Journal of Neurology, Neurosurgery, and Psychiatry 1994;57:460–463

Lessons from a remarkable family with dopa-responsive dystonia

G Harwood, R Hierons, N A Fletcher, C D Marsden

Abstract

A family is described in which dopa-responsive dystonia affected six members and segregated in an autosomal dominant fashion. Patients either presented in childhood with dystonia of the legs, going to develop parkinsonism and pseudo-pyramidal deficits, or in adult life with parkinsonian tremor and rigidity, with pseudo-pyramidal signs. Remarkably, in the three cases with childhood onset the symptoms and signs of the condition were abolished 36 to 52 years later by small doses of levodopa. No long term side effects of levodopa have appeared after 15 years of treatment.

(*J Neurol Neurosurg Psychiatry* 1994;57:460–463)

Regional Neurological Unit, Brook General Hospital, Shooters Hill Road, Woolwich, London, SE18 4LW
G Harwood
R Hierons

University Department of Clinical Neurology, Institute of Neurology, The National Hospital for Neurology & Neurosurgery, Queen Square, London, WC1N 3BG
N A Fletcher
C D Marsden

Correspondence to:
Professor C D Marsden, University Department of Clinical Neurology, Institute of Neurology and National Hospital for Neurology and Neurosurgery, Queen Square, London, WC1N 3BG.

Received 22 March 1993.
Accepted 17 May 1993

Dopa-responsive dystonia (DRD) is characterised by the appearance of dystonia, usually commencing in the lower limbs to cause a bizarre gait, in childhood or adolescence.[1 2] Other clinical features such as brisk tendon reflexes in the legs, parkinsonism and "striatal" plantar responses (pseudo-Babinski sign[3]) are variably present. It has been suggested that up to 10% of cases of dystonia with onset at this age might be due to DRD.[2] The clinical importance of this condition lies in the fact that it is effectively cured with continued administration of small doses of levodopa.[2 4 5] Segawa *et al*[4] drew recent attention to the condition, but numerous reports of cases with very similar clinical features exist in earlier publications.[6–11]

The family described here is of interest for a number of reasons: (1) it adds to the evidence for autosomal dominant inheritance of this condition,[12 13] with reduced penetrance and greater expression in women than men[1 13 14]; (2) it confirms that affected adults may present with parkinsonism[2 13 15 16]; (3) it shows that despite onset in childhood, and progression to severe disability with no effective treatment, administration of small doses of levodopa can lead to rapid and dramatic improvement 36 years (case IV·5), 47 years (case III·17), and 52 years (case III·9) after the beginning of the disease; (4) it confirms that such patients continue to have a sustained, smooth, therapeutic response to levodopa therapy.[5] All three cases have remained more or less normal on doses of levodopa (with carbidopa) of 50 to 200 mg daily for 15 years, without the need to increase levodopa intake, and with none of the long term side effects of chronic levodopa therapy seen in Parkinson's disease.

Cases

The figure shows the pedigree of this family; we have examined 11 members.

Case I.2

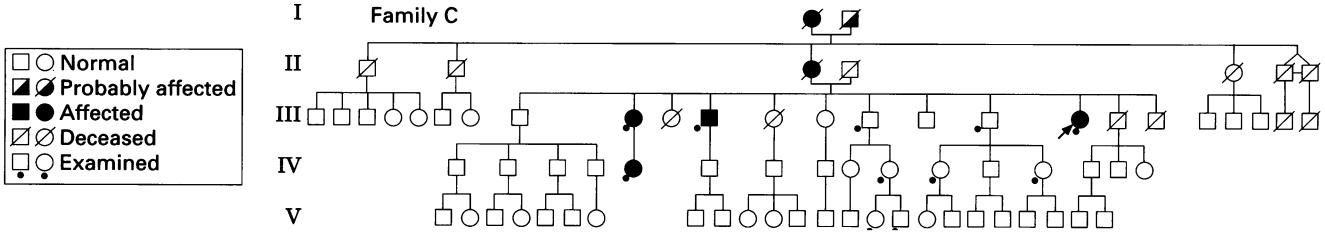
Case I.2 died at an advanced age but he is remembered as having a pronounced tremor and difficulty walking, with a tendency to fall forwards and a stiff and stooped posture. The onset was probably in middle age but the details are scanty.

Case II.3

Case II.3 is also deceased. At age 39 she developed a tremor of the hands and family members recall that she had "bad legs". She was examined in 1964 at the age of 78; there was a parkinsonian tremor of the hands and the left leg together with cogwheel rigidity of the arms and bilateral apparently extensor plantar responses.

Case III.17

Case III.17 (the proband) is now aged 68. Birth and development were normal. At the age of six, it was noted that both feet were beginning to invert, the left more than the right. Walking became difficult and she had



Pedigree of family with dopa-responsive dystonia.

frequent falls, particularly when running. At the age of 10 she was sent to a school for the physically handicapped where it was said that she could walk and even run quite well but that after several hundred yards she became "tired". At the age of 16 she underwent surgery to lengthen both Achilles tendons without benefit. By now there was a pronounced scissors gait and a longstanding tremor of the hands became more prominent. When examined by one of us (RH) in 1961 she was 39 years old. The gait was very abnormal; the posture was anteflexed with plantar flexion and inversion of the feet and the knees rubbed together so that she often caught her feet on the opposite leg. She used her arms, shoulders, and trunk to help in the movement, giving rise to a lurching, elaborate gait with dystonic posturing of the arm, particularly the left. The cranial nerves were normal although speech was slightly dysphonic and there was a resting tremor of the limbs and head. Plastic rigidity in the limbs, slight weakness of hip flexion, exaggerated tendon reflexes, and apparently extensor plantar responses were noted. Sensory examination was normal.

Five years later, she had deteriorated and was barely able to walk without assistance. Speech was worse and dysphagia had developed; her tremor had become more noticeable. The symptoms showed considerable fluctuation and were always worse in the evenings or when she was anxious. In the mornings she could manage shopping and housework; by the evening she had difficulty with walking, ascending or descending stairs, and eating. On examination, the physical signs were more prominent and there was pronounced axial rigidity.

Slow deterioration continued over the next seven years; treatment with benzhexol, orphenadrine, and amantadine was ineffective. By 1974, aged 54, she was mostly confined to a wheelchair and there was dystonic posturing at rest. At this stage, 47 years after the onset of the disorder, she received levodopa for the first time (Sinemet 275, one tablet twice daily); eight hours later the patient was taken out to the theatre in her wheelchair. During the interval, she stood up and was able to walk unaided; over the course of the next week she rapidly improved to the point where she walked virtually normally. She took only one Sinemet 275 tablet per day throughout this period and was then able, to all intents and purposes, to lead a perfectly normal life. Fifteen years later, she had required no increase in dose and none of the side effects of long term levodopa therapy seen in Parkinson's disease had appeared. There was minimal chorea of the limbs and a fine postural tremor; her gait, although much improved, remained slightly dystonic and the plantar responses remained apparently extensor.

Investigations, including a cranial CT scan, EEC, examination of CSF, copper studies, liver function tests, and blood and urinary amino acid analyses were normal.

Case III.9

Case III.9, the sister of the proband, was followed up to 80 years of age. She developed an abnormal gait at the age of 13, with limping on the left leg, poor balance, and frequent falls; throughout her life she has noted difficulty maintaining any physical effort such as holding a cup in the hand or writing; the hand seems to "tighten up". In 1966, at the age of 58, she was found to have a kyphoscoliosis and to drag the feet when walking. The cranial nerves were normal and there was extrapyramidal rigidity of the limbs; muscle power, tendon reflexes, plantar responses, and sensation were normal. During the next 11 years she deteriorated. Her symptoms fluctuated and became worse during the day; at times she was unable to stand. In 1974, 52 years after the onset, this patient also received levodopa; she became rapidly symptom free. Fifteen years later she remained symptom free on half a tablet of Sinement 275 per day. On examination the physical signs were confined to the gait, which was minimally abnormal with mild stiffness and flexion of the legs and slight inversion of the feet.

Case III.11

Case III.11 was followed up to the age of 75. As a child he had seizures treated with phenobarbitone. The family had always noticed that he was "slow getting around" but he had never sought medical advice for this problem. There was no diurnal fluctuation of symptoms although the history was not reliable. On examination in 1988 he was dysphonic but the examination of the cranial nerves was otherwise normal; there was cogwheel rigidity of the arms, a resting tremor, and pronounced bradykinesia. Muscle power was normal as were the tendon reflexes; the plantar responses were apparently extensor, sensation was normal. The gait was slow, flexed, and shuffling and was indistinguishable from that typical of Parkinson's disease. This patient has never received levodopa or any other treatment.

Case IV.5

Case IV.5 is the daughter of III·9 and was followed up to age 59. Birth and developmental milestones were normal until the age of eight when she noted that her right foot tended to invert and that she was clumsy on walking or running although she could play games normally. About four years later, she developed torticollis to the right which increased in severity over the next few years. By the age of 24, she noted that walking was becoming more difficult and she tended to drag her legs, particularly towards the end of the day. By the evening, she had "run out of steam completely" and it would take her half an hour to undress for bed. About five years later she developed spasms of stiffness and immobility in the arms.

She was first seen by a neurologist in 1963 at the age of 34. There was torticollis to the right; a tremor of the lower lip and hands was present, more pronounced on action. The

cranial nerves, muscle tone, and power and sensation were normal. Tendon reflexes were increased and the plantar responses apparently were extensor. These physical signs were very slight, however, in comparison with the gait, which was highly abnormal. She dragged both legs, especially on the right where the foot was everted. A year later she was worse; the gait was now more stiff-legged and plastic rigidity had appeared in the arms. She was given benzhexol at a dose of 2 mg twice daily together with a small nocturnal dose of benztropine; on this regime, unlike III-17, she showed considerable improvement. The torticollis disappeared and she became able to walk independently.

Ten years later, she had deteriorated again to a point where she was unable to walk on her own, although still better than in 1963, and still free of torticollis. Thirty six years after the onset of symptoms, levodopa (Sinemet 110, half a tablet daily) was given. All residual symptoms disappeared within one week. Fifteen years later, she was free of symptoms other than a slight tremor or the left leg in the evening. Her walking was almost normal and there were no other physical signs.

This patient underwent the same investigations as III·17 and all were normal.

Discussion

Cases III.9, III.17, and IV.5 resemble previously reported cases of DRD in their onset in childhood with dystonia of the legs, diurnal fluctuation, and sustained response to levodopa. In other respects the clinical features were variable; dystonia elsewhere, parkinsonian tremor and rigidity, brisk reflexes in the legs, and apparently extensor plantars responses (pseudo-Babinski responses) were prominent. By contrast, case III.11, a 75 year old man, had only mild parkinsonism with pseudoextensor plantar responses and had never been moved to seek medical advice. According to history, cases I.2 and II.3 also presented with parkinsonian tremor and rigidity in adult life. Recently, Nygaard *et al*[13] have demonstrated normal striatal uptake of fluorodopa by PET in two cases of adult onset parkinsonism in a family with DRD. Their finding clearly shows that adult onset parkinsonism in such DRD families is not due to coincidental Parkinson's disease, but is a manifestation of DRD. In our family, case II·3, the affected mother, presented at the age of 39 with parkinsonian tremor and rigidity, along with pseudopyramidal signs.

All this evidence supports the conclusion that children with DRD usually present with leg dystonia, sometimes with superimposed elements of parkinsonism, whereas adults present with parkinsonism.[13]

The inheritance in our family also suggests autosomal dominant inheritance with varied expression as noted in previous studies.[1 2 12] The DRD gene seems to show a sex influenced expression; the preponderance of female cases—four out of our six cases and 23 out of 32 cases reviewed by Nygaard and Duvoisin[2] were female—is striking. An excess of female cases (3:1) has also been noted by Nygaard *et al*[17] and Segawa *et al*[14] who have suggested that there may be physiological differences in dopaminergic neurons between the two sexes. There is a suggestion that the expression in females tends to be more severe and of the classical dystonic type whereas that in males tends to be milder and akinetic-rigid, but the numbers are too small to draw a firm conclusion concerning this. Such a phenomenon might, however, explain the excess of female cases in published reports; males may be less likely to come to medical attention or may be diagnosed as having Parkinson's disease. It should be noted that male to male transmission has been recorded in other families[1] thereby excluding X-linked inheritance in the absence of disease heterogeneity.

The response of one of our cases (IV·5) to a small dose of benzhexol and benztropine deserves comment; the dose was certainly much lower than that used to obtain therapeutic effects in idiopathic torsion dystonia.[18] There are, however, other reports of such pronounced responses to benzhexol in DRD. Corner[6] described a similar response to low dose anticholinergic treatment in two patients with the clinical features of DRD. Other cases were reported by Burns,[19] Mucklow and Metz,[20] and by Nygaard and Duvoisin,[1] who suggested that the effect may be due to inhibition of dopamine reuptake.

Several of the patients in this report have been followed up for over 25 years, much of this before the availability of levodopa, so that the evolution of the condition with time is apparent. The extraordinary feature of these cases is the remarkable length of time elapsing between the onset of symptoms and the successful treatment with levodopa leading to almost complete resolution of symptoms. Case III·17 had been affected for 47 years and wheelchair bound for over 30 years; case IV·5 had been affected for 36 years and III·9 for 52 years. All experienced the dramatic and sustained impact of levodopa on their disability without complications, which is so characteristic of this condition.[5] None developed any of the features of long term levodopa treatment found in idiopathic Parkinson's disease,[21] even after 15 years of therapy.

These cases graphically illustrate the clinical course of DRD over many years and the extent to which the clinical response to levodopa is independent of the duration of the symptoms or therapy. This has important implications for the pathogenesis of this movement disorder. A purely biochemical (and hereditary) abnormality of dopaminergic pathways is implied; the therapeutic response in a degenerative disease would not be expected to be independent of disease duration. The absence of long term side effects such as dose-response fluctuations and loss of efficacy suggests that dopamine receptor function is normal. The clinical features of DRD suggest a partial deficiency of dopamine,

which is corrected by treatment with a small daily dose of levodopa.

Striatal uptake of fluorodopa studied by PET has been normal or near normal in DRD,[13 22 23] implying normal dopa decarboxylation and presynaptic dopaminergic nerve terminal storage. In fact, cases III·17 and IV·5 were studied by PET and their mean Ki values for ^{18}F-dopa uptake into caudate and putamen were within two standard deviations of those of normal control subjects.[22] The metabolic defect in DRD might, therefore be in tyrosine hydroxylation to levodopa. Tyrosine hydroxylase is the rate limiting enzyme in catecholamine synthesis and a genetic abnormality of tyrosine hydroxylase has been suggested to be the cause of DRD.[14] A molecular genetic study has, however, failed to show linkage between the DRD locus and restriction-fragment length polymorphisms detected by a tyrosine hydroxylase gene probe and other closely linked genetic markers.[24] The precise nature of the biochemical abnormality in DRD therefore remains elusive. Abnormalities of biopterin metabolism have been demonstrated in patients with DRD[25 26] and patients with biopterin deficiency have features of DRD[25 27]; tetrahydrobiopterin is a cofactor for tyrosine hydroxylase and therefore is important in dopamine neurotransmission.

Whatever the nature of the underlying biochemical derangement in DRD, it is clear that a hereditary biochemical abnormality can produce a profound movement disorder and that this is rapidly and permanently reversible, even when symptoms have been present for over 50 years. The implications of this finding for idiopathic torsion dystonia, another common movement disorder with no consistent demonstrable structural pathology, are considerable.

1 Nygaard TG, Duvoisin RC. Hereditary dystonia-parkinsonism syndrome of juvenile onset. *Neurology* 1986; **36**:1424–8.

2 Nygaard TG, Marsden CD, Duvoisin RC. Dopa responsive dystonia. In: Fahn S, Marsden CD, Calne DB, eds. *Dystonia 2. Advances in Neurology*. Vol 50. New York: Raven Press, 1988:377–84.

3 Hunt JR. Progressive atrophy of the globus pallidus (primary atrophy of the pallidal system). A system disease of the paralysis agitans type. *Brain* 1917;**40**:58–148.

4 Segawa M, Hosaka A, Miyagawa F, *et al.* Hereditary progressive dystonia with marked diurnal fluctuation. In: Eldridge R, Fahn S, eds. *Advances in Neurology*. Vol 14. New York: Raven Press, 1976:215–33.

5 Nygaard TG, Marsden CD, Fahn S. Dopa-responsive dystonia: long-term treatment response and prognosis. *Neurology* 1991;**41**:174–81.

6 Corner BD. Dystonia musculorum deformans in siblings treated with artane (trihexyphenidyl). *Proc R Soc Med* 1952;**45**:451–2.

7 Davision C. Pallido-pyramidal disease. *J Neuropathol Exp Neurol* 1954;**13**:50–9.

8 Horowitz G, Greenberg J. Pallido-pyramidal syndrome treated with l-dopa. *J Neurol Neurosurg Psychiatry* 1975; **38**:238–40.

9 Allen N, Knopp W. Hereditary parkinsonism-dystonia with sustained control by l-dopa and anticholinergic medication. In: Eldridge R, Fahn S, eds. Dystonia. *Advances in Neurology*. Vol 14. New York: Raven Press, 1976:201–14.

10 Gordon N. Fluctuating dystonia and allied syndromes. *Neuropaediatrics* 1982;**13**:152–4.

11 Ouvrier RA. Progressive dystonia with marked diurnal fluctuation. *Ann Neurol* 1978;**4**:412–7.

12 Nygaard TG, Trugman JM, de Yebenes JG, Fahn S. Dopa-responsive dystonia: the spectrum of clinical manifestations in a large North American family. *Neurology* 1990;**40**:66–9.

13 Nygaard TG, Takahashi H, Heiman GA, Snow BJ, Fahn S, Calne DB. Long-term treatment response and fluorodopa positron emission tomography scanning of parkinsonism in a family with dopa-responsive dystonia. *Ann Neurol* 1992;**32**:603–8.

14 Segawa M, Nomura Y, Tanaka S, *et al.* Hereditary progressive dystonia with marked diurnal fluctuation—consideration of its pathophysiology based on the characteristics of clinical and polysomnographic findings. In: Fahn S, Marsden CD, Calne DB, eds. *Dystonia 2. Advances in Neurology*. Vol 50. New York: Raven Press, 1988:367–76.

15 Nomoto M, Kumamoto K, Sano Y, *et al.* A family with benign familial Parkinson's disease with a child having severe dopa-responsive fluctuating dystonia [abstract]. *Rinsho Shinkeigaku* 1984;**24**:1388.

16 Nygaard TG, Gardner-Medwin D, Marsden CD. Dopa-responsive dystonia: the spectrum of clinical manifestations in a family. In: Crossman AR, Sambrook MA, eds. *Neural mechanisms of disorders of movement*. London: John Libbey, 1989:367–70.

17 Nygaard TG, Snow BJ, Fahn S, Calne DB. Dopa-responsive dystonia: clinical characteristics and definition. In: Segawa M, ed. *Hereditary progressive dystonia*, London: Parthenon Publishing, 1993:21–35.

18 Fahn S. High dosage anticholinergic therapy in dystonia. *Neurology* 1983;**33**:1255–61.

19 Burns CLC. The treatment of torsion spasm in children with trihexyphenidyl (Artane). *The Medical Press* 1959; **241**:148–9.

20 Mucklow ES, Metz HT. Remarkable response to benzhexol hydrochloride (Artane) in children with an unusual progressive straital syndrome. *Dev Med Child Neurol* 1964;**6**:598–605.

21 Marsden CD, Parkes JD. "On-off" effects in patients with Parkinson's disease on chronic levodopa therapy. *Lancet* 1976;**i**:292–6.

22 Sawle GV, Leenders KL, Brooks DJ, *et al.* Dopa-responsive dystonia: [^{18}F]dopa positron emission tomography. *Ann Neurol* 1991;**30**:24–30.

23 Snow BJ, Okada A, Martin WRW, *et al.* PET scanning in dopa-responsive dystonia, parkinsonism-dystonia, and young-onset parkinsonism. In: Segawa M, ed. *Hereditary progressive dystonia*. London: Parthenon Publishing, 1993:181–6.

24 Fletcher NA, Holt IJ, Harding AE, Nygaard TG, Mallet J, Marsden CD. Tyrosine hydroxylase and levodopa responsive dystonia. *J Neurol Neurosurg and Psychiatry* 1989;**52**:112–4.

25 Fink JK, Barton N, Cohen W, *et al.* Dystonia with marked diurnal variation associated with biopterin deficiency. *Neurology* 1988;**88**:707–11.

26 LeWitt PA, Miller LP, Levine RA, *et al.* Tetrahydrobiopterin in dystonia: identification of abnormal metabolism and therapeutic trials. *Neurology* 1986; **36**:760–4.

27 Tanaka K, Yoneda M, Nakajima T, *et al.* Dihydrobiopterin synthesis defect: an adult with diurnal fluctuation of symptoms. *Neurology* 1987;**37**:519–22.