

Epidemiology of Frontotemporal Dementia

Introduction

Frontotemporal dementia (FTD) is a neurodegenerative disorder, characterised by progressive behavioural change and a disturbance of language and frontal functions. Memory problems are not prominent at the initial stage. The introduction of criteria according to the Lund-Manchester Groups has helped to distinguish FTD from Alzheimer's disease (AD) in clinical practice.¹ Semantic dementia (SD) and primary progressive aphasia (PPA) are clinical subtypes of FTD that present with prominent language disturbance; both show the same neuropathological characteristics as in typical FTD cases (although mainly restricted to the temporal lobe), suggesting a common aetiology. Therefore, in this chapter we will use the term FTD to describe all clinical variants of this neuropathological spectrum. The frequency of patients with respectively SD or PPA in cohorts of patients with FTD ranges between 10 and 25% in most studies.²⁻⁶ The demographic features of patients with SD and PPA (age at onset, duration of disease, gender distribution, and family history) do not differ in general from patients with FTD.

Patient characteristics

Most patients with FTD are of Caucasian origin.⁷ However, patients of African and Asian descent have also been reported.^{5,7} Most studies show an equal incidence of FTD in men and women (in the Dutch study 49% men, 51% women).⁷ The average age at onset is 50 to 60 years, with a broad range of 21 to 85 years. About twenty percent of patients are older than 65 years at onset of symptoms.⁷ Disease duration is on average 8 years, with a broad range of 2 to 20 years. Symptoms of motor neuron disease are associated with significantly shorter disease duration of 3 years on average. About forty percent of patients have at least one first-degree family member with dementia; half of these patients come from a family with a clear autosomal dominant pattern of inheritance of dementia. The age of onset in familial and sporadic cases does not differ significantly.

The aetiological and pathological heterogeneity of FTD has been the object of extensive research over the past decade. The pathological hallmark of FTD is circumscribed atrophy of the frontotemporal cortex, as described by Arnold Pick,⁸ with neuronal loss, gliosis and spongiosis of the superficial layers of the cortex in all cases. Upon immunohistochemical analysis however, FTD is pathologically heterogeneous with at least three different subtypes being recognised: tau pathology, ubiquitin pathology, and cases without distinctive histology. There is no correlation between the type of neuropathological substrate and clinical syndrome. The term Pick's disease is now exclusively designated for FTD with intraneuronal argyrophilic inclusions, so-called Pick bodies, which consist of abnormal tau protein. Only 10-30% of sporadic FTD cases show Pick bodies.⁹⁻¹⁰ In contrast, 30-60% of familial FTD is pathologically characterised by tau pathology.¹¹

Familial FTD

Although the exact figures vary somewhat between different populations, roughly about 20 to 25% of FTD patients have an autosomal dominant pattern of inheritance. Rare recessive forms have also been described,¹²⁻¹³ but the mode of inheritance is not obvious in the remaining families due to a lack of information on family history or the possibility of non-paternity.¹⁴ Furthermore, the phenomenon of incomplete penetrance has convincingly been demonstrated in one family, making it even more difficult to recognise the pattern of inheritance.¹⁵

In 1998, three research groups identified mutations in the

tau gene in eight families,¹⁶⁻¹⁸ and more than 35 different tau mutations have been recognised in families in Europe, North America, Japan, and Australia over the past years. The frequency of tau mutations varies considerably in different FTD populations, ranging from zero to 18%.¹⁹⁻²³ Mutations in the tau gene have been identified in most familial FTD cases with tau pathology.^{7,11,22} However, a considerable proportion (40-70%) of the total group of hereditary FTD cases shows neither tau mutations nor tau pathology, suggesting a different aetiology.¹¹ The pathological hallmark of a large number of these cases is the presence of ubiquitin-positive inclusions in the hippocampus and frontotemporal cortex. Some of these families have also shown linkage to chromosome 17q21-22 in the absence of tau mutations, suggesting that there may be a second gene involved located close to the tau gene.²⁴⁻²⁷ Furthermore, linkage to chromosome 3 has been reported in a Danish family and a mutation in the *CHMP2B* (charged multivesicular body protein 2B, also known as chromatin-modifying protein 2B) gene has recently been identified in this family.²⁸

Prevalence studies

Several population-based studies addressing the prevalence of FTD have been reported over the past few years. Although the prevalence estimates differ somewhat between studies, it is evident that FTD is much more common than previously suspected. There are two population-based studies from the United Kingdom (UK), one from Cambridge and one from London,²⁹⁻³⁰ one study from the province Zuid-Holland in the Netherlands,⁷ and one regarding the incidence of FTD from Rochester, Minnesota in the United States of America.³¹ Finally, a study in Gothenburg, Sweden estimated the prevalence of FTD in a population-based sample of 85 year olds.³²

The two UK studies are similar in design, investigating all patients with presenile dementia referred to a centre specialising in dementia; older patients were not included. They found an identical FTD prevalence of 15 per 100,000 inhabitants in the age group 45 to 64 years. However, there was a difference of more than factor two in the prevalence of patients with AD in these studies: 15 per 100,000 in Ratnavalli et al²⁹ and 35 per 100,000 in Harvey et al.³⁰ This difference may be due to incomparable rates of ascertainment and/or diagnostic methods between the two studies. The prevalence figures from the Cambridge study²⁹ suggest that FTD may be as common as AD before the age of 65 (both FTD and AD showed a prevalence of 15 per 100,000 inhabitants). However, clinical studies with post-mortem confirmation do not support this view. In a series of 158 consecutive dementia patients in Lund, Sweden only 13% had FTD, compared to 45% with AD, half with a presenile onset.³³ Similarly, in Japan a ratio of FTD to AD has been reported in presenile cases of about 1 to 4.5. In the Dutch study, the maximum prevalence estimate of FTD in patients aged 45 to 64 was 4.0 per 100,000, significantly lower than both UK studies.⁷ This difference may be partly explained by the fact that both UK studies examined all patients with presenile dementia in a defined population, in contrast to examination of only referred suspected FTD patients in the Dutch study.

In the Dutch study, the highest prevalence estimates of FTD were seen at ages 60 to 69, with prevalence estimates of 3.6 per 100,000 at age 50-59 years, rising to 9.4 per 100,000 at age 60-69 years and declining to 3.8 per 100,000 in the 70-79 year age group.⁷ A similar profile was seen in Rochester, Minnesota, where the incidence (new cases per 100,000 person-years) of FTD was shown to be 2.2 for ages 40 to 49, 3.3 for ages 50 to 59 and 8.9 for ages



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60 to 69; no older patients were found.³¹ However, a study in Gothenburg, Sweden estimated the prevalence of FTD in a population-based sample of 85 year olds to be 3.1 per 100 inhabitants.³² This is one of the first studies to address the presence of FTD in older patients and has revealed surprisingly high prevalence estimates. Drawbacks of the Swedish study are a lack of neuroimaging (CT-scanning was available in only 6 of 14 (43%) FTD patients) and neuropathological confirmation.

Conclusion

Epidemiological studies have shown that FTD is more common than previously suspected, but still relatively rare compared to AD, even at younger ages. The highest prevalence is found at ages 60 to 70, although patients older than 85 years have been reported. About 25% of patients have a hereditary form of FTD with autosomal dominant inheritance. Mutations in the tau gene are present in less than half of familial FTD cases. A mutation in the *CHMP2B* gene on chromosome 3 is probably even rarer. Therefore, it is very likely that more common disease-causing genes, one of them possibly located on chromosome 17q²¹⁻²² close to the tau gene, have still to be identified.

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Neutralising Anti-interferon-beta Antibodies in Multiple Sclerosis (NABINMS) – EU Grant

The European Commission Framework Programme 6 has recently awarded a specific grant to establish and validate neutralising anti-interferon-beta antibody (NAB) assays in the EU and to further study the impact of NABs on interferon-beta therapy (IFN β) in subjects with multiple sclerosis (MS). As part of this programme we have developed a novel NAB assay and are now in a position to test for NABs in subjects on IFN β therapy as part of our research programme. If over the next 6-12 months there is sufficient demand for this assay we will be able to provide it as part of our routine laboratory service. The evidence that NABs impacts negatively on the efficacy of IFN β is beyond doubt and has significant implications for the cost-effectiveness of IFN β therapy.¹ Subjects with MS treated with IFN-beta should be offered routine NAB testing within the first 24 months of starting treatment as standard clinical practice.² We would advise routine testing at

12 and 24 months. If subjects are NAB-ve at 24 months, repeat NAB testing is not indicated, unless a positive result is likely to affect a treatment decision. NAB testing should also be considered in subjects with clinical evidence of disease activity who have been on IFN β therapy for at least 6 months. It is recommended that in subjects who are persistently NAB+ve (≥ 100 NU on two consecutive occasions) IFN β therapy should be discontinued.² It is debatable about what to do with subjects who are persistently positive at lower titres (20-100 NU), as some subjects with low titres may still have evidence of in vivo IFN β bioactivity, eg induction of IFN β -specific genes, albeit at a lower level. In addition, there is greater tendency for subjects with low titres to spontaneously revert to NAB negative over the next 3-4 years; the chances of this occurring are up to 20% for subjects treated with IFN β -1a and up to 60% for subjects treated with IFN β -1b.³



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