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ORIGINAL COMMUNICATION

Parkinsonian traits in amyotrophic lateral sclerosis (ALS): a prospective population-based study

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Abstract

Background Amyotrophic lateral sclerosis (ALS) is characterized by a spectrum of phenotypes, but only a few studies have addressed the presence of parkinsonian (PK) symptoms. The aim of our study was to investigate the occurrence of PK features in a prospective population-based cohort of ALS patients, determining their demographic, clinical, neuropsychological and genetic characteristics, and identifying their morphological and functional imaging correlates.

Methods A consecutive series of ALS patients were enrolled and prospectively followed for 2 years. Patients were classified according to the presence (ALS-PK) or absence (ALS) of PK signs, and they underwent neuropsychological testing, genetic analysis for the main ALS and PD genes, brain MRI and ^{18}F-FDG-PET. ALS-PK patients underwent ^{123}I-ioflupane SPECT.

Results Out of 114 eligible patients, 101 (64 men; mean age at onset 65.1 years) were recruited. Thirty-one patients (30.7%) were classified as ALS-PK. Compared to ALS patients, ALS-PK patients were more frequently male, but did not differ for any other clinical, demographic or neuropsychological factors. ^{123}I-ioflupane SPECT was normal in all but two ALS-PK patients. At ^{18}F-FDG-PET, ALS-PK patients showed a relative hypometabolism in left cerebellum and a relatively more preserved metabolism in right insula and frontal regions; MRI fractional anisotropy was reduced in the sagittal stratum and increased in the retrolenticular part of the internal capsule.

Conclusions In our study, about 30% of ALS patients showed PK signs. Neuroimaging data indicate that PK signs are due to the involvement of brain circuitries other than classical nigrostriatal ones, strengthening the hypothesis of ALS as a complex multisystem disease.

Keywords Amyotrophic lateral sclerosis · Parkinsonian · Positron emission tomography · Population-based study

Abbreviations

ALS	Amyotrophic lateral sclerosis
PD	Parkinson's disease
PARALS	Piemonte and Valle d'Aosta Register for ALS
FTD	Frontotemporal dementia
ALS-PK	ALS patients with co-morbid parkinsonian disorder

Introduction

Amyotrophic lateral sclerosis (ALS) causes progressive degeneration of upper and lower motor neurons [1]. Approximately 50% of cases show various degrees of cognitive impairment, up to frontotemporal dementia (FTD) [2, 3] suggesting that ALS and FTD are part of a continuum [4].

An association between sporadic and familial Parkinson's disease (PD) and ALS, i.e., Brait–Fahn–Schwartz disease, has been proposed as a syndrome characterized

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by the co-presence of these two disorders without dementia or dysautonomia [5]. More recently, parkinsonian (PK) symptoms and signs have been described in cross-sectional studies in ALS patients, with frequency from 5 to 17% [6, 7]. The presence of bradykinesia associated with rigidity or tremor in patients with upper and lower motor neuron signs (spasticity, hyperreflexia, weakness, atrophy, fasciculations) suggests a concomitant dysfunction of the basal ganglia and the corticospinal system. However, studies on the occurrence of PK features in ALS are lacking, and neuroimaging correlates of co-morbid patients have not been systematically explored.

The aims of this study were: (1) to determine the presence of PK features in a prospective population-based ALS cohort; (2) to describe the motor and cognitive characteristics of ALS patients with PK signs (ALS-PK); (3) to investigate the differences between ALS and ALS-PK with morphological and functional neuroimaging.

Methods

Patients residing in Piemonte and Valle d'Aosta (PARALS), Italy, and diagnosed between January 1st 2013 and December 31st 2013 with definite, probable or probable laboratory-supported ALS, according to El Escorial criteria revised [8], were eligible for the study.

Patients underwent clinical, neurophysiological, and neuropsychological examination, and were classified as classical, bulbar, flail arm, flail leg, or prevalent upper motor neuron ALS [9]. We collected age at onset, age at diagnosis, age at enrollment, birth place, family history of ALS, PD or extrapyramidal disorders, dementia, and other neurological diseases, physiological and past medical history, pharmacological therapy and disease duration. Patients were evaluated at baseline and at a quarterly basis, using the ALS Functional Rating Scale-Revised (ALSFRS-R), the Medical Research Council (MRC) score, and the Ashworth scale. To identify patients with a co-morbid parkinsonian disorder (ALS-PK), defined as the presence of bradykinesia associated with either resting tremor or rigidity, or both [10], they were examined by a neurologist expert in movement disorders. The presence of PK signs was carefully evaluated, due to possible misleading motor ALS-related symptoms, and the neurological examination was video recorded. All videos were subsequently and independently examined by two other neurologists expert in movement disorders. Patients were classified as ALS-PK when there was agreement in the evaluation of at least two out of three neurologists. The evaluators were blinded to the ALSFRS-R and MRC scores. The severity of PK features was rated through the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) [11], but the score was not used for the diagnosis of ALS-PK.

Cognitive assessment The neuropsychological battery is reported in Supplementary Methods. Patients were classified as ALS-FTD, ALS with cognitive impairment (ALS-Ci), ALS with behavioral impairment (ALS-Bi) and cognitively normal (CN) [13].

Genetic testing All patients were assessed for the main ALS-related genes: *SOD1, TARDBP, FUS* and *C9orf72* (see Supplementary Methods). MLPA (multiplex ligation-dependent probe amplification) was used to detect complete or partial deletions or duplications on these PD-related genes: *SNCA, PARK2, UCHL1, PINK1, PARK7, LRRK2, GCH1* and *ATP13A2* (see Supplementary Methods).

^{123}I-ioflupane (^{123}I-FP-CIT) SPECT Patients with PK features underwent, at the time of the PK symptoms onset, a ^{123}I-ioflupane SPECT. The brain scan was acquired following the standard procedures using a dual-head GE Millennium camera and filtered back projection. Acquired sequences were analyzed qualitatively and semi-quantitatively (see Supplementary Methods)

^{18}F-FDG-PET ^{18}F-FDG-PET was performed, at the time of ALS diagnosis, by a Discovery ST-E System (General Electric) and reconstructed using iterative ordered subset expectation maximization (OSEM) (2 iterations, 28 subsets) resulting in FWHM of 6 mm (see Supplementary Methods).

MRI MRI was performed, at the time of ALS diagnosis, by MRI HDXT Echo-Speed GE Signa 1.5 T. Diffusion tensor imaging (DTI) was acquired using a 2D single-shot spin-echo planar imaging sequence and T1-weighted MRI using a standard 3D magnetization prepared rapid acquisition gradient-recalled echo (3D MPRAGE) pulse sequence at 1 mm isotropic spatial resolution (see Supplementary Methods).

Data analysis The clinical characteristics of patients in the two groups were compared using the Chi square test (discrete variables) or the Student's *t* test/ANOVA (continuous variables). Survival was calculated from onset to death/tracheostomy or the censoring date (31st October 2017), using the Kaplan–Meier method, and compared with the log-rank test. No patients were lost to follow-up. Multivariate analysis was performed with Cox proportional hazards model (stepwise backward). Data were analyzed using the SPSS 22.0 statistical package. For further details see Supplementary Methods.

Standard protocol approval, registration, and patient consent

The local Ethical Committee (Comitato Etico Azienda Ospedaliero-Universitaria Città della Salute e della Scienza) approved the study. All patients provided written informed consent before enrollment. Data were anonymized according to the Italian law for the protection of privacy.

Data availability

Anonymized data will be shared by request from any qualified investigator.

Results

114 newly diagnosed consecutive patients were eligible for the study (Fig. 1). Two patients were excluded because the diagnosis changed (benign fasciculation syndrome; nemalinic myopathy). Four patients refused to participate. Seven patients gave their consent but were not assessable for extrapyramidal signs due to their severe clinical condition. The final study population included 101 patients, 64 men and 37 women (mean age at onset 65.1 years, SD 11.7; mean age at enrollment 66.6 years, SD 11.7). 40 cases showed bulbar onset and 61 spinal onset. The phenotype was classified as classical ALS ($n=37$), bulbar ($n=40$), flail arm ($n=2$), flail leg ($n=15$), and prevalent upper motor neuron ALS ($n=7$). This proportion was kept in the 67 patients who underwent PET.

Basal visit Twenty-eight patients (27.7%) were diagnosed as ALS-PK. All three experts in movement disorders agreed in diagnosing ALS-PK for 26 cases, while it was excluded in 73 cases. The remaining two cases were classified as ALS-PK by two out of three experts, but were included in the final ALS-PK group after a consensus discussion.

Two of the ALS-PK patients had already been diagnosed with PK disorder before the onset of ALS. One patient in his 1970s had an idiopathic PD diagnosed 2 years before the onset of ALS and underwent effective dopaminergic therapy. QueryThe latter, who was in his 1980s, had an atypical asymmetrical parkinsonism, poorly responsive to dopaminergic therapy, with an onset of 18 months before the diagnosis of ALS and considered as possible corticobasal degeneration (CBD) [14].

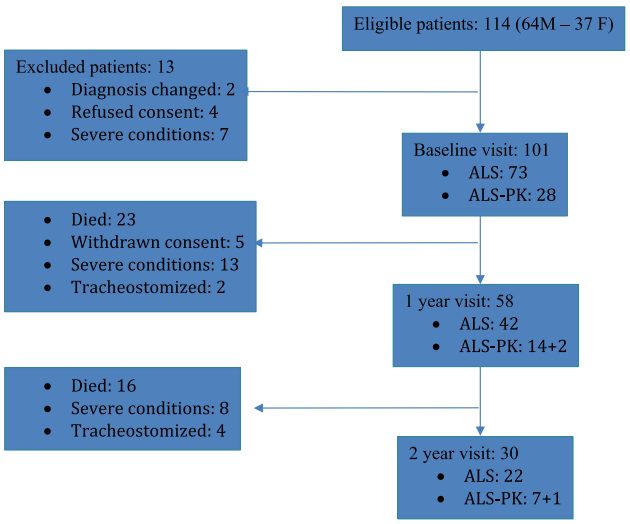

Fig. 1 Flow chart of the study. *ALS* amyotrophic lateral sclerosis patients without parkinsonian signs, *ALS-PK* amyotrophic lateral sclerosis patients with parkinsonian signs

Table 1 reports a comparison of clinical and demographic characteristics of ALS and ALS-PK. Men were overrepresented in the ALS-PK group ($p=0.05$), with an odds ratio of 3.31 (CI 1.20–9.08). Age at onset, type of onset, diagnostic delay, mean ALSFRS-R, MRC scores, survival and family history for ALS, PD or dementia were similar for the two groups.

The scores and subscores of the MDS-UPDRS are reported in Tables 2 and 3.

Bradykinesia was present in all ALS-PK and 71 (97.3%) ALS patients ($p=0.93$). Median bradykinesia subscore was higher in the ALS-PK patients [18 (IQR 12–25) vs 13 (IQR 9–19); $p=0.02$].

All but three ALS-PK patients (89.2%) showed rigidity at least in one limb compared to 36 ALS patients (49.3%) ($p=0.0001$). Rigidity was significantly more severe in the ALS-PK group [median score 18 (IQR 2–6) vs. 0 (IQR 0–2), $p=0.0001$].

Tremor was present in 16 (57.1%) ALS-PK and in 33 (45.2%) ALS ($p=0.0001$), and the median composite tremor subscore was significantly different in the two groups [1 (IQR 0–6) vs 0 (IQR 0–2), $p=0.01$]. Resting tremor was present in 10 ALS-PK (35.3%) and in 5 ALS patients (6.8%)

Table 1 Demographic and clinical characteristics of patients

	ALS-PK	ALS	*p*
Sex (female)	6 (21.4%)	31 (42.5%)	0.05
Site of onset (bulbar)	10 (35.7%)	30 (41.1%)	0.62
Mean age at onset (SD)	67.4 (12.1)	64.3 (11.5)	0.24
Mean age at basal visit (SD)	68.8 (12.1)	65.7 (11.5)	0.25
Mean ALSFRS-R score at basal visit (SD)	38.5 (6.3)	40.7 (5.0)	0.10

ALS amyotrophic lateral sclerosis patients without parkinsonian signs, *ALS-PK* amyotrophic lateral sclerosis patients with parkinsonian signs

Table 2 Comparison of overall scores of the MDS-UPDRS scale

	ALS-PK	ALS	*p*
UPDRS-I (SD)	12.5 (6.5)	9.4 (5.6)	0.018
UPDRS-II (SD)	17.8 (8.7)	12.4 (8.0)	0.004
UPDRS-III (SD)	39.1 (13.9)	27.1 (15.0)	0.0001
Hoehn & Yahr (SD)	3.0 (1.0)	2.2 (1.5)	0.009

ALS amyotrophic lateral sclerosis patients without parkinsonian signs, *ALS-PK* amyotrophic lateral sclerosis patients with parkinsonian signs

Table 3 Comparison of subscores of the section III of the MDS-UPDRS scale

MDS-UPDRS-III subscores		ALS-PK	ALS	*p*
Rigidity subscore	# of cases	25/28 (89.3%)	36/73 (49.3%)	0.0006
	Mean (SD)	4.00 (2.78)	1.74 (2.48)	0.0001
	Median (range)	4 (2–6)	0 (0–2)	0.0001
Bradykinesia subscore	# of cases	28/28 (100%)	71/73 (97.3%)	0.93
	Mean (SD)	18.46 (7.8)	14.66 (8.7)	0.05
	Median (range)	18 (12–25)	13 (9–19)	0.02
Tremor subscore	# of cases	16/28 (57.1%)	33/73 (45.2%)	0.0001
	Mean (SD)	2.89 (3.54)	1.16 (1.58)	0.001
	Median (range)	1 (0–6)	0 (0–2)	0.01
Axial subscore	# of cases	28/28 (100%)	66/73 (90.4%)	0.21
	Mean SD)	7.36 (4.31)	5.40 (4.19)	0.04
	Median (range)	7 (4–10)	4 (2–9)	0.04

Rigidity subscore is the sum of items 3a-e. Bradykinesia subscore is the sum of items 4a–b, 5a–b, 6a–b, 7a–b, 8a–b, 14. Tremor subscore is the sum of items 15a–b, 16a–b, 17a–e, 18. Axial subscore is the sum of items 9, 10, 11, 12, 13

ALS amyotrophic lateral sclerosis patients without parkinsonian signs, *ALS-PK* amyotrophic lateral sclerosis patients with parkinsonian signs

($p=0.0001$). The median composite MDS-UPDRS-III score for resting tremor was significantly different in the two groups [0 (IQR 0–2) vs 0 (IQR 0–0); $p=0.001$]. No significant differences were found for postural and action tremor.

Axial symptoms were detected in all ALS-PK and 66 (90.4%) ALS cases ($p=0.21$). Median axial subscore was higher in ALS-PK patients [7 (IQR 4–10) vs 4 (IQR 2–9); $p=0.04$].

One-year follow-up visit 58 patients underwent the 1-year visit with a movement disorder neurologist. In 14, PK signs had already been detected at the first visit. Two patients who had no PK signs at baseline showed PK signs at the second evaluation. The former had rest tremor and mild to moderate rigidity in the upper limbs. The latter showed postural tremor, bradykinesia, hypomimia, and moderate rigidity.

Two-year follow-up visit 30 patients underwent the 2-year visit. In seven, PK signs had already been detected in the previous visits. One patient developed PK signs at the third assessment (kinetic tremor, mild resting tremor, and rigidity at the upper limbs).

Genetic analysis All patients underwent screening for ALS and PD genes. The analysis of ALS-related genes showed in nine patients (7.8%) a pathological expansion of *C9orf72*, in one (0.9%) the c.800a > g (p.Asp267Ser) missense mutation of *TARDBP*, and in one patient (0.9%) the c.435 g > c (p.Leu145Phe) missense mutation of *SOD1*. Only one out of nine patients with *C9orf72* expansion showed PK signs. The patient carrying a *TARDBP* mutation developed PK signs at the 1-year follow-up visit. The patient with *SOD1* mutation had no PK signs.

Two mutations of Parkinson-related genes were detected (2%), in two subjects with ALS-PK. The former carried a p.Gly2019Ser missense mutation in the exon 41 of *LRRK2*; he had a family history of PD (father, paternal uncle, and paternal grandmother) and had been diagnosed with PD 2 years before the onset of ALS. The latter carried a heterozygous (non-pathogenic) deletion of exon 4 (delex 4) of *PARK2*; he did not have a familial history of PD, ALS or FTD.

Cognitive evaluation 93 cases underwent cognitive evaluation (92.1%). Eight cases were not tested (3 ALS-PK and 5 ALS): two patients were not of Italian mother language, four declined, and two were too clinically impaired. The cognitive profile was similar in the two groups: FTD was diagnosed in 4 ALS-PK (14.3%) and in 11 ALS (16.9%), ALS-Ci in 5 ALS-PK (17.8%) vs 14 ALS (21.5%), and ALS-Bi in 1 ALS-PK (3.6%) vs 3 ALS (4.6%). Overall, cognitive impairment was identified in 10 (35.7%) ALS-PK and 28 (43.1%) ALS patients ($p=0.51$). Among patients that underwent PET, cognitive impairment was found in 46.2% of ALS-PK and 31.2% of ALS.

^{123}I-FP-CIT SPECT Nineteen ALS-PK patients underwent ^{123}I-FP-CIT *SPECT*. The distribution of the ligand of the dopamine transporter in the basal nuclei was within the normal values for all but two patients, both with a diagnosis of PK syndrome pre-dating ALS.

^{18}FDG-PET 66 patients underwent ^{18}F-FDG-PET (16 ALS-PK, 50 ALS). Compared to ALS-PK, ALS patients showed a relative hypometabolism in right insula (BA 13) and in several right frontal regions (Supplementary Table 1; Fig. 2). A relatively higher metabolism was found in ALS compared to ALS-PK patients in left cerebellum.

MRI Seventy-three patients underwent brain MRI (17 ALS-PK, 56 ALS), that showed a significant reduction of fractional anisotropy (FA) in ALS-PK compared to ALS in the sagittal stratum and a significant increase of FA

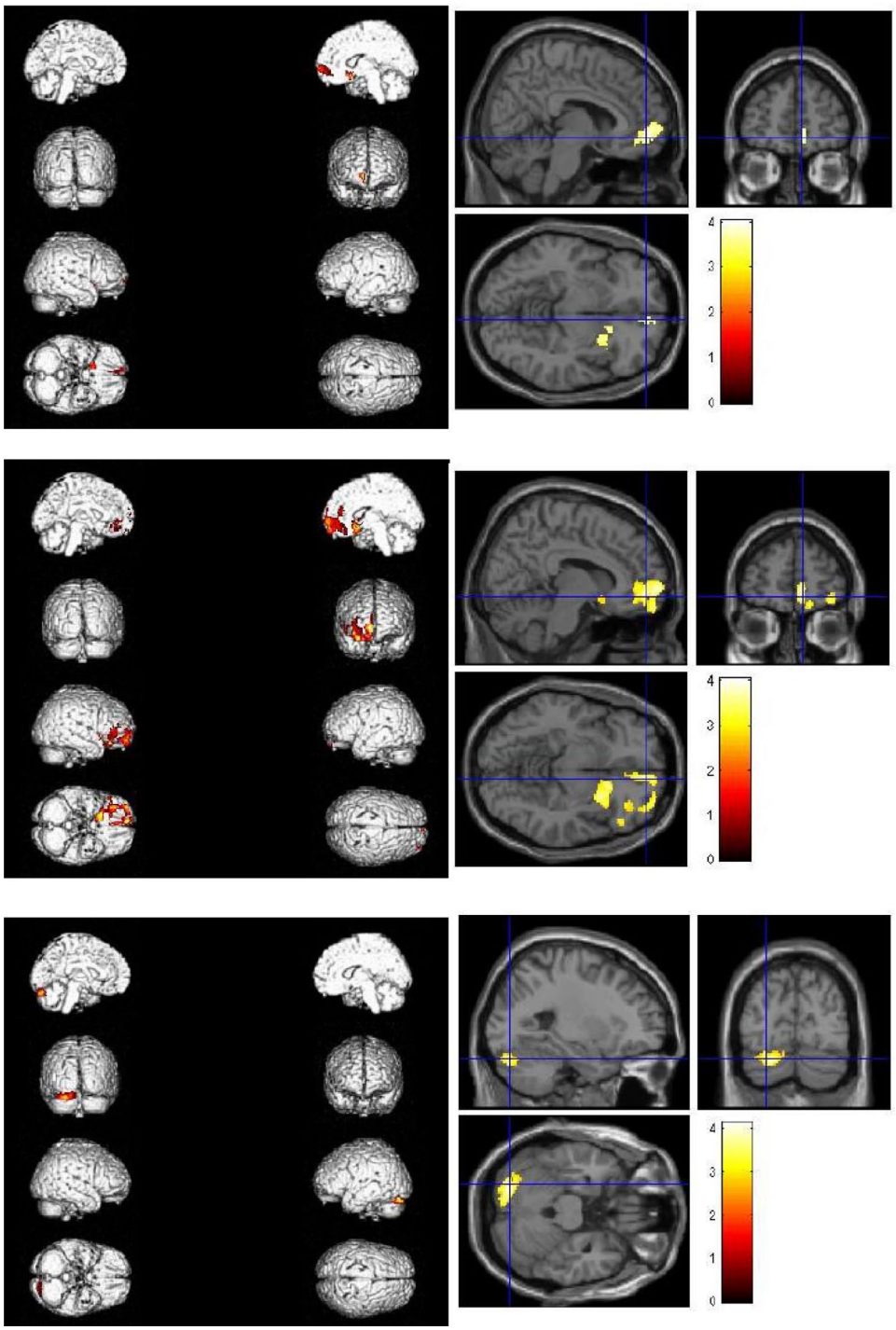

Fig. 2 PET imaging. ALS-PK vs ALS (peak level p_{height} of less than 0.005, cluster level $p_{FDR\text{-}corr} < 0.05$ and a cluster extent threshold (k_E) set at 100 voxels). Top row: relative hypermetabolism in ALS-PK vs ALS (top left: brain surface rendering; top right superimposition on an MRI template). Bottom row: hypometabolism in ALS-PK vs ALS (bottom left: brain surface rendering; bottom right superimposition on an MRI template)

of the retrolenticular part of the internal capsule (Supplementary Table 2; Fig. 3). Volumetric studies demonstrated a reduction of thickness in the left pre-central and occipital cortex in ALS-PK (Fig. 4).

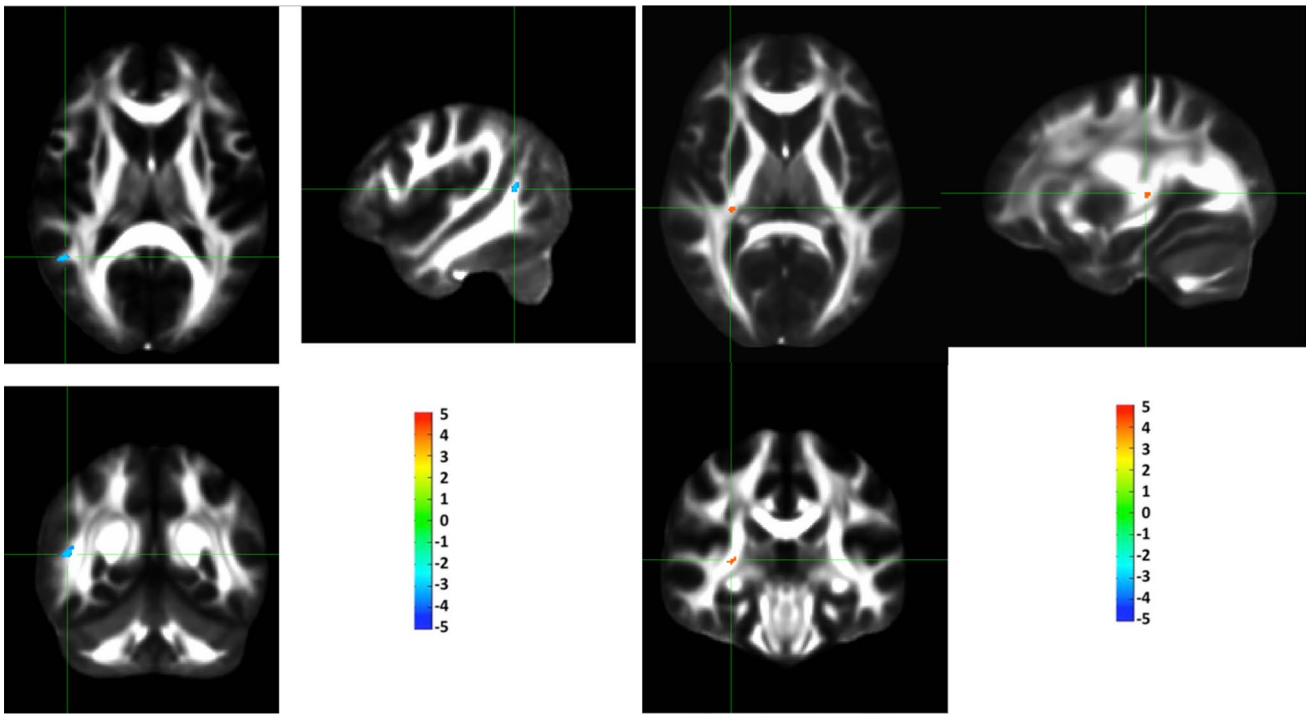

Fig. 3 ALS-PK compared to ALS. Reduction of FA in the sagittal stratum (left) and increase of FA in the retrolenticular part of the internal capsule (right)

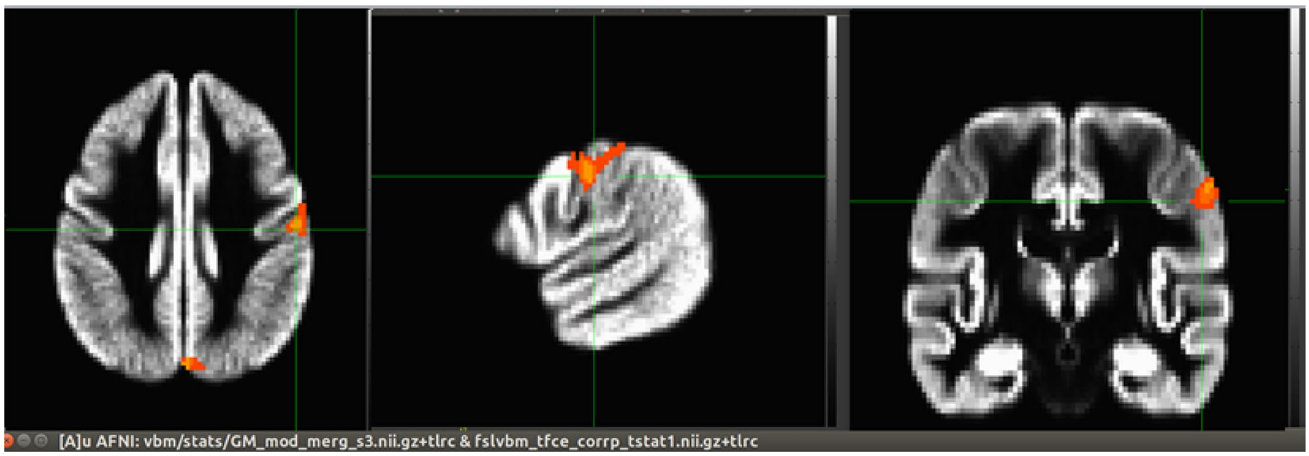

Fig. 4 Reduction of cortical thickness in ALS-PK compared to ALS. The significant clusters are superimposed on a gray matter template. Left: transversal view; center: sagittal view; right: coronal view

Discussion

In this prospective population-based study, about 33% of ALS patients (31/114) showed PK features meeting the diagnostic criteria for parkinsonism [10].

Two ALS-PK patients had already been diagnosed with parkinsonism before the onset of ALS. The former had a familial dominantly transmitted PD, due to a *LRRK2* p.Gly2019Ser missense mutation, while the latter had possible CBD. There are a few reports of the coexistence of LRRK2 mutation and TPD-43 pathology in the literature, and the possible influence of TDP-43 protein in the clinical presentation of LRKK2 mutated patients is still to be clarified [11].

The other 29 ALS-PK patients had signs meeting the criteria for parkinsonism, which were detected at the time of ALS diagnosis or during the follow-up, also in the late stage

of the disease. Besides bradykinesia, rigidity and rest tremor were also present in 89.2% and 35.3% of patients, respectively, in keeping with a previous report on a small ALS series [15]. ALS-PK patients were more frequently male, but they did not show any other clinical or demographic difference compared to ALS patients without PK signs. The neuropsychological profile did not differ between ALS-PK and ALS patients.

The comorbidity of ALS and parkinsonism had been described in 1973 in four patients in whom familial or sporadic parkinsonism predated ALS, without cognitive impairment or dysautonomia [5]. Subsequently, several case reports and small series were published, confirming this association [15–20]. The clinical picture of patients with comorbid ALS and parkinsonism appears to be heterogeneous, including cases with primary lateral sclerosis, ALS-FTD, and multisystem atrophy [21]. Our series further widens the spectrum of the possible associations, including CBD.

A recent case–control study compared 146 ALS patients with 146 age- and sex-matched controls to evaluate if the risk of cardinal PK signs at diagnosis was higher than expected by chance [7]. An increased risk was found for bradykinesia and rigidity but not for tremor and postural instability, although only 6% of cases had at least two PD cardinal signs. The authors concluded that newly diagnosed ALS patients are at a higher than expected chance to show PK signs. Similarly, rigidity was found in at least one muscle in 69% of a series of 39 consecutive ALS patients, indicating that extrapyramidal involvement plays a role in stiffness and balance impairment in a subset of ALS patients [6]. However, in that study, other PK signs were not assessed and patients had a prevalent upper motor neuron phenotype.

We did not find any difference in genetic mutation frequencies comparing ALS-PK and ALS patients. Only one of the nine patients with *C9orf72* expansion had PK signs. In a series of *C9orf72* expansion carriers, parkinsonism has been described in about one-third of the patients with FTD or FTD/ALS but in none of those with ALS [22]. However, only a small proportion (less than 1%) of patients with PD or atypical PD has been reported to carry the *C9orf72* expansion [23].

ALS-PK patients, with the only exception of the two patients with a diagnosis of familial PD and possible CBD, had a normal ^{123}I-FP-CIT SPECT, demonstrating that the nigrostriatal (NS) pathway was preserved and therefore indicating that PK symptoms in ALS patients are likely to be related to mechanisms different from the impairment of the NS pathway. Our findings differ from those of a series of 18 ALS patients in whom a moderately reduced striatal uptake was found, possibly due to the longer disease duration in that series (38.7 months vs. 15 months) [24]. In fact, a cross-sectional study with 6-Fluorodopa-PET on 16 patients with sporadic ALS without extrapyramidal signs found a significant correlation between a reduction of 6-Fluorodopa uptake and disease duration and a reduced dopaminergic function in 3 patients with ALS of long duration compared to controls [25]. The integrity of both preganglionic and postganglionic NS was described in five ALS patients with PK signs in a study performed using [^{18}F] L-dopa and [^{11}C] *N*-methylspiperone positron emission tomography [26]. These authors inferred that the parkinsonism in ALS patients could be related to pathological changes in brain areas other than the NS pathway.

In the present study, ^{18}F-FDG-PET showed a relative hypometabolism in the right insula and in several right frontal regions and a cerebellar relative hypermetabolism in ALS as compared to ALS-PK patients. The relative preservation of frontal metabolism in ALS-PK patients might be due to the nature of the neurobiological changes causing PK signs in ALS, which seem to be different from that observed in idiopathic PD, where the NS pathway involvement determines a relative decrease of metabolism in the lateral premotor cortex and parieto-occipital areas [27, 28]. This phenomenon is here described for the first time and investigations with larger cohorts may be necessary to better understand its significance.

The relative cerebellar hypometabolism might underscore the involvement of subcortical motor circuitry in ALS-PK. A similar finding has been described in parkinsonian-type MSA [29], and could be interpreted as a sign of the spread of the pathological process in different brain areas in ALS-PK patients.

Volumetric MRI showed that ALS-PK patients had a reduction of cortical thickness in the left pre-central region, despite having similar ALSFRS-R mean scores compared to ALS patients. Beside the possibility of being a sparse result, such relative atrophy in premotor cortex might mimic PK signs, being correlated with the ideomotor apraxia circuits.

In ALS-PK patients, FA was reduced in the sagittal stratum and increased in the retrolenticular part of the internal capsule. Recent studies indicate that microstructural changes in these pathways may have a role in motor and cognitive phenomenology of extrapyramidal disorders such as PD, progressive supranuclear palsy [30, 31] and traumatic brain injury [32].

A limitation of this study is represented by the difficulty to detect PK signs in ALS patients, where confounding factors are relevant. For example, bradykinesia was detected in a high percentage of non-ALS-PK patients. The experience of the examiner is crucial to decide if PK signs are only due to the confounding features [10]. We tried to overcome this difficulty through an independent evaluation of three movement disorder experts. Moreover, we used the MDS-UPDRS scale to score the severity of PK signs, despite it being expressly developed for PD patients. Thus, this scale could not be the best instrument to assess PK signs in ALS

patients. The MDS-UPDRS scale provides for the investigator "rate what you see" [12]; therefore, we used this tool just to give an overall judgement on motor signs and symptoms severity, independently from the diagnosis of ALS-PK.

Another limitation is the relative small size of the population in relationship with the interpretation of imaging features, because we know that some current opinions consider ALS as a syndrome, and different phenotypes should be considered as nosographic entities.

In conclusion, in this prospective multiparametric study, we found that about one-third of the ALS patients showed PK signs (bradykinesia and rigidity or resting tremor), mainly already detectable at the time of diagnosis. This phenotype was more common in males, but no other clinical, genetic, and demographic features differentiated the two groups. ^{123}I-FP-CIT SPECT showed that PK signs were not related to a functional impairment of the NS pathway. On the other hand, PET and MRI seem to converge in describing altered neuronal functions in ALS-PK in regions with motor valence, represented by relative hypermetabolism in frontal regions, hypometabolism in cerebellum, reduced cortical thickness in the left pre-central region and increased FA in the retrolenticular part of the internal capsule and reduced FA in the sagittal stratum. The latter, associated with metabolic changes in insula and prefrontal cortex observed in PET, is in accordance with an implication of regions with cognitive valence in ALS-PK patients [30]. These distinct functional and anatomical patterns indicate that PK signs in ALS-PK are related to the involvement of pathways different from those impaired in PD or other movement disorders and this further widens the clinical and pathological spectrum of ALS.

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Author contributions AC, AC, LL and MGR contributed to the fund raising, literature search, figures, study design, data collection, data analysis, data interpretation, writing, and revision of the manuscript. AC, AC, SC, FD, UM, CM, AR, BI and EM contributed to the data collection, data analysis, and revision of the manuscript. LS, UM, CAA and AC contributed to writing, data analysis and revision of the manuscript. MP, QT and FN contributed to data analysis, data interpretation, and revision of the manuscript. TM, MB, GC, MB, AC, GC and CV contributed to data collection, data analysis, data interpretation, and revision of the manuscript.

Compliance with ethical standards

Conflicts of interest Andrea Calvo reports no disclosure. Adriano Chiò reports personal fees from Biogen Idec, Cytokinetics, Mitsubishi Tanabe, and Neuraltus, outside the submitted work. Marco Pagani reports no disclosure. Stefania Cammarosano reports no disclosure. Francesca Dematteis reports no disclosure. Cristina Moglia reports no disclosure. Luca Solero reports no disclosure. Umberto Manera reports no disclosure. Tiziana Martone reports no disclosure. Maura Brunetti reports no disclosure. Michele Balma reports no disclosure. Giancarlo Castellano reports no disclosure. Marco Barberis reports no disclosure. Angelina Cistaro reports no disclosure. Carlo Alberto Artusi reports no disclosure. Elisa Montanaro reports no disclosure. Alberto Romagnolo reports no disclosure. Barbara Iazzolino reports no disclosure. Antonio Canosa reports no disclosure. Giovanna Carrara reports no disclosure. Consuelo Valentini reports no disclosure. Tie-Qiang Li reports no disclosure. Flavio Nobili reports no disclosure. Leonardo Lopiano reports no disclosure. Mario G. Rizzone reports no disclosure.

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