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Frequency and caregiver's burden of frontotemporal dementia in ALS patients and their caregivers

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Sommario

Chapter 1

1.1 Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS), described in 1869 by Jean-Martin Charcot, is a fatal motor neuron disease (MND) characterized by degenerative changes to upper and lower motor neurons.

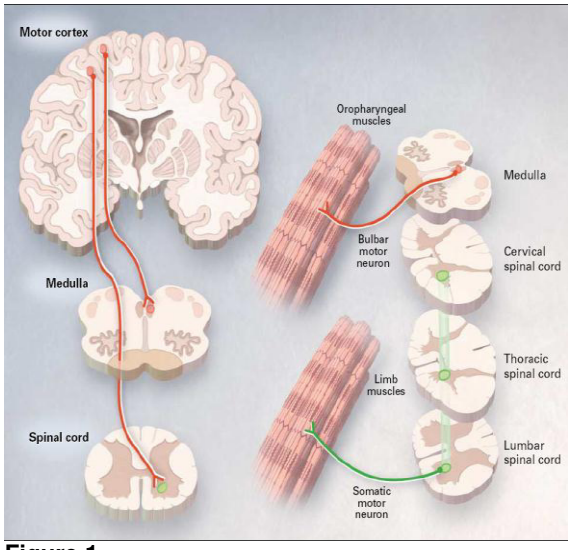

Figure 1.

The pathology and epidemiology of Amyotrophic Lateral Sclerosis (ALS) have been intensively studied. The term "Amyotrophic" refers to the presence of muscle atrophy, weakness and fasciculations due to the disease of the lower motor neurons; "lateral sclerosis" refers to the gliosis following the degeneration of the corticospinal tracts resulting in the hardness to palpation of the lateral columns of the spinal cord in autopsy specimens[1]. Median survival is 2 to 4 years from onset; only 5–10% of patients survive beyond 10 years.

Motor neurons arise from the motor cortex and extend from the brain stem throughout the spinal cord, forming the pathway to control voluntary movement. (***Figure 1***). Upper motor neurons carry impulses to lower motor neurons which then innervate muscles. In ALS upper motor neuron signs, with the presence of clonus, hyperreflexia (overactive tendon reflexes), Hoffmann signs, spasticity and Babinski signs, are present together with lower motor neuron signs,
determining a condition of progressive spinal muscle atrophy, weakness, fasciculations and paralysis, with a loss of motor neurons in the spinal ventral horns, most brainstem motor nuclei, and motor cortex[2] (***Table 1***).

ALS is characterized by the involvement of both the I and II motor neuron, and usually by distal and asymmetric limb onset. Typically, urethral and sphincter

function, and motor neurons in the oculomotor, trochlear and abducens cranial nerve nuclei are spared .

Nevertheless, the disease of upper and lower motor neurons may develop as independent syndromes: the Primary Lateral Sclerosis (PLS), characterized by the exclusive involvement of the I motor neuron, and the Progressive Muscular Atrophy (PMA), in which there is an exclusive involvement of the II motor neuron. Both are considered variants of ALS because, at autopsy, there are likely to be abnormalities in both upper and lower motor neurons. A different form is the Progressive bulbar palsy (PBP), marked with the involvement of motor neurons in the brainstem nuclei.

	Brainstem	Cervical	Thoracic	Lumbosacral
Lower motor neuron signs weakness, atrophy, fasciculations	• jaw, face, • palate, • tongue, • larynx	• neck, arm, hand, • diaphragm	• back, • abdomen	• back, abdomen, • leg, foot
Upper motor neuron signs pathologic spread of reflexes, clonus, etc.	• clonic jaw jerk, • gag reflex, • exaggerated snout reflex, • pseudobulbar features, • forced yawning, • pathologic DTRs, • spastic tone	• clonic DTRs, • Hoffmann reflex, • pathologic DTRs, • spastic tone, • preserved reflex in weak wasted limb	• loss of superficial abdominal reflexes, • pathologic DTRs, • spastic tone	• clonic DTRs, • extensor plantar response, • pathologic DTRs, • spastic tone, • preserved reflex in weak, wasted limb

Table 1. El Escorial revised diagnostic criteria for ALS: Lower motor neuron and upper motor neuron signs in four central nervous system (CNS) regions

The spectrum of neurodegenerative syndromes characterised by the progressive degeneration of motor neurones includes other ALS variants in which the disease is limited to one or two extremities for many years: the monomelic variant, in which only one limb is affected, and the flail arm/leg variant, with the involvement of both upper (the so-called “man in the barrel”) or lower limbs respectively (Flail Arm syndrome also known as Vulpian-Bernhardt Syndrome and Bernhardt syndrome and Brachial amyotrophic diplegia; Flail Leg syndrome, also known as Pseudopolyneuritic form of ALS)[3].

The term "Motor neuron disease" (MND) was introduced in 1932 by Lord Russell Brain to incorporate all these conditions into a single spectrum of disorders

of which ALS is the most common form of the disease, accounting for about 80% of cases[4].

Typically there is no cognitive impairment or loss of sensory nerve functions, although there are ALS variants that include these symptoms (e.g. ALS-Dementia).

With regard to the course of the disease, patients suffering from PBP, PMA and PLS generally progress to a situation involving the degeneration of both upper and lower motor neurons. However, this occurrence is not always observable and there are cases with a more favourable prognosis in which this eventuality does not take place. Milder variants of ALS may occur in 10 to 20% of cases and patients may survive for more than 10 years[5.] Patients with bulbar symptoms onset are considered to have a shorter survival[6-9.] Prediction of progression and survival is difficult and might be associated with the site of initial clinical involvement and to a number of non-specific factors including muscle athropy, dysphagia, other diseases, and the patient's age at the time of the onset[6,10].

The diagnosis of ALS is made according to the number of body regions involved (clinical examination and electromyography), and require upper and lower motor neuron loss with progression of signs within a body region and to other body regions[11-13]. According to the El Escorial criteria, ALS combined with other neurological disorders, such as dementia and parkinsonism, is defined as ALS plus[13].

The Revised El Escorial research diagnostic criteria for ALS (with the Awaji elecrodiagnostic algorithm included)
Clinically definite ALS UMN and LMN clinical sings or electrophysiological evidence in three regions
Clinically definite ALS – laboratory supported UMN and/or LMN clinical sings in one region *and* the patient is a carrier of a pathogenic SOD-1 gene mutation
Clinically probable ALS UMN and LMN clinical or electrophysiological evidence by LMN and UMN in two regions with some UMN signs rostral to the LMN signs
Clinically possible ALS UMN and LMN clinical or electrophysiological signs in one region only, or UMN signs in at least two regions, or UMN and LMN signs in two regions with no UMN signs rostral to LMN signs. Neuroimaging studies have excluded other diagnoses.

Table 2. ALS, amyotrophic lateral sclerosis; UMN, upper motor neuron, LMN, lower motor neuron.

The differential diagnosis of the motoneurone disease from other neurological condition[14] was considered by the El-Escorial World Federation of Neurology Criteria. The El Escorial revised criteria (EEC-R)[15] distinguish four levels of diagnostic certainty: definite, probable, possible, and suspected ALS. EEC-R has

abolished the suspected level and introduced two other categories: probable ALS laboratory supported and definite familial ALS laboratory supported[15].

Categorizations as "clinically definite, "clinically probable," and "clinically possible" are expressed on the basis of the number and location of the cardinal signs. The diagnosis is made by clinicians on the balance of the probabilities, excluding other diseases and waiting for the disease to progress to meet the full diagnostic criteria.

Recently, the new Awaji electrodiagnostic algorithm[16] was added to the EEC-R to improve diagnostic sensitivity (with no loss in specificity7) and also to facilitate early diagnosis[18-21] as the EEC-R were considered excessively restrictive and not designed for use in routine[22] (***Table 2***). Electrodiagnostic examination is important to exclude conductions block and electromyography can confirm muscle denervation[23].

The mean time from the onset of symptoms to confirmation of the diagnosis raises from 10 to 18 months[24]. Even if an early diagnosis may provide opportunities for treatment with neuroprotective agents, to date there are no cure or therapeutic strategies to significantly alter the course of the disease[25].

Amyotrophic lateral sclerosis, together with dementia and parkinsonism, is considered as an "age-related" rather than "ageing-related" disorder with a worldwide age-specific prevalence of 33/100.000 observed at 60-75 years, responsible for approximately 1/800 deaths, with 10% occurring before 40 years of age[26-29]. This means that is more likely to occur within a specific age range rather than being caused by the ageing process itself[30]. An increasing age at onset predicts worse survival[31,9].

There are multiple factors underlying the disease mechanism and a variety of environmental exposures have been investigated. Experimental evidences have considered the effects of many potential factors, including oxidative damage, excitotoxicity, apoptosis, abnormal neurofilament function, defects in axonal transport, aberrant protein processing and degradation, increased inflammation, and mitochondrial dysfunction[32-35].

Also occupational exposure has been considered among potential causes of ALS and an increased relative risk of ALS was noted in workers potentially exposed to chemicals as 2,4-dichlorophenoxyacetic acid (2,4-D) and to lead, suggesting a

potential role for lead exposure in the aetiology of the disease[36,37]. Genetic susceptibility has been considered as modifying the relationship of ALS to chemicals and to lead exposure.

Understanding the pathophysiology and the molecular pathogenesis of neurodegeneration is fundamental for the treatment of the disease but, despite all the hypothesis, more than 140 years after Charcot described the selective degeneration and death of motor neurons, it is still difficult to determine which process is most important in triggering cell dysfunctions and death, and what determines the selective vulnerability of motor neurons, so the aetiology remains for the moment substantially unknown.

1.2 EPIDEMIOLOGY

Prospective epidemiological studies indicated that the incidence of ALS is uniform in Western countries.

In the past years a range between 0.4 and 2.6 cases/100.000/year was identified with a uniform worldwide distribution in space and time[38] , with a life-time risk of 1/800[32] and a slight male to-female preponderance (1.3:1–1.6:1), in a decreasing tendency[38]. Therefore male sex, increasing age, and hereditary are recognized as being the main risk factors[6,40,41].

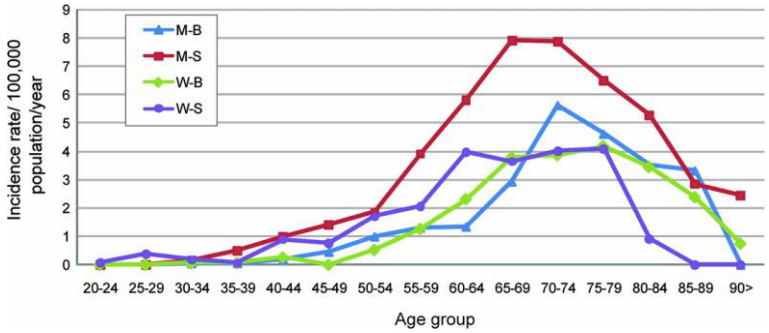

Figure 2. Age-specific incidence rates by gender (men and women) and site of onset (spinal vs bulbar) Courtesy of A. Chiò, 2009

European and American studies reported similar incidence rates, ranging from 1.5 to 2.5 cases/100,000 population/year[42-47] and a recent study by Chiò et al. (2009)[23] indicated an annual crude incidence of 2.9 cases/100.000 /year (95% CI 2.72-3.09). Chiò described the temporal pattern of incidence and demographic characteristics of ALS in Piemonte and Valle d'Aosta (Italy), in a 10-year period, (1995-2004), through the observation of incident cases of ALS collected in a prospective register through the Central Regional Archive and the Italian Statistical Bureau (the Piemonte and Valle d'Aosta Register for ALS)[24.]

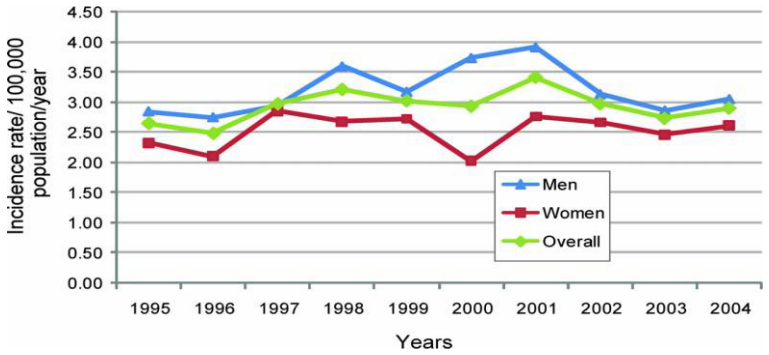

Figure 3. Incidence rates for amyotrophic lateral sclerosis in Piemonte and Valle d'Aosta, 1995 to 2004

Courtesy of A. Chiò, 2009

The Piemonte and Valle d'Aosta Register for ALS (PARALS) is a prospective epidemiologic register established in 1995 collecting all ALS incident cases in these 2 Italian regions (population: 4,332,842)[43]. In the examined decade the mean annual incidence rate was of 2.64/100.000 population, with a men to women rate ratio of 1.28:1. The incidence rate was higher in men than in women (***Figure 2***) with a peak in the 70–74 age class in men, and in the 75–79 age class in women. The presence of bulbar onset was identified in about one third of patients, significantly more frequently among women[24], identical to that of spinal onset for the 65–79 age groups and increasing at older age. The age-specific incidence of bulbar onset in the oldest age groups may indicate that older persons have a greater risk of developing bulbar ALS.

The possible involvement of different genes may explain the pathogenesis of the various clinical presentations of ALS and the different susceptibility of bulbar and spinal motor neurons at different ages.

During the 10-year period of the study in Piemonte and Valle d'Aosta the incidence rate was relatively stable, with a men to women rate ratio ranging from 1.04 (in 1997) to 1.71 (in 2000). The cumulative lifetime risk for ALS was estimated as being 1/278 for men and 1/432 for women so that 1 out of 278 men and 1 out of 432 women in Piemonte will develop ALS during their life (***Figure 3***).

The crude prevalence rate of ALS in Piemonte was 7.9/100,000 population; prevalent patients were found to be significantly younger than incident ones, and are less likely subject to a bulbar presentation. However, Chiò (2009)[24] reported that the prevalent population, generally corresponding to the patients who are enrolled in clinical trials, is substantially different from the incident population, having more favourable prognostic factors (e.g. younger age, spinal onset). Data suggest that the incidence of ALS in Italy has been stable and no relevant modifications regarding the clinical and demographic characteristics of the patients have been recorded[24].

Furthermore, ALS incidence in Piemonte and Valle d'Aosta is reported to be similar to the Irish and Scottish registers[45,46], but higher than that observed in other Italian Regions as Lombardia and Puglia[44-47], although some differences are probably due to the accuracy of the investigations, differences in requesting health facilities by

the elderly and to the high frequency misdiagnosis. However, the incidence has been decreasing in recent years[24].

Figure 4. Rate of familial amyotrophic lateral sclerosis in individual European countries.

1.3 GENETICS

Genetic susceptibility is recognized and approximately 90% of patients are sporadic (SALS) and almost 10% are familial (FALS) with multiple autosomal dominant and recessive forms.

Almost 20% of the familial cases are caused by dominantly inherited mutations in the protein Cu/Zn superoxide dismutase (SOD1)[48].

There are no clinical/neuropathological differences between sporadic cases and familial forms of ALS but for the lower age at onset in familial forms[6].

A systematic review and meta-analysis of reported rates of FALS indicated that their rate among prospective population based registries is 5.1% (CI 4.1 to 6.1%), and not 10% as often stated[49]. Geographic variation (***Figure 4***) may reflect variability in the underlying genetic structure of the European population.

A study population including all ALS cases diagnosed in Piemonte and Valle d'Aosta (Italy) during a 4.5-year period (Jan. 1, 2007 – Jun. 30, 2011) revealed that out of the 475 patients included in the study, 51 (10.7%) carried a mutation of an ALS-related gene, and that younger patients are nearly 3 times more likely to carry a mutation in one of the known ALS genes compared to older patients[50] (***Table 3***).

	≤54y. n(%)	55-69 y. n (%)	≥70 y. n(%)	Total, n (%)
Mutated	12 (16.0)	29 (12.3)	10 (5.6)	51 (10.7)
Wild-type	62 (85.1)	207 (87.9)	155 (94.4)	424 (89.3)
Overall	74	236	165	475

*Cochran –Armitage test for trend, p=0.03

Table 3. Frequency of mutated patients (all tested genes) according to age

Courtesy of Chiò A, 2012

The detected mutations concern the following genes: C9ORF72, *superoxide dismutase 1* (*SOD1*)[48], *TAR DNA binding protein* (*TARDBP*)[51,] *angiogenin* (*ANG*)[52], *fused in sarcoma* (*FUS*)[53,54] *optineurin* (*OPTN*), (Maruyama,2010)[55] and the *chromosome 9 open reading frame 72* (*C9ORF72*)[56,57].

ALS cases carrying genetic mutations share some clinical peculiarities, such as a significantly lower age at onset.

The presence of ALS with a comorbid FTD is more common in patients carrying a genetic mutation (either *C9ORF72* or *TARDBP*). A positive family history for ALS or frontotemporal dementia (FTD) was found in 46 (9.7%) patients[50].

This huge epidemiologic study concludes highlighting that at least 10% of patients with ALS carry a genetic mutation of one of the major ALS genes, with the *C9ORF72* being the commonest genetic alteration and a major cause of both ALS and FTD[50]. So, the presence of comorbid FTD or a young age at onset are strong indicators of a possible genetic origin of the disease. Another finding is that the frequency of FALS in the Piemonte population is unexpectedly higher than that reported by previous epidemiologic studies[58,49].

1.4 AMYOTROPHIC LATERAL SCLEROSIS AND DEMENTIA

Even if cognition has traditionally been considered preserved in ALS, non-motor involvement can be observed: cognitive decline with cortical degeneration may occur in approximately half of the ALS patients, with 5 to 10% of subjects developing an overt frontotemporal lobar dementia (FTLD), characterized by personality changes, irritability, language difficulty, poor insight and deficits in frontal executive tests[59-64].

A relationship between dementia and ALS was first noted in the late 1800s, and the first researches on cognition in ALS date back to the 1930[65]. The growing evidence of the association of FTD and motor neuron disease has been documented by numerous articles and reviews[66,67] but the term *frontotemporal dementia with motor neuron disease* was first used by the Lund and Manchester groups in 1994[68] describing a continuum with cognitive and behavioural impairment. This conception has been constantly subject to investigations and considerations[69-71].

Over the past years the clinical pattern of ALS-associated dementia has been explored with neuropsychological testing, imaging studies, and neuropathological data[72,73].

A helpful nomenclature was identified by Lomen-Hoerth et al.[74] who introduced the term *behaviourally impaired* (ALSbi) to describe ALS patients who displayed frontal lobe-based behavioural signs and did not meet the full criteria for FTD. The use of the Neuropsychiatric Inventory or other behavioural interviews to provide caregivers of a useful structure for the assessment of specific frontal lobe-based behaviour changes was recommended (***Table 4***)[69].

Terminology	Clinical Characteristics
ALS	A pure motor system disorder as defined by the EEC-R; no clinical evidence of frontotemporal dysfunction
ALSci	Deficits (1,5 SDs below the age-matched mean) on ≥2 neuropsychologic tests of executive functioning but insufficient to meet the Neary criteria for FTD
ALSbi	Frontal lobe-type behavioural impairment in ≥2 areas as measured by means of a standardized caregiver interview
ALS-FTD	ALS patients meeting the Neary criteria for FTD
ALSci= ALS with cognitive impairment ALSbi= ALS with behavioural impairmeny	

Table 4. Specific Characteristics Used to Distinguish ALSci, ALSbi, and ALS-FTD as summarized by Murphy et al, 2007[69]

Cortical degeneration may occur and the cognitive impairment can precede, accompany, or follow the features of ALS. Also non-demented patients with ALS may be affected with cognitive difficulties[75].

The cognitive and behavioural abnormalities vary in severity and the need to detect and uniformly describe even subtle cognitive deficits lead to the development of international criteria to facilitate their recognition and study[70].

An international research workshop on frontotemporal dementia and ALS was held in London, Canada, in June 2007, and expressed some recommendations: *1)* performing a concise clinical diagnosis of the underlying motor neuron disease (Axis I), *2)* defining the cognitive and behavioural dysfunction (Axis II), *3)* describing additional non-motor manifestations (Axis III) and *4)* identifying the presence of disease modifiers (Axis IV) (***Table 5***).

Table VI. Application of Axis I and Axis II diagnostic classification for ALS.

Heading	Subheadings	Existing, synonymous terms within the literature	Characteristics
Axis I. Motor neuron disease variant			
ALS	Sporadic ALS	SALS; classic ALS; Charcot disease	A progressive motor system disorder with both upper and lower motor neuron involvement, with the degree of diagnostic certainty further defined by the El Escorial criteria (definite ALS, probable ALS, laboratory-supported probable ALS, possible ALS)
	Familial ALS	FALS	As indicated for sporadic ALS with the additional components: 1. confirmed genetic linkage, or 2. clinical evidence of autosomal dominant, autosomal recessive, or X-linked inheritance
	Western Pacific variant	Lytico bodig	ALS arising with a hyper-endemic region of the western Pacific (e.g. Kii Peninsula, Guam, Rota)
Axis II. Cognitive/behavioural characterization			
Frontotemporal lobar degeneration with ALS			
ALS-FTD	ALS-bvFTD	ALS-dementia (ALS-D)*, FTD-MND	ALS patient meeting either the Neary criteria (51) or Hodge's criteria (2) for FTD
	ALS-PNFA		ALS patient meeting Neary criteria for PNFA
	ALS-SD		ALS patient meeting Neary criteria for SD
ALSbi			ALS patient meeting at least two non-overlapping supportive diagnostic features from either the Neary criteria (51) or Hodge's criteria (2) for FTD
ALSci			Evidence of cognitive impairment at or below the 5th percentile on at least two distinct tests of cognition that are sensitive to executive functioning
FTD-MND-like			A neuropathological diagnosis in which FTLD is the primary diagnosis but in which there is neuropathological evidence of motor neuron degeneration, but insufficient to be classified as ALS
ALS-dementia		ALS-dementia (ALS-D)*	ALS with dementia, not typical of FTLD
	ALS-AD		ALS in association with AD
	ALS-vascular dementia		ALS in association with vascular dementia
	ALS-mixed dementia		ALS in association with a mixed dementia (e.g. AD-vascular dementia)
ALS-Parkinsonism-dementia complex		Western Pacific variant of ALS; lytico bodig.	ALS concurrent with dementia and/or Parkinsonism occurring in hyperendemic foci of the western Pacific

*Note that the term 'ALS-dementia' has been used generically within the literature to imply the presence of any clinical or neuropathological evidence of cognitive or behavioural impairment and thus appears in two synonymous categories. The participants recommend restriction of the use of 'ALS-dementia' to refer to specific dementias.

Table 5. Strong (2008): The syndromes of frontotemporal dysfunction in amyotrophic lateral sclerosis.

Different Authors have been investigating differences in psychometric testing characterizing the cognitive impairment. Evidences from neuropsychological examination[76] show that ALS patients are significantly impaired in tests of working memory, sustained attention, response inhibition, naming, verbal fluency and complex visuo-spatial processing. The memory impairment seems to be secondary to deficits in forming learning strategies and retrieval. Dysfunctions in cognitive and behavioural aspects may be present in 20–50% of cases and 5-15% ALS patients may develop a dementia of the frontotemporal type[63,77,70]. When encountered, an insidiously progressive behavioural disorder with affective symptoms may occur, with impairments of verbal fluency, word-finding difficulties, lexical disorganization, and reliance on stereotypic utterances[72,67]. Behavioural and/or language impairments, in some cases, are severe enough to account for a diagnosis of FTD[78].

Compared to ALS with spared cognition, patients with ALS-FTD are reported to have a reduced survival[79,80]. Ascertaining the presence of a frontotemporal syndrome in ALS is extremely important since it influences the compliance and efficacy of life-prolonging therapies: patients may demonstrate a reduced decision

making and a diminished ability in undertaking information and assuming decisions about invasive treatments[81,82].

Finally, a dysfunction of the prefrontal cortices may be responsible for a Theory of Mind (ToM) deficit which can contribute to patients' difficulty in understanding and managing social interactions appropriately[83,84].

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Chapter 2

2.1 PROJECT

It is now recognized that 10% to 50% of patients with ALS present a subtle cognitive decline [1,2] and 5% to 10% have an overt frontotemporal dementia (FTD), characterized by personality changes, irritability, poor insight, and deficits in frontal executive functions.[3,4] Compared to ALS with spared cognition, patients with ALS-FTD are reported to have a reduced survival.[5,6]

As ALS progresses, patients become more and more dependent on caregivers for everyday tasks; therefore, the required caregiver time progressively increases, and with it the burden on caregivers. Caregiver time is, at least for >informal caregivers, a hidden economic cost, affecting their income by denying other occupational possibilities and reducing their quality of life. An analytical study on ALS caregiver time allocation found that mean time spent in caregiving was 570 min each day (range 15–3,051 min), and caregiver time and the mean number of caregivers (both paid and unpaid) for each patient increased with increasing disability score[7].

As ALS patients become weaker, they require greater care. This burden usually falls to the caregiver, and thus, as patients lose independence, so do caregivers. Patient and caregiver may be considered a dyad as each one influences the other at various levels, physically, psychologically and emotionally. Although patients and caregivers each overestimate the psychosocial impact of the disease on the other, there is generally agreement between them when assessing certain issues such as pain, control over ALS, optimism, and will to live[8].

Usually, caregivers become the main source of information about how the patient is functioning at home, since it has been shown that they can accurately report information about the patient's physical function, even at the end of life [8].

The personal experiences of ALS patients and caregivers differ somewhat: patients are initially shocked by their symptoms (existential shock) and ambivalent about knowing the diagnosis, struggle with their increasing loss of control and have to learn to be cared for, have to create meaning, face the change in relationships and,

finally, abandon the concept of ‘‘normality’’ accepting that of ‘‘dynamic normality”[9]. Their caregivers, on the other hand, are initially de-stabilized and search for answers, have to face forced life changes, have to learn through caring, and accept ‘‘a false normality’’ while preparing for loss [9].

A better knowledge of ALS patients’ and caregivers’ psychological reactions would certainly help health care providers to better plan their interventions.

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2.3 AIMS OF THE PRESENT PROJECT

The aim of the present project was to assess the frequency and the clinical and radiological pattern of cognitive impairment in series of patients with ALS.

In addition we evaluated the effect of neurobehavioral dysfunctions on survival and on the quality of life in patients with ALS and their caregivers. We considered the influence of the cognitive impairment on the course of the disease: the acceptance of the diagnosis, the decision making, the compliance, the use and the tolerance of life-prolonging therapies, and, finally, the survival.

Furthermore, we assessed the presence of anxiety and depression in the caregivers. We evaluated the caregivers' burden to understand if the neurobehavioral dysfunctions could negatively influence the patient-caregiver relationship.

The final purpose of this study was to improve the burden of care and the compliance of ALS patients with cognitive impairment and their caregivers.

2.4 METHODS

We invited to participate to the study all patients with ALS, consecutively seen in our ALS Center and diagnosed between 1 January 2009 and 31 December 2013, meeting El-Escorial revised diagnostic criteria for definite, probable and probable laboratory-supported ALS.

Disease severity was assessed with the amyotrophic lateral sclerosis-functional rating scale revised (ALSFRS-R) scale.

At the diagnosis, the patients underwent the neurological examination and an extensive neuropsychological battery, selected according to Clinical Diagnostic Criteria for Frontotemporal Lobar Degeneration, and ALS-FTD Consensus Criteria, and it was administered by a neuropsychologist skilled on ALS and working in our Center.

The battery included: Mini Mental State Examination; Wisconsin Card Sorting Test; Trail Making A and B; Stroop Colour-Word Interference Test; letter and category fluency test; Wechsler Memory Scale II—revised (Form 2); Rey-Osterrieth Complex Figure Test; Token test; Wechsler Adult Intelligence Scale revised; Raven's Progressive Colored Matrices; Frontal Assessment Battery. In some cases supplementary tasks were administered for a comprehensive evaluation of language; the following tests were used: semantic systems tests of the Battery for the Analysis of Aphasic Deficits[10] and the Silhouette trial of the Visual Object and Space Perception battery.[11] Depression was evaluated using Zung Depression Scale (ZDS), a self-reported scale with 20 items, each rated from 1 to 4, obtaining a total score ranging from 20 to 80; a score between 50 and 59 indicates mild depression, a score between 60 and 69 indicates moderate depression, and a score over 70 indicates severe depression. Quality of life (QoL) was assessed with the McGill Quality of Life Questionnaire (MQoL), a 16-item questionnaire, each rated from 0 (not at all) to 10 (extremely) widely used to assess QoL in ALS patients and caregivers. MQoL includes 5 domains, three of which are health related (physical well-being, physical symptoms, psychological symptoms) and two non-health related (existential wellbeing, support). Moreover, the respondent is also asked to indicate her/his self-perceived quality of life in the past 2 days in a single-item scale (MQoL-SIS), rated from 0 (very bad) to 10 (excellent). Both patients and caregivers were assessed with MQoL. Caregiver burden was assessed with the Caregiver Burden Inventory (CBI), a 24-item self-administered rating scale. Its scores range from 0 (lowest level) to 100 (highest level). CBI includes five domains of burden: time dependence, developmental, physical, social, and emotional. All the patients were invited to undergo a MRI fiber-tracking and a Brain PET-CT with 18FFDG.

All patients were prospectively followed with clinic or home visits scheduled at 2 to 3 months interval. Enteral nutrition (EN) and non- invasive ventilation (NIV) were proposed according to the current clinical guidelines. Both interventions are given free of charge by the Italian National Health System. We have considered as NIV-treated each patient who was prescribed the use of NIV and used it for at least 1 day (intention-to-treat analysis). A patient was defined tolerant to NIV if he or she was able to use the ventilator for at least 4 consecutive hours/day.

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Chapter 3

Cognitive correlates in amyotrophic lateral sclerosis: a population-based study in Italy

3.1 INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterised by a progressive loss of spinal, bulbar and cortical motor neurons, leading to voluntary muscles weakness and wasting and ultimately to death due to respiratory failure. While in about 90% of patients ALS occurs sporadically, in 10% it is genetically transmitted.[1 2] Extramotor features in ALS include cognitive changes, which have been described in 10–50% of patients.[3 4]

Frequency and clinical correlates of cognitive impairment in ALS are still poorly understood. With only one exception,[4] all studies have been performed on small clinic-based cohorts and did not use standardised methodologies for the evaluation of cognition. Recent consensus criteria proposed a classification of frontotemporal cognitive and behavioural syndromes in ALS[5] which includes ALS with frontotemporal dementia (ALS-FTD) and two milder forms of ALS with behavioural impairment (ALS-Bi) and ALS with cognitive impairment.

The aim of this study was to assess the frequency and the clinical pattern of cognitive impairment in a population-based series of patients with ALS, identified through the Piemonte and Valle d'Aosta register for ALS (PARALS), fully characterised from the clinical and genetic point of view.

3.2 METHODS

We invited to participate to the study all patients with ALS resident in the provinces of Torino and Cuneo of Piemonte region, Italy, (n=281), and diagnosed between 1 January 2009 and 31 December 2011, identified through the Piemonte and Valle

d'Aosta register for ALS,[6] meeting El Escorial revised diagnostic criteria for definite, probable and probable laboratory-supported ALS.[7] Disease severity was assessed with the amyotrophic lateral sclerosis—functional rating scale revised (ALSFRS-R) scale.[8] All patients underwent pulmonary function tests within 4 weeks before or after the neuropsychological evaluation.

Patients with history of neurological disorders affecting cognition (major stroke, severe head injuries, mental retardation), alcohol-dependence and drug-dependence, severe mental illness and use of high-dose psychoactive medications were tested but not included in data analysis. Patients resident in the area but who were not of Italian mother tongue were assessed only through an unstructured interview and therefore were excluded from the analysis.

Patients were invited to participate to the study at the time of the diagnosis or during the first scheduled follow-up visit (~2 months later) and were interviewed at home or at the ALS clinic. In no case cognitive examination was performed more than 12 months after diagnosis. A total of 127 healthy age-matched, gender-matched and education-matched controls underwent the same neuropsychological battery. Controls were enrolled thought patients' general practitioners (GPs) and were interviewed at home, at the GP office or at the hospital. Only nine subjects asked to participate as controls denied their participation. Most GPs were willing to collaborate (~85%). When a GP did not collaborate, another GP practicing in the same area was contacted.

Neuropsychological battery

Patients and controls underwent a battery of neuropsychological tests encompassing executive function, memory, visuospatial function and language, selected according to Clinical Diagnostic

Criteria for Frontotemporal Lobar Degeneration,[9] and ALS-FTD Consensus Criteria.[5] The neuropsychological battery included: Mini Mental State Examination; Wisconsin Card Sorting Test; Trail Making A and B; Stroop Colour-Word Interference Test; letter and category fluency test; Wechsler Memory Scale II—

revised (Form 2); Rey-Osterrieth Complex Figure Test; Token test; Wechsler Adult Intelligence Scale revised; Raven's Progressive Colored Matrices; Frontal Assessment Battery. In some cases supplementary tasks were administered for a comprehensive evaluation of language; the following tests were used: semantic systems tests [7 and 8] of the Battery for the Analysis of Aphasic Deficits[10] and the Silhouette trial of the Visual Object and Space Perception battery.[11] Neurobehavioral dysfunction was determined on the basis of direct observation and patient's history,[9] [12] and with the Frontal Systems Behavior Scale,[13] using the Family-form evaluated by a close relative (scores: normal ≤59, borderline 60–64; pathological ≥65). If a subject had scores reflecting a frontal systems abnormality in the premorbid and in the postillness forms, he/ she was considered pathological only if there was an increase of ≥10 points at the T score between the two forms.[14] Anxiety and depression were assessed with the Hospital Anxiety and Depression Scale; the item 'I feel slowed down' was discussed with patients in order not to refer to physical disability. Cognitive impairment was defined as impairment on two tests of executive or non-executive function that was below the 5th centile of healthy controls. The battery was administered following the same sequence in order to avoid the possible differential interference of the answers of one test over the others. The administration of the battery required ~2 h, and was usually performed in the morning. If the subject felt too tired, a further session was scheduled to complete the battery, within 2 weeks after the first one. Patients' and controls' O2 saturation at the time of the neuropsychological testing was measured with a pulse oximetry; none of the patients and controls had evidence of hypoxaemia (oxygen saturation <92 mm Hg).

Cognitive classification.

Clinical diagnosis and cognitive classification were performed with the collaboration of two neurologists specialist in ALS and FTD and two neuropsychologists. Patients' cognitive status was classified as follows:

A. ALS with normal cognition.

B. ALS with frontotemporal dementia (ALS-FTD). The diagnosis of frontotemporal dementia was defined according to Clinical Diagnostic Criteria for Frontotemporal Lobar Degeneration.[9]

C. ALS comorbid with non-FTD dementias. The diagnoses of non-FTD dementias were based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders-IV-TR15 and those of the National Institute of Neurological and Communicative Disorders and Stroke— Alzheimer's Disease and Related Disorders Association.[16]

D. ALS with executive cognitive impairment (ALS-ECI). Patients with ALS who did not meet criteria for FTD or other types of dementia, but who had an impairment in two tests of executive dysfunction compared with healthy controls, that is, had an executive dysfunction, were classified as ALS with executive cognitive dysfunction. A more conservative cut-off than that proposed by the ALS-FTD Consensus Criteria5 was used (2.3rd centile).[4]

E. ALS with non-executive cognitive impairment (ALS-NECI). This group includes patients with ALS with impairment in two non-executive domains, in particular visuopraxic abilities, and no impairment in executive function.

F. ALS with behavioural impairment (ALS-Bi). This group includes patients with predominant behavioural disturbances and with impairment in none or only one test of executive dysfunction and no impairment in non-executive domains.

G. ALS with non-classifiable cognitive impairment (ALS-NCCI). This group includes patients with ALS with impairment in one executive and/or one non-executive test, sometimes associated with smooth behavioural changes.

Genetic analysis

All coding exons and 50 bp of the flanking intron-exon boundaries of SOD1, of exon 6 of TARDBP, and of exons 14 and 15 of FUS and exons 5, 9, 12 and 14 of OPTN and the single exon of ANG have been PCR amplified, sequenced using the Big-Dye

Terminator v3.1 sequencing kit (Applied Biosystems), and run on an ABIPrism 3130 genetic analyser. In patients with positive family history for ALS or FTD all coding exons of VCP have also been assessed. These exons were selected as the vast majority of known pathogenic variants are known to lie within these mutational hot spots. A repeat-primed PCR assay was used to screen for the presence of the GGGGCC hexanucleotide expansion in the first intron of C9ORF72.[17] A cut-off of ≥30 repeats was considered pathological.

Statistical methods

Comparisons between means were made with Student t test or analysis of variance; comparisons between categorical variables were made with $\chi 2$ test; for all comparisons, Levene's test was used to confirm the equality of variances. Survival was calculated from onset to death/tracheostomy or censoring date (30 June 2013), using the Kaplan-Meier method, and compared with the log-rank test. No patients were lost to follow-up. Multivariable analysis was performed with Cox proportional hazards model (stepwise backward) (for details, see table 3). For the analysis of the relationship between cognitive status and disease progression, the progression rate for the ALSFRS-R score, its four subscores (bulbar, fine motor, gross motor and respiratory) and forced vital capacity per cent of predicted (FVC%) was calculated as the mean monthly number of points lost from disease onset to the time of cognitive evaluation. For example, the progression rate for the ALSFRS-R score was calculated as follows: (48-ALSFRS-R at time of cognitive evaluation)/duration from onset to diagnosis (months). In the Cox model, these variables were dichotomised on the basis of their median value. The list of all variables included in the Cox model is reported in table 3. A p level <0.05 was considered statistically significant. All tests were two-tailed. Statistical analyses were carried out using SPSS V.20.0 (SPSS, Chicago, Illinois, USA).

Standard protocol approvals, registrations and patient consents The study design was approved by our institutional Ethical Committee. Patients and controls signed a written informed consent. The database was managed according to the Italian law for the protection of privacy.

3.3 RESULTS

A flow chart of the sequence of participants' selection is reported in figure 1. Of the 281 patients diagnosed in the study area in the 2009–2011 period, 202 (71.9%) underwent the neuropsychological battery. Of the 79 non-captured patients, 34 were not able to undergo the battery of tests due to their motor disability (7 patients were tracheostomised or used non-invasive ventilation for more than 16 h; 18 patients had severe difficulties in writing and speaking; 9 patients had a severe fatigue and, although willing to collaborate, could not adequately perform the whole battery), 5 were not of Italian mother tongue, 30 declined participation and 10 died before being tested. Nineteen tested patients were excluded from the analysis due to previous neurological disorders affecting cognition (seven patients), severe mental illness (six), drug or alcohol abuse (two), use of high-dose psychoactive medications (one due to bipolar disorder, one due to paranoid schizophrenia), analphabetism (one) and mental retardation (one). Non-captured patients did not differ demographically and clinically from those who underwent the examination (table 1). The median time from diagnosis to the neuropsychological assessment was 1.9 months (IQR 1.2–3.8 months).

Cognitive classification

According to the classification criteria for patients' cognitive status, 23 (12.6%) had ALS-FTD, 36 (19.7%) ALS-ECI, 10 (5.5%) ALS-NECI, 11 (6.0%) ALS-Bi and 11 (6.0%) ALS-NCCI; 91 (49.7%) patients were cognitively normal (see online E-figure S1). One patient had comorbid Alzheimer disease (AD). Twenty-two out of the 23 patients with ALS-FTD presented with behavioural changes typical of behavioural variant fronto-temporal lobar dementia (FTLD); one patient had semantic dementia. Cognitive groups were clinically and demographically different (table 2). Patients with ALS-FTD, ALS-ECI and ALS-Bi had a higher mean age (~70 years) than those with normal cognition and ALS-NECI. ALS-NCCI had the lowest age at onset. Patients with ALS-FTD and those with ALS-NECI had a higher frequency of bulbar onset than all other groups (p=0.003). The mean number of education years was significantly lower in patients with ALS-FTD than in all other groups. ALSFRS-R

score and FVC% at the time of the cognitive examination did not show significant differences. However, the ALSFRS-R bulbar subscore (items 1, 2 and 3 of the ALSFRS-R scale) was significantly lower in the group with ALS-FTD (data not shown). The rate of decline of ALSFRS-R, of its subscores and of FVC% was similar in the various groups.

Patients' cognitive status and genetics

Of the nine cases carrying the GGGGCC hexanucleotide repeat expansion in the first intron of the C9ORF72 gene, six had ALS-FTD, two ALS-ECI and one was cognitively normal. One of the five patients with SOD1 mutations and one of the five patients with TARBDP mutation had ALS-Bi. Both patients with FUS and OPTN mutations were cognitively normal. Genetic status was significantly correlated to the presence/absence of cognitive impairment ($p=0.0001$).

Survival analysis

The overall median survival time was 2.7 years (95% CI 2.4 to 2.9) (figure 2). Patients with ALS-FTD had a significantly shorter survival (1.9 years, 95% CI 1.7 to 2.2) than any other group of patients with cognitive impairment, with the only exception of those with ALS-NECI (2.0 years, 95% CI 1.6 to 2.4). Patients with ALS-Bi (3.0 years, 95% CI 0.8 to 5.3) had a survival time similar to that of cognitively normal patients (3.1 years, 95% CI 2.7 to 3.4). Patients with ALS-ECI had an intermediate survival between the two groups (2.6 years, 95% CI 2.0 to 3.1). Cognitive status remained significant in Cox multivariable analysis (table 3). The presence of FTD significantly increased the risk of death compared with non-demented patients; also ALS-NECI and ALS-ECI resulted to be independently related to a worse outcome.

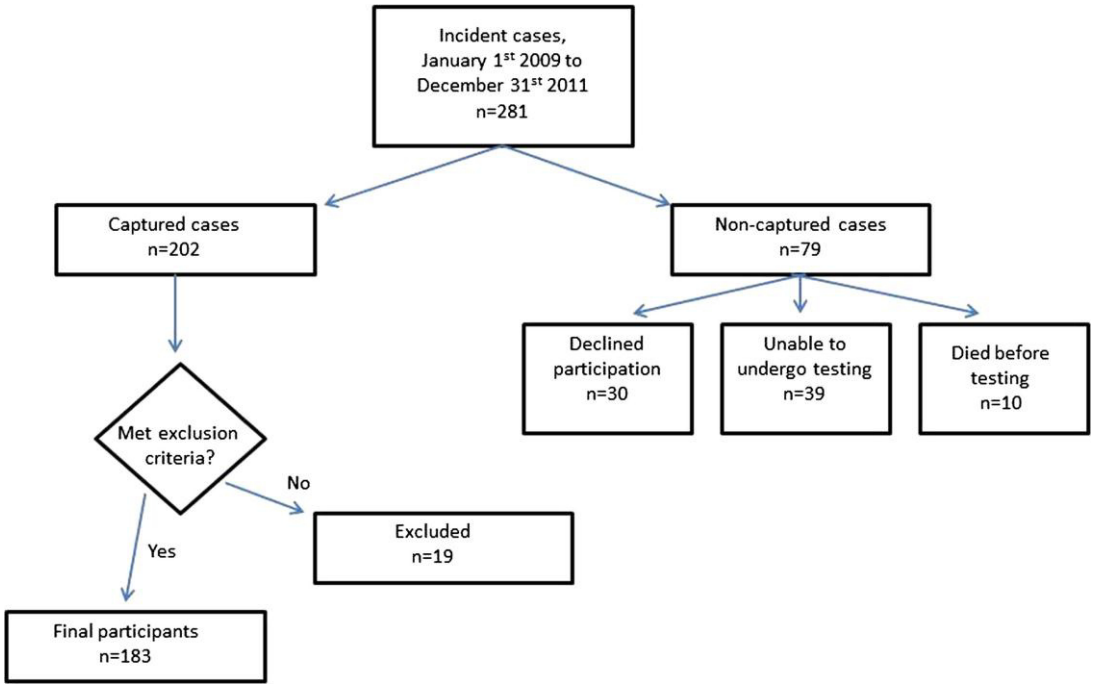

Figure 1 Flow chart showing capture rate and the sequence of participant selection. ALS, amyotrophic lateral sclerosis

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Table 1 Demographic and clinical characteristics of patients with ALS and controls

	Patients with ALS enrolled for the study (n=183)*	Non-captured patients with ALS (n=79)	Healthy controls (n=127)
Mean age at onset (years, SD)	67.0 (9.9)	66.9 (10.3)	66.5 (11.4)
Gender (female, %)	76 (41.5%)	35 (44.3%)	54 (42.5%)
Education (number of years, SD)	8.3 (4.1)	8.5 (4.2)	8.7 (4.3)
Site of onset (bulbar, %)	62 (33.9%)	26 (32.9%)	–

All comparisons are non-significant.
*Nineteen patients tested but not included in the study due to exclusion criteria (see text) are not shown in the table.
ALS, amyotrophic lateral sclerosis.

3.4 DISCUSSION

We have studied cognitive status in a population-based series of patients with ALS in Italy using an extensive battery of tests evaluating multiple cognitive domains. In our series, 13% of patients had a comorbid FTD, while 50% had normal cognition. The remaining patients who did not meet the criteria for FTD, but otherwise had some clinical significance, including a negative effect on disease outcome, showed various degrees of cognitive impairment. The frequency of cognitive impairment in our epidemiological series was similar to that described in Irish patients.[4] However, differently from that study, according to ALS-FTD Consensus Criteria[5] we identified a group of patients with cognitive impairment, that is, patients with isolated behavioural impairment, accounting for 6% of cases. These patients did not show impairment in more than one executive or one nonexecutive test, but had a behavioural impairment at extensive clinical observation and at the Frontal Systems

Behavior Scale test. Interestingly, one control patient also met the criteria for cognitive behavioural impairment. We also identified a group of patients (6% of our series) (NCCI) with impairment in one executive and/or one nonexecutive test who did not fulfil criteria for other cognitive groups. These patients largely differed from cognitively normal patients and from all other cognitive subgroups, being younger, less frequently bulbar, and with a higher mean education level. It is possible that this group includes premorbid FTD cases, that is, patients who did not meet the criteria for other cognitive impairments but who could have developed more severe impairment later in the course of the disease.

In our series, patients with ALS-FTD with full-blown comorbid dementia had a significantly lower educational level, in keeping with another population-based study.[4] The lower mean educational level in Italian patients and controls in this series compared with that of the Irish study[4] reflects the low level of education in the Italian population born before 1950.[18] Educational level, as well as higher occupation attainment, are considered proxies of cognitive reserve.[19] The role of cognitive reserve in protecting from AD is widely accepted,[19] although the underlying mechanisms are still unclear. Cognitive reserve is also involved as a protective mechanism in several cognitive functions impaired in FTD, in particular speed of processing/ executive functioning, visual spatial abilities and verbal memory.[20–22] Our finding suggests that either a long-standing frontal dysfunction interferes with learning and might underline the future development of cognitive impairment or low education level puts patients at higher risk of developing FTD. Differently from patients with ALS-FTD, those with ALS-ECI, ALS-NECI and ALS-Bi did not differ from normal controls regarding educational level, and those with ALS-NCCI had a higher educational level than other cognitive groups and controls. This finding may indicate that either cognitive reserve does not have a role in these variants of cognitive impairments in ALS, or that some patients develop cognitive impairment not meeting the full criteria for FTD because they are protected by their cognitive reserve. Patients with ALS-FTD and ALS-ECI had an older age at onset than controls, ALS-Bi and ALS-NECI, in keeping with various papers,[3 23] but not all.[4,24] This difference may be due to the higher mean age of our patients compared with other series.[4 24] In our series, bulbar onset was significantly more frequent in ALS-

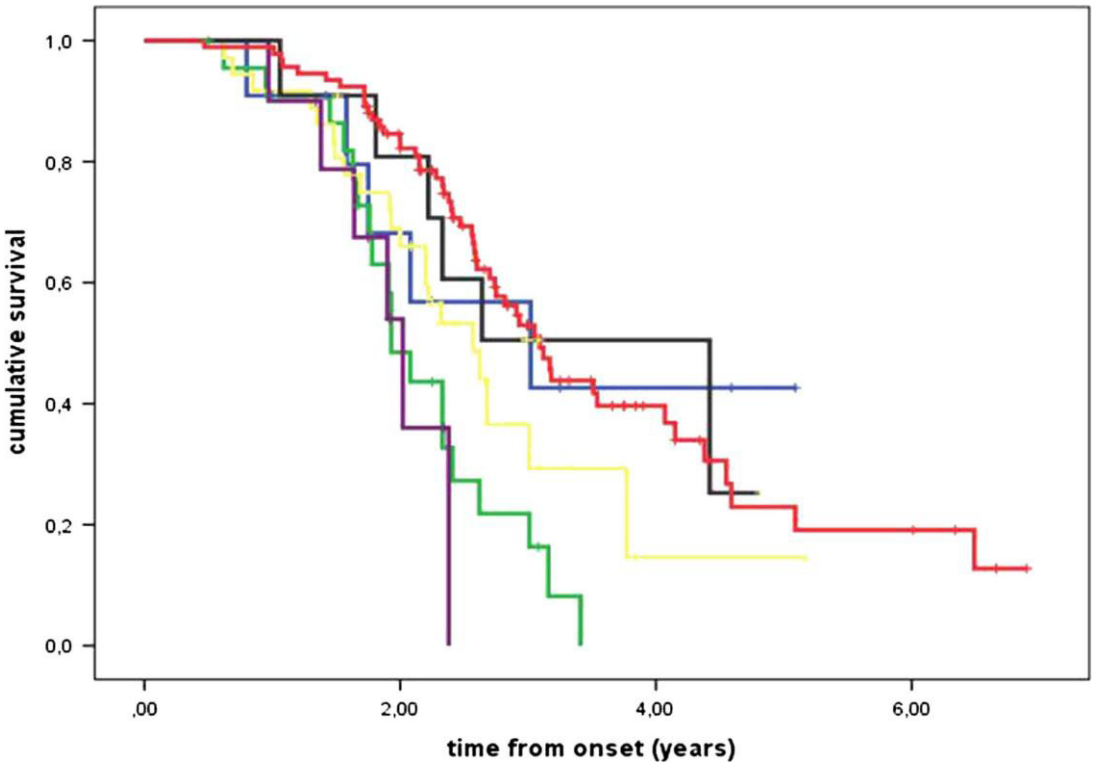
FTD and ALS-NECI. Bulbar onset has been found to be more commonly related to FTD features in several series,[3 25 26] but not in all.[4 23] Supporting our findings, a [18F]2-fluoro-2- deoxy-D-glucose (FDG) Positron Emission Tomography (FDGPET) study showed a significantly higher relative decrease in metabolism in large frontal and parietal regions in bulbar onset patients compared with spinal ones.[27]

Table 2 Demographic and clinical characteristics of patients with ALS according to cognitive status

	Cognitively normal (n=91)	ALS-FTD (n=23)	ALS-ECI (n=36)	ALS-NECI (n=10)	ALS-Bi (n=11)	ALS-NCCI (n=11)	p Value
Mean age at onset (years, SD)	65.9 (10.6)	69.1 (7.7)	70.0 (7.4)	64.9 (12.8)	68.1 (9.9)	61.9 (9.5)	0.04
Gender (female, %)	40 (43.5%)	11 (47.8%)	14 (38.9%)	4 (40.0%)	4 (36.8%)	4 (36.8%)	0.97
Disease duration at time of interview (years, SD)	1.23 (1.11)	1.28 (0.60)	1.18 (0.76)	1.03 (0.63)	1.19 (1.17)	1.20 (0.62)	0.99
Site of onset (bulbar, %)	28 (30.4%)	10 (60.9%)	10 (27.8%)	6 (60.0%)	2 (18.2%)	2 (18.2%)	0.015
Time lapse between diagnosis and interview (years, SD)	0.25 (0.23)	0.35 (0.31)	0.26 (0.26)	0.12 (0.05)	0.18 (0.12)	0.31 (0.32)	0.12
Mean education (years, SD)	8.6 (3.7)	4.7 (1.9)	7.8 (4.0)	9.5 (5.1)	9.9 (5.2)	12.4 (4.4)	0.0001
FALS (%)	11 (12.1%)	7 (30.4%)	2 (5.6%)	0	0	0	0.015
Mean ALSFRS-R score at time of interview (SD)	38.8 (7.6)	34.9 (7.3)	36.4 (7.6)	40.9 (6.4)	34.5 (12.8)	39.7 (6.3)	0.086
Mean FVC% at time of interview (SD)	91.2 (25.5)	80.7 (25.0)	88.4 (28.7)	83.2 (22.3)	83.7 (26.6)	92.3 (23.1)	0.181

One patient with comorbid Alzheimer's disease is not included in the table.
p Value is calculated with analysis of variance (age, education, time lapse, ALSFRS-R, FVC) or χ^2 (gender, site of onset, FALS status).
ALS, amyotrophic lateral sclerosis; Bi, behavioural impairment; ECI, executive cognitive impairment; FALS, familial ALS; FTD, frontotemporal dementia; FVC%, forced vital capacity per cent of predicted; NECI, non-executive cognitive impairment; NCCI, non-classifiable cognitive impairment.

Figure 2 Survival curves from disease onset to death/tracheostomy of the incident amyotrophic lateral sclerosis (ALS) cohort according to their cognitive classification; p=0.004. Ticks are censored patients. Red, patients with ALS with normal cognition; green, patients with ALS with comorbid frontotemporal dementia (ALS-FTD); yellow, patients with ALS with executive cognitive impairment (ALS-ECI); violet, patients with ALS with non-executive cognitive impairment (ALS-NECI); blue, patients with ALS with behavioural impairment (ALS-Bi); black, patients with ALS with non-classifiable cognitive impairment (ALS-NCCI). The single patient with ALS with comorbid dementia of Alzheimer's type is not included.


1,0
0,8
0,6
0,4
0,2
0,0
cumulative survival
,00
2,00
4,00
6,00
time from onset (years)

In this study a genetic characterisation of all patients with ALS was performed. C9ORF72 hexanucleotide repeat expansion was the more frequent mutation, and, as expected,[1 28] it was also the one significantly associated with FTD compared with other gene mutations or no genetic mutations. However, patients with FTD with C9ORF72 mutation accounted only for a fourth of all cases with ALS-FTD, indicating that other genetic, epigenetic or environmental mechanisms underlie the involvement of prefrontal cortex in ALS. The role of still unknown genes is supported by the fact that ALS-FTD was more commonly related to a positive family history of ALS than all other cognitive conditions. Cognitive impairment has a strong negative impact on ALS outcome.[4 14 26 29 30] The survival of our patients with ALS-FTD and ALS-ECI was about 1 year shorter than that of cognitively normal, patients with ALS-Bi and ALS-NECI. The reason of this finding is still not completely understood. The presence of neurobehavioral dysfunction or of isolate dysexecutive behaviour in ALS at diagnosis has been found to be a strong predictor of a poor outcome, partially related to a reduced efficacy of life-prolonging therapies such as non-invasive ventilation and percutaneous endoscopic gastrostomy,[14] while the decline in cognitive function was faster in patients who were cognitively impaired at baseline.[31] However, we could not find any significant correlation between ALS progression, evaluated with ALSFRS-R at the time of the interview, and patients' cognitive status, indicating that the shorter survival of patients with ALS with cognitive impairment is not completely explained by the progression rate of their motor impairment. Cox multivariable analysis confirmed that cognitive status was independently related to ALS outcome. A limitation of this study is that it is based on a single observation shortly after the diagnosis of the disease. However, at least two series with a follow-up cognitive assessment in patients with ALS found that an onset of FTD or other forms of cognitive impairment is rare during the disease course.[31 32] In this study of cognitive status of incident Italian patients with ALS, the frequency of cognitive impairment was similar to that reported by a population-based study performed in Ireland,[4] despite the different genetic backgrounds of the two populations,[1 2] that is, the higher frequency of C9ORF72 mutations in Ireland, and of SOD1 and TARDBP mutations in Italy.

We found that ~15% of patients had ALS-FTD and another 35% had some degree of cognitive impairment. Comorbid FTD was associated with higher age at onset, bulbar onset and lower educational level, likely to represent a proxy for a reduced cognitive reserve, and has a significantly reduced survival than any other cognitive group. It remains to be understood whether ALS-ECI and ALS-NECI represent incomplete forms of cognitive impairment or discrete cognitive syndromes within the spectrum of ALS and FTD, with strong effect on the disease outcome.

Table 3 Cox's multivariable analysis

Variable		OR (95% CI)	p Value
ALS-FTD	No	1	0.0001
	Yes	3.7 (2.1 to 6.6)	
ALSFRS total score	<0.7 points/month	1	0.003
	≥0.7 points/month	1.9 (1.3 to 2.9)	
ALS-NECI	No	1	0.004
	Yes	3.6 (1.5 to 8.7)	
ALS-ECI	No	1	0.025
	Yes	1.8 (1.1 to 3.1)	
Type of onset	Spinal	1	0.03
	Bulbar	1.7 (1.1 to 2.7)	

The following variables were included in the Cox model: age (18–59, 60–69, 70–79, 80–99) years, gender, FALS status (FALS vs SALS), gene mutation (*C9ORF72, SOD1, TARDBP, FUS, OPTN*, no mutation identified), years of education (≤5, 6–8, 9–13, ≥14), progression rate of ALSFRS-R total score (<0.7 vs ≥0.7 point/months), ALSFRS-R bulbar score (<0.15 vs ≥0.15 points/month), ALSFRS-R fine motor score (<0.2 vs ≥0.2 points/month), ALSFRS-R gross motor score (<0.22 vs ≥0.22 points/month), ALSFRS-R respiratory score (<0.1 vs ≥0.1 points/month), FVC% (<0.50 vs ≥0.50 months). Cognitive status was included as ALS-FTD (yes vs no), ALS-ECI (yes vs no), ALS-NECI (yes vs no) ALS-Bi (yes vs no) and ALS-NCCI (yes vs no). Enteral nutrition and non-invasive ventilation were included as time-dependent variables. ALS, amyotrophic lateral sclerosis; Bi, behavioural impairment; ECI, executive cognitive impairment; FALS, familial ALS; FTD, frontotemporal dementia; FVC%, forced vital capacity per cent of predicted; NECI, non-executive cognitive impairment; NCCI, non-classifiable cognitive impairment.

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Chapter 4

Neurobehavioral dysfunction in ALS has a negative effect on outcome and use of PEG and NIV

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder characterized by progressive weakness of upper and lower limbs and bulbar and respiratory muscle, due to a loss of upper and lower motor neurons. Traditionally, cognition has been considered preserved in patients with ALS. However, it is now recognized that 10% to 50% of patients with ALS present a subtle cognitive decline1,2 and 5% to 10% have an overt frontotemporal dementia (FTD), characterized by personality changes, irritability, poor insight, and deficits in frontal executive functions.3,4 Compared to ALS with spared cognition, patients with ALS-FTD are reported to have a reduced survival.5,6

The aim of the present study was to assess the effect of neurobehavioral dysfunction on survival and the use of life-prolonging therapies in a population-based setting of patients with ALS.

Table Demographic and clinical characteristics of patients with and without neurobehavioral impairment

	Patients without neurobehavioral impairment (n = 87)	Patients with neurobehavioral impairment (n = 41)	*p*
Female, n (%)	36 (41.4)	21 (51.2)	NS
Bulbar site of onset, n (%)	20 (23.0)	16 (39.0)	0.05
Age at onset, y, mean (SD)	64.9 (11.7)	64.2 (9.3)	NS
Time delay to diagnosis, mo, mean (SD)	10.1 (7.5)	9.3 (8.7)	NS
Enteral nutrition, n (%)	31 (35.6)	11 (26.8)	NS
Noninvasive ventilation, n (%)	31 (35.6)	13 (31.7)	NS

Abbreviation: NS = not significant.

4.1 METHODS

The Piemonte and Valle d'Aosta Register for ALS (PARALS) is a prospective epidemiologic register established in 1995 collecting all ALS incident cases in 2 Italian regions (population: 4,332,842). Methods and epidemiologic data have been reported in detail elsewhere.7 ALS diagnosis was based on the El Escorial diagnostic criteria (EEC) and the EEC revised criteria.8,9 All the 132 patients with ALS diagnosed in the Province of Torino (population, 2,236,941) between January 1, 2007, and June 30, 2008, identified through the PARALS, were invited to participate in this longitudinal study. Of these, 128 agreed, 2 refused, and 2 had no caregivers available for completing the questionnaire. Only subjects with definite, probable, and probable laboratory-supported ALS according to EEC were eligible. The interview was performed within 4 months from ALS diagnosis.

Neurobehavioral dysfunction was assessed with the Frontal Systems Behavior Scale (FrSBe),10 a 46-item questionnaire. Each question is rated from 0 (almost never) to 5 (almost always). Fourteen questions are reverse-scored. The questionnaire includes a version for the patients (Self-Rating form) and a version for the caregivers (Family Rating form). Moreover, each item is rated indicating the behavior before the illness (premorbid period) and at the present time (postillness). Raw scores are converted to T scores according to gender, age, and years of education. These scores were used in data analyses. A T score between 60 and 64 is considered borderline while a T score >65

reflects frontal systems abnormalities. The FrSBe has 3 subscales: apathy, disinhibition, and executive dysfunction. The questionnaire, which has already been effectively used in ALS,11–14 has been translated in Italian and internally validated.12 For the present study, we have considered the results of the premorbid and post illness Family Rating forms. If a patient had a score reflecting a frontal systems abnormality both in the in the premorbid form and the post illness form, he or she was considered pathologic only if there was an increase of at least 10 points at the T score between the premorbid and the post illness form. This difference was the

median increase of the score observed in a previous series of patients with ALS followed in our center.

In order to exclude that FrSBe overall score or the score of one of its subscales was influenced by the declining of ALS disability, a progression rate of the disability scale (Amyotrophic Lateral Sclerosis Functional Rating Scale–revised [ALSFRS-R]) was calculated as follows: [48 _ ALSFRS-R score at the time of the interview]/time in months where 48 is the maximum ALSFRS-R score. The progression rate was then correlated to FrSBe scores.

All patients were prospectively followed with clinic or home visits scheduled at 2 to 3 months interval. Enteral nutrition (EN) and non-invasive ventilation (NIV) were proposed according to the current clinical guidelines.15 Both interventions are given free of charge by the Italian National Health System. We have considered as NIV-treated each patient who was prescribed the use of NIV and used it for at least 1 day (intention-to-treat analysis). A patient was defined tolerant to NIV if he or she was able to use the ventilator for at least 4 consecutive hours/day.

Statistical analysis.

Survival was calculated to death/tracheostomy or censoring date (June 30, 2011), using the Kaplan-Meier method, and compared with the log-rank test. Multivariable analysis was performed with Cox proportional hazards model (stepwise backward). EN and NIV were included as time-dependent variables. Correlations were calculated with Pearson coefficient. No patient was lost to follow-up. A *p* level _0.05 was considered significant. All tests were 2-tailed. Statistical analyses were carried out using SPSS 18.0 (SPSS, Chicago, IL).

Standard protocol approvals, registrations, and patient consents.

The study design was approved by the institutional Ethical Committee of our center. Patients and caregivers signed a written informed consent. Database was managed according to the Italian law for the protection of privacy.

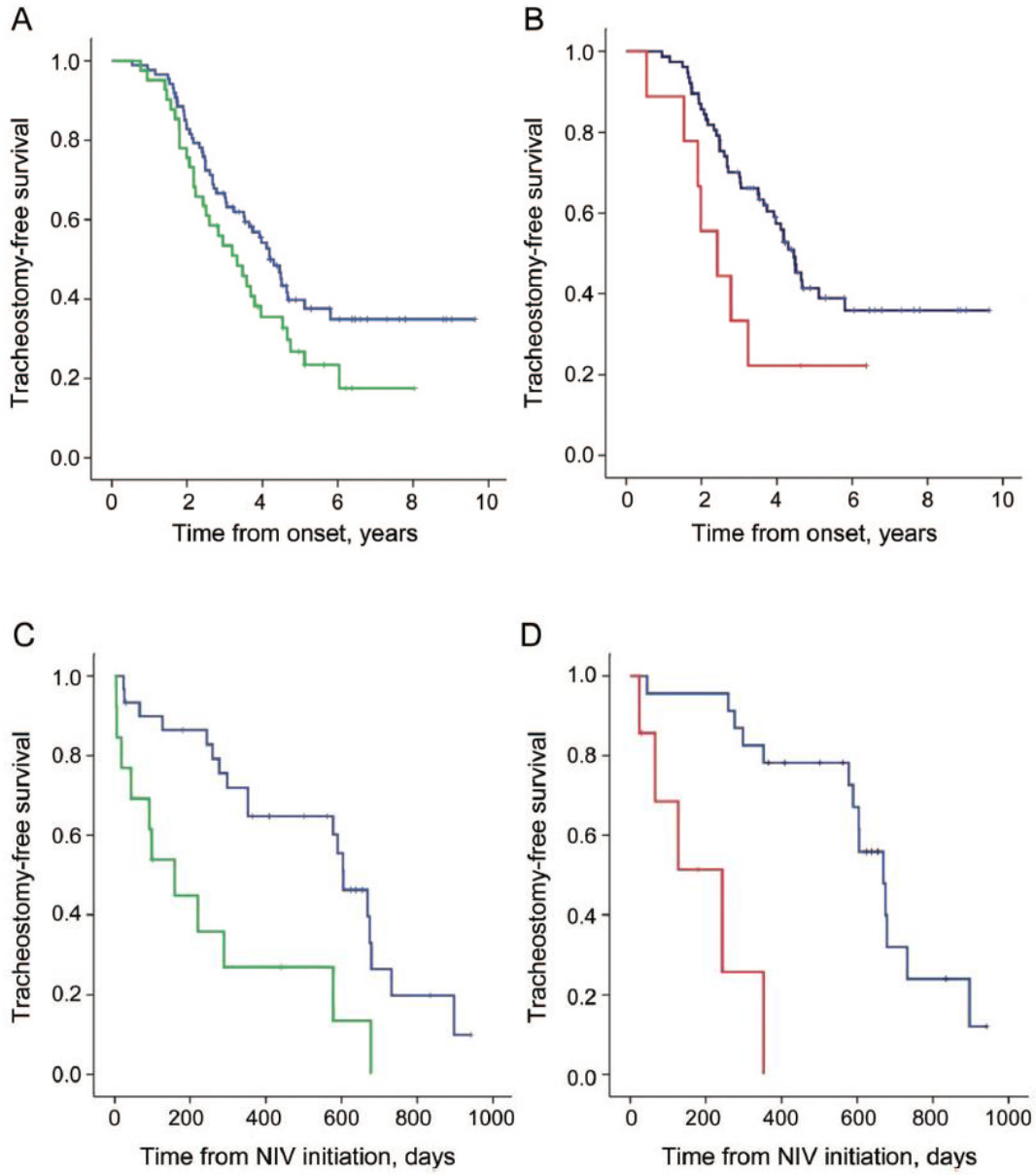
4.2 RESULTS

The 128 patients included 71 men and 57 women, with a mean age at onset of 64.7 years (SD 11; range 25.4–87.4). The mean disease duration at time of interview was 1.1 year (SD 0.9). Ninety-two patients (71.9%) had a spinal onset and 36 (28.9%) a bulbar onset. According to FrSBe (Family rating form), 41 patients (32.0%) had an overall score _65, indicating neurobehavioral dysfunction; apathy was detected in 52 patients (40.6%), disinhibition in 23 (18.0%), and dysexecutive behavior in 44 (34.4%). Nine patients (7.0%) had an isolated dysexecutive behavior. The demographic and clinical differences between patients with and without neurobehavioral dysfunction are shown in the table. No correlation was found between total FrSBe score and its subscores and the ALSRFS-R progression rate, indicating that FrSBe findings were not related to the progression of the disease. EN and NIV were performed with similar frequencies in patients with and without neurobehavioral dysfunction (EN: neurobehavioral dysfunction 11 [26.8%], without neurobehavioral dysfunction 31 [35.6%], *p*=NS; NIV: neurobehavioral dysfunction 13 [31.7%], without neurobehavioral dysfunction 31 [35.6%], *p* _ NS). Overall median survival time from ALS onset was 3.9 years (95% confidence interval 3.4–4.4). Patients with a FrSBe overall pathologic score had a significantly shorter survival than patients with a normal score (median survival, 3.3 [3.8–4.8] vs 4.3 years [2.4–4.3]) (*p* _ 0.02) (figure, A). When considering only the patients without neurobehavioral dysfunction, those subjects with a pathologic score at the dysexecutive behavior subscale had significantly a shorter survival than those without a pathologic score at the same subscale (median survival, 2.5 [1.1–3.7] vs 4.5 [3.9–4.9]; *p* _ 0.03) (figure, B). Patients with pathologic score in 1 of the 2 other subscales (apathy and disinhibition), or in both, had a similar survival as patients with no pathologic scores. Patients with a FrSBe pathologic overall score had a shorter survival after EN (median survival, 143 days [38 –248] vs 333 days [99 – 567]; *p* _ 0.007), and also after NIV (median survival, 159 days [48– 270] vs 605 days [505–705]; *p* _ 0.002) (figure, C). Patients without a pathologic overall FrSBe score but with an isolated pathologic score at the dysexecutive behavior subscale had a shorter survival after NIV (median survival, 243 days [74–412] vs 669 days [565–

774]; *p* _ 0.0001) (figure, D) but not after EN (median survival, 321 days [123–519] vs 333 days [171– 495]; *p* _ NS). Six (13.6%) of the 41 patients undergoing NIV died within 30 days after the initiation of treatment (early deaths). Of these patients, 4 had a neurobehavioral dysfunction (30.8% of those undergoing NIV) and 2 a normal overall FrSBe score (6.5% of those undergoing NIV) (*p* _ 0.03); however, both patients with a normal overall FrSBe score had an isolated dysexecutive behavior. Tolerance to NIV, as indicated by the ability to perform NIV for at least 4 consecutive hours/day, was lower in patients with neurobehavioral dysfunction (5 patients vs 1 patient with normal FrSBe score, who however had an isolated dysexecutive behavior).

The negative effect of comorbid neurobehavioral dysfunction on survival persisted in a multivariate model that included neurobehavioral dysfunction, age, gender, site of onset (bulbar vs spinal), time delay to diagnosis, NIV, EN, ALSFRS-R score at diagnosis, and forced vital capacity percent of predicted (FVC%) at diagnosis (hazard ratio 1.72; 95% confidence interval 1.22–2.92; *p* _ 0.02). The presence of dysexecutive behavior in patients without comorbid neurobehavioral dysfunction remained significant in a multivariable model including dysexecutive behavior, age, gender, site of onset (bulbar vs spinal), time delay to diagnosis, NIV, EN, ALSRFRS-R score at diagnosis, and FVC% at diagnosis (hazard ratio 2.56; 95% confidence interval 1.20–4.11; *p* _ 0.03).

Figure **Tracheostomy-free survival in patients with amyotrophic lateral sclerosis (ALS) with and without neurobehavioral impairment**



(A) Tracheostomy-free survival of patients with neurobehavioral impairment (green line) was significantly shorter than that of patients without neurobehavioral impairment (blue line). Marks indicate censored patients. (B) Tracheostomy-free survival of patients with isolated dysexecutive behavior (red line) was significantly shorter than that of patients without neurobehavioral impairment (blue line). Marks indicate censored patients. (C) Tracheostomy-free survival after noninvasive ventilation (NIV) initiation of patients with neurobehavioral impairment (green line) was significantly shorter than that of patients without neurobehavioral impairment (blue line). Marks indicate censored patients. (D) Tracheostomy-free survival after NIV initiation of patients with isolated dysexecutive behavior (red line) was significantly shorter than that of patients without neurobehavioral impairment (blue line). Marks indicate censored patients.

4.3 DISCUSSION

In this study we have assessed the effect of neurobehavioral impairment, evaluated with FrSBe, in a population-based series of patients with ALS. We have found that the presence of neurobehavioral impairment was significantly correlated to shorter patient survival and that subjects with dysexecutive behavior but without neurobehavioral impairment have a worse outcome than patients cognitively spared or with impairment limited to other neurobehavioral domains. This negative effect was independent from other prognostic factors, as indicated by the multivariable model. In our series, the negative effect of neurobehavioral impairment on survival was partly due to the reduced benefit of NIV and EN.

The frequency of neurobehavioral dysfunction in our epidemiologic series is in the range of literature. 11,12,14,16 The effect of cognitive impairment and FTD on survival of patients with ALS have been assessed in a few studies in the last decade. A shorter survival of patients with ALS–FTD was first reported in a series of 81 patients attending a tertiary ALS center.5 In that study, patients with ALS-FTD were those subjects who met Neary's criteria for FTD or had abnormal executive function on neuropsychological testing. A recent population-based prospective study on Irish patients with ALS showed that comorbidity with FTD significantly reduced survival and, similarly to our series, patients without FTD but with dysexecutive dysfunction had a shorter survival. 6 Another study, comparing patients with a simultaneous onset of ALS and FTD symptoms to those with an onset with FTD symptoms and a later development of motor symptoms, demonstrated that the co-occurrence of ALS and FTD carried a significantly shorter survival.17 Conversely, 3 studies performed on clinical series did not find any effect of cognitive impairment on ALS outcome after controlling for ALS severity.16,18,19 The observed discrepancies between these reports could be due to several reasons. First, some studies were underpowered to detect differences of survival due to the few patients included16,18,19; second, the different setting of the various studies, ranging from tertiary ALS centers to population-based series, probably determined a patient selection bias in some of them20; third, the different neuropsychological batteries used could have caused a different rate of detection of neurobehavioral impairment.

Our study has some strengths. The major strengths are the representativeness of the ALS population, with a complete ascertainment of cases from a population-based epidemiologic register7 and the enrollment of 128 out of the 132 incident cases, and the longitudinal prospective design.

The major limitation of our study is that for the assessment of cognitive impairment we did not perform a full series of cognitive testing but we relied on the FrSBe questionnaire. In fact, FrSBe is heavily based on the subjective feeling of the caregiver, which can be confounded by the loss of patients' physical abilities, as well as by his or her mood status. However, the FrSBe is a simple and validated test allowing the detection of behavioral dysfunction in patients with ALS, comparing the premorbid to the present time behavior according to the caregivers' rating.11–14 Using this questionnaire we could demonstrate that behavioral dysfunction has a great negative influence on patient survival.

We found that neurobehavioral dysfunction, and isolated dysexecutive behavior as well, significantly reduced patient survival related to the use of NIV and EN. Interestingly, patients with neurobehavioral dysfunction underwent NIV and EN with a similar frequency as patients without behavioral dysfunction. The reasons why neurobehavioral dysfunction impairs the use of these interventions are unclear. It is has been reported that compliance with both interventions, in particular NIV, is reduced in cognitively impaired patients with ALS, but this assumption was based only on indirect data, such as the time delay after the neurologist recommendation or the modality of use of EN and NIV.5 In our series, the 30-day mortality rate after NIV initiation, a marker of reduced compliance, was significantly higher in patients with neurobehavioral dysfunction and in those with isolated dysexecutive behavior than in patients with no neurobehavioral dysfunction. Moreover, more patients with neurobehavioral dysfunction and isolated dysexecutive behavior had a reduced tolerance to NIV. This finding deserves further study, with an ad hoc prospective assessment of the use of NIV and EN in patients with ALS with and without cognitive impairment. However, poor compliance with NIV and EN does not fully explain the negative effect of neurobehavioral dysfunction on ALS survival, which is likely to be related to other biological or clinical factors. The role of comorbid

cognitive and neurobehavioral dysfunction in the clinical course of ALS is becoming increasingly evident, including the reduced efficacy of life-prolonging therapies. Therefore, measures of patients' cognitive and behavioral assessment should be included both in the diagnostic workup of patients with ALS and in the evaluation of patients for enrollment in clinical trials.

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Chapter 5
Neurobehavioral symptoms in ALS are negatively related to caregivers' burden and quality of life

5.1 Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder characterized by progressive weakness involving upper and lower limbs, and bulbar and respiratory functions. Traditionally, cognition in ALS has been considered spared. However, there are now indications that 10–50% of ALS patients present a subtle cognitive decline [1,2] or an overt frontotemporal dementia (FTD), characterized by personality changes, irritability, poor insight, and deficit in frontal executive tests [3] It has been also proposed that patients with ALS-FTD are less compliant with recommended treatments and have a shorter survival than those with classic ALS [4]. There are, however, very few data about the impact of ALS patients neurobehavioral symptoms on their caregivers burden and quality of life.

The aim of this study was to evaluate the frequency of neurobehavioral symptoms related to FTD in ALS patients and to assess their influence on patients and caregivers mood, burden, and quality of life.

5.2 Methods

A total of 70 couples of ALS patients and their caregivers consecutively seen in our ALS clinic were separately interviewed using a battery of tests assessing frontotemporal-related neurobehavioral symptoms, emotional status, and quality of life. Only patients with definite, probable, and probable laboratory-supported ALS according to El-Escorial criteria were included [5]. Patients with positive family history for ALS were excluded; no patient of this series carried mutations of SOD1

or TARDBP genes. No patient had a history of disorder which could affect cognition or behavior. The primary caregiver was the person indicated by the patient as the ‘‘main informal caregiver.’’ Paid caregivers were excluded from the study.

Behavioral abnormalities were assessed with the Frontal Systems Behavior Scale (FrSBe) [6], a 46-item questionnaire evaluating neurobehavioral symptoms. Each question is rated from 0 (almost never) to 5 (almost always). Fourteen questions are reverse-scored. The questionnaire includes a version for the patients (self-rating form) and a version for the caregivers (family-rating form). Moreover, each item is rated indicating the behavior before the illness (premorbid period) and at the present time (post-illness). Raw scores are converted to T-scores according to gender, age, and years of education. These scores were used in data analyses. A T-score between 60 and 64 is considered borderline, while a T-score ‡65 reflects frontal systems abnormalities. The scale has 3 subscales: apathy, disinhibition, and executive dysfunction. The questionnaire has already been effectively used in ALS [7]. The questionnaire has been translated in Italian and internally validated. Patients were also assessed with Mini Mental State Examination (MMSE) [8]. Data were corrected for age and education according to Italian norms. Depression was evaluated using Zung Depression Scale (ZDS) [9], a self-reported scale with 20 items, each rated from 1 to 4, obtaining a total score ranging from 20 to 80; a score between 50 and 59 indicates mild depression, a score between 60 and 69 indicates moderate depression, and a score over 70 indicates severe depression. Quality of life (QoL) was assessed with the McGill Quality of Life Questionnaire (MQoL) [10,11], a 16-item questionnaire, each rated from 0 (not at all) to 10 (extremely) widely used to assess QoL in ALS patients and caregivers [12,13]. MQoL includes 5 domains, three of which are health related (physical well-being, physical symptoms, psychological symptoms) and two non-health related (existential wellbeing, support). Moreover, the respondent is also asked to indicate her/his self-perceived quality of life in the past 2 days in a single-item scale (MQoL-SIS), rated from 0 (very bad) to 10 (excellent). Both patients and caregivers were assessed with MQoL. Caregiver burden was assessed with the Caregiver Burden Inventory (CBI) [14], a 24-item self-administered rating scale. Its scores range from 0 (lowest level) to 100 (highest level). CBI includes five domains of burden: time dependence, developmental, physical, social, and emotional. Patients

physical status was evaluated with the ALS Functional Rating Scale (ALS-FRS) [15], a 10-item scale evaluating various physical functions involved in ALS (swallowing, speech, use of hands, walking, breathing, etc.). Each item is rated from 0 (worse) to 4 (best), corresponding to a total score ranging from 0 to 40.

Statistical methods

Comparisons between means were evaluated with Student s t-test; binary correlation was evaluated with Pearson's correlation; multivariable analyses were performed with linear regression (stepwise). In multivariable analyses, the following variables were included: patients' age, gender, number of years of formal education, site of onset (bulbar vs. spinal), ZDS score, MMSE score, MQoL total score, ALS-FRS score, FrSBE total score, and FrSBE domains, including before and present time ratings (according to caregiver evaluation); caregivers' age, gender, number of years of formal education, ZDS score, MQoL total score, and CBI score. FrSBE before scores were included to control for caregivers response style to patients baseline behavior. In multivariable analyses, FrSBE scores were included as T-scores. Because of the multiple statistics, according to Bonferroni correction, significance was set at $P < 0.01$. All tests were two-sided. Analyses were performed with SPSS 12.0 (SPSS, Chicago, IL, USA). The study has been approved by the Ethical Committee of our institution. Each participant signed a written informed consent.

5.3 Results

The patients included 37 men and 33 women, whose mean age was 61.9 (±10.0); 54 patients had a spinal onset and 16 a bulbar onset. Their mean educational level was 10.1 (±4.7) years. Their mean disease duration at the time of the interview was 16.5 (±9.3) months. Patients' mean ALS-FRS score was 29.2 (±6.1), mean MMSE score was 28.4 (±1.8, range 26– 30, median 29), and mean ZDS score was 42.1 (±9.6); 9 (12.9%) patients had a ZDS score between 50 and 59 (mild depression) and 6 (8.6%) between 60 and 69 (moderate depression). The caregivers included 23 men and 47

women. Their mean age was 54.7 (±13.3),and their mean educational level was 11.0 (±4.8) years. The caregivers were 56 spouses, 11 children, and 3 other relatives. Their mean ZDS score was 39.1 (±7.6); eight (11.4%) caregivers had a ZDS score between 50 and 59 (mild depression) and none over 59. Frequency of neurobehavioral symptoms According to caregivers' evaluations, 15 (21.4%) patients had premorbid pathological scores and 34 (48.6%) had pathological scores at the time of the interview. According to patients' evaluation, 2 (2.9%) patients had pre-morbid pathological scores and 9 (12.9%) had pathological scores at the time of the interview. Although caregivers reported higher T-scores than patients, there was a good correlation between the two parties, because all patients who self-reported with pathological scores were also considered over the cut-off by their caregivers. In caregivers' assessment, at the time of the interview the most commonly impaired neurobehavioral domain was apathy (39 patients, 55.7%), followed by executive dysfunction (32 patients, 45.7%) and disinhibition (18 patients, 25.7%). According to patients' evaluation, the most commonly impaired domains were executive dysfunction (14 patients, 20%), followed by disinhibition (7, 10%), and apathy (6, 8.6%). FrSBe mean T-scores and pathological scores are reported in Table 1.

Table 1 FrSBe mean *T*-scores (SD) and number of patients over pathological scores, according to caregivers (family-rating score) and patients (self-rating scores). Both pre-morbid (before) and post-illness (present time) scores are reported

Family rating form	Mean *T*-scores (SD)	Pathological scores	Self-rating form	Mean *T*-scores (SD)	Pathological scores
FrSBe – before	53.3 (12.2)	15	*FrSBe – before*	44.7 (10.5)	2
Apathy	55.7 (14.0)	17	Apathy	43.0 (9.7)	3
Disinhibition	51.6 (12.8)	12	Disinhibition	45.8 (10.8)	3
Executive dysfunction	51.3 (11.1)	10	Executive dysfunction	47.6 (10.0)	2
FrSBe – present time	64.2 (14.7)	34	*FrSBe – present time*	53.1 (11.7)	9
Apathy	67.4 (16.6)	39	Apathy	50.9 (13.1)	6
Disinhibition	56.9 (14.1)	18	Disinhibition	49.7 (11.1)	7
Executive dysfunction	62.6 (13.9)	32	Executive dysfunction	55.9 (11.6)	14

FrSBe, Frontal Systems Behavior Scale.

Neurobehavioral symptoms were not related to patients' age, gender, or physical status (ALS-FRS score). Patients who at the time of the interview had bulbar symptoms had significantly higher mean total FrSBe scores (68.3 vs. 57.3; P = 0.002), and also apathy (71.5 vs. 60.3; P = 0.006), and executive dysfunction scores (65.0 vs. 56.5; P = 0.008). Patients' ZDS depression scores were not significantly correlated with apathy both in patients' and in caregivers' evaluations (Pearsons correlation coefficient, patients) 0.009; caregivers 0.131), indicating that depression

and apathy are different constructs. Correlation between patients' neurobehavioral symptoms and caregivers' strain and quality of life Caregivers depression was significantly related to patients total FrSBe score reported by caregivers (r = 0.386; P = 0.001), and also to apathy and executive dysfunction scores (r = 0.353; P = 0.003, and r = 0.387; P = 0.001, respectively), but not to disinhibition (r = 0.201; P = n.s.). Caregivers burden was related to patients total FrSBe score reported by caregivers (r = 0.384; P = 0.001) and to apathy (r = 0.313; P = 0.008) and executive dysfunction scores (r = 0.435, P = 0.0002), but not to disinhibition (r = 0.134; P = n.s.). The emotional and developmental components of CBI were the domains more correlated to the presence of neurobehavioral symptoms (Table 2).

Table 2 Correlation coefficients between neurobehavioral symptoms and CBI domains (Pearson's coefficients)

	Apathy score	Disinhibition score	Executive dysfunction score	Total FrSBe score
Time dependence burden	0.114	−0.116	0.240*	0.139
Developmental burden	0.424****	0.267*	0.387***	0.443****
Physical burden	0.021	−0.024	0.204	0.094
Social burden	0.229	0.131	0.330**	0.297*
Emotional burden	0.410***	0.429***	0.482****	0.534****
Total burden	0.384***	0.313**	0.134	0.435***

CBI, caregiver burden inventory. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$; ****$P < 0.0001$.

Caregivers quality of life was correlated to patients total FrSBe score and to all its components; the most impaired MQoL domains related to neurobehavioral symptoms were existential wellbeing and support (Table 3). In multivariable analysis, caregivers' depression was independently related to MQoL score (P =

0.0001), FrSBe executive dysfunction domain (P = 0.015), and caregiver female gender (P = 0.036); caregivers MQoL score was related to depression score (P = 0.0001), and FrSBe total score (P = 0.022); caregivers' burden was independently related to FrSBe total score (P = 0.002) and caregivers' depression score (P = 0.04). Correlation between patients' self-rated neurobehavioral symptoms and patients' depression and quality of life Patients MQoL and depression scores were not correlated to their neurobehavioral symptoms (data not shown).

Table 3 Correlation between neurobehavioral symptoms and MQoL domains (Pearson's coefficients)

	Apathy score	Disinhibition score	Executive dysfunction score	Total FrSBe score
Physical well-being	−0.091	−0.024	−0.187	−0.139
Physical health	−0.076	−0.112	−0.074	−0.100
Psychological health	−0.335**	−0.112	−0.198	−0.273*
Existential well-being	−0.339**	−0.275*	−0.312**	−0.372**
Support	−0.383***	−0.440***	−0.171	−0.373**
Total MQoL score	−0.362**	−0.331**	−0.310**	−0.387***

MQoL, McGill Quality of Life Questionnaire. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

5.4 Discussion

In our consecutive series of ALS patients, we found that half of the cases showed an impairment of behavior according to their caregivers' evaluations with the FrSBE, a frequency similar to that found in other ALS series [1,4]. The most impaired function was apathy. The patients did not fully recognize their neurobehavioral problems, as

expected in a condition reducing their insight, and they were particularly unaware of apathy. Patients' neurobehavioral symptoms had a profound impact on their caregivers' emotional status: they are related to caregivers depression and burden and were negatively correlated to their QoL. Although a FrSBE pathological score does not indicate by itself a FTD, it reveals a pathological neurobehavior of the frontotemporal type. FrSBE has been already effectively used in ALS patients [7], as well in other disorders, such as dementia [16,17] and multiple sclerosis [18]. According to their caregivers' evaluation, ALS patients presented a marked behavioral change, mainly involving the aspects of apathy and executive dysfunction. Because only eight caregivers had a ZDS score over the cut-off, it is unlikely that depression has influenced their appraisal of patients behavioural changes. Similarly to a previous observation in ALS [7], apathy was independent of mood, indicating that depression and apathy are different constructs. The dissociation of apathy from depression has been recently demonstrated in Parkinson's disease [19] and has led to propose an operative definition of apathy as a primary lack of motivation that manifests itself in three domains (behavioral domain, including lack of effort, lack of productivity, and dependence on others to structure activities; cognitive domain, including loss of interest in new experience and lack of concern about ones problems; and affective domain, including flattened affect and lack of response to positive or negative events) [20]. Recognition of ALS patients with higher scores on apathy, which is currently not appropriately treated, may be useful to assay new therapies targeted toward this particular symptom. In our series, neurobehavioral symptoms, in particular apathy and executive dysfunction, were strongly related to the presence of bulbar symptoms at the time of the interview, more than to a bulbar onset. Although some items of the FrSBe may be influenced by the presence of bulbar symptoms (i.e., speaks only when spoken to), probably spuriously increasing the association between bulbar symptoms and apathy, this finding confirms previous observations that cognitive dysfunction is more frequent in bulbar onset than in non-bulbar onset patients [7,21–24]. According to some studies, the involvement of the bulbar function per se increases the likelihood to develop neurobehavioral symptoms [23]. Our patients had a good respiratory function at the time of the interview (mean forced vital capacity percent of expected, 83.5, SD 10.3; mean respiratory score at the ALS-FRS-R scale,

3.7, SD 0.6, median 4). Therefore, it is unlikely that our findings may be related to hypoxia or hypercapnia. Previous articles have shown that ALS caregivers psychological status is negatively influenced by the progression of motor symptoms [25,26] and that caregivers' burden is related to the worsening of patients' clinical status and the increase of disease duration [27]. Moreover, the reduction of intimacy rating has been found to correlate significantly with the strain felt by caregivers [28]. We have now found that the presence of neurobehavioral abnormalities negatively affects ALS caregivers QoL and increases their depression and burden. Closer analysis of the subscales revealed that behaviors associated with apathy and executive dysfunction were correlated to the worsening of caregivers' psychological status, whereas disinhibition in the patients was not predictive of caregivers' psychological strain. This finding is different from what observed in caregivers of patients with dementia, who have been found to be more affected by executive dysfunction and disinhibition [16]. This difference could be because of the fact that in ALS, disinhibition is present in less than 25% of patients, and its score is largely lower than that observed in demented patients [16]. When considering the components of caregivers' burden, the most affected in patients who showed neurobehavioral abnormalities were the emotional and developmental domains. The latter indicates the caregivers feeling to be out of life or out of sync compared to their peers [14]. As for QoL, existential well-being and support were mostly influenced, indicating the feeling of being alone in facing the disorder in presence of modification of patients behavior and confirming a recent observation on the caregivers of FTD patients without ALS [29]. This should not surprise, because dementia and FTD deteriorate interpersonal and social relationships, reducing closeness, communication, and sharing viewpoints [29]. In patients with FTD, neurobehavioral symptoms have been found to be related to caregivers burden [30].

Contrarily to what found in dementia patients [16,31], we did not find any correlation between caregivers reports of patients pre-morbid behavior and current burden.

The current study may have been limited by the lack of objective neuropsychological measures of executive dysfunction; however, the aim of the study was not to evaluate objectively executive dysfunction, but to determine the effect of frontal systems

dysfunction as perceived by caregivers on their burden and depression. In addition, several authors have demonstrated in FTD important differences between male and female caregivers [32], though this relationship remained unclear. Although we found a correlation between female gender and depression, a more in-depth assessment of these differences was not possible because of the overrepresentation of women in our sample.

In conclusion, neurobehavioral symptoms were quite frequent in our series ALS patients, in particular in those with bulbar symptoms. Neurobehavioral symptoms have a profound negative impact on caregivers psychological status, being a strong predictor of caregivers' burden. It is therefore important to discuss the characteristics of behavioral symptoms both with ALS patients and their caregivers. ALS caregivers need to become aware that patients may change their behavior over time, to be able to face the modification of the interpersonal relationship. Our findings support interventions that address both caregivers' mood and the specific types of behavioral disturbances in patients. For example, problem-solving strategies to compensate for executive dysfunction and behavioral interventions to address inappropriate behaviors and apathy in the patients may be beneficial.

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Chapter 6
Conclusions

The aim of the present project was to assess the frequency and the clinical and radiological pattern of cognitive impairment in a series of patients with ALS.

In addition we evaluated the effect of neurobehavioral dysfunctions on survival and on the quality of life in patients with ALS and their caregivers. About 50% of Italian patients with ALS had some degree of cognitive impairment, in keeping with a previous Irish study, despite the largely different genetic background of the two populations. The frequency of cognitive impairment in our epidemiological series was similar to that described in Irish patients. However, differently from that study, according to ALS-FTD Consensus Criteria we identified a group of patients with cognitive impairment, that is, patients with isolated behavioural impairment, accounting for 6% of cases. Neurobehavioral symptoms were quite frequent in our series ALS patients, in particular in those with bulbar symptoms.

We considered the influence of the cognitive impairment on the course of the disease: the acceptance of the diagnosis, the decision making, the compliance, the use and the tolerance of life-prolonging therapies, and, finally, the survival.

The presence of neurobehavioral dysfunction or of isolate dysexecutive behavior in ALS at diagnosis is a strong predictor of a poor outcome, partially related to a reduced efficacy of life-prolonging therapies.

We found that neurobehavioral dysfunction, and isolated dysexecutive behavior as well, significantly reduced patient survival related to the use of NIV and EN. Interestingly, patients with neurobehavioral dysfunction underwent NIV and EN with a similar frequency as patients without behavioral dysfunction. The reasons why neurobehavioral dysfunction impairs the use of these interventions are unclear. It is has been reported that compliance with both interventions, in particular NIV, is reduced in cognitively impaired patients with ALS, but this assumption was based only on indirect data, such as the time delay after the neurologist recommendation or the modality of use of EN and NIV.5 In our series, the 30-day mortality rate after

NIV initiation, a marker of reduced compliance, was significantly higher in patients with neurobehavioral dysfunction and in those with isolated dysexecutive behavior than in patients with no neurobehavioral dysfunction. Moreover, more patients with neurobehavioral dysfunction and isolated dysexecutive behavior had a reduced tolerance to NIV.

The final purpose of this study was to improve the burden of care and the compliance of ALS patients with cognitive impairment and their caregivers.

Neurobehavioral symptoms were present in 50% of our ALS patients and were related to bulbar symptoms. They have a profound negative impact on caregivers_ psychological status and were highly related with caregivers-burden.

Neurobehavioral symptoms have a profound negative impact on caregivers psychological status, being a strong predictor of caregivers' burden. Furthermore, we assessed the presence of anxiety and depression in the caregivers. We evaluated the caregivers' burden to understand if the neurobehavioral dysfunctions could negatively influence the patient-caregiver relationship.

It is therefore important to discuss the characteristics of behavioral symptoms both with ALS patients and their caregivers. ALS caregivers need to become aware that patients may change their behavior over time, to be able to face the modification of the interpersonal relationship. Our findings support interventions that address both caregivers' mood and the specific types of behavioral disturbances in patients.