Heart Disease in Friedreich's Ataxia

— Observation of a Case for Half a Century —

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A case of Friedreich's ataxia was followed for 47 years, beginning in 1930; this patient had an abnormal electrocardiogram (flat or inverted T waves in leads II and III with prolonged QT interval) from the very beginning of the onset of neurological symptoms. Cardiac and neurological disturbances progressed slowly but steadily, and the patient died suddenly at the age of 67. The autopsy revealed typical findings of Friedreich's ataxia and hypertrophic cardiomyopathy with thickened left ventricular wall and myocardial fiber disarray. To the authors' knowledge, this is the longest continuous follow-up study of Friedreich's ataxia, and it will provide invaluable information on the natural history and development of the cardiac and neurological disorders in this condition. (*Jpn Circ J* 2000; 64: 229–236)

Key Words: Friedreich's ataxia; Hypertrophic cardiomyopathy; Myocardial fiber disarray; Natural history

Friedreich's ataxia is one of the rare heritable neurologic diseases, and the cardiac involvement associated with this disease was already described in the original work by Friedreich in 1863¹. Since then, these cardiac aspects have been a matter of intensive interest. The present report deals with a case of typical Friedreich's ataxia, in which electrocardiographic abnormalities were already recognized on admission, when ataxia was noted 2 years previously, suggesting the heart being involved at about the same time as the onset of neurological symptoms. The cardiac disease took a very slow course over half a century, and exhibited complex features. Recent observation of the rather frequent association of hypertrophic cardiomyopathy with Friedreich's ataxia might shed some light on the pathogenesis of both the diseases. We believe that this is the longest continuous follow-up study and provides an invaluable legacy which our predecessors gave to the medical profession of succeeding generations.

Case Report

In November 1930, a 20-year-old female with the diagnosis of Friedreich's ataxia was admitted to the Kyoto University Hospital complaining of gait disturbance, inability to perform fine movements, and speech disturbance. Her parents were cousins. Only one sister among her 9 siblings had Friedreich's ataxia, and she had died at the age of 22. The present patient had noted muscle weakness of the lower extremities at the age of 16. Speech disturbance and difficulty in walking began at the age of 18 after a full-term delivery. At the age of 38, she suffered a fracture of

the right tibia. After that, she was dependent on a wheel chair, with a gradual increase of thoracic kyphosis and muscle atrophy in the limbs. After the age of 52, a swaying sensation disabled her from sitting or walking. At the age of 66, her speech became very slow and explosive. The movement of her fingers and hands were clumsy, and there was marked thoracic kyphoscoliosis and pes cavus with hammer toes and claw hands. However, she never complained of cardiovascular symptoms throughout her 47 years of hospitalization.

Cardiovascular examination at the age of 20 revealed a regular pulse of 70/min and the blood pressure of 120/70 mmHg. The lungs were clear on percussion and auscultation. There were neither abnormal sounds nor significant murmurs on auscultation of the heart. At the age of 66, after 47 years of hospitalization, she had a regular pulse rate of 60/min. Her blood pressure was 120/80 mmHg. No dilatation of the jugular veins was present. The lungs were clear. On auscultation, a systolic ejection sound was audible in the third left sternal border, and there was a grade 2/6 low-pitched midsystolic murmur with an occasional third sound at the apex. The liver was palpable 3 cm below the ribs on the right midclavicular line. There was no edema in the lower extremities, and no other evidence of congestive heart failure.

Neurological examination at the age of 20 revealed slurred speech and horizontal nystagmus in the lateral gaze. The finger–nose–finger test and Romberg's sign were positive. Ankle and knee jerks were completely lost, but there was neither sensory disturbance nor muscle atrophy. During her long-term hospitalization, the neuromuscular disturbance progressed very slowly. Neurological examination at the age of 66 revealed spontaneous horizontal and vertical nystagmus, incoordination, dysmetria and decreased or absence of all tendon reflexes. In addition, hypotonicity of the muscles and moderate sensory impairment in the lower extremities were noted.

With the aid of an Educational Grant for Rare Diseases from the Japanese government, she spent all her life after the age of 20 in the Kyoto University Hospital until the age

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Fig 1. Computed tomography scan of the head at the age of 65. (Left) Dilatation of the cerebellopontine-angle cistern and enlargement of the fourth ventricle, suggesting marked cerebellar atrophy. (Right) Slightly enlarged lateral ventricles and lack of a markedly atrophic cerebrum.

Fig 2. (A) Antero-posterior chest X-ray at the age of 30 (1941). Enlarged cardiac silhouette with cardiothoracic ratio of 0.56. (B) Chest X-ray at the age of 66 (1977). Marked kyphoscoliosis and aneurysmal dilatation of the aorta. (Left) Antero-posterior view, (Right) lateral view.

of 67, when she was found dead in her bed during the night of August 6, 1977, without any preceding signs except for mild to moderate fever for the previous week.

Laboratory Examinations

At the age of 66, the erythrocyte sedimentation rate (34.8 mm/h) was slightly accelerated; serum aspartate aminotransferase (AST, SGOT) (76 mU/ml; normal range, 20–60) and creatine kinase (CK) (38 mU/ml; normal range, 5–30) were both slightly elevated, suggesting possible skeletal muscle damage. Lactate dehydrogenase (LDH) was 360 U (normal range, 50–406), but LDH isozyme was slightly elevated in fraction 1 (41.5%), which may imply latent myocardial damage. Serum electrolytes, serum cholesterol, total protein, albumin, fasting blood sugar and urinary catecholamines (epinephrine: 3.4 µg/day, norepinephrine: 41.4 µg/day) were all within normal limits. Radiocardiographic studies revealed that the cardiac output was 3.51 L/min, the cardiac index was 2.69 L min⁻¹ m⁻², and the stroke index was 40.8 ml beat⁻¹ m⁻², all of which were slightly lower than normal.

Computed Tomography

A computed tomography (CT) scan of the head (Fig 1) at the age of 65 demonstrated marked cerebellar atrophy, identified by the dilatation of the cerebellopontine-angle cistern and enlargement of the fourth ventricle, but the cerebrum was not markedly atrophic.

Electromyogram

Electromyograms in all 4 limbs showed the presence of fibrillation and fasciculation, giant spike and complex neuromuscular unit (NMU), and poor interference during forced contraction. The motor nerve conduction velocity of the posterior tibial nerve was decreased (39.1 m/s) and the sensory nerve action potential of the sural nerve was not evoked.

Chest X-ray

At the age of 30, a radiograph of the chest revealed a cardiothoracic ratio of 0.56 with protrusion of the left first and fourth cardiac segments. Slight kyphoscoliosis was present, but no abnormality of the lung field was noted (Fig 2A). At the age of 66, anteroposterior and lateral chest X-ray films showed marked kyphoscoliosis without abnormality in the lung. Marked dilatation of the aorta was noted (Fig 2B).

Radio-Isotope Angiogram

A radio-isotope angiogram showed kinking of a tortuous thoracic aorta just above the diaphragm, with narrowing at the level of the diaphragm. There was no evidence suggesting aneurysm of the thoracic aorta (Fig 3).

Electrocardiogram

In 1932, at the age of 21, the standard ECG showed flat or inverted T waves in leads II and III with prolongation of the QTc to 0.45 (Fig 4A). The QTc interval was calculated by the formula,

$$QTc = \frac{QT}{\sqrt{R-R}}$$

During the following 20 years, no particular changes of the ECG were noticed in the standard limb leads, but the abnormal ST-T segments intermittently reverted to normal. At the age of 43, the 10-lead ECG showed flat or inverted T

Fig 3. Radio-isotope angiography of the aorta with ^{99m}Tc at the age of 66 (1976). The lateral view demonstrates kinking of the tortuous descending aorta just above the diaphragm, with narrowing at the diaphragm. There was no evidence suggesting aneurysm of the aorta.

waves in leads II, III, -VL and CR₁₋₆ (almost equivalent to V₁₋₆), combined with prolongation of the QTc to 0.47 (Fig 4B). At the age of 51, the ECG simulated an inferior myocardial infarction, with deep and narrow Q waves in leads II, III and aV_F, and flat or inverted T waves in all limb and precordial leads, with prolongation of the QTc to 0.50 (Fig 4C). At the age of 53, left ventricular hypertrophy with depressed ST segments, inverted T waves and high voltage in the left precordial leads were noted. The QT interval was progressively prolonged (QTc: 0.51) (Fig 4D). At the age of 66, the ECG revealed left ventricular hypertrophy with ischemic changes of the ST segments and inverted T waves, but the abnormal Q waves in leads II, III and aV_F had disappeared. The QT interval became further prolonged (QTc: 0.52) (Fig 4E). Throughout the follow-up period, neither rhythm disturbance nor axis deviation was noted. There was a gradual but progressive prolongation of the QT interval.

Vectorcardiogram

A vectorcardiogram by the Frank system at the age of 66 revealed the maximum QRS vector located anteriorly and to the left with increased spatial magnitude. The initial 20-ms vector was located anteriorly and to the right with increased magnitude, but the magnitude of the posterior component was not increased. These findings were compatible with left ventricular hypertrophy, especially at the septal region. Fibrosis or necrosis of the posterior wall could not be ruled out.

Echocardiogram

The echocardiogram at the age of 66 showed features of hypertrophic cardiomyopathy; namely, the interventricular septum and the left ventricular posterior wall were thickened, measuring 14 mm and 12 mm in width, respectively, with an enlarged left ventricular cavity. Movement of the

Fig 4. Serial electrocardiograms. (A) Age 21 (1932). Standard limb leads only. Flat or inverted T waves in leads II and III with prolonged QT intervals (QTc: 0.45). (B) Age 43 (1954). Ten-lead ECG (photographic recording). -VL refers to the negative VL, one of the unipolar extremity leads. CR₁-6 are the unipolar precordial leads with the indifferent electrode in the right arm instead of the Wilson's central terminal. This lead system was used during a certain period of time at the Kyoto University Hospital. There are flat or inverted T waves in all limb and precordial leads with prolonged QT intervals (QTc: 0.47). (C) Age 51 (1962). Twelve-lead electrocardiogram (photographic recording). Deep and narrow Q waves in leads II, III and aV_F, simulating inferior myocardial infarction. Flat or inverted T waves in all limb and precordial leads with prolonged QT intervals (QTc: 0.50). (D) Age 53 (1964). Twelve-lead electrocardiogram (direct recording). High voltage with depressed ST segments and inverted T waves in the left precordial leads suggesting left ventricular hypertrophy. Flat or inverted T waves in all the rest of the leads. The QT interval was progressively prolonged (QTc: 0.51). (E) Age 66 (1976). Twelve-lead ECG (direct recording). Left ventricular hypertrophy with high voltage and ischemic ST-T changes in the left precordial leads. Abnormal Q waves in leads II, III and aV_F have disappeared. Further prolongation of QT intervals (QTc: 0.52).

interventricular septum and left ventricular posterior wall were poor in the middle to the apical area (Fig 5A,B).

Autopsy Findings

At death, the patient was small and kyphotic, weighing 40kg and with a height of 140 cm.

Heart

Gross Findings The heart weighed 350g and the surface was partially opaque white without pericardial adhesion, due to thickening of the pericardium.

Serial sections of the 3 major coronary arteries cut transversely at 0.2–0.3 cm intervals revealed 75% narrowing of the stem of the left anterior descending artery, 50% narrowing of the right coronary artery and 10% narrowing of the left circumflex artery without thrombus, secondary to atherosclerotic changes. Moderate to severe stenosis in the extracardiac branches of the coronary artery was not detected. The left circumflex artery was large, supplied the posterior surface of the left ventricle, and continued beyond to cross the crux of the heart.

The heart was incised serially and latitudinally at about

0.5-cm intervals and observed macroscopically. Both ventricles, especially the left, were hypertrophied; the left and right ventricles were 13 mm and 5 mm thick, respectively. There was no evidence of asymmetric hypertrophy of the left ventricle. All the cardiac valves were normal.

Microscopic Findings In approximately the middle third of the myocardium, fibrosis, degeneration and hypertrophy of myocardial fibers with large nuclei were noted throughout both ventricles. There was evidence of extensive whirled disarrangement (disarray) of the hypertrophied muscle fibers with short runs of the fibers interrupted by fibrosis (Fig 6). These changes were most severe in the postero-septal, posterior and lateral walls in the left ventricle, which are the areas nourished by the blood from the left circumflex artery, which showed only 10% luminal stenosis. Multiple and focal fatty infiltration, which was diffuse in the right ventricle, was evident in both ventricles. Inflammatory cell infiltration was rare. There was no evidence of coagulation necrosis or of moderate to severe stenosis of intramural coronary vessels. These findings suggest that the myocardial damage in this patient was compatible with hypertrophic cardiomyopathy, not ischemic changes. In the subepicardium and subendo-

Echocardiography K.O. (66yr.) 1976

Fig 5. Echocardiogram at the age of 66 (1976). (A) Two-dimensional parasternal long axis view demonstrates an enlarged left ventricular cavity. (B) M-mode study shows thickened interventricular septum, 14 mm, and left ventricular posterior wall, 12 mm. Movement of the interventricular septum and the left ventricular posterior wall is poor. Ao, aorta; LA, left atrium; LV, left ventricle; IVS, interventricular septum; LVPW, left ventricular posterior wall.

Fig 6. Microscopic findings of the myocardium. Note the marked disarrangement of bizarre-shaped myocardial fibers with hypertrophy and interstitial fibrosis (H&E, $\times 400$).

Fig 7. Transverse section of the upper thoracic cord. Marked demyelination of the posterior funiculi, more severely in the gracile (Goll) tract than in the cuneate (Burdach) tract, and in the anterior and posterior spinocerebellar tracts. Pallor of the pyramidal tract was also noted (Klüver-Barrera's stain).

cardium of the left ventricle, myocardial fibers were atrophic and contained brown pigment. There was no hypertrophy or abnormal arrangement of myocardial fibers or fibrosis in these portions.

Spinal Cord, Cerebellum, Cerebrum and Other Systemic Organs

Demyelination was evident in the posterior funiculi, more severely in the gracile (Goll) tract than in the cuneate (Burdach) tract, and in the anterior and posterior spinocerebellar tracts of the spinal cord (Fig 7). There was very slight atrophic degeneration of the anterior horn cells. The dorsal nucleus (Clarke's nucleus) was atrophic and degenerative. Loss of Purkinje cells and degeneration of the granule neurons were prominent in the cerebellum. There were degeneration and cell loss in the dorsal root ganglia. Cerebral arteries were generally sclerotic. There was degeneration of nerve cells in the cerebrum (weight: 1270 g) and the brain stem. Atrophy of the lower leg muscles, kyphoscoliosis, and peculiar deformities of the hands and the feet, such as claw hand and pes cavus, were noted. There was generalized arteriosclerosis, and congestion in the lungs (left: 210 g, right: 300 g), the liver (815 g), the kidneys (left: 100 g, right: 95 g) and the spleen (55 g). Atrophy of the following organs was noted: the adrenals (left: 2.8 g, right: 3.2 g), the ovaries (left: 1.7 g, right: 1.8 g), the thyroid gland (10.5 g), and the pancreas (50 g).

Anatomical Diagnosis

Friedreich's ataxia with cardiac involvement, particularly hypertrophic cardiomyopathy.

Discussion

Cardiac involvement in Friedreich's ataxia has been extensively investigated since the original report by Friedreich in 1863. The most important diagnostic modality of the cardiac involvement in Friedreich's ataxia has been the ECG²⁻⁴ Hewer reported electrocardiographic abnormalities in 100% of cases examined⁵ The most frequent abnormalities were sinus tachycardia and labile, flat, biphasic or inverted T waves in leads I, II, III, aV_F and the left precordial leads^{3,6,7} Left ventricular hypertrophy was commonly found in patients with slight to moderate involvement of the heart.

In the advanced cases, supraventricular premature beat, paroxysmal atrial tachycardia, atrial fibrillation, atrioventricular block and bundle branch block were reported. In addition, right ventricular hypertrophy with right axis deviation was also observed.^{6,8} Deep Q wave simulating myocardial infarction often appeared in leads II, III, aV_F and/or the precordial leads^{2,6,7} Some authors stated that this finding was suggestive of interventricular septal hypertrophy⁸ In the present patient, cardiac morbidity was followed by ECG for 47 years, and at one time exhibited a pattern simulating myocardial infarction, which may suggest interventricular septal hypertrophy. These abnormal Q waves, however, disappeared in later recordings. The loss of the abnormal Q waves may indicate cancellation of electric potential in the hypertrophic septum due to compensatory hypertrophy of the free wall of the left ventricle, or due to fibrosis of the interventricular septum. In the vectorcardiogram, Gregorini et al found left ventricular hypertrophy, abnormal axis deviation, ischemic changes or diffuse myocardial damage in all 10 asymptomatic patients even

without kyphoscoliosis.⁹ In both the scalar ECG and vectorcardiogram, So et al found disturbances of the repolarization in 94% of their 17 cases and signs of left ventricular hypertrophy in 27%.¹⁰

In the present patient, the repolarization disturbance was observed early in her life, manifested as inverted T waves, followed by prolongation of the QT interval, suggesting progressive myocardial damage or sympathetic nerve disturbance.¹¹⁻¹³ It has been reported that 56% of the patients with this disease die of heart failure.⁵ The present patient had had no cardiac complaints throughout her life, in spite of extensive and complex cardiac involvement, including myocardial fiber disarray, diffuse fibrosis of the myocardium, and left ventricular hypertrophy, including hypertrophy of the interventricular septum. Reduced physical activity due to the neurological disturbance, as well as the markedly slow progression of the cardiac morbidity, may have resulted in a balanced circulatory demand and supply relationship.

Gauthier noted that cardiac involvement in Friedreich's ataxia approached 100% at the time of death, based on previously published autopsy reports.¹⁴ Cardiac involvement in this disease was referred to grossly as a biventricular hypertrophy, especially of the left ventricle, with microscopic findings of hypertrophy and degeneration of muscle fibers and interstitial fibrosis with cellular infiltration, combined with obliteration of intramural coronary arteries.^{7,15,16} Hypertrophic obstructive cardiomyopathy was found in some cases of Friedreich's ataxia by cardiac catheterization and echocardiography.¹⁷⁻¹⁹

Goodwin speculated that the disturbances of sympathetic nerve supply to the heart muscles or an abnormality of catecholamine metabolism or response might result in the hypertrophic obstructive cardiomyopathy.²⁰ In patients with Friedreich's ataxia, sinus tachycardia, rhythm and repolarization disturbances were found, as described previously. It is therefore suspected that abnormal sympathetic discharge plays an important role in the genesis of heart disease in Friedreich's ataxia.²¹

James and Fish proposed that the cardiac involvement in Friedreich's ataxia is caused by narrowing or obliteration of the small coronary arteries in the myocardium. They claimed that this arteriopathy, like the nervous system disease, is also inherited and that the 2 traits coexist.¹⁵ On the other hand, based on his careful counting of coronary arteries of different diameters, Hewer concluded that the vast majority of cardiac arteries were not obviously narrowed, and that the arterial narrowing that does occur was secondary to involution of the cardiac muscle, and not the cause of diffuse myocardial fibrosis.⁹

It is unlikely that the cardiac disturbances are secondary to neurological ones, because the ECG abnormalities sometimes appear before the neurological manifestations^{3,4,7} and in autopsy cases there are no pathological changes in the medulla or the vagal nerve.^{2,4,14}

Recent reports have indicated the association of hypertrophic cardiomyopathy with Friedreich's ataxia. Smith et al reported that approximately one-third of their group of patients with Friedreich's ataxia had hypertrophic cardiomyopathy.²² It is now established that hypertrophic cardiomyopathy is a heritable disease caused by an autosomal dominant gene with incomplete penetrance.²³ Affected members of the same family with Friedreich's ataxia often show similar abnormal findings in the ECG and vectorcardiogram,^{6,7,9} suggesting that they have similar cardiac

disease. Some affected siblings have been reported to have hypertrophic cardiomyopathy.^{18,19} Friedreich's ataxia is also been known to be a heritable disease caused by an autosomal recessive trait. Recently, the locus of the genetic defect and the responsible gene were identified,^{24,25} and it is now believed that mitochondrial dysfunction contributes to the pathophysiology of Friedreich's ataxia.^{26,27} Moreover, it was demonstrated that in Friedreich's ataxia, the frequency of cardiac involvement and the severity of left ventricular hypertrophy are related to the number of GAA trinucleotide repeats.^{28,29} These studies suggest that hypertrophic cardiomyopathy is a specific cardiac disease of classical Friedreich's ataxia, and that the cardiac and neurological abnormalities represent pleiotropic effects of the same deleterious gene.^{2,14,22}

Summary

A typical case of Friedreich's ataxia with follow-up observation for half a century is reported with reference to changes in the cardiac involvement. Cardiac disturbance was recognized from a very early age, and progression of this cardiac morbidity was markedly slow. Despite extensive and complex cardiac involvement, the patient never had cardiac complaints throughout her life. This may have been due to a well-maintained equilibrium between the slowly progressive myocardial impairment and the decreasing circulatory demand due to limited physical activity resulting from the neurological disturbances. Both the cardiac and neurological abnormalities in this disease are suspected to stem from a common genetic origin.

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