CHAPTER 9

FRONTOTEMPORAL LOBAR DEGENERATION

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Abstract: Frontotemporal Lobar Degeneration (FTLD) is an heterogeneous neurodegenerative disorder characterized by behaviour and language disturbances, associated with degeneration of the frontal and temporal lobes. Three different clinical presentations have been described, namely behavioural variant Frontotemporal Dementia (bvFTD), Semantic Dementia (SD) and Progressive Non-Fluent Aphasia (PNFA). The associated histopathology includes different neuropathological hallmarks, the most frequent being tau-positive inclusions (FTLD-TAU) or tau-negative and TDP-43 positive inclusions (FTLD-TDP). The majority of familial FTLD cases are caused by mutations within *Microtubule-Associated Protein Tau (MAPT)* gene, leading to FTLD-TAU, or *Progranulin (PGRN)* gene, leading to FTLD-TDP. In the last few years, imaging, biological and genetic biomarkers have been developed, helping in clinical evaluation and diagnostic accuracy. Though current pharmacologic interventions are only symptomatic, recent research argues for possible disease-modifying strategies in the near future.

INTRODUCTION

At the end of the XIX century, Arnold Pick described a series of patients with progressive aphasia, apraxia and behavior changes, associated with severe frontotemporal atrophy.[1,2] Initially, these cases were grouped under the same label of Alzheimer's disease pathology. Thereafter, the identification of the round silver staining inclusions (Pick's bodies) allowed the researchers to characterize the specific hallmark of this entity.[3-5]

By a clinical point of view, patients with behavioural disturbances, deficits of executive functions and language impairment were labeled under the term of Frontotemporal Lobar Degeneration (FTLD).[6] However, at autopsy, Pick's bodies were found only in a subgroup

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of these patients, suggesting that FTLD is characterized by a more heterogeneous histopathology than previously thought.

Different diagnostic criteria have been developed over years, with the attempt to better define the clinical correlates of FTLD neuropathology.[6,7] The first criteria were developed by the Lund and Manchester group in 1994.[8] These criteria permitted a good discrimination between FTLD and Alzheimer's disease,[9] but no hints on the number of clinical features necessary for FTLD diagnosis were defined. In 1998, new diagnostic criteria were published by Neary et al[10] and the three major clinical syndromes were described. Indeed, behavioural variant Frontotemporal Dementia (bvFTD) and two language variants (Progressive Non-Fluent Aphasia, PNFA and Semantic Dementia, SD) were considered.[11] Finally, in 2001 revised clinical criteria were published by McKhann and colleagues.[12] In these criteria, Progressive Supranuclear Palsy (PSP) and Corticobasal syndrome (CBS) were considered under the label of FTLD, as overlapping both clinically and neuropathologically.

EPIDEMIOLOGY

FTLD is considered the second cause of presenile dementia, accounting for 20% of all the cases under the age of 65 years.[13] The disease onset is usually in the sixth decade, but it can be from the third to the ninth decade. In FTLD, the mean age at onset is lower than in Alzheimer's disease and other neurodegenerative dementias.[14,15]

The prevalence of FTLD in population-based studies has varied between 2.7/100,000 inhabitants in the Netherlands,[16] to 15.1/100,000 in subjects aged <65 years in Cambridgeshire, UK.[14] In early-onset cases, the incidence was 3.5/100,000 person-year in the Cambridge study[17] and 3.3/100,000 person-year in the Rochester study.[18]

A population-based study in Northern Italy reported an overall prevalence of 17.6/100,000 inhabitants, with a higher prevalence in patients aged 66-75 (78/100,000 inhabitants).[19] Taken together these data suggest that FTLD is a common cause of early-onset dementia, but it is frequent in advanced age as well.

The estimated median survival is approximately of 6-11 years from symptom onset and 3-4 years from diagnosis.[20] Some studies suggested that in FTLD survival is shorter than that found in Alzheimer's disease.[21] The worse predictor of survival in FTLD is the presence of associated motor neuron disease.

CLINICAL PRESENTATION

bvFTD is the most common clinical presentation, characterized by changes in personality and social conduct (including breaches of interpersonal etiquette and tactlessness). Disturbances could range from inertia, loss of interest in personal affairs and responsibility, to social disinhibition and socially inappropriate behaviors.[9] Distractibility, overactivity, pacing and wandering are common,[22] with relative preservation of memory functions. Perseverations, stereotyped and compulsive behaviors are present,[23] as emotional blunting and loss of insight. Dietary changes typically take the form of overeating and a preference for sweet foods.[24] Sometimes, personality changes have been defined as a "change in self".[25] At onset, language deficits are less common than in other clinical subtypes, but these can arise during disease course. Cognitive deficits occur in the domains of attention, abstraction, planning, problem solving and judgment. Attention and working memory

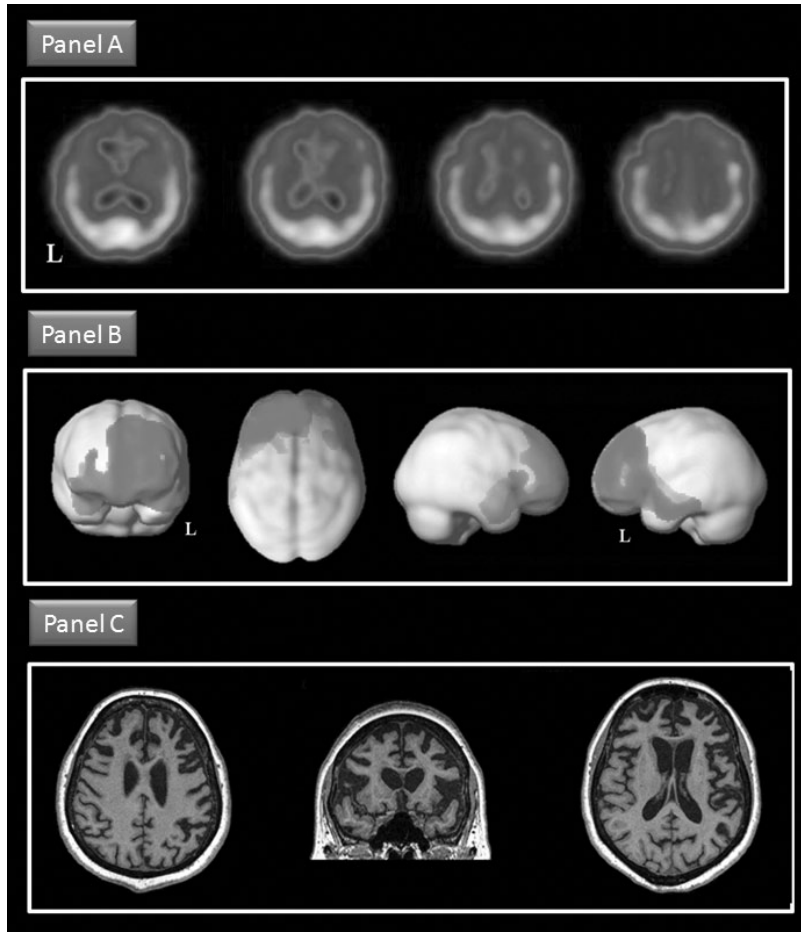

Figure 1. Panel A) Brain Perfusion analisys (*^{99m}Tc-ECD SPECT*) in bvFTD patient. Panel B) single subject Statistical Parametric Mapping analysis on SPECT image (patient vs healthy control group, $P < 0.005$); hypoperfusion pattern in bvFTD patient is highlighted in red. Panel C) MRI atrophy in bvFTD patient. As described in the text, there is a deep and selective fronto-temporal atrophy/hypoperfusion.

may be involved, with a variable preservation of episodic memory. However, memory test performances may be affected, because of patient's frontal disturbances rather than a primary amnesia. In contrast to Alzheimer's disease, at onset visuospatial functions are well preserved.[26] Behavioral disturbances may help to distinguish FTLD from Alzheimer's disease, as in the former lack of concern and insight, presence of repetitive stereotyped behaviors and confabulations are more common.[27] Neuroimaging studies have demonstrated structural (gray matter atrophy) and functional (hypoperfusion and hypometabolism) frontal involvement[28-31] (see Fig. 1). More recently, it has been reported that white matter is affected as well and damage in frontal tracts (superior longitudinal fasciculus) is specific for bvFTD and correlates with behavioral disturbances.[32] The heterogeneous clinical presentation reflects specific brain damage: dorsomedial frontal atrophy correlated with apathy and orbitofrontal atrophy is associated with disinhibited syndrome.[33] Atrophy in medial paralimbic region

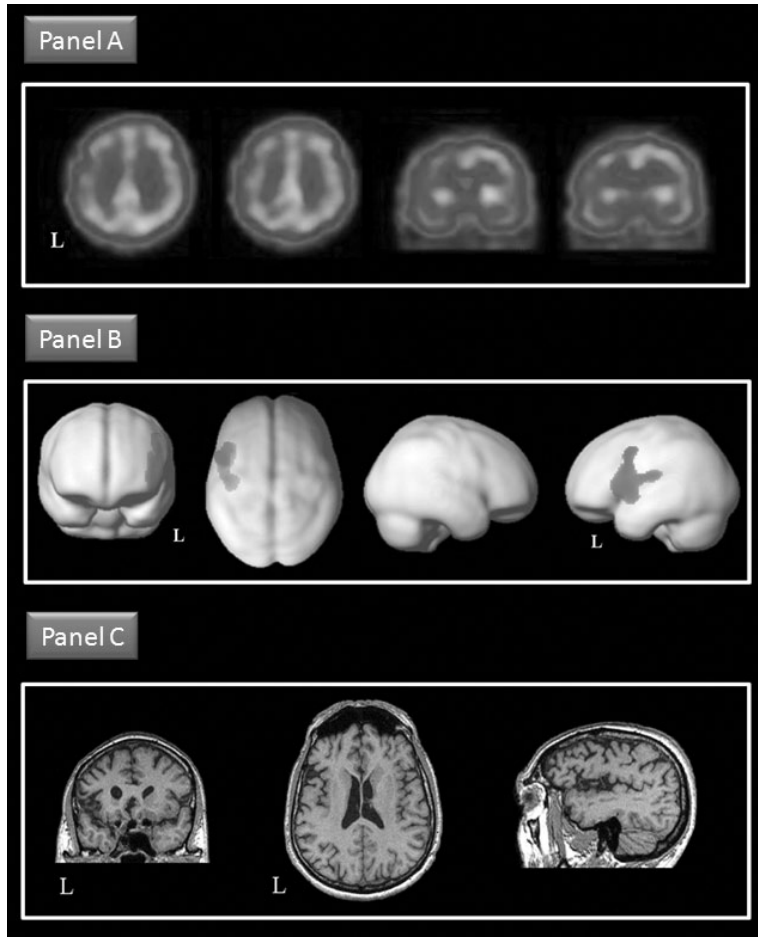

Figure 2. Panel A) Brain Perfusion analisys (*^{99m}Tc-ECD SPECT*) in PNFA patient. Panel B) single subject Statistical Parametric Mapping analysis on SPECT image (patient vs healthy control group, $P < 0.005$); hypoperfusion pattern in PNFA patient is highlighted in red. Panel C) MRI atrophy in PNFA patient. As described in the text, there is a selective left inferior frontal atrophy/hypoperfusion.

(anterior cingulated, orbitofrontal and frontoinsular cortices) help to differentiate FTLD from Alzheimer's disease.[34] Motor neuron disease (MND) can co-occur with any of the FTLD clinical variants, but is more commonly associated with bvFTD.[35]

The second prototypic syndrome, namely PNFA, is a disorder of expressive language with difficulty in initiating speech, slow rate of speech, with phonologic and grammatical errors, word retrieval difficulties, as well as difficulties in reading and writing. The disorder of language occurs in the absence of impairment in other cognitive domains, although behavioral changes may emerge later in the disease course. Neuropsychological evaluation could show impairment in working memory and executive functions, with a substantial preservation of episodic memory and visuospatial ability.[36] Behavioural abnormalities are less severe than in bvFTD and SD.[37] PNFA is characterized by atrophy in left frontal operculum, premotor and supplementary premotor areas and anterior insula[38] (Fig. 2).

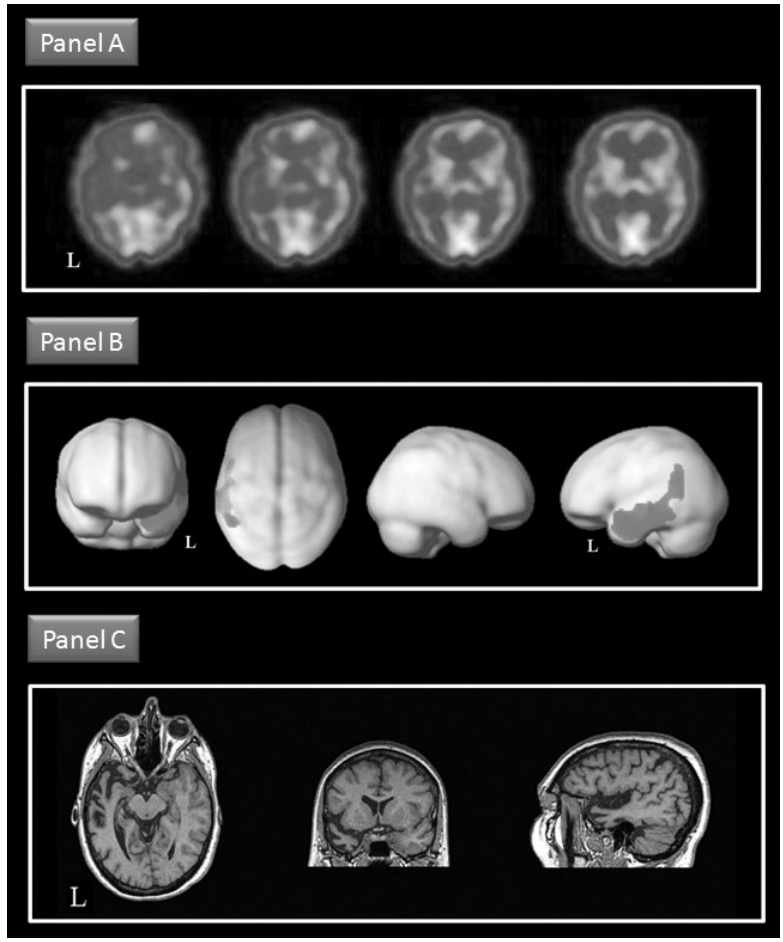

Figure 3. Panel A) Brain Perfusion analisys (*^{99m}Tc-ECD SPECT*) in SD patient. Panel B) single subject Statistical Parametric Mapping analysis on SPECT image (patient vs healthy control group, $P < 0.005$); hypoperfusion pattern in SD patient is highlighted in red. Panel C) MRI atrophy in SD patient. As described in the text, there is a selective left temporal atrophy/hypoperfusion.

SD is characterized by fluent, anomic aphasia and behavioural changes, with asymmetric degeneration of the temporal poles and white matter damage (inferior longitudinal fasciculus)[32] (Fig. 3). Cognitive testing denotes profound semantic loss, with deficit in word comprehension and naming, deficits in face and object recognition; visuospatial ability and episodic memory are well preserved.[10] Primary left-side involvement is associated with progressive loss of semantic knowledge of words, objects and concepts. On the other side, patients with right involvement present with prosopagnosia and behavioral abnormalities.[39,40]

HISTOPATHOLOGY

At autopsy, FTLD patients are characterized by gross atrophy of the frontal and anterior temporal lobes,[41] with relative sparing of posterior brain regions until the most advanced stages of disease.[42] Microscopic examination shows loss of pyramidal neurons and microvacuolar degeneration in layers II and III of the frontal and temporal cortex, with a variable degree of cortical gliosis. White matter shows both axonal and myelin loss and gliosis.[43] Recent advances in neuropathology have defined a new histopathological classification of FTLD, barely overlapping with clinical diagnoses. Mackenzie et al have recently published an update on nosology of FTLD.[44] Virtually all cases of FTLD can be subclassified into the following four major categories, which are based on the presence or the absence of specific inclusion bodies: (i) FTLD with tau inclusions (FTLD-TAU), (ii) FTLD with tau-negative and TDP-43-positive inclusions (FTLD-TDP) and (iii) FTLD with tau/TDP-43 negative and FUS-positive inclusions (FTLD-FUS), (iv) FTLD with positive immunohistochemistry against proteins of the ubiquitin proteasome system (FTLD-UPS).

Tau-Positive FTLD (FTLD-TAU)

FTLD-related tauopathies are classified based on both the morphologic features and the biochemical composition of tau inclusions. Pick's disease, the prototypical tauopathy of FTLD, is characterized by the presence of Pick's bodies, which are solitary, round or oval, argyrophilic inclusions found in the cytoplasm of neurons. In Pick's disease, hyperphosphorylated and aggregated forms of tau accumulate in neurons and, in certain cases, glia.[45] Tau is a complex protein that regulates microtubules dynamics,[46] and six different isoforms resulting from alternative splicing of exons 2, 3 and 10 exist.[47] The splicing-in of exon 10 introduces an extra microtubule-binding domain leading to the so-called four-repeat tau (4R), whereas the splicing-out of exon 10 leads to three-repeat tau (3R). The composition of the different isoforms of tau can be identical to those observed in Alzheimer's disease, with all six alternatively spliced forms present as neurofibrillary tangles. Alternatively, a predominance of three- or four-repeat forms may be present. The histological profile of Pick's disease is defined by predominant 3R tau neuropathology.[48] Anatomically, Pick's bodies are most commonly localized in the dentate gyrus of hippocampus, amygdala and frontal and temporal neocortex.[43] They are detected by Bielschowsky staining.

Less common FTLD-related tauopathies include the argyrophilic grain disease, the sporadic multiple system tauopathy with dementia, the neurofibrillary tangle dementia and the Amyotrophic Lateral Sclerosis (ALS) parkinsonism-dementia complex of Guam.[49]

TAR DNA-Binding Protein 43 (TDP-43)-Positive FTLD (FTLD-TDP)

Tau-negative FTLD pathology has been termed as FTLD tau-negative ubiquitin positive (FTLD-U) for ages.[50] In 2006, the hallmark of a subgroup of FTLD-U cases was identified and TDP-43 protein was found in the vast majority of FTLD-U brains (FTLD-TDP). Up to now, FTLD-TDP represents the most common histological profile observed in FTLD.[51] This protein accumulates in cytoplasm, neuritis and

occasionally it forms intranuclear lentiform inclusions.[52] Phosphorylation of S409/410 residue is a consistent feature of FTLD-TDP.[53] Antibodies against this residue do not stain nuclear TDP-43 in physiological conditions, thus suggesting a pathological role of phosphorylation of this site. TDP-43 is usually ubiquitinated and cleaved (probably by caspase-3[54] to produce C-terminal fragments.[55] The overexpression of these fragments appears to evoke splicing abnormalities, leading to the pathological process.[56] Protein inclusions are found in the dentate gyrus of hippocampus, in layer II of the frontotemporal cortex, in cranial nerve nuclei and in the anterior horn cells of the spinal cord.[49] FTLD-TDP can present with any of the major clinical phenotypes of the FTLD syndrome[57] and, rarely it may lead to clinical diagnosis of Parkinson's disease or Corticobasal syndrome.[58]

TDP-43 pathology is characterized by four different patterns with clinical and genetic correlations, based on the anatomical distribution, morphology and inclusion type. Clinical presentation of Type 1 is primarily bvFTD or PNFA. Type 1 histopathology is associated with progranulin mutations. Type 2 usually presents with sporadic SD, while Type 3 is correlated with FTD-ALS presentation (including familial cases linked to chromosome 9p). Type 4 is correlated with *Valosin Containing protein (VCP)* mutations.[57,59-61]

However, TDP-43 inclusions are also found in patients with sporadic ALS and the mutations have been correlated to inherited and sporadic ALS.[62]

Little is known about the role of TDP-43 in neurodegeneration. The abnormal redistribution of TDP-43 to cytoplasm correlated with a loss-of-function mechanism.[63] In support of this hypothesis, reduction of TDP-43 in mouse models correlated with motor impairment and structural abnormalities of motor neurons.[64] However, many other studies postulated a toxic gain of function mechanism induced by pathological cellular inclusions.[65,66] The pathogenic mechanism associated with TDP-43 proteinopathy is still under investigation, but multiple disease mechanism remains the most probable working hypothesis.

FUS-Positive FTLD (FTLD-FUS)

Five to 20% of FTLD-U cases present a negative staining for TDP-43.[67] Recent advances have shown that the majority of these cases consist of positive staining for the protein fused in sarcoma (FUS).[68] Furthermore, abundant FUS-positive pathology was found in cases previously termed as neuronal cytoplasmic inclusions of basophilic inclusions body disease (BIBD) and in cases of neuronal intermediate filament inclusion disease (NIFID).[44,69] This ubiquitously expressed DNA/RNA binding protein regulates gene expression and translocation of FUS and it leads to sarcoma and hematological malignancies.[70] Mutations within *FUS* gene are associated with familial ALS, while the majority of FTLD-FUS cases do not show any genetic mutation within *FUS*. Clinically, patients with FUS pathology are characterized by very early age at onset, behavioural syndrome and MRI caudate atrophy.[68] The latter has been proposed as a useful clinical predictor of this FTLD subtype.[71] As for TDP-43 proteinopathies, complex pathogenic mechanism (gain and loss of function) is plausible. Several works have suggested that altered nuclear import is a key event in the pathogenesis.[72] Modifications of FUS include phosphorylation and arginine methylation. As in other RNA binding proteins, these interactions are crucial for nuclear-cytoplasmic shuttling.[73]

FTLD with Positive Immunohistochemistry against Proteins of the Ubiquitin Proteasome System (FTLD-UPS)

FTLD-UPS encompasses cases with tau/TDP-43/FUS negative inclusions.[74] FTLD-UPS remains appropriate for familial FTLD linked to chromosome 3, caused by mutation in *CHMP2B* gene.[75,76] It is possible that the inclusions herein detected have a more heterogeneous composition resulting from a defect of endosomal function.[77]

GENETICS

FTLD patients present a high rate of positive family history (up to 40%), with approximately 10% of patients showing an autosomal dominant inheritance pattern.[78] Familial FTLD is more common in patients with bvFTD and FTLD-ALS than in patients with PNFA and SD. In 1994, FTLD was firstly linked to chromosome 17q21-22, defining frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17).[79] In 1998, *Microtuble Associated Protein Tau (MAPT*) gene, encoding for protein tau, was identified as the causal gene in FTDP-17 families with tau-positive histopathology.[80] In 2006, *Progranulin (PGRN*) gene mutations were identified in FTDP-17 families with tau-negative histopathology.[81] *MAPT* and *PGRN* mutations account for the majority of familial FTLD (http://www.molgen.ua.ac.be/FTDMutations).

FTLD Associated with *MAPT* Gene Mutations

The microtubule-associated protein tau in neurons binds to axonal microtubules, promoting microtubule assembly and it is involved in stabilization and in signal transduction. Two different types of mutations have been described, either exonic (which lead to aminoacid change) or intronic (which disturb the regulation of the alternative splicing). As in other proteinopathies, mutations may lead to loss (decrease) of function, with decreased binding affinity to microtubules (and consequent deficit in axonal transport). On the other side, a toxic gain-of function mechanism can be represented by an increased self aggregation into toxic filamentous inclusions. These mechanisms are not mutually exclusive and often act synergistically. As stated, many *MAPT* mutations are located in or adjacent to the alternatively spliced exon 10, altering the normal 1:1 ratio between 3R and 4R isoforms in favour to 4R.[82] *MAPT* mutations are characterised by a disease onset between the ages of 40 and 60 years (mean 55) and by a wide spectrum of clinical phenotypes, i.e., bvFTD, SD, PNFA, CBD, PSP and even ALS.[84]

Furthermore, *MAPT* haplotype, i.e., H1 and H2, can modify the risk for developing a tauopathy and can modulate disease phenotype. H1/H1 haplotype has been associated with PSP and CBS.[85-89]

FTLD Associated with *PGRN* Gene Mutations

Progranulin is a secreted growth factor with a wide range of functions (inflammation, tumor growth in nonbrain tissue, promotion of neural survival, stimulation of neuritic outgrowth).[90-92] It is secreted as a precursor protein.[93] Mutations (nonsense or missense) are found in all *PGRN* exons and lead to the loss of at least 50% of functional *PGRN*, suggesting an haploinsufficiency mechanism.[94,95] In patients with *PGRN* mutations,

expression pattern of many genes in the frontal cortex are altered, compared to controls.[96] Compared with *MAPT*, *PGRN* mutations are associated with more variable age at onset (range 35-89 years, mean 60 years) and penetrance (estimated at only 50% by age 60 years and 90% by age 70 years).[97] *PGRN* gene mutations accounted for 5%-10% of sporadic FTLD cases and for 20%-25% of the familial ones.[98-100] However, in Europe a lower prevalence was reported.[101] Clinical presentation is heterogeneous: 20-25% of patients present with PNFA, but also bvFTD and CBS are common clinical phenotypes. In some cases, clinical diagnosis of Alzheimer's disease has been postulated.[102] Parkinsonism may be the leading feature, whereas motor neuron disease is uncommon.[103]

Rare Mutations

Mutations in the *CHMP2B* gene were found only in a single Danish family. CHMP2B is part of the endosomal complex (ESCRTIII) involved in endosomal/lysosomal system.[103] Cases of myopathy with succeeding development of FTLD were found to be associated with mutations in the *VCP* gene.[104] *VCP* is an adenosine triphosphatase that is involved in protein degradation in the endoplasmic reticulum. *VCP* mutation carriers show variable penetrance and phenotypic heterogeneity, with myopathy (frequently inclusion body myositis) in the most of cases, while FTLD and Paget's disease occur in fewer than 50%.[105] Mutations in *TARDP* gene and *FUS* gene are associated with familial ALS and seldom with FTLD.[106-111]

International genome-wide association studies are underway with the attempt to identify additional causative and risk-modifying genes.[112] As initial finding, an association with locus 9p13.2-21.3 has been consistently identified in patients with clinical presentation ranging from FTLD to ALS or a combined phenotype.[113] Another genome wide-scan has shown an association between FTLD-TDP and variants in *TMEM106B*.[114]

TREATMENT

No specific treatment is currently available.[115] Neurochemical[116] and functional PET[117] studies have demonstrated impairment of serotonin metabolism. Furthermore, many of the behavioural symptoms of FTLD (depression, compulsions, disinhibition) respond to selective serotonin reuptake inhibitors (SSRI). Different clinical trials have been performed with SSRIs, but different biases limited the obtained results, i.e., small sample size, absence of placebo group, short-term follow-up. However, Huey and collaborators have published a meta-analisys suggesting that the use of serotoninergic drugs in FTLD is associated with a significant reduction of behavioral disturbances.[118]

In clinical practice SSRI are often prescribed as first-line drugs for behavioural symptoms in FTLD. Second-line therapy (in patients that are refractory to SSRI and only in selected cases as first choice) may be represented by atypical antipsychotics.[119] However, extrapyramidal adverse effects and the reported increase mortality risk in the elderly represent important red flags to keep in mind.[120] From this perspective, quetiapine is preferred for its relatively low dopamine D_2 receptor antagonism. Acetylcholinesterase inhibitors, commonly used in Alzheimer's disease, have been tested in FTLD patients; however, no study has shown a cholinergic deficit in FTLD.[121,122] Memantine is a noncompetitive NMDA antagonist, used in Alzheimer's disease. A case series has shown improvement of behavioral disturbances in FTLD as well.[123] Several clinical trials are currently in progress in FTLD (www.clinicaltrials.gov).

CONCLUSION

FTLD is challenging not only for clinicians, that face up every day with the management of the disease, but also for researchers, as actors in disentangling phatogenic and molecular basis leading to neurodegeneration. As in other neurodegenerative diseases, clinical and research perspectives represent the two faces of the same coin. The progressive knowledge of the genetic and pathological bases of FTLD has allowed us to define new type of biomarkers to trace the disease[124,125] and to speculate about new therapeutic targets.[126] Nevertheless, the precise definition of the underlying phatogenetic mechanisms, for setting pharmacological targets and disease-modifying drugs and a world-wide collaborative strategy to recruit a large cohort of patients to demonstrate treatment effect in FTLD, are mandatory.[127]

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