Extrapyramidal and cognitive signs in amyotrophic lateral sclerosis: A population based cross-sectional study

ELISABETTA PUPILLO¹, ELISA BIANCHI¹, PAOLO MESSINA¹, LUCA CHIVERI², CHRISTIAN LUNETTA³, MASSIMO CORBO³, MASSIMILIANO FILOSTO³, LORENZO LORUSSO⁴, BENOIT MARIN⁵, JESSICA MANDROLI⁶, NILO RIVA⁶, FRANCESCO SASANELLI¹⁰, LUCIO TREMOLIZZO¹¹ & ETTORE BEGHI¹ AND THE EURALS CONSORTIUM (*)

¹Laboratory of Neurological Disorders, IRCCS-Istituto di Ricerche Farmacologiche ‘Mario Negri’, Milan, ²Ospedale Valduce, Como, ³Centro Clinico NEMO, Fondazione Serena Onlus, Milano, ⁴Department of Neurorehabilitation Sciences, Casa CURA Policlinico, Milan, ⁵Spedali Civili di Brescia, Brescia, ⁶U.O. di Neurologia, A.O. Mellino Mellini, Chiaravalle, Brescia, Italy, ⁷INSERM UMR1094, Tropical Neuroepidemiology, Limoges, France, ⁸Sant’Agostino-Estense’ Hospital, University of Modena and Reggio Emilia, Modena, ⁹Department of Neurology and Institute of Experimental Neurology (INSPE), IRCCS San Raffaele Scientific Institute, Milan, ¹⁰Azienda Ospedaliera di Melegnano, Vizzolo Predabissi, Milan, and ¹¹Ospedale San Gerardo, Monza, University of Milano-Bicocca, Italy

Abstract
Our objective was to assess the association between amyotrophic lateral sclerosis (ALS) and other neurodegenerative diseases such as Alzheimer’s disease (AD), frontotemporal dementia (FTD) and Parkinson’s disease (PD). From May 2007 through August 2012 we investigated 146 patients with newly diagnosed ALS and 146 age- and gender-matched controls. Each individual was screened for cardinal extrapyramidal signs (neurological examination) and cognitive dysfunction (Mini Mental State Examination, MMSE and Frontal Assessment Battery, FAB). Results demonstrated that rigidity was present in 8.2% of cases and 2.1% of controls (adjusted odds ratio, adjOR 5.7; 95% CI 1.5–22.0). The corresponding percentages for bradykinesia and postural instability were, respectively, 8.2 vs. 2.7% (adjOR 4.8; 95% CI 1.4–16.5) and 2.7 vs. 9.6% (adjOR 0.3; 95% CI 0.1–0.9). FAB ≤ 13.4 was recorded in 24.8 vs. 9.6%; adjOR 2.9; 95% CI 1.5–5.7). Tremor and abnormal FAB score were predicted by an older age at onset while an abnormal FAB score was associated with cramps and family history of neurodegenerative diseases. In conclusion, our data support the notion that newly diagnosed ALS carries a higher than expected risk of extrapyramidal signs and FTD.

Keywords: Amyotrophic lateral sclerosis, Parkinson’s disease, frontotemporal dementia, Alzheimer’s disease, heterogeneity, population based

Introduction
Amyotrophic lateral sclerosis (ALS) is a rare, progressive and fatal neurological disorder characterized by degeneration of both upper motor neurons (UMNs) and lower motor neurons (LMNs). The disease has an unknown aetiology and a fairly heterogeneous phenotype in terms of age at onset, site of onset, degree of involvement of UMNs and LMNs, genetic background, and comorbidities (1,2). The association between ALS and other neurodegenerative diseases (the so-called ALS-plus syndrome) is well known. The clinical, pathologic and genetic overlap between ALS and frontotemporal dementia (FTD) is clearly documented (3,4). Several studies have reported imaging (5–7) and pathologic (8–10) evidence of degeneration of substantia nigra, caudate

(*) Members of EURALS Consortium: E. Vitelli, A. Padovani, N. Leali, E. Maestri, M. Perini, M.S. Cotelli, M. Comi, F. Tavernelli, P. Perrone, M. Cerioni, E. Alvistu, C. Cereda C, P. Buzzi, A. Galbussera, G.L.Vertuè, M.L. Monticelli, C. Ferraresi.
Correspondence: E. Beghi, IRCCS-Istituto di Ricerche Farmacologiche ‘Mario Negri’, Via G. La Masa, 19 Milano, Italy. Fax: 02 39 001916. E-mail: ettore.beghi@marionegri.it.

(Received 9 December 2014; accepted 13 March 2015)

ISSN 2167-8421 print/ISSN 2167-9223 online © 2015 Informa Healthcare
DOI: 10.3109/21678421.2015.1040028
and striatum in ALS. However, the possible association with Parkinson’s disease (PD), except for the ALS/PDC of Guam (11), is still based on few case reports or small series from referral centres (12–14), and data are inconsistent on the association with Alzheimer’s disease (AD), mostly reflecting the differing validity of the screening instruments (15). With few exceptions (1,4,16), the ALS-plus syndrome has been investigated in prevalent populations and the results cannot be applied to incident ALS cohorts that better represent the full disease spectrum. In addition, in the absence of matched controls, the possibility cannot be excluded that extrapyramidal signs and cognitive dysfunction are present in some of these elderly patients as a reflection of the aging process. Against this background, we planned a population-based matched cross-sectional study in representative samples of incident ALS and normal individuals. The research hypothesis was that newly diagnosed ALS carries a higher than expected risk of cardinal extrapyramidal signs and/or cognitive dysfunction, with special reference to the executive functions.

Material and methods

The study design and reporting was in line with the STROBE guidelines for observational studies (17). Informed consent was obtained from each study participant.

Population

The study population was represented by patients with newly diagnosed ALS included in two population based registries located in northern Italy (Figure 1). Case ascertainment in both registries is virtually complete (18,19). During the study period (May 2007 through August 2012), a random sample of all registered patients was selected for this study. The baseline characteristics of the sample compared to the origin ALS populations are illustrated in the Supplementary Tables 1 and 2 to be found online at http://informahealthcare.com/doi/abs/10.3109/21678421.2015.1040028. A patient was included if (s)he was 18 years of age or older and had definite, probable or possible ALS according to the El Escorial (EE) diagnostic classification (20). For each patient, a control was selected from the lists of local general practitioners (GPs), matched for age (±2.5 years), gender and province of residence.

Data collection

After obtaining an informed consent, a board certified neurologist or a GP with neurological training performed the medical interviews and neuropsychological testing with the Mini Mental State Examination (MMSE) (21) and the Frontal Assessment Battery (FAB) (22) to each case and control. The GPs (two in total) received a video with the details of a neurological examination and proper instruction on how to perform neuropsychological testing. The neurological examination was performed in search of cardinal extrapyramidal signs (bradykinesia, tremor, rigidity, postural instability), and other motor findings and signs suggesting an ALS mimic. For ALS patients, details were collected on the EE diagnostic category, site of onset of symptoms (bulbar, spinal), duration of symptoms at diagnosis, fasciculations, cramps, other motor findings, and treatment with riluzole. The following data were recorded in a structured questionnaire: date of enrolment, date of birth, gender, years of education, family history of any neurodegenerative disease among AD, PD, FTD and ALS, family history of each disease separately, cardinal extrapyramidal signs, MMSE and FAB scores. Data were entered for analysis in a password protected web-database with personal login. The following analyses were planned in the study protocol: 1) number and proportion of cases and controls with any of the extrapyramidal signs and with each separate sign; 2) number and proportion of cases and controls with abnormal neuropsychological tests (corrected MMSE score, <24; corrected FAB score, ≤13.4) (23); 3) number and proportion of cases with family history of AD, PD, FTD, ALS; 4) ALS demographics (age and gender) and clinical findings (age at onset, site of onset, EE diagnostic category, family history of neurodegenerative diseases), and extrapyramidal signs; 5) ALS demographics and clinical findings, and MMSE and FAB scores.

Statistical analysis

Descriptive statistics are reported as count and percentage or median and range/interquartile range (IQR). Bivariate analyses were performed using Fisher’s exact test and Wilcoxon-Mann Whitney test.
as appropriate. Five conditional logistic models were used to compare the risk of ALS patients vs. controls in the occurrence of tremor (model I), bradykinesia (model II), rigidity (model III), postural instability (model IV) and at least one of the four cardinal signs (model V). All models were adjusted for age, gender, years of education. MMSE and FAB were also dummyed (normal vs. abnormal) and used as dependent variables in conditional logistic models VI and VII. Abnormal scores were based on normative values obtained in the Italian population (24,25). ALS patients were also tested to assess any possible relation between the demographic and clinical variables and extrapyramidal signs, MMSE and FAB scores using multivariable (logistic regression) models. Variables to be maintained in the multivariable models were selected using a stepwise selection method. A 5% significance level was required for a variable to enter and stay in the model. The results of multivariate analyses are presented as adjusted odds ratios (adjOR) with 95% confidence intervals (95% CI). Given the exploratory nature of this investigation, the sample size was not predetermined. All analyses were performed using the SAS statistical analysis system version 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

One hundred and forty-six patients and 146 matched controls entered the study. The median (range) age at the time of evaluation was 68 years (27–92) and 67 years (26–92) for cases and controls, respectively. Each group included 91 (62%) males and 55 (38%) females. The median (range) MMSE score was 28 (18.4–30) in ALS patients and 28 (13.5–30) in controls (p = 0.85) while the median (range) FAB score was 15.9 (5.7–18) in cases and 16.5 (6.4–18) in controls (p = 0.01). The clinical characteristics of the disease in ALS patients are illustrated in Table I. Of note, family history of AD was reported by 5.5% of cases. The corresponding values for PD, FTD and ALS were 1.4, 0.7 and 3.4%, respectively.

ALS patients and controls reporting cardinal extrapyramidal signs and abnormal MMSE and FAB scores are illustrated in Table II. None of the cases and controls received treatment for extrapyramidal signs, or for cognitive dysfunction because these signs were mild and did not interfere with daily living activities. Significant differences were observed for rigidity (adjOR 5.7; 95% CI 1.5–22.0), bradykinesia (adjOR 4.8; 95% CI 1.4–16.5), postural instability (inverse correlation: adjOR 0.3; 95% CI 0.1–0.9), and abnormal FAB score (adjOR 2.9; 95% CI 1.5–5.7). An abnormal MMSE score was reported in similar proportion in cases and controls.

In evaluating the ALS group, the occurrence of fasciculations was inversely correlated with having at least one cardinal symptom of PD (adjOR 0.2; 95% CI 0.1–0.7) (Table III). Age at ALS onset was correlated with tremor (adjOR 1.1; 95% CI 1.01–1.2) and with an abnormal FAB score (adjOR 1.1; 95% CI 1.01–1.1) (Table III). Cramps and family history of neurodegenerative diseases were correlated to an abnormal FAB score (adjOR 4.9; 95% CI 1.5–18.0).

Table I. Demographic and clinical characteristics of patients with ALS.

| Variable                  | n (%)       |
|---------------------------|-------------|
| Gender                    |             |
| M                         | 91 (62.3)   |
| F                         | 55 (37.7)   |
| Site of onset             |             |
| Limb                      | 87 (59.6)   |
| Bulbar                    | 49 (33.6)   |
| Generalized               | 10 (6.9)    |
| El Escorial criteria      |             |
| Definite ALS              | 69 (47.3)   |
| Probable ALS              | 54 (37.0)   |
| Possible ALS              | 23 (15.7)   |
| Family history of FDT     |             |
| Yes                       | 1 (0.7)     |
| No                        | 142 (97.2)  |
| Don’t know                | 3 (2.1)     |
| Family history of PD      |             |
| Yes                       | 2 (1.4)     |
| No                        | 143 (97.9)  |
| Don’t know                | 1 (0.7)     |
| Family history of AD      |             |
| Yes                       | 8 (5.5)     |
| No                        | 133 (91.7)  |
| Don’t know                | 4 (2.8)     |
| Missing                   | 1           |
| Family history of ALS     |             |
| Yes                       | 5 (3.4)     |
| No                        | 139 (95.2)  |
| Don’t know                | 2 (1.4)     |
| Family history of ND      |             |
| Yes                       | 11 (7.5)    |
| No                        | 135 (92.5)  |
| Muscle weakness           |             |
| Yes                       | 12 (8.2)    |
| No                        | 134 (91.8)  |
| Fasciculations            |             |
| Yes                       | 69 (47.6)   |
| No                        | 76 (52.4)   |
| Missing                   | 1           |
| Cramps                    |             |
| Yes                       | 45 (31.0)   |
| No                        | 45 (31.0)   |
| Missing                   | 1           |
| Riluzole                  |             |
| Yes                       | 112 (76.7)  |
| No                        | 34 (23.3)   |

Table II. Demographic and clinical characteristics of patients with ALS.

| Variable                  | 1st quartile | Median | 3rd quartile |
|---------------------------|--------------|--------|--------------|
| Education                 | 5.0          | 8.0    | 11.0         |
| Age at symptoms onset     | 57.2         | 67.0   | 73.7         |
| Disease duration at        | 9.3          | 13.2   | 20.2         |
| evaluation (months)       |              |        |              |
| MMSE                      | 26.0         | 28.0   | 30.0         |
| FAB                       | 13.5         | 15.9   | 18.0         |

ALS: amyotrophic lateral sclerosis; PD: Parkinson’s disease; AD: Alzheimer’s disease; ND: neurodegenerative diseases (AD and/or PD and/or FTD and/or ALS); MMSE: Mini Mental State Examination; FAB: Frontal Assessment Battery.
Table II. PD cardinal symptoms and cognitive impairment in cases and controls.

| Variable                        | Cases | Controls | adjOR | 95% CI |
|---------------------------------|-------|----------|-------|--------|
| At least one PD cardinal symptom|       |          |       |        |
| Yes                             | 23 (15.7) | 25 (17.1) | 1.1   | 0.5; 2.1 |
| No                              | 123 (84.2) | 121 (82.9) |       |        |
| Tremor                          |       |          |       |        |
| Yes                             | 11 (7.5)  | 11 (7.5)  | 1.03  | 0.4; 2.6 |
| No                              | 135 (92.5) | 135 (92.5) |       |        |
| Bradykinesia                    |       |          |       |        |
| Yes                             | 12 (8.2)  | 4 (2.7)   | 4.8   | 1.4; 16.5 |
| No                              | 134 (91.8) | 142 (97.3) |       |        |
| Rigidity                        |       |          |       |        |
| Yes                             | 12 (8.2)  | 3 (2.1)   | 5.7   | 1.5; 22.0 |
| No                              | 134 (91.8) | 143 (97.9) |       |        |
| Postural instability            |       |          |       |        |
| Yes                             | 4 (2.7)   | 14 (9.6)  | 0.3   | 0.1; 0.9  |
| No                              | 142 (97.3) | 132 (90.4) |       |        |
| MMSE < 24                       | 18 (12.3) | 15 (10.3) | 1.1   | 0.5; 2.3  |
| MMSE ≥ 24                       | 128 (87.7) | 131 (89.7) |       |        |
| FAB ≤ 13.4                      | 36 (24.8) | 14 (9.6)  | 2.9   | 1.5; 5.7   |
| FAB > 13.4                      | 109 (75.2) | 132 (90.4) |       |        |
| At least two PD cardinal symptoms|       |          |       |        |
| Yes                             | 10 (6.8)  | 7 (4.8)   | 1.1   | 0.5; 2.1   |
| No                              | 136 (93.2) | 139 (95.2) |       |        |

PD: Parkinson's disease; MMSE: Mini Mental State Examination; FAB: Frontal Assessment Battery; adjOR: adjusted odds ratio (age, gender, years of education); 95% CI: 95% confidence interval.

CI 2.0–12.4 and 5.7; 95% CI 1.4–23.4, respectively). All the other variables were unremarkable.

Discussion

Our population based case-control study suggests that patients with newly diagnosed ALS are at higher than expected chance to report extrapyramidal signs and to present impairment of executive functions. The odds are almost five-fold for bradykinesia and six-fold for rigidity. The odds of having an abnormal FAB score are three-fold. Each additional year of age corresponds to a 10% increased risk of tremor and/or to perform poorly when tested with the FAB scale. The odds to present an abnormal FAB score was almost five-fold and six-fold in patients with cramps and in those reporting a family history of neurodegenerative diseases, respectively.

Our findings on the impairment of executive functions are in keeping with other reports (4,26,27). In a comprehensive review of the literature, Ravits et al. (2) confirmed a partial overlap between ALS and FTD as up to 15% of FTD patients and 30% of ALS patients experience symptoms and signs suggestive of both clinical conditions. The overlap between ALS and FTD has a strong genetic basis, represented by the C9orf72 gene expansion which is known to cause familial ALS-FTD syndrome and accounts for about 10% of sporadic ALS (28).

Our findings on the increased risk of extrapyramidal signs are supported by few other observations. In a large cohort of patients with ALS from an integrated clinical database, 13.6% of cases were diagnosed with ALS-plus syndrome (16). Extrapyramidal signs and cognitive impairment were present in 22.7% and 8.0%, respectively, of cases. The only other study assessing the possible association between ALS and Parkinsonism in a clinical series was that of Wolf Gilbert et al. (12) who reviewed the Columbia Movement Disorder database of about 5500 PD patients and identified 27 patients with both Parkinsonism and ALS. Three of them were also found to have dementia. Bradykinesia, rigidity and postural instability were present in nearly all cases. However, the present study cannot be strictly compared with the U.S. report because our target

Table III. PD cardinal symptoms and cognitive impairment in patients with ALS. Results of multivariate analyses.

| Variable                        | adjOR | 95% CI | p-value |
|---------------------------------|-------|--------|---------|
| At least one PD cardinal symptom|       |        |         |
| Fasciculations                  | 0.2   | 0.1–0.7 | 0.0124  |
| Age at onset (\*)               | 1.1   | 1.01–1.2 | 0.0039  |
| FAB Age at onset (\*)           | 1.1   | 1.01–1.1 | 0.0248  |
| Cramps                          | 4.9   | 2.0–12.4 | 0.0007  |
| Family history of ND            | 5.7   | 1.4–23.4 | 0.0015  |

ALS: amyotrophic lateral sclerosis; PD: Parkinson’s disease; ND: neurodegenerative diseases; (\*): one-year increase; adjOR: adjusted odds ratio (age, gender, years of education); 95% CI: 95% confidence interval.
population was represented by patients with ALS, the number of individuals fulfilling the diagnosis of PD (i.e. at least two of the four cardinal signs) was similar among cases and controls (6.8 vs. 4.8%, \( p = 0.45 \)), and an active search was made of each extrapyramidal sign.

A family history of neurodegenerative diseases was associated with an increased risk of reporting abnormal executive functions in our ALS patients. Our data are in keeping with other epidemiologic and genetic studies supporting common pathophysiologic mechanisms for ALS, AD and PD. Involvement of the extrapyramidal system was more prevalent in 134 patients with probable AD than in 167 controls (29). Evidence for a shared genetic susceptibility to the three neurodegenerative diseases was found in a familial aggregation study on a hospital based cohort (30). However, more recent work from a population based case-control family aggregation study did not support this observation (31).

Neurodegenerative diseases have also in common a number of exogenous risk or protective factors, including low education, trauma, pesticide exposure, diet, coffee, smoking, occupation, exercise, and drug exposure (32,33).

One of the mechanisms linking ALS to PD is an increased frequency of variants in the gene encoding angiogenin (\( \text{ANG} \)), a strong neuroprotective factor (34). Isolated TDP-43 disorders were found to be associated with an ALS-plus syndrome with extrapyramidal features (9,35).

Except for age at onset, we found no association between demographic and clinical features in ALS patients and extrapyramidal signs, cognitive dysfunction and family history of AD, PD, FTD or ALS separately. Given the small number of cases and controls, our study may be underpowered to detect minor differences.

In addition, we did not find ALS-emergent abnormal MMSE scores. The use of this screening measure, which is fairly inaccurate in detecting mild cognitive impairment, might lead to under-ascertainment of cases with altered cognition.

Surprisingly, we found an inverse correlation between ALS and postural instability, one of the cardinal PD signs. A chance finding cannot be excluded. However, postural instability is generally observed in advanced PD and can be caused by several clinical conditions other than PD in elderly individuals. We did not investigate the cause of balance disorders in our controls, but old age, musculo-skeletal disorders and vertigo were frequently reported in their medical history.

Our study has strengths and limitations. Our major strength is the population base coupled with the representativeness of the inception cohort. The prevalence of family history of ALS in our sample corresponds to that of other Italian population-based studies (36,37). The study of newly diagnosed ALS patients favours the identification of other neurological signs early in the course of the disease and, in this regard, can help assessing comorbid disorders when the disease is not so advanced as to mask independent symptoms and signs. The second strength is the inclusion of strictly matched controls in order to disentangle symptoms and signs attributable to the disease from coincidental age-related findings. The third strength is the direct screening rather than a retrospective search of extrapyramidal signs and cognitive functions. The first limitation is the cross-sectional assessment of neurological signs.

In the absence of a follow-up, we cannot exclude the possibility that PD and dementia might occur later in the course of the disease. However, the functional impairment caused by the disease may mask extrapyramidal signs and the ability to comply with cognitive testing. The second limitation is the use of very simple scales to investigate executive functions. However, the similarity of our findings with other, more accurate reports and the validity of FAB, compared to other neuropsychological tests measuring frontotemporal functions (38), supports the value of our screening method. The third limitation is the limited sample size. Some associations may have thus gone undetected.

In conclusion, our data confirm a possible link between ALS, extrapyramidal disorders and impairment of executive functions. Whether this link is the result of a specific genetic susceptibility is a research hypothesis to be tested by future genetic studies.

Acknowledgements

The study has been funded by the Italian Ministry of Health (RFFS-2006-7-335969).

Declaration of interest: E. Pupillo has received funding from the American ALS Association and Italian Ministry of Health for data management and data monitoring of an observational study protocol. She receives funding from Italian Drug Agency (AIFA) for data monitoring and study management of randomized clinical trials. P. Messina has received funding from Sanoﬁ-Aventis, EISAI, Lombardy Region, and the American ALS Association for the data analysis and data management of RCT and observational study protocol. C. Lunetta has received compensation for board membership by ITALFARMACO. M. Corbo has received compensation for board membership by ITALFARMACO. M. Filosto has received funding from Genzyme, CSL Behring and Baxter.

J. Mandrioli has received research grants from Regione Emilia Romagna (Programma di ricerca Regione-Università 2010–2012, area 2, Ricerca per il Governo Clinico), and she has received compensation for board membership by ITALFARMACO. Emilia Romagna Registry for ALS is supported by a
grant from the Emilia Romagna Regional Health Authority. E. Beghi has received payment for board membership by VIROPHARMA and EISAI; has received funding for travel and speaker honoraria from UCB-Pharma, GSK and also for educational presentations from GSK; has received grants for research activities from the Italian Drug Agency, Italian Ministry of Health, Sanofi-Aventis and the American ALS Association.

Bianchi, Chiveri, Lorusso, Marin, Riva, Sasanelli and Tremolizzo report no conflicts of interest.

References

1. Chio A, Calvo A, Moglia C, Mazzini L, Mora G; PARALS study group. Phenotypic heterogeneity of amyotrophic lateral sclerosis: a population based study. J Neurol Neurosurg Psychiatry. 2011;82:740–6.

2. Ravits J, Appel S, Baloh RH, Barohn R, Brooks BR, Elman L, et al. Deciphering amyotrophic lateral sclerosis: what phenotype, neuropathology and genetics are telling us about pathogenesis. Amyotroph Lateral Scler Frontotemporal Degener. 2013;14 (Suppl 1):5–18.

3. Phukan J, Pender NP, Hardiman O. Cognitive impairment in amyotrophic lateral sclerosis. Lancet Neurol. 2007;6:994–1003.

4. Phukan J, Elamin M, Bede P, Jordan N, Gallagher L, Byrne S, et al. The syndrome of cognitive impairment in amyotrophic lateral sclerosis: a population based study. J Neurol Neurosurg Psychiatry. 2012;83:102–8.

5. Takahashi H, Snow BJ, Bhatt MH, Peppard R, Eisen A, Calne DB. Evidence for a dopaminergic deficit in sporadic amyotrophic lateral sclerosis on positron emission scanning. Lancet. 1993;342:1016–8.

6. Desai J, Swash M. Extrapyramidal involvement in amyotrophic lateral sclerosis: backward falls and retropulsion. J Neurol Neurosurg Psychiatry. 1999;67:214–6.

7. D’Ascenzo C, Cecchin D, Santelli L, Palmieri A, Gaiani A, Querin G, et al. Parkinson-like features in ALS with predominant upper motor neuron involvement. Amyotrophic Lateral Sclerosis. 2012;13:137–43.

8. Geser F, Brandmeir NJ, Kwong LK, Martinez-Lage M, Elman L, McCluskey L, et al. Evidence of multisystem disorder in whole-brain map of pathological TDP-43 in amyotrophic lateral sclerosis. Arch Neurol. 2008;65:636–41.

9. McCluskey LF, Elman LB, Martinez-Lage M, van Deerlin V, Yuan W, Clay D, et al. Amyotrophic lateral sclerosis-plus syndrome with TAR DNA-binding protein-43 pathology. Arch Neurol. 2009;66:121–4.

10. Brettschneider J, Arai K, del Tredici K, Toledo JB, Robinson JL, Lee EB, et al. TDP-43 pathology and neuronal loss in amyotrophic lateral sclerosis spinal cord. Acta Neuropathol. 2014;128:423–37.

11. Steele JC, McGeer PL. The ALS/PDC syndrome of Guam and the cycad hypothesis. Neurology. 2008;70:1984–90.

12. Wolf Gilbert RM, Fahn S, Mitsumoto H, Rowland LP. Parkinsonism and motor neuron diseases: 27 patients with diverse overlap syndromes. Mov Disord. 2010;25:1868–75.

13. Manno C, Lipari A, Bono V, Taciello AG, La Bella V. Sporadic Parkinson’s disease and amyotrophic lateral sclerosis complex (Brain-Fahn-Schwartz disease). J Neurol Sci. 2013;326:104–6.

14. Luigetti M, Quaranta D, Conte A, Lattante S, Romano A, Silvestri G, et al. Frontotemporal dementia, Parkinsonism and lower motor neuron involvement in a patient with C9orf72 expansion. Amyotroph Lateral Scler. 2013;14:66–9.

15. Goldstein LH, Abrahams S. Changes in cognition and behaviour in amyotrophic lateral sclerosis: nature of impairment and implications for assessment. Lancet Neurol. 2013;12:368–80.

16. McCluskey L, Vandriel S, Elman L, van Deerlin VM, Powers J, Boiler A, et al. ALS-plus syndrome: non-pyramidal features in a large ALS cohort. J Neurol Sci. 2014;345:118–24.

17. Von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP; STROBE Initiative. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Bull World Health Organ. 2007;85:867–72.

18. Beghi E, Millul A, Micheli A, Vitelli E, Logroscino G; SLALOM Group. Incidence of ALS in Lombardy, Italy. Neurology. 2007;68:141–5.

19. Georgoulopoulos E, Vinceti M, Bonvicini F, Sola P, Goldoni CA, de Girolamo G, et al. Changing incidence and subtypes of ALS in Modena, Italy: a 10-years prospective study. Amyotrophic Lateral Scler. 2011;12:451–7.

20. Brooks BR. El Escorial World Federation of Neurology criteria for the diagnosis of amyotrophic lateral sclerosis. Subcommittee on Motor Neuron Diseases/Amyotrophic Lateral Sclerosis of the World Federation of Neurology Research Group on Neuromuscular Diseases and the El Escorial ‘Clinical limits of amyotrophic lateral sclerosis’ workshop contributors. J Neurol Sci. 1994;124 (Suppl):96–107.

21. Folstein MF, Folstein SE, McHugh PR. Mini Mental State. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12:189–98.

22. Dubois B, Slachevsky A, Litvan I, Pillon B. A frontal assessment battery at bedside. The FAB. Neurology. 2000;55:1621–6.

23. Slachevsky A, Villalpando JM, Sarazin M, Hahn-Barma V, Pillon B, Dubois B. Frontal assessment battery and differential diagnosis of frontotemporal dementia and Alzheimer’s disease. Arch Neurol. 2004;61:1104–7.

24. Appollonio I, Leone M, Isella V, Piamarta F, Consoli T, Villa ML, et al. The Frontal Assessment Battery (FAB): normative values in an Italian population sample. Neurol Sci. 2005;26:108–16.

25. Magni E, Binetti G, Bianchetti A, Rozzini R, Trabucchi M. Mini-Mental State Examination: a normative study in Italian elderly population. Eur J Neurol. 1996;3:198–202.

26. Monttuschi A, Iazzolino B, Calvo A, Moglia C, Lopiano L, Restagno G, et al. Cognitive correlates in amyotrophic lateral sclerosis: a population based study in Italy. J Neurol Neurosurg Psychiatry. 2014 doi: 10.1136/jnnp-2013-307223. [Epub ahead of print]

27. Ringholz GM, Appel SH, Bradshaw M, Cooke NA, Mosnik DM, Schulz PE. Prevalence and patterns of cognitive impairment in sporadic ALS. Neurology. 2005;65:586–90.

28. Al-Chalabi A, Jones A, Troakes C, King A, Al-Sarraj S, van den Berg LH. The genetics and neuropathology of amyotrophic lateral sclerosis. Acta Neuropathol. 2012;124:339–52.

29. Funkenstein HH, Albert MS, Cook NR, West CG, Scherr PA, Chown MJ, et al. Extrapyramidal signs and other neurologic findings in clinically diagnosed Alzheimer's disease. A community based study. Arch Neurol. 1993;50:51–6.

30. Majoar-Kraukauer D, Ottman R, Johnson WG, Rowland LP. Familial aggregation of amyotrophic lateral sclerosis, dementia, and Parkinson’s disease: Evidence of shared genetic susceptibility. Neurology. 1994;44:1872–7.

31. Byrne S, Heverin M, Elamin M, Bede P, Lynch C, Kenna K, et al. Aggregation of neurologic and neuropsychiatric disease in amyotrophic lateral sclerosis kindreds: a population based case-control cohort study of familial and sporadic amyotrophic lateral sclerosis. Ann Neurol. 2013;74:699–708.

32. Kieburtz K, Wunderle KB. Parkinson’s disease: evidence for environmental risk factors. Mov Disord. 2013;28:8–13.
33. Sutherland GT, Siebert GA, Kril JJ, Mellick GD. Knowing me, knowing you: can a knowledge of risk factors for Alzheimer’s disease prove useful in understanding the pathogenesis of Parkinson’s disease? J Alzheimers Dis. 2011;25:395–415.

34. van Es MA, Schelhaas HJ, van Vught PWJ, LeClerc AL, Keagle P,Bloem BR, et al. Angiogenin variants in Parkinson’s disease and amyotrophic lateral sclerosis. Ann Neurol. 2011;70:964–73.

35. Fujita Y, Ikeda M, Yanagisawa T, Senoo Y, Okamoto K. Different clinical and neuropathologic phenotypes of familial ALS with A315E TARDPB mutation. Neurology. 2011;77:1427–31.

36. Mandrioli J, Biguzzi S, Guidi C, Venturini E, Sette E, Terlizzi E, et al. Epidemiology of amyotrophic lateral sclerosis in Emilia Romagna Region (Italy): a population based study. Amyotroph Lateral Scler Frontotemporal Degener. 2014;15:262–8.

37. Piemonte and Valle d’Aosta Register for Amyotrophic Lateral Sclerosis (PARALS). Incidence of ALS in Italy: evidence for a uniform frequency in Western countries. Neurology. 2001;56:239–44.

38. Oskarsson B, Quan D, Rollins YD, Neville HE, Ringel SP, Arciniegas DB. Using the Frontal Assessment Battery to identify executive function impairment in amyotrophic lateral sclerosis: a preliminary experience. Amyotroph Lateral Scler. 2010;11:244–7.

**Supplementary material available online**

Supplementary Tables I–II.