Paper V

Associations between family history of Parkinson's disease and dementia and risk of dementia in Parkinson's disease. A community-based, longitudinal study.

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Abstract

Dementia is common in patients with Parkinson's disease (PDD). The etiology of PDD is still unclear but exciting advance has been made in discovering pathogenetic components in Parkinson's disease (PD) implicating the role of genetic factors. It is, however, still controversial whether genetic factors also contribute to the development of dementia in PD. Thus we investigated the association between development of dementia and a positive family history of PD or dementia in a community-based study of PD in Rogaland county, Norway (n=219). The patients were followed prospectively with neurological and neuropsychological assessments. Dementia was more common in patients with a strong family-association of PD (first-degree relatives>second degree relatives>no family history) ($p<.05$). However, time to dementia did not differ between the two groups. No associations between dementia in PD and familial occurrence of dementia could be shown. Further studies with larger samples are needed to explore a possible relationship between a family history of PD and development of dementia in PD and its potential pathogenetic mechanisms.

Key words: Parkinson's disease, dementia, genetics, pathogenesis, family history

Introduction

Parkinson's disease (PD) is a neurodegenerative disorder with a high prevalence among the elderly. Progress in the study of genetics of PD has enhanced our understanding of basic disease mechanisms highlighting the central role of the ubiquitin-proteasome system [1]. Neuropsychiatric features like cognitive impairment and hallucinations are common in the course of the disease. In a systematic literature search it could be shown that approximately 30% of the overall PD-population has dementia (PDD) [2], and over a 8 year disease duration, a cumulative prevalence could be shown to be as high as 78% [3]. Dementia is a key symptom for PD patients as it increases the risk of nursing home admission [4] and mortality [5], and has a substantial impact on quality of life.

Exciting recent studies have identified several genes such as *presinilin 1* and *2*, *Apolipoprotein e (Apo e)*, and *amyloid precursor protein* involved in the development of Alzheimer disease (AD) [6, 7], the most common cause of dementia, which have enabled important advances in our understanding of the molecular biology and facilitated the development of novel therapeutic approaches.

The etiology of dementia in PD is not yet clear, but both Lewy bodies [8, 9] and Alzheimer changes [10] have been reported to contribute. Since both AD and PD have genetic determinants [11-13], and both diseases share common risk factors [14, 15], genetic factors may also contribute to the development of dementia in PD. However, little is known regarding the potential genetic contributions to dementia in PD. Therefore, we have longitudinally studied the associations of parkinsonism or dementia in the family and risk of dementia in PD.

Materials and Methods

Overall design

A community-based cohort of patients with PD in the county of Rogaland, Norway was established and clinically followed prospectively over 12 years (4 and 8 years after baseline and thereafter annually) with assessment of dementia and neuropsychological features in regular intervals.

Patient recruitment and diagnosis of PD

The study population comprised all subjects with PD living in nine municipalities with 220 000 inhabitants in the southern part of Rogaland, Western Norway on the prevalence day of January 1st 1993. Total ascertainment of patients with PD was attempted through a detailed community study in the study area [16]. After a screening procedure, 400 patients were invited to participate in the study. Among the 400 patients with possible PD 245 patients (120 men and 125 women) were diagnosed with PD according to published diagnostic criteria [17] (prevalence: 110.9 per 100 000 inhabitants). Further details on patient selection, demographic and clinical factors of the patients have been published previously [16, 18]. A subgroup of PD patients (n=27) has been assessed neuropathologically. All 27 patients had neuronal cell loss and alpha-synuclein positive Lewy-bodies in the surviving neurons of the substantia nigra confirming the diagnosis of PD [8].

Diagnosis of dementia and clinical assessment

Information on clinical and demographic patient characteristics was obtained through a semi-structured interview and with rating scales. During the interview a caregiver with intimate knowledge of the patient and the patient's family accompanied the patient. Severity of parkinsonism was examined by the Unified Parkinson's Disease Rating Scale (UPDRS) [19], including the Hoehn and Yahr staging [20]. Dementia was diagnosed according to DSM-III-R

criteria [21], using these criteria as a guide during a caregiver-based interview and taking into consideration the physical disability that occurs in patients with PD, in addition to the performance on cognitive screening tests (Mini-Mental State Examination (MMSE) [22] and Dementia Rating Scale (DRS) [23]). Patients with a MMSE score of 16 or above underwent a neuropsychological battery assessing executive functioning, visual memory, and visuospatial functioning. Beginning in 2002, the MMSE was administered annually together with the clinical interview. Further details of the dementia diagnosis have been published elsewhere [3].

Assessment of familial aggregation and heredity of dementia and parkinsonism in PD

At baseline, patients and their closest relative were asked to complete a questionnaire that asked for detailed information about the occurrence of PD or dementia in their families. The probands' and informants' report of additional cases in the family was based on their own information of diseases in the family. The relatives that should be considered by the patients and/or their caregiver were all siblings, parents, children, siblings of parents, and grandparents. We have examined the frequency of familial occurrence of the disorders both among first-degree and second-degree relatives.

The study was performed in accordance with the ethical standards laid down in the Declaration of Helsinki, and approved by the appropriate ethical committees, and all participants provided informed consent.

Statistics

The software programs SPSS 12.0 (SPSS, Chicago, IL) and STATA (StataCorp LP) were used for statistical analysis. Comparisons between groups were performed using 1-way ANOVA and t-test for normally distributed continuous variables, and chi square test for

categorical variables. Analyses of the associations between dementia and PD in the family with dementia in PD were performed using the gamma test of linear association (PD or dementia in first degree, second degree, or in no family). We used Cox proportional hazards to determine whether a positive family history of dementia or PD was independently associated with time to a diagnosis of dementia. P values less than 0.05 were considered significant.

Results

Seven patients were re-diagnosed as not having PD during the first 4-year period, and in 19 no reliable family history could be obtained. Thus, 219 patients were eligible for the present study and performed the baseline assessment in 1993. In 1997, 139 patients, were seen, 87 after 8 years, 67 in 2002, 48 in 2003, 36 in 2004 and 35 in 2005. Drop-out was nearly exclusively due to death, less than 10% at each assessment refused to participate. The majority of those who died during the study period were demented, but 65 subjects dropped out of the study without dementia being diagnosed.

28 (12.8%) patients with PD reported to have a first degree relative and 23 (10.5%) to have a second degree relative affected with PD. 21 (9.6%) reported a first-degree and 21 (9.6%) a second degree relative affected with dementia. Baseline characteristics of these groups are shown in table 1. As seen, the groups did not differ regarding sex, age, or age at onset, and no differences were found at baseline for UPDRS motor scale, Hoehn and Yahr staging, MMSE, or drug intake. Dementia was present in 49 patients (22.4%) at baseline, and was diagnosed in another 72 (32.9%) (incident dementia) during follow-up, with a total number of 121 (55.3%).

Relationship between familial occurrence of PD and dementia in PD:

The association between dementia and family history of PD is shown in table 2. There was a linear relationship between dementia prevalence and strength of family-association of PD: PD in first-degree relative (75%), second degree (57%), and no family history (52%) ($p=0.036$). However, the Cox hazard analyses failed to detect a significant association between family history of PD and time to develop dementia in PD ($p>0.05$) (figure 1a).

Relationship between familial occurrence of dementia and dementia in PD:

The association between dementia and family history of dementia is shown in table 2. There was a numerical trend towards a higher proportion with dementia in those with dementia in a first-degree (67%) or second-degree (57%) relative compared to no family history of dementia (53%), but this difference was not statistically significant ($p=0.28$). The Cox hazard did not reveal any relationship between dementia in the family and time to develop dementia in PD ($p>0.05$) (fig 1b).

Discussion

This is the first longitudinal study exploring the association between a family history of PD or dementia with the risk of developing dementia in patients with PD. We found an association between a positive family history of PD and a higher risk for developing dementia in PD. However, in the survival analysis there was no significant association with time to develop dementia. No association between a family history of dementia with dementia or time to dementia in PD was found.

Few studies have explored whether genetic factors may contribute to dementia in PD. In contrast to our results a family history of PD was previously reported to correlate with a milder motor and mental decline [24]. Age and age at onset, which has been found to be associated with the risk for dementia and may represent influence of different genes [25], differed in the two studies and may contribute to the different findings. Our finding of no association between a family history of dementia and dementia in PD is consistent with a recent study reporting a lack of familial aggregation of PD and AD [26].

There are several plausible genetic candidates which could contribute to the emergence of dementia in PD. A pathomorphological correlation between cortical alpha-synuclein inclusions and development of dementia in PD has been shown [8]. To date three mutations are found in the *alpha-synuclein gene* (*A53T, A30P, E46K*) leading to misfolding of the protein and subsequent protein aggregation in Lewy bodies [27-30]. The possibility that PDD and dementia with Lewy bodies, another syndrome mainly related to cortical Lewy bodies, have common genetic determinants [31] supports the hypothesis that mutations in the *alpha-synuclein* gene contributes to dementia in PD.

Associations between *Apo e* ε genotype and familial occurrence of PD, development of dementia in PD [32-35], and with the number of neocortical Lewy bodies and amyloid

plaques has been found in some but not all studies [36, 37] suggesting that *Apo e ε* polymorphisms are associated with the emergence of dementia in PD.

This study has some methodological limitations which may have influenced the findings. Firstly, the relatively few cases with PD or dementia in a first-degree relative limits the statistical power for detecting a significant relationship with dementia in the probands. We had a 75% probability for detecting a 50% increased risk of dementia associated with a family history of PD. Secondly, assessing family history data of PD patients is not always straightforward, and patients with PD tend to overstate PD in their relatives when compared to controls [38]. However a current study demonstrated that a family history interview similar to the one used in our study is a reliable method [39]. Misclassification may also occur because relatives are still at risk or had died before expression of disease symptoms. These types of bias would more likely lead to an underestimation of associations. Thirdly, 40% of our PDD-patients had dementia already at baseline. Accordingly, in this subgroup, the time from onset of PD to dementia was made retrospectively, which is subject to recall bias. In addition, since the interval between assessments during the first 8 years of the study was 4 years, the accurate timing of onset of dementia cannot be accurate. Since mortality is higher in PDD than in PD, some patients may have developed dementia and died in the 4-year interval. Finally, although confounders like rural and urban living or education grade do not differ between the groups (table 1) other environmental risk factors for dementia can not be totally excluded.

Future studies with a large number of patients should further explore the possible association between a family history of PD and dementia in PD including the role of possible confounders. Molecular investigations are needed to clarify the underlying principles and to explore processes involved at the molecular level.

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Table 1. Baseline characteristics of PD patients with and without PD or dementia in their families.

	PD				Dementia			
	in first degree	in sec. degree	not in family	P*	in first degree	in sec. degree	not in family	P*
Number of PD patients	28	23	168		21	21	176	
Age at onset, years	66.2 (8.2)	60.5 (11.7)	64.2 (9.7)	0.96	63.4 (9.0)	66.3 (8.1)	63.9 (10.1)	0.81
Age, years	76 (6.7)	70.6 (10.4)	73.2 (8.3)	0.62	73.7 (7.3)	74.2 (7.2)	73.1 (8.7)	0.95
Females, No. (%)	15 (53.6)	9 (39.1)	79 (47)	0.45	14 (66.7)	9 (42.9)	89 (50.6)	0.27
Rural living, No. (%)	10 (35.7)	9 (39.1)	46 (27.4)	0.22	7 (33.3)	3 (14.3)	55 (31.3)	0.4
Education, years	8.63 (2.9)	10.45 (4.09)	9.06 (2.78)	0.7	8.42 (2.42)	10.05 (2.98)	9.12 (3.01)	0.69
Dementia, No. (%)	7 (25)	3 (13)	38 (22.6)	0.53	9 (42.9)	3 (14.3)	36 (20.5)	0.06
MMSE, mean score	24.1 (6.7)	26.7 (3.9)	24.6 (6.3)	0.55	22.9 (5.6)	26.5 (5.3)	25.1 (6.3)	0.4
UPDRS Motor, score	29.2 (16.4)	25.4 (12.8)	28.5 (16.6)	0.71	30.5 (15.4)	24.1 (14.4)	28.6 (15.9)	0.49
Hoehn & Yahr, stage	2.9 (1.2)	2.8 (0.9)	2.8 (1.1)	0.22	3.0 (1.2)	2.6 (0.9)	2.8 (1.1)	0.63
Levodopa-dose	519.6 (232.7)	578.3 (290.7)	487.3 (235.4)	0.79	457.1 (235.7)	514.6 (254.8)	505.6 (242.6)	0.52

*Groups were compared using 1-way ANOVA or chi square

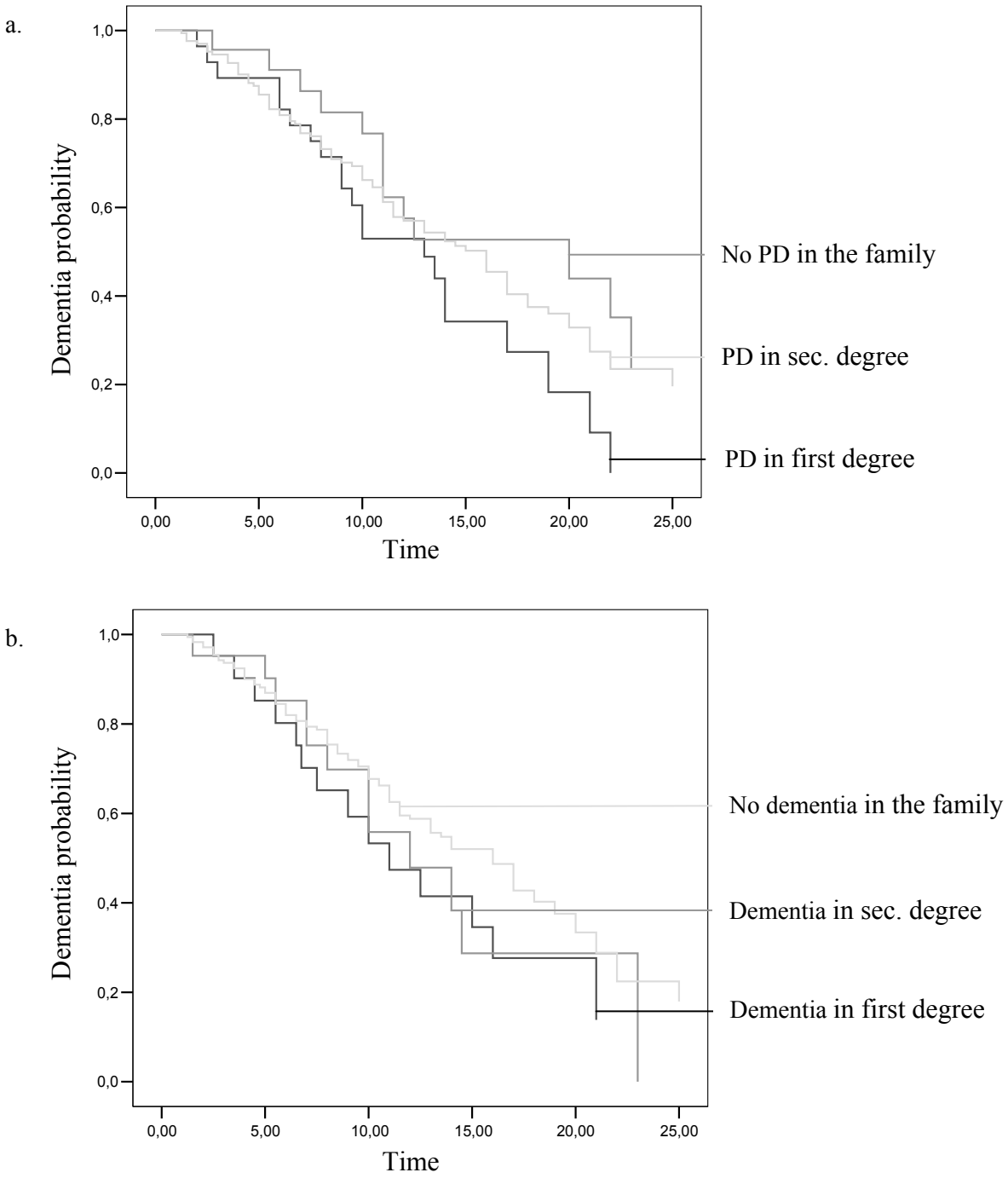
Table 2. Relationship of a family history of PD or dementia and development of dementia during 12 years of follow-up in patients with PD.

	Family history of PD					Family history of dementia				
	in first-degree	in sec. degree	not in family	n	P*	in first-degree	in sec. degree	not in family	n	P*
Dementia	21	13	87	121		14	12	94	120	
No dementia	7	10	81	98	0.036	7	9	82	98	0.28
Total	28	23	168	219		21	21	176	218	

Numbers represent number of patients

*Comparison between groups were made using the gamma test of linear associations

Figure 1.
Cox hazard analysis between PD (figure 1a) or dementia (figure 1b) in the family and time to develop dementia in PD.



- Figure legend: X-axis: Time (years) from diagnosis of PD. Y-axis: Proportion without dementia: all demented = 0, all non-demented=1.0