6. ALZHEIMER’S DISEASE AND OTHER DEMENTIAS

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Dementias represent a major health problem because the number of patients is increasing in most countries, due to aging of the populations. Alzheimer’s disease was the first to be individualized and is by far the most frequent. More recent, clinical and neuropathological studies have distinguished a second major form of dementia, frontotemporal dementia, although less frequent. Interestingly, both Alzheimer’s disease and frontotemporal dementia have features in common, such as neuronal loss in a number of brain structures and the intra or extracellular accumulation of misfolded proteins which constitute markers for the diseases. Sub-groups of Alzheimer’s disease and frontotemporal dementia are monogenic. Several of the responsible genes have been identified, making possible to approach the physiopathology of the disease and to generate in-vivo and in-vitro models.

1. INTRODUCTION

Alzheimer disease (AD) is the most common cause of dementia. In the past decade, many advances have been made in the understanding of AD etiology. Advances in neuropathology have helped to accurately describe the lesions responsible for this disease. More recently, the identification of mutations involved in familial early onset AD (EOAD), has permitted to characterize the physiopathological cascade. In the future, it could be possible to develop new therapeutic strategies targeted against the causative alterations.

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2. CLINIC

Clinical AD is diagnosed according to the NINCDS-ADRDA criteria (McKhann 1984): National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association. Whereas clinical findings may provide possible diagnosis, final confirmation is only obtained based on pathological results. Diagnosis of AD is often preceded by a predementia state during several years, described as mild cognitive impairment (MCI). The diagnosis of MCI is made if the patient met the following criteria: memory complaint, normal activities of daily living, normal general cognitive function, abnormal memory for age, and not demented (Petersen 1999). Individuals with MCI develop AD at the rate of 10% to 12% per year. The initial characteristics of AD are mainly disorders of episodic memory reported by the family, but can also appear as changes in behavior, reduction in attention, word finding difficulties or time and space disorientation. In some cases, the disease is revealed by a confusion syndrome. The patient is often anosognosic at the dementia state of AD and the diagnosis is therefore carried out with the help of a family member.

Reduction of cognitive functions are assessed either by different global scales, as the Mattis Dementia Rating Scale (Schmidt) or more specific tools evaluating memory, as the Grober and Buschke test (Grober), temporal and space orientation, image identification, verbal fluency and executive functions, praxis and gnosia (knowledge of famous faces, drawings of objects) and judgment. Cognitive functions initially affected are memory (encoding, recall, temporal areas) but initially normal. Whereas clinical findings may provide possible diagnosis, final confirmation is only obtained based on pathological results. Diagnosis of AD is often preceded by a predementia state during several years, described as mild cognitive impairment (MCI). The diagnosis of MCI is made if the patient met the following criteria: memory complaint, normal activities of daily living, normal general cognitive function, abnormal memory for age, and not demented (Petersen 1999). Individuals with MCI develop AD at the rate of 10% to 12% per year. The initial characteristics of AD are mainly disorders of episodic memory reported by the family, but can also appear as changes in behavior, reduction in attention, word finding difficulties or time and space disorientation. In some cases, the disease is revealed by a confusion syndrome. The patient is often anosognosic at the dementia state of AD and the diagnosis is therefore carried out with the help of a family member.

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Neurological examination is frequently normal at the onset of the disease. At an advanced stage, patients are confined to bed and stiffness, myoclonic jerks or epileptic seizures may occur.

3. COMPLEMENTARY EXAMINATIONS

Cerebral CT-scan is necessary to eliminate other causes of dementia (vascular, tumoral or different), and may reveal both global and regional atrophy (initial temporal areas) but initially, the CT-scan can appear completely normal.
There is currently no blood nor sufficiently specific cephalo-spinal liquid biological marker for AD that could be used to achieve an accurate diagnosis.

4. NEUROPATHOLOGY

The two neuropathological hallmarks of AD are the presence of senile (neuritic) plaques and neurofibrillary pathology (Tolnay 2003). Senile plaques are extra cellular lesions constituted by amyloid deposits, surrounded by neurofibrillary tangles. The amyloid deposits, present in the core of the senile plaques and in the vascular walls, contain a 40 to 42 amino-acids (AA) long peptide, named Aβ, which is a fragment of the amyloid precursor protein (APP). Antibodies directed against the Aβ peptide also label diffuse deposits that are devoid of the tinctorial affinities and biochemical properties of amyloid substances. While Aβ in the β-sheet conformation is the main component of senile plaques, several other proteins are found in senile plaques such as the apolipoprotein E which could act as a chaperone protein, inducing or facilitating the formation of amyloid.

Neurofibrillary pathology includes neurofibrillary tangles and neuropil threads. Neurofibrillary lesions are characterized by the same ultrastructure, i.e. the accumulation of paired helical filaments and the same immunological characteristics: they are labeled by antibodies directed against the Tau protein. The Tau protein constitutes the principal component of neurofibrillary pathology and is bound to ubiquitin, which means that it is intended to be degraded by the proteasome.

5. DOMINANTLY INHERITED FAMILIAL ALZHEIMER DISEASE

Early-onset autosomal dominant Alzheimer’s disease (EOAD) is a heterogeneous disorder that can be caused by mutations in at least three different genes. These monogenic forms of AD account for approximately 0.25% of the entire pathology (Campion 1999). Presenilin 1 (PS1) mutations account for the majority of monogenic forms (70%), mutations of amyloid precursor protein (APP) are rare (15%) while Presenilin 2 (PS2) are exceptional.

5.1. APP gene

The first APP mutation was identified in 1991 (Goate 1991). This mutation causes an amino acid (AA) substitution (Val717Ile) located near the carboxy terminus of the Aβ peptide on its precursor. The APP gene is located in q21 region of chromosome 21 and has several isoforms generated by alternative splicing. All of these encode multidomain proteins with a single membrane-spanning region. This gene is triplicated in trisomy 21 (Down Syndrome) a condition in which senile plaques appear very early, from the age of 20.

Missense APP mutations are concentrated in three sites which are APP physiological cleavage sites (see Fig. 1). Val717Ile mutation is most frequent
and was found in 23 pedigrees. Other substitutions at the same codon are Val717Phe mutation (Murrell 1991), Val717Gly mutation (Chartier-Harlin 1994) and Val717Leu mutation (Murrell 2000). Other mutations are clustered around this site including the Ile716Val mutation (Eckman 1997), the Val715Met mutation (Ancolio 1999), the Thr714Ile mutation (De Jonghe 2000), the Thr714Ala mutation (Pasalar 2002) and the Leu723Pro mutation (Kwok 2000). In two large families linked by genealogy and containing multiple cases of Alzheimer disease (Mullan 1992), found a double mutation in exon 16, the Swedish mutation. Two nucleotide transversions, G to T and A to C, were observed in affected individuals at codons 670 and 671, respectively. These changes resulted in the substitution of a lysine to an asparagine and a methionine to a leucine (Lys670Asp, Met671Leu).

Finally, five mutations located in the middle of the Aβ sequence at the vicinity of the α-secretase cleavage site have been described: Ala692Gly, Flemish mutation (Hendriks 1992), Glu693Gln, Dutch mutation (Levy 1990), Glu693Gly, Arctic mutation (Kamino 1992), Glu693Gly, Italian mutation and Asp694Asn, Iowa mutation (Grabowski 2001). Some patients bearing these mutations have classical AD whereas cerebral hemorrhages occur in others. Currently, 17 pathogenic changes of APP have been reported.

Mutations around codon 717 in one hand and the Swedish mutation on the other hand, correspond to the sites where APP is cleaved by γ-secretases and by β-secretases, respectively releasing the Aβ peptide from its precursor. The consequence of the Swedish mutations is a quantitative increase in the production at the same time of the short form (Aβ-40, 40 AA) and long (Aβ-42, 42 AA) of the Aβ peptide. The other changes modify the Aβ42/Aβ40 ratio, thus favoring the production of the longer form of the peptide, which is more prone to aggregation. Indeed, the last two AA play an important role in the conformation of the peptide in β-pleated sheet, which are characteristic of senile plaque deposits (Jarrett 1993). Aβ peptide in fibrillar form is toxic for neurons (Lorenzo 1994), although the exact mechanisms which act as mediators of this toxicity still remain to be defined i.e. disruption of calcium homeostasis, oxidative stress, and induction of apoptosis.

5.2. Presenilin 1 (PS1) gene and Presenilin 2 (PS2)

In 1995, two other genes were discovered, which were implicated in monogenic forms of EOAD. These genes, known as PS1 and PS2, were located respectively on chromosomes 14 and 1 and present major sequence homologies (Sherrington 1995; Levy-Lahad 1995). PS1 mutations are extremely diverse, as
opposed to APP (see Fig. 2). The same mutation is rarely found in both non-related families. Currently, 134 PS1 missense mutations have been reported. It therefore appears that the structure of this protein is extremely sensitive and the slightest variation of AA composition can provoke AD.

In several families, a mutation on the splicing site produced a deletion of exon 9, conserving the reading frame and generating a missense mutation at the splice junction (PS1 δ9 S290C). In a Finnish family, the loss of exon 9 was due to a major deletion which equally including adjacent introns (Crook 1998). In 7 families, who were thought to have a common ancestor, an intron 4 mutation produced three different transcripts, two coding for truncated PS1 and the third for a protein with an AA insertion: T113-114Ins (De Jonghe 1999). Finally, another insertion of one AA after codon 352 in exon 10 has been described (Rogaeva 2001).

PS2 mutations are exceptional and only 9 missense mutations have been reported in the literature (Rogaeva 1995).
5.3. Clinical characteristic of dominantly inherited alzheimer disease

5.3.1 Age of onset

As regards APP mutations, the age of onset of the illness varies between 37 years and 64 years for the same Val717Ile mutation. This onset age diversity has prompted to search for factors, primarily genetic, which may modulate disease expression. It has been suggested that APOE gene polymorphism could modify age of onset. In fact, a difference has been found for the same mutation and APOE genotype, which suggest that either genetic or environmental factors should be further investigated.

As regards PS1, comparison of numerous mutations confirms major diversity of onset age among mutations. Age of onset is always below age 60. Early occurrences are possible: from 24 to 33 years for Pro117Leu mutation (Wisniewski 1998); from 24 to 29 years for Leu173Trp mutation (Campion 1999). One hypothesis is that these mutations involve particular modifications of PS1 structure, which may be particularly deleterious. The role played by biochemical properties of substituted AA is illustrated by comparing both mutations at codon 143: the average age of onset is 35 years in cases of non-conservative substitution (Ile143Thr), whereas onset age is approximately 55 years in cases with semi-conservative substitution (Ile143Phe).
However, a great intra-familial diversity has been reported in certain families with a large number of cases. Therefore, the concept of diversity according the specific type of mutation remains questionable. For example, age of onset varied from 34 to 62 years in a large family with Leu392Val mutation. Recently, it has been shown that APOE genotype may play a role to modulate age of onset in a cohort of 52 affected subjects bearing the same Glu280Ala PS1 mutation (Pastor 2003)\textsuperscript{31}.

5.3.2 Neurological signs associated to AD

Most of the PS1 mutations are associated with classical AD; however, some families develop AD and spastic paraparesis. The relevant mutations are a deletion of 2 AA in exon 4 (\textit{6183/M84}) (Houlden 2000), an insertion of 2 AA in exon 5 (\textit{InsFl}) (Rogaeva 2001) and the complete deletion of exon 9 (69) (Kwok 1997; Crook 1998; Sato 1998). This phenotype was also observed with certain specific point mutations such as Phe237Ile, Val261Phe, Pro264Leu and Arg278Thr, but it is not constant. Spastic paraparesis may occur before cognitive impairment. In family Finn 2, memory impairment was preceded by walking difficulty due to spasticity of the lower extremities among 10 patients out of 14 (Verkkoniemi 2000). These forms are characterized on the hispathological ground by “cotton wool” plaques lacking congophilic dense core or marked plaque related neuritic pathology (Crook 1998).

In two families harboring either the Leu113Pro mutation (Raux 2000) or the insertion of one codon in position 352 (Rogaeva 2001), patients had personality changes and behavioral disorders, whereas spatial orientation and praxis were unchanged late in the course of the illness. This presentation was consistent with the diagnosis of fronto-temporal dementia. Recently a novel PS1 missense mutation associated with Pick’s disease but not senile plaques has been described (Dermaut 2004).

6. BIOLOGICAL CONSEQUENCES

6.1. Amyloid cascade hypothesis: \textit{APP} mutations

There are two pathways of APP maturation. The first one consists of APP cleavage by the $\alpha$-secretase enzyme in the middle of A$\beta$ peptide. This pathway which produces a soluble APP$\alpha$ fragment is non amyloidogenic because it avoids the A$\beta$ peptide production.

The second maturation pathway which consists in the sequential cleavage of APP by $\beta$- and $\gamma$-secretases is amyloidogenic. It produces the amyloid-peptide, a soluble APP-$\beta$ fragment and also releases an intracellular fragment (AICD) which is translocated in the nucleus where it has a role of transcriptional activator (Cao 2004). A$\beta$ peptide has an unknown exact function and as long as this function is not known, it will be difficult to consider therapeutic blocking the A$\beta$ peptide production which could be noxious.
APP mutations were localized on the 3 APP cleavage sites, by α-, β- and γ-secretases. All these mutations have the same biological consequence: overproduction of Aβ peptide, by blocking α-secretase in one case, or by increasing β- and γ-secretase activities in other cases. To specify the mutation characterization, animal models were assessed, which overproduced Aβ peptide.

6.2. APP transgenic mice

Transgenic mice expressing normal or mutant human APP were evaluated (Calhoun 1998). Mice have an APP homolog gene, containing the Aβ peptide sequence but this sequence is slightly different and no senile plaque was observed in mice, probably because aggregation capacity was less significant.

Brains of transgenic mice expressing human mutant APP exhibit typical pathologic features of AD, including numerous extracellular Aβ deposits, neuritic plaques, synaptic loss, astrocytosis, and abnormal phosphorylated Tau protein. However, it should be stressed that neurofibrillary tangles were never observed. Neurofibrillary tangles can be formed in transgenic mice; they have indeed been observed in transgenic mice with Tau mutations, whereas this gene is never mutated in AD (Lewis 2001).

APP transgenic mice are thus suffering of cognitive deterioration and neuronal loss without neurofibrillary tangles whereas in human, cognitive deterioration is correlated with neurofibrillary lesions. Observation of these transgenic mice raises another problem: cognitive deterioration appears before senile plaques. Together, these observations show that cognitive deterioration related to Aβ toxicity can occur very early, before neurofibrillary tangles and senile plaques, suggesting that these lesions would be a late event in AD evolution and emphasize the pathogenic role of soluble, incompletely aggregated forms of Aβ, so called “protofibrils.”

6.3. Presenilin mutations

Immunohistochemical analyses indicated that PS1 and PS2 localize to similar intracellular compartments, such as the endoplasmic reticulum and Golgi complex, where APP undergoes biochemical maturation.

Consequences of Presenilin mutations are the same than that of APP mutations i.e. an overproduction of Aβ peptide and particularly of the Aβ42 form. Cell lines transfected with mutant PS1 produce a more significant increase in Aβ42 than cells transfected with wild type PS1 (Murayama 1999). Transgenic mice overexpressing mutant PS1, but not wild type PS1, show a selective increase in brain Aβ42 (Duff 1996). Thus, mutations of three different genes have the same biological consequence and this observation strongly support the conclusion that progressive cerebral deposition of amyloid β protein is a seminal event in familial AD pathogenesis.

Asides from APP, Presenilin interact with several proteins, including the transmembrane protein Notch. Signaling through the receptor Notch, which is involved in crucial cell fate decisions during development, requires ligand-induced cleavage of Notch. This cleavage occurs within the predicted
transmembrane domain, releasing the Notch intracellular domain (NICD), and is reminiscent of the γ-secretase-mediated cleavage of APP. Indeed, deficiency of presenilin-1 inhibits processing of APP by γ-secretase in mammalian cells, and genetic interactions between Notch and PS1 homologs in C. elegans indicate that the presenilins may modulate the Notch signaling pathway. De Strooper et al. (1999) reported that in mammalian cells PS1 deficiency also reduces the proteolytic release of NICD from a truncated Notch construct, thus identifying the specific biochemical step of the Notch signaling pathway that is affected by PS1.

Moreover, several γ-secretase inhibitors block this same step in Notch processing, indicating that related protease activities are responsible for cleavage within the predicted transmembrane domains of Notch and APP. Presenilins are now known to be members of a large multimolecular complex (also including Nicastrin, APH1 and PEN2) which is responsible for the γ-secretase activity (Mattson 2003). Targeting of γ-secretase activity for the treatment of Alzheimer disease may risk toxicity caused by reduced Notch signaling. Ye et al. (1999) described loss-of-function mutations in the Drosophila PS1 gene that caused lethal Notch-like phenotypes such as maternal neurogenic effects during embryogenesis, loss of lateral inhibition within proneural cell clusters, and absence of wing margin formation. They showed that PS1 is required for the normal proteolytic production of carboxy-terminal Notch fragments that are needed for receptor maturation and signaling, and that genetically it acts upstream of both the membrane-bound form and the activated nuclear form of Notch. Thus, to interfere with the Notch signaling could be very deleterious but there is now an inhibitor of γ-secretase able to alterate only APP signaling (Netzer 2003).

7. GENETIC RISK FACTOR: APOE

In the central nervous system Apolipoprotein E (APOE) is primarily synthesized by astrocytes. APOE assures the transport role of different lipoproteins and binds to neurons via LDL receptors (LDL, VLDL, LRP, and gp330) (Poirier 1994). APOE is present in three isoforms APOE2, APOE3 and APOE4, with respective frequencies of 7%, 78% and 15% in a European or American caucasian population (Strittmatter 1995). These isoforms are encoded by three alleles ε2, ε3, ε4 of the APOE gene localized in the q13.2 region of chromosome 19. While the APOE3 isoform has a cystein to codon 112 and an arginine to codon 158, the APOE4 contains an arginine in 112 and APOE2 a cysteine in 158. An increase of ε4 allele frequency was initially reported in groups of old subjects with familial cases of AD. This association was further confirmed in groups with late and early sporadic AD (Chartier-Harlin). Numerous studies have now reported this association between AD and the ε4 allele. In a meta-analysis study including 6262 subjects and 5107 AD patients of caucasian origin, respective percentages of different genotypes were 61% versus 36% of ε3/ε3, 21% vs 41% of ε3/ε4, 1% vs 15% of ε4/ε4, and 17% vs 8% of
The genotype relative risk is calculated by taking ε3/ε3 as a genotype reference (odds ratio (O.R.) = 1). This risk is multiplied by 2.7 (2.2-3.2) for ε3/ε4 genotype, by 12.5 (8.8 - 17.7) for ε4/ε4 genotype, and 0.6 for ε2/ε3 (Farrer 1997). Therefore, a genetic dosage effect exists with a greater risk occurring in homozygotes ε4/ε4 as compared to ε3/ε4. The ε2/ε3 genotype has a protective effect as the risk is lower compared to genotype ε3/ε3. The imputable risk of allele ε4 remains present whatever the age range but it is most significant between 60 and 69 years [O.R.= 4.1(2.3-7.5)] than before 59 years [O.R.= 1.9 (.96-3.7)] and over 80 years [O.R.=1.7 (.9-3.4)] (Bickeboller 1997). In cases of genotype ε3/ε4, the risk of AD is higher for women; the adjustment for age range eliminates all bias due to their greater longevity (Farrer 1997).

This gender effect therefore suggests the intervention of another factor. The importance of the risk associated with the allele ε4 and the frequency of this allele in the general population raises the question of the involvement of the APOE genotype in familial, non autosomal dominant, aggregation. The cumulated risk of developing AD at the age of 90 years was estimated in the first degree relatives of a proband, according to the propositus genotype. These risks were respectively 30% (±11), 46% (±13) and 61% (±16) in relatives of a ε3/ε3, ε3/ε4, or ε4/ε4 propositus (Martinez 1998). These estimates were comparable with those reported by Farrer et al. (1995). These figures should be compared to predictive percentages of carriers who have at least one ε4 allele in family member, which are on average 14 %, 58 % et 90% depending on ε3/ε3, ε3/ε4, and ε4/ε4 genotype of propositus. The first conclusion is that the allele ε4 is a major risk factor, which may explain significant family aggregation in relatives of a propositus bearing at least one ε4 allele. The presence of several cases in the same family may therefore result from the effects of this sole genetic risk factor, particularly in relatives old and ε4/ε4 proband. The second conclusion is that AD aggregation (30%) observed in the propositus family with a genotype ε3/ε3, may be due in part to another risk factor as allele ε4, which only would explain approximately 50% of observed cases. Finally, allele ε4 is only a risk factor as certain allele ε4 carriers will not develop the disease even beyond 90 years of age. Similarly, approximately 30% of family related women and 60% family related men, carriers of one or two ε4 alleles would not experience AD if they reach that age. Nevertheless, the previously mentioned data may be under estimated as ε4 allele is a risk factor for myocardial infarction. A large number of deaths due to cardiovascular disease have been observed in relatives, primarily men, of AD patients who are ε4 carriers (Li 1996).

The direct role played by APOE on peptide Aβ deposits has been demonstrated by using transgenic mice, which not only overexpress mutated APP but are knock out for the mouse APOE gene. The number of amyloid deposit is very low in APOE knock out mice, intermediary in hemizygototes and increased in those mice which express mutated APP in a normal APOE background (Bales 1997). In transgenic mice expressing the human APOE gene, an APOE isoform dependent amyloid deposition and neuritic degeneration has been reported.
In addition, APOE may also intervene in cholesterol metabolism and reduction of oxydative stress induced by the Aβ peptide on neurons. APOE 4 has been shown to have a reduced anti-oxydative effect as compared to the other two isoforms56.

8. GENES AND THERAPY

Cholinesterase inhibitors are established for the treatment of mild-to-moderate Alzheimer’s disease. Memantine is the first drug to demonstrate a clinical benefit in the treatment of patients with moderately-severe to severe AD. Acetylcholinesterase inhibitors had comparable efficacy as well as similar significant side effects. Some patients are very receptive to anticholinesterasic drugs whereas other patients are only slightly or not at all. Predictive factors of positive response to anticholinesterasic drugs have been poorly reported. Nevertheless, Poirier et al. (1995) have reported the influence of APOE4 on Tacrine effects. Allele ε4 was considered to be predictive of less satisfactory response to treatment as compared to allele ε3 or ε2. Cacabelos (2002)58 reported a similar effect with galantamine. However, this effect remains debatable since not reported by others (Farlow 1999; Aerssens 2001) but the understanding of functional genomics in AD will foster productive pharmacogenomic studies in the search for effective medications and preventive strategies in AD.

8.1. New therapeutic strategies

Enormous effort is devoted to develop drugs that slow neurodegeneration in Alzheimer’s disease, although insights into AD genetics and molecular pathogenesis only arose in the last 15 years. The existence of pathogenic mutations in APP and the presenilin genes provides strong support for the hypothesis that Aβ-production and deposition contribute to the etiology of AD. A variety of approaches are being tried to interrupt the disease process, including reducing the production of the Abeta peptide, inhibiting its aggregation, and promoting its removal, for example via immunotherapy. γ-Secretase activity is involved in the generation of Aβ and therefore likely contributes to the pathology of AD. Blocking this activity would have been a major therapeutic target to slow down or arrest Aβ-related AD progression. Drugs that modulate the production of Aβ by inhibiting γ-secretase could provide an effective therapy for AD, but like most disease targets, the γ-secretase appear to have more than a single function. The discovery of drugs that could selectively inhibit β-APP cleavage is an important objective. Several inhibitors seem to be able to prevent Aβ production without triggering unwanted cleavages of other proteins (Netzer 2003). The efficacy of these inhibitors in reducing Aβ without affecting Notch cleavage may prove useful as a basis for developing novel therapies for Alzheimer’s disease. Little is known about exchange of the β-peptide between the brain and blood. Increased understanding
of this process in experimental animal models and humans, and how it changes
with aging, will likely open new therapeutic approaches.

Finally, discovery of abnormally phosphorylated tau protein in neurofibrillary
tangles in AD brain has led to strategies for identifying selective inhibitors of tau
kinases and central nervous system/brain-permeable drugs that help maintain
microtubule integrity.

All the future knowledge of physiopathological neurodegeneration will help
to develop neuroprotective strategies.

FRONTOTEMPORAL DEMENTIAS

During the past decade, neurologists and psychiatrists have become
increasingly aware that a significant proportion the degenerative dementias are
of the “non-Alzheimer” type. The frontotemporal dementias, characterized by
progressive personality changes and language impairment related to a
frontotemporal atrophy, account for approximately 5-20% of these diseases
(Jackson 1996; Sleegers 2004). The first pathological description of a particular
form of frontotemporal dementia (FTD) was made by Arnold Pick in the early
20th century, but the first clearly indexed cases of patients with FTD were
reported in 1987 by Gustafson in Lund-Sweden (Gustafson 1987), and in 1988
by Neary et al. in Manchester-United Kingdom (Neary 1988). The clinical and
pathological nosology was further clarified in 1994 and the term frontotemporal
dementia adopted during a consensus conference bringing both the teams of
Lund and Manchester (The Lunds and Manchester groups 1994). The
frontotemporal dementias in fact included a wide range of distinct entities,
which are now divided into subgroups, according to their genetic and
pathological characteristics (D.M.A. 2000). The term Pick disease, sometimes
used as a clinical term for patients presenting progressive frontal syndrome with
frontotemporal lobar atrophy, should now be restricted to a minority of
pathologically proven cases with specific Pick bodies.

8.1.1. Epidemiology

The prevalence of FTD is age-depandant and varies from 3.6 per 100 000 at
age 50-59, and 9.4 at age 60-69 (Rosso 2003; Bird 2003). A positive family
history is noted in 33 to 56% of patients (Stevens 1998; Morris 2001; Hodges
2003). Approximately 25% of the probands presenting a family history
compatible with an AD mode of inheritance have a mutation in the tau gene

8.1.2. Diagnosis

FTD are characterised by prominent personality changes (apathy, agitation,
agression, disinhibition, depression, inappropriate affect), impaired reasoning
and insight, lack of thematic understanding and difficulty planning, in the
absence of ideomotor apraxia or agnosia. Most of cases begin between the age
of 45 and 65, with a mean age at onset at 58.0 years (Rosso 2003). The phenotypes and age at onset may vary, however, in patients with a microtubule associated protein tau (MAPT) gene mutation, also referred to as FTDP-17, according to the type of mutation (Van Swieten 2004). Indeed, a subset of patients with the P301L and R406W develop the disease after 60 (Van Swieten 1999), whereas those with the P301S mutation have earlier age at onset, around age 35 (Bugiani 1999; Yasuda 2000; Lossos 2003; Werber 2003). The clinical diagnosis of FTD, based on the criteria established by the Lund and Manchester group, later revised by Neary, includes: (i) progressive behavioural disorder with insidious onset; (ii) affective symptoms; (iii) preserved orientation and praxis; (iv) selective frontotemporal atrophy on brain imaging or frontotemporal hypoperfusion on single photon emission computed tomography (SPECT) (The Lund and Manchester groups 1994; Neary 1998).

Clinical presentation depends on whether the frontal or the temporal cortex is first affected (Perry 2000; Hodges 2001). The frontal - or behavioural-variant is characterized by progressive changes in personality and social cognition, with disinhibition, loss of empathy, changes in eating patterns, stereotyped behaviours, apathy. The temporal variant – or semantic dementia- is characterized by the deficits in language and semantic knowledge. Physical manifestations are limited to frontal signs as grasping, sucking and rooting reflexes, and the occasional late development of parkinsonism. Motor neuron disease (MND) is associated with frontotemporal dementia in approximately 15% of patients. Mean survival after onset is approximately 6.0 to 10.4 years (Hodges 2003; Pasquier 2004).

Brain morphology visualized by MRI or CT can be normal at onset. As the disease progresses, bilateral atrophy of the frontal lobes, sometimes asymmetrical, and of the anterior region of the temporal lobes becomes visible. Atrophy of the hippocampal area can also be associated with frontotemporal atrophy (Frisoni 1996). SPECT studies show hypoperfusion in the frontal lobe and anterior region of the temporal lobes, often before atrophy can be visualized by CT or MRI (Miller 1991).

8.1.3. Neuropathology

The definite diagnosis of frontotemporal dementia is made by neuropathological examination. Circumscribed focal atrophy may be seen in the frontal and/or temporal lobes, and may be accompanied by ventricular dilatation. Although microscopic pathological changes are variable, neuronal loss, gliosis and diffuse spongiosis in superficial layers of the cortex are lesions observed in
all forms of FTD. The substantia nigra, hippocampus, and others subcortical structures show neuronal loss. Immunohistochemistry has greatly facilitated the diagnosis of these conditions, with the identification of disease specific abnormalities, including Pick bodies, tau inclusions or motor neuron disease-type ubiquitin positive inclusions. A classification of frontotemporal dementias has been proposed based on to the pathological hallmarks (Morris 2001; Munoz 2003). However, the lesions are heterogeneous not only among the different entities, but also among families with the same mutation, and even in the same brain.

DFT with tauopathy is characterized by frontotemporal neuronal loss, gliosis, and the presence of tau-positive inclusions in neurons and glial cells. They account for approximately 30-40% of the DFT (D.M.A. 2000), among which 50% have FTDP-17 with tau mutations. The neuropathological characteristics of patients with tau mutations are variable, although all cases reported to date had filamentous pathology made of hyperphosphorylated tau protein in neurons and glial cells (Götz 2001; Rosso 2002). The morphology of tau filaments and the tau isoform involved is determined by whether the mutation affects or not the splicing of exon 10, but most of the mutations cause aggregation predominantly of insoluble four repeats (4R) tau proteins (Bué 1999). Pick disease, another form of FTD, is characterized neuropathologically by the presence of ballooned neurons (Pick cells) containing granulofilamentous material in cortical layers of the most severely affected areas. Pick cells are immunostained with antibodies against alpha-B crystalline and phosphorylated neurofilaments, but only inconsistently with tau and ubiquitin antibodies. In addition, intraneuronal argyrophilic tau-positive round inclusions, called Pick’s bodies, that constitute the pathological hallmark of the disease, are found essentially in the hippocampus, dentate fascia, amygdala and ventral temporal lobe. They are composed of tau- and ubiquitin-positive straight and twisted filaments, that do not contain alpha-synuclein reactivity (Dickson 2001). The insoluble tau proteins contains only the 3R isoform in most cases (Bué 1999; Taniguchi 2004), or more rarely a mixture of 3R and 4R tau (Taniguchi 2004).

The major form of FTD without pathologically confirmed tauopathy includes dementia with motor neuron disease (MND)-type type inclusions, progressive subcortical gliosis and dementia lacking distinctive histology. Dementia with MND-type inclusions is characterized by ubiquitinated neurites in neocortex and neuronal inclusions in neocortex and dentate gyrus, containing intermediate filaments. The inclusions are ubiquitin-positive but tau-negative (Wightman 1992). Dementia lacking distinctive histologic features (DLDH) is characterised by neuronal loss and gliosis only; there are no tau- or ubiquitin-positive neuronal inclusions and no senile plaques (Knopman 1990). Zhukareva
et al. (2001) reported a particular form of DLDH characterized by the absence of native tau protein (Zhukareva 2001). Progressive subcortical gliosis is characterized by frontotemporal atrophy and fibrillary astrogliosis in superficial and deep cerebral cortical layers, and in the white matter immediately subcortical. Immunoreactive tau is either absent (Lanska 1994), or may be present in both neurons and glial cells in rare families with tau mutations (Goedert 1999).

Dementia lacking distinctive histologic features is the most common neuropathological form of FTD in a recent Japanese neuropathological study of 55 autopsied cases. The relative frequencies are 42% for DLDH, 18% for FTD with ubiquitin inclusions, 15% for Pick disease and 11% for FTDP-17 with identified tau mutation and inclusions (Taniguchi 2004).

8.1.4. Genetic of familial FTD

The MAPT gene and tau protein

Many cases of FTD are sporadic, but some pedigrees strongly support the existence of an autosomal dominant entity with high penetrance. Mutations in the MAPT gene (microtubule associated protein tau) have been identified in approximately 25% of the probands with family histories compatible with an autosomal dominant mode of inheritance (Heutink 1997; Dumanchin 1998; Hutton 1998; Poorkaj 1998). The reported frequency of MAPT gene mutations in familial forms of FTD varies among different populations and studies, ranging from 10% to 50% (Houlden 1999; Morris 2001; Rizzu 1999). The MAPT gene on chromosome 17 (17q21-22) encodes the tau protein, which is widely expressed in adult human tissues including central nervous system. In neurons, tau is mainly present in axons, where it binds to microtubule and promotes their assembly and stabilizes the cytoskeleton. Tau is a major component of neurofibrillary tangles, a pathological characteristic of Alzheimer disease. In addition, the accumulation of filamentous deposits of hyperphosphorylated tau in various brain areas is a hallmark of several neurodegenerative diseases including frontotemporal dementia linked to chromosome 17 (FTDP-17), and other tauopathies such as Pick disease, progressive supranuclear palsy and corticobasal degeneration (Bué 1999).

Six major tau isoforms, resulting from alternative splicing of exons 2, 3 or 10, are expressed in the adult human brain. Exons 2 and 3 encode for a N-terminal insertion of 29 or 58 amino acids respectively, which may play a role in the spacing of microtubules. Alternative splicing of exon 2, or 2+3, results in the absence (0N) or the presence of one (1N) or two (2N) 29 amino-acid domains. Exons 9 to 13 encode the C-terminal region of the protein, containing 3 or 4 imperfectly repeated domains involved in interaction and binding to microtubules, one of which being encoded by exon 10 (E10). Alternative splicing of E10 results in two distinct isoforms containing either 3 (3R, exon 10) or 4 (4R, exon 10+) repeated domains. Splicing of E10 is regulated by at least 8 cis-acting regulatory elements affecting the efficiency of normally weak 5’ and 3’ splice sites (D’Souza 2000 and 2002). The 5’splice sites regulatory sequences enhance (exon splicing enhancer, ESE) or inhibit (exon splicing silencer, ESS)
the use of the E10 5′ splice site (Lee 2001). The binding affinities of the 3R and 4R isoforms for tubulin differ. The 4R isoform binds tubulin with a 3-fold higher affinity and assembles microtubules more efficiently than the 3R isoform (Goedert 1990; Goode 2000). In contrast to adult human brain, in which all six isoforms are found, with slight preponderance of 3R over 4R forms (Goedert 1990), fetal human brain expresses only the 3R isoform. This may explain the greater stability of the cytoskeleton in adult compared to fetal neurons in development.

In addition to E10 alternative splicing, tau is also affected by posttranslational modifications, including glycosylation, glycation and ubiquitination. The major post-translational modification, however, is phosphorylation of the tau protein at at least 25 different sites. Phosphorylation of tau affects its potential to form aggregates, in a positive or a negative manner, depending on the site of phosphorylation (Yen 1999). Hyperphosphorylation of tau at physiological or additional sites, alter its ability to bind to microtubules, increasing the pool of soluble tau that may promotes tau filament assembly.

8.1.4a. MAPT mutations

Thirty-five mutations, including 21 missense mutations, 8 intronic mutations found in the 5′ splice donor site of exon 10, 3 silent mutations and two 3-basepair deletion in positions 280 and 296, have been identified so far in more than 100 families. The mutations are listed in Table 1. Most are clustered in exons 9 to 13 that encode the microtubule-binding domain, or in flanking regions, except for two mutations in exon 1. The P301L and E10+16 are the most frequent mutations (Rosso 2002). Ancestral founder events have been identified for the E10+16 mutation in British, Australian and North American families (Pickering-Brown 2004) and for the N279K in Japanese families (Tsuboi 2002). Phenotypic heterogeneity is observed in families with MAPT gene mutations. Some mutations give rise to variable phenotypes and/or pathologic hallmarks in classical FTD, Pick disease (K257T, G272V, S305N, S320F, Q336R, G389R, K369I) (Spillantini 1998; Ghetti 2000; Murrell 1999; Pickering-Brown 2000 and 2004; Rizzini 2000; Neumann 2001; Rosso 2002; Kobayashi 2004), pallido-ponto-nigral degeneration (N279K, V337M) (Tsuboi 2002; Clark 1998), progressive subcortical gliosis (E10+16) (Petersen 1995; Goedert 1999), progressive supranuclear palsy (R5L, N279K, S305S, ΔN296, E10+16) (Poorkaj 2002; Delisie 1999; Svolieri 2003; Stanford 2000; Wszolek 2001; Pastor 2001; Morris 2003), corticobasal degeneration (N296N, P301S) (Spillantini 2000; Bugiani 1999), dementia with epilepsy (P301S) (Rosso 2003), and tauopathy with respiratory failure (S352L) (Nicholl 2003).
Table 1. Mutations of the MAPT gene and their consequences on the expression and function of the tau protein.

<table>
<thead>
<tr>
<th>Mutations</th>
<th>Exon</th>
<th>Tau isoforms</th>
<th>Pathologic alteration</th>
</tr>
</thead>
<tbody>
<tr>
<td>R5L</td>
<td>1</td>
<td>-</td>
<td>↓ MT assembly, ↑ FF</td>
</tr>
<tr>
<td>R5H</td>
<td>1</td>
<td>-</td>
<td>↓ MT assembly, ↑ FF</td>
</tr>
<tr>
<td>K257T</td>
<td>9</td>
<td>-</td>
<td>↓ MT assembly, ↑ FF</td>
</tr>
<tr>
<td>I260V</td>
<td>9</td>
<td>-</td>
<td>↓ MT assembly, ↑ FF</td>
</tr>
<tr>
<td>L266V</td>
<td>9</td>
<td>-</td>
<td>↓ MT assembly, ↑ FF</td>
</tr>
<tr>
<td>G272V</td>
<td>9</td>
<td>Normal ratio</td>
<td>↓ MT assembly, ↑ FF</td>
</tr>
<tr>
<td>N279K</td>
<td>10</td>
<td>Increase 4R</td>
<td>E10 splicing</td>
</tr>
<tr>
<td>AK280</td>
<td>10</td>
<td>Increase 3R</td>
<td>E10 splicing</td>
</tr>
<tr>
<td>L284L</td>
<td>10</td>
<td>Increase 4R</td>
<td>E10 splicing</td>
</tr>
<tr>
<td>aN296</td>
<td>10</td>
<td>Increase 4R</td>
<td>E10 splicing</td>
</tr>
<tr>
<td>N296H</td>
<td>10</td>
<td>Increase 4R</td>
<td>E10 splicing</td>
</tr>
<tr>
<td>N296N</td>
<td>10</td>
<td>Increase 4R</td>
<td>E10 splicing</td>
</tr>
<tr>
<td>P301L</td>
<td>10</td>
<td>-</td>
<td>↓ MT assembly, ↑ FF</td>
</tr>
<tr>
<td>P301S</td>
<td>10</td>
<td>-</td>
<td>↓ MT assembly, ↑ FF</td>
</tr>
<tr>
<td>S305N</td>
<td>10</td>
<td>Increase 4R</td>
<td>E10 splicing</td>
</tr>
<tr>
<td>S305S</td>
<td>10</td>
<td>Increase 4R</td>
<td>E10 splicing</td>
</tr>
<tr>
<td>IVS10+3</td>
<td>Intron 10</td>
<td>Increase 4R</td>
<td>E10 splicing</td>
</tr>
<tr>
<td>IVS10+11</td>
<td>Intron 10</td>
<td>Increase 4R</td>
<td>E10 splicing</td>
</tr>
<tr>
<td>IVS10+12</td>
<td>Intron 10</td>
<td>Increase 4R</td>
<td>E10 splicing</td>
</tr>
<tr>
<td>IVS10+13</td>
<td>Intron 10</td>
<td>Increase 4R</td>
<td>E10 splicing</td>
</tr>
<tr>
<td>IVS10+14</td>
<td>Intron 10</td>
<td>Increase 4R</td>
<td>E10 splicing</td>
</tr>
<tr>
<td>IVS10+16</td>
<td>Intron 10</td>
<td>Increase 4R</td>
<td>E10 splicing</td>
</tr>
<tr>
<td>IVS10+19</td>
<td>Intron 10</td>
<td>Increase 3R</td>
<td>E10 splicing</td>
</tr>
<tr>
<td>IVS10+29</td>
<td>Intron 10</td>
<td>Increase 3R</td>
<td>E10 splicing</td>
</tr>
<tr>
<td>L315R</td>
<td>11</td>
<td>Normal ratio</td>
<td>↓ MT assembly, No effect on FF</td>
</tr>
<tr>
<td>S320F</td>
<td>11</td>
<td>-</td>
<td>↓ MT assembly, ↑ FF</td>
</tr>
<tr>
<td>Q336R</td>
<td>12</td>
<td>-</td>
<td>↑ MT assembly, ↑ FF</td>
</tr>
<tr>
<td>V337M</td>
<td>12</td>
<td>Normal ratio</td>
<td>↓ MT assembly, ↑ FF</td>
</tr>
<tr>
<td>E342V</td>
<td>12</td>
<td>Increased 4R</td>
<td>↑ MT assembly, ↑ FF</td>
</tr>
<tr>
<td>S352L</td>
<td>12</td>
<td>-</td>
<td>Not available</td>
</tr>
<tr>
<td>K369I</td>
<td>12</td>
<td>-</td>
<td>↓ MT assembly, ↑ FF</td>
</tr>
<tr>
<td>G389R</td>
<td>13</td>
<td>Normal ratio</td>
<td>↓ MT assembly</td>
</tr>
<tr>
<td>R406W</td>
<td>13</td>
<td>Normal ratio</td>
<td>↓ MT assembly</td>
</tr>
</tbody>
</table>

MT: microtubule, FF: filament formation
8.1.4b. Effects of MAPT mutations on tau function

The electrophoretic tau profiles and functional consequences of tau mutations vary according to the type and location of the mutations in the protein (Hong 1998). Missense mutations in constitutively expressed exons affect all six major isoforms and result in neurofibrillary tangles similar to those present in Alzheimer disease (Goedert 1992). These mutations are associated with predominantly neuronal tau pathology. Conversely, mutations that affect the alternatively spliced E10, or its 5’ splice regulatory region alter the ratio of the tau isoforms constituting tangles, resulting in filamentous inclusions resembling those seen in other tauopathies such as progressive supranuclear palsy, corticobasal degeneration and Pick disease. These mutations are associated with both glial and neuronal tau pathology.

Most of the missense mutations identified so far (K257T, I260V, L266V, G272V, N279K, L284L, N296N, N296H, P301L, P301S, S305N, S305S, V337M, E342V, S352L, K369I, G389R, R406W) and two deletions (ΔK280, ΔN296) are localized in the microtubule-binding domain. All intronic mutations and most of the mutations located in exon 10 affect alternative splicing of the exon 10 by altering cis-acting regulatory sequences, changing the ratio of 4R to 3R isoform (Hasegawa 1998). Most of these mutations increase E10 containing mRNA, leading to a preponderance of the 4R isoform. The 5’ splicing site is predicted to form a stem-loop RNA structure, that might regulate the E10 splicing by partially blocking access by the splicing machinery to the splice site. Intrinsic mutations might destabilize this critical stem-loop, facilitating access to and the binding of splicing factors to the splice site, increasing inclusion of exon 10. Three mutations (E10+19, E10+29, ΔK280), however, increase the 3R isoform by disrupting an intron silencer modulator (E10+19) or a splicing enhancer near the 3’ splice site (ΔK280) with consequent exclusion of E10.

Additionally, most missense mutations lead to a partial loss of function by altering the ability of tau protein to bind to tubulin and to promote microtubule assembly, and increasing its ability to aggregate (Hasegawa 1998). Most of the missense mutations are located in the microtubule binding domain and are hypothesized to alter tau-microtubule interactions. In vitro studies using recombinant 4R tau have confirmed that the P301L, P301S, V337M, R406W and ΔK280 mutations significantly reduce the affinity of tau for microtubules.133 G272V, ΔK280, P301L, V337M and R406W mutations reduce the ability of 3R and 4R to polymerize tubulin. Reduced microtubule binding increase the pool of unbound tau which is consequently available for pathological aggregation in neurons, consistent with a toxic gain of function. In vitro aggregation studies with recombinant wild-type and mutant 4R tau (P301L, V337M, R406W) incubated with arachidonic acid or heparin, demonstrated that the missense mutations alter the ability of tau to interact with itself, accelerate tau polymerization and increase the tendency of tau to polymerize into insoluble filaments (Barghorn 2000; Götz 2001).

Animal models have been generated with overexpressed normal tau protein or with a number of different human tau mutations (P301L, P301S, G272V,
8.1.4. Other monogenic forms of FTD

The genetic basis of familial FTD has not yet been elucidated in the 3/4 of cases not caused by mutations in the MAPT gene. Several families with FTD, or FTD with amyotrophic lateral sclerosis are linked to the MAPT locus on chromosome 17 but no mutations have been found in the coding sequence of gene, suggesting variations in non-coding regions or in another that maps close to MAPT (Wilhelmson 2004). In a large family, a second locus has been identified in a 13cM region on chromosome 3, but the responsible gene has not yet been identified (Brown 1995; Gydesen 2002).

8.1.4d. Genetic risk factors

Non-monogenic FTD has been less well studied. Several groups have examined the potential association of FTD with the apolipoprotein E gene, but the results have been contradictory. Initially, Gustafson et al. and Stevens et al. reported a higher frequency of E4 alleles and E4E4 genotypes in patients with FTD than in controls (Gustafson 1997; Stevens 1997). Other studies have indicated that the E2 allele might represent a risk factor for FTD. A recent study confirmed that the E2E2 genotype was overrepresented in a large group of 94 FTD patients and 392 controls, suggesting that patients homozygous for allele E2 are at increased risk for developing FTD (Verpillat 2002). The extended tau H1 haplotype, that covers the entire human tau gene, and the H1H1 genotype were significantly overrepresented in patients with FTD compared with controls with an odds ratio at 1.95, confirming the primary role of tau in FTD (Verpillat 2002). The genotype QQ for the Q7R polymorphism in the saitoxin gene, a novel determinant of the H1 haplotype, was also associated with FTD.

8.1.5. Therapy

No effective therapy for FTD is available at present. Several neurotransmitter systems are altered in the frontal cortex of patients with FTD, and a conservative approach to restore deficient neurotransmission with pharmacologic agents has been proposed. The principal neurotransmitters involved in frontal lobe function are serotonin, catecholamines and acetylcholine. Since cholinergic neurons are not affected in FTD patients, anticholinesterases are not indicated. Decreased serotonin receptor binding has been reported, however, in frontal and temporal cortex of FTD patients, as well as decreased serotonin levels in CSF. The effect of serotoninergic re-uptake inhibitors has, therefore, been evaluated. Fluoxetine, sertraline, and paroxetine...
are reported to reduce signs such as disinhibition, depression, hyperorality and compulsive behaviours (Swartz 1997). Decreased CSF dopamine levels and reduced binding of dopaminergic receptor ligands in the superior frontal cortex have also been described in FTD patients (Frisoni 1994). Evaluations of dopamine agonists have shown that bromocriptine might improve some frontal functions, such as performances of executive functions and perseveration (Imamura 1998). The effect of dopaminergic therapy still need further study (Litván 2001).

Another potential approach, is target the consequences of tau dysfunction or aggregation (Trojanowski 1999). Phosphorylation of tau appears to be critical for its toxicity. Tau phosphorylation, which requires the intervention of several successive kinases in a temporally ordered sequence, has partially identified. It has been shown that the drosophila PAR-1 kinase initiate tau toxicity by phosphorylating tau at S262 and S356. The phosphorylation of S262 and S356 is a prerequisite for the action of downstream kinases (GSK-3, Cdk5) that phosphorylate other sites and generate disease associated phospho-epitopes (Nishimura 2004). Disrupting the phosphorylation process by inactivating the PAR-1 kinase might be expected to reduce tau toxicity. PAR-1 and the other tau kinases may therefore be interesting targets for future therapeutic intervention in tauopathies.

9. ACKNOWLEDGMENTS

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