Hereditary whispering dysphonia

NEVILLE PARKER

SUMMARY An Australian family group is described where at least twenty members have inherited torsion dystonia and two siblings with an affected mother have similar clinical manifestations, but have also the biochemical and pathological changes found in Wilson's disease. Whispering dysphonia was the commonest presenting symptom, and a diagnosis of hysteria was invariably made if the family history was not known. This group emphasises the enormously varied ways in which torsion dystonia may be manifested in one family, and raises the possibility of a disturbance in copper transport in diseases of the basal ganglia other than Wilson's disease.

A small handful of people, all related and living in North Queensland, Australia, have a most unusual speech disorder. They are able to shout and yell when emotional, have no trouble communicating after drinking alcohol and talk normally in their sleep, yet when they try to speak their voices come out only in a faint whisper. Eventually they may be unable to utter a sound when trying to talk. This whispering dysphonia may continue throughout life as an isolated feature, but more commonly is the initial presentation of a more pervasive disease with extremely varied expression. A sister and brother have Wilson's disease yet none of their immediate or distant relatives have any of the biochemical changes found in that recessive disease. At least three deceased members were diagnosed as having Huntington's chorea at the time of presentation before details of other affected family members became known, while the only living affected person with involuntary movements is a classical example of idiopathic dystonia musculorum deformans. Others have isolated dystonic features particularly torticollis and spastic dysphonia; two had life threatening dysphagia and one of these was diagnosed prior to surgery as having pseudobulbar palsy. Four have been admitted to hospital with atypical psychoses, several were demented and manifested personality deterioration prior to becoming grossly intellectually impaired. It is very unlikely that this diverse collection of extremely rare syndromes occurs in the one family group purely by chance, and the conclusion is inescapable that a unique family has been identified.

Address for reprint requests: Dr N Parker, Temple Court, 422 Collins Street, Melbourne 3000, Australia.

Revised 26 August 1983 and in final revised form 29 March 1984.
Accepted 1 April 1984

Patients

The pedigree of the Australian members of this family group is illustrated in fig 1, which indicates an autosomal dominant mode of inheritance with complete penetrance and variable expressivity. Assuming that the cases diagnosed as Huntington's chorea, idiopathic dystonia musculorum deformans and pseudobulbar palsy are all suffering from the same underlying disorder, and that whispering dysphonia is a "forme fruste", then the numbers affected are as listed in table 1.

Of the twenty definitely established cases, seventeen had affected mothers, who had more than three times as many children as affected males or unaffected members of either sex. The original migrants included a brother, two sisters, and an illegitimate daughter; the brother (IA) had six children of whom all married and had large families; none of this group has suffered from any neurological disorders.

The younger sister (IC) had fifteen subsequent children, eight of whom died in infancy; she developed "a peculiar way of walking" in her early fifties and died twenty three years later. The other sister (IB) also had an illegitimate child, born shortly after arriving, then married and went on to rear six additional children, three of whom developed the disease. Her diagnosis was established by inference for her grandchildren were unaware of anything unusual about her, and she too lived to an old age.

Information about the next generation is patchy, and I examined only one of them (IIF), but in subsequent generations everyone in the pedigree has been personally examined over a period of thirty years and several have been thoroughly investigated.

There has been apparent change in the pattern of symptoms with succeeding generations; those in the second and third generations are remembered for their choreiform movements while only one in the fourth generation has marked involuntary movements and these are clearly an expression of torsion dystonia, associated with other dystonic features. Whispering dysphonia is the usual presenting feature and in living affected members dystonia is usually mild.

As the disease is usually not obvious before the early

Table 1

		Male	Female
Deceased	affected	5	8
	suspect	1	3
	unaffected	8	12
Living	affected	6	1
	suspect	0	1
	unaffected	1	1
	not yet determined	28	19
Totals		49	45

twenties the children in the fifth generation are too young to show clinical signs and are all included in the "not yet determined" category together with those in the fourth generation who now appear to be normal—symptoms may only become obvious after the age of 50 years. Indeed the age of onset is as varied as the clinical presentation but the general tendency is for it to show in the early twenties.

Case reports

Case histories of some affected members will be briefly outlined to give an indication of the diversity of expression of the gene, and to highlight the unsolved riddles which this family presents.

"**ARTHUR**" (*Case IVS*), a mild example of transient torticollis and spastic dysphonia, when first examined in 1974 was aged 19. There was a slightly forced quality about his voice and a suggestion of mild torticollis. When re-examined in 1982 he had classical "spastic dysphonia" as described by Critchley:¹ the voice is "almost as though the patient were trying to talk whilst being choked and sounds are emitted in a peculiarly harsh and constrained fashion". This is how Arthur speaks now, but there were no other abnormalities on careful examination; however, when going through his photo album there was a picture taken two years earlier (fig 2) illustrating marked torticollis, and he mentioned that his neck pulls over to the left for brief periods, particularly when he is upset. Arthur was a nervous teenager, performed poorly at school and was repeatedly attempting to have intercourse with his step-sisters aged 9 and 5 (the natural children of the parents, for he was adopted). The child psychiatrist to whom he was sent noted that he was a timid, apprehensive 15 year old, and was tense and restless throughout the consultation. There were no abnormalities on clinical examination and psychological testing revealed an IQ of 68 on the WISC (Verbal IQ 79, Performance IQ 62). He was admitted to a residential centre for sub-normal children, then graduated to a sheltered workshop, living in a home which provides accommodation for up to twenty of the workers. He is happy there and not giving any trouble.

The woman who gave birth to Arthur (IIIT) died in 1973 at the age of 46 years, from pneumonia and when examined during a survey of Huntington's chorea in Queensland,² had marked choreiform movements, and was demented; she had two brothers (IIIR and IIIV) and a mother (IIM) with similar movements commencing in their thirties. In her twenties she presented with whispering dysphonia, but her spectacular expression of early dementia overshadowed this feature. She was extremely aggressive, her personal habits deteriorated and she became blatantly

Fig 2 "Arthur" *Case IVS* (1980) demonstrating transient torticollis.

promiscuous, drank heavily and made several suicide attempts.

Arthur's sister (IVP) had suffered from whispering dysphonia as an isolated feature for many years. His elder brother now aged 36 years (IVQ) is a normal and responsible member of the community; the other brother (IVR) has never been sighted as his foster parents did not let him know of my interest in examining him.

"**BERYL**" (*Case IVX*) is a severe example with gross involuntary movements. When first examined in June 1975 she was 23 years old and had noticed a change in her voice commencing about six weeks previously; as she explained "It fades out". At that time neurological examination was completely normal and extensive biochemical investigations were all negative. In July 1978 her dysphonia was obvious, and in addition to its soft volume there was a forced quality to her speech. One week earlier she developed right sided torticollis, most apparent when she was walking. The torticollis rapidly became severe with extensor spasms and within months she became progressively unable to walk or talk and developed involuntary movements of both arms and legs with inversion spasm and violent jerking of the pelvis; tone was increased with normal reflexes. There was no improvement following anti-Parkinsonian therapy, and the wide variety of drugs which

Hereditary whispering dysphonia

were tried were equally ineffective. By mid 1979 she was bedridden and severe extensor spasms resulted in several broken ribs; a diagnosis of idiopathic dystonia musculorum deformans was beyond doubt and in March 1980 bilateral sterotaxic lesions were made in both ventro-lateral nuclei of the thalamus in four stages; this resulted in a marked improvement and she was soon mobile. When examined in January 1982 spastic dystonia had redeveloped and torsion spasms of the left leg; at the time of writing six months later, the torticollis had returned and is quite marked.

Her mother (IIW) developed the disease in her late thirties but the only abnormal movements are mild persistent blepharospasm. She is completely mute except when angered and then she shouts expletives at full volume. There is marked kyphoscoliosis and she walks bent over with her head turned to the left. An older sister (IVW) and a younger brother (IVAB) have mild spastic dysphonia as the only abnormality demonstrated to date; another sister "Emily" (IVAD) and brother (IVAE) both developed Wilson's disease.

"COLIN" (Case IVA) presented to a general hospital in August 1968 at the age of 22 years complaining of difficulty in speaking for the previous six weeks but had no trouble shouting and swearing. In September 1971 he attended again, this time complaining that for the previous two months he could not swallow and had lost approximately half a stone in weight. At that stage his speech was almost inaudible but no other abnormalities were detected on clinical examination and biochemical and neurological investigations were normal; he was diagnosed as having hysteria and referred to a psychiatrist.

Dysphagia became more marked with time and by August 1972 he was having difficulty in swallowing fluids. A barium swallow was reported as follows: "No actual organic lesion was shown in the pharynx, but there appeared to be a periodic spasm about the level of the crico-pharyngeus. No other lesion was shown in the oesophagus. There was inhalation of some barium into the bronchial tree".

His mother was noted to have "shuffled in" a few weeks later and explained in her faint voice that she was worried about her son's choking; although his speech was almost inaudible, his mother agreed that he talked clearly in his sleep. It was difficult to understand him for he spoke in a very faint whisper. No treatment had been initiated for he was still considered to have an untreatable psychiatric disorder. When his mother died from pneumonia in the winter of 1975 Colin moved to Sydney to stay with his brother. While there he attended a major teaching hospital and underwent a crico-pharyngeal myectomy operation in October 1980. There was considerable improvement after the operation; unfortunately the improvement was short lasting and when examined again in January 1982 he was living a miserable existence and limited to a fluid diet.

Severe dysphagia was present in two other cases and one of these (IIIV) had difficulty breathing, dying at the age of 32 years after an unsuccessful tracheotomy operation.

"DAISY" (Case IIIL) Daisy's mother (IIF) was admitted in a demented state to a mental hospital at the age of 62 years, the certificates recording that she became gradually more confused over the previous two years and was restless, wakeful and wandering at night; she was unable to

give an account of herself. A year later it was recorded that she had to be locked in a room all day otherwise she would hit the other patients: "She is dirty in her habits and very destructive; all clothing she has is torn to pieces, the windows in her room are broken, she shouts abuse at the other patients and cannot be encouraged to enter into conversation". The brief note relating to the clinical examination has her as a "frail little person with multiple bruises and abrasions. No audible speech. Champing movements of the jaw. Hypertonus all limbs". After an attack of pneumonia her health rapidly deteriorated and she died five years later after admission in 1953 (before the introduction of neuroleptic drugs).

Daisy (IIIL) had been admitted to the same mental hospital only six months before her mother in 1952 when aged 41 years. She appeared apprehensive without cause, vague and incoherent, with thought blocking. She was bewildered with causeless weeping outbursts. She gave the impression of being mentally retarded but achieved an IQ on the WAIS of 90. She had found it increasingly difficult to manage her home and four children and was considered to be potentially suicidal. After seven electro-shock treatments there was "a brief remission" and after fourteen more treatments she had improved sufficiently to return home on trial leave.

During her declining years she was cared for in a hospital for the incurable and the Matron recalled her as being a restless, agitated woman who was demented and featured marked choreiform movements. It may be that her dystonia was secondary to drug therapy for she was prescribed Serenace, but in view of the family history and affected mother it is reasonable to diagnose her as also suffering from a primary dystonia. She died from pneumonia in June 1974.

Her brother (IIIK) has become unreasonably aggressive more recently and had assaulted his wife on several occasions.

None of Daisy's four children have any physical or psychiatric abnormalities to date.

"EMILY" (Case IVAD) On Boxing Day 1971 an 11-year-old girl was admitted to the Mackay Hospital, North Queensland, with what was thought to be acute infectious hepatitis complicated by haemolytic anaemia. At the time her haemoglobin was recorded as 4.5 g/dl and serum iron 92 g/dl, and this gradually improved without the need for transfusion. She had a further haemolytic episode but by early March 1972 was well enough to return home; haemolysis had settled and the haemoglobin was at 12.5 g/dl; however, liver function tests remained abnormal. In May 1972 she fractured the right humerus; it healed well but radiographs suggested some thinning of bones. Serum calcium and phosphate and three day faecal fat were all normal, but liver function tests were still abnormal (bilirubin 0.2 mgm/100ml, SGOT 62 iu, SAP 160 iu, ESR 40 mm in one hour). In November 1972 she was complaining of pain in the shins and radiographs showed a cortical fracture of the medial border of the distal tibia. There was no evidence of rickets or scurvy but there was diminution of bone density. Detailed biochemical investigations were undertaken and a wedge biopsy of the liver confirmed the diagnosis of Wilson's disease (fig 3A and B). The liver copper content was 245 mg/g (normal approximately

Fig 3(a) Wedge biopsy of liver from "Emily" Case IV AD showing fibrous septa separating nodules of liver tissue. **(b)** The same biopsy demonstrating chronic inflammatory cells infiltrating in the portal tracts and septa. Some liver cells show fatty change and other are swollen. There is piecemeal necrosis and proliferation of bile ducts in the portal tracts and septa.

7 mg/g).

In August 1973 this young girl became extremely ataxic and there was marked lability of mood. Normal schooling became impossible; she had severe dystonia and would frequently fall over backwards. She then developed severe flexion rigidity of the upper limbs, to such a degree that she dislocated her elbow joints in spasm. She became dysarthric and although she lost co-ordination when speaking, was able to phonate. Her mouth remained open in a facile smile.

Pencillamine was commenced but her condition continued to deteriorate until she was bedridden lying with her upper limbs flexed and she was unable to talk. However with time her speech returned sufficiently for her to manage a few words. Athetoid movements and the gross dystonia improved and she was able to leave her bed and

Fig 4 "Emily" Case IV AD (1982) Wilsons Disease.

move around with assistance. Her improvement continued and at age 21 years she is now a useful employee in a sheltered workshop making leather goods. She walks with a slow jerking gait with spasticity of all four limbs and still has a somewhat facile expression (fig 4). Voluntary speech is not possible but she can make herself understood when emotional. Her intelligence is not affected and she is able to communicate by printing out comments on a pocket computer.

Her brother (IVAE), born two years later, was well until December 1973 when he became jaundiced, with no preceding suggestion of infectious hepatitis and no drugs or injections had been given in the preceding weeks. The jaundice fluctuated during the next four months and the only other feature was marked emotional lability which had been present for three years. There were no abnormal movements and his speech was normal.

On examination in September 1974 there was some increased tone in all four limbs, he displayed dysidiadokynesia and an abnormal heel knee test. He had an enlarged firm liver and Kayser Fleischer rings were noted on slit-lamp examination. Biochemical investigations revealed low serum caeruloplasmin, low serum copper and increased urinary copper excretion following commencement of penicillamine (table 2). Biochemical investigations

Table 2 Biochemical findings

Case	Serum copper (12–24 mol/l)	Serum caeruloplasmin (200–450 mg/l)	24 hour urine copper (0–1.57 mol/day)	Liver biopsy
IV AD ("Emily")	6.0	127*	29.3*	Wilson's disease
IV AE	2.8†	37*	25.6†	Wilson's disease
IV X ("Beryl")	16.1*	278*	1.2†	Normal
IV Y	20.3*	—	1.3†	Normal

*—average of two separate readings

†—average of three separate readings

and liver biopsy of other family members did not reveal any significant abnormalities (table 2) and there was no suggestion of consanguinity in this branch of the family.

Discussion

In the early years it was felt that we were dealing with an atypical Westphal variant of Huntington's chorea and the family was included in a Queensland survey of the disease undertaken in the 1950's.³ When Bruyn⁴ published his authoritative review of over 700 articles on Huntington's chorea the torsion dystonias were not featured in the differential diagnosis and this is still the position today. In their seminal study of 70 recorded cases of the rigid and akynetic forms of Huntington's chorea Bittenbender and Quadfasel⁵ did not include one example of torsion dystonia among the 27 patients incorrectly diagnosed. Myriantopoulos⁶ when considering this group mentioned that in some the clinical signs and epidemiological features depart significantly from typical cases of Huntington's chorea and warrant separate consideration. Certainly the family group reported by Curran⁷ in his widely quoted article "Huntington's chorea without choreiform movements" sounds more like the family group described here than a variant of Huntington's chorea.

It is not surprising that idiopathic dystonia musculorum deformans is not included in the differential diagnosis of Huntington's chorea for the majority with onset in adult life do not have affected relatives and can be readily excluded by its distinctive features and absence of autosomal dominant inheritance. When "Beryl" developed violent jerking spasms of the trunk and limbs in association with torticollis in 1978 Huntington's chorea was clearly excluded from the differential diagnosis. Her involuntary movements were quite unlike the serpentine writhings of the arms and legs seen in affected members in the third generation, yet on rechecking they too had signs of torsion dystonia.

Zemen *et al*⁸ made an important contribution to the understanding of idiopathic dystonia musculorum deformans when they drew attention to the minor variants so frequently found in this disease. Among the cases outlined in this paper several are

expressing "formes fruste" of this disease—"Arthur" with transient torticollis and spastic dysphonia, "Beryl's" mother with kyphoskiolosis and mild blepharospasm, and a brother (IVAB) with spastic dysphonia as an isolated symptom; "Colin's" mother with mild involuntary movements of the hands and a shuffling gait and "Daisy's" mother with champing movements of the jaw and hyper-tonus of all limbs. I would regard all these people as having "formes fruste" of idiopathic dystonia musculorum deformans.

von Keyserlingk⁹ concluded that difficulties of speech occurring in families affected with dystonia should be considered as "formes fruste" of this hereditary condition. Marsden and Sheehy¹⁰ in a personal series of 53 patients with Mieg's disease (or Brueghel's syndrome) found 31 with involvement of the mouth and jaw by dystonic spasms which distorted speech and commented that the evidence linking that disease to the other types of torsion dystonia and other extra-pyramidal disorders is now quite impressive. Marsden¹¹ also encountered cases of isolated focal laryngeal dystonia where spastic dysphonia was the only manifestation.

In this family group whispering dysphonia may usher in the disease, may be present throughout life with no other dystonic signs or may be found in various combinations with spastic dysphonia, involuntary movements and other dystonic features. In my opinion this too is yet another "forme fruste" of idiopathic dystonia musculorum deformans, affecting the abductor muscles of the larynx while the more frequent manifestations of spastic dysphonia are produced from spasm of the abductor muscles involved in phonation. As Marsden pointed out, laryngeal dystonia would be a more appropriate a label for these symptoms.

The only other organic diagnosis which was considered in an affected family member was pseudobulbar palsy, but this was tentatively proposed because no other satisfactory label could be made to cover "Colin's" symptoms. Not one case has any real resemblance to this disease, or for that matter any of the other rare syndromes with symptomatic dystonia (such as Hallervorden-Spatz syndrome, Leigh's disease, neuro-acanthocytosis or dysphonia associated

with degenerative neurological disorders with cerebellar and pyramidal features).

When patients presented to doctors who did not know the family they were invariably diagnosed as having hysteria and many have been given extensive courses of hypnosis, psychotherapy of all different shades of emphasis, electro-convulsive therapy, acupuncture, faith healing techniques as well as tranquillising drugs and the like in a vain bid to have them talking again. Patients with whispering dysphonia as an isolated complaint have an absence of organic disease, cough without difficulty and on direct examination the vocal cords function normally. Additionally the dysphonia is worse under stress and there are incongruities such as an ability to talk normally during sleep and under the influence of alcohol and drugs; it is not surprising that a diagnosis of hysteria is made.

Diseases of the basal ganglia show a high incidence of behaviour disturbance in their course. Dementia is one of the characteristic features of Huntington's chorea and the personality changes which commonly occur such as aggressiveness, irresponsibility and general lowering of standards, are usually the early expression of a slowly progressive dilapidation of all cognitive functions.

In this family "Arthur's" mother, "Daisy" and her mother, and other affected members not described in this paper gradually deteriorated to a state of severe dementia and were very disturbed before intellectual deterioration became obvious. On this basis "Arthur's" explosive outbursts and "Daisy's" brother's violence can be seen as early manifestations of the family illness.

Basal ganglia disorders are also frequently complicated by a psychotic illness with paranoid or depressive features and again this appears to be secondary to an underlying organic lesion; this would also seem to be the explanation in the family group described here. The fact that drugs effective in controlling schizophrenic symptoms can cause dystonic and Parkinsonian features implies that there should be an inverse relationship between psychoses and basal ganglia disorders if the two are related to cerebral dopamine levels. Perhaps there is a fundamental common link between the two groups of diseases; if so the answer will be more complex than our present simplistic biochemical theories of schizophrenia

and depression lead us to believe.

Wilson's disease is frequently misdiagnosed in cases of juvenile Huntington's chorea and vice versa, but the biochemical changes and liver biopsies in "Emily" and her brother demonstrate convincingly that they do in fact have Wilson's disease. No other Australian members of the family have any suggestive signs of this diagnosis. It is now for the biochemists to explain a possible connection between these two clinically similar disorders; perhaps this may modify our thinking about the relationship between abnormalities of copper transport, and diseases of the basal ganglia.

References

- 1 Critchely Macdonald. Spastic dysphonia (inspiratory speech). *Brain* 1939; **62**:96-103.
- 2 Wallace DC. Huntington's chorea in Queensland—a not uncommon disease. *Med J Aust* 1972; **1**:229-310.
- 3 Wallace DC, Parker N. Huntington's chorea in Queensland: the most recent story. *Adv Neurol* 1973; **1**:223-35.
- 4 Bruyn GW. Huntington's Chorea—a review. In: *Handbook of Clinical Neurology Vol. 6. Disease of the Basal Ganglia*. Amsterdam: North Holland Publishing Company 1968:298-378.
- 5 Bittenbender JB, Quadfasel FA. Rigid and akinetic forms of Huntington's chorea. *Arch Neurol* 1962; **7**:275-88.
- 6 Myrianthopoulos NC. Huntington's Chorea: an appraisal of the genetic problem. *Proc. Int. Cong. Neurogenetics and Neuroophthalm.* Montreal 1969; **2**:509-16.
- 7 Curran D. Huntington's Chorea without choreiform movements. *J Neurol Psychopath* 1930; **10**:305-10.
- 8 Zemen W, Kaebler R, Pasamanick B. Idiopathic Dystonia Musculorum Deformans II the formes frustes. *Neurology (Minneapolis)* 1960; **10**:1068-75.
- 9 von Keyserlingk H. Zum Familiären Vorkommen der Idiopathischen Torsiondysonie. *Nervenarzt* 1980; **27**:34.
- 10 Marsden CD, Sheehy MP. Spastic Dysphonia, Meigs' disease and Torsion Dystonia. *Neurology (NY)* (in press).
- 11 Marsden CD. Dystonia: the spectrum of the disease in *The Basal Ganglia*. Yahr MD, ed. New York, Raven Press 1976:351-67.
- 12 Marsden CD. The focal dystonias. *Seminars in Neurology* 1982; **24**:324-33.