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Increased prenatal exposure to methylmercury does not affect the risk of Parkinson's disease

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ABSTRACT

This study aimed to determine whether prenatal methylmercury (MeHg) exposure is a risk factor for Parkinson's disease (PD). A total of 172 clinically confirmed PD cases and 1018 controls matched by vital status, sex and age were included. The cases were ascertained in 1995 or were diagnosed during 1995–2005 in the Faroe Islands where the prevalence of PD is twice as high as elsewhere in northern Europe. Because the main single source of increased MeHg exposure in the Faroes is whale meat, retrospective exposure assessment was possible using detailed whaling records, rules of whale meat distribution and census lists. The share for each resident was calculated from the total amount of whale meat landed divided by the number of residents in the district entitled to a share. Utilizing the calculated share per resident at the mother's residence prior to the date of parturition, maternal body burden profiles were calculated as the average hair Hg concentration during the whole pregnancy, during the third trimester, and at the beginning of the third trimester. The exposures were compared between cases and controls using Mantel–Haenszel odds ratios (ORs), χ^2 and logistic regressions. All analytical methods gave ORs close to 1.0, none of them approaching statistical significance. The upper confidence limit was clearly below 2.0 in all analyses. No significant association between PD and prenatal MeHg exposure was found in this study, thus providing no support for prenatal MeHg exposure as an important risk factor that might explain the doubling of PD prevalence in this population.

1. Introduction

The nervous system is thought to be the most sensitive target for many toxic chemicals (Grandjean and Landrigan, 2006). The greatest vulnerability seems to occur during brain development (Andersen et al., 2000; Costa et al., 2004), as indicated by prospective studies of birth cohorts exposed to lead, methylmercury (MeHg), and polychlorinated biphenyls (PCBs) (Grandjean and White, 2002; Grandjean and Landrigan, 2006). Some neurotoxic effects, e.g., experienced during fetal development, may be latent and thus temporarily non-detectable; the full spectrum of neurotoxic damage therefore includes subclinical effects or silent toxicity that may become unmasked by challenges later in life, e.g., as a result of cumulative neurotoxicity over the life span (Calne et al., 1986; Cory-Slechta et al., 2005; Reuhl, 1991).

Experience with MeHg shows that developmental neurotoxicity may have long-term consequences (Grandjean and White, 2002; Grandjean, 2007; National Research Council, 2000), as illustrated by latent or delayed neurotoxicity evident after the environmental poisoning outbreak with MeHg in Minamata, Japan (Ninomiya et al., 1995). Brain functions affected in patients with Parkinson's disease (PD) are known also to be sensitive to environmental neurotoxicants (Feldman, 1999; White, 1992), such as MeHg and PCBs, which might therefore cause exacerbation of PD-associated deficits and may accelerate physiological aging. Such evidence has led to the hypothesis that degenerative diseases of the nervous system, such as PD, may be due to environmental damage, either prenatally or postnatally, to specific regions of the central nervous system and that the damage may remain silent for up to several decades (Barlow et al., 2007; Calne et al., 1986; DiMonte et al., 2002). Thus, the initial event that leads to PD may occur many years prior to the onset of symptoms. A few studies of MeHg exposure as risk factor for PD have been conducted, though with inconsistent results (Gorell et al., 1999; Ngim and Devathasan, 1989; Ohlson and Hogstedt, 1981; Semchuk et al., 1993).

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Prenatal exposure to MeHg as a risk factor for PD has not been studied so far.

The residents of Faroe Islands, a North Atlantic fishing community, have an increased MeHg exposure from eating the meat from the pilot whale (Andersen et al., 1987). Of further interest, PD in the Faroes has a prevalence about twice as high as expected (Wermuth et al., 1997, 2000, 2007). In 2005, the crude prevalence of idiopathic PD was 206.7 per 100,000 (Wermuth et al., 2007), i.e., about twice as high as the crude prevalence in Rogaland, Norway (110.9 per 100,000) (Tandberg et al., 1995), Als in Denmark (102.0 per 100,000) (Wermuth et al., 2000) and Østergøtland in Sweden (115 per 100,000) (Fall et al., 1996) where comparable methods for case-finding were used. As heritable cases mainly occur in cases diagnosed before age 50 years (Langston, 1998), the excess occurrence in the Faroes above this age (Wermuth et al., 2007) would likely be mainly due to environmental factors or combinations of genetic and environmental factors. The high prevalence could conceivably be linked to the increased prenatal exposure to MeHg, an exposure that has occurred for a long time due to the tradition of catching pilot whales that bioaccumulate this neurotoxicant that originates in part from natural sources. Over time and between the islands, whale meat intake varies substantially with availability. Consequently, subjects of the same age may have had widely different prenatal MeHg exposure potentials due to differences in access to whale meat. Because the MeHg exposure in the Faroes mainly originates from a single source, i.e., the pilot whale meat (Andersen et al., 1987; Weihe et al., 2005), retrospective MeHg exposure assessment is possible by using the unique historical sources available. The whaling records provide the exact location of each whale catch, the date, the number of whales, and the total amount of meat and blubber (Department of Foreign Affairs, 2000). By using census lists and the detailed rules of distribution, the whale meat allowance and thereby the potential MeHg exposure can be estimated. Thus, given the increased exposure to MeHg and the high prevalence of PD, this study aims at elucidating whether prenatal MeHg exposure, based on detailed whaling records at the child's birth place, is a risk factor for PD. Only MeHg is relevant as whale meat pollutant, because the present study focuses on people born in the first half of the 20th century, and exposure to organochlorine substances (e.g., PCBs) became important only after about 1950 (Eisenreich et al., 1989; Vartiainen et al., 1997).

2. Method

2.1. Subjects

All 181 Faroese PD patients (cases) identified in 1995 or diagnosed between 1995 and 2005 were considered for inclusion in this study (Wermuth et al., 1997, 2007). Nine PD cases were born before 1912 and were excluded, because population numbers at village level were lacking. Hence, a total of 172 PD cases was included. The cases were assessed based on the clinical information, the course of disease development, and the response to levodopa. Subjects were diagnosed as having PD if they had at least two of the three cardinal signs of resting tremor, bradykinesia, and rigidity (Wermuth et al., 1997, 2007). The mean age at appearance of symptoms was 66.0 years and the mean age at treatment initiation was 67.9 years (Wermuth et al., 2007). For comparison, the mean age at disease onset was 64.4 years in Rogaland, Norway (Tandberg et al., 1995). Information on smoking history is available on 79 interviewed cases and 154 controls, and 53.2% cases and 59.1% controls reported being current or former smokers (Petersen et al., 2008).

Six controls for each case were retrieved from the Faroese Population Registry. They were matched by vital status, date of birth and sex. For the PD cases who had first been identified in 1995, the controls were identified as Faroese residents alive on 1 July 1995. Similarly, matched cases were alive at the time of identification of the PD cases. Because of the small population in the Faroes (about 47,000 inhabitants) and the old age of the cases, matching was based on the closest possible birthday. A total of 1032 controls was drawn from the population registry. However, for six controls, information on the birth place was missing and eight subjects were known PD cases and thus excluded as controls. A total of 1018 controls was therefore included in the analysis. Thirty-six controls were controls for more than one PD case.

No contact was attempted to the subjects in this study, and the only information retrieved from the population registry on both PD cases and controls was place and date of birth. The Ethical Review Committee covering the Faroe Islands approved the protocol.

2.2. Methodology

We assessed, on an ecological basis, the potential prenatal MeHg exposure of each resident. The assignment of whale meat per resident was computed from the size of each whale catch, the detailed rules of distribution, and the number of residents entitled to receive a share according to the rules of distribution. Hence, each resident was assumed to receive a share calculated from the total amount of whale meat landed divided by the number of residents in one or more of the nine major districts of distribution entitled to a share.

Utilizing the calculated share that each resident received at the mother's residence prior to the date of parturition, estimation of the maternal body burden profiles could be performed assuming an average MeHg concentration of 2 μg/g whale meat, a regular consumption of the meat at a rate of 3 kg/month, and that any remaining supply after 2 years would be discarded. The body burden profiles took into account the average biological half-life of MeHg of 45 days (National Research Council, 2000). A decay of four biological half-lives after depletion of whale meat stores was assumed to be required for a woman to decrease her accumulated MeHg burden to background levels. The increased MeHg body burden after a large whale catch could therefore last for up to 2.5 years.

Although many of a district's whale catches occurred at considerable time intervals, some districts experienced more than one catch within a short period of time. In such cases, the supplies had not run out before the next catch occurred or, alternatively, the supply may have run out, but the body burden from the previous catch had not yet reached background levels. Therefore, we incorporated the contributions of all relevant whale catches 2 years prior to the birth date. All subjects were assumed to be born at term. The protocol was uploaded at the project web site (Petersen et al., 2005), and data were entered before cases and controls were identified.

Calculations of average hair mercury (Hg) concentration during the whole pregnancy, during the third trimester, and a point estimate at the beginning of the third trimester (i.e., 3 months before child birth) were performed using the individual body burden profiles. These numbers were then used to compare prenatal exposures of PD cases with those of the controls.

2.3. Validation on birthplace information

The exposure of subjects is dependent on their birthplace, this being the only independent variable differentiating the cases from the controls. Therefore the accuracy of this information is crucial. Self-reported birthplace is considered to be very accurate, and registry data in the Faroes are considered of high quality. In order to assess the reliability of the information from the population registry, we examined the data on 154 controls who had been interviewed in connection with another study (Petersen et al., 2008). Only six disagreements were apparent between the two sources and only one of the disagreements had an impact on the district and thereby the exposure estimates.

2.4. Data analysis

Fisher's exact-test was used to assess differences in the number of cases and controls born abroad and a χ^2-test to assess differences between groups of districts. Mantel–Haenszel odds ratios (ORs) for matched data stratified by age and sex was used, categorizing Hg exposure as a binary exposure variable where 'not exposed' was defined as hair Hg levels equal to zero or within the lowest tertile of the non-zero hair Hg distribution, while 'exposed' was defined as hair Hg levels in the second and third tertiles of non-zero hair Hg distribution.

For sensitivity analysis, ORs were compared without matching using (1) χ^2 to assess differences in odds between PD and hair Hg levels, categorized as a binary variable or as three categories (not exposed, some exposure and high exposure) based on the tertiles of the hair Hg distribution and (2) logistic regressions to assess the relationship between PD and Hg exposure categories, adjusted for age and sex. In addition, district adjustment was included in further multivariate logistic models for the assessment of the potential effects on the association between PD and Hg exposure.

3. Results

The average hair Hg concentration estimates for PD cases and controls are shown in Table 1. From the assumptions made, the maximum hair mercury concentration at steady state would be about 30 μg/g, but very few subjects approached this level. Thirty controls were born abroad while only two cases were born abroad. This difference is not statistically significant ($p = 0.30$). An attempt was made to classify the nine whaling districts into three groups from the amount of whale meat landed during the period of 1915–1943 where most PD patients were born ($n = 152$). No clear tendency was seen ($\chi^2 = 2.74$; $p = 0.25$), but this approach did not take into account the timing of whale meat availability in regard to each subject's prenatal MeHg exposure.

The Mantel–Haenszel OR was close to 1.0 for the three exposure measures (Table 2). Similar results were found with the various methods for non-matched data and methods of categorizing; Table 3 shows results for a non-matched multivariate logistic model, adjusted for sex and age. Although not significant, some ORs suggested that subjects with high Hg exposure had slightly greater odds of having PD than those who were not exposed.

Table 2
Mantel–Haenszel odds ratios and confidence intervals (CI) for matched data on prenatal methylmercury exposures (expressed as maternal hair mercury concentrations) in subjects with Parkinson's disease and controls

	OR[a,b]	95% CI
Average hair Hg during the whole pregnancy[a]	1.03	0.68–1.54
Average hair Hg during the third trimester[a]	1.04	0.68–1.59
Hair Hg at the beginning of third trimester[a]	1.11	0.70–1.76

Abbreviations: Hg, mercury; CI, confidence interval; OR, odds ratio.
[a] 'Not exposed': hair Hg levels equal zero and lowest tertile of the non-zero hair Hg distribution.
[b] 'Exposed': hair Hg levels in the second and third tertile of the non-zero hair Hg distribution.

Overall, no significant association between PD and prenatal MeHg exposure was found in this study. The upper confidence limits were all below 2.0.

The three hair Hg measures were highly correlated with Spearman correlation coefficients ranging from 0.84 to 0.91. Generally, the hair Hg levels at the beginning of the third trimester suggested slightly stronger, though insignificant associations with PD (data not shown).

There were differences in Hg distribution among the districts, but the overall associations between PD and Hg exposure did not change after further adjustment for district in the multivariate logistic models (data not shown).

4. Discussion

This study is, to our knowledge, the first to examine the possible association of prenatal MeHg exposure and PD risk. It is also the first to estimate prenatal exposures by taking advantage of historical data on whaling. Overall, no significant association between estimated prenatal MeHg exposure and PD was found in this study.

Several assumptions were made to develop the methodology for exposure assessment, as based on the most appropriate information available, while taking into regard the feasibility of the calculations. Some sources of inaccuracy cannot be eliminated, and the choices made may confer some imprecision to the results. The bias due to the assumptions is most likely non-differential affecting both the cases and controls and thus leading to an underestimation of the true effect. Further, unknown confounders and interaction parameters, impossible to adjust for, could have occurred due to the retrospective nature of the study.

The accuracy of the historical data, i.e., the whaling records, population numbers and birthplace is regarded to be excellent. Some inaccuracy of the data cannot be ruled out, but this would tend to result in small random errors. Only one disagreement was observed between the birth place given by the population registry and the self-reported birthplace that had an impact on the district

Table 1
Characteristics of the cases and controls; median and interquartile range (IQR) of the average hair mercury (Hg) concentration during the full pregnancy, during the third trimester only and at the beginning of the third trimester

	Cases	Controls	Wilcoxon two-sample rank-sum test[a]
Participants (number)	172	1018	
Sex (%)[b]	52/48	52/48	
Age in years[c]	68.7 ± 9.6	68.4 ± 9.3	
Average hair Hg during the whole pregnancy[d]	5.52 (0.00–16.50)	5.40 (0.00–15.20)	0.38
Average hair Hg during the third trimester[d]	1.67 (0.00–8.85)	1.73 (0.00–10.64)	0.40
Hair Hg at the beginning of third trimester[d]	0.00 (0.00–12.00)	0.00 (0.00–9.73)	0.30

Abbreviations: Hg, mercury; IQR, interquartile range.
[a] 1-Sided p-value.
[b] Men/women.
[c] Mean ± S.D. Age on July 1, 1995.
[d] Unit: μg/g.

Table 3
Multivariate logistic assessment of the association between estimated maternal hair mercury (Hg) concentrations and Parkinson's disease (PD)

	Cases $N = 172$	Controls $N = 1018$	Adjusted OR[d]	95% CI
Average hair Hg during the whole pregnancy				
Not exposed[a]	95	565	1.00	
Some exposure[b]	35	230	0.91	0.60–1.38
High exposure[c]	42	223	1.13	0.76–1.67
Average hair Hg during the third trimester				
Not exposed[a]	107	639	1.00	
Some exposure[b]	33	189	1.06	0.70–1.62
High exposure[c]	32	190	1.12	0.72–1.73
Hair Hg at the start of the third trimester				
Not exposed[a]	116	699	1.00	
Some exposure[b]	28	160	1.06	0.68–1.66
High exposure[c]	28	159	1.07	0.68–1.70

Abbreviations: Hg, mercury; CI, confidence interval; OR, odds ratio.
[a] No exposure: hair Hg levels equal zero (NE) and lowest tertile of the non-zero hair Hg distribution.
[b] Some exposure: hair Hg levels in the second tertile of the non-zero hair Hg distribution.
[c] Heavy exposure: hair Hg levels in the third tertile of the non-zero hair Hg distribution.
[d] Adjusted for age and sex.

distribution, providing us with confidence of the validity of this information.

All whale catches were assumed to be shared between the local inhabitants and their immediate neighbours entitled to a share according to the rules of distribution. But small whale catches were probably only divided between the active participants and close-by residents. The exposure estimates did not take such simplified distributions into account, and many subjects may therefore be considered exposed MeHg at low concentrations, while the level of exposure of the people truly exposed is underestimated, thereby diluting the effect of MeHg.

While the data on whale catches are thought to be highly reliable, deviations in whale distributions and differences in food habits would affect the validity of the exposure estimates. Still, these sources of error are likely to be of small importance in comparison with the substantial differences between whale availability over time and between communities. Thus, some districts had uninterrupted supplies of whale for several years, while no whales were caught elsewhere. In the past, the diet varied much less than today and was to a large extent dictated by the food available. Our estimates of average whale intake – and therefore the maximum mercury exposure at steady state – are based on historical accounts and interviews. Although an estimate of the uncertainty would be desirable, no approach to assessing individual exposure levels retrospectively in the first half of the 20th century is available.

Another possible source of error is that the mother's residence some time before and during pregnancy is assumed to be the same as the child's birth place. This assumption could be inaccurate, but the limited possibilities to travel from one place to another in those days would speak against any great influence on the results due to this assumption. (Further discussion on the rationale for the assumptions regarding the methodology is available elsewhere (Petersen et al., 2005).)

Higher numbers of controls were born abroad compared with cases, although not significantly so. It is possible that the tendency of a higher risk of PD in subjects born in the Faroes may be related to prenatal MeHg exposure, but it could also be related to the greater life-time reliance on traditional foods among locally born Faroese. Additional postnatal factors, such as smoking, may have affected the development of PD and a possible MeHg-related pathogenesis. Because the present study is register-based, no information on such lifestyle factors has been obtained. In regard to smoking, our interviews with live PD cases and matched controls showed that smoking had a protective effect, as anticipated (Petersen et al., 2008).

A few studies have assessed the postnatal MeHg exposure and PD, but the results have been equivocal. In a case–control study of 54 cases and 95 controls, increased blood-mercury concentration was associated with an increased risk of PD (Ngim and Devathasan, 1989). However, this was not the case in other studies (Gorell et al., 1999; Ohlson and Hogstedt, 1981; Semchuk et al., 1993). A possible explanation for the lack of evidence for Hg and other metals as well as risk factors for PD could be that most epidemiological studies have been focused on recent exposures, with few epidemiological studies considering environmental factors encountered early during the life span or even during pregnancy (Barlow et al., 2007; Logroscino, 2005).

Our focus was on idiopathic Parkinson's disease due to its doubled prevalence in the Faroe Islands as compared to other Scandinavian populations. The plausibility of a MeHg-related etiology is supported by experimental data that MeHg may interfere with the dopaminergic system (Bemis and Seegal, 1999). The number of cases with a-typical parkinsonism in this population is too small and too variable in clinical appearance to allow meaningful exposure comparisons (Wermuth et al., 1997, 2007).

In conclusion, no significant association between PD and prenatal exposure was found in this study, and all upper confidence limits were below 2.0. Thus, prenatal MeHg exposure is unlikely to explain the doubling of PD prevalence in the Faroes, even when taking into account the possible effect of misclassified exposures. The assumptions made can have introduced some imprecision, leading to a dilution of the effect, but with the uniformly high p-values, such bias is not a likely explanation for the lack of association. Also, the levels of MeHg exposures likely to be achieved after large whale catches were very high, thereby providing a wide exposure interval. However, a weak role of prenatal MeHg exposure cannot be ruled out as a contributing factor in etiology of PD based on this study, perhaps in conjunction with postnatal exposure.

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