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Motor neuron dysfunctions in the frontotemporal lobar degeneration spectrum: A clinical and neurophysiological study

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ABSTRACT

Background: Although only a few frontotemporal lobar degeneration (FTLD) patients develop frank amyotrophic lateral sclerosis (ALS), motor neuron dysfunctions (MNDys) occur in a larger proportion of patients. The aim of this study is to evaluate MNDys and ALS in a sample of consecutively enrolled sporadic FTLD patients.
Methods: Clinical and neurophysiological evaluations (i.e. needle electromyography) assessed lower (LMN) and upper (UMN) motor neuron function at the baseline in 70 probable FTLD patients (i.e., 26 behavioural variant-bvFTD, 20 primary progressive aphasias-PPAs and 24 corticobasal syndrome-CBS). To obtain a more accurate estimation, quantitative scales were also applied (i.e. ALSFRS-r and UMN scale). Patients were screened for *MAPT*, *GRN* and *C9orf72* mutations. A mean clinical follow-up of 27.8 ± 22.4 months assessed MNDys progression and the clinical presentation of ALS.
Results: Five genetic cases were identified. Within the sample of sporadic patients, a relative low rate of FTLD patients was diagnosed as probable ALS (5%), while a higher proportion of patients (17%) showed clinical and neurophysiological MNDys. Thirteen patients (20%) presented with isolated clinical signs of LMN and/or UMN dysfunction, and 8 patients (12%) showed neurogenic changes at the electromyography. No differences in FTLD phenotype and disease duration were found between MNDys positive and negative patients. Clinical MNDys were highly associated with positive electromyographic findings. At follow-up, no MNDys positive patient developed ALS.
Conclusion: Neurophysiological and clinical examinations revealed mild MNDys in FTLD patients not fulfilling criteria for ALS. This condition did not evolve at a mean follow-up of two years. These results, indicating a subclinical degeneration of corticospinal tracts and lower motor neurons, suggest that FTLD patients may be more at risk of MNDys than the general population.

1. Introduction

A considerable amount of clinical and neuropathological evidence supports a shared basis for frontotemporal lobar degeneration (FTLD) and amyotrophic lateral sclerosis (ALS) disorders [1–4]. In particular, in the last ten years, many researchers suggested the idea of a continuum between these two neurological conditions. The identification of trans-activating responsive (TAR) sequence DNA binding protein (TDP-43) as common pathogenetic substrate of many sporadic and familial FTLD and motor neuron disorder (MND) patients [5–7], as well as the discovery of large hexanucleotide (GGGGCC) repeat expansion of the chromosome 9 open reading frame 72 (*C9orf72*) gene as the major responsible for many familial FTLD, ALS or combined phenotypes [8,9] provided important support for this hypothesis. Moreover, many clinical studies have indicated the presence of a clinical–neuropsychological continuum also in patients with sporadic FTLD and ALS [10,11].

In particular, in-depth phenotypical characterization of non demented ALS patients revealed the presence of cognitive and behavioural disorders mirroring those observed in the behavioural variant of frontotemporal dementia (bvFTD) [12–17]. These, in some instances, may be severe enough to fit the criteria for dementia. In further support of commonality, a proportion of FTLD patients develops motor neuron disorder in association to cognitive symptoms (i.e., FTD-ALS patients), usually within a year from the onset of cognitive and behavioural changes [18–21]. Observational studies have shown that it accounts for almost 15% of all FTLD cases [19,20,22]. Typical FTD-ALS patients

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present with prominent behavioural changes and psychotic symptoms, but they may also have language disorders [23,24]. Although this phenotype is relatively uncommon, motor neuron dysfunctions (MNDys) has been reported in a larger proportion of FTLD patients. In the study of Lomen-Hoerth and co-workers [17], in a cohort of 36 frontotemporal dementia cases, the 14% of patients met the criteria for ALS [25], and received a diagnosis of FTD-ALS, while the 36% had electromyographic findings supporting subclinical MNDys.

Only a few studies have systematically investigated MNDys in FTLD subtypes and estimated their incidence, distribution, severity and functional significance [12,17–19], and, to the best of our knowledge, only one study investigated clinical and neurophysiological findings in a prospective study [22]. In this study, that includes 40 patients (bvFTD and non fluent (nf-PPA) and semantic (sv-PPA) variants of primary progressive aphasia), MNDys was found in the 12.5% of patients and clinical evidence of minor motor system dysfunction (i.e., occasional fasciculations, mild wasting or weakness) in a further 27.3%.

In the present study, we aimed at estimating the incidence of MND/ALS in a sample of consecutively enrolled FTLD patients (i.e., bvFTD, PPA and also corticobasal syndrome (CBS) subtypes). We evaluated patients with a full neurological examination targeted to disclose signs of upper and lower MNDys and to report their site, severity and extent. We also performed needle electromyography (EMG) in each case in order to identify electromyographic findings of MNDys. A mean clinical follow-up of two years assessed the possible progression to ALS.

2. Materials and methods

2.1. Participants

The study sample includes patients evaluated for possible FTLD at Department of Clinical Neurosciences, San Raffaele Hospital (Milan, Italy) in the years between 2005 and 2011. At the time of diagnosis both patients and caregivers underwent a structural clinical interview. A standard neuropsychological battery included measures of global cognitive efficiency, memory, executive functions, language, and visuospatial abilities. Behavioural changes were explored, using caregiver questionnaires (i.e., Neuropsychiatric Inventory and Frontal Behavioral Inventory). For a better diagnostic accuracy, starting from 2009 patients also underwent a socio-emotional battery including emotion recognition (i.e., Ekman 60-Faces task [26,27]) and emotion and intention attribution (i.e., Story-based Empathy task [28]) tasks. Carers completed also the Interpersonal Reactivity Index (IRI) [29], a standardized questionnaire of empathy.

Neuroimaging (i.e., brain MRI or CT, and/or cerebral [^{18}F]FDG-PET or SPET) data were collected to support the diagnosis. Family history of dementia or MND/ALS was systematically investigated. Genetic screening for mutations or polymorphisms of progranulin (*GRN*) and *C9orf72* genes were performed in each case in agreement with previously reported procedures [30,31]. In absence of known *GRN* or *C9orf72* mutations and in the case of positive family history suggestive of autosomal dominant inheritance, patients were offered genetic testing for microtubule-associated protein tau (*MAPT*) mutations.

According to the new diagnostic criteria for the three main subtypes of FTLD (i.e., bvFTD, PPA and CBS) [32–34], both clinical–neuropsychological data and imaging supportive features were reviewed by two experienced behavioural neurologists (C.C. and A.M.) in order to correctly classify patients within each specific diagnostic group.

All subjects, or their informants/caregivers, gave informed consent to the experimental procedures that had been approved by the local Ethical Committee.

2.2. Cinical motor assessment and needle EMG examination

Patients were submitted to a full neurological examination with particular attention to clinical motor assessment and a needle EMG examination in order to assess clinical signs of upper (UMN) and lower (LMN) motor neuron dysfunction and to record neurophysiological evidence of acute and chronic neurogenic change. Full nerve conduction studies were also performed in order to exclude other neurological disorders.

The clinical examination included the evaluation of brainstem, cervical, thoracic and lumbar districts, while the EMG study included only cervical and lumbosacral regions. Muscles of craniobulbar region were evaluated only if brainstem involvement was suspected on clinical ground.

The clinical evaluation of UMN signs included the identification of overactive reflexes (i.e., deep tendon reflexes elicited with minimal stimulus or pathological spread of reflexes), spasticity and Babinski sign. The presence of the Hoffmann's sign and clonus was also noted. Patients were categorized as having definite (overactive reflexes, spasticity and Babinski sign/Hoffman sign/clonus) or probable (overactive reflexes and/or spasticity in the same limb, without Babinski sign, Hoffmann's sign or clonus) UMN involvement.

Clinical LMN signs included focal muscular atrophy, fasciculations and muscle weakness. Seven body regions were inspected for fasciculations: face/chin, tongue, shoulders/back, upper arms, forearms/hands, thighs, and lower leg. The presence of fasciculations was reported as mild, moderate or severe. Any degree of fasciculations higher than zero was considered clinically relevant. If present, the severity and distribution of muscle weakness was graded according to the Medical Research Council (MRC) grading system. Patients were categorized as having definite (fasciculations and wasting, plus weakness in the same muscle) or probable (fasciculation or focal muscle wasting) LMN involvement.

A quantitative scale [35] was applied to obtain a more accurate estimation of UMN damage. It reports the total number of pathologically brisk reflex on the biceps, supinator, triceps, finger, knee, and ankle, plus extensor plantar responses and brisk facial and jaw jerks (maximum score = 16). ALS-Functional Rating Scale-Revised (ALSFRS-r) [36] was administered to caregivers during the clinical interview in order to assess motor functional status.

The neurophysiological study included the evaluation of at least two muscles innervated by different roots and peripheral nerves for each limb in the cervical and lumbar districts. For the definition of ALS, stringent neurophysiological criteria were applied in accordance with the El Escorial criteria [25,37]. ALS was diagnosed when combined LMN and UMN signs were identified in at least two regions.

A clinical follow-up (mean 27.8 ± 22.4 months) was carried out on all patients, to evaluate the likely progression of MNDys and the possible appearance of ALS.

2.3. Statistical Analyses

Statistical analysis was performed using the Statistica software (https://www.statsoft.com). Chi-square test was used for comparisons among patient subgroups (bvFTD, PPA and CBS). In particular, we first compared the proportion of cases showing signs of MNDys across the subgroups. Then, we estimated the association between the presence of MNDys observed at the clinical level and the emergence of MNDys from the needle EMG in the whole sample, as well as in the three patient subgroups separately. Finally, we correlated the presence/absence of MNDys with the clinical variables (Pearson's correlation coefficient).

3. Results

Among a larger group of 86 cases, a final sample of 70 patients (39 men, 31 women; mean age = 66.6 ± 9.3 years; mean education = 10.1 ± 4.6 years; Clinical Dementia Rating (CDR) scale global score range = 0.5–2) was identified. Sixteen patients were excluded (i.e., mixed or logopenic/phonological variants of PPA, and possible bvFTD or CBS cases without a complete diagnostic

agreement between the two experts and not fulfilling criteria for probable dementia). Enrolled patients were sub-categorized as probable bvFTD (n = 26), PPA (n = 20; 13 nf-PPA and 7 sv-PPA) and CBS (n = 24; 13 progressive supranuclear palsy-PSP; 10 probable corticobasal degeneration-CBD and 1 CBD plus nf-PPA).

Twenty-eight patients reported a positive family history for cognitive decline or behavioural disorders (at least 1 other family member), but only two patients for ALS. Two cases with family history for dementia, two apparently sporadic cases (with no familiar history either for ALS or for dementia) and one case with familiar ALS carried mutations for known genes associated with FTLD: 1 FTD-ALS with sv-PPA phenotype (*C9ORF72* +), 2 bvFTD (*C9ORF72* and *GRN* +), 1 nf-PPA (*GRN* +) and 1 sv-PPA (*GRN* +) (for details on the clinical phenotype of these cases see [30,31,38]). They were thus excluded from the analyses, which included a final sample of 65 sporadic FTLD patients (24 bvFTD, 17 PPA and 24 CBS) (Table 1).

Within the sporadic patients, only 3 cases (2 bvFTD and 1 nf-PPA; 5%) had frank MND, meeting El Escorial criteria for clinically probable ALS [25,37]. They were thus classified as FTD-ALS. They all presented with spinal onset.

Thirty patients (13 bvFTD, 7 PPA and 10 CBS; 46%) did not show MNDys either at the neurological examination or at the needle EMG.

Among the rest of patients (32/65), 13 subjects (3 bvFTD, 4 PPA and 6 CBS; *Clinically positive group* = 20%) presented with isolated clinical signs of UMN and/or LMN dysfunction in one or two districts. Eight patients (i.e., 1 bvFTD, 4 PPA and 3 CBS; *EMG positive group* = 12%) showed isolated neurogenic changes at the needle EMG: chronic denervation/reinnervation (e.g., MUPs of increased amplitude and duration, with reduced inference pattern) in one or two regions. Chronic neurogenic abnormalities were associated with active denervation (i.e., fibrillation potentials (fibs) in bilateral anterior tibialis and right gastrocnemius), suggesting possible MND/ALS, in only one case.

Finally, 11 patients (i.e., 5 bvFTD, 1 PPA and 5 CBS; *Clinically-EMG positive group* = 17%) showed both clinical and neurophysiological MNDys findings. Critically, 8 patients showed clinical signs and neurogenic changes confined to muscles dependent from the same root (mainly C7–C8 and L5–S1), suggesting a radiculopathy. Two subjects (1 bvFTD and 1 CBD) presented isolated diffuse acute denervation (i.e., fasciculation potential-FP) on the upper and lower limb with the simple morphology of benign fasciculations; one bvFTD showed FP and fibs plus chronic denervation/reinnervation on the gastrocnemius and tibialis anterior. See Fig. 1 for a summary.

At the neurological examination, apart from the 3 FTD-ALS, only 8 patients (i.e., 4 *Clinically positive* and 4 *Clinically-EMG positive* cases) showed LMN signs. Mild to moderate fasciculations in two or more muscles (gastrocnemius, tibialis anterior, biceps and triceps) were found in 7 patients, while one patient had slight focal wasting of the thenar and hypothenar eminences and forearm muscles (Table 2). No patient with definite LMN was found; normal muscle power was recorded in each case except in the patient with forearm/hand wasting (MRC scale 4/5 on wrist and finger flexo-extension). Three clinically positive patients presented UMN signs (upper and lower limb hyperreflexia and positive Babinski sign) associated to rostral LMN signs (forearm/hand fasciculations or hand wasting), suggesting possible MND. Unexpectedly, none of these subjects showed MNDys at the needle EMG either at the baseline or at a twelve-month neurophysiological follow-up.

Hyperreflexia was the most frequent UMN sign. It was reported in isolation in nine patients, and in association with Babinski signs, clonus or spasticity in ten further cases. Isolated spasticity plus Babinski sign/clonus was reported only in three cases.

FTD-ALS patients scored below the 5th percentile of the non-ALS ALSFRS-r score distribution. The latter group showed only little or no motor functional impairment. Similarly, UMN scale scores in FTD-ALS patients were equal or higher than the 95th percentile of the non-ALS UMN score distribution.

Group analyses showed no significant difference in the proportion of patients presenting MNDys – in terms of clinical signs and/or EMG findings – across patients' subgroups (Table 3A). However, overall, the presence of clinical (UMN and LMN) signs was highly associated with the presence of EMG findings ($Chi^2 = 7.05$, $p = 0.007$). Finally, correlation analyses between the presence/absence of MNDys and clinical variables highlighted that patients displaying a positive profile for MNDys at the clinical evaluation and/or at the needle EMG scored significantly worse in the UMN and ALSFRS-r scales than patients showing no evidence of MNDys. No difference in disease duration was found between MNDys positive and negative patients (Table 3B).

At the clinical follow-up (27.8 ± 22.4 months), no patient either developed further MNDys signs or progressed in terms of both severity and spreading of MNDys to other districts. MNDys presented at the baseline assessment did not produce any functional impairment at the follow-up. No patient with clinical or EMG positive findings developed ALS in the months following the baseline evaluation.

4. Discussion

In this study, we assessed MNDys in a sample of sporadic FTLD with a combined clinical and neurophysiological approach. We carried out a longitudinal study and evaluated the distribution of LMN and UMN clinical and neurophysiological signs, and their clinical progression expanding knowledge on this field. Though the efforts toward characterizing the clinical overlap between FTLD and MND disorders, there have been only few formal attempts to systematically examine cohorts of FTLD patients for features of MND [17,18,22]. A considerably lower rate of FTD-ALS cases (5%) was found in our sample compared to the prevalence reported in literature (12.5–14%) [18,22]. This discrepancy could be due to differences in patients' enrolment (e.g., FTLD subtypes enrolled and diagnostic criteria used for the classification) or in the study design (i.e., we left out known genetic cases). The previously reported greater prevalence of FTD-ALS cases [18,22] could be indeed attributed to the presence of a higher number of genetic cases (e.g., *C9ORF72* mutated patents), still unknown at the time of those publications. Moreover, the list of newly identified gene loci (i.e., 6p21.3 and 11q14 [39]) possibly contributing to the pathological mechanisms of FTD-ALS is continuously increasing.

Apart from the MND/ALS cases, our data confirmed previous findings [22] showing that a considerable proportion of FTLD patients had mild evidence of motor system dysfunction, insufficient to satisfy

Table 1
Clinical and demographic characteristic of sporadic frontotemporal lobar degeneration patients.

	bvFTD	PPA	CBS	Total	P-value
No. (male)	24 (14)	17 (6)	24 (14)	65 (34)	–
Age in years (mean ± st.dev.)	63.8 ± 10.6	66.9 ± 9.2	69.2 ± 7.4	66.6 ± 9.3	NS
Education in years (mean ± st.dev.)	10 ± 4.2	10.2 ± 5.6	9.9 ± 4.6	10.1 ± 4.6	NS
Disease duration in months (mean ± st.dev)	46.5 ± 31.5	40.2 ± 26.1	28 ± 15.2	38 ± 26	p = 0.042*
Follow-up (mean ± st.dev)	31.5 ± 22.8	25.4 ± 24.6	25.5 ± 20.8	27.8 ± 22.4	NS
CDR global score (range)	0.5–2	0.5–1	1–2	0.5–2	–

bvFTD = behavioural variant of Frontotemporal Dementia; PPA = primary progressive aphasia; CBS = corticobasal degeneration syndrome; CDR = Clinical Dementia Rating scale; * = bvFTD > CBS.

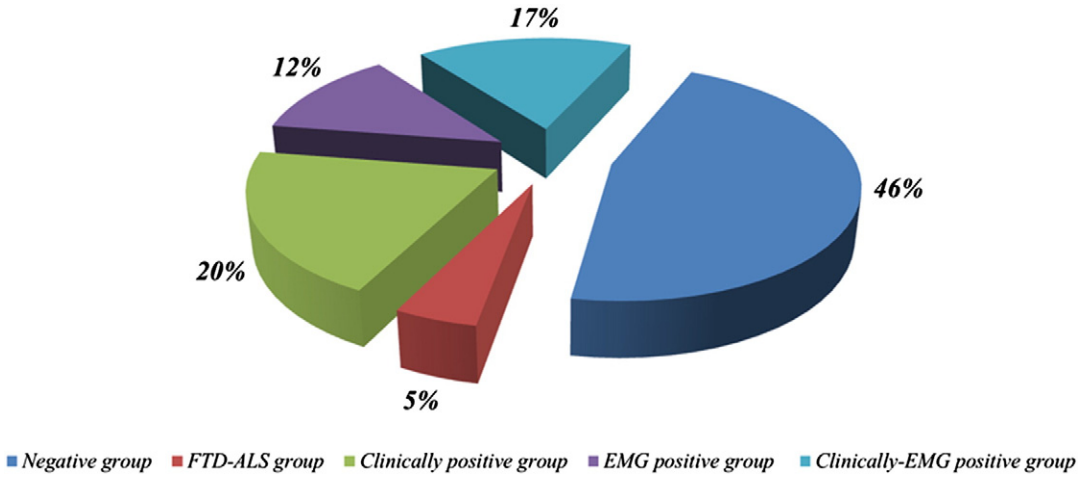

Fig. 1. Distribution of motor neuron dysfunction signs in the sample of 65 FTLD sporadic patients. FTD-ALS = Frontotemporal dementia plus Amyotrophic Lateral Sclerosis; EMG = Electromyography.

diagnostic criteria for ALS. FTLD patients may be indeed more at risk of MNDys than the general population. Within the *EMG positive group* of patients, we identified indeed two patients exhibiting active denervation and collateral reinnervation in the same districts. The denervation involved at least two muscles innervated by different roots and peripheral nerves, with a high likelihood to be due to primitive motor neuron pathology [25]. Similarly, in the *Clinically positive group*, three patients presented UMN signs plus rostral LMN signs clinically suggesting MND. None of the MNDys positive patients presented positive family history for MND/ALS. At the clinical examination, UMN signs were more common in CBS subgroup. Like in the primary lateral sclerosis, these patients showed primary motor cortex degeneration associated with astrocytosis and microglia activation, and corticospinal tract damage with deposits of cytoplasmic inclusions immunoreactive for 4R-tau [40,41].

The follow-up study documented a benign course in the *Clinically positive group* confirming that the presence of fasciculations and/or muscle wasting in the setting of a normal EMG certainly carries a benign prognosis. The lack of progression of MNDys in the *EMG positive* cases suggests that also this detectable subclinical neurophysiological motor system dysfunction is not associated to a fast clinical progression. None of the MNDys positive patients progressed toward MND/ALS or developed further MNDys in other districts during the follow-up period. No relevant functional impact documented by high ALS-FSRr scores was recorded.

No significant difference was found in the proportion of MNDys positive and negative patients among clinical subtypes (bvFTD vs. PPA variants and CBS), suggesting that MNDys do not present an association with a specific clinical syndrome related to distinct patterns of cortical atrophy. In particular, we did not prove a specific association not even with nf-PPA, whose main locus of pathology in the inferior frontal region (Broca's area) and anterior insula is close to the primary motor cortex. This result, however, may be influenced by the relative small sample size. Though the number of the enrolled subjects of our sample is in line with those of the previous studies [18,22], a larger sample size could provide increased statistical power of detecting significant associations within the different FTLD subgroups. In addition, the presence of MNDys was not related in the whole group to disease duration, supporting the existence of subtle motor system dysfunction occurring simultaneously to the damage to frontotemporal cognitive brain areas. Noteworthy, this finding was confirmed in single cases by the lack of progression over time during the follow-up period.

In conclusion, our findings indicate that MND/ALS is not frequent in sporadic (*C9orf72*, *GRN* or *MAPT* negative) patients. In contrast, subclinical MNDys or neurophysiological changes are frequently observed and may occur even in the case of negative family history for MND/ALS.

Table 2
Motor neuron dysfunction sings distribution at the clinical examination and the needle electromyography.

	bvFTD = 24	PPA = 17	CBS = 24	All = 65
Clinical examination				
LMN signs (number (%) of patients)	4 (16.6%)	2 (11.7%)	2 (8.3%)	*8 (12.3%)*
Fasciculation	4 (16.6%)	2 (11.7%)	1 (4.1%)	7 (10.7%)
Focal muscle wasting and weakness	–	–	1 (4.1%)	1 (1.5%)
UMN signs (number (%) of patients)	7 (29.1%)	4 (23.5%)	11 (45.8%)	22 (33.8%)
Hyperreflexia	4 (16.6%)	2 (11.7%)	3 (12.5%)	9 (13.8%)
Spasticity plus Babinski sign/clonus	–	2 (11.7%)	1 (4.1%)	3 (4.6%)
Hyperreflexia plus Babinski sign/clonus	3 (12.5%)	–	6 (25%)	9 (13.8%)
Hyperreflexia plus spasticity	–	–	1 (4.1%)	1 (1.5%)
Motor functional impairment (mean global score ± st.dev.)				
ALS-FRS-r global score	46.5 ± 2.5	46.5 ± 2.1	47.1 ± 1.3	46.7 ± 2
UMN scale score	2.6 ± 3.7	1.6 ± 2.9	2.8 ± 3.6	2.4 ± 3.4
Needle EMG (number (%) of patients)				
Acute denervation	4 (16.6%)	3 (17.6%)	3 (12.5%)	11 (16.9%)
Chronic denervation/reinnervation	5 (20.8%)	5 (29.4%)	7 (29.1%)	17 (26.1%)

bvFTD = behavioural variant of Frontotemporal Dementia; PPA = primary progressive aphasia; CBS = corticobasal degeneration syndrome; LMN = lower motor neuron; UMN = upper motor neuron; ALS-FRS-r = Amyotrophic Lateral Sclerosis Functional Rating Scale revised; EMG = electromyography.

Table 3
Group statistics — A) Group comparison on the proportion of cases showing MNDys in terms of clinical signs and needle EMG findings across the three patients' subgroups; B) Correlation analysis between the presence/absence of MNDys in the whole group and clinical variables assessing motor neuron impairment severity and duration.

	Clinical signs (UMN & LMN) and EMG	Clinical signs (UMN & LMN)	EMG
A			
bvFTD vs CBS	$Chi^2 = 0.75$, $p = 0.39$	$Chi^2 = 0.08$, $p = 0.77$	$Chi^2 = 0$, $p = 1$
bvFTD vs PPA	$Chi^2 = 0.39$, $p = 0.53$	$Chi^2 = 0.30$, $p = 0.58$	$Chi^2 = 0$, $p = 1$
CBS vs PPA	$Chi^2 = 0.03$, $p = 0.86$	$Chi^2 = 0.67$, $p = 0.41$	$Chi^2 = 0$, $p = 1$
B			
ALS-FRS-r global score	$r = -0.20$, $p = 0.102$	$r = -0.23$, $p = 0.057$	**$r = -0.24$, $p = 0.044$**
UMN scale score	**$r = 0.58$, $p < 0.000001$**	**$r = 0.77$, $p < 0.000001$**	$r = -1.03$, $p = 0.305$
Disease duration (months)	$r = -0.09$, $p = 0.45$	$r = -0.04$, $p = 0.712$	$r = -0.16$, $p = 0.191$

bvFTD = behavioural variant of frontotemporal dementia; CBS = corticobasal degeneration syndrome; PPA = primary progressive aphasia; LMN = lower motor neuron; UMN = upper motor neuron; EMG = electromyography; ALS-FRS-r = Amyotrophic Lateral Sclerosis Functional Rating Scale revised.
Significant correlations are reported in bold.

These changes, however, do not appear to represent an early stage of MND or to predict an inevitable progression toward ALS, even if a longer follow-up is necessary to support this conclusion. Overall, they are compatible with the hypothesis that the motor system can be involved in FTLD, without necessarily implying a clinical progression to ALS. As previously documented by Burrell et al. [22], FTLD patients may show a prolongation of the central motor conduction time, presumably due to axonal loss and consistent with a degeneration of corticospinal tracts. This condition that is typical of ALS patients may occur also in the proportion of FTLD patients with MND signs. The hypothesis needs further confirmation, in particular on a single-subject basis. Diffusion-Tensor Imaging tractography may be particularly useful to evaluate corticospinal tract integrity in pure FTLD patients with subclinical MNDys.

As a practical point, in the absence of clinical suspicion of MND/ALS a full clinical–neurophysiological study is probably unwarranted. Although at a one-year re-evaluation Lomen-Hoerth and co-workers [18] reported in a MNDys positive patient a progression into a definite ALS, we cannot exclude that the clinical presentation of this case was influenced by a genetic cause. Similarly, we cannot exclude that other genetic causes, not yet known [39], influenced the high rate of MNDys present in our sample.

The lack of genetic screening for the recently discovered genes' mutations responsible for FTLD makes it really difficult to compare these results with our data. More in general, this and other previous evidence [18–20] support indeed the presentation of ALS in FTLD patients within a year from the clinical onset of cognitive decline.

The main limitation of the study is the relatively limited sample size, which does not allow us to identify the association between the presence of specific MNDys signs and precise FTLD phenotypes. Large follow-up and survival studies on different populations are certainly needed to establish whether MNDys positive patients may actually progress to a fully-expressed MND/ALS, or rather if in some cases MNDys signs are not associated with any clinical progression. In conclusion, an in-depth characterization of the extent of MND dysfunctions in FTLD syndromes is not simply of academic interest but has important clinical implications on disease progression and patient management. Further prospective studies are needed to provide definite answers to these important questions.

Conflict of interest

None.

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