Clinical Observations in Geriatrics

Depression or prodromal fronto-temporal dementia?

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Introduction. Frontotemporal dementia (FTD) is a rare neurodegenerative disease, occasionally late onset, whose prevalence is underestimated especially in the geriatric population. The initial symptoms can be confused with some psychiatric disorders, such as depression, so the differential diagnosis may require careful investigations. Here we report the case of a 75 years old patient presenting with severe anxiety symptoms, initial social withdrawal and mild cognitive impairment.

Materials and methods. Longitudinal observational clinical study of 3 years. The patient underwent three successive cognitive assessments that included the Mini Mental State Examination (MMSE) and a battery of neuropsychological tests, imaging studies of the brain with a computer tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) and genetic analysis of a few possible mutations involved in FTD (C9ORF72, progranulin).

Results. The results after the first visit showed a picture of non amnesic single cognitive domain (dysexecutive) Mild Cognitive Impairment (MCI) associated with anxious-depressive symptomatology. The initial neuroimaging demonstrated fronto-temporal cortical atrophy with mild enlargement of the frontal horns of the lateral ventricles, and moderate glucose hypometabolism of bilateral prefrontal cortex. Genetic tests were instead negative. These data were suggestive of a diagnosis of prodromal FTD. However, in the three years follow-up, following a treatment with paroxetine the patient completely resolved her depressive symptoms, and in parallel she did not worsen her cognitive status nor developed behavioural disorders. Therefore we concluded for a depressive disorder and we diminished our suspects for a prodromal dementia.

Key words: Fronto-temporal dementia, Depression, Elderly

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INTRODUCTION

Frontotemporal dementia (FTD) is a rare neurodegenerative disease, with a typical pre-senile onset (on average at 58 years old) [1], rarely after 75 years old [2].
FTD can be classified into 3 main clinical phenotypes: the behavioural FDT, the most common one, characterized by changes in personality; the progressive non-fluent aphasia, in which the language deficit is the most prominent feature; the semantic dementia, dominated by semantic language disorders and semantic memory deficits. Overlapping syndromes, in which the FTD occurs associated with a motor neuron disease (amyotrophic lateral sclerosis) or atypical parkinsonism (corticobasal degeneration or progressive supranuclear paralysis) [3] also exist.
Because of diagnostic difficulties, especially in the elderly, the prevalence of this disease is underestimated [2]. Despite a strong hereditary component has been demonstrated [4] and genetic mutations (most frequently C9ORF72, progranulin and MAPT) have been identified in familial cases, sporadic cases are reported in literature, in which the mutations occur de novo, or the clinical phenotype is not associated to known gene defects [5]. Especially in those forms not associated with a known genetic substrate, the diagnosis is particularly challenging because it relies on clinical symptoms and imaging techniques to rule out other diseases that may present similar manifestations. The differential diagnosis between a late onset sporadic FTD and depression might be particularly difficult. Depression is indeed a very common disorder in the elderly, and it can be developed for the first time in the old age, or become manifest with aging in subjects who have been suffering from sub-threshold mood disorders [6]. Both FTD and depression can be characterized by positive symptoms, such as excessive emotionality, distractibility and impulsiveness, or negative ones, such as apathy, social withdrawal, feelings of sadness, mental rigidity, loss of spontaneity and empathy. The two diseases differ in the type of management required, and in the impact they can have not only on the quality but also on the quantity of life. Indeed, some forms of FTD can lead to the patient exitus in only 4 years [7].
Our work aim is to show the difficulties encountered in practice in the differential diagnosis between depression and a prodromal geriatric onset of FTD, through the presentation of a clinical case.

CLINICAL CASE

We report the case of a 75-year old patient, who, during her first geriatric visit, in December 2012, complained of anxious symptoms, progressive loss of interests, social withdrawal, and initial fears related to unknown situations. Moreover, she reported difficulties in finding words and recent episodic memory loss (i.e. she lost objects at home). The symptoms had begun insidiously a year before, without apparent triggers. Her general practitioner had prescribed bromazepam without any benefit.
The patient's familiar anamnesis was positive for unspecified late onset dementia. Her father's cognitive disorder started when he was 80 years old and he died 5 years later for a stroke; whereas in her 79 year-old brother the first symptoms of cognitive impairment appeared insidiously, when he was 77 years old.
The patient's anamnesis was positive for hypertension, osteoporosis, chronic gastritis and gastro-oesophageal reflux disease. She had undergone a right mastectomy for breast cancer in 1978; subsequent follow-up had always been negative. When she was 30 years old, she had presented an episode of depression deemed as reactive to her father's death.
Functional assessment scales showed a complete preservation of autonomy in performing basic and instrumental activities of daily living (Activity of Daily Living - Index Katz - (ADL) = 6/6; Instrumental Activity of Daily Living - Home Lawton - (IADL) = 8/8). The screening cognitive tests, despite the reported memory loss, were normal: Mini Mental State Examination (MMSE) = 30/30; Clock Drawing Test (CDT) = 4/5. The assessment of the affective state, as reported by the patient, confirmed the presence of deflected mood (Geriatric Depression Scale (GDS) = 14/30).
To rule out any organic cause, blood tests were carried out and they excluded thyroid dysfunction or vitamin deficiencies. Complete blood count, coagulation, liver and kidney function indexes, electrolytes, glycaemia, glycated haemoglobin, lipid profile, serum uric acid concentration, reactive C protein, creatine phosphokinase and albumin were all normal.
The patient was investigated with brain computed tomography (CT) scan, which demonstrated a mild vasculopathy and a slight enlargement of the frontal horns of the lateral ventricles (Fig. 1A). A carotid Doppler ultrasound detected only a diffuse myointimal thickness.
Despite the normality of the cognitive screening, considering the relatively young age of the patient, the presence of psychiatric symptoms characterized predominantly by apathy and anxiety, the abrupt onset of the symptoms without any apparent trigger, and the enlargement of the frontal horns of the lateral ventricles detected by CT scan, we prudently decided to consider the hypothesis of a possible neurodegenerative disease, like FTD, in a prodromal phase.
Therefore we further evaluated the patient's cognitive state with neuropsychological tests, which showed a

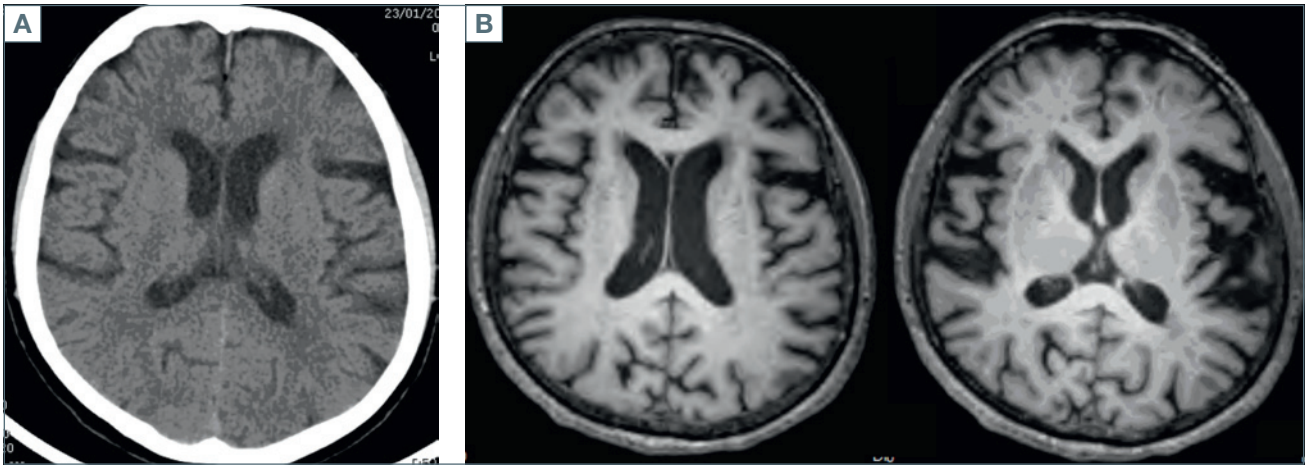

Figure 1. A. Brain CT showing off the slight enlargement of bilateral frontal horns of the lateral ventricles. **B.** Brain MRI: the frontal and temporal atrophy.

focal pre-frontal executive dysfunction (phonological fluency, bizarre cognitive estimates) associated with bradyphrenia, adynamic behavioural traits (characterized by a reduction of spontaneity and variability of emotional responses) and confirmed the anxious symptoms. The assessment was therefore conclusive for a non-amnestic (dysexecutive) single domain Mild Cognitive Impairment (MCI).

The result of the cognitive evaluation, although not specific and common to other aetiologies too (i.e. vascular disorders), could be compatible with the hypothesis of prodromal FTD.

Therefore we proceeded to a more sensitive neuroimaging study with brain magnetic resonance imaging (MRI), and with brain positron emission tomography (PET) to early detect hypo-functioning cerebral areas. The MRI confirmed the mild vasculopathy and the modest expansion of the anterior horns of the lateral ventricles already seen with CT, and demonstrated an initial cortical atrophy of the frontal and temporal cortex (Fig. 1B). The PET detected a moderate glucose hypometabolism in the bilateral prefrontal cortex (Fig. 2).

Considering the neuroimaging results, which seemed to support the hypothesis of prodromal FTD, and the family history of cognitive disorders we performed genetic analyses. We checked the presence of esanucleotidic expansion of the C9ORF72 gene and dosed plasmatic progranulin, which, if reduced, is suggestive of the presence of a genetic mutation causing gene haploinsufficiency. However we found no expansion of the C9ORF72 gene and normal plasmatic progranulin levels (75 ng/ml [normal values > 61.5 ng/ml]). Additionally, in the hypothesis of a frontal variant of Alzheimer's disease (AD) [8], apolipoprotein E (ApoE) was genotyped and resulted homozygous for epsilon 3.

In the meanwhile, we modified the psychopharmacological therapy to cope with the patient's symptoms. We tried with sertraline, later substituted due to inefficacy, with escitalopram, levosulpiride and alprazolam, but we achieved only modest results. Finally, in January 2014, the patient was evaluated by a neurologist who, because of the high degree of anticipatory anxiety, avoidance behaviours and irritability presented by the patient, replaced escitalopram and levosulpiride with paroxetine. Subsequently the patient's depressive and anxious symptoms gradually improved with practically a complete resolution in June 2015 (Tab. I).

During the three year follow-up, from 2012 to 2015, the cognitive state of the patient remained substantially stable. Table II shows the results of longitudinal neuropsychological assessments; the neuropsychological phenotype remained unchanged: non amnestic (dysexecutive) single domain MCI.

DISCUSSION

A clinically overt dementia can be preceded by an early stage, now formally called Mild Cognitive Impairment (MCI), in which the activities of everyday life are not compromised, but deficits in one or more cognitive domains are already detectable through neuropsychological tests [9]. This phase may be also characterized by mild personality changes and behavioural symptoms.

The diagnosis of MCI-FTD is mainly clinical and is very complicated, because, the initial symptoms (behaviour or mood changes) are often similar to those found in psychiatric disorders. Moreover, depression in the elderly may be one of the first manifestations of dementia, either as an initial behavioural disorder, or as an emo-

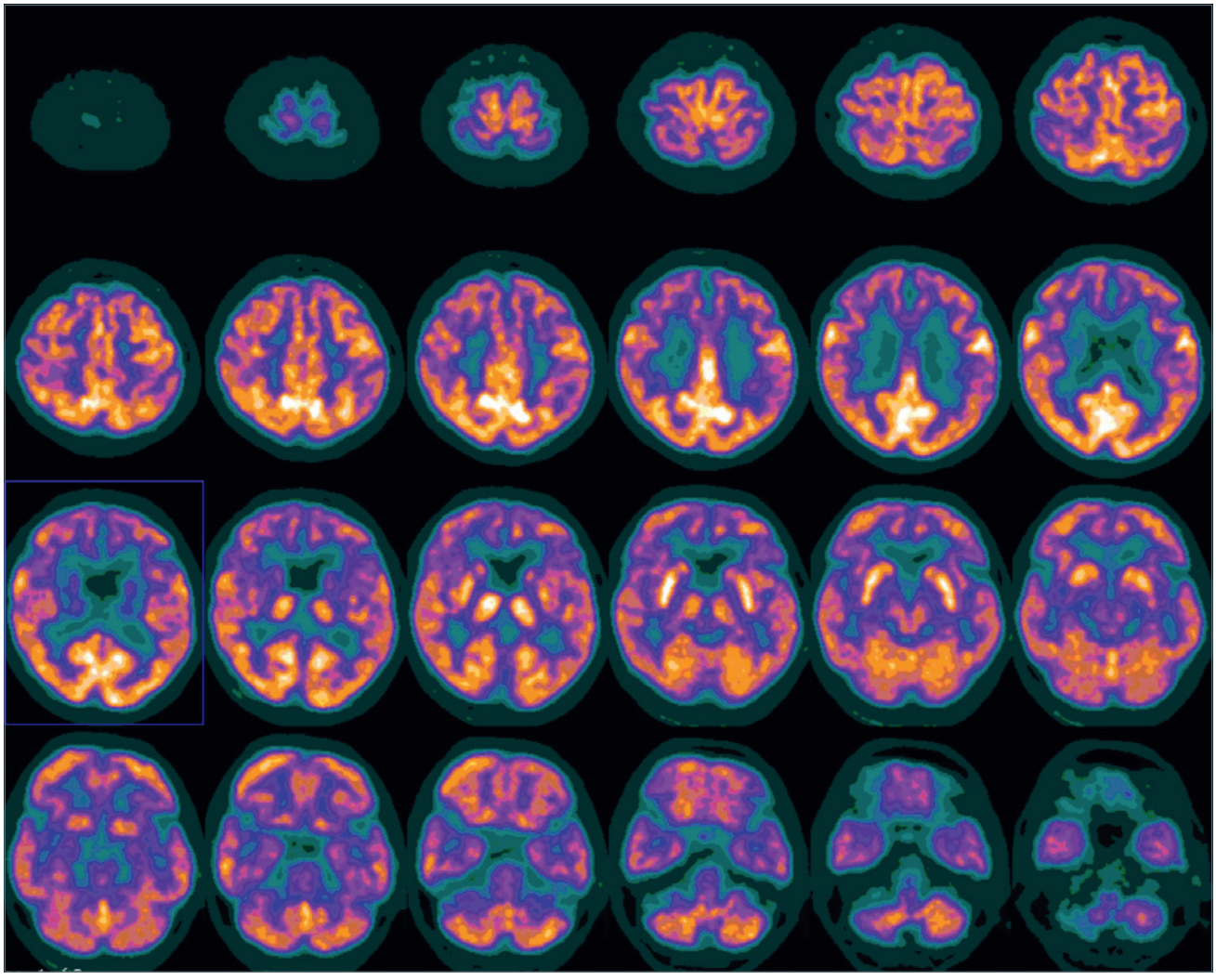

Figure 2. Brain PET showing a moderate bilateral prefrontal glucose hypo-metabolism.

Table I. Evolution of anxious-depressive symptoms over time and parallel changes in psychopharmacological therapy.

	Feb. '13	Nov. '13	Mar. '14	Sept. '14	Dec. '14	Jun. '15
Symptoms	Insecurity, tension, agitation, anticipatory anxiety overall for activities outside the daily routine; deflected mood; insomnia	Deflected mood; anxiety and apathy	Improvement of the mood and the anxious state since it was introduced paroxetine (January 2014). Social withdrawal persist	Fair compensation of mood, no more anxiety	Improvement of anxiety symptoms and mood; no more social withdrawal	Neither deflected mood nor anxiety
Treatment	Sertraline (25 mg x 2) Alprazolam (0.25 mg)	Escitalopram (8 mg) Alprazolam (0.25 mg) Levosulpiride (25 mg x 2)	Paroxetine (20 mg) Alprazolam (0.25 mg)	Paroxetine (10 mg) Alprazolam (0.25 mg)	Unchanced	Unchanged
GDS (0-30)	14	15				3

Table II. Neuropsychological assessment.

	March 2013		December 2013		February 2015		
Test	**Raw score**	**Equivalent score or qualitative**	**Raw score**	**Equivalent score or qualitative**	**Raw score**	**Equivalent score or qualitative**	**Maximum score**
Global							
MMSE	30	+	26	+	28	+	/30
Attention							
Matrices test (visual search)	53	4	49	4	52	4	/60
Bells test	34	+	32	+	34	+	/35
Psychomotor speed							
Trail Making Test A	64	3	48	4	46	4	-
Memory							
Prose memory	11.3	2	11.8	2	12.5	3	/16
Rey-Osterrieth Figure (recall)	14.5	4	11.5	4	12	4	/36
Digit span forward	5	3	5	3	5	3	-
Prefrontal functions							
Digit span backward	3	+	3	+	3	+	-
Trail Making Test B	122	4	96	4	126	4	-
Raven test (coloured)	29	4	30	4	27	3	/36
Phonological fluency	16	0**	17	1*	22	1*	-
Short Stroop test (times)	25.5	4	34.5	3	21.5	4	-
Short Stroop test (errors)	0	4	3	2	2.5	3	/0
Cognitive Estimates CET (tot)	14	+	18	+	17	+	/0
CET (bizarre errors)	6	Deficit**	2	+	6	Deficit**	/0
Weigl's Sorting test					12	4	/15
Language							
Picture naming	73	+	70	+	69	+	/80
Praxis							
De Renzi's test (right)	69	+	67	+	69	+	/72
De Renzi's test (left)	65	+	70	+	65	+	/72
Visuospatial functions							
Copy of geometrical drawings	12	3	13	4	13	4	/14
Copy of Rey-Osterrieth Figure	30	3	31	4	29	2	/36

** impaired scores (< 5th percentile); scores in the lower normal range (< 20th percentile).

tional reaction to the awareness of one's own cognitive deficits. Depression is also known to be an independent risk factor for the development of dementia [10]. Alzheimer's dementia (AD) should also be contemplated among the possible diagnoses since its frontal variant could appear clinically indistinguishable from a behavioural FTD, especially in its early stages. The ApoE genotype (more frequently homo- or heterozygous for the allele epsilon 4 in AD cases) and the neuroimaging (showing a different distribution of the areas of brain atrophy) can help [11].

A comprehensive neuropsychological assessment can detect an early deficit in executive functions, such as the ability to plan, initiate and complete tasks, typically compromised in the FTD and less easily identifiable through the standard interview with the patients and/or caregiver compared with amnesic deficits. Nevertheless, even depression, especially if associated with a cerebrovascular disease may be associated with executive dysfunctions.

Neuroimaging studies can help to exclude organic diseases (e.g. tumors or infarction in the frontal lobes etc),

and support the diagnosis of behavioural FTD if there is evidence of focal atrophy of the frontal/anterior temporal lobes and/or a dilation of the frontal horns of the lateral ventricles. However, in the early stages of the disease, atrophy may not be detectable. At these stages functional studies, such as PET, can show a glucose hypometabolism in the fronto-temporal lobes when the brain parenchyma is still volumetrically intact.
Genetic tests are used to identify the mutations that cause familial forms of FTD but if negative do not rule out sporadic variants.
Unfortunately, often, only the disease course can help in the differential diagnosis. A condition of MCI can, in some cases, remain clinically stable for long periods. This is less likely if it is the manifestation of a prodromal FTD because this dementia type has usually a rapid course towards death (4-8 years). During the three-year follow-up, our patient did not reveal either psychotic symptoms or language disorders, which are instead typical during the progression of FTD. Finally, the response of our patient to the therapy with paroxetine, an antidepressant of the class of selective serotonin reuptake inhibitors (SSRIs), was impressive. Serotonin neurotransmission is involved in social control (basal orbitofrontal circuit), attention and planning (dorsolateral circuit), and in motivation and selective thinking (frontomedial circuit). It is known that in FTD serotonin concentration is reduced in the frontal subcortical circuits and that SSRIs, and in particular paroxetine, can improve non-cognitive symptoms and reduce the use of antipsychotic drugs [12]. However, it is unlikely that these molecules can lead to a complete resolution of behavioural symptoms in a neurodegenerative disorder [13], as much as when they are used for the treatment of depression [14].
Finally, the presence of a chronic cerebrovascular disease should be taken into consideration. Cerebrovascular diseases increase the vulnerability of the elderly to the development of depression through various neurobiological mechanisms, such as damage to the frontal subcortical circuits important in emotional control [15]. In our patient it is possible that the cerebrovascular disease detected at the neuroimaging, although mild, could have played a role in the development of both depressive symptoms and executive dysfunction.

CONCLUSIONS

The early recognition of prodromal forms of FTD in the elderly remains a difficult challenge of fundamental importance for the geriatrician. It is of particular importance the differential diagnosis with the forms of depression in the elderly, which are often difficult to detect, and which, if not properly treated, can amplify the disability of patients, reducing their quality of life, increase the mortality rate and increase the economic burden of the healthcare system. Unlike the FTD, whose prognosis is necessarily unfavourable, depression can be treated effectively, especially if therapy is started early, so it is of fundamental importance to make a proper early diagnosis which allows a therapeutic approach able to improve the life quality both of patients and family members.

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