.885, 5.443)
Years	−0.121	(−0.432, 0.190)
ASA		
Ever regular use ^a	Not available	Not available
Years	−0.066	(−0.406, 0.274)

^a By direct questioning. All models adjusted for years of education, years of tobacco use and years living within a mile of an agricultural area.

this disease are very difficult to conduct but will be the only way to obtain a more definitive answer to this question.

Our result is consistent with that of Vidal et al. [5] who did not find a significant association between PSP and anti-inflammatory use in a much smaller case-control study. It is unclear from their report exactly how they defined anti-inflammatory use, including the frequency of use and the period of exposure. To our knowledge, no other studies have examined the association between anti-inflammatory use and PSP.

An open-label futility study of the NSAID salsalate is currently being conducted in a small number of patients with PSP. Our results are not inconsistent with a beneficial effect of Salsalate which is an NSAID that has been shown to enhance tau turnover and reduce tau levels [10], and thus may have the potential to influence the pathological process of PSP in ways that other NSAIDs cannot. Furthermore, as explained above, our results cannot rule out a clinically meaningful negative association with PSP. A strength of this work is the detailed clinical evaluation by expert centers, minimizing diagnostic error and allowing us to examine several outcomes describing the clinical expression of PSP in addition to its occurrence. Limitations of this work should be considered, however. Information on NSAID use was collected retrospectively, such that recall is likely to be inaccurate to some degree. Given that participants were not aware of the hypothesis and NSAID use was embedded in a questionnaire including many other topics, it seems unlikely that this issue would bias toward finding an association in either direction. Rather, it may bias toward the null result that we found. In addition, we lacked dosage data that could provide additional relevant information on exposure. Prospective studies

of lifetime exposure are ideal to address this issue, or studies accessing databases containing drug dispensing data. Given the low incidence of PSP the latter approach will likely be necessary.

To address the hypothesis that NSAID exposure is associated with later onset of PSP we used a linear regression approach. This approach can introduce a bias toward observing an association between longer exposure and later age at onset simply because there is more opportunity to accumulate any exposure, related or not to the outcome of interest when patients have a later age at onset. However, we did not find any suggestion of such an effect. This issue protects us against false positive conclusions.

In conclusion, we found no evidence of a protective effect of NSAIDs against PSP using multiple outcome measures.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.parkreldis.2017.11.346>.

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