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FRIEDREICH’S ATAXIA AND ITS CARDIAC MANIFESTATIONS
HENRY H. GALE, M.D.*

Associated system disease is a particularly interesting facet of medicine. The association of neurologic disease and cardiovascular disease is well known in syphilis, less known in myotonia atrophica and in progressive muscular dystrophy and relatively unknown in Friedreich’s ataxia. This is particularly interesting since Friedreich in his original description in 1863 of six cases described clinical cardiac abnormalities in five.

Friedreich’s ataxia is classified among the hereditary ataxias, (Table 1) a group of closely related disorders having a familial basis. They usually breed true but there are occasionally transitional forms. They are characterized by localized degeneration of parts of the nervous system in various combinations and by a slowly progressive course.

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<th>Hereditary Ataxias (2)</th>
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<td>3. Sanger-Brown’s ataxia.</td>
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<td>4. Friedreich’s ataxia.</td>
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<td>5. Marie’s cerebellar ataxia.</td>
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<td>6. Progressive cerebellar degeneration.</td>
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These diseases share certain common pathologic features. There is degeneration of ectodermal elements of the nervous system, the nerve fibres are more severely affected than the ganglion cells and the cerebellum and spinal cord are smaller than normal and bear the brunt of the degenerative process. With all these common features clinically and pathologically it is not surprising that differential diagnosis is often difficult. This review is to re-emphasize the importance of the cardiovascular examination and in particular the electrocardiogram as an aid in differential diagnosis.

Friedreich’s ataxia is a chronic, progressive, heredo-degenerative disease having its onset usually between 5 and 15 years, though abnormalities such as pes cavus may be discovered in apparently normal members of affected families in early childhood. It is the most common of the hereditary ataxias.

The characteristic pathology of the nervous system reveals degenerative changes especially in the posterior and lateral columns of the spinal cord. These changes are most severe in the lower cord and diminish towards the medulla. The degeneration involves the fasciculus gracilis and cuneatus, the dorsal spino cerebellar tracts, the corticospinal tracts and the cells of Clarke’s column. Occasionally the medulla oblongata and cerebellum are involved. The dorsal roots are involved but rarely the anterior horn cells. There is a reactionary gliosis in the degenerated fiber tracts.

The cardinal neurologic symptoms of Friedreich’s ataxia include the following. Ataxia is invariably present. It is most marked in the lower limbs. The patient walks

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Loiseau reviewed the literature in 1938 putting forward the theory of degeneration of vagal nuclei resulting in sustained sympathetic hypertonia. In his collected series there were sixteen autopsied cases, six with cardiac hypertrophy, four with dilatation and three with valvular lesions. Fatty degeneration was found in six.

In 1946 Dorothy Russell reviewed four autopsied cases, three of whom had clinically manifested heart failure. Hypertrophy of the heart, diffuse interstitial myocardial fibrosis, and fatty degeneration with normal valves and endocardium was present in all four cases. Two cases revealed atheromatous involvement of the coronary arteries. She proposed the "toxin" theory as the underlying etiologic factor in both cardiac and neurologic manifestations. She did not find any significant changes involving the vagal nuclei.

From the clinical and electrocardiographic viewpoints Evans and Wright in 1942 described thirty-eight cases. Twelve showed definite and significant ECG abnormalities. An additional ten cases revealed minor abnormalities. The more widespread the nervous changes the more heart involvement was present. A positive family history gave more cardiac involvement and affected members of the same family tended to show identical ECG changes.

In 1946 Piron theorized that the cardiac manifestations are caused by lesions of the nervous system. In support of this he presented a case of a twenty-two year old male who had a fatal myocardial infarction after a skiing injury that damaged the dorsal spine. The similarity of the cardiac manifestations and nervous system lesions in this case to those observed with Friedreich's ataxia led him to consider the cardiac involvement in Friedreich's ataxia an additional manifestation of neurologic damage.

More recently Nadas, Alimurung and Sieracki in 1951 described the ECG changes in more detail. They found patterns uniformly showing inverted T waves in the complexes representing left ventricular potentials, that is AVF (in vertical hearts) and V5 and V6. Some of the chest leads showed inverted T waves in V1 through V4 which can occur normally in children. The inverted T's in V5 and V6 are however completely abnormal suggesting ischemia of the left ventricle. On the basis of the now numerous reports of anginal syndrome, autopsy reports of atheromatous involvement of the coronary arteries and now ECG evidence of coronary artery disease, theories have been advanced that the coronary artery involvement may play a role in the production of myocardial fibrosis. There is, alas, no explanation of the etiology of this arterial change.

The pathology of the heart and coronary arteries has been inconsistent and has not followed any definite pattern. Grossly there is cardiac hypertrophy involving all chambers but especially the left ventricle. The endocardium and valves are normal while the coronary arteries are highly variable ranging from normal to diffuse atheromatous involvement with or without obstruction. There is seen to be fatty degeneration and diffuse interstitial fibrosis of the myocardium with dilatation. Occasionally pericardial effusion is found with fibrous pericardial thickening and epicardial petechiae and hemorrhage.
Friedreich's Ataxia

Microscopically there is found to be destruction of the cardiac muscle by focal coagulation necrosis of its fibres. There is collagenous tissue replacement of the degenerating myocardium with a compensatory hypertrophy of the remaining un-involved fibres. The nuclei of the muscle fibres are large, vacuolated and hyperchromatic. The cross-striations are usually absent. There are longitudinal fibrils occupying the peripheral sarcoplasm with a granular cytoplasm in the center of the cell and with lipochrome pigment present. The Purkinje fibres of the node and conducting system are separated by fibrous tissue and a sparse cellular infiltrate, usually lymphocytes and eosinophiles but occasionally mast cells or neutrophilic leukocytes.

Pathologic examination of the remainder of the organs revealed only chronic passive congestion in liver, spleen and lungs with occasional pleural effusions.

It is noteworthy that the cardiac disorder was the presenting complaint in a significant number of patients. Clinically the signs and symptoms varied with the heart size, that is, with the stage of the disease. The common findings were arrhythmias, congestive failure, and anginal syndrome.

Many different arrhythmias have been reported including normal sinus rhythm with numerous atrial or ventricular premature systoles, paroxysmal atrial tachycardia, atrial fibrillation, parasystolic ventricular rhythm, bundle branch block and complete heart block. These are probably due to involvement of the conducting system by fibrosis with disruption of the normal pathways.

The described murmurs were also variable and were heard over the mitral, aortic and pulmonary areas. The murmurs varied in timing being either systolic or diastolic (proto-, mid-, or presystolic). In numerous autopsies there was complete failure to account for these murmurs by organic valvular damage.

Considerable difficulty is often encountered during life in deciding whether there is coexistent rheumatic valvulitis to account for the heart murmurs. Careful search histopathologically has failed to reveal these characteristic changes in all the series reviewed. The murmurs then are probably due to the marked dilatation of the left ventricle relative to the mitral orifice. Further evidence in this regard is that tachycardia often emphasized the murmurs showing the importance of blood velocity in the production of the murmur.

The presence of electrocardiographic abnormalities suggests the eventual onset of heart failure or arrhythmia. Cardiac signs and symptoms can occur in the absence of left ventricular enlargement especially in association with rapid irregular heart action. The addition of cardiac enlargement however worsens the prognosis and heralds further or progressive cardiac failure. The arrhythmias and congestive failure respond for a time to the standard therapeutic measures for their relief.

The etiology remains obscure. Early workers ascribed the myocardial changes to bulbar sclerosis involving the vagal nuclei and thereby facilitating sympathetic
overactivity. Careful review histopathologically has failed to corroborate this theory. Later an unknown toxic agent was held responsible for both the myocardial and the neurological lesions. Fatty degeneration may be caused by toxins or by lack of oxygen. The bacterial toxins are organic poisons, and fatty degeneration is frequently seen in acute and chronic infections. Phosphorous, chloroform and alcohol are the most common inorganic poisons resulting in fatty degeneration. Pernicious and secondary anemias both cause insufficient oxygenation leading to fatty degeneration. Investigation along these lines has failed to unearth any clues etiologically.

The association of abnormal ECG changes and a positive family history with affected members of one family showing the same type of change certainly suggests the inheritance of a lethal gene affecting both heart and nervous system. There are no racial, geographic or social factors related to the disease. The primary cause appears to be an inherited abnormality. Since the condition usually appears before the age of puberty, the chance of inheritance beyond a single generation is reduced. The lethal gene may result in true Friedreich's ataxia, Friedreich's ataxia associated with the cardiac disorders, variants of Friedreich's, and intermediate forms of the degenerative processes within the central nervous system. Certain authors have suggested the heart alone may be affected.

Roth reports a family with Friedreich's ataxia in a mother and a daughter and heart disease in five other members of the same family over three generations. The mother with Friedreich's ataxia had six siblings, four of whom had heart disease. Her father died suddenly of heart disease at age 62 and one brother died at 34 of heart disease. The details of the cardiac disorder is unknown in these cases but it does lend support to the concept of a lethal gene responsible for Friedreich's ataxia and familial cardiac disorders.

CONCLUSIONS

Friedreich's ataxia should not be regarded as a disease of the nervous system alone but as a degenerative disease of unknown origin with a predilection for the nervous and cardiovascular systems.

Since it has been estimated that electrocardiographic changes are observed in 30 per cent of patients with Friedreich's ataxia, the electrocardiogram is a diagnostic aid which may help to establish the diagnosis of Friedreich's ataxia when the neurologic manifestations are not altogether typical. While a normal tracing does not exclude diagnosis of this disease, an abnormal record lends valuable support to the diagnosis. Conversely in a young patient showing signs of coronary insufficiency or unexplained cardiac symptoms a complete neurological investigation may establish the diagnosis.

The frequent presence of myocardopathy in Friedreich's ataxia is now well established, although the cause remains obscure. The rarity of its observation may be due to failure to investigate this association. The diagnosis of Friedreich's ataxia should demand a thorough evaluation of the cardiac status.
Friedreich's Ataxia

REFERENCES


