

Low Prevalence of Cancer in Patients with Frontotemporal Lobar Degeneration

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Abstract. Several studies have reported reduced risk of cancer in patients with Alzheimer's disease (AD) or Parkinson's disease. The relationship between cancer and frontotemporal lobar degeneration (FTLD) has not been previously reported. Here, our aim was to evaluate the occurrence of cancer in Finnish FTLD patients with a high proportion of *C9ORF72* repeat expansion carriers in comparison to age- and sex-matched group of AD patients and control subjects classified as not cognitively impaired (NCI). The prevalence of cancer was 9.7% in FTLD, 18.7% in AD, and 17.4% in NCI (FTLD versus AD $p=0.012$, FTLD versus NCI $p=0.029$) groups. No differences were observed between *C9ORF72* repeat expansion carriers and non-carriers inside the FTLD group. To our knowledge, this is the first study showing significantly lower prevalence of cancer in FTLD patients compared to patients with AD or NCI subjects. Our data suggest an inverse association between neurodegeneration and cancer and that FTLD-specific mechanisms may underlie the especially strong inverse association observed in this study.

Keywords: *C9ORF72*, cancer, comorbidity, frontotemporal dementia, frontotemporal lobar degeneration

INTRODUCTION

Frontotemporal lobar degeneration (FTLD) is a clinically and pathologically heterogeneous group of progressive neurodegenerative diseases that can be divided into four main clinical subtypes. These include behavioral variant of frontotemporal dementia (bvFTD) [1], nonfluent variant of primary progressive aphasia (nfvPPA), semantic variant of

primary progressive aphasia (svPPA), and logopenic variant of primary progressive aphasia (lvPPA) [2].

The most common genetic cause of FTLD and amyotrophic lateral sclerosis is a hexanucleotide repeat expansion in chromosome 9 open reading frame 72 (*C9ORF72*). In Finland, the *C9ORF72* repeat expansion is the underlying cause for a great majority of familial cases [3], whereas other known mutations causing FTLD are extremely rare [4–6]. It is noteworthy, however, that most of the FTLD cases in Finland and worldwide are sporadic without any identified pathogenic mutations. So far, specific risk factors for FTLD have not yet been identified.

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Several studies have reported bidirectional inverse association between cancer and Alzheimer's disease (AD) [7–12]. The risk of subsequent cancer was substantially decreased in patients with probable AD (hazard ratio 0.39) [8] and conversely prevalent cancer was associated with reduced risk of AD (hazard ratio 0.57) [11]. Similarly, the evidence for decreased occurrence of cancer in Parkinson's disease (PD) patients has also been reported [13–15]. The aim of this study was to analyze the occurrence of cancer in Finnish FTLD patients and to investigate whether there is a similar inverse association between cancer and FTLD than previously observed between cancer and AD.

MATERIALS AND METHODS

Ethical considerations

The study was performed according to the principles of the Declaration of Helsinki. Written informed consent was obtained from the participants. The study protocol was approved by the research ethics committees of Northern Savo hospital district and Northern Ostrobothnia hospital district.

Participants

Total of 195 patients with FTLD were identified during the years 1999–2016 from the memory outpatient clinics of Kuopio University Hospital and Oulu University Hospital. Patients were examined by experienced neurologists, specialized in memory diseases. Altogether 131 patients were diagnosed with bvFTD, 19 patients with combined features of FTLD and motoneuron disease (FTLD-MND), 37 patients with nvPPA, and eight patients with svPPA. Most of the patients with bvFTD were diagnosed according to the latest diagnostic criteria by Rascovsky and colleagues [1], and patients with language variants were diagnosed according to the Gorno-Tempini diagnostic criteria [2]. Those patients, who were diagnosed with bvFTD, nvPPA, or svPPA before the publication of the most recent criteria, were retrospectively classified according to the Rascovsky (2011) and Gorno-Tempini (2011) criteria. Only patients fulfilling at least probable bvFTD, nvPPA, or svPPA criteria were included in the study. No patients with lvPPA were identified.

Patients with FTLD were divided based on their *C9ORF72* repeat expansion status into two groups:

the *C9ORF72* repeat expansion carriers (*C9+*) (*N* = 55) and patients without the *C9ORF72* repeat expansion (*C9-*) (*N* = 103). The *C9ORF72* repeat expansion was detected in 39 out of 105 bvFTD patients, in six out of 30 nvPPA patients, in one out of six svPPA patients and in nine out of 17 FTLD-MND patients. For 37 FTLD patients, the *C9ORF72* repeat expansion status was not available (26 bvFTD, seven nvPPA, two svPPA, and two FTLD-MND). Six patients with unknown *C9ORF72* repeat expansion status were neuropathologically confirmed as FTLD, leading to a total of 61 patients with definite and 134 with probable FTLD according to the latest criteria [1, 2].

For comparison, age- and sex-matched group of AD patients (*N* = 193) was identified from memory outpatient clinics in Kuopio University Hospital and Oulu University Hospital by experienced neurologist specialized in memory diseases. The AD patients were diagnosed according to the McKhann criteria for probable AD between the years 1999–2017 [16]. The diagnoses were based on clinical and neuropsychological examination, brain imaging, and cerebrospinal fluid AD biomarkers.

For another control group, we screened age and sex matched group of participants without any neurodegenerative disorder classified as not cognitively impaired subjects (NCI, *N* = 184). These participants had either undergone investigations in Kuopio University Hospital due to a suspected memory disorder and were shown not to have any neurodegenerative disorder (88/184) or recruited without any diagnosed neurodegenerative disorder among patients scheduled for hip or knee arthroplasty surgery due to primary osteoarthritis at the Department of Anesthesia and Operative Services at Kuopio University Hospital (96/184). Patients with suspected memory disorder (88/184) underwent neurological and neuropsychological testing with structural brain imaging (CT or MRI) and patients who were recruited from the Department of Anesthesia and Operative Services (96/184) underwent cognitive testing (CERAD or TELE interview) to exclude mild cognitive impairment or dementia.

Characteristics of the study cohort are shown in Table 1.

Genetic analyses

The *C9ORF72* repeat expansion status was analyzed using the repeat-primed polymerase chain reaction assay [17]. Five patients of the *C9+* group

Table 1
Clinical characteristics of the study cohort and prevalence of observed neoplasms

Characteristics	FTLD ² n = 195	C9+ ² n = 55	C9- ² n = 103	AD n = 193	NCI n = 184
Age ¹ , y, mean (SD)	68.0 (8.0)	64.6 (8.2)	68.8 (7.3)	68.0 (7.8)	68.4 (8.8)
Gender, % female	49.2%	50.9%	49.5%	49.7%	52.2%
Cancer total, n (%)	19/195 (9.7%) ^{3,4}	5/55 (9.1%)	12/103 (11.7%)	36/193 (18.7%) ³	32/184 (17.4%) ⁴
Carcinomas, n (%)	17/195 (8.7%) ³	4/55 (7.3%)	11/103 (10.7%)	31/193 (16.1%) ³	25/184 (13.6%)
Non-melanoma skin cancer, n	3	1	2	8	10
Breast cancer, n	6	2	3	8	3
Prostate cancer, n	2	1	1	9	3
Lung cancer, n	0	0	0	0	1
Gastrointestinal cancer, n	2	0	2	5	4
Other carcinoma, n	5	0	4	6	4
Hematologic cancers, n (%)	1/195 (0.5%)	1/55 (1.8%)	0/103 (0.0%)	4/193 (2.1%)	6/184 (3.3%)
Leukemia, n	0	0	0	2	1
Lymphoma, n	1	1	0	2	4
Myeloma, n	0	0	0	0	1
Melanomas, n (%)	1/195 (0.5%)	0/55 (0.0%)	1/103 (1.0%)	1/193 (0.5%)	2/184 (1.1%)
Mesotheliomas, n (%)	0/195 (0.0%)	0/55 (0.0%)	0/103 (0.0%)	0/193 (0.0%)	1/184 (0.5%)
Gliomas, n (%)	0/195 (0.0%)	0/55 (0.0%)	0/103 (0.0%)	0/193 (0.0%)	1/184 (0.5%)

¹Age at last visit in special health care; ²FTLD-total group includes 37 cases without known *C9ORF72* repeat expansion status; ³FTLD versus AD, total cancer: Chi-square $p=0.012$, FTLD versus AD, carcinomas: Chi-square $p=0.028$; ⁴FTLD versus NCI, total cancer: Chi-square $p=0.029$. One patient with FTLD, five patients with AD, and three NCI participants had two separate cancers.

carried an intermediate expansion (20–40 repeats) and the rest (N = 50) a full expansion (>40 repeats). The patients of the C9- group had less than five repeats.

Clinical review

Medical histories were retrospectively screened for evidence of malignant neoplasms. Screening was continued until the patients' last visit at the university hospital. Malignant neoplasms were divided into carcinomas, melanomas, hematologic cancers, gliomas, and mesotheliomas. The prevalence of all cancer types in total and specific cancer subtypes were compared between FTLD, AD, and NCI. We also compared these groups based on the number of different types of cancers per participant.

Statistical analyses

All statistical analyses were performed by using SPSS statistic version 23 (IBM corp. USA). Independent sample *t*-test was used to compare continuous variables (age and number of cancers per patient) and chi square test (or Fisher's exact test when frequencies were less than five) for categorical variables such as gender and occurrence of cancer (dichotomous variables). *P*-values < 0.05 were considered statistically significant.

RESULTS

Characteristics of the study population and comparison of the prevalence of malignant neoplasms between FTLD, AD, and NCI groups are presented in Table 1. The number of cancers per patient varied between 0–2. No other types of malignant neoplasms, for example, sarcomas, were detected in any of the individuals.

The prevalence of cancer in general was significantly lower in FTLD (9.7%) compared to both AD (18.7%, $p=0.012$) and NCI (17.4%, $p=0.029$) (Chi-square). No differences were observed within the FTLD group depending on the *C9ORF72* repeat expansion status ($p=0.789$) or between the AD and NCI groups ($p=0.790$, Chi-square). The prevalences of carcinomas (FTLD versus AD $p=0.028$ Chi-Square, FTLD versus NCI $p=0.131$ Chi-Square) and hematologic cancers (FTLD versus AD $p=0.214$ Fisher's exact test, FTLD versus NCI $p=0.061$ Fisher's exact test) differed most prominently between the groups (Table 1).

Age at the cancer diagnosis was for FTLD patients 61.6 ± 10.0 years, for C9+ FTLD patients 63.0 ± 9.8 years, for C9- FTLD patients 62.3 ± 11.0 years, for AD patients 64.4 ± 8.8 years, and for NCI subjects 62.9 ± 11.1 years (mean \pm SD), indicating no significant differences between the groups. In addition, there were no significant differences between sexes when comparing the cancer prevalence inside each

study group based on gender. In patients with FTLD, 55% of the cancer diagnoses were made before the diagnosis of FTLD and 45% of the cancer diagnoses after the diagnosis of FTLD. In the AD patients, 80% of the cancer diagnoses were made before the AD diagnosis, and 20% after the AD diagnosis. Mean age at the time of the neurological diagnosis was 65.7 years in FTLD and 68.5 years in AD.

In the FTLD clinical subgroups, the prevalence for cancer was 13/131 (9.9%) in bvFTD, 5/37 (13.5%) in nvPPA, 0/8 (0.0%) in svPPA, and 1/19 (5.3%) in FTLD-MND. The number of cancer per patient (mean \pm SD) was in bvFTD: 0.11 ± 0.334 (95% CI=0.05–0.16, range=0–2), in nvPPA: 0.14 ± 0.347 (95% CI=0.02–0.25, range=0–1), in svPPA: 0.00 ± 0.00 (95% CI=not available, range=0), and in FTLD-MND: 0.05 ± 0.229 (95% CI=–0.06–0.16, range=0–1).

The number of different types of cancers per each participant (mean \pm SD) in different groups were as follows: FTLD (N=195), 0.1 ± 0.32 , (95% CI=0.06–0.15, range=0–2); C9+ (N=55), 0.09 ± 0.29 (95% CI=0.01–0.17, range=0–1); C9- (N=103), 0.13 ± 0.36 (95% CI=0.06–0.20, range=0–2); AD (N=193), 0.21 ± 0.47 (95% CI=0.15–0.28, range=0–2); NCI (N=184), 0.19 ± 0.43 (95% CI=0.13–0.25, range=0–2). One FTLD, five AD, and three NCI participants had two separate types of cancers. The number of different types of cancers per patient were compared between different groups. Statistically significant difference was detected between FTLD versus AD (independent sample *t*-test, $p=0.008$) and FTLD versus NCI (independent sample *t*-test, $p=0.027$) groups.

DISCUSSION

To our knowledge, this is the first paper analyzing cancer prevalence in FTLD patients. We found a significantly lower prevalence of cancer in FTLD patients as compared to AD patients or NCI subjects. Differences in cancer prevalence between these groups were the most prominent with carcinomas and hematologic cancers. No differences were observed within the FTLD group in relation to the *C9ORF72* repeat expansion status. Patients in the C9+ group were somewhat younger, which most likely explains the slight but not statistically significant difference in cancer prevalence between *C9ORF72* expansion carriers and non-carriers (9.1% in C9+ and 11.7% in C9-).

A large amount of previous studies have reported bidirectional inverse associations between AD and cancer [7–11]. Although it has been suggested that these findings could be due to survival bias, these associations have persisted after correcting for such bias [8]. In addition, co-occurrence of cancer and PD have been inversely associated in several studies [13–15]. Intriguingly, no associations were found with pure vascular dementia and cancer [11]. We found an extremely low prevalence of cancer in FTLD patients regardless of the *C9ORF72* repeat expansion status, supporting the idea that cancer and neurodegeneration are inversely associated. Since the etiology of vascular dementia substantially differs from that of neurodegeneration in AD, FTLD, and PD, the mechanisms leading to neurodegeneration in non-vascular neurodegenerative diseases may be protective against cancer. As hypothesized in previous studies [8, 18], a common biological pathway that regulates the cell cycle homeostasis towards either cell proliferation (tumorigenesis) or apoptosis (neurodegeneration) might underlie the observed inverse association of cancer and neurodegenerative diseases.

It is noteworthy that the cancer prevalence in our FTLD cohort is significantly lower than that in the AD cohort, suggesting that disease-specific underlying pathogenic mechanisms may influence the cancer prevalence. For example, studies in *C9ORF72* knockout mouse models have indicated that immune system dysfunction might be associated with the potential haploinsufficiency caused by the *C9ORF72* repeat expansion [19, 20]. On the other hand, we did not observe significant differences in the cancer prevalence between *C9ORF72* expansion carriers and non-carriers, rather implying that FTLD in general could be associated with immune system dysfunction. This hypothesis is supported by a recent genome-wide association study that provided evidence linking immune system dysfunction with FTLD pathogenesis [21] and the fact that in addition to *C9ORF72* mouse models, also PGRN (protein encoded by *GRN* gene) knockout mice show inflammatory phenotypes [22]. Therefore, it is possible that overactive immune system might provide protection against cancer in FTLD in general. Yet, it is also possible that other currently unknown mechanisms may underlie the decreased cancer prevalence in FTLD patients when compared to AD patients or NCI subjects.

Interestingly, we found no differences in cancer prevalence between AD patients and NCI subjects. This is in contrast with previous reports based on

larger cohorts, which have shown that there is an inverse association between AD and cancer occurrence [8–11]. However, the fact that we did not observe differences between the AD and NCI groups may be due to the limited AD cohort size in this study. On the other hand, the observation that the FTLD patients had significantly lower cancer prevalence in our cohort suggests that the inverse association between cancer and neurodegeneration is particularly evident in FTLD patients.

One limitation of this study is that our cohort size for epidemiologic data is rather small. Another limitation is that common risk factors for cancer (other than age), such as smoking, were not included in the analyses. However, since the inverse association between cancer and AD are particularly, but not exclusively, found in cancers highly associated with smoking [8] (i.e., smoking-related cancers are even more rare than other cancers in AD), we hypothesize that higher cancer prevalence in AD may not result from smoking. In addition, in our screening, we did not detect high amounts of cancers strongly related to smoking [23] in any of our clinical groups. Possible differences in the likelihood of detecting cancer in our study groups could also have an impact on our results, since patients with severe FTLD or AD may not readily seek or receive medical attention to symptoms of cancer due to dementia diagnosis.

The greatest strength of this study is our exceptionally large and well-characterized FTLD cohort with extremely high proportion of definite FTLD cases according to the latest criteria, increasing the validity of our results. Our cohort reliably represents *C9ORF72* repeat expansion carriers and sporadic FTLD cases, since based on our previous studies, the other common FTLD-associated mutations are extremely rare in Finland; In our previous studies, *GRN* and *MAPT* mutations have been excluded in approximately half of the cases in this FTLD cohort [4–6]. The comparison AD and NCI groups were also accurately identified at the university hospitals by experienced neurologists specialized in memory diseases.

In conclusion, our novel finding of lower prevalence of cancer in FTLD patients compared to AD patients or NCI subjects indicates that the previously observed inverse association between cancer and AD or PD can also be detected between cancer and FTLD, linking the biological mechanisms causing neurodegeneration and cancer. In addition, the significantly lower prevalence of cancer in FTLD compared to AD indicates that the biological mecha-

nisms in neurodegenerative disorders, which appear to provide possible protection against cancer, are the most evident with FTLD patients. This hypothesis opens new horizons for further studies for defining the exact biological pathways underlying neurodegeneration and cancer and subsequently designing possible therapeutic approaches.

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