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Estimating the Number of Persons with Frontotemporal Lobar Degeneration in the US Population

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Abstract

There are many challenges for determining the prevalence and incidence of frontotemporal lobar degenerations (FTLD). Consequently, the number of cases of behavioral variant frontotemporal dementia (bvFTD) or primary progressive aphasia (PPA) in the USA is unknown. Our objective was to derive a consensus estimate of bvFTD and PPA prevalence and thereby to estimate the total number of these syndromes in the USA. We identified five prevalence and three incidence studies of FTLD based on passive surveillance and seven studies of survival in FTLD. Data from these studies were used to estimate the number of cases of PPA or bvFTD in the USA. Because prevalence and incidence estimates outside of the 45–64-year age range were either not available or widely divergent, we used data from clinical and pathological series to estimate the proportion of FTLD cases aged <45 or >64 years. The prevalence estimates in the age categories of 45–64 years old have ranged from 15 to 22 per 100,000 person-years in studies where both bvFTD and PPA were identified. The incidence estimates for the same age group ranged from 2.7 to 4.1 per 100,000 person-years. Using a survival rate of 6 to 9 years from onset and rates from the incidence studies, a calculated prevalence estimate (prevalence = incidence × duration) was similar to the previously reported prevalence rates. We estimated that 10% of cases were less than age 45 years and 30% were 65 years and older. We estimate that there are approximately 20,000 to 30,000 cases of the cognitive syndromes of FTLD in the USA. The main threat to the accuracy of the estimates is the difficulty in diagnosing the clinical syndromes that comprise the FTLD group of disorders.

Keywords

Frontotemporal lobar degeneration; Prevalence; Incidence

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Introduction

Frontotemporal lobar degenerations (FTLDs) are a distinct group of neurodegenerative diseases of mid- and later life. The FTLDs are defined by a constellation of pathological findings that include a number of distinct molecular types (Mackenzie et al. 2009). There are several clinical phenotypes associated with FTLD pathology. The two cognitive syndromes are behavioral variant frontotemporal dementia (bvFTD) (Neary et al. 1998; Rascovsky et al. 2007) and primary progressive aphasia (PPA) (Neary et al. 1998; Gorno-Tempini et al. 2011). Other phenotypes include the syndromes of progressive supranuclear palsy and corticobasal degeneration; these syndromes will not be considered in the current analysis.

Epidemiological studies of the prevalence and incidence of the FTLDs have been challenging for two reasons. First, the diagnoses of bvFTD and PPA require a level of expertise in behavioral neurology that is usually not present in primary care. Equally daunting for epidemiological studies is the rarity of the FTLDs. In neuropathological series, they are considerably less common than Alzheimer's disease (AD; Barker et al. 2002). Because the age of onset of the FTLDs extends from the fourth to the eighth decade of life, the number of persons to be examined in a research effort using active surveillance—that is, prospective examinations and diagnoses performed by a research team—would be enormous.

As an alternative approach, several research groups in the USA, Europe, and Japan have used passive surveillance methods to estimate prevalence or incidence of the cognitive syndromes of the FTLDs. With passive surveillance, case detection depends upon the availability of neurological expertise in the community; medical records are reviewed to enumerate cases of clinically diagnosed bvFTD or PPA. This article reviews all of the published studies of prevalence and incidence of the cognitive syndromes of FTLD as of January 2011. The goals of the analysis were, first, to derive a consensus estimate of bvFTD and PPA prevalence, and second, to estimate the total number of cases of the cognitive syndromes of FTLD (CS-FTLD) in the USA.

Methods

All articles on the prevalence and incidence of early onset dementia that specifically enumerated cases of bvFTD or PPA were assembled. In addition to personal knowledge of citations, a search strategy in PubMed used the following: "prevalence or incidence" and "frontotemporal dementia or primary progressive aphasia" or "progressive aphasia or frontotemporal lobar degeneration" and "population." There were five prevalence studies (Table 1) and three incidence studies (Table 2) that explicitly discussed the CS-FTLD syndromes.

The methodology of each study was reviewed, and the diagnostic criteria used, the catchment area, age range investigated, type of health records reviewed, and number of prevalent or incident cases were abstracted. A summary of the case ascertainment methods, diagnostic criteria used, and other methodological details of the eight studies is found in the Appendix. The diagnostic criteria published in 1998 (Neary et al. 1998) were the first that included bvFTD and PPA under the rubric of FTLD and explicitly distinguished between bvFTD and PPA. The 1994 Lund–Manchester criteria (The Lund and Manchester Groups 1994), the first to define the behavioral syndrome of what is now called bvFTD, but did not explicitly identify PPA, although language difficulties were mentioned among the diagnostic criteria. Therefore, when the 1994 diagnostic criteria were used, there is a concern that PPA cases were undercounted or not counted.

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Survival studies of CS-FTLD were also identified. Survival rates and incidence rates were utilized to calculate prevalence (prevalence=duration × survival), and the calculated prevalence was compared to the measured prevalence. The calculated prevalence rates were then applied to data from the projected 2010 US census (http://www.census.gov/population/www/projections/usinterimproj/natprojtab02a.pdf) to estimate the number of cases of CS-FTLD in the US population.

Results

Prevalence of CS-FTLD

Of the five studies of the prevalence of CS-FTLD, four were from Western Europe and one was from Japan (Table 1). Three of the four European studies used the 1998 diagnostic criteria (Neary et al. 1998). The London, UK, and Ibaraki, Japan studies used the original Lund–Manchester criteria (The Lund and Manchester Groups 1994) which did not explicitly recognize PPA. Three studies examined only bvFTD (Rosso et al. 2003; Harvey et al. 2003; Ikejima et al. 2009). Prevalence estimates from these three studies ranged from 2 to 15.4 per 100,000 persons in the 45–64-year-old age range. In the two studies that identified both syndromes (Ratnavalli et al. 2002; Borroni et al. 2010), the point estimates of prevalence were 15 and 22 cases per 100,000 in the 45–64-year-old age range.

Incidence of CS-FTLD

There were three incidence studies of CS-FTLD (Table 2), one from the USA (Knopman et al. 2004) and two from Western Europe (Mercy et al. 2008; Garre-Olmo et al. 2010). The incidence rates in the age range that included 45–64 years were similar, ranging from 2.7 to 4.1 per 100,000 person-years. The lower estimate from Girona, Spain (Garre-Olmo et al. 2010) may have occurred because the only two CS-FTLD syndromes considered were bvFTD and semantic dementia (and not progressive nonfluent aphasia); bvFTD was by far the most common syndrome. In the Cambridge study (Mercy et al. 2008), bvFTD comprised 76% of the CS-FTLD cases.

Estimating Proportion of Cases Outside of the 45–64-year Age Range

The prevalence study from the Netherlands (Rosso et al. 2003) reported that 13% of cases were under age 50 years, and 15% of the 55 cases were 70 years or older. In contrast, 66% of cases were over 65 years in the prevalence study in Brescia, Italy (Borroni et al. 2010), and 80% were over 65 years in the incidence study from Girona, Spain (Garre-Olmo et al. 2010). Neither of the two studies identified any cases under age 45 years.

To address the wide divergence of extant prevalence estimates in the younger and older age ranges, we drew on other data. First, we examined the age range of a series of autopsy-proved cases of FTLD drawn from an international consortium of centers with expertise in bvFTD (Rascovsky et al. 2011). The study set included 176 cases, of which approximately 63% had an age of onset between 45 and 64 years, 9.7% an age of onset <45 years, and 27.3% an age of onset >64 years. We also examined a clinical series of 353 patients drawn from three centers that specialized in FTLD disorders (Johnson et al. 2005). In that series, about 30% had onset after age 65 years. Using these two alternate resources together with the prevalence data from the Netherlands (Rosso et al. 2003), we therefore estimated that 10% of CS-FTLD patients were <45 years of age and 30% were over age 65 years of age at onset.

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Survival in CS-FTLD

From the time of diagnosis, the estimates of mean survival times ranged from 3 to 4 years and were consistent across most studies (Table 3). Survival from symptom onset ranged from 6.6 to 9 years, reflecting the long delays in diagnosis that occur in FTLD.

Convergence of Prevalence and Incidence Estimates

Based on the incidence and survival data described above, the calculated prevalence of CS-FTLD in the 45–64-year age range is (incidence of 3–4 per 100,000 person-years × survival from onset of 6 to 9 years) 18 to 36 per 100,000 persons.

Estimating the Number of Cases of CS-FTLD in the US

Since the calculated prevalence was comparable to the values from the three studies that estimated prevalence of CS-FTLD, we used the prevalence estimate in the 45–64-year-old age group of 15 to 22 per 100,000 in those studies as optimal for estimating the number of CS-FTLD cases in the USA. Given a 2010 US census estimate of approximately 81 million persons between the ages of 45 and 64 years, we therefore estimate that there are between 12,000 and 18,000 CS-FTLD cases in this age range. If the 45–64-year-old age range represents 60% of all CS-FTLD patients who come to autopsy (Johnson et al. 2005), with the remainder younger or older, we would estimate that the total number of cases in the USA is 1.67 times that of the 45–64-year-old number, that is, roughly 20,000 to 30,000.

If, instead, the majority of cases of CS-FTLD were older than age 65 years as reported in two studies (Borroni et al. 2010; Garre-Olmo et al. 2010) (i.e., 66% and 80%), the estimate of the total number of cases would double or triple. In contrast, if the lowest estimate of prevalence of bvFTD in the 45–64-year-old age range of 2 per 100,000 was used in the calculation, and one assumed that there was one case of bvFTD for every case of PPA based on the large multinational series (Johnson et al. 2005), the number of CS-FTLD in the USA in this age range would be only about 1,800 cases.

Discussion

The incidence estimates for CS-FTLD were clustered in a tight range, but the prevalence estimates differed by a factor of 10. We believe that the low estimates of prevalence (Rosso et al. 2003; Ikejima et al. 2009) resulted from insensitive diagnostic criteria and inadequate recognition. Indeed, the studies that reported lower prevalence estimates were ones that used the older 1994 criteria (The Lund and Manchester Groups 1994). It is possible that the very high estimates of prevalence in persons over age 65 years in some studies (Borroni et al. 2010; Garre-Olmo et al. 2010) do not reflect neuropathological FTLD and therefore represent an overdiagnosis of bvFTD. Neuropathological studies typified by the large multicenter study (Rascovsky et al. 2011) simply do not support the contention that most FTLDs occur in persons over age 65. Based on the best available data, we believe that the most plausible figures are that roughly 60% of CS-FTLD occurs in the 45–64-year-old age range, and that the prevalence of CS-FTLD is 15–22 per 100,000 in that age range.

Because of the rarity of PPA and bvFTD, none of the studies reviewed here employed active case detection methods. Instead, they all relied on passive surveillance and case detection by medical record review. The basis for claiming that a prevalence or incidence could be calculated was that each study was able to define a geographic catchment area for their case review and claim that any case of FTLD in a resident of the catchment region that was diagnosed would have been captured by their methodology.

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The main threat to the validity of these observations is the accuracy of clinical diagnoses. Undercounting of cases is a distinct possibility because the clinical detection of bvFTD or PPA requires a level of expertise in behavioral neurology that is possessed by few neurologists and even fewer non-neurologists. We believe that the very low estimate of CS-FTLD prevalence from Ibaraki, Japan (Ikejima et al. 2009) reflected the use of insensitive diagnostic criteria for, and, simultaneously, a limited awareness of, the clinical syndromes of FTLD in the practitioners in Ibaraki.

Overdiagnosis and misclassification of bvFTD or PPA are also possible and could occur if some of the cases that were labeled clinically as bvFTD or PPA were actually due to the pathology of Alzheimer's disease, Lewy body disease, or cerebrovascular disease. A number of the behavioral features of bvFTD may occur in the dementia of AD or in dementia with Lewy bodies. AD pathology sometimes occurs in persons diagnosed clinically with bvFTD or PPA (Mesulam et al. 2008; Forman et al. 2006; Davies et al. 2005; Hodges et al. 2004; Knopman et al. 2005).

It is not possible to estimate quantitatively the extent of under- or overdiagnosis of CS-FTLD syndromes. To resolve both misclassification problems, very large, longitudinal clinical–pathological studies would be required that were free of biases during recruitment that would compromise the estimates. Patients with dementia of any presumed etiology would have to be recruited and followed to death and autopsy confirmation of diagnosis.

The similarities in prevalence and incidence of CS-FTLD syndromes and Alzheimer's disease (AD) in younger persons are notable. Our estimates of CS-FTLD prevalence are lower than a prevalence of AD of 35 per 100,000 in the 45–64-year age range in London, UK (Harvey et al. 2003). Unlike any of the other studies, the Japanese study found the prevalence of vascular dementia exceeded that of dementia due to AD, 38.6 vs. 22.3 per 100,000 persons in the 45–64-year age range (Ikejima et al. 2009).

Each of the incidence studies (Knopman et al. 2004; Mercy et al. 2008; Garre-Olmo et al. 2010) also analyzed cases of dementia due to AD. Incidence rates of CS-FTLD were similar to rates observed for AD: 4.2 per 100,000 person-years in 45–64 year olds in Cambridge (Mercy et al. 2008) and 5.7 per 100,000 person-years in 30–64 year olds in Girona (Garre-Olmo et al. 2010). The Rochester, MN study found that CS-FTLD and AD incidence rates were identical in 50–59 year olds; in contrast, the incidence of AD considerably exceeded CS-FTLD in the 60–69-year-old age range (88.9 for AD versus 8.9 per 100,000 person-years for CS-FTLD) (Knopman et al. 2004).

A study of progressive supranuclear palsy from the UK reported a prevalence rate of 25 per 100,000 in a population of 55 years and older, a value similar to our estimate of CS-FTLD (Nath et al. 2001). The incidence of ALS in three European countries in the 65–84-year-old age range was greater than five new cases per 100,000 person-years (Logroscino et al. 2010), higher than the peak rate for CS-FTLD reported in the three incidence studies described above.

In summary, our review of these studies suggests that prevalence rates of CS-FTLD range between 15 and 22 per 100,000, incidence rates are between 2.7 and 4.0 per 100,000 person-years, and between 20,000 and 30,000 persons in the USA have CS-FTLD.

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Appendix

Table 4

A summary of the case ascertainment methods, diagnostic criteria used, and other methodological details of the eight studies

Location	Diagnostic approach to FTLDs	Method of ascertainment	Age range	Focus	Comments
Prevalence					
Zuid-Holland (Rosso et al. 2003)	1994 Lund–Manchester Criteria for bvFTD, supplemented by imaging and genotyping	All neurologists and physicians in nursing homes received yearly postal inquiries about suspected FTD cases	All ages	bvFTD only	A positive family history in 43%
Cambridgeshire, UK (Ratnavalli et al. 2002)	1998 Consensus criteria	Review of case records of three specialist clinic databases and in-patient admissions to University Hospital, Cambridge. All suspected cases were then	< age 65	All degenerative dementias	Strong male predominance (14:3)

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Location	Diagnostic approach to FTLDs	Method of ascertainment	Age range	Focus	Comments
		seen by study team and underwent imaging			
London, UK (Harvey et al. 2003)	1994 Lund–Manchester Criteria	Clinicians in catchment area were polled and contacted; hospital and clinic records reviewed; half of all cases identified by passive method were examined in person by authors	< age 65	All dementias	AD prevalence higher than FTD >50 years old
Brescia, Italy (Borroni et al. 2010)	1998 Consensus criteria or McKhann criteria	Cases identified through a network of Neurology and Geriatric specialty centers. All cases alive on prevalence day based on contact with each center	All ages	FTLD only	bvFTD=80% of cases; + family history in 35%; prevalence higher in >65 year olds
Ibaraki, Japan (Ikejima et al. 2009)	1994 Lund–Manchester criteria	Cases identified by a two-step postal survey to 2,475 institutions that provided medical care in the prefecture.	< age 65	All dementias	Very high rate of vascular dementia
Incidence					
Rochester MN (Knopman et al. 2004)	1998 Consensus criteria	Passive identification through review of medical records	All Ages	All dementias	
Cambridgeshire, UK (Mercy et al. 2008)	1998 Consensus criteria	Same as described above for Cambridgeshire, UK	< age 65	All dementias	bvFTD=75%; ratio of AD/FTLD=1.6:1
Girona, Spain (Garre-Olmo et al. 2010)	1994 Lund–Manchester criteria	Registry of all cases of dementia diagnosed in the seven hospitals of the region. All diagnoses are made by specialists in neurology or geriatrics	All ages	All dementias	bvFTD/semantic dementia=13:1; AD/FTLD = 5.7:1.3

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Table 1

Studies of prevalence of FTLD

Location	No. of cases	Case definition	Point estimate per 100,000 in 45–64 year olds	95% CI
Zuid-Holland, Netherlands (Rosso et al. 2003)	55	bvFTD only	4.0	2.8 to 5.7
Cambridgeshire, UK (Ratnavalli et al. 2002)	11	bvFTD+PPA	15	8.4 to 27.0
London, UK (Harvey et al. 2003)	18	bvFTD	15.4	9.1 to 24.3
Brescia, Italy (Borroni et al. 2010)	213	bvFTD+PPA	22	17 to 27
Ibaraki, Japan (Ikejima et al. 2009)	17	bvFTD only	2.0	1.3 to 3.2

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Table 2

Studies of incidence of FTLD

Location	No. of cases	Case definition	Rate per 100,000 per year	95% CI
Rochester, MN (Knopman et al. 2004)[a]	4	bvFTD+PPA	4.1 (age range, 40–69)	1.1 to 10.4
Cambridgeshire UK (Mercy et al. 2008)[b]	16	bvFTD+PPA	3.5 (age range, 45–64)	2.0 to 5.7
Girona, Spain (Garre-Olmo et al. 2010)[c]	14	bvFTD+semantic dementia	2.7 (age range, 45–64)	1.5 to 4.6

[a] All cases between ages 40 and 69 years

[b] 1/16 cases < age 45 years. Only ages <65 years were considered

[c] Of 70 cases of bvFTD or semantic dementia, 14 were under age 65 at onset

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Table 3

Studies of survival in FTLD

Location	Basis of diagnosis	No. of subjects	Mean age at diagnosis	Delay in diagnosis	Survival from onset or diagnosis
Survival from diagnosis					
San Francisco (Roberson et al. 2005)	Clinical diagnoses	177	58.5+9.4	4.5+2.9	3.6+0.4
San Diego (Rascovsky et al. 2005)	Pathologically confirmed	70	65+9.4	4.0+2.8	4.2
Sydney (Garcin et al. 2009)	Clinical diagnoses	91	57.2+8.2 (onset)	3.6+2.5	4.2+0.8[a]
Cambridge and Sydney (Hodges et al. 2003)	Pathologically confirmed	61	61.5+7.6	3	3.0+0.4
Survival from onset					
Rochester MN (Josephs et al. 2005)	Pathologically confirmed	45	57.3+11.1 (onset)	–	6.6
Philadelphia (Xie et al. 2008)	Pathologically confirmed	71	61+9.5 (onset)	1+1	6.6+0.5
Netherlands (Chiu et al. 2010)	Clinical diagnoses	354	57.5+8.9	–	9.9+0.7

[a] Cases of “bvFTD phenocopy were excluded” (Davies et al. 2006). If those cases were included, survival from diagnosis was 5.5+4.1