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Fluctuating dystonia responsive to levodopa

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SUMMARY Four cases of hereditary progressive dystonia with diurnal fluctuation were studied. All were sporadic; three of them mimicked spastic diplegia; and the fourth showed some similarity to torsion dystonia. Emotional or cognitive disturbance, or both, was seen in three. The correct diagnosis was suggested by fluctuating signs and symptoms, which worsened towards evening, but this was reached only after many years of handicap, hospital admissions, and invasive diagnostic procedures. Typically there was a prompt, pronounced, and sustained response to moderate doses of levodopa. Sleep recordings were obtained in three patients and showed increased body movements during rapid eye movement sleep. Several close relatives had periods of increased leg movements during sleep. It is suggested that hereditary dystonia responsive to levodopa should be considered as the diagnosis in children with fluctuating signs of motor disability syndromes, simulating torsion dystonia or spastic diplegia. Polysomnographic studies may be helpful in diagnosis and may also detect early or subclinical cases.

Chronic dystonia in childhood has traditionally been regarded as an incurable and progressive disease. Over the past 15 years some cases have responded to treatment with modest doses of levodopa. Most of these were characterised by definite diurnal fluctuation of symptoms. Twenty five such cases have been described;[1–6] an additional 11 cases lacking diurnal variation have also been reported.[5 7 8] Because this disease or group of diseases presents in childhood and responds to treatment paediatricians should be aware of it.

We report four patients and discuss common diagnostic pitfalls and the use of polysomnographic studies in diagnosis.

Case 1: A girl began to stumble and fall at the age of 4. Walking became progressively more difficult and she tired easily. Bad school work and emotional difficulties led to ineffective psychotherapy and a transfer to a class for slow learners. From the age of 7, obesity, slack facies, and slow reactions and speech were noted; her sleep cycle was disturbed with waking before dawn and going to bed in the late afternoon. She had several episodes during which she could not walk and resorted to crawling. During these episodes, each of which lasted several hours, her head, arms, and fingers were flexed, her legs were extended, and her left foot assumed an equinovarus position.

Between the ages of 6 and 9 she was seen by various physicians who found different signs at different times—for example, normal and increased muscle tone; positive, equivocal, and absent Babinski signs; ankle clonus; and wide based gait with slow rigid movements most of the time.

Investigations in five centres included electroencephalography; pneumoencephalography; air myelography; visual evoked potentials; nerve conduction velocity; electrocardiography; muscle biopsy; estimation of the activity in serum of creatine kinase and other muscle enzymes, thyroxine, ceruloplasmin, lactate and pyruvate (at rest and during ischemic effort); tensilon test; and electromyography at rest and on repetitive supramaximal nerve stimulation. All were within normal limits, except for the finding of a large fourth ventricle on pneumoencephalography, and the presence of type 2 fibre atrophy on histological examination of the muscle biopsy specimen. Tentative diagnoses included spastic diplegia, spinocerebellar degeneration, metabolic myopathy, and dystonia musculorum deformans.

Examination at the age of 9 showed obesity (weight 42 kg, height 126 cm) with dull facial

expression, coarse features, protruding tongue, drooling, and an occasional inappropriate transverse smile. She was alert and oriented, but only partly cooperative, with a short attention span and obvious distractibility. Her speech was monotonous and slurred. She stood on a wide base with her head slumped forward. Her gait was awkward, and characterised by short steps, toe walking, and abrupt stopping. The right arm tended to assume a wing position. These abnormal findings were least noticeable in the early morning and extremely striking in the late afternoon.

Treatment with levodopa resulted in a prompt diminution of motor handicap, loss of weight, increase in alertness, and return of a normal sleep cycle. The abnormalities of facial appearance, gait, and posture disappeared, with the exception of mild residual clumsiness and minimal residual dystonic signs. When last seen her weight was normal for her age after a loss of 20 kg during the first few months of treatment. At the time of writing, she is now doing well in a normal school class and leading a normal social life with no motor disability. She has been maintained for seven years on 100 mg levodopa and 10 mg carbidopa (Sinemet, Merck) daily, without deterioration or side effects. She discontinued the drug herself on several occasions and this resulted in immediate reappearance of dystonic equinovarus posturing of the legs.

Case 2. A young girl had been slightly clumsy since infancy. Her disability worsened at age 6 with progressive bradykinesia, tiredness, dystonic leg posturing, kyphoscoliosis, and leg twitching. By the age of 13 she needed help in the afternoons to get up from a chair and walk 20 metres. The diurnal fluctuation of her symptoms was noted and the diagnosis was established at the age of 13½. She responded within an hour to a single test dose of 250 mg levodopa. At the time of writing she had been asymptomatic for six years on 250 mg levodopa and 25 mg carbidopa daily.

Case 3. A 12 year old girl developed progressive bilateral equinovarus, spastic paraparesis, and scoliosis, and was confined to a wheelchair by the age of 13½. She had bilateral hand tremor from the age of 15, when additional findings included slowing of the basic electroencephalographic rhythm, impairment of spatial orientation on neuropsychological testing, bilateral ankle clonus, spasticity of leg adductors and flexors, nystagmus on right lateral gaze, and hypomimia. The diurnal fluctuation of her symptoms was noted and the diagnosis suggested at the age of 15½. She responded well to levodopa within 24 hours. At the time of writing she had been symptom free for two years of daily treatment with 375 mg levodopa and 37·5 mg carbidopa. Electroencephalogram and neuropsychological state reverted to normal.

Case 4. A 5 year old girl developed a progressive tendency to fall, particularly in the afternoons, clumsy gait, inturning of both legs, torticollis, scoliosis, and behavioural disturbances. By the age of 9 she could walk only five or six steps at a time during the afternoon, and showed torticollis, truncal torsion, leg inturning, bilateral intention tremors, mild bradykinesia, depressed affect, mutism, and negativism. Psychotherapy did not help. The diurnal fluctuation of her symptoms was obvious from the outset, but the diagnosis was first suggested at the age of 9. Her neurological disability responded within 48 hours to levodopa. Her behaviour became normal within a month and psychotherapy was stopped. She was still asymptomatic after two years of receiving 125 mg levodopa and 12·5 mg carbidopa daily.

Diagnoses

Onset of symptoms in our patients varied from 4 to 12 years. The correct diagnosis was made three to eight years later. All four were girls and none had affected relatives. Parental consanguinity was noted in case 3. They all had the distinctive diurnal variation of disability and dystonic signs, with striking improvement after sleep. All four patients underwent numerous investigations in major medical centres. Table 1 lists the previous diagnoses considered and the various major diagnostic and therapeutic procedures, many of them invasive. Results of all tests were within normal limits, except for the non-specific pneumoencephalography and muscle biopsy histology mentioned in case 1.

The eventual diagnosis was suspected on clinical findings alone. These included various pyramidal signs in three of the four patients and disturbances of higher function, in addition to the main features of fluctuating dystonia, accompanied in all four cases by other signs of basal ganglia dysfunction. Table 2 lists these findings. One patient was confined to a wheelchair for two years before diagnosis, while the other three were handicapped but still partially ambulant. Three had been referred to rehabilitation centres with the diagnosis of chronic, incurable motor handicap.

Complete and repeated polysomnographic studies were performed on two consecutive nights in three of the patients, and in 11 unaffected immediate relatives. In all three patients increased body movements occurred during rapid eye movement

Table 1 *Previous diagnoses, investigations, and treatment in four dystonic patients*

	Case No			
	1	*2*	*3*	*4*
Suggested diagnoses:				
Spastic diplegia	yes	yes	yes	no
Spinocerebellar degeneration	yes	yes	yes	no
Metabolic myopathy	yes	no	no	no
Torsion dystonia	yes	no	no	yes
Primary lateral sclerosis	no	no	yes	no
Huntington's chorea	no	no	no	yes
Wilson's syndrome	no	no	no	yes
Psychogenic ties	no	no	no	yes
Investigations and treatment:				
Pneumoencephalography or computed tomography	yes	yes	yes	yes
Myelography	yes	*	yes	yes
Electromyography	yes	yes	yes	yes
Muscle biopsy	yes	no	no	no
Femoral angiography	no	yes	no	no
Psychotherapy	yes	no	no	yes
Tenotomy	no	*	no	no

*Recommended but not carried out.

Table 2 *Clinical findings in four patients with fluctuating dystonia*

	Case No			
	1	*2*	*3*	*4*
Pyramidal motor signs:				
Spastic paraparesis	yes	yes	yes	no
Ankle clonus	yes	no	yes	no
Hyper-reflexia	yes	no	yes	no
Hip flexor contractures	no	yes	no	no
Babinski signs	yes	no	no	no
Non-pyramidal motor signs:				
Fluctuating dystonia	yes	yes	yes	yes
Bradykinesia	yes	yes	yes	yes
Tremor, chorea, mask face	yes	yes	yes	yes
Torticollis	no	no	no	yes
Higher functions:				
Emotional disturbance	yes	no	no	yes
Impaired spatial orientation	no	no	yes	no
Failure to learn	yes	no	no	no
Other findings:				
Scoliosis	no	yes	yes	yes
Pes cavus	no	yes	no	no
Sleep disorder	yes	yes	no	no
Drooling, slurred speech	yes	no	no	no

(REM) sleep, mixed with numerous awakenings, but without obvious impairment of sleep structure. In two patients studies were performed both before and during treatment with levodopa. No noticeable decrease in body movements resulted from the treatment, although the sleep cycle abnormality disappeared. Among 11 relatives, all three fathers and two of the three mothers showed definite periods of leg movement during stage 2 sleep; a paternal grandfather and two of four siblings were similarly affected.

The effect of levodopa on these patients was prompt, effective, and sustained. All responded fully within 24–96 hours of starting treatment and all now function normally. Examination at the time of writing showed none of the patients had the previously apparent pyramidal signs nor disturbances of higher mental functions. Daily doses ranged from 375 mg (levodopa) and 37·5 mg (carbidopa) to 100 mg and 10 mg, respectively. Treatment has been continued for two to seven years without side effects or need for a change in dose.

Discussion

'Childhood onset levodopa responsive dystonia' was first described by Segawa *et al* in 1971,[1] and nine cases from the same clinic were reviewed in detail five years later.[2] The syndrome was named 'hereditary progressive dystonia with marked diurnal fluctuation'. All cases responded promptly to levodopa. Six of the nine cases were familial, with a pattern that suggested autosomal dominant inheritance with low penetration. An additional 16 cases have been reported since.[3–6] Our cases fit the described pattern of childhood dystonia with pronounced diurnal variation; this is sufficient for diagnosis and predicting a good response to levodopa. Eleven other cases of chronic dystonia which responded to levodopa have been reported; in these diurnal fluctuation was absent.[5 7 8] Three families have also been reported to have cases both with and without diurnal fluctuation.[5] This implies that there is no genetic distinction between cases with and without diurnal fluctuation and that this striking and useful finding is not invariably present. It is uncertain, however, whether all families with this syndrome share the same autosomal dominant genes. Our four sporadic cases, including one with parental consanguinity, suggest the possibility of a recessive phenocopy.

None of the cases reported has shown an addiction to levodopa, even after 12 years of treatment.[2–8]

Homovanillic acid concentrations in the cerebrospinal fluid were studied in three patients.[3 7] These were low before treatment, and increased immediately after the levodopa was started. One of the three patients did not have diurnal fluctuation;[7] the authors suggest that concentration of homovanillic acid in the cerebrospinal fluid may be of use in predicting response to treatment with levodopa.

Several other patients have been reported who may or may not have this syndrome. These include two brothers with dystonia, without diurnal variation, and with a less than complete response to medication,[9] and two unrelated children with immediate response to levodopa, but with neither dystonia nor diurnal fluctuation.[10] In addition, at

least 18 cases have been reported in Japan of early onset Parkinsonism, usually familial, who showed both pronounced diurnal fluctuation and an unusually good response to chemotherapy.[11–12] These reports suggest that chronic childhood levodopa responsive basal ganglia disease may, in fact, comprise several different diseases.

The precise interrelations between response to levodopa, diurnal fluctuation, body movements during sleep, and catecholamine concentrations in cerebrospinal fluid remain to be clarified. Segawa *et al* performed polysomnography in four patients and found body movements mainly during stage 2 sleep.[2] A decrease in body movements during sleep was reported in Parkinson's disease and an increase in such movements occurs in Huntington's chorea and Gilles de la Tourette syndrome.[13] Increased body movements were found in our patients. These movements, however, occurred during REM rather than stage 2 sleep, and they seemed unresponsive to levodopa.

A unique finding was the presence of periodic leg movements during sleep in first degree relatives of three patients; we can find no other reports of familial periodic leg movements in an isolated form. A few instances of such movements have been seen in the familial restless leg syndrome.[14 15]

In summary, what characterises virtually all these reported cases is the onset between 1 year of age and puberty of a progressive and chronic motor handicap, which, in some cases, mimics spastic diplegia and in others mimics torsion dystonia. In most cases closer examination shows pronounced diurnal fluctuation of signs and symptoms, together with evidence of dystonic posturing; these are often associated with other signs of dysfunction of the basal ganglia such as choreiform movements, bradykinesia, and mask like facies. Emotional disturbance, leading to referral for psychotherapy, may be common but does not contradict the diagnosis.

In cases with diurnal fluctuation a four day trial of levodopa in a daily dose of 10 to 25 mg/kg is mandatory, and an immediate improvement will usually confirm the diagnosis. In cases or families without diurnal fluctuation the diagnosis is more difficult. Either the polysomnographic findings of body movements during REM sleep, or the finding of abnormally low concentrations of dopamine or homovanillic acid, or both, in the cerebrospinal fluid, may predict response to levodopa. In case of doubt a four day trial should provide the answer.

We do not know what proportion of the cases presently diagnosed as late onset spastic paraplegia in chronic rehabilitation centres are, in fact, treatable cases of hereditary progressive dystonia. We believe that this possibility should not be ignored in view of the fact that three of our four patients and at least three other published cases had been referred to such care.

The presence of body movements during sleep in the patients and of periodic leg movements in healthy first degree relatives suggests that these two phenomena may be related although different expressions of a fundamental disorder of the basal ganglia. Such movement could serve as a genetic marker in affected families.

Dr Amos Korczyn of the Tel Aviv Municipal Hospitals was the first to suggest the correct diagnosis in case 1.

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