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Original Research Article

Epidemiology of Frontotemporal Lobar Degeneration in Northern Finland

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Key Words

Epidemiology · Prevalence · Incidence · Behavioral variant · Frontotemporal dementia · Semantic dementia · Progressive nonfluent aphasia

Abstract

Background: Frontotemporal lobar degeneration (FTLD) is responsible for as many as every fifth case of early-onset dementia. Very few epidemiological studies of FTLD have been conducted; there are no published epidemiological data of FTLD from Finland or the other Nordic countries. The *C9ORF72* expansion-associated FTLD is common in Finland; thus, the prevalence of FTLD is expected to be high in this population. **Methods:** We retrospectively evaluated the incidence and prevalence of FTLD in university hospital settings in Northern Finland. **Results:** The mean 1-year incidence of FTLD was 5.54/100,000 (range 1.9–11.3/100,000) in the population aged 45–65 years. The prevalence of FTLD in the same age group was 20.5/100,000. **Conclusion:** The incidence and prevalence of FTLD in Finland seem to be the highest in Europe. However, studies from different countries may not be directly mutually comparable due to methodological issues.

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Introduction

Frontotemporal lobar degeneration (FTLD) is the second most common degenerative dementing disease; it is thought to be responsible for 10–20% of patients with early-onset dementia (onset under the age of 65 years). FTLD is divided into three clinical syndromes: behavioral variant frontotemporal dementia (bvFTD), semantic dementia and progressive

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Table 1. Previously published studies investigating the incidence of FTLD

Study	Study area, country	Inhabitants in the study area	Study population	Cases with different types of FTLD	Age group(s), years	Study time period/census day	Diagnostic criteria	Incidence/100,000 (95% confidence interval)
Knopman et al. [18], 2011	Rochester, Minn., USA	NA	60 patients with dementia onset <70, and 504 cases >70, and 114 autopsied cases	4 FTLD	40–69	1990–1994	Neary et al. [1]	4.1 (1.1–10.4)
Mercy et al. [16], 2008	Cambridge City, East Cambridgeshire and South Cambridgeshire, England, UK	326,200	54 new dementia cases	12 bvFTD 1 FTD-MND 2 SD 1 PFNA	45–64	2000–2006/ the census population estimates from 2003	Neary et al. [1]	3.5 (2.0–5.7)
Garre-Olmo et al. [17], 2010	Girona, Catalonia, Spain	690,207	2,083 new dementia cases from the ReDeGi register	56 bvFTD 14 SD	30–64 >65	2007–2009/ the census population estimates from every year	–	<65: 1.3 (0.7–2.2) bvFTD: 1.2 (0.6–2.1) SD: 0.1 (<0.01–0.5) >65: 16.7 (12.6–21.7) bvFTD: 12.8 (9.3–17.3) SD: 3.9 (2.0–6.6)
Present study	Finland, Northern Ostrobothnia	398,355	40 patients with FTLD	34 bvFTD 1 FTD-ALS 2 SD 1 PFNA	45–70	2006–2010/ December 31, 2010	Neary et al. [1], Rascovsky et al. [7], Gorno-Tempini et al. [8]	45–70: 6.7 (range 4.1–11.5) 45–65: 5.54 (range 1.9–11.3)

NA = Not available; FTD-MND = frontotemporal dementia with motor neuron disease; SD = semantic dementia; PFNA = progressive nonfluent aphasia; FTD-ALS = frontotemporal dementia with amyotrophic lateral sclerosis.

nonfluent aphasia [1]. The presence of different pathologies and genetic backgrounds is the basis for allocation to the clinical syndromes [2]. There have been very few epidemiological studies conducted focusing on FTLD, and the epidemiology has been studied mainly in the age group of under 65-year-olds (table 1, 2). These studies have been conducted with different study designs, and this may explain why there are such extensive variations in the reported prevalence of FTLD from several European studies (4.0–29.9/100,000; table 1) [3–5]. There have been no previous epidemiological data of FTLD from any of the Nordic countries. In Finland, the *C9ORF72* expansion-associated FTLD is rather common [6], thus prevalence of FTLD would be expected to be high in this population. The aim of this study was to evaluate the prevalence and 1-year incidence of FTLD in the Finnish population.

Methods

Northern Ostrobothnia is a province in the north of Finland with a population of 398,355 on December 31, 2010, i.e. 7.4% of the total population of Finland. The female/male ratio was 0.99. This study was conducted at the outpatient memory clinic of the Department of Neurology of Oulu University Hospital (OUH) with the approval of the Ethics Committee of the Northern Ostrobothnia Hospital District following the principles of the Declaration of Helsinki. The OUH is the primary referral center for all patients under 70 years with memory or cognitive complaints. Patients over 70 years with memory/cognitive complaints were excluded from the study as they are mainly referred to other local memory clinics.

The data were collected from the hospital discharge register using the ICD-10 diagnoses G31.0 and F03, and the exact date of the diagnosis was confirmed to be within the time frame of January 1, 2006–December 31, 2010. All patients underwent a full neurological exami-

Table 2. Previously published studies investigating the prevalence of FTLD

Study	Study area, country	Inhabitants in the study area	Study population	Cases with different types of FTLD	Age group, years	Study time period/census day	Diagnostic criteria	Prevalence/100,000 (95% confidence interval)
Ratnavalli et al. [5], 2002	Cambridge City, East Cambridgeshire and South Cambridgeshire, England, UK	326,019	108 cases of early-onset dementia	11 FTD	45–64*	1997–2000/ May 30, 2000	Neary et al. [1]	45–64: 15.1 (8.4–27.0)
Harvey et al. [4], 2003	The London boroughs of Kensington, Chelsea, Westminster and Hillingdon, England, UK	567,500	185 patients with early-onset dementia	23 FTD	30–64	NA	Lund and Manchester [20]	30–64: 7.5 (4.4–11.8) 45–64: 15.4 (9.1–24.3)
Rosso et al. [12], 2003	The province of Zuid-Holland, The Netherlands	2,043,949	245 patients with probable FTD	174 FTD	30–79	1994–2002/ January 1, 1998	Lund and Manchester [20]	40–49: 1.2 (0.6–2.7) 50–59: 3.6 (2.1–6.0) 60–69: 9.4 (6.4–13.8) 70–79: 3.8 (1.9–7.4) overall prevalence: 2.7 (2.1–3.5)
Borroni et al. [3], 2011	Brescia County, Northern Italy	NA	94 patients with FTLD	94 FTLD	45–65	since 2000/ December 1, 2009	Neary et al. [1]	29.6 (23.7–35.6)
Bernardi et al. [14], 2012	Community in Biv., Province of Reggio Calabria, Italy	1,568	30 patients with dementia	18 FTD	≥50	–/January 1, 2004	NA	overall prevalence: 35
Gilberti et al. [15], 2012	Vallemonica Valley in the Province of Brescia, Northern Italy	119,647	42 patients with FTLD	34 bvFTD 1 SD 7 PNFA	≥45	since 2000/ January 1	Neary et al. [1]	45–65: 31 (20–42) 66–75: 156 (131–180) >75: 135 (112–158) overall prevalence: 35 (26–46)
Wada-Isoe et al. [13], 2012	Tottori prefecture, Japan	587,722	66 patients with FTLD	62 bvFTD 3 PNFA 1 SD	≥45	–/October 1, 2010	Neary et al. [1]	45–55: 4.0 (–5.3 to 8.6) 55–64: 5.6 (0.7–10.5) ≥45: 20.7 (15.7–26.0) overall prevalence: 11.2
Present study	Finland, Northern Ostrobothnia	398,355	40 patients with FTLD	34 bvFTD 1 FTD-ALS 2 SD 1 PFNA	45–70	2006–2010/ December 31, 2010	Neary et al. [1], Rascovsky et al. [7], Gorno-Tempini et al. [8]	45–70: 26.8 (18.5–37.6) 45–65: 20.5 (12.8–31.0)

NA = Not available; SD = semantic dementia; PNFA = progressive nonfluent aphasia; FTD-ALS = frontotemporal dementia with amyotrophic lateral sclerosis.
* Patients in whom dementia was diagnosed before they were 65 years old but who were older on the census day were included in the study.

nation, evaluation of behavioral and neuropsychiatric symptoms and structural brain imaging. A neuropsychological examination was conducted in 96% (n = 42) of patients. Neuropsychological tests were initially carried out as a part of the clinical diagnostics, and therefore, no uniform neuropsychological test battery was applied. However, concentration, executive function, verbal knowledge, literacy, verbal memory, nonverbal knowledge, nonverbal memory, spatial orientation, constructive and fine motor skills were evaluated with appropriate tests. After the examinations, the diagnoses of FTLD were made by neurologists specializing in memory disorders and were based on the consensus criteria by Neary et al. [1] from 1998. All of the cases also fulfilled the revised criteria for bvFTD prepared by the International Behavioural Variant FTD Criteria Consortium (FTDC) or the criteria for progressive aphasia in retrospective evaluation [7, 8]. Possible or probable Alzheimer's disease was excluded by applying the criteria of the National Institute of Neurological Disorders and Communicative Disorders – Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA), and vascular dementia was excluded by applying the criteria proposed by the National Institute of Neurological Disorders and Stroke (NINDS) and the Association Interna-

Table 3. One- and 5-year incidence of FTLD in the population of the 45- to 65-year-old people living in Northern Ostrobothnia

Year	Population (45–65 years old)	New FTLD cases (45–65 years old)	Incidence/ 100,000	Confidence interval
2006	102,212	9	8.81	4.03–16.72
2007	102,832	3	2.92	0.60–8.53
2008	104,983	3	2.86	0.59–8.35
2009	106,193	12	11.30	5.84–19.74
2010	107,516	2	1.86	0.23–6.72
2006–2010	523,736	29	5.54	3.71–7.95

tionale pour la Recherche et l’Enseignement en Neurosciences (AIREN). The clinically borderline cases which did not fulfill exactly Neary et al.’s criteria and those patients with concomitant symptoms more typical of the other dementias were excluded.

The data were processed with IBM SPSS Statistics for Windows (versions 20.0. and 21.0., IBM Corp., Armonk, N.Y., USA, released in 2011 and 2012). The 1-year incidence in the age group of 45- to 70-year-olds was calculated using the population of Northern Ostrobothnia on December 31 in the time frame 2006–2010. These values were extracted from the free database of Statistics Finland. The confidence intervals were calculated using Confidence Interval Analysis (CIA) software, version 2.0.0. The prevalence rates were calculated using the population of Northern Ostrobothnia on December 31, 2010. All patients who were diagnosed within the time frame of January 1, 2006–December 31, 2010 and who were confirmed to be alive according to the patient records on December 31, 2010 were included in the prevalence rates.

Results

During the 5-year period, a total of 40 new FTLD diagnoses were made at OUH. The majority of patients were diagnosed with bvFTD (90%, $n = 36$). Semantic dementia was diagnosed in 2 (5%) cases, and there was 1 subject with progressive nonfluent aphasia and 1 with FTD with motor neuron disease in the study group. The female/male ratio of the patients was 1.4. The mean age at disease onset was 58.4 years (range 47–67), and the mean age at diagnosis was 61.7 years (range 50–70). During the study period, 29 new FTLD diagnoses were made in the 45- to 65-year age group. DNA samples were available from 34% ($n = 10$) of these early-onset FTLD cases. Mutations of microtubule-associated protein tau (MAPT), progranulin (PGRN) and charged multivesicular body protein 2b (CHMP2B) as well as the presence of the *C9ORF72* expansion had been analyzed from these cases in our previous studies [6, 9–11]. No mutations in MAPT, PGRN or CHMP2B were detected in this cohort, but 40% ($n = 4$) of genetically studied cases were *C9ORF72* expansion carriers.

The mean annual incidence of FTLD was 5.54/100,000 (range 1.9–11.3/100,000), and the prevalence was 20.5/100,000 (confidence interval 12.8–31.0) in the population aged 45–65 years (table 3, 4). The mean annual incidence was 6.7/100,000 (range 4.1–11.5/10,000), and the prevalence was 26.8/100,000 (confidence interval 18.5–37.6) in the population of 45–70 years.

Table 4. Prevalence of FTLD in Northern Ostrobothnia

Age group, years	Population of the research area	FTLD cases alive	Prevalence/100,000
45–65	107,516	22	20.5
45–70	123,111	33	26.8
<65	341,164	22	6.5
<70	356,759	33	9.3

Discussion

Recently, there has been increasing interest focused on FTLD because of new neuropathological and genetic findings about this disease group. However, there are very little epidemiological data about FTLD, and even in the published reports, the study designs and the age distribution have been variable. Surprisingly, there are no previous epidemiological data on FTLD from any of the Nordic countries. Our hypothesis was that FTLD would be more common in the Finnish population compared to other European populations because the frequency of *C9ORF72* expansion-associated FTLD is very high in the Finnish population, although other genetic causes of FTLD in the Finnish population are rare [9–11]. We found that the prevalence of FTLD was 20.5/100,000 in the group aged 45–65 years. The prevalence of FTLD is higher in Finland than in England (15/100,000), the Netherlands (4.0–6.7/100,000) or Japan (4.8/100,000) in the same age group [4, 5, 12, 13]. The highest prevalence of FTLD has been reported from Italy (22–29.6/100,000) [3, 14, 15]. In the present study, the mean of the 5-year incidence of FTLD was 5.5/100,000 per year in the group aged 45–65 years, which is also slightly higher than in the published values for FTLD in England (3.5/100,000) or bvFTD and semantic dementia in Spain (1.3/100,000) [16, 17]. The prevalence of FTLD in the USA (15–22/100,000) is about the same as the Finnish figures [18].

In the previous studies, the overall prevalence of FTLD in all age groups has varied from 2.7/100,000 in the Netherlands to 35/100,000 in Italy [12, 14, 15]. In the Finnish population, the prevalence of FTLD over a broader age range (the age group of 45–70 years) was 26.8/100,000, which is lower than in other European countries such as Germany (47.9/100,000) and Italy (35/100,000) [19]. However, the varying study designs and different age distributions in these study populations make it difficult to conduct a valid comparison.

As all patients under the age of 65 years with memory disorders in this region are examined and diagnosed at OUH, these results can be considered to be reliable, especially those related to the age group of 45- to 65-year-olds. There is, however, a possibility that the number of FTLD patients has been underestimated and some cases have been misdiagnosed as a psychiatric disorder or some other dementia. Another reason for underestimation is that we excluded all of those cases which did not totally fulfill the FTLD clinical criteria. In contrast, we would argue that overestimation is unlikely. The weaknesses of our study are the lack of genetic information and neuropathological evaluation in the whole cohort as well as the relatively short study period.

In conclusion, this is the first epidemiological study of FTLD from any of the Nordic countries. We found the prevalence rates to be in line with the previous European studies, whereas the annual incidence rates were slightly higher in the group aged less than 65 years. Further studies with larger populations with genetically or neuropathologically confirmed diagnoses will be needed to clarify the epidemiology of FTLD in European countries.

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Disclosure Statement

The authors disclose no conflicts of interest.

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