Review

Frontotemporal dementia and related syndromes: a review

S. LUZZI, S. BALDINELLI

Department of Experimental and Clinical Medicine, Polytechnic University of Marche, Ancona, Italy

SUMMARY: *Frontotemporal lobar degeneration is a clinically, pathologically and genetically heterogeneous group of disorders characterized by frontal and temporal lobes atrophy. Three major clinical syndromes are described: behavioural variant frontotemporal dementia, progressive non-fluent aphasia and semantic dementia. Patients with behavioural variant frontotemporal dementia present with changes in personality and behaviour such as disinhibition, apathy, loss of sympathy and empathy, compulsive behaviours, altered eating and drinking with sweet preference, hyperphagia and alcohol abuse. Neuroimaging shows frontal atrophy, hypometabolism and hypoperfusion. Semantic dementia is characterized by a prominent breakdown of semantic knowledge with fluent aphasia, single word comprehension deficit, associative agnosia and prosopoagnosia. Asymmetrical degeneration of the anterior temporal lobes is found. Patients with left-sided semantic dementia present with progressive fluent aphasia while patients with right-side atrophy usually have problems to recognize objects or familiar/famous persons. Patients with PNFA show effortful speech, impaired production with agrammatism and relatively preserved comprehension. PNFA is associated with atrophy, hypometabolism and hypoperfusion of the left perisylvian area. Overlap between the syndromes can occur, particularly later in the course. There is considerable heterogeneity in clinical presentations. Frontotemporal lobar degeneration may present with atypical parkinsonism such as corticobasal syndrome or progressive supranuclear palsy syndrome. Association with motor neurone disease is found. In the absence of definitive biomarkers, the diagnosis is dependent on clinical symptoms. Frontotemporal lobar degeneration is a pathologically heterogeneous spectrum of disorders. Three main histologies are described, involving tau, TDP-43 and FUS proteins. Principal gene mutations are found in the MAPT, GRN and C9orf72 genes. There is no available etiological therapy for frontotemporal lobar degeneration; symptomatic drugs and nonpharmacological intervention can help in management of symptoms.*

KEY WORDS: *Corticobasal syndrome, Frontotemporal dementia, Non fluent aphasia, Progressive aphasia, Progressive supranuclear palsy, Semantic dementia.*

INTRODUCTION

Frontotemporal dementia is an "umbrella" term that includes different clinical phenotypes due to FTLD[41]. The prototypic clinical picture is characterized by profound alteration in personality with behavioural changes associated to a dysexecutive syndrome that nowadays constitutes the bvFTD. Two clinical variants pertain to the domain of language. Semantic dementia is characterized by impairment of the semantic system with progressive aphasia and associative prosopoagnosia. Nonfluent progressive aphasia is characterized by a prominent non fluent aphasia with alteration of verbal production (anomias,

Correspondence: Prof.ssa Simona Luzzi, Dipartimento di Medicina Sperimentale e Clinica, Università Politecnica delle Marche, via Tronto 10/A, 60126 Ancona (AN), Italy, phone: +39-(0)71-5966560, e-mail: s.luzzi@univpm.it
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LIST OF ACRONYMS AND ABBREVIATIONS: **AD** = Alzheiemer's Disease; **ALS** = Amyotrophic Lateral Sclerosis; **bvFTD** = behavioral variant of FrontoTemporal Dementia; **bvFTD-PS** = behavioral variant of FrontoTemporal Dementia phenocopy syndrome; **CBS** = Corticobasal Syndrome; **CHMP2B** = CHarged Multivesicular body Protein 2B; **CSF** = CerebroSpinal Fluid; **EEG** = ElectroEncephaloGram; **FDG-PET** = FluoroDeoxyGlucose Positron Emission Tomography; **FTD** = frontotemporal dementia; **FTLD**= FrontoTemporal Lobar Degeneration; **FUS** = Fused in Sarcoma; **LBD** = Lewy Body Dementia; **lvPPA** = logopenic variant of Primary Progressive Aphasia; **MAPT** = Microtubule-Associated Protein Tau; **MND** = Motor Neuron Disease; **MRI** = Magnetic Resonance Imaging; **NFPA** = Nonfluent Progressive Aphasia; **nfvPPA** = non-fluent variant of Primary Progressive Aphasia; **PPA** = Primary Progressive Aphasia; **PRGN** = progranulin; **PSP** = Progressive Supranuclear Palsy; **SD** = Semantic Dementia; **svPPA** = semantic variant of Primary Progressive Aphasia; **TARDBP** = TAR DNA-binding protein; **TDP-43** = TAR DNA-binding protein 43; **VCP** = Valosin-Containing Protein.

phonological parahasias, agrammatism) and relatively spared comprehension. FTLD has a broad spectrum of clinical syndromes that include among the most frequent syndromes the corticobasal syndrome and progressive supranuclear palsy[1,3]. Association with motoneuron disorder is present[4].

Accurate diagnosis of patients in life is crucial, both on clinical and scientific grounds. From a clinical point of view it helps the patient and his caregiver to know the prognosis of the disease and it is of importance for optimal clinical care and management. From a scientific point of view it is crucial for clinical trials and genetic studies[14].

Distinct cognitive/behavioural syndromes reflect different topographical localization of pathology[45].

There is growing evidence that a comprehensive analysis of patients' clinical

history, neuropsychological profile, together with a full neurological examination, lead to a high degree of confidence in clinical diagnosis[45,47].

The present review aims to focus on the clinical spectrum of FTD to give a brief guide to the clinician to suspect and recognize FTD syndromes in the daily clinical routine.

Other aspects - epidemiology, genetics, pathology - will be briefly summarized.

□ HISTORICAL BACKGROUND

The first description of patients affected by FTD came from Arnold Pick[2] who described a series of subjects whose psychological and cognitive deficits were associated with a focal atrophy of the frontal and temporal lobes. After Pick description for most part of the last century focal atrophies included FTD have received little attention from neurologists, neuropsychologist and pathologists. The renewed attention came from the Manchester Group[41]. In 1992 J. Snowden described a clinical syndrome characterized by progressive fluent aphasia with alteration of semantics and loss of word meaning that she named "semantic dementia"[42].

The first diagnostic criteria for FTD have been formulated by the Lund and Manchester groups (the "Lund-Manchester criteria"[29,49]). Three clinical syndromes were identified and criteria for each syndrome were provided: frontemporal dementia characterized by prominent behavioural symptoms, semantic dementia characterized by semantic memory breakdown and primary nonfluet aphasia characterized by altered language production. Recently, the International Behaviouaral Variant FTD Criteria Consortium developed revised guidelines for the diagnosis of bvFTD[35]. The two language variants have been reclassified within the primary progressive aphasias where semantic dementia constitutes the svPPA and the NFPA constitutes the "nonfluet variant" of PPA[10].

□ EPIDEMIOLOGY

Frontotemporal lobe degeneration is considered the third most common cause of dementia, after Alzheimer's disease and dementia with Lewy bodies. Frontotemporal lobe degeneration incidence is estimated between 1.61 and 4.1 cases per 100.000 people/year and prevalence about 10.8/100.000 people, with the highest prevalence reached between 65 and 69 years of age[15,30].

Clinic-based studies in dementia hypothesise that FTLD is responsible of about 5% of all cases of degenerative cognitive impairment, in particular presenile dementia.

Frontotemporal lobe degeneration is the most common cause of dementia of degenerative origin below 65 years of age, despite in the literature have been described some cases with age of onset included between 30 and 90 years.

Frontotemporal lobe degeneration mean age at onset is about 60 years[15].

Among all dementias, FTLD is the form with the most rapid clinical progression: the time between cognitive symptoms onset and death is variable from a minimum of 6 years and a maximum of 10 years approximately. In particular, the fastest progression has been documented in the behavioural variant of frontotemporal dementia[15].
In frontotemporal lobar degeneration there are no sex differences.
bvFTD is the most common variant, comprising about half of patients. Within the progressive primary aphasias the non-fluent variant is the most frequent[15].

□ BEHAVIOURAL VARIANT OF FRONTOTEMPORAL DEMENTIA

❐ Clinical features

The behavioural variant is characterized by personality changes and alteration in personal and social behaviour. The onset of symptoms is usually insidious. Loss of social awareness and insight is quite common and it is reported by the patient' relatives as a "reduction of courtesy" or "loss of manners". The patient is often referred as "less polite" with visitors and commits false steps in social life without concern. Relatives usually describe the patients as "instinctive", "primitive" as they notice that the patient progressively tends to "obey to instinctual behaviour" avoiding to respect the social context[32].
Changes are typically noticed in the personal hygiene. The patients avoid contact with water or avoid to change their clothes and do not show interest in their physical appearance[49].
Dressing is usually reported as bizarre (winter clothes during the summer or vice versa). Women may show alteration in applying make-up (they can stop to apply make-up or by contrast can use garish make-up); details in dressing are usually omitted (shoes unlaced, fasteners unclosed, blouses unbuttoned)[41].
Altered eating and drinking are very common. Patients may over-eat with tendency to eat sweet foods. Typically the relatives notice that the patient has lost the capacity to "stop eating" and it is frequently reported that the patient can eat huge amount of food (cakes, biscuits, piece of butter etc). Selective food fads can be present. Less frequent is the tendency to eat inedible objects or fluids (e.g. soap) often due to the presence of semantic breakdown (the patient mistakes a white fluid for something edible such as milk)[33].
Loss of empathy or sympathy is very frequent as well. Affective symptoms vary from fatuous jocularity to emotional indifference and shallowness. The patients can be described by relatives as "emotionless" and they do not show interest for autobiographical events or social events highly emotive. By contrast, they can be "over-emotive" and show an inappropriate and exaggerate emotional reaction[34,46].
Psychosis is not very frequent in bvFTD phenotype. A powerful association between C9ORF72 mutations and psychosis is reported. In these patients behavioural characteristics are qualitatively distinct with presence of with paranoid, deluded or irrational thinking[16,44].
Sphincter control may be altered from the early stage with not criticised incontinence. Sexual alterations can be present as well, even they are not very frequent. The patients can show increased sexual demand to the partner as part of their behavioural disinhibition or loss of libido and sexual indifference (more frequent in apatethic patients)[41].
Motor behaviour varies from akinesia in apatethic patients (they usually tend to sit on a chair or on the sofa without any movement) to wandering behaviour or presence of repetitive movements[41]. Perseverations and behavioural stereotypies can take a variety of forms, from simple repetitive movements (e.g. rubbing hands) to obsessive-compulsive behaviour with rituals and can assume the form of utilization behaviour. In this last case the patient's attention is captured by objects within his reach that are grasped by the patient and used (e.g. if a bottle of water is on the table next to the patient, he can picks up and drinks from the bottle several times). This un-controlled behaviour can sometime be responsible of over-eating (when the food is in front of the patient he will eat the food until t is not finished)[33,34,41].
Even if the patient does not show primary language deficits the quality of speech is altered. Usually economy of speech is frequent especially in the moderate and severe stages (within the so called "akinetic mutism"). Typically the patient does not initiate conversation and can avoid to answer to the questions of the examiner. Laconic speech is frequent with minimal sentences with a single or few words ("yes", "no" "I don't know"). Echolalia can be present ("How are you?" -"How am I?"; "Where are you from?" -"Where am I from?"). Verbal stereo-

typies are frequently noted and are part of a stereotyped behaviour[35,41,49].

❒ Neurology

bvFTD patients are typically physically well and they do not show neurological signs. In some cases, clinical sign of striatal involvement can be present with akinetic extrapyramidal syndrome. Ataxia is not present. Early primitive reflexes (e.g. grasping, sucking etc.) can be present. Incontinence can be an early sign; typically the patient does not criticize incontinence[35,41].

❒ Neuropsychology

Frontal-dysexecutive syndrome is invariably present in bvFTD. Anyway, especially in the early stage an accurate and detailed evaluation of cognitive functions, in particular the ones pertaining to the frontal lobe, should be carried out, because a very mild bvFTD patient could not show problems in most domains and not invariably all executive functions could be impaired. In the more advanced stages the dysexecutive syndrome with poor attention, abstraction, planning and verification of activities can be responsible of poor performance in several cognitive domains such as memory, calculation, spatial skills, language. Neuropsychological examination should be carried out in these patients by an expert neuropsychologist to avoid judgement bias (very mild FTD with subtle frontal syndrome can be interpreted as normal subjects, while moderate-severe FTD patients can be interpreted as Alzheimer's disease cause of the overall bad performance in several tasks)[14,29,35,41,49].
The examination of "quality" of errors committed and the patient's behaviour during the cognitive examination can be of help (perseverations, stereotypies, concreteness of thought, absence of mental effort, wandering or utilization behaviour etc.)[5].

❒ Investigations

Neuroimaging can help clinicians in making differential diagnosis. MRI scan shows bilateral frontal atrophy with possible involvement of anterior temporal lobes. Usually, posterior cortex is spared.
MRI scan can also contribute to exclude other potential causes of frontal lobe syndrome such as brain tumours, vascular encephalopathy, normal pressure hydrocephalus[7].
FDG-PET may be more sensitive than MRI in the early stages of disease and reveals a decrease metabolism in frontal, anterior cingulate and anterior temporal regions[7].
EEG is normal in bvFTD[29,41,49].
CSF examination may reveal high levels of tau and phospho-tau with beta amyloid in the normal range[39].
Laboratory exams can help to exclude hypothyroidism, syphilis, cobalamine deficiency.

❒ Differential diagnosis

Within the chapter of neurodegenerative brain diseases differential diagnosis includes Alzheimer's disease and less frequently Lewy body dementia[18,38,45].
Memory loss constitutes the prototypical presentation of Alzheimer's disease. Even FTD patients can be described by their relatives as "forgetful". Anyway, memory problem is not the dominating feature and it is usually reported to vary according the different contexts and situations. The "frontal variant" of Alzheimer's disease may be difficult to distinguish from FTD. Usually, frontal syndrome is present from the early stages in patients with familiar AD. In these cases a deep neuropsychological examination together with neuroimaging and biomarkers can help in differential diagnosis[38,41,45].
Clinical presentation of Lewy body dementia is usually very different from FTD and the presence of cognitive decline, together with extrapiramidal signs, fluctuation of symptoms, delusions and hallucinations can orient toward LBD. Hallucinations have been described also in FTD and when present can be confounding. Hallucinations are reported to be present in patients carrying C9ORF72 mutation. Cognitive assessment can help in differential diagnosis. In LBD neuropsychological evaluation reveals visuoperceptual and spatial prominent alterations (usually absent in FTD) together with a dysexecutive syndrome and a variable and usually mild involvement of memory[38,41].
bvFTD can start with indiscriminate over-drinking leading the clinician to impute the cognitive symptoms to excessive alcohol intake. Anyway, a careful history can contribute to rule out alcoholism. Even if frontal lobe syndrome and amnesia are

typical of both patients suffering from chronic alcoholism and from Wernicke-Korsakoff symdrome, patients with FTD do not show the classical neurological complications (e.g. cerebellar syndrome, peripheral neuropathy), neither shows the systemic effects (e.g. epatopathy)[41].

The behavioural alterations, with apathy, personality changes, obsessive compulsive behaviour, can be interpreted as part of a psychic disorder.

Especially in the early stage, the bvFTD patient can perform well neuropsychological tests and this can reinforce the diagnosis of "non-organic" disorder. Furthermore, the presence of familiar history (presence of "psychiatric disorders" in other family members with institutionalisation) can reinforce the idea of a psychic disorder. In the clinical routine it is quite common that bvFTD are referred to a memory clinic from psychiatrists after several pharmacological attempts without clinical benefit[18].

Traumatic encephalopathy frequently leads to damage of the frontal lobes and behavioural alterations can be persistent. Anyway, the temporal coincidence with the head trauma and development of behavioural symptoms, together with the patient's follow-up (absence of progressive decline of performance) can help in differential diagnosis[41].

Syphilis can mimic the presence of a bvFTD because often the patient tends to manifest behavioural problems such as disinhibition, hyperphagia, wandering behaviour.

Within the differential diagnosis of bvFTD the clinician should consider the bvFTD-PS. This is a well-documented syndrome in which the patient who manifests typical signs and symptoms of bvFTD do not show clear biomarker evidence of FTLD. These patients do not clearly demonstrate progressive clinical deterioration[17]. Usually these patients suffer from a psychiatric disorder. Anyway, very slowly progressive forms of bvFTD, with disease duration upwards of 20 years have been described[18,48].

☐ SEMANTIC DEMENTIA/ SEMANTIC VARIANT OF PRIMARY PROGRESSIVE APHASIA

❐ Clinical features

Semantic dementia is one of the two clinical variants that impair language[13,41,49]. Although SD is currently reclassified within the primary progressive aphasias, the language disorder is only one of the clinical equivalents of the disease that primarily concerns an alteration of the semantic system. Therefore, if it is true that in most cases the patient manifests a language disorder, it does not represent the only cognitive alteration and often the patients may exhibit an associative prosopagnosia.

SD is more properly the clinical correlate of an alteration of the semantic system, a wide and complex brain network that stores and processes all aspects relative to word knowledge[41]. The semantic system is mainly localized within the temporal cortex (temporal poles and middle and inferior temporal gyris) and because the degenerative process is confined to these regions of the brain, the clinical syndrome pertains to a multimodal breakdown of meaning. Left temporal cortex is mainly implicated in linguistic aspects of word knowledge, while the non verbal equivalents are mainly processed by the right temporal lobe. It follows that, depending on the left or right prevalence of the degenerative process, the patient can manifest primarily language disorders or an associative agnosia and prosopagnosia, respectively[8,19].

The designation of semantic variant of primary progressive aphasia reflects the predominance of the language problems that are apparent to the clinician, as the alterations of language are easily detected by the patient's family and by the clinician during the visit[13,41].

However, the disorder is usually not confined only to the verbal domain and problems in recognise objects and faces are often present[8,19].

Language alterations are the hallmark features of the svPPA and they are usually characterized by anomies and semantic paraphasias. The patient substitutes a semantically related alternative for the correct word, i.e. pertaining to the same category of the target word ("cat" instead of "dog", "fork" instead of "spoon"). Phonemic paraphasies (sound based errors) are never reported. Word comprehension is altered, especially in the moderate to severe stages of the disease. Language is fluent and often garrulous without detectable syntactic errors[13,36,41,49].

Loss of meaning can involve objects, faces, and voices. The patient can therefore manifest problems in recognizing objects and familiar faces or famous persons[8,13,19,41].

Behavioural problems are not very frequent. When present, alterations in behaviour are qualitatively distinct from the behavioural changes of bvFTD with

prevalence of compulsive and stereotypic traits, loss of awareness of danger, preference for fixed routine (e.g. clock-watching), inappropriate preoccupations. Parsimony is frequent and the patient avoids spend money and tends to limit expenses by buying low-cost products (food, clothes, shoes, etc.). Unlike the bvFTD where there is indiscriminate hyperphagia, patients with SD tend to eat a narrow range of foods[13,41,49].

❒ Neurology

Neurological examination is normal. Articulation and prosody are intact. Only in the advanced stages of the disease can appear primitive reflexes, frontal signs or akinetic extrapiramidal syndrome[41].

❒ Neuropsychology

Neuropsychological examination can be of extreme value to corroborate the diagnosis of semantic dementia. Neuropsychological findings are highly characteristic and uniform and consist of an almost selective impairment of semantic tasks that involve both the verbal and non verbal aspects. Language is fluent and effortless. Some pauses can be due to anomies. Semantic paraphasies are often present and the patient tends to use broad generic terms (e.g. "thing"). Semantic fluency is very poor[36]). Syntax is preserved. No phonological errors are detected. Tasks exploring comprehension reveal altered single word comprehension, with a characteristic "word frequency effect", where common words (high frequency words - e.g. "cat") are better understood than unusual words (low-frequency words - e.g. "penguin"). Reading and writing are fluent, but regularization errors are often present due to surface dyslexia and surface dysgraphia respectively[14,41,49].
Object recognition difficulties are often present in SD. Typically the patient tend to recognize better common objects used in the day-to-day life than unusual objects. For example, the patient can recognize and use his shaving razor without problems, but is unable to recognize a new razor purchased at the supermarket. Similarly, the patient may not recognize known faces or famous personalities[8,19]. Usually the faces of family members (high frequency stimuli) are recognized until the advanced stages of the disease.
Autobiographical memory is preserved and patients have no difficulties to remember facts, appointments and episodes of their life[41,47].
Calculation and reckon change is usually preserved[21].
They do not show neither spatial nor visuoperceptual problems and they do not get lost in the environment. They can drive on known routes until the late stages of the disease without get lost and the main problem they can manifest is the inability to recognize road signs[20].

❒ Investigations

Traditional neuroimaging (CT scan or MRI scan) is usually helpful in diagnosis because it shows a selective atrophy of temporal lobes extending mainly to the temporal pole and inferior and middle convolutions. Atrophy is clearly asymmetric in the two hemispheres. The degree of asymmetry is usually proportional to the phenotypic expression of the disease, with a prevalent language disturbance in predominantly left atrophy and conversely a prominent associative agnosia and prosopoagnosia in patients with predominantly right brain atrophy[29,35,49].
FDG-PET show hypometabolisms in the anterior temporal lobes and can reveal alterations in the mild stage of the disease when the mild atrophy is not necessarily detectable by the structural brain imaging[7].
EEG is normal. CSF examination may reveal high titres of tau and phospho-tau with normal levels of beta-amyloid[39].

❒ Differential diagnosis

In the first instance SD should be differentiated from the other two variants of primary progressive aphasia(10).
Usually an expert neuropsychologist in language disorders can help the clinician because the neuropsychological pattern of SD is characteristic and the features of the language disorder are easily differentiated from the pattern of NFPA and lvPPA. The main aspects that allow to make the diagnosis are the presence of semantic breakdown without neither orthographic nor syntactic errors and single-word comprehension deficit with a spared verbal working memory[10].
Semantic dementia should also be differentiated from

Alzheimer's disease. The absence of prominent amnestic syndrome, the absence of visuospatial symptoms makes reasonably easy the diagnosis[15,41].
A very similar clinical picture to that of semantic dementia is appreciable in herpetic encephalitis that is characterized by the presence of a fluent aphasia with main impairment of the lexico-semantic level. Anyway, the temporal trend (abrupt or subacute onset of symptoms in herpetic encephalitis) and the clinical spectrum of related symptoms and signs (fever, headache, etc.) allow to rule out this disease without problems[41]. In rare cases Creutzfeld-Jakob disease can contemplate the presence of aphasic syndrome but the temporal trend and constellation of other neurological signs (cerebellar syndrome, cortical blindness, etc.) helps the clinician to make the correct diagnosis.
SD in one of the clinical syndrome more difficult to appreciate and recognize especially in the mild stage of disease, where other cognitive domains except semantics are spared and the patient is reported to be completely autonomous in the daily routine. Usually the patient is dismissed as "normal" or may be misdiagnosed as suffering from psychic disorder[41].

□ PROGRESSIVE NON-FLUENT APHASIA/ NON-FLUENT VARIANT OF PRIMARY PROGRESSIVE APHASIA

❒ Clinical features

PNFA, now relabelled as the non-fluent variant of PPA, is characterized by a selective disorder of language. Patients usually show a long history of slow and insidious trouble in speech production in contrast to spared speech comprehension. The patient come to the attention of the neurologist because notes errors both in oral and written language. Errors in writing may precede alteration in speech production of several years[11,12,26]. Typically the patient has good insight and can describe his symptoms carefully. Phonemic paraphasias are frequent and the patient refers that he makes errors in "pronunciation". Vowels and consonant may be altered ("car" → "bar") with deletions, substitution, insertions, and duplications. At the beginning of the disease language may have a stuttering quality due to multiple attempts to pronounce the right word and try to correct the paraphasias. During the course of the disease oral and written language becomes more and more telegraphic and assumes the form of "agrammatism" where all functions, such as prepositions, articles, adverbs are omitted[11,12,29,41,49].
Speech apraxia may be present and is usually mistaken for dysartria. Speech apraxia reveals its linguistic (and not merely articulatory) form in relation to the type of speech output of the patient. Typically speech apraxia varies as a function of the orthographic complexity of the word pronounced and may "disappear" in recitation of verbal series[10,11,12,41].
Other cognitive functions are usually spared in the mild to moderate stage and both patient and relatives do not refer problem in day-to-day memory or spatial orientation. Usually frank behavioural symptoms are absent, even they can arise during the course of the disease. Patients can be relatively independent in their routine functioning until the severe stages of the disease[10,41,49].

❒ Neurology

Usually neurological examination is within the normal range. A mild to moderate rigid-akinetic extrapyramidal syndrome may be present[41,49].

❒ Neuropsychology

Neuropsychological examination reveals a selective impairment of language in absence of a diffuse cognitive decline. Language is agrammatic and hesitant. Phonemic errors can be detected in oral and written language. Repetition is altered as well. Lexical comprehension is relatively preserved. Memory is usually normal. Non verbal memory should be preferred as the performance in verbal memory tests is invariably altered cause of the language problem. Episodic memory is normal. Visuoperception and spatial skills are preserved as well[10,12].
Mild to moderate (according to the stage) dysexecutive syndrome can be present[12].

❒ Investigations

Structural neuroimaging (CT scan or MRI scan) reveals asymmetric left perisylvian atrophy and conversely FDG-PET shows hypometabolism in the same regions[7,11,12].
EEG is usually normal[10,49]. CSF examination shows similar findings of bvFTD[39].

❒ Differential diagnosis

The differential diagnosis of NFPA primarily relates to other forms of progressive aphasia[10].
Detailed language assessment provides considerable help to the clinician[10,12].
NFPA is characterized by agrammatism, presence of speech apraxia and phonological paraphasias. Semantic domain is usually spared and single word comprehension is within the normal range.
NFPA is now counted among the phenotypic variant of corticobasal degeneration (*see below*). The presence of neurological sign (often extrapiramidal signs such as limb apraxia, unbalance etc) can be of help in the differential diagnosis[1,3].
The cognitive findings of NFPA are very similar to the Broca's aphasia a common presentation of left anterior strokes. Anyway the abrupt onset of symptoms typical of stroke allows to make a differential diagnosis without problems[41].

□ OVERLAPPING SYNDROMES

Phenotypic presentation of the frontotemporal lobar degeneration is heterogeneous.
In several cases patients demonstrate variable mixtures of symptoms and sign pertaining to progressive supranuclear palsy syndrome, corticobasal syndrome and motor neuron disease[1,3].
The association between FTD and MND is well established[4,44]. Patients presenting with FTD may develop MND and patients with MND may develop FTD[9].
The association between FTD and MND is frequent in subjects carrying C9ORF72 mutation[44]. Distinct clinical characteristic have been described in these patients[31,44].

□ ATYPICAL PHENOTYPES IN FRONTOTEMPORAL LOBAR DEGENERATION

Due to the focal onset and the slow progression of degeneration, in some cases unusual cognitive profiles can be observed where a single domain is compromised in the absence of other canonical signs of the disease[41]. We described a case of a woman presenting with a two-year history of selective FAS in absence of other neuropsychological signs[27] and a patient who showed a seven-year history of slowly progressive pure dysgraphia[26].
Unusual associations of syndromes pertaining to FTLD have been described[41]. We reported two cases of patients showing both the features of semantic dementia and corticobasal syndrome[22,24]. A similar case was described by Clerc et al.[6] with autoptical evidence of 4R tauopathy.

□ GENETICS

Frontotemporal lobar degeneration has a marked component of familiarity: in about 17-43% of affected individuals there is a familiarity for a similar disorder[9].
Currently, the rate of familiarity seems underestimated even because of the frequent difficulty to perform an exhaustive family history.
In FTLD causal genetic mutations are often reported in apparently non-familiar cases. This phenomenon is probably attributable to several factors: the occurrence of a new mutation, an incomplete penetrance or an unrecognised familiarity (for example, due to families deaths at an early age).
Recruitment of large cohorts of familiar cases of FTLD and actual genome sequencing technology are significantly increasing about the genetic basis of familiar FRTL.
About 40-50% of familiar FTLD cases are explained by causal mutations of known causative genes but the remaining familiar cases causative mutation has not been discovered yet.
The genetic forms of FTLD represent a substantial percentage variable from 25 to 50%; in most cases the transmission is attributable to an autosomal-dominant pattern, with extremely variable clinical phenotype[37]. The first genetic mutation responsible for FTLD to be detected was in the MAPT gene (which encodes the associated microtubular protein), located on chromosome 17 (17q21) and coding the tau protein, estimated as responsible for 10-20% about all cases of familial FTLD[40]. Since 1998, about 44 different mutations have been identified in 132 different families of this gene, which seem globally responsible for 5-20% of familiar FTLD. In 2006, PRGN gene was identified on chromosome 17. In following years, about 70 different mutations of this gene were discovered in 199 families affected by FTLD, responsible of about 6-10% of cases of familial cases[23,43]. Recently, C9orf72 gene involved

in FTLD has been identified, located on chromosome 9. Its mutation seems not only related to the FTD/MND (motoneuron disease) phenotype, but it also appears to be the most frequently documented in the familial forms of FTLD (11.7% of cases) and in familial amyotrophic Lateral Sclerosis (23.5% of cases)[25,28,40].

Less common mutations (found in about 1% of cases of familial frontotemporal lobe degeneration), refer to other genes such as VCP, CHMP2B and TARDBP[40].

□ PATAHOLOGY

From a macroscopic point of view, the FTLD is characterized by frontal and temporal lobes atrophy; in particular, at least at the onset, this atrophy appears to be confined at the level of the anterior cingulate cortex, the fronto-insular regions and the lateral orbit-frontal cortex. As the pathology progresses, atrophy also tends to spread to the dorsolateral prefrontal cortex and to the anterior and posterior portions of the temporal lobes. In the case of nfvPPA, anterior atrophy of the lower left and insula frontal atrophy occurs, while in the svPPA the first brain area to be involved is the anterior portion of the left temporal lobe (initially the antero-inferior portion and only later the posterior one), then the contralateral analogous area, the posterior insula and the ventro-medial frontal lobe are involved[18,28,41].

From the histological point of view the first protein recognized having a role in FTLD was the tau protein (FTLD-tau). Tau protein is encoded by a gene composed by 16 exons in chromosome 17 and the central nervous system isoforms are generated by alternative RNA splicing of their exons. This protein, involved in axonal transmission, in FTLD is hyperphosphorylated and present as aggregates in a series of pathologies consequently defined taupathies, which include AD, Pick's disease, cortical-basal degeneration and progressive supranuclear paralysis. Neuronal tau deposit included pretangles, neuro-fibrillary tangles and Pick bodies. These histological finding are not documented in all cases of frontotemporal lobe degeneration, but only in a small number of them[18,28].

Another histological marker present in about half of patients with frontotemporal lobe degeneration is ubiquitin, present in the form of intracellular inclusions. Only a decade ago was identified the TDP-43. TDP-43 is a RNA-binding domain protein involved in multiple cellular processes and it is the most important component of tau-negative, ubiquitine-positive intracellular inclusion in frontotemporal lobe degeneration[16,28].

Another protein found to be present as intracellular inclusions is the FUS protein, another RNA-binding protein[28].

FUS protein is a RNA-binding protein. In ALS and FTLD brain tissues, FUS and TDP-43 result partially lost from the nucleus in neuron and glia and aggregate in cytoplasm and, less frequently, in the nucleus[28].

TDP-43 and FUS are nuclear carrier proteins that have a role in RNA metabolism regulation, whereas tau protein (a MAPT product) is involved in intracellular transport, in particular microtubules assembly/disassembly[16,28].

Histologically, FTLD is characterized by the accumulation at the cellular level of aggregated abnormal proteins of neuronal and glial origin. In 45% of the cases approximately, intracytoplasmic neuronal inclusions are formed by microtubule associated protein tau (FTLD-tau). Round bodies (Pick bodies) and glial inclusions of the tau protein coexist in about half of the intracellular tau-positive forms. About 50% of FTLD cases are characterized by the presence of neuronal intracytoplasmic inclusion and neuronal intranuclear inclusion formed by TDP-43 protein (a RNA and DNA binding protein). These forms are called FTLD-TDP. The remaining 5% of cases the neuronal intracytoplasmic and neuronal inclusion are characterized by the FUS protein, and are called FTLD-FUS[16,28].

□ TREATMENT

Until now there are not approved treatments to manage FTD syndromes. Cholinesterase inhibitors and memantine have not demonstrated clinically significant efficacy in treating FTD patients[50].

Symptomatic drugs can have some benefit on behavioural symptoms. SSRI treatment has some benefit on eating, agitation, irritability, dysphoria, and depression. Antipsychotics have been used to treat agitation and psychosis although the presence of side effect limits their utilization[50].

Nonpharmacological interventions and caregiver support can help to improve symptoms in FTLD[50].

Although recent advances suggest potential novel

therapeutic targets, data concerning their effectiveness are still preliminary or preclinical. Further studies are required to develop pharmacological interventions[50].

□ CONCLUSION

The purpose of the present review was to describe the clinical features of the variegated phenotypic spectrum of FTLD in order to provide a practical aid to the clinician to make a correct diagnosis.
FTLD is a heterogeneous group of disorders characterized by disturbances of behaviour and personality and different types of language impairment associated to atrophy of the frontal and anterior temporal lobes.
Together with the three more frequent syndromes (bvFTD, SD and NFPA) there is a significant clinical, pathological and genetic overlap between FTD and motor neuron disease/amyotrophic lateral sclerosis and the atypical parkinsonian syndromes, such as PSP and CBS.
The clinical history together with the neuropsychological evaluation provides fundamental information for the diagnosis of the different clinical variants. Instrumental examinations as well as genetics are helpful for a correct diagnostic classification.

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