

Michele T. M. Hu  
Jeremy Bland  
Chris Clough  
Catherine M. Ellis  
K. Ray Chaudhuri

## Limb contractures in levodopa-responsive parkinsonism: a clinical and investigational study of seven new cases

Received: 3 September 1998  
Received in revised form: 3 December 1998  
Accepted: 17 December 1998

M. T. M. Hu · J. Bland · C. Clough  
C. M. Ellis · K. R. Chaudhuri (✉)  
Movement Disorders and Autonomic Unit,  
Department of Neurology,  
Mapother House, King's College Hospital,  
De Crespigny Park, Denmark Hill,  
London SE5 8AF, UK  
Tel.: +44-171-3465319  
Fax: +44-171-3465332

M. T. M. Hu · C. M. Ellis  
K. R. Chaudhuri  
Medical School and Institute of Psychiatry,  
King's College Hospital,  
De Crespigny Park, Denmark Hill,  
London SE5 8AF, UK

K. R. Chaudhuri  
University Hospital of Lewisham,  
London, UK

**Abstract** We describe six patients with classical levodopa-responsive Parkinson's disease (PD) and one case of levodopa-responsive familial juvenile dystonia-parkinsonism with fixed contractures of the hands, feet or legs. In most patients contractures became established over a short period (2 months–2 years) but a considerable time after onset of parkinsonism (mean 13 years). Mean disease duration was 17 years, and all patients had severe levodopa-induced dyskinesias, either biphasic or peak dose, in the affected limb prior to onset of the contracture. Nerve conduction studies excluded peripheral ulnar nerve lesions in all patients with one exception, who was found to have a mild bilateral ulnar entrapment neuropathy. Transcranial magnetic stimulation performed in five

of the seven patients showed shorter mean central motor conduction time in the affected than in the unaffected limb. Results of magnetic resonance imaging of the brain performed in a subgroup of patients were normal, with no evidence to suggest multiple system atrophy, cerebral infarction or focal abnormalities of the basal ganglia. We conclude that hand and feet contractures are not necessarily restricted to parkinson plus syndromes and may complicate otherwise typical PD in the absence of a structural or peripheral nervous cause. Striatal dopaminergic deficiency, particularly long-standing, may have a role in the pathogenesis of limb contractures in PD.

**Key words** Limb contracture · Parkinson's disease

### Introduction

Axial and limb deformities in parkinsonism, although rare, are known to occur. Charcot [2] in 1877 first noted the typical deformities of the hands and feet seen in Parkinson's disease (PD) and pointed out their resemblance to those seen in chronic rheumatoid arthritis. He was able to make the distinction because in cases of parkinsonism there was no swelling or stiffness in the joints, and he described the deformity of the toes as a 'grifte' or claw. Sporadic cases were reported by Jackson [8], who likened these deformities to tetany. Cooper [3], Bravo [1] and Gortvai [6] reported correction of hand and foot deformities in severe parkinsonian patients after stereotactic thalamotomy. Skeletal deformities including

hand contractures were also described in post-encephalitic parkinsonian patients by Martin [12] and Onaguluchi [15] and in the parkinsonism-dementia syndrome in Guam [9].

Fahn and Jankovic [4] described the dystonic striatal hand incorporating flexion at the metacarpophalangeal joints and extension of the proximal interphalangeal joints, occurring in de novo and levodopa-treated parkinsonian patients. This dystonia appeared to be reversible and completely resolved with levodopa treatment. However, in our series of contractures the deformity is fixed and uncorrectable with either levodopa, through passive movement or during sleep. There are few reports of specific hand contractures in parkinsonism [6, 10, 17] and Quinn et al. [17] felt the contractures in their patients might possibly be linked to bromocriptine therapy.

**Table 1** Clinical details of the seven contracture patients

	1	2	3	4	5	6	7	Mean
Age (years)	73	58	66	56	75	41	76	61.5
Hoehn and Yahr stage (off)	III	IV	IV	V	IV	IV	II	IV
Symptom duration (years)	8	17	24	16	16	24	3	17.5
Time for contractures to develop (years)	2/12	2	1	9/12	1	1	1	1
Duration of dyskinesias (years)	1	2	9	6	5	8	2	5
Duration of levodopa therapy (years)	7	15	21	14	14	21	2	13
Daily levodopa dose (mg)	400	1400	1000	600	600	200	300	700

**Table 2** Dopamine agonist (DA) therapy in the seven contracture patients

Pa-tient no.	DA treatment prior to onset of contracture	Mean daily dose (mg)	Time between initiation of therapy and contracture onset	Duration of treatment	Current DA treatment
1	Nil	–	–	–	Nil
2	Pergolide	0.75	5 years	4 months	Nil
	Apomorphine	48	2 years	2 months	Nil
3	Apomorphine	36	1 year	1 month	Nil
4	Pergolide	0.30	7 years	1 month	Apomorphine
	Apomorphine	80	10 months	3 years	
5	Pergolide	0.45	2 years	3 years	Pergolide, apomorphine, cabergoline
	Apomorphine	120	1.5 years	2.5 years	
6	Pergolide	0.75	4 years	3 years	Apomorphine, cabergoline
	Apomorphine	120	2 years	4 years	
7	Nil	–	–	–	Nil

Deformities of the hands and feet with subsequent progression to contractures add to the functional disability of patients already compromised by advanced disease. The aetiology of contractures in PD remains unclear. We present a series of seven parkinsonian patients with contractures, all of whom had previously developed severe dyskinesias. Results of transcranial magnetic stimulation performed on affected and unaffected limb; neuroimaging and their relevance to the aetiology of this disorder are also discussed.

## Case reports

In six of the seven patients having contractures, the clinical picture was that of typical idiopathic PD, with a combination of asymmetric rigidity, bradykinesia and tremor. Clinical details of these six patients are summarised in Table 1 (patient 6, who had an atypical presentation of parkinsonism, is described separately below). Their mean age was 61.5 years, mean duration of symptoms 17 years, and mean 'off period' Hoehn and Yahr scale IV (range II–V). Interestingly, the female to male sex ratio was 6:1. There was no clinical evidence of other conditions which may cause contractures, such as rheumatoid arthritis and Dupuytren's contracture. All patients had an excellent response to initiation of levodopa therapy, taking a mean daily levodopa dose of 700 mg/day (range 200–1400) over a mean duration of 13 years. Details of dopamine agonist therapy are summarised in Table 2.

All patients developed severe interdose dyskinesias following levodopa therapy initiation, either biphasic or peak dose. The duration of dyskinesias prior to onset of the contracture varied be-

tween 1 and 8 years (mean 5). All patients experienced bilateral dyskinesias; however, two patients gave a history of recurrent dystonic posturing in the affected limb several months prior to the development of a fixed contracture. The majority of patients developed contractures over a short period (range 2 months–2 years) despite having had parkinsonian symptoms for a much longer period (mean 17 years). Five of the seven patients had hand or arm contractures (Figs. 1, 2) which were bilateral in one case, and two patients had foot inversion contractures (Fig. 3), bilateral in one case. Unlike off-period or 'wearing-off' dystonia, which causes transient abnormal posturing of a limb usually relieved by levodopa, in our series of patients the deformity was fixed and uncorrectable with either levodopa or passive movement. In none of the patients were the contractures abolished by sleep.

### Patient 6

A 41-year-old Madeiran Portuguese man presented in his late teens with tremor of the limbs and trunk (legs more than arms), rigidity and gait disturbance without any diurnal variation. There was an excellent response to levodopa, and he was diagnosed to have juvenile onset dystonia-parkinsonism at the age of 21 years. Over the next 5 years the tremor became more marked, and was associated with bradykinesia, rigidity and postural instability. Extensive investigations excluded other causes of extrapyramidal disorder. In particular, screening for Huntington's disease, dentato-rubro-pallidolusian atrophy and spinocerebellar ataxia 1, 2 and 3 mutations was negative. The patient's maternal grandfather and paternal grandmother were siblings, and an older sister developed inversion of the feet on walking, tremor and gait disturbance, becoming wheelchair-bound at the age of 13 years. In 1994 the patient was admitted to a nursing home with behavioural problems, severe peak-dose dyskinesias and 'on-off' periods. He was then main-



**Fig. 1** Photograph showing bilateral hand deformities with flexion at the metacarpophalangeal and proximal interphalangeal joints of both hands, more severe on the left. The left 4th and 5th fingers could not be passively straightened, giving rise to a fixed contracture. There is bilateral ulnar deviation of the fingers

tained on an apomorphine infusion and Sinemet with excellent response.

In 1997 the patient was noted to have a right hand contracture with fixed flexion of the wrist, 'thumb in hand' deformity and a flexed elbow contracture (Fig. 4). He received three courses of botulinum toxin type A injections under electromyographic (EMG) guidance at a mean dose of 400 mouse units distributed to the forearm flexors over a period of 1 year, with no improvement to the contractures. When 'on', he currently walks unaided, requiring some assistance with activities of daily living, but there is very poor right hand function. He still has excellent responsiveness to levodopa and apomorphine, and because of severe diphasic dyskinesias he has undergone unilateral ventromedial pallidotomy with moderate improvement in dyskinesias and 'off' period symptoms, but no change in the hand-arm contractures.

#### Nerve conduction and transcranial magnetic stimulation

Peripheral ulnar nerve conduction was assessed by measuring motor conduction velocities in the forearm and elbow segments and the terminal motor latency to the abductor digiti minimi. Sensory studies were made difficult by the hand deformity and considered unreliable. Results are summarised in Table 3. All values fell within our normal range except those of patient 1 who was felt to



**Fig. 2** Photograph demonstrating a flexion contracture of the left arm with fixed flexion of the elbow, wrist and proximal interphalangeal joints. The metacarpophalangeal joints of the left hand are held in hyperextension



**Fig. 3** Photograph demonstrating an inversion contracture of the left foot

have mild bilateral ulnar entrapment neuropathies at the elbow on nerve conduction velocity grounds. Concentric needle EMG was not performed. Central motor conduction time (CMCT) in the same five patients was measured using magnetic cortical and cervical stimulation. As a group, these patients showed a non-significant trend ( $P = 0.16$ ) toward shorter CMCT in the affected than the unaffected arm, with four of six values falling outside our normal range (Table 4).





**Fig. 4** Photograph showing a right hand contracture with fixed flexion of the wrist and metacarpophalangeal joints and a 'thumb in hand' deformity. The right elbow is held in fixed flexion. The patient is maintained on a apomorphine infusion pump, as is evident from the photograph

#### Neuroimaging

Because hand contractures may be more common in multiple system atrophy (MSA) [21] we also performed T1- and T2-weighted magnetic resonance imaging in three patients, including patient 6 who had atypical parkinsonism, to look for changes in intensity of the putamen. The images were also examined for evidence of cerebrovascular infarction, particularly in putamen and globus pallidus, by an independent radiologist (J.D.) unaware of the clinical diagnosis, as putaminal infarction is a documented cause of contralateral dystonia [5]. All three scans were normal. To exclude compressive myelopathy, we performed magnetic resonance imaging of the cervical spine in three patients with normal results.

**Table 3** Summary of peripheral ulnar nerve conduction studies in the five patients with hand contractures

Patient no.	Side	Contracture	Nerve conduction velocity (m/s)		Conduction block (% peak/peak amplitude)	
			Forearm	Elbow	Below/above elbow	Above elbow (worst)
1	R	Yes	55	33 <sup>a</sup>	7%	16%
	L	Yes	Unrecordable	31 <sup>a</sup>	ND	ND
3	R	No	66	46	0%	22%
	L	Yes	51	43	0%	11%
4	R	No	ND	50	ND	ND
	L	Yes	50	53	0%	0%
6	R	Yes	63	46	4%	13%
	L	No	50	62	8%	0%
7	R	Yes	56	50	6%	25%
	L	No	ND	57	ND	ND

<sup>a</sup>Outside normal range

## Discussion

We believe that this is the largest series of patients highlighting the poorly understood issue of limb contractures in PD. The exact incidence of limb contractures in PD is unclear, perhaps because it is rare and often unrecognised. In a series of 86 parkinsonian patients Reynolds et al. [19] in 1965 found that 34 (40%) had some deformity in the hands. These deformities were more frequent among those with post-encephalitic parkinsonism (71%) than without (24%). Onaguluchi [15] in 1964 reported an incidence of hand contractures as high as 66% of the 67 patients studied in a post-encephalitic ward of a general hospital. These figures contrast with the much lower frequency of hand contractures found in 1988 by Kyriakides et al. [10]. In this study only three cases of hand contractures – all with levodopa responsive PD of non-post-encephalitic origin – were identified over a 1-year period in a busy neurological department. The much higher figures previously found may be a result of biased patient selection or a higher incidence of post-encephalitic parkinsonism in the 1960s and a greater propensity for these patients to develop contractures.

The frequency and aetiology of hand and feet contractures in PD and parkinsonism are unclear. We excluded coexistent conditions which may cause contractures such as rheumatoid arthritis and Dupuytren's contracture and compressive myelopathy, particularly of cervical spine, the latter by normal magnetic resonance imaging of cervical spine in three cases. Focal infarction, particularly of the putamen, has been suggested as a cause of acute dystonia which may lead to contractures [5]. However, careful clinical and radiological examination failed to show any evidence for this in the subgroup of patients examined. Wenning et al. [21] suggested that hand contractures are more common in MSA, occurring in up to 6% of cases. However, the majority of cases in the present series, with the exception of patient 6, appear to have typical levodopa-responsive PD, with no autonomic, cerebel-

**Table 4** CMCT (ms) in affected and unaffected hand with mean (SD) values

	1	2	3	4	6	7	Mean
Affected hand	6.25	5.93	5.60	8.98	8.60	6.55	6.98±1.43
Unaffected hand	–	–	8.98	7.00	9.82	7.68	9.34±1.27

CMCT of age-matched healthy controls, 9.21 ± 1.21 ms (range, 6.79–11.63)

lar or pyramidal features to suggest an alternative diagnosis [18, 21]. Patient 6, extensively investigated, has juvenile onset dystonia parkinsonism. Contractures in parkinsonism, have also been linked to bromocriptine therapy, possibly secondary to peripheral fibrosis [17]. None of our seven patients took bromocriptine prior to the onset of contractures, although five had taken the ergot dopamine agonist pergolide. Four patients had taken pergolide in combination with apomorphine – a potent parenteral non-ergot dopamine agonist (see Table 2 for review). Thus, although association with bromocriptine therapy does not explain the contractures in this series of patients, the role of other dopamine agonists in contractures needs to be explored further.

Analysis of clinical features in patients with hand and feet contractures suggest that these appear not to be related to the degree or duration of tremor in patients, but are correlated with the degree of rigidity in the affected limb [6, 15, 19]. It has been suggested that hand contractures are related to overactivity of the small muscles of the hand which are supplied by the ulnar nerve [15]. Gortvai [6] demonstrated that local anaesthetic block of the ulnar nerve corrected hand deformities in patients with parkinsonism of all types. Furthermore, ulnar nerve stimulation in a patient with only sensory signs and symptoms and no muscular weakness produced the characteristic hand deformity [1]. In our series one of the five patients with hand contractures showed evidence of a mild bilateral ulnar entrapment neuropathy at the elbow on nerve conduction studies, all other values fell within the normal range.

As might be expected with a mean disease duration of 17 years and a mean of 13 years treatment with levodopa, all seven patients experienced severe levodopa-induced dyskinesias prior to the onset of contractures. However, Charcot [2] described limb contractures in PD long before the introduction of levodopa therapy. PD patients may demonstrate transient dystonic posturing leading to an ulnar deviated hand, flexion of the metacarpophalangeal joints and hyperextended interphalangeal joints [11]. It is possible that recurrent dystonic posturing over a long period of time leads to a fixed contracture. Interestingly, some of the patients in our series had noted intermittent dystonic posturing of the affected limb several months prior to the onset of contractures. There might be a direct link between the degree of striatal dopaminergic deficiency and development of limb contractures, particularly when one considers the severity and long duration of disease in

our patients. The observation of limb dystonia in monkeys treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine and also shown to have low striatal dopamine levels, suggests that striatal dopaminergic deficiency (even in the absence of treatment) plays a role in development of dystonic posturing, which may over time lead to fixed contractures [16]. Unlike the cases of Fahn and Jankovic [4], in our patients the contractures were fixed deformities and uncorrectable with levodopa, during sleep or passive manipulation, although for ethical reasons this was not attempted under general anaesthesia.

In keeping with previous studies [10, 17], there was a strong female preponderance in those affected with limb contractures in our series (6:1 female to male), although the relevance of this to aetiological factors is unclear. Transcranial magnetic stimulation is a noninvasive technique that has been used to investigate a variety of neurological disorders, including PD [7, 13], corticobasal degeneration [14] and task-specific focal dystonia [20]. Studies in PD using transcranial magnetic stimulation have shown normal or reduced CMCT in the more severely affected limb [7, 13]. Our finding of a trend toward a reduced CMCT in the affected compared to unaffected limb may reflect reduced excitability of cortical inhibitory circuits contributing to excessive and inappropriate muscle contraction similar to that possibly contributing to the aetiology of focal dystonia and levodopa-induced dyskinesias [20]. However, this is speculative, and only limited conclusions can be drawn from this study which involved a small number of patients. Our experience of treatment of these contractures has been disappointing, possibly because any attempts were initiated too late in the course of contracture development, when the deformity was already well established. We have tried a combination of three repeated courses of botulinum toxin injections (mean dose 400 mouse units) to the forearm finger flexors under EMG guidance followed by physiotherapy and passive splinting in two patients, with no significant improvement. As noted previously, manipulation of drug therapy, including the addition of subcutaneous apomorphine infusions was ineffective. Ventromedial pallidotomy in one case also failed to improve the contractures.

In summary, we present a series of seven patients with predominant hand contractures developing on a setting of levodopa-responsive parkinsonism. Transcranial magnetic stimulation and nerve conduction studies performed in these patients suggest a largely central rather than peripheral aetiology, and further neurophysiological and functional imaging studies are required to investigate the role of striatal dopamine deficiency, dopamine agonist therapy and the pattern of parkinsonism in the development of contractures.

**Acknowledgements** We thank Dr. Steve Pollock and Dr. Fred Schon for allowing us to study their patients, and Susie Clift for performing autonomic function tests. M.T.M.H. is supported by a clinical training fellowship from Action Research, UK.

## References

1. Bravo GJ (1958) In: Fields WS (ed) Pathogenesis and treatment of parkinsonism: sixth annual scientific meeting of the Houston Neurological Society. Thomas, Springfield, p 325
2. Charcot JM (1877) Lectures on the diseases of the nervous system. New Sydenham Society, London
3. Cooper IS (1961) Parkinsonism – its medical and surgical therapy. Thomas, Springfield
4. Fahn S, Jankovic J (1984) Practical management of dystonia. In: Jankovic J (ed) Neurological clinics, vol 2, Saunders, Philadelphia
5. Giroud M, Lemesle M, Madinier G et al (1997) Unilateral lenticular infarcts; radiological and clinical syndromes, aetiology, and prognosis. *J Neurol Neurosurg Psychiatry* 63:611–615
6. Gortvai P (1963) Deformities of the hands and feet in parkinsonism and their reversibility by operation. *J Neurol Neurosurg Psychiatry* 26:33–36
7. Ikoma K, Mano Y, Takayanagi T (1994) Pulsed magnetic stimulation and F-waves in Parkinson's disease. *Intern Med* 33:77–81
8. Jackson JH (1899) *Brain* 22:621–623
9. Chen K-M, Chase TN (1986) Parkinsonism-dementia. In: Vinken PJ, Bruyn GW, Klawans HL (eds) *Handbook of clinical neurology*, vol 49. Elsevier, Amsterdam, pp 172–173
10. Kyriakides T, Langton Hewer R (1988) Hand contractures in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 51:1221–1223
11. Marsden CD, Parkes JD, Quinn N (1992) Fluctuations of disability in Parkinson's disease – clinical aspects. In: Marsden CD, Fahn S (eds) *Movement disorders*. Neurology 2. Butterworths, London, pp 96–122
12. Martin JP (1967) *The basal ganglia and posture*. Pitman Medical, London
13. Mochio S, Oka H, Katayama K, et al (1997) Central motor conduction time using magnetic and vibratory stimulation in Parkinson's disease, especially in patients with rigidity. *Nippon Rinsho* 55:173–179
14. Morimatsu M, Negoro K (1995) Corticobasal degeneration: symptomatological, brain-imaging and electrophysiological studies. *Rinsho Shinkeigaku* 35:1459–1462
15. Onugaluchi G (1964) Parkinsonism. Butterworths, London, pp 94–105
16. Perlmutter JS, Tempel LW, Black KJ, Parkinson D, Todd RD (1997) MPTP induces dystonia and parkinsonism. Clues to the pathophysiology of dystonia. *Neurology* 49:1432–1438
17. Quinn NP, Ring H, Honavar M, et al (1988) Contractures of the extremities in parkinsonian subjects: a report of three cases with a possible association with bromocriptine treatment. *Clin Neuropharmacol* 11:268–277
18. Quinn N (1989) Multiple system atrophy – the nature of the beast. *J Neurol Neurosurg Psychiatry* 129–133
19. Reynolds F, Petropoulos G (1965) Hand deformities in parkinsonism. *J Chronic Dis* 18:593–595
20. Ridding MC, Sheean G, Rothwell, et al (1995) Changes in the balance between motor cortical excitation and inhibition in focal, task specific dystonia. *J Neurol Neurosurg Psychiatry* 59:493–498
21. Wenning GK, Tison F, Ben Shlomo Y, Daniel SE, Quinn NP (1997) Multiple system atrophy: a review of 203 pathologically proven cases. *Mov Disord* 12: 133–147