Lessons from a remarkable family with dopa-responsive dystonia

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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 pseudopyramidal 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.

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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. Other clinical features such as brisk tendon reflexes in the legs, parkinsonism and "striatal" plantar responses (pseudo-Babinski sign) 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. The clinical importance of this condition lies in the fact that it is effectively cured with continued administration of small doses of levodopa. Segawa et al4 drew recent attention to the condition, but numerous reports of cases with very similar clinical features exist in earlier publications. 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,1 13 14 with reduced penetrance and greater expression in women than men; (2) it confirms that affected adults may present with parkinsonism;3 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. 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.](image-url)
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 be-
came "tired". At the age of 16 she underwent
surgery to lengthen both Achilles tendons
without benefit. By now there was a pro-
nounced 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 ab-
normal; 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 move-
ment, giving rise to a lurching, elaborate gait
with dystonic posturing of the arm, particu-
larly 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 weak-
ness of limb 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 de-
volved; her tremor had become more notice-
able. 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 ineffect-
ive. By 1974, aged 54, she was mostly con-
fined to a wheelchair and there was dystonic
posturing at rest. At this stage, 47 years after
the onset of the disorder, she received lev-
odopa 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 exten-
sor.

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 diffi-
culty 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 cra-
nial 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 fluctu-
ated 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 Sinemet 275 per day. On
examination the physical signs were confined
to the extreme, exaggerated plantar
stiffness, and 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 pheno-
barbitone. 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 oth-
erwise 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 developmen-
tal 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 plantar 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 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. The inheritance in our family also suggests autosomal dominant inheritance with varied expression as noted in previous studies. 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 were female—is striking. An excess of female cases (3:1) has also been noted by Nygaard et al and Segawa et al 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 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 female transmission has been recorded in other families 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 benztoprine deserves comment; the dose was certainly much lower than that used to obtain therapeutic effects in idiopathic torsion dystonia. There are, however, other reports of such pronounced responses to benzhexol in DRD. Corner described a similar response to low dose anticholinergic treatment in two patients with the clinical features of DRD. Other cases were reported by Burns, Mucklow and Metz, and by Nygaard and Duvoisin, 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 30 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. None developed any of the features of long term levodopa treatment found in idiopathic Parkinson's disease, 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,
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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, 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 9F-dopa uptake into caudate and putamen were within two standard deviations of those of normal control subjects. 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. 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. The precise nature of the biochemical abnormality in DRD therefore remains elusive. Abnormalities of biotin metabolism have been demonstrated in patients with DRD and patients with biotin deficiency have features of DRD; tetrahydrobiopterin is a cofactor for tyrosine hydroxylation 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.


