PAPER

Predictors of falls and fractures in bradykinetic rigid syndromes: a retrospective study

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Background: Falls and fractures contribute to morbidity and mortality in bradykinetic rigid syndromes.
Methods: The authors performed a retrospective case notes review at the Queen Square Brain Bank for Neurological Disorders and systematically explored the relation between clinical features and falls and fractures in 782 pathologically diagnosed cases (474 with Parkinson's disease (PD); 127 progressive supranuclear palsy (PSP); 91 multiple system atrophy (MSA); 46 dementia with Lewy bodies (DLB); 27 vascular parkinsonism; nine Alzheimer's disease; eight corticobasal degeneration).
Results: Falls were recorded in 606 (77.5%) and fractures in 134 (17.1%). In PD, female gender, symmetrical onset, postural instability, and autonomic instability all independently predicted time to first fall. In PD, PSP, and MSA latency to first fall was shortest in those with older age of onset of disease. Median latency from disease onset to first fall was shortest in Richardson's syndrome (12 months), MSA (42), and PSP-parkinsonism (47), and longest in PD (108). In all patients fractures of the hip were more than twice as common as wrist and forearm fractures. Fractures of the skull, ribs, and vertebrae occurred more frequently in PSP than in other diseases.
Conclusion: Measures to prevent the morbidity associated with falls and fractures in bradykinetic rigid syndromes may be best directed at patients with the risk factors identified in this study.

T he diagnoses of Parkinson's disease (PD) and progressive supranuclear palsy (PSP) are contingent on the presence of postural instability and falls.[1] [2] In these and other bradykinetic rigid syndromes, falls occur frequently and are associated with a poorer quality of life.[3] [4] The risk of bone fracture increases with a history of falls, impairment of mobility, low body mass index, and low bone mineral density.[5] [6] In patients with disturbances of gait due to parkinsonism, fractures are more common than in those with gait disturbances due to other neurological conditions such as peripheral neuropathies.[7] In PD the femur is the most commonly fractured bone[8–10] but in the community the forearm is more frequently broken. This difference is thought to be due to the manner in which patients with PD fall.[11] [12] Despite the greater frequency of falls in atypical parkinsonism, falls and their relation to bone fractures have not been systematically analysed in progressive supranuclear palsy (PSP), multiple system atrophy (MSA), corticobasal degeneration, or vascular parkinsonism (VP).[10] [13] Falling within the first year of disease is required by the National Institute for Neurological Disorders and Stroke (NINDS) diagnostic criteria for a diagnosis of probable PSP, although in practice only 61% of patients with this diagnosis had fallen that early on.[2] [14] Together with a supranuclear gaze palsy, nuchal dystonia, and early frontostriatal cognitive deficits, falls complete the cardinal clinical quartet of PSP first described by Richardson.[15] We have recently defined a subgroup of patients designated PSP-parkinsonism (PSP-P), in whom the PSP tau pathology more frequently causes early asymmetrical levodopa responsive bradykinesia and in whom falls, cognitive changes, and supranuclear gaze palsy occur later than in classic Richardson's syndrome (RS).[14] A number of factors contribute to falls in other bradykinetic rigid syndromes. Gait unsteadiness and cognitive impairment contribute to falls in corticobasal degeneration (CBD), dementia with Lewy bodies (DLB) and in those with pathological changes diagnostic of Alzheimer's disease (AD)

who present with parkinsonism. In MSA, on the other hand, orthostatic hypotension and cerebellar or parkinsonian gait disorder are important precipitants.[16]

We have retrospectively analysed data from a large number of pathologically diagnosed PD, PSP, MSA, CBD, DLB, VP, and AD patients and have investigated the relation between pathological diagnosis and the bones fractured. We have also quantified the temporal evolution of falls in each disease group and analysed the relation between time from disease onset to first fall (latency) and disease.

SUBJECTS AND METHODS
Subjects
A retrospective analysis was performed using the clinical files of 782 patients with a lifetime diagnosis of a bradykinetic rigid syndrome or parkinsonism with a pathologically confirmed diagnosis (PD, n = 474; PSP, n = 127; MSA, n = 91; DLB, n = 46; VP, n = 27; AD, n = 9; CBD, n = 8) archived at the Queen Square Brain Bank for Neurological Disorders. Patients were recruited from around the United Kingdom and died between 1988 and 2003. A few cases (2% of total) could not be included in the analysis because of insufficient clinical data (10 PD, three PSP, one MSA, one AD, one VP). The PSP group were further divided according to the number of clinical features reported associated with each clinical phenotype: RS (supranuclear gaze palsy, abnormality of saccadic eye movements, cognitive changes in first two years), PSP-P (tremor and non-axial dystonia in the first two years, asymmetric onset, and response to levodopa).

Table 1 Characteristics of patients according to pathological diagnosis

	PD	PSP	MSA	DLB	CBD	VP	AD
Number	474	127	91	46	8	27	9
Mean age at onset, years (range)	60.4 (28.6–84.2)	65.7 (40.1–87.5)	56.4 (33.5–79)	66.7 (43.0–82.6)	66.2 (55.6–76.1)	69.6 (39.5–81.3)	69.4 (59.6–84.8)
Mean age at death, years (range)	76.4 (49.8–93.4)	73.7 (45.4–95.8)	64.4 (39.4–86.0)	74.9 (54.9–88.3)	73.0 (65.8–81.6)	82.5 (72.4–93.6)	80.2 (71.0–94.6)
Women (%)	39.9	37.3	53.8	20	20	48	44.4
Fallers (%)	73.3	98.3	77.6	58.1	100	73.9	85.7
Median time to first fall, months (range)	108 (0–384)	16.8 (0–244)	42 (0–165)	54 (0–158)	30 (0–90)	40.8 (0–304)	66.6 (36–228)
Fractures (%)	16.9	28.6	11	4.3	0	11.1	22.2

Data collection

A systematic chart review was performed; specifically the case notes of the family doctor were scrutinised together with all the correspondence between the medical specialist and family doctor. Hospital inpatient notes, inpatient consultations, and emergency room admission notes were also reviewed. The clinical features were recorded as present or absent early in the disease (within two years of first symptom onset) and at anytime during the disease. These features included: age of onset (age at the time of the first reported symptom considered to be attributable to disease), disease duration (time from onset until death), falls, time to first fall (time from onset to fall), bones fractured (confirmed radiologically), bradykinesia, cognitive dysfunction (reported by family, patient or physician, not attributed to affective disorder), symmetry of disease at onset, tremor, rigidity, postural reflexes (if reported by physician), supranuclear gaze palsy, impaired saccadic or pursuit eye movements, non-axial dystonia, pyramidal signs, autonomic dysfunction (abnormal autonomic function tests or any two of: urinary urgency, frequency, and nocturia without hesitancy; chronic constipation; postural hypotension; sweating abnormalities; erectile dysfunction), dyskinesias, and response to levodopa (graded by patient or clinician as nil/slight, moderate, good, excellent) were recorded. Standardised forms were not used by the doctors recording the antemortem medical history. We recorded symptoms as being *absent* if not reported, and clinical signs were recorded as *missing* if they were not specifically mentioned in the notes. Where conflicting clinical features were reported the findings of the neurologist were used.
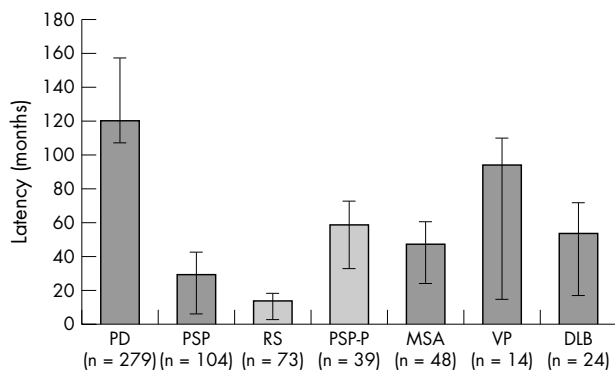
Statistics

The report and timing of any falls from the time of disease onset until death and/or fractures was the primary outcome measure. Descriptive statistics were used to analyse the latency to first fall and frequency of different skeletal bones fractured in each diagnostic group. Clinical characteristics in different diseases were compared. We investigated the associations between bradykinesia, rigidity, tremor, cognitive dysfunction, speech disturbance, dysphagia, dystonia, dyskinesias, autonomic dysfunction, gender, symmetry of clinical features, visual hallucinations, and age at disease onset with falls and fractures in all diseases. Univariable analyses using χ^2 for categorical and two tailed t test or the Mann Whitney U test, as appropriate, for continuous variables were applied. In PSP univariable analysis was performed on falls in the first two years (that is, early falls, rather than any falls) because of the high frequency of falls. In PSP, RS, and PSP-P the effect of falls on prognosis was assessed by calculating the mean disease duration in patients who fell in the first two years of disease and comparing it to those who fell after two years. Kaplan-Meier plots were used to graphically assess survival. Cox multiple stepwise regression analysis was performed in all diseases for latency to first fall, using clinical factors present around disease onset (within the first two years) and gender as categorical covariates and age at onset as a continuous variable. This work was approved by the local ethics committee.

RESULTS

Among the 782 cases the incidence of falls from disease onset to death was 77.5%. It was highest in CBD (100%) and PSP (97.5%) and lowest in MSA (77.6%) and PD (73.3%) (table 1).

Falls occurred earlier in those with PSP (median 17 months; range 0–244 months) than all other diseases (fig 1). Median time to first fall was significantly shorter in RS (12; range 0–95) compared to both PSP-P (47; 0–228, p<0.001), PD (108; 0–384, p<0.001), and MSA (42; 0–165). In PD univariable analysis showed an association between the occurrence of falls and the late clinical features of cognitive dysfunction, speech disturbance, dysphagia, autonomic dysfunction, and hallucinations and a negative association between the falls and early and late tremor (table 2).

In PSP, early falls (within the first two years of disease) were associated with symmetrical disease onset and early cognitive dysfunction, axial rigidity, postural instability, eye movement abnormalities, and speech disturbance (occurring within two years of disease onset). In common with PD, in those with early falls tremor was less frequent. In MSA falls at any time were associated with the late clinical features of limb rigidity, speech disturbance, dysphagia, and pyramidal

Figure 1 Latency to first fall according to disease, showing interquartile range.

Table 2 Clinical features in fallers and non-fallers: percentage, χ^2

	Parkinson's disease			PSP			MSA		
	Fallers	Non-fallers	p Value	Early fallers	Early non-fallers	p Value	Fallers	Non-fallers	p Value
Number	313	114		75	49		66	19	
Gender (% female)	43.1	27.2	0.002	36	40.8	NS	59	36.8	NS
Early clinical features									
Cognitive dysfunction	0	0	NS	70.7	28.6	<0.001	4.8	0	NS
Tremor	72.4	86.2	0.004	6.8	35.4	<0.001	42.2	42.1	NS
Axial rigidity	5.6	8.1	NS	54.7	32.5	0.024	16.7	5.9	NS
Limb rigidity	75	81.9	NS	63.9	61.4	NS	61.1	68.9	NS
Asymmetric onset	84.8	88.2	NS	34.8	83.1	<0.001	60.3	50	NS
Postural instability	8.7	1.9	0.017	91.9	41.9	<0.001	28.6	21.1	NS
Vertical gaze palsy	6.2	0	NS	54.9	11.5	<0.001			
Abnormal saccades	12	0	NS	83.3	45.0	0.002			
Speech disturbance	9.6	6.5	NS	66.7	41.7	0.006	19.3	38.9	NS
Dysphagia	0.7	2.9	NS	26.7	12.5	NS	4.9	17.6	NS
Pyramidal signs	3.3	0	NS	12.3	15.2	NS	17.4	16.7	NS
Dyskinesias	0.7	0.9	NS	0	0	NS	0	1.6	NS
Autonomic dysfunction	5.7	3.6	NS	1.4	2.0	NS	55.6	58.9	NS
Late clinical features									
Cognitive dysfunction	71.7	49.5	<0.001				31.6	12.5	NS
Tremor	85.7	93.6	0.018				60.3	68.4	NS
Axial rigidity	30.1	22.3	NS				47.5	41.2	NS
Limb rigidity	98	98.2	NS				96.7	77.8	0.008
Postural instability	45.6	83.8	<0.001				94.7	88.2	NS
Speech disturbance	78.8	59	<0.001				98.4	82.4	0.007
Dysphagia	59.7	46.9	0.033				94.9	68.8	0.003
Dyskinesias	58.1	53.3	NS				22.2	22.2	NS
Autonomic dysfunction	46.9	21.5	<0.001				88.9	100	NS
Pyramidal signs	5.4	9.4	NS				66.7	33.3	0.018
Hallucinations	53.3	37.5	0.004				10.6	5.9	NS

NS, not significant.

tract signs. There were no significant associations between falls and clinical features in VP, DLB, CBD, and AD; this may be due to the small sample sizes for these diseases.

Multivariate analyses were performed using the Cox multiple stepwise regression model on early clinical features, age, and gender identified several clinical factors which independently influence time to first fall (table 3).

In PD female gender, older age, symmetrical onset, and autonomic dysfunction were all independent predictors of earlier falls. Age of onset was also an important independent factor predicting time to first fall in PSP and MSA as was postural instability.

Almost all patients with PSP had falls at some point in their clinical history; patients with falls in the first two years had mean life expectancy 3.3 years lower than other PSP patients (table 4).

This difference was greater in the PSP-P group, and there was no difference in the RS group. This is illustrated graphically by the Kaplan-Meier plot (fig 2).

There were 166 fractures recorded in 134 (17.1%) patients. Eighty patients (16.9%) with PD sustained a total of 96 fractures, 36 (28.6%) patients with PSP sustained 52 fractures, and 10 (11%) patients with MSA sustained a fracture.

Hip fractures comprised 46.9% of all fractures in PD and one third of fractures occurred in the upper limb. In PSP the proportion of hip fractures was less than in PD (30.7% *v* 46.9%, p = 0.053 *t* test), and the proportion of ''other upper limb fractures'' (including the clavicle, scapula, and bones in the hand) was higher than in PD (p = 0.109, *t* test) (table 5). Comparing all patients (with and without fractures), multiple fractures were significantly more common in PSP than in both PD (6.4% *v* 1.9%, p = 0.007 *t* test) and MSA (6.4% *v* 0%, p = 0.014 *t* test). Skull fractures (3.2% *v* 0.8%, p = 0.43 *t* test) and truncal fractures (5.6% *v* 1.9%, p = 0.24 *t* test) were both more common in PSP than in PD. There were no substantial or significant differences in fracture site between the two subgroups of PSP.

The clinical features that were significantly associated with fractures in PD were early falls (9.3% with fractures *v* 3.2% no fractures, χ^2 p = 0.024), late falls (100% *v* 66.7%, χ^2 p<0.001), and late postural instability (88.4% *v* 71%, χ^2 p = 0.003)); in PD fractures were also more frequent in women (28.6% *v* 11.3%, χ^2 p<0.001). In PSP early bradykinesia (77.8% with fractures *v* 92% without fractures, χ^2 p = 0.027), early limb rigidity (47% *v* 68.7%, χ^2 p = 0.028), and early pyramidal signs (2.5% *v* 18.8%, χ^2, p = 0.02) occurred less frequently in those with fractures. Sex distribution was not significantly

Table 3 Factors affecting time to first fall in PD, PSP and MSA: independent predictors from Cox multiple regression analysis on early clinical features, age and sex
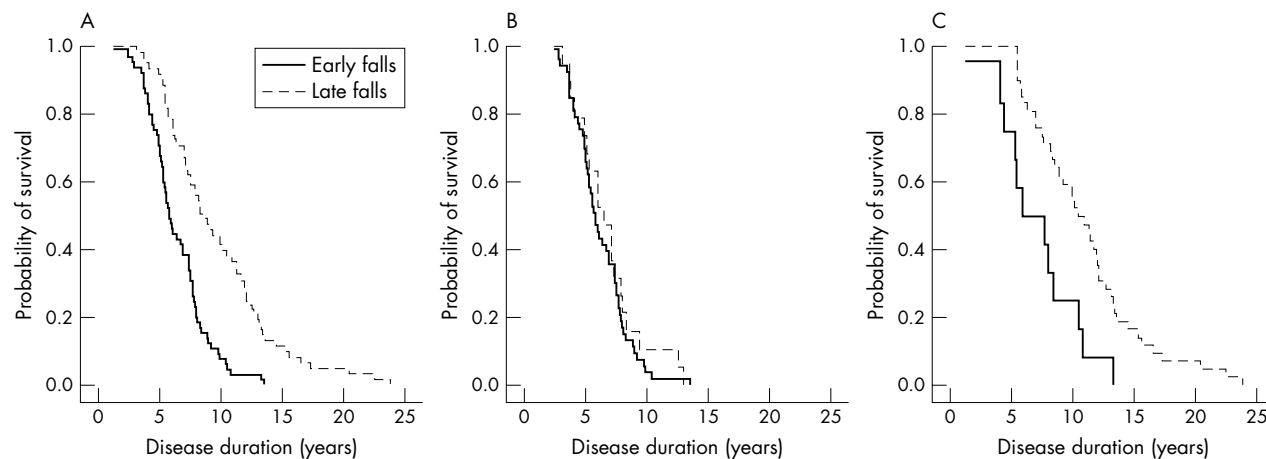
PD	HR	95% CI	p Value	PSP	HR	95% CI	p Value	MSA	HR	95% CI	p Value
Age of onset	1.07	1.05–1.08	<0.001	Age of onset	1.05	1.01–1.09	0.007	Age of onset	1.04	1.02–1.08	0.003
Symmetrical onset	1.86	1.25–2.77	0.002	Early postural instability	3.4	1.7–6.8	0.001	Early postural instability	2.08	1.07–3.94	0.03
Early autonomic dysfunction	2.56	1.32–4.98	0.005								
Female gender	1.39	1.05–1.83	0.021								

Table 5 Distribution of fracture location in bradykinetic rigid syndromes: number (% of all fractures)

	PD	PSP	RS	PSP-P	MSA	VP	DLB	AD
Forearm	17 (17.7)	7 (13.5)	5 (16.7)	2 (9.1)	3 (30)	1 (33.3)		
Humerus	10 (10.4)	5 (9.6)	2 (6.6)	3 (13.7)	1 (10)	1 (33.3)		
Other upper limb	6 (6.3)	8 (15.4)	5 (16.7)	3 (13.7)	0	1 (33.3)		1 (50)
Hip	45 (46.9)	16 (30.7)	10 (30.0)	7 (31.8)	4 (40)		2 (100)	
Distal leg	5 (5.2)	4 (7.7)	3 (10)	1 (4.5)	0			1 (50)
Pelvis	1 (1.0)	1 (1.9)	0	1 (4.5)	0			
Trunk	8 (8.3)	7 (13.5)	3 (10)	4 (18.2)	1 (10)			
Skull	4 (4.2)	4 (7.7)	3 (10)	1 (4.5)	1 (10)			
Multiple	9	8	7	5	0			
Total fractures	96 (100)	52 (100)	30 (100)	22 (100)	10 (100)	3 (100)	2 (100)	2 (100)

given the retrospective nature of the study, it is possible that the recording of this clinical feature was more likely in those who had fallen than those who had not.

Patients were selected on the basis that they died during a specified period of time. If the diagnosis is becoming increasingly or decreasingly common over time, or if the criteria for diagnosis is changing subtlety over time, then this may cause some bias in the type of patients included in our study. For instance, people diagnosed more recently need to die sooner after diagnosis to be included in this study.

Falls in MSA

Clinical factors that were more common in falls in MSA were similar to those in PD, in particular axial symptoms and signs (early axial rigidity, speech disturbance, and dysphagia) and early pyramidal tract signs. Less than 15% of our cases presented with prominent cerebellar symptoms, the MSA-C clinical phenotype, perhaps explaining the lack of association with cerebellar signs and falls. Interestingly autonomic dysfunction, which was present in more than 50% of patients in the first two years of disease, was not significantly associated with falling. The clinical features which significantly and independently influenced latency to first fall were the same as PSP: age of disease onset and postural instability.

Fractures

More than one quarter of patients with PSP (28.6%) fractured at least one bone and the frequency of fractures was significantly higher than in the other diseases (Fisher's exact test, p<0.02). The clinical features that were more frequent in those with fractures and PSP were also different to other diseases. Whereas in PD and MSA and control populations women were more at risk[12] and falls and postural instability were strongly associated with fractures, in PSP there was no association with female gender. In PSP only the absence of early bradykinesia, limb rigidity, and pyramidal signs were significantly associated with fractures. We speculate that when early bradykinesia, limb rigidity, and pyramidal signs are present patients are less likely to attempt to independently mobilise. In these patients there are fewer opportunities of succumbing to the poor balance and "motor recklessness" of PSP and fractures are less frequent. Among the elderly in residential care facilities men fall more than women but fractures are more frequent in women.[32] In contrast, men with PSP had a similar propensity to fracture bones, perhaps reflecting the type of falls associated with the disease and the frontal cognitive deficits in these patients. A similar pattern was seen in patients with VP, who were likely to have had frontal cognitive impairment.

The proportion of hip fractures was higher in PD than in PSP and MSA (table 4). There was a significantly smaller proportion of fractures in the distal leg in MSA than in PD and PSP. We found that fractures of the trunk (ribs, vertebrae, and sternum) were proportionally more in PSP and MSA than in PD. In contrast to previous reports[10] rib and vertebral fractures were proportionally less than hip and proximal upper limb fractures in PSP. These studies have different methodology and the discrepancy may be explained if rib and vertebral fractures occur earlier in the disease, and hip and proximal upper limb fractures later. In other respects, the location of fractures was similar between disease groups.

Nordell *et al* reported that in a community dwelling population of 65–74 year olds fractures of the upper extremities, and in particular the distal radius, were most common[12] and fractures of the proximal femur or hip were half as common as radial fractures. In all bradykinetic rigid syndromes diagnosed in our study this proportion is reversed, reflecting a common disturbance of postural reflexes. Bradykinesia prolongs reaction times following a postural challenge and thereby limiting the protective responses, including outstretching of the arm, thus limiting fractures of the distal upper limb.

CONCLUSION

Falls and fractures are frequently associated with bradykinetic rigid syndromes. Patients with PD, PSP, MSA, DLB, and VP should be assessed for the independent risk factors identified in this study. The disease burden associated with disturbances of posture, resulting in falls and fractures, appears to be highest in PSP. The significant difference between RS and PSP-P in latency to first fall supports a division of these clinical syndromes. Furthermore, the presence of early supranuclear gaze palsy, cognitive change, and a lack of response to levodopa predicts early falls and bone fractures.[14] Patients with RS, and those with other bradykinetic rigid syndromes with symmetrical disease onset, postural instability, autonomic dysfunction, and cognitive disturbance, and in particular women, may benefit from early assessment for osteoporosis, treatment of decreased bone mineral density, and physiotherapy intervention to limit falling related morbidity.[5]

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