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Frontotemporal dementia in The Netherlands: patient characteristics and prevalence estimates from a population-based study

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Summary

Since 1994, a population-based study of frontotemporal dementia (FTD) in The Netherlands has aimed to ascertain all patients with FTD, and first prevalence estimates based on 74 patients were reported in 1998. Here, we present new prevalence estimates after expansion of our FTD population to 245 patients, with emphasis on the prevalence in the province Zuid-Holland where the main study centre is located. All neurologists and physicians in nursing homes received a yearly postal enquiry about suspected FTD cases. FTD was diagnosed in 245 patients according to the Lund-Manchester criteria, supported by neuroimaging and neuropsychology. *tau* mutation analysis was performed in a subgroup of 154 patients (63%), and 40 out of 98 patients (41%) who died during follow-up were autopsied during the course of the study. The prevalence of FTD in the province Zuid-Holland was 3.6 per 100 000 at age 50–59 years, 9.4 per 100 000 at age 60–69 years and 3.8 per 100 000 at age 70–79 years. The median age at onset of the 245 patients (51% female) was 58.0 years (range 33–80 years). Dementia in one or more first-degree family members was found in 43% of patients and mutation analysis of the *tau* gene showed mutations in 34 patients (19 P301L, five L315R, four G272V, four R406W, one ΔK280 and one S320F), all with a positive family history for dementia (14% of the total population, 32% of patients with a positive family history). Pathological findings in the 40 autopsied patients consisted of dementia lacking distinctive histology in 22%, FTD with ubiquitin-positive inclusions in 33%, Pick's disease in 15% and tauopathy in the remaining 30% of patients, with *tau* mutations identified in more than half of the latter patients. We conclude that the prevalence of FTD in The Netherlands is higher than previously reported, confirming that FTD is more common than was previously thought. The finding of *tau* mutations in 32% of patients with a positive family history for dementia justifies mutation screening in FTD patients with a positive family history, while *tau* mutations in non-familiar cases are rare.

Keywords: frontotemporal dementia; prevalence; *tau* mutation; ubiquitin

Abbreviations: DLDH = dementia lacking distinctive histology; FTD = frontotemporal dementia; MND = motoneuron disease; NBB = The Netherlands Brain Bank

Introduction

Frontotemporal dementia (FTD) has become increasingly recognized by clinicians and pathologists as a major cause of dementia over the past decade. Reliable clinical criteria for the diagnosis FTD have been established (Lund and

Fig. 1 Map of The Netherlands showing the Zuid-Holland province (dark grey) and the four cities in which the medical centres specialized in dementia are located (including the main study centre).

Manchester Groups, 1994; Neary *et al*., 1998), and several pathological subtypes are now distinguishable using immunohistochemical techniques (Mann *et al*., 1993; Cooper *et al*., 1995). The identification of mutations in the *Microtubule-associated protein tau* gene has led to a new classification of familial FTD, in which subclasses show specific pathological features (Morris *et al*., 2001). The frequency of *tau* mutations varies considerably in different FTD populations, ranging from 0 to 18% (Houlden *et al*., 1999; Rizzu *et al*., 1999; Fabre *et al*., 2001; Kowalska *et al*., 2001; Poorkaj *et al*., 2001). Although the number of different *tau* mutations is still increasing, some FTD families show neither tau pathology nor *tau* mutations, and may be distinguished by typical ubiquitin-positive inclusions (Kertesz *et al*., 2000; Morris *et al*., 2001; Rosso *et al*., 2001*a*; Savioz *et al*., 2000), emphasizing genetic heterogeneity.

Since 1994, a population-based study aims to ascertain all patients with FTD in The Netherlands. Preliminary results indicated a maximum prevalence of 3 per 100 000 inhabitants at age 60–69 years (Stevens *et al*., 1998). However, a recent study in the Cambridge area of the UK found a substantially higher prevalence of 15 per 100 000 inhabitants aged 45–64 years (Ratnavalli *et al*., 2002). Although FTD is known to occur at older age, the prevalence of FTD in patients older than 65 years has not yet been investigated. In the current study, we describe a large cohort of FTD patients ascertained between January 1994 and June 2002 in The Netherlands, and present estimates of the prevalence of FTD at different ages, the frequency of *tau* mutations and the distribution of different pathological subtypes. We also attempt to evaluate the proportion of misdiagnosis and non-referral by looking at all patients with a neuropathological diagnosis compatible with FTD, autopsied during the same period at The Netherlands Brain Bank (NBB).

Patients and methods

Study design and diagnosis

A complete ascertainment of patients with FTD in The Netherlands was attempted from January 1994 until June 2002 (Stevens *et al*., 1998). All hospital-based neurological and psychiatric practices (n = 183) and physicians in psychogeriatric hospitals or nursing homes (n = 269) received a yearly postal enquiry requesting referral of all new patients with suspected FTD, irrespective of their family history. This study was given publicity at local meetings over the years, and in national expert journals. In addition, we went through the databases of four university medical centres specialized in dementia in June 2002 (P.S., Amsterdam, H.P.K., Nijmegen, F.V., Maastricht, and the Academic Medical Centre, Amsterdam) and systematically pulled out all coded cases of suspected FTD and reviewed medical records (including neuropsychological evaluation and hard copies of neuroimaging) of patients examined after 1994 to assess whether they fulfilled the criteria for probable FTD. Together with the main study centre, these four university medical centres cover most referrals in The Netherlands: two university centres are in the most densely populated area around Amsterdam, and the other two centres more distant (60 miles east and 150 miles south-east of Rotterdam; Fig. 1).

The diagnosis of FTD was based on the criteria of Lund and Manchester (Lund and Manchester Groups, 1994; Neary *et al*., 1998) and included: (i) a progressive behavioural disorder with insidious onset; (ii) affective symptoms; (iii) speech disorder; (iv) preserved spatial orientation and praxis; and (v) selective frontotemporal atrophy (CT or MRI) or selective frontotemporal hypoperfusion [single photon emission computed tomography (SPECT) with 99mTc-hexamethyl propyleneamine oxime (HMPAO)]. Consensus about the clinical diagnosis between research physician, neurologist and neuropsychologist was obtained, and in case of uncertain diagnosis, the final decision was made based on supplementary clinical, neuropsychological and neuroimaging data later in the course of the disease.

Spouses and first-degree relatives assisted in obtaining detailed clinical history on the onset and evolution of the disease, with emphasis on frontal symptoms, speech and spatial functions, as well as memory problems. The age at onset was defined as the age at which the first symptom compatible with the diagnosis FTD was observed by a close relative or caretaker. The duration of the disease was determined in all patients who died during the course of the

study. A positive family history was defined as at least one first-degree relative with dementia before the age of 80 years. An autosomal dominant pattern of inheritance was considered present if at least three affected individuals (including the proband) over two or more generations were identified, and through genealogical research we attempted to link these familial cases in order to determine the number of individual families. The pattern of cerebral atrophy on CT or MRI was evaluated, and patients were classified according to the predominance of either frontal or temporal atrophy as described previously (Rosso *et al*., 2001*b*). Left-right asymmetry was considered to be present if there was at least one grade difference.

tau mutation analysis was performed in a subgroup of 154 patients (63%). Mutation analysis for 90 patients has been described previously (Rizzu *et al*., 1999). For another 50 cases, all 11 coding exons of the *tau* gene, including flanking intronic sequences, were amplified from genomic DNA. Sequence analysis was performed on exons 1, 2, 3, 4, 5, 7, 9, 11 and 13. For the remaining 14 patients only exons 9 to 13 of the *tau* gene were sequenced by our clinical testing laboratory.

The possibility and desirability of *post mortem* examination was discussed with relatives of all patients before death. Over the past decade, the NBB has been willing to carry out autopsy on all patients suspected of having FTD or other types of presenile dementia in The Netherlands. In addition to FTD patients registered by one us for future autopsy at the NBB, nursing home physicians or other physicians could follow the same procedure for their patients with dementia at the NBB independently of us. In collaboration with the NBB, all brains that became available for autopsy were processed for routine staining, including Bodian silver staining, as well as immunohistochemistry with tau (AT8, 1 : 40; Innogenetics, Ghent, Belgium) and ubiquitin (1 : 500, Dako, Glostrup, Denmark) antibodies as described previously (Rosso *et al*., 2001*a*). The NBB complies with all relevant ethical and legal guidelines regarding obtaining consent from autopsy, anonymity of the donors and the collection use and transport of tissue samples, as well as the safety procedures of working with human *post mortem* tissues (Ravid *et al*., 1995). The study was approved by the Medical Ethics Committee of the Erasmus Medical Centre of Rotterdam. Informed consent for participation (including DNA studies) was obtained from the spouse or a first-degree relative of each patient.

Prevalence estimates

Point prevalence estimates for both The Netherlands and the province of Zuid-Holland, in which the main study centre is located, were calculated for January 1 of each year between 1995 and 2000 (population number corrected for each year) to evaluate consistency of ascertainment over the years. Subsequently, age-specific prevalences were calculated for 10-year periods for the chosen census day, January 1, 1998. The number of patients with FTD resident in the appropriate target area and alive on the census day was divided by the total number of inhabitants in the same area. Information about population size was derived from the Central Bureau for Statistics in The Netherlands. The 95% confidence intervals (CIs) were calculated using a recommended method for small numbers with confidence interval analysis (CIA) software (Altman *et al*., 2000). Differences in prevalence ratios between different target areas, as well as between the present study and published studies, were compared using the recommended method for unpaired samples (Newcombe) with CIA software (Altman *et al*., 2000).

Evaluation of accuracy of prevalence estimates

In order to assess the accuracy of our prevalence estimates, we looked at all patients autopsied at the NBB during the course of the study who had a neuropathological diagnosis compatible with FTD. First, we determined the proportion of autopsied patients with a clinical diagnosis other than FTD, in order to assess the proportion of misdiagnosis of FTD. Secondly, we looked for autopsied patients from Zuid-Holland with a clinical diagnosis of FTD, to determine whether non-referral occurred in our study. Subsequently, we evaluated what effect correction for the proportion of misdiagnosis and non-referral would have on our prevalence estimates.

Results

Demographic and clinical features

During the entire study period a total of 245 patients (125 women, 120 men) with probable FTD were identified according to the Lund-Manchester criteria. FTD patients referred by neurologists and psychiatrists (n = 135) were examined at out-patient clinics and the remaining patients were seen at nursing homes (n = 110). The median duration of symptoms at ascertainment was 3.7 years in the former group and 4.3 years in the latter group. The median age at onset was 58.0 years, with a broad range from 33 to 80 years. Fifty-four patients (22%) were >65 years at onset of symptoms. Ninety-eight patients died during the course of the study, after a median duration of symptoms of 6.9 years (range 2–19 years). The family history was positive for dementia in 105 patients (43%). Forty-nine of these patients (20%) had an autosomal dominant pattern of inheritance, and genealogical research showed that they came from 18 independent families. The information on affected family members was too limited to determine whether there was a true familiar form of FTD in the remaining 56 patients (23%). Symptoms of motoneuron disease (MND) developed during the course of the illness in 11 patients (4%), six of whom had a positive family history for either dementia or amyotrophic lateral sclerosis. Parkinsonian features, early in the course of the disease, were present in 34 patients (14%), whereas most patients developed a hypokinetic-rigid syndrome later in the course of

the disease. Predominantly temporal atrophy on neuroimaging was seen in 97 pateints (40%), which was asymmetric in 70 patients (72%). In patients with frontotemporal atrophy, asymmetry was seen in only 27% of patients.

Prevalence estimates

The estimated overall prevalence of FTD in The Netherlands rose from 0.9 per 100 000 in 1995 to 1.1 per 100 000 in 1997, and remained stable thereafter. A total of 174 patients were alive and suffering from FTD in The Netherlands on January 1, 1998, our census day, resulting in an overall prevalence of 1.1 per 100 000 inhabitants (95% CI 1.0–1.3). The overall prevalence in the Zuid-Holland province was at least twice as high, namely 2.7 per 100 000 inhabitants (95% CI 2.1–3.5), based on 55 patients. Because there is no evidence that familial aggregation in Zuid-Holland is more common, this difference is most likely due to underascertainment in regions further away from the main study centre. The age-specific prevalence in Zuid-Holland, summarized in Table 1, was highest in patients aged 60–69 years (9.4 per 100 000 inhabitants). The prevalence of FTD at age 45–64 years was 4.0 (95% CI 2.8–5.7) per 100 000 inhabitants, based on 31 patients.

At the NBB, we identified 50 patients autopsied after January 1, 1994 with a pathological diagnosis compatible with FTD. Thirty-three (66%) patients had been ascertained in the current study, whereas non-ascertainment (34%) was due to non-referral in nine cases and clinical misdiagnosis in the remaining eight cases. Two of the nine non-referred cases with the clinical diagnosis FTD came from Zuid-Holland. Assuming that the proportion of misdiagnoses in similar throughout The Netherlands, correction for a non-referral of 34% would increase the prevalence of FTD at ages 45–64 years in Zuid-Holland (based on 31 and 52 patients, respectively) from 4.0 to 6.7 per 100 000 inhabitants (95% CI 5.1–8.8).

Table 1 *Age-specific prevalence estimates of FTD in Zuid-Holland on January 1, 1998 (per 100 000 inhabitants)*

Age group (years)	No. patients	Population	Prevalence (95% CI)
30–39	1	556 346	0.2 (0.03–1.0)
40–49	6	488 269	1.2 (0.6–2.7)
50–59	14	391 154	3.6 (2.1–6.0)
60–69	26	276 581	9.4 (6.4–13.8)
70–79	8	212 754	3.8 (1.9–7.4)
Total population	55	2 043 949	2.7 (2.1–3.5)

Genetic studies

tau mutation analysis was carried out in 154 (63%) out of 245 patients. This group consisted of 72 patients with sporadic FTD and 82 FTD patients with positive family history (Table 2). Mutations were found in none of the 72 patients with sporadic FTD. Forty-eight out of 82 sequenced FTD patients with positive family history did not show mutations, 15 of whom had an autosomal dominant form of FTD. Of these 15 patients, nine came from two large FTD pedigrees with ubiquitin-positive, tau-negative inclusions and significant linkage to chromosome 17q21-22 (Rosso *et al*., 2001*a*; Rademakers *et al*., 2002). The remaining six patients came from unrelated families with autosomal dominant form of FTD, which were too small for significant linkage analysis.

The frequency of *tau* mutations for the total FTD population was 14%. Missense mutations in the *tau* gene were identified in 34 out of 82 (41%) FTD patients with positive family history, and out of 49 (70%) patients with autosomal dominant FTD (19 P301L, five L315R, four G272V, four R406W, one ΔK280 and one S320F). After genealogical research, we concluded that these 34 patients came from 10 independent families at most (three P301L, two L315R, one G72V, two R406W, one ΔK280 and one S320F). The median age at onset in the four G272V patients (44 years) was significantly lower than in those with other mutations. Patients with P301L, G272V, L315R and ΔK280 presented with behavioural changes, whereas memory problems were prominent in the early stage in patients with R406W and S320F mutations (Table 3).

Table 2 *Family history, autosomal dominant forms of FTD and tau mutation analysis in 245 FTD patients*

	Total group (n = 245)	*tau* sequencing (n = 154)	*tau* mutations (n = 34)	No *tau* mutations (n = 120)
Sporadic form	140	72	0	72
FTD + positive family history	105	82	34 (41%)	48 (59%)
Possible familial FTD	56	33	0	33 (100%)
Autosomal dominant FTD	49	49	34 (70%)	15 (30%)*

*Including nine patients from two large FTDP-17 pedigrees with ubiquitin-positive inclusions.

Table 3 *Demographic and clinical data of 34 patients with six different tau mutations*

Mutation	No. patients	Age at onset [years (range)]	Follow-up [years (range)]	Age at death [years (range)]	Clinical symptoms	Autopsy*
P301L	19	53 (44–65)	6 (1–12)	63 (49–76)	Disinhibition, apathy, word finding difficulties, compulsive behaviour	3 (6)
G272V	4	44 (42–47)	9 (3–20)	–	Disinhibition, apathy	1 (1)
R406W	4	55 (51–58)	16 (13–19)	71 (70–71)	Apathy, memory loss	2 (4)
L315R	5	57 (54–64)	5 (1–8)	63	Apathy, memory loss, word finding difficulties	1 (1)
ΔK280	1	53	8	–	Restlessness, apathy	–
S320F	1	43	11	54	Memory loss, disinterested, word findings problems	1 (1)

*The number of patients who died during follow-up is shown in parentheses.

Pathological findings

Brain autopsy was performed in 40 out of 98 (41%) patients who died during the course of the study (16% of the total population). This group consisted of nine (22%) patients with the pathological diagnosis dementia lacking distinctive histology (DLDH), 13 (33%) patients had ubiquitin-positive inclusions in neurons of the second layer of the frontotemporal cortex and dentate gyrus of the hippocampus (FTD-MND type), and 18 (45%) patients showed tauopathy (*tau* mutations in seven, sporadic Pick's disease in six, other tauopathy without *tau* mutations in three and other tauopathy without *tau* mutation screening in two patients).

Discussion

The present population-based study, consisting of the largest series (n = 245) of FTD patients reported so far, showed a maximum prevalence of 9.4 per 100 000 at age 60–69 years in the Zuid-Holland province of The Netherlands. Prevalence estimates for The Netherlands as a whole were a factor of two lower, probably due to underascertainment in regions further away from the study centre. An age at onset >65 years was found in 22% of patients. The family history was positive for dementia in 43% of patients (n = 105), and *tau* mutation screening showed mutations in 32% of these patients (n = 34), 14% of the total population. Pathology in 40 of the patients who died during follow-up showed DLDH in 22%, FTD with ubiquitin-positive inclusions in 33%, Pick's disease in 15% and tauopathy in the remaining 30% of patients.

One limitation of the present study is the possibility of underascertainment due to misdiagnosis and non-referral by other neurologists, psychiatrists and nursing home physicians. Besides the 55 patients with FTD from Zuid-Holland ascertained in our study, an additional two FTD cases from Zuid-Holland came to autopsy at the NBB without referral to our centre. Although we can make a correction of prevalence for misdiagnosis and non-referral based on NBB data, we are not informed about non-ascertained and non-autopsied cases. A second limitation is the possibility of referral bias for familial cases of FTD. However, our percentage of patients with positive family history is similar to that found in other studies (Fabre *et al*., 2001; Poorkaj *et al*., 2001).

The highest prevalence of 9.4 per 100 000 emphasizes that FTD is much more common than was previously thought. This was also apparent in the only other study on the prevalence of FTD in the UK, where a prevalence of 15 per 100 000 was found at ages 45–64 years (Ratnavalli *et al*., 2002). In the current study, the maximum prevalence estimate in patients aged 45–64 was 4.0 per 100 000, significantly lower than in the UK study. The lower prevalence estimate in The Netherlands may be explained by methodological differences between the two studies. In the latter study, case identification occurred after systematic evaluation of all patients with potential dementia. In the autopsy series of the NBB, 34% of patients had not come to our attention, due to either misdiagnosis or non-referral by the primary specialist. A correction for a non-referral proportion of 40% would increase the prevalence of FTD at ages 45–64 in Zuid-Holland from 4.0 to 6.7 per 100 000 inhabitants, still considerably lower than in the UK study. Other factors that may contribute are the ethnic background of the population. The population of Zuid-Holland consists for a considerable part (10%) of non-Caucasian ethnic groups, which do not have the same risk of FTD as Caucasians. In the current study, over 99% of patients were indeed of Caucasian origin. In contrast, Ratnavalli *et al.* explicitly mention that ethnic minorities were underrepresented in the Cambridge study population (Ratnavalli *et al*., 2002).

An important observation of the present study was that 22% of our patients had an age at onset >65 years (63% between ages 65 and 70 years, and 37% aged >70 years). Interestingly, two of the four original patients described by Pick had an age at onset of 69 and 73 years (Pick, 1904). However, Van Mansvelt, in his large literature review of Pick's disease, emphasized its presenile onset (Van Mansvelt, 1954). The older age at onset in a subgroup of patients has not been given much attention in more recent literature, although the frequency in several studies varied from 10% up to 44% in a pathologically confirmed series by Giannakopoulos

(Murayama *et al*., 1990; Kosaka *et al*., 1991; Snowden *et al*., 1992; Mendez *et al*., 1993; Frisoni *et al*., 1995; Giannakopoulos *et al*., 1995).

A positive family history was present in 43% of Dutch FTD patients, similar to that reported previously (Stevens *et al*., 1998). These patients have proven (*tau* mutation) or convincing autosomal dominant inheritance of FTD in 20%, whereas the presence of a familial form of FTD could not be confirmed in the remaining patients due to small pedigrees or limited information on affected family members. *tau* mutations were seen in 14% of Dutch patients, similar to the 18% reported in our previous study of 90 FTD patients (Rizzu *et al*., 1999) and to 14% in the stringently diagnosed Manchester series (Houlden *et al*., 1999). However, most other studies show fewer *tau* mutations, with percentages in Sweden, the USA and Japan of 0, 6 and 8%, respectively (Fabre *et al*., 2001; Kowalska *et al*., 2001; Poorkaj *et al*., 2001). As also observed in series from France and Northern America (Dumanchin *et al*., 1998; Poorkaj *et al*., 2001), the most common *tau* mutation in The Netherlands was P301L (19 patients), which may be due to a founder effect in these populations. The absence of intronic splice-site mutations appears to be common on the European continent, in contrast to the UK, where mainly intronic mutations downstream of exon 10 are found (Dumanchin *et al*., 1998; Houlden *et al*., 1999; Poorkaj *et al*., 2001).

More than half of the pathologically confirmed cases did not have deposition of hyperphosphorylated tau in affected brain regions, as also reported in other pathological series (Cooper *et al*., 1995; Mann *et al*., 2000). DLDH was the diagnosis in 22% and FTD with ubiquitin-positive inclusions in 33% of these cases. MND was present in only three of 13 cases with ubiquitin-positive inclusions. Tauopathy was found in 45% of our patients, which is quite a high percentage compared with other series (Mann *et al*., 1993; Cooper *et al*., 1995; Bergmann *et al*., 1996), although the frequency of classical Pick's disease, diagnosed in 15% of our patients, varies considerably in different studies, ranging from 8 to 35% (Constantinidis *et al*., 1974; Brun, 1987; Mann *et al*., 1993; Cooper *et al*., 1995; Bergmann *et al*., 1996). The cause of tauopathy in five other patients (two with a positive family history) has yet to be elucidated. Boeve *et al.* recently presented a similar family characterized by tauopathy, but extensive sequencing of the *tau* gene also did not reveal a *tau* mutation (Boeve *et al*., 2002). It may be that a gene other than *tau* is responsible for the extensive tauopathy in these familial cases.

In conclusion, frontotemporal dementia is more common in The Netherlands than previously reported, with a maximum prevalence at ages 60–69 years. As nearly one-quarter of patients had an age at onset >65 years, more attention should be paid to FTD at older ages in epidemiological studies. The presence of *tau* mutations in 32% of patients with a positive family history justifies *tau* mutation analysis in familial cases of FTD.

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