Hereditary Non-Progressive Torsion Dystonia with Intellectual Disturbance

Kenji Nakashima, Manabu Shimoda, Kazuhiko Sato, Eiji Nanba*, Masayuki Igo**, Kenzo Sato*** and Kazuro Takahashi

Three siblings of a consanguineous parents with involuntary movements are reported. The mother had only a very slight neck tremor, without any other neurological abnormality, and the father had died. The 38-year-old son (Case 1) complained of involuntary movements at the age of 6. His involuntary movements were observed in the tongue, perioral region and upper and lower extremities: jerky movements with dystonic features. The 46-year-old elder brother (Case 2) experienced involuntary movements at the age of 18. Involuntary movements were observed in the upper extremities; he also had torticollis and tremulous movements in the neck, and jerky movements in the perioral region. They showed gait disturbance and dysarthria. The 35-year-old sister (Case 3) also experienced involuntary movements. When she was writing, her involuntary movements were obvious: dystonia and myoclonic jerks. Tremor in the neck was also seen. Their intelligence was below average. We concluded that this family had hereditary torsion dystonia, with myoclonus, and low intelligence. This condition may be associated with an autosomal recessive gene.

Key words: dystonia, myoclonus, tremor, autosomal recessive

Introduction

There are some types of hereditary movement disorders with a non-progressive course (1–3). We treated a family of three siblings with non-progressive involuntary movements consisting of jerks and dystonic features, and a slight degree of intellectual impairment associated with an autosomal recessive trait. Typically, hereditary torsion dystonia has an autosomal dominant gene (4) and does not show intellectual disturbance (5). Therefore, this family showed a peculiar form of movement disorder. To our knowledge, no similar cases have been reported; here so we describe these three siblings with hereditary non-progressive torsion dystonia.

Case Reports

The parents of the patients were consanguineous: first cousins (Fig. 1). The father died of gastric carcinoma and liver cirrhosis at the age of 64. The mother showed only a very slight degree of postural tremor in the neck. Except for this neck tremor, she did not show any neurological abnormality. She stated that she had had normal intelligence and no movement disorders when she was young.

Case 1: 38-year-old male (Fig. 1: III-4)

Case 1 started to walk late, at the age of 20 months. He noticed involuntary movements in the perioral region at the age of 6 and in the upper extremities at the age of 12. When he was a primary school student, his academic scores were low. His involuntary movements and low degree of intelligence continued. To our knowledge, no similar cases have been reported; here so we describe these three siblings with hereditary non-progressive torsion dystonia.

Case 1 started to walk late, at the age of 20 months. He noticed involuntary movements in the perioral region at the age of 6 and in the upper extremities at the age of 12. When he was a primary school student, his academic scores were low. His involuntary movements and low degree of intelligence continued. When he was 32 years of age (1988), he was admitted to our clinic for these problems. He was admitted again at the age of 38 (1992). Compared to his condition at the age of 32, his involuntary movements were unchanged.

His intelligence was slightly low. His Wechsler Adult Intelligence Scale (WAIS) was 60 in the verbal IQ, 93 in the performance IQ and 70 in the total IQ; at the age of 32, he had shown WAIS scores of 62 in the verbal IQ, 79 in the performance IQ and 68 in the total IQ. He showed dysarthria and a slight degree of rigidity in his extremities. He spoke slowly and in a
low voice. Involuntary movements were observed in the tongue, perioral region, neck and extremities. Jerky movements in the perioral region and fingers, choreo-athetotic movements in the feet, and a slight degree of neck dystonia were seen. When he spoke, the involuntary movements in the perioral region were enhanced. The jerky movements showed variable amplitudes and non-rhythmic, repeated occurrence (Fig. 2). Tremulous movement of the left wrist was also observed. Grimacing, upward jerking of the eyebrows and gait disturbance were also noticed. Tendon reflexes were normal. No pathologic reflex was observed. Ataxia and sensory disturbance were not present.

The count and morphology of the red blood cells were normal. Hepatogram, serum lipids and amino acids, and serum beta-lipoprotein were normal. The level of serum copper (110 μg/dl: normal range 82–134) and ceruloplasmin (17 mg/dl: normal range 15–35) were normal. Serum calcium and phosphate were normal, and the level of serum parathyroid hormone was less than 0.6 ng/ml (normal range: less than 1.3 ng/ml). Serum levels of epinephrine, norepinephrine and dopamine, MHPG, 5-HIAA and HVA in the cerebrospinal fluid, and urinary levels of total catecholamine and 5-HIAA were normal.

The enzyme levels in the lymphocytes were normal: alpha-galactosidase 21.9 nmol/mg protein/h (normal range 24.2±3.5), beta-galactosidase 126.4 nmol/mg protein/h (106.8±13.0), alpha-glucosidase 11.2 nmol/mg protein/h (8.0±3.5), beta-glucosidase 1.85 nmol/mg protein/h (2.6±0.8), beta-hexosaminidase 1,060 nmol/mg protein/h (1,138±414), beta-hexosaminidase A 162.0 nmol/mg protein/h (165.2±522.0), alpha-mannosidase 26.2 nmol/mg protein/h (28.8±7.5), alpha-fucosidase 24.4 nmol/mg protein/h (32.5±5.0), beta-glucuronidase 30.2 nmol/mg protein/h (28.3±10.3), arylsulfatase A 73.0 nmol/mg protein/h (63.1±12.6) and hypoxanthine-guanine phosphoribosyl-transferase 108 nmol/mg protein/h (87–115). Cerebrospinal fluid was normal. Electroencephalography (EEG), nerve conduction velocities of the peripheral nerve, somatosensory evoked potentials (SEPs), and visual evoked potentials (VEPs) were normal. There was no EEG abnormality preceding the involuntary movements – no spike, nor movement related cortical potentials, as confirmed with back-averaging techniques. Electromyography (EMG) showed two types of involuntary movements; one was a continuous EMG discharge, and the other was jerky, repetitive EMG discharges (Fig. 2). Computerized tomography (CT) of the head was normal.

According to the methods described by Warner et al (6) and Nagafuchi et al (7), DNA analyses for Huntington’s disease and for dentatorubro-pallidoluysian atrophy (DRPLA) were performed. It was confirmed that the patient did not have Huntington’s disease or DRPLA.

L-dopa increased the involuntary movements. Trihexyphenidyl and tiapride were slightly effective. Clonazepam was effective for his involuntary movements. Haloperidol, isonicotinic acid hydrazide, bromocriptine, valproic acid, carbamazepine, and diazepam were not effective, although carbamazepine and diazepam were not used for a long period because they caused skin eruptions. Alcohol was effective for
Serum level of parathyroid hormone was less than 0.6 ng/ml. Calcium and phosphate were normal (Ca: 9.6 mg/dl, P: 3.9 mg/dl).
Levels of copper and ceruloplasmin were normal. Serum calcium and phosphate were normal (Ca: 8.8 mg/dl, P: 3.8 mg/dl).

The count and morphology of the red blood cells, hepatogram, and 6th decades, apart from choreo-athetosis (and sometimes slight intention tremor) no abnormal neurological signs, normal intellect, and familial incidence, probably autosomal dominant with reduced penetrance. In the present cases, though choreo-athetoid movements in the lower extremities of Case 1 were observed, the majority of jerky movements were considered as myoclonus, rather than chorea.

Mahloudji and Pikielny (11) proposed the diagnostic criteria of hereditary essential myoclonus, such as onset of myoclonus in the first or second decade, a benign course, often variable but compatible with an active life of normal span, dominant mode of inheritance with variable severity, normal intellect and absence of other neurological deficits. In the present cases, an autosomal recessive trait was suggested, and intellectual distur-

The jerky movements in the three patients were considered as myoclonus. In Case 1, a slight degree of torticollis, writer’s cramp, oromandibular dystonia and dystonia in the feet were observed. In Case 2, obvious torticollis, writer’s cramp and oromandibular dystonia were observed. In Case 3, writer’s cramp, torticollis and oromandibular dystonia were observed. Thus, these patients had dystonic features, associated with tremor and myoclonus, and were therefore they were diagnosed as having hereditary torsion dystonia.

There is some confusion in the classification of hereditary essential myoclonus, hereditary myoclonic dystonia, hereditary torsion dystonia and benign hereditary chorea (2). These disorders could show non-progressive courses, and the combination of jerky movements and dystonic features (2). Quinn (3) reported family cases with torsion dystonia, who had been previously reported as having hereditary progressive chorea without dementia. Essential features of benign familial chorea were defined by Sleigh and Lindenbaum (1): choreic or choreo-athetoid symmetrical movements, non-progressive, same intensity, or slight improvement from childhood into 5th, 6th, and 7th decades, apart from choreo-athetosis (and sometimes slight intention tremor) no abnormal neurological signs, normal intellect, and familial incidence, probably autosomal dominant with reduced penetrance. In the present cases, though choreo-athetoid movements in the lower extremities of Case 1 were observed, the majority of jerky movements were considered as myoclonus, rather than chorea.

Mahloudji and Pikielny (11) proposed the diagnostic criteria of hereditary essential myoclonus, such as onset of myoclonus in the first or second decade, a benign course, often variable but compatible with an active life of normal span, dominant mode of inheritance with variable severity, normal intellect and absence of other neurological deficits. In the present cases, an autosomal recessive trait was suggested, and intellectual distur-

The count and morphology of the red blood cells, hepatogram, serum lipids, amino acids and endocrinological studies, serum levels of copper and ceruloplasmin were normal. Serum calcium and phosphate were normal (Ca: 9.6 mg/dl, P: 3.9 mg/dl).
Serum level of parathyroid hormone was less than 0.6 ng/ml.

Cerebrospinal fluid, EEG, nerve conduction velocities of the peripheral nerve, CT of the head, SEPs and VEPs were normal.

Haloperidol was effective for her involuntary movements.

Discussion

These three patients had consanguineous parents, early onset of involuntary movements, slightly low intelligence and non-progressive course. All three patients showed the involuntary movements of tremor, dystonic features and myoclonus. Tremor was seen in the hand of Case 1, in the hands and in the neck of Case 2, and in the hand of Case 3 when writing. Tremor is often observed in dystonia. Myoclonus, chorea and tics may be associated with dystonia (5, 8–10). The jerky movements of myoclonus should be differentiated from those of chorea and tics. Myoclonus is a sudden, rapid, brief and simple muscle jerk. Chorea is irregular, unpredictable, brief jerk movement that flits from one part to another in a continuous, random sequence. In these patients, such a random flow of movement was not observed. Tics are repetitive, irregular stereotypic movements. In these patients, irregular vocalization was not observed, and we could not see the complex movements, which is observed in tics. The jerky movements in the three patients were considered as myoclonus. In Case 1, a slight degree of torticollis, writer’s cramp, oromandibular dystonia and dystonia in the feet were observed. In Case 2, obvious torticollis, writer’s cramp and oromandibular dystonia were observed. In Case 3, writer’s cramp, torticollis and oromandibular dystonia were observed. Thus, these patients had dystonic features, associated with tremor and myoclonus, and were therefore they were diagnosed as having hereditary torsion dystonia.

There is some confusion in the classification of hereditary essential myoclonus, hereditary myoclonic dystonia, hereditary torsion dystonia and benign hereditary chorea (2). These disorders could show non-progressive courses, and the combination of jerky movements and dystonic features (2). Quinn (3) reported family cases with torsion dystonia, who had been previously reported as having hereditary progressive chorea without dementia. Essential features of benign familial chorea were defined by Sleigh and Lindenbaum (1): choreic or choreo-athetoid symmetrical movements, non-progressive, same intensity, or slight improvement from childhood into 5th, 6th, and 7th decades, apart from choreo-athetosis (and sometimes slight intention tremor) no abnormal neurological signs, normal intellect, and familial incidence, probably autosomal dominant with reduced penetrance. In the present cases, though choreo-athetoid movements in the lower extremities of Case 1 were observed, the majority of jerky movements were considered as myoclonus, rather than chorea.

Mahloudji and Pikielny (11) proposed the diagnostic criteria of hereditary essential myoclonus, such as onset of myoclonus in the first or second decade, a benign course, often variable but compatible with an active life of normal span, dominant mode of inheritance with variable severity, normal intellect and absence of other neurological deficits. In the present cases, an autosomal recessive trait was suggested, and intellectual distur-

Case 2: 46-year-old male (the elder brother of Case 1, Fig. 1: III-1)

Case 2 started to walk at the age of 18 months. He experienced involuntary tremulous movements in the right hand at the age of 18. At the age of 28, he showed abnormal gait. At the age of 36, he showed torticollis in the neck. The degree of intelligence was low to moderate during his school years. He was admitted to our clinic at the age of 41 (1988).

His WAIS was 71 in the verbal IQ, 92 in the performance IQ and 78 in the total IQ at the age of 41; at the age of 46, he showed WAIS scores of 61 in the verbal IQ, 89 in the performance IQ and 69 in the total IQ and Kohs IQ of 108. Involuntary movements were observed in the upper extremities, neck and perioral region. Tremulous movements in the hands and the neck, torticollis and grimacing were seen. He elevated his left shoulder. When he tried to write, he declined his neck to the left. He could not write well with his right hand. The jerky movements of the perioral region produced retraction of the mouth angle. Dysarthria and gait disturbance were also seen. The tendon reflexes were normal. Pathologic reflex, ataxia or sensory disturbance were not observed.

The count and morphology of the red blood cells, hepatogram, serum lipids and endocrinological studies were normal. Serum calcium and phosphate were normal (Ca: 8.8 mg/dl, P: 3.8 mg/dl), and serum level of parathyroid hormone was less than 0.6 ng/ml. Serum levels of copper and ceruloplasmin were normal. Cerebrospinal fluid was normal. EEG, nerve conduction velocities of the peripheral nerve, CT of the head, SEPs and VEPs were normal.

Tiapride was slightly effective, and beta-blocker decreased neck tremor. Alcohol was slightly effective for neck tremor.

Case 3: 35-year-old female (the younger sister of Cases 1 and 2, Fig. 1: III-5)

Case 3 started to walk when she was 13 months old. At the age of 12, she noticed tremulous movements when she used her right hand. She was admitted to our clinic at the age of 30 (1987).

Her WAIS was 79 in the verbal IQ, 83 in the performance IQ and 80 in the total IQ. Involuntary movements were observed in the upper extremities and neck. She showed spasm in the arms, when she stretched them. When she was writing, the involuntary movements in her neck and right hand increased; jerky movements in the right arm and oromandibular dystonia were also observed. When using scissors, she had less neck tremor, than when writing. She showed dysarthria and gait disturbance. She had normal tendon reflexes and no pathologic reflex. Ataxia and sensory disturbance were not present.

The count and morphology of the red blood cells, hepatogram, serum lipids, amino acids and endocrinological studies, serum levels of copper and ceruloplasmin were normal. Serum calcium and phosphate were normal (Ca: 9.6 mg/dl, P: 3.9 mg/dl).
Serum level of parathyroid hormone was less than 0.6 ng/ml.
bance and other movement disturbances such as tremor and dystonia were also observed. Thus, these patients were different from hereditary essential myoclonus.

Patients with dystonia and myoclonus are categorized as having myoclonic dystonia (9). Recently, some familial cases with myoclonic dystonia were reported (2, 12, 13). Quinn et al (2) proposed that hereditary myoclonic dystonia is distinct from hereditary torsion dystonia based on the following points: more "shock-like" jerks, non-affectedness of the legs and dramatic response to alcohol. Patients with hereditary myoclonic dystonia, associated with intelligence impairment and an autosomal recessive trait, have not been reported yet. In Cases 1 and 2, alcohol was slightly effective in decreasing myoclonic or tremulous movements, but not dramatic. Myoclonic jerks in these cases were not "shock-like" and were compatible with those seen in hereditary torsion dystonia.

The mother showed only a very slight degree of postural tremor in the neck. However, she did not show any other neurological abnormality. We concluded that she did not have the same movement disorders as the three patients, and that they showed an autosomal recessive trait. In non-Jewish families with hereditary torsion dystonia, an autosomal recessive trait or intelligence impairment are not common (14). Fletcher et al (4) showed that idiopathic torsion dystonia in the United Kingdom was autosomal dominant inherited, and that there was no evidence for the existence of an autosomal recessive form. In order to confirm the diagnosis of these patients, we may be able to use molecular genetic analysis and/or find some biochemical evidence of the symptomatic dystonia in the near future. For the present, we conclude that this family may belong to an atypical form of idiopathic torsion dystonia with intellectual disturbance, non-progressive course, and movement disturbances of dystonia, tremor and myoclonus, perhaps associated with an autosomal recessive gene.

Acknowledgements: We are indebted to Dr. J. Goto and Prof. I. Kanazawa, Department of Neurology, Institute of Brain Research, University of Tokyo, for their analysis of DNA, and Miss S. Ito for her preparation of figures.

References
3) Quinn N. Benign hereditary chorea or hereditary idiopathic dystonia? Mov Disord 8: 401, 1993.