Movement Disorders
Vol. 24, No. 12, 2009, pp. 1836–1847

Brief Reports

Handedness Does Not Predict Side of Onset of Motor Symptoms in Parkinson's Disease

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Abstract: **This study focused on the relationship between the asymmetry of initial motor symptoms of Parkinson's disease (PD) and premorbid handedness of patients. Structural equation modeling has been used for this purpose. The survey consisting of validated items measuring handedness and questions related to side of occurrence of initial symptoms was administered to 472 patients with PD [277 men, 195 women, mean age 66.5 (9.3), mean duration of the disease 10 (6.1) years]. The unidimensional model of handedness fits the data well (χ^2 = 37.86, df = 20, *P* = 0.009, Root Mean Square Error of Approximation = 0.044, Comparative Fit Index = 1.00, Standardized Root Mean Square Residual = 0.042) and side of initial motor symptoms is not significantly related to the factor of handedness (*r* =0.11, SE = 0.07, *P* = 0.14). In contrast to several other studies, the results indicate that the side of first occurrence of PD signs cannot be predicted from premorbid handedness of patients.** © 2009 Movement Disorder Society

Key words: laterality; handedness; Parkinson's disease; asymmetry; motor symptoms

INTRODUCTION

The motor symptoms of Parkinson's disease (PD) are usually asymmetric,[1–4] particularly in the beginning of the disease. The commonly used Unified Parkinson's Disease Rating Scale (UPDRS)[5] incorporates items for evaluation of this asymmetry.

The asymmetry of motor symptoms in PD is said to remain unchanged overtime,[6] and patients with unilateral onset of PD manifestations have greater degeneration of contralateral substantia nigra at postmortem examination[7] as well as in early-stage PD.[8] Right-left asymmetry has been considered as an important classification factor used to distinguish between pathologically demonstrated PD and other movement disorders with similar characteristics.[9,10]

Relationships between body laterality and asymmetry of PD symptoms have been reported rather rarely. Laterality is based on the brain hemisphere dominance and its manifestations include performance asymmetry of hands, legs, eyes, and ears. Anatomic and functional brain asymmetry has been demonstrated with regard to handedness.[11] In an early clinical survey, no relationship was found between handedness and side of symptoms onset in idiopathic PD,[12] whereas dominant side was found to be more frequently involved in another small study, supposedly because of greater attention the patient pays to the affliction of the dominant hand.[13] One study[14] aiming to identify predictive factors associated with asymmetric symptoms of PD found that left-handed individuals tended to have more severe disease on the left side of the body. Further, it was shown that initial PD symptoms start to manifest more frequently on the right-sided extremities than on the left.[15] This might account for the potential relationship between dominance of the extremities and laterality of PD motor symptoms because there are almost 90% of right-handed people in the population. A recent study also identified the trend toward symptom onset on the dominant side.[16] By contrast, another study[17] showed that enhanced physical activity associated with preferred limb has a neuroprotective effect in experimental model of PD.

On the basis of the above-mentioned results, it is not clear whether there is a relationship between side of appearance of initial motor symptoms of PD and handedness. The aim of this study is to uncover the real level of association between the premorbid handedness and side of onset of PD motor symptoms by using advanced statistical procedures.

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Potential conflict of interest: Nothing to report.

Received 24 February 2009; Revised 14 April 2009; Accepted 16 April 2009

Published online 9 June 2009 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/mds.22653

TABLE 1. *Table of frequencies of side of onset*

	Right-handers		Left-handers	
	Right onset	Left onset	Right onset	Left onset
Writing	218	168	2	4
Hair dressing	196	151	13	13
Knocking	185	148	10	9
Unlocking	190	149	7	13
Spoon	211	167	2	4
Teeth	192	151	11	14
Knife	207	157	13	18

Right-handers (left-handers) are considered as those who responded "always use right (left) hand" or "rather use right (left) hand" for the corresponding motor activity.

PATIENTS AND METHODS

Sample

The questionnaire was mailed to 683 patients with PD that were seen at the Prague Movement Disorders Center between June 2006 and February 2007. All subjects provided informed consent. The study was approved by the local human studies committees.

Methods

The seven-item handedness questionnaire was part of a larger (27 items) survey of laterality. The other items of this survey regarded individual preferences of legs, eyes, and ears and therefore were not included in the analyses as this study focuses on handedness only. Because there is no handedness questionnaire standardized for PD, the items for handedness were taken from previously standardized tools such as Edinburgh Handedness Inventory[18] or Annet's laterality questionnaire.[19] These items have been assessed and validated for the use in patients with PD independently by four neurologists, two kinanthropologists, and a statistician experienced in questionnaire development. This resulted in seven-item questionnaire of handedness and one additional question about side of appearance of initial motor symptoms. The patients were asked which hand they used before the signs of PD occurred for specific motor activities such as handwriting, hairdressing, brushing teeth, holding a spoon, unlocking, knocking, and cutting with knife. Responses have been recorded on five-point ordinal scale (always used right hand, rather used right hand, used both hands equally often, rather used left hand, always used left hand). Responses for side of onset of initial motor symptoms were recorded on three-point scale (right side, both sides, or left side of the body). The Spearman correlations were estimated and structural equation model has been developed to study how the lateral hand preference is related to the side of occurence of first signs of PD. The LISREL program[20] has been used for the estimation of model parameters. Regarding the ordinality of the data, the covariance matrix and corresponding asymptotic covariance matrix were estimated. Robust maximum likelihood was used as an estimator of model parameters.

RESULTS

The response rate among the 683 patients was 77% (523), and 51 were excluded prior to analyses for incomplete or inconsistent answers. Thus, the data from 472 PD (69%) patients were analyzed (277 men, 195 women). Mean age of the patients was 66.5 (SD 9.3) years and mean duration of the disease 10 (6.1) years. Asymmetric onset of PD was reported by 398 patients (221 right side onset, 177 left side onset), and 42 patients reported onset on both sides. Thirty-two patients did not remember the side of occurrence of first PD signs. Mean percentage of right-handedness was 89%, left-handedness 5.4% (Table 1).

The individual relationships between the side of onset of first PD motor signs and items measuring handedness is expressed by means of Spearman correlations (Table 2), and the overall relationship is subsequently estimated by a LISREL model shown in Figure 1.

Spearman Correlations

Values of correlations between side of onset and handedness items were low (ranging from 0.01 to

TABLE 2. *Correlation matrix (Spearman)*

	1.signs	Writing	Hair dressing	Knocking	Unlocking	Spoon	Teeth	Knife
1.signs	1.00							
Writing	0.04	1.00						
Hair dressing	0.07	0.38	1.00					
Knocking	0.01	0.29	0.58	1.00				
Unlocking	0.06	0.25	0.61	0.71	1.00			
Spoon	0.08	0.37	0.52	0.40	0.45	1.00		
Teeth	0.05	0.27	0.63	0.54	0.61	0.55	1.00	
Knife	0.09	0.31	0.61	0.51	0.52	0.56	0.66	1.00

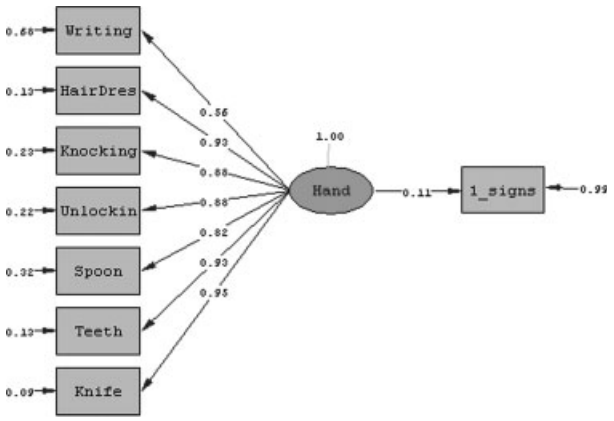

FIG. 1. Path diagram and parameter estimates of the model of relationship between handedness and occurrence of the first signs of PD.

0.09). None of these correlations reached 5% level of statistical significance (*P*-values were ranging from 0.06 to 0.89).

LISREL Model

To quantify the overall relationship between side of onset of PD motor signs and handedness, the model shown in Figure 1 was empirically tested. Handedness is expressed as unidimensional latent variable. The internal consistency of handedness items assessed by Cronbach's alpha was satisfactory (0.90). Goodness of fit statistics suggested this model fits the data very well [Satorra-Bentler Scaled $\chi^2 = 37.86$, df = 20 ($P = 0.009$), Root Mean Square Error of Approximation = 0.044; Normed Fit Index = 0.99; Comparative Fit Index = 1.00; Standardized Root Mean Square Residual = 0.042; Goodness of Fit Index = 0.86].

The regression equation which predicts the 1.signs from handedness in the model is 1.signs = 0.11 × Handedness + 0.99. The regression coefficient (0.11) can be interpreted as overall correlation between premorbid handedness and side of onset of initial motor symptoms. The value of this correlation equals to 0.11 and it is nonsignificant (SE = 0.07, $P = 0.14$). In addition, the percentage of variance of item 1.signs explained by this model is only 0.01. These values indicate that the side of the occurence of the first parkinsonian signs (right or left side of the body) cannot be predicted from the premorbid handedness of patients.

DISCUSSION

Unlike previous investigations on the relationship between handedness and side of onset of PD symptoms, this study does not confirm a relationship between them.

Previous studies evaluated handedness on binary scale (right-handed/left-handed) and single activity (handwriting). Results of this study are based on handedness data from multiple unilateral activities, each on five-point ordinal scale, which allows studying the relationship in greater detail. In addition, more advanced and suitable statistical procedures were used than in previous studies, which minimize the threat of over/underestimation of correlations between studied phenomena.

Proportion of patients experiencing the side of onset on their dominant hand is comparable with previous study[16] and gives impression of tendency toward dominant side onset. However, the between-items correlations of side of onset of PD symptoms and handedness items were very low (ranging from 0.02 to 0.09) and nonsignificant. The overall correlation was subsequently estimated using structural equation modeling. This relationship was also found very low ($r = 0.11$) and nonsignificant ($P = 0.14$).

Indeed, these findings do not correspond with majority of previous studies. The large (1,277 individuals) study[14] has identified hand dominance as one of the predictors of the side of asymmetric disease such that left-handed individuals tended to have more severe disease on the left side of the body. However, results of this study may not be very convincing because of the following: First, handedness has been assessed just by clinical rating of handwriting on binary scale (right-handed or left-handed). Handedness is not a binary variable, though, its distribution in the population is rather bimodal. Thus, it should be quantified on a continuum or at least on an ordinal scale. Second, the assessment of handedness was based on clinical rating of single activity (handwriting), which may be biased by cultural and social factors. Third, their predictive multiple regression model explained only 16% of variance, which is not satisfactory. It should be noted, however, that authors of this study were not interested in predicting the side of symptom onset but rather in the degree of asymmetry of symptoms. The most recent study[16] reported a tendency toward symptom onset on dominant hand although statistical significance has not been reached. Authors argued that it was due to small sample size (over 300 patients). Also, in this study, handedness was defined as the hand used for the single activity (handwriting) and assessed on a binary scale, which may bias the inferences about the level of association.

With regard to the previous studies, it is rather interesting observation that the item *Handwriting* features

the lowest factor validity in our model (correlation with handedness equals to 0.56; see Fig. 1). This suggests that this item reflects handedness less than the other items and should be used with caution. The similar holds for the item *Holding a spoon* (although its factorial validity is comparable with other items). As mentioned earlier, responses from these items may be affected by cultural or social pressures toward using right hand for these activities.

In conclusion, this study shows that premorbid handedness is not related to the side of the body where the first signs of PD occur. The limitation of this study is that it is based on self-reported hand preference of patients as well as side of onset of PD symptoms. Other limitation is that only preference is taken into account and not the real difference in performance of hands. Hence, further studies are needed using performance-based measures.

Acknowledgments: This work is supported by Czech Science Foundation (grant nr. 406/07/P513), Czech Ministry of Education (MSM 0021620864 and MSM 0021620849), and Czech Ministry of Health (grant NR 9220-3).

Author roles: Jan Stochl: Conception of research project, conception and execution of statistical analyses, writing of the first draft of the manuscript. Knut Arne Hagtvet: Conception, review and critique of statistical analyses, review and critique of the manuscript. Hana Brozova: Organization and execution of research project, data collection. Jiri Klempir: Organization and execution of research project, data collection. Jan Roth: Data collection, review and critique of the manuscript. Evzen Ruzicka: Conception, organization and execution of research project, review and critique of the manuscript.

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No Evidence for Cognitive Dysfunction or Depression in Patients with Mild Restless Legs Syndrome

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Abstract: **Restless legs syndrome is a common disoder that may interrupt sleep and has been reported to produce daytime fatigue and/or mood changes. This study assessed whether patients with RLS have more cognitive dysfunction and depression than individuals of the same age and education who do not have RLS. The study showed that older individuals with mild RLS for at least 1 year do not have cognitive dysfunction and are not depressed compared with a control group of similar age and education.** © 2009 Movement Disorder Society

Key words: restless legs syndrome; cognitive dysfunction

Restless legs syndrome (RLS) affects up to 25% of the adult population.[1] RLS is characterized by uncomfortable sensations in the legs, which are relieved by movement but commonly worsen at night. This often interrupts sleep and may cause daytime fatigue. It has been reported that patients with RLS suffer from increased rates of irritability, anxiety, and depression.[2–5] However, almost all previous studies (both population-based and clinic-based) have used varying RLS diagnostic criteria and various depression scales and have not completely assessed the associated cognitive function.[5] This study assessed whether patients with RLS have more cognitive dysfunction and depression than individuals of the same age and education who do not have RLS.

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Potential conflict of interest: None reported.

Received 7 August 2008; Revised 20 April 2009; Accepted 12 June 2009

Published online 16 July 2009 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/mds.22701

SUBJECTS AND METHODS

The Sun Health Research Institute Brain and Body Donation Program (BBDP) database was reviewed for subjects with and without RLS. All subjects had received annual movement disorder and neuropsychological evaluations. Subjects with Parkinson's disease, parkinsonism, essential tremor, other tremor disorders, progressive supranuclear palsy, dystonia, peripheral neuropathy, fibromyalgia, or dementia were excluded from this analysis. The diagnosis of RLS was made by a movement disorder specialist using the IRLSSG criteria.[6] Neuropsychological testing included Rey-AVLT, Trails A and B, stroop, controlled oral word association, animal fluency, judgment of line orientation, digit span, Folstein mini-mental status examination (MMSE), and clock drawing. The 30-item Geriatric Depression Scale (GDS) was used to assess depression.

Data were compiled from the subject's most recent visit that had both movement and cognitive testing. The mean level of each measure in the RLS group was compared with that of the control group and the statistical significance was calculated by using the two-sample *t* test.

RESULTS

After exclusion criteria were applied there were 26 subjects with RLS, 208 without RLS (control group), and 79 subjects were excluded. There was no difference in mean age (RLS, 77 years; control, 78 years) (Table 1). The 95% CI for the difference in mean age (95% CI = −5.0 to 2.3) indicates that the mean age is equivalent within 5 years. The mean duration of education was 15 years in both groups. The mean duration of education was equivalent within 1 year (95% CI = −0.9 to 1.3).

The mean RLS rating scale score for the RLS group was 11.0 (SD = 7.6, N = 25) and the mean duration of RLS was 11.0 years (range, 1–51 years). Ten RLS subjects had a family history of RLS and one had a family history of Parkinson's disease.

Twelve of the 26 subjects had been or were being treated for RLS (6-gabapentin, 1-ropinirole, 1-pramipexole, 3-narcotics, 1-quinine), 9 had been or were on antidepressants, and 8 had been or were using benzodiazepines. Only 4 patients were using an antidepressant or benzodiazepine at the time of cognitive testing. There were no significant differences in neuropsychometric testing between these two groups of RLS patients. Therefore, they were combined into one group for comparison with controls. Also, no significant

TABLE 1. *Demographic and cognitive measures of subjects with and without restless legs syndrome*

	With RLS: mean (SD), N	Without RLS: mean (SD), N	Δ	95% CI	P*
Age (yr)	76.8 (9.2), 26	78.1 (9.0), 208	−1.4	−5.0 to 2.3	0.46
Duration of education (yr)	15.3 (2.8), 26	15.1 (2.6), 208	0.2	−0.9 to 1.3	0.71
Folstein MMSE	28.2 (1.7), 25	28.7 (1.6), 204	−0.5	−1.2 to 0.2	0.15
AVLT total learning	47.7 (9.1), 26	44.7 (11.3), 205	3.0	−1.6 to 7.5	0.19
AVLT Trial 1	5.7 (1.7), 26	5.5 (2.1), 205	0.2	−0.6 to 1.0	0.64
AVLT Trial 2	8.5 (1.9), 26	8.2 (2.6), 205	0.2	−0.8 to 1.3	0.67
AVLT Trial 3	10.0 (2.5), 26	9.6 (2.7), 205	0.4	−0.7 to 1.5	0.49
AVLT Trial 4	11.4 (2.2), 26	10.3 (2.7), 205	1.1	0.01 to 2.2	0.048
AVLT Trial 5	12.1 (2.1), 26	11.0 (2.7), 205	1.1	0.01 to 2.2	0.047
AVLT intrusions (1–5)	0.6 (1.2), 25	1.5 (2.3), 200	−0.9	−1.8 to 0.0	0.06
AVLT STM (A6)	9.6 (3.4), 26	9.0 (3.3), 205	0.5	−0.8 to 1.9	0.43
AVLT intrusions (STM)	0.36 (0.70), 25	0.50 (0.96), 200	−0.14	−0.52 to 0.25	0.50
AVLT LTM (A7)	9.0 (3.5), 26	8.9 (3.7), 205	0.1	−1.4 to 1.6	0.88
AVLT LT % recall	73 (24), 26	79 (26), 205	−6	−17 to 4	0.25
AVLT List B	5.2 (2.0), 26	4.8 (2.0), 204	0.4	−0.4 to 1.2	0.33
AVLT recognition TP	13.5 (1.7), 25	13.2 (2.3), 199	0.3	−0.7 to 1.2	0.56
AVLT recognition FP	0.20 (0.41), 25	0.64 (1.25), 199	−0.44	−0.94 to 0.05	0.08
WAIS digit span - forward	8.6 (1.5), 24	9.6 (2.0), 188	−1.0	−1.8 to −0.2	0.02
WAIS digit span - backward	6.2 (1.8), 24	6.4 (2.0), 187	−0.2	−1.1 to 0.6	0.60
WAIS digit span - total	14.8 (2.6), 24	16.0 (3.3), 187	−1.2	−2.6 to 0.2	0.09
WAIS digit span - backward span	4.6 (1.2), 23	4.7 (1.2), 182	−0.1	−0.6 to 0.4	0.74
WAIS digit span - forward span	5.7 (0.9), 23	6.3 (1.2), 183	−0.6	−1.1 to −0.1	0.03
Clock drawing	9.0 (1.6), 25	9.2 (1.1), 204	−0.3	−0.8 to 0.2	0.26
STROOP word (#)	87 (15), 24	89 (16), 199	−2	−8.9 to 5.0	0.58
STROOP color (#)	63 (12), 23	63 (12), 196	0	−5 to 5	0.98
STROOP word/color (#)	32.6 (7.0), 23	33.0 (10.1), 196	−0.4	−4.6 to 3.9	0.86
STROOP uncorrected W/C errors	0.4 (1.1), 22	0.4 (1.0), 191	0.1	−0.4 to 0.5	0.72
STROOP interference	−4.0 (5.4), 23	−4.0 (7.2), 195	0.0	−3.1 to 3.0	0.99
TRAILS A/B - time (3 min limit)	37 (16), 24	38 (22), 203	−1	−10 to 78	0.79
TRAILS A/B - A errors	0.13 (0.34), 24	0.12 (0.42), 203	0.01	−0.17 to 0.18	0.94
TRAILS A/B - B (5 min limit)	101 (43), 24	102 (53), 200	−1	−24 to 21	0.90
TRAILS A/B - B errors	0.46 (0.72), 24	0.57 (1.11), 201	−0.11	−0.57 to 0.35	0.64
COWA (CFL) total	38 (16), 26	38 (12), 205	1	−4 to 6	0.79
COWA (CFL) perseverations	2.8 (2.9), 25	2.8 (2.7), 200	0.0	−1.2 to 1.1	0.97
COWA (CFL) intrusions	0.08 (0.28), 25	0.29 (0.64), 200	−0.21	−0.46 to 0.05	0.12
Animal fluency	16.7 (5.2), 26	16.8 (5.0), 204	−0.1	−2.2 to 2.0	0.91
Animal fluency perseverations	1.0 (1.4), 25	1.0 (1.3), 199	0.0	−0.5 to 0.5	1.00
Judgment of line orientation	23.6 (3.9), 23	23.7 (4.3), 191	−0.1	−2.0 to 1.7	0.89
GDS	3.7 (3.2), 26	3.4 (3.7), 206	0.4	−1.1 to 1.8	0.63

*Two sample *t* test.

difference was found in cognitive testing between the RLS patients on medications for RLS and those who were not on treatment medications. Therefore, these subjects were not separated from the RLS group in the comparative analysis. Medications for the control subjects were not recorded.

None of the mean cognitive scores differed by more than half of the standard deviation of the group without RLS (Table 1). All of the mean cognitive scores were equivalent within one standard deviation of the group without RLS. The mean GDS scores differed by less than 1 point on a 30-point scale. The percentage of subjects with GDS ≥ 10 was 6% (n = 3/208) among controls and 4% (n = 1/26) among RLS cases ($\Delta = -0.02$, 95% CI = −0.08 to 0.13, $P > 0.99$). The sample was too small to assess for a correlation between the GDS score and severity of RLS.

DISCUSSION

These findings suggest that older individuals with mild RLS for at least 1 year do not have cognitive dysfunction and are not depressed compared with a control group of similar age and education. Previous epidemiological studies have reported that patients with RLS have more anxiety and depression.[2–5] Whether this is secondary to the actual RLS symptoms, insomnia or another sleep disorder, or other factors is unclear. These prior reports varied significantly in their methodology, including study design (population to random sampling), sample size (range, seven subjects to over 3,000), the RLS diagnostic criteria (the IRLSSG was not normally used), the exclusion or inclusion of patients with a known history of depression, and various assessment scales for evaluation of depression.[2–5] Furthermore, cognitive dysfunction in

this population has not been systematically or extensively evaluated. In two previous conflicting reports, untreated RLS patients showed cognitive deficits similar to that seen in sleep-deprived patients, yet the follow-up study found untreated RLS patients to perform better than sleep-deprived controls.[7,8] These studies were limited by a small sample size (n = 16), the RLS cases being withdrawn from treatment, and no correlation with RLS severity.[7] These factors make it difficult to assess for medication-withdrawal effects and RLS severity on the cognitive dysfunction found.

The current study used the International RLS Study Group criteria assessed by a movement disorder specialist, the RLS rating scale for quantifying the symptoms, and prospective neuropsychological testing to objectively assess cognitive function. Additionally, patients with depression were not prospectively excluded. Limitations of this study included the cases having relatively mild RLS, no treatment withdrawal for RLS medications (n = 12), no controlling for the use of antidepressants or benzodiazepines (n = 4), and no measurement for sleep disturbances in either group. Further prospectively designed studies of RLS and control populations are needed to determine if cognitive or neuropsychiatric symptoms occur in more severe cases of RLS and what factors may be correlated with these disorders.

Acknowledgments: This work was funded by Federal Grants NS40669 and P30 AG019610, the Arizona Biomedical Research Commission (contracts 04-800, 4001, 05-901), the Michael J. Fox Foundation for Parkinson's Research (Prescott Family Initiative), Mayo Foundation for Medical Research, and Sun Health Research Institute.

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Financial Disclosures: Erika Driver-Dunckley MD = none; Donald Connor PhD = consulting and advisory board - MedAvante; Joseph G. Hentz MS = Research funding from Allergan, Astellas Pharma US, Dynatherm Medical, Genentech, and Millenium Pharmaceuticals. Marwan Sabbagh MD = on advisory boards for Elan, Wyeth, Lilly, and Amerisciences. Receives royalty income from Amerisciences and consults for them as well. Nina Silverberg PhD = none; Jose Hernandez BA = none; Linda Vedders = none; Virgilio GH Evidente MD = Consulting for: Teva Neurosciences. Speaking honorarium from: GSK. Research support from: Allergan, Merz Pharmaceuticals, Boehringer, UCB-Schwarz, Neurogen. Holly Shill MD = Consulting fees from Medtronics and Ipsen. Honoraria from Allergan and Teva. Research funding from Boehringer-Ingleheim, Chelsea, Schering-Plough, International Essential Tremor Foundation, Nexalin. John N. caviness MD = none; Charles H. Adler MD, PhD = Consulting fees for advisory boards from GlaxoSmithKline, Ipsen, MerckSerono. Contracts with Ipsen and MerckSerono. Research funding from Allergan and Novartis.

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TARDBP Variation Associated with Frontotemporal Dementia, Supranuclear Gaze Palsy, and Chorea

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Abstract: **TDP-43 has been identified as the pathological protein in the majority of cases of frontotemporal lobar degeneration and amyotrophic lateral sclerosis (ALS). *TARDBP* mutations have so far been uniquely associated with familial and sporadic ALS. We describe clinicopathological and genetic findings in a carrier of the novel K263E *TARDBP* variation, who developed frontotemporal dementia, supranuclear palsy, and chorea, but no signs of motor neuron disease. Neuropathologic examination revealed neuronal and glial TDP-43-immunoreactive deposits, predominantly in subcortical nuclei and brainstem. This is the first report of a *TARDBP* variation associated with a neurodegenerative syndrome other than ALS.** © 2009 Movement Disorder Society

Key words: TDP-43; atypical dementia; amyotrophic lateral sclerosis; movement disorders; neuropathology

Transactive response DNA binding protein with molecular weight of 43 kDa (TDP-43) constitutes the major pathologic component of neuronal and glial ubiquitinated inclusions observed in frontotemporal lobar degeneration with tau-negative, ubiquitin-positive inclusions (FTLD-U), in the large majority of cases of amyotrophic lateral sclerosis (ALS), and FTLD with motor neuron disease (FTLD-MND).[1–3] These disorders are referred to as TDP-43 proteinopathies. Mutations in the *TARDBP* gene, located on chromosome 1p36 and encoding TDP-43, have been associated with both sporadic and familial ALS.[4–6] Although previous studies have failed to show an association between *TARDBP* mutations and FTD,[7,8] two patients with FTLD-MND, carriers of a *TARDBP* mutation, have been recently reported.[9] We describe clinical, neuropathologic, and genetic findings in a subject, carrier of the novel K263E *TARDBP* variation, who developed FTD, supranuclear palsy and choreiform movements, but no signs of MND.

MATERIALS AND METHODS

Clinical Assessment

The subject was referred to psychiatric evaluation due to insidiously progressive personality and behavioral changes. He underwent general, neurological, and psychiatric evaluations. Neuropsychological assessment was carried out using the Hungarian version (*MAWI*) of Wechsler Adult Intelligence Scale. Neuroimaging examination included CT and MRI scans of the brain. Informed consent for this study was obtained from the subject's wife.

Neuropathology

Formalin-fixed, paraffin-embedded blocks were obtained from the following regions: frontal, cingulate, temporal, parietal, and occipital cortices and subcortical white matter, basal ganglia, thalamus, hippocampus, amygdala, cerebellum, and brainstem. Additional samples of fresh brain were frozen for genetic and biochemical studies. Sections were stained using hematoxylin and eosin, luxol fast blue, Bielschowsky, and Gallyas methods. Immunohistochemistry (IHC) was carried out using the following monoclonal antibodies (mAb): anti-tau AT8 (1:200, Pierce Biotechnology, Rockford, IL, pS202/pT205), anti-β-amyloid (1:100, Novocastra Lab, Newcastle, UK), anti-phospho-TDP-43 (pS409/410, 1:2,000, Cosmo Bio, Tokyo, Japan), anti-TDP-43 (1:2,000, Abnova, Taipei, Taiwan), anti-HLA-DR (1:100, Dako, Carpinteria, CA), and anti-α-synuclein (1:10,000, clone 4D6, Signet, Dedham, MA). In addition polyclonal anti-p62 (guinea pig, 1:4,000, Progen Biotechnik GmBh, Heidelberg, Germany), anti-glial fibrillary acidic protein

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Potential conflict of interest: None reported.

Received 3 February 2009; Revised 7 May 2009; Accepted 12 June 2009

Published online 16 July 2009 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/mds.22697

(GFAP, 1:3,000, Dako), and anti-TDP-43 (1:100, Protein-Tech Group, Chicago, IL) Ab were used.

Genetics

Genomic DNA was extracted from the subject's frozen brain samples, as described.[10] *TARDBP* exons 1-6, *Progranulin* (*PGRN*) exons 0-12 and respective flanking intronic regions were amplified as described.[11,12] Products were examined by agarose gel electrophoresis, treated with ExoSAP-IT (USB, Cleveland, OH), asymmetrically amplified using the DTCS Quick Start Kit (Beckman Coulter, Fullerton, CA), and analyzed on a CEQ 8000 GeXP Genetic Analysis System (Beckman Coulter). The resulting sequences were compared to published *TARDBP* and *PGRN* sequences (www.ncib.nlm.nih.gov). *Huntingtin* (*HTT*) sequencing was carried out as described.[13]

The K263E *TARDBP* variation introduces a restriction site for Bsp1268I. Amplification of *TARDBP* exon 6 followed by enzymatic digestion was carried out on subject's DNA as well as on 530 DNA samples from neurologically healthy control individuals, including 160 Hungarian, from the Biobank of the Clinical and Research Centre for Molecular. Neurology of the Semmelweis University, the National Cell Repository for Alzheimer's Disease and the Centre d'Etude du Polymorphisme Humain (CEPH) reference panel, after obtainment of informed consent.

RESULTS

Clinical Data

A 35-year-old Hungarian man, known to be pleasant, quiet, and cooperative showed marked personality changes and become less enganged in conversation. Progressive reduction in attention and critical thinking was also noted. The onset of symptoms followed an accidental fall with consequent collarbone fracture, but no head trauma. Later, he developed anxiety, hyperactivity, psychomotor agitation, reading difficulties, mannerisms, severe insomnia, and nocturnal wandering. In addition, he started complaining of erectile dysfunction. At age 36, he was initially admitted to the psychiatry unit and later on to the neurology unit.

Neurological examination revealed reduced vertical gaze (upward > downward), hyperkinetic (choreiform) involuntary movements of the upper extremities, blepharospasms, motor stereotypies, and primitive reflexes. No rigidity, paresis, motor neuron disease signs, cerebellar ataxia, Kayser-Fleischer ring, or sensory deficits were noted. Routine laboratory parameters of blood and urine were in the normal range. Neuropsychological testing revealed prominent emotional blunting and lability, childish behavior, disinhibition, and loss of insight. He obtained a score of 100 on the IQ test. He underwent a CT scan of the head and an EEG that were reported as normal. An MRI of the brain revealed prominent atrophy of the mesencephalic tectum and, to a lesser extent, caudate nuclei (Fig. 1 A–C). He was diagnosed with FTD according to published criteria.[14] The disease rapidly progressed, and he eventually died at age 37 for pulmonary edema secondary to cardiac failure.

Family History

The proband's father died at age 52 secondarily to lung cancer. The proband's mother, aged 60, is alive and healthy. She has two brothers and three sisters, aged 50 to 63, who were reported free from neuropsychiatric disorders 7 years prior to this report. The proband's brother died at the age of 18 in a traffic accident; another brother, diagnosed with mental retardation, and a healthy sister are alive and in their late 30's, early 40's. The proband had two healthy offspring, a 16-year-old daughter and a 13-year-old son.

Neuropathology

The weight of the fixed brain was 1,130 g. Moderate atrophy of the frontal lobes and caudate nuclei, severe atrophy of tectum and tegmentum as well as severe depigmentation of the substantia nigra were observed. Microscopically, mild microvacuolar changes were observed in the superficial cortical layers of the frontal and cingulate gyri (Fig. 1D). Neuronal loss and astrogliosis were prominent in the subcortical gray matter (Table 1 and Fig. 1E,F). Phospho-TDP-43 IHC revealed a larger number of deposits as compared to what observed using anti-TDP-43 Abs. Phospho-TDP-43-immunoreactive deposits were observed (Table 1) as either thin and long inclusions in either morphologically normal or enlarged dystrophic neurites (Fig. 1G,H). Spherical or skein-like neuronal cytoplasmic inclusions (NCI) (Fig. 1I,J), as well as lentiform or rounded neuronal nuclear inclusions (Fig. 1K,L) were also seen. Phospho-TDP-43 immunoreactivity in neurites was mild to moderate in the upper and lowest neocortical layers, including the primary visual cortex (Fig. 1M), while only sparse NCI were seen (Table 1). The precentral gyrus was mildly affected (Fig. 1N). Phospho-TDP-43 pathology was not seen in the dentate gyrus (Fig. 1O). In contrast, abundant NCI were seen in subcortical and brainstem nuclei. Neuronal intranuclear inclusions (moderate) were seen in the striatum (Fig.

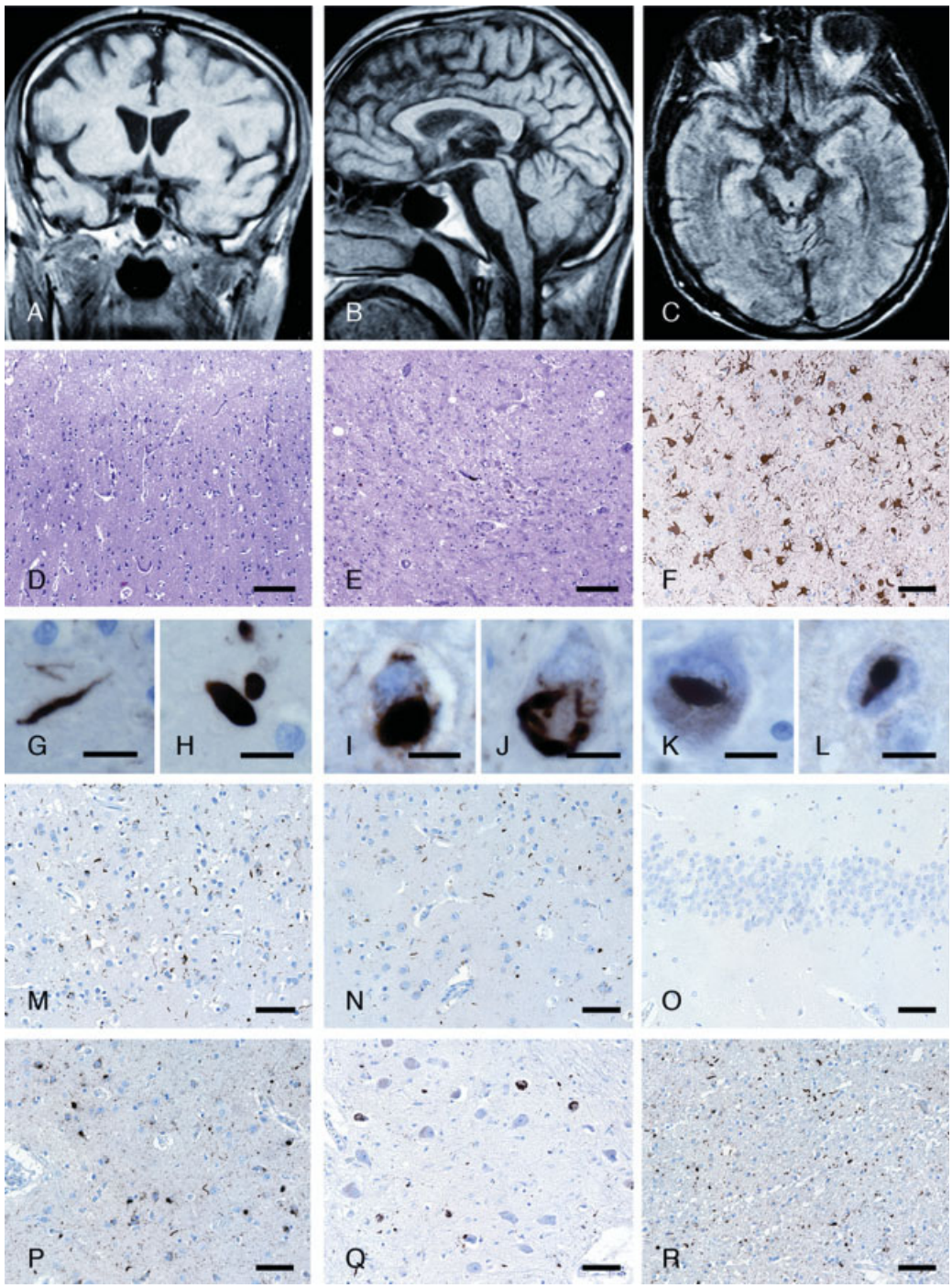

FIG. 1. T1 MRI sequences, 1 year prior to death, revealed mild atrophy of the caudate nucleus (**A**) and prominent tectal and tegmental atrophy in the mesencephalon (**B, C**). Mild spongiosis in the superficial layers of the frontal cortex (**D**, Hematoxylin-eosin). Severe loss of neurons in the substantia nigra (**E**; Hematoxylin-eosin). Severe reactive gliosis in the caudate nucleus demonstrated by anti-GFAP immunostaining (**F**). Immunohistochemistry for phospho-TDP-43 revealed: thin and long (**G**) as well as globular neurites (**H**); spherical (**I;** caudate nucleus) and skein-like (**J**; inferior olives) neuronal cytoplasmic inclusions; neuronal intranuclear inclusions (**K**; inferior olive and **L**; caudate nucleus). Moderate neuritic phospho-TDP-43-immunoreactivity in the primary visual cortex (**M**). Mild phospho-TDP-43-pathology in the precentral gyrus (**N**). Absence of phospho-TDP-43 pathology in the dentate gyrus (**O**). Phospho-TDP-43-immunoreactive neurites and neuronal inclusions in the caudate nucleus (**P**) and inferior olive (**Q**). Thread-like pathology and sparse glial cytoplasmic inclusions in the internal capsule (**R**). Scale bars = Bar graphs: 150 μm (D, E), 20 μm (G–L), 100 μm (F, M–R).

TABLE 1. *Anatomical distribution of neuronal loss, gliosis, and phospho-TDP-43 immunoreactivity*

Region	Neuronal loss/Gliosis	pTDP-43 immunoreactivity			
		NCI	Skein-like NCI	NNI	Neurites
Frontal cortex*	+/++	+	–	–	++
Temporal cortex	+	+	–	–	++
Insular cortex	–	+	–	–	++
Cingulate cortex	+	+	–	–	++
Parietal cortex	–	+	–	–	+
Motor cortex	–	–	–	–	+
Occipital	–	+	–	–	++
Entorhinal cortex	+	–	–	–	+
Hippocampus CA1	–	–	–	–	+
Subiculum	–	–	–	–	+
Fascia dentata	–	–	–	–	–
Amygdala	+++	++	–	–	++
Caudate nucleus	+++	+++	–	++	++
Putamen	+++	+++	–	++	++
Globus pallidus	+++	++	–	–	++
Medial thalamus	++	++	++	–	++
Lateral thalamus	++	++	–	–	+
Subthalamic nucleus	+++	++	++	–	+
Basal nucleus	–	–	–	–	+
Hypothalamus	–	–	–	–	+
Oculomotor complex	+++	++	–	–	++
Substantia nigra	+++	++	++	–	++
Locus coeruleus	+	+	+	–	++
Pontine base	+	+	–	–	++
Hypoglossal nucleus	–	+	–	–	++
Dorsal vagal nucleus	–	+	–	–	++
Medullary raphe	–	+	–	–	++
Inferior olive	++	++	+++	+	++
Dentate nucleus	–	–	–	–	–
Cerebellar cortex	–	–	–	–	+

NCI, neuronal cytoplasmic inclusion; NNI, Neuronal nuclear inclusion; –, none; +, occassional/mild; ++, few/moderate; +++, many/prominent.

*Findings were more severe in the frontobasal region.

1P,Q). Thread-like deposits, as well as occasional cytoplasmic glial inclusions were observed in the white matter from all regions (Fig. 1R). IHC for ubiquitin and p62 displayed a smaller amount of deposits, with similar pattern of distribution, compared to that observed using anti-phospho-TDP-43 antibodies. IHC for β-amyloid, α-synuclein, and hyperphosphorylated tau protein was negative in all examined sections.

Genetic Analysis

An adenine to guanine substitution was found at the first position of codon 263 (exon 6) in one allele of the proband's *TARDBP* gene. The variation, resulting in a glutamate for lysine (K263E) change, was confirmed in the proband and excluded in 530 controls individuals by restriction enzyme digestion. No mutations in *PGRN* and *HTT* genes were found. The number of *HTT* trinucleotide repeats was in the range of healthy controls.

DISCUSSION

We report the association of the novel K263E *TARDBP* variation with the clinical phenotype of FTD, supranuclear gaze palsy and chorea in the absence of signs of motor neuron disease, as well as with neuronal and glial pathologic deposition of TDP-43 in the brain. As clinical information on the proband's family is limited and no DNA from relatives is available, we are not able to prove segregation of this variation with the disease. The variation was not found in 530 control individuals. Indicative of the pathogenic role of the K263E variation are its location in exon 6 of *TARDBP*, the highly conserved C-terminus of TDP-43 where virtually all reported pathogenic mutations cluster, and the strong correlation between the proband's clinical phenotype and predominately subcortical (striatum > brainstem) distribution of phospho-TDP-43 pathology.[15] Clinical presentations of genetic disorders associated with TDP-43 proteinopathy comprise amyotrophic lateral sclerosis (*TARDBP* mutations), FTD with or without parkin-

sonism or corticobasal syndrome (CBS) (*PGRN* mutations),[16] or FTD with inclusion body myopathy and Paget's disease of the bone (*VCP* mutations).[17] Atypical disease presentations, such as the one characterized by stuttering, oculomotor abnormalities and choreic buccolingual movements, severe striatal degeneration and TDP-43 pathology, associated with the c.26C>A *PGRN* mutation, have been described.[18] On the other hand, the autosomal dominantly inherited Perry syndrome, characterized by predominant pallidonigral TDP-43 pathology, has not been associated with either *TARDBP* or *PGRN* mutations.[19]

Some of the proband's clinical (FTD and chorea) and neuropathologic (severe striatal gliosis and presence of ubiquitin-immunoreactive intranuclear inclusions) findings are reminiscent of Huntington's disease (HD). Sequencing of *HTT* ruled out the presence of typical genetic changes associated with HD. Interestingly, phospho-TDP-43-immunoreactive deposits have been found in colocalization with neuronal cytoplasmic but no nuclear deposits of huntingtin in genetically proven HD cases.[20]

Our observation suggests that *TARDBP* variations may be associated with a clinicopathologic spectrum of disorders wider than familial and sporadic ALS, and supports the utility of *TARDBP* genetic testing of all cases of atypical FTD.

Acknowledgments: Supported by NIH AG010133 and EU Grant FP6, BNEII No LSHM-CT-2004-503039. S. Spina is partly supported by the Department of Neurological, Neurosurgical and Behavioral Sciences, University of Siena, Siena, Italy. Samples from the National Cell Repository for Alzheimer's Disease (NCRAD), which receives government support under a cooperative agreement grant (U24 AG21886) awarded by the National Institute on Aging (NIA), were used in this study. We thank contributors, including the Alzheimer's Disease Centers who collected samples used in this study, as well as patients and their families, whose help and participation made this work possible.

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