Virchows Arch [Pathol Anat] (1982) 397:301–311

Virchows Archiv A

The Cardiomyopathy of Wilson's Disease

Myocardial Alterations in Nine Cases

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Summary. Though myocardial alterations are well recognized in haemochromatosis, little attention has been paid to the cardiac changes in Wilson's disease. To define the extent of myocardial degeneration in newly diagnosed or chronically treated Wilson's disease, we reviewed the autopsy findings in 9 cases with this condition. We compared our observations with those in 3 control cases, selected for comparable age and with liver disease having no known association with cardiac degeneration. Our results revealed cardiac hypertrophy in 5 out of 9 cases of Wilson's disease. There was evidence of interstitial and replacement fibrosis, intramyocardial small vessel sclerosis and focal inflammatory cell inflammation to a variable degree in all cases. One case had AV nodal degeneration, and a 15 year old boy had severe atherosclerosis of the left main coronary artery. Two patients died suddenly, presumably secondary to an arrhythmia; one of these patients had the most marked myocardial alterations. We could not correlate these changes specifically with the tissue levels of copper, treatment with D-penicillamine, or the presence of cirrhosis. We conclude that there are definite morphological abnormalities in the hearts of patients with Wilson's disease consistent with a cardiomyopathy. Though the myocardial changes were non-specific, the fact that 2 patients died suddenly, suggests the need for a prospective study of cardiac function in these patients in the future.

Key words: Wilson's disease – Cardiomyopathy – Copper toxicity – Myocardial degeneration

The deposition of copper in the liver and brain of patients with Wilson's disease leads to recognized morphological degeneration and clinical dysfunc-

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Supported in part by NIH Grants HL 21756 and NIAMD 17702, and The Foundation for the Study of Wilson's Disease, Inc.

0340-1227/82/0397/0301/$02.20

tion (Scheinberg and Sternlieb 1965; Sass-Kortsak 1965; Goldfischer and Sternlieb 1968). Though cardiac alterations have been associated with intoxication by other metals, particularly lead (Khan et al. 1977), cobalt (Olsen 1972), and iron (Nicholas et al. 1971; Buja and Roberts 1971), myocardial abnormalities secondary to copper overload are less well known. Although two recent reports describe histological (Azevedo et al. 1978) and ultrastructural (Kaduk et al. 1980) cardiac damage in Wilson's disease associated with increased tissue copper levels, several papers report increased myocardial copper content without morphological damage (Butt et al. 1958; Bottiger and Mollerberg 1959; Brandt 1972). To determine the extent of myocardial degeneration in Wilson's disease, we reviewed the autopsy findings in 9 cases with this condition. We conclude that a clinical and pathological cardiomyopathy can occur in Wilson's disease.

Materials and Methods

During the years 1960–1980, 9 autopsies were performed on patients with documented Wilson's disease in the Bronx Municipal Hospital Center and the Hospital of the Albert Einstein College of Medicine. Two of these autopsies did not have adequate histological sections of the heart for evaluation and they were eliminated from the study, but 2 cases, submitted for review and consultation by outside institutions, were included.

All tissue had been fixed in neutral formalin, embedded in paraffin, and stained with haematoxylin and eosin, and Masson's trichrome. Sections were prepared from each case and were stained for copper employing 2 methods: 5(p-dimethylamino-benzylidene) rhodanine (Eastman No. 2748) (Lindquist 1969; Irons et al. 1977), and rubeanic acid (dithiooxamide) (Eastman) (Uzman 1956). All cases had quantitative determination of cardiac copper content utilizing spectrophotometric analysis of unembedded tissue (Morell et al. 1968). The normal heart contains 16.5 μg/g dry weight copper, with a range of 10.0–22.9 μg/g (Fell et al. 1968).

Each case had 4–5 histological sections of myocardium selected mainly from the left ventricle available for analysis. Sections of left atrium, coronary artery, and cardiac conduction system were reviewed from several cases. Two pathologists independently evaluated all sections for the degree and localization of interstitial and replacement fibrosis, and graded the cases 1+ to 3+ depending on the extent and severity of the changes. We also evaluated the intramyocardial small muscular vessels (50 to 200 microns in diameter) for the presence of vessel wall sclerosis and perivascular fibrosis, of the type reported in alcoholic heart disease (Factor 1976). The presence or absence of interstitial inflammation was noted in each case. Since the tissue sections were evaluated retrospectively, it is possible that the original prosectors selected myocardium for sectioning which was grossly abnormal, thereby biasing the sample. In most cases this is unlikely because the gross descriptions were normal or did not refer to myocardial lesions (7/9 cases, see Table 2). However, we cannot entirely rule out the possibility that errors were introduced in our grading of the histological alterations.

The clinical summaries were reviewed for evidence of overt symptomatology referable to the heart, and laboratory or clinical evidence of cardiac disease. The duration of therapy with D-penicillamine was recorded for each patient.

Control cases were selected from the autopsy files of our affiliated institutions. For inclusion, patients had to be between 10 and 50 years of age (comparable to our study group), with significant hepatic fibrosis or cirrhosis. Cases were eliminated if the liver disease was secondary to a condition known to be associated with cardiac disease, i.e. chronic alcoholism, haemochromatosis, or schistosomiasis with pulmonary involvement. Three cases fulfilled these criteria. It should be noted that in our general hospital population, most patients with cirrhosis in the appropriate age range are chronic alcoholics.

Results

The clinical features of the 9 cases are summarized in Table 1. The mean age of the group was 29.4 years. All but 2 cases were diagnosed as having Wilson's disease before their acute hospitalization, and they were treated with D-penicillamine chronically. Cases 2 and 6 were treated with D-penicillamine for only a brief period before their death. Five patients died secondary to either hepatic failure or ruptured oesophageal varices. One patient (case 1) died following the onset of Goodpasture's syndrome due to D-penicillamine therapy, while another (case 7) had necrotizing enteritis and sepsis. Patients 4 and 8 died suddenly and unexpectedly, most likely from acute cardiac arrhythmias.

Two patients had clinical manifestations of cardiovascular disease. Case 4, the only patient in our series without hepatic cirrhosis, had recurrent tachycardia for 21 years. His electrocardiograms revealed supraventricular

Table 1. Clinical features of patients with Wilson's disease

Case #	Age	Sex	Age at diagnosis	Duration of therapy (D-penicillamine)	Cardiac signs and symptoms	ECG	Other
1	47	M	44	3 years	0	WNL	Uraemia, Haemoptysis, Goodpasture's Syndrome, Cirrhosis
2	20	F	20	3 days	0	N/A	Acute Hepatic, Failure, Cirrhosis
3	26	M	22	4 years	0	N/A	Ruptured Oesophageal, Varices, Cirrhosis
4	25	M	21	4 years	Recurrent tachycardia, palpitations	Supraventricular tachycardia, PAT, VPC's	Sudden Death
5	54	F	34	17 years	II/IV SEM	WNL	Hepatic Failure, Cirrhosis, Sepsis
6	15	M	15	1–2 months	0	N/A	Hepatic Failure, Cirrhosis, Sepsis
7	33	M	20	13 years	0	WNL	Sepsis, Necrotizing Enteritis, Cirrhosis
8	22	F	18	4 years	0	N/A	Neurological Dysfunction, Cirrhosis, Sudden Death
9	24	F	16	8 years	0	N/A	Ruptured Oesophageal Varices, Cirrhosis

Abbreviations: N/A = not available; SEM = systolic ejection murmur; PAT = paroxysmal atrial tachycardia; VPC's = ventricular premature contractions

Table 2. Pathology of hearts in Wilson's disease

Case #	Heart weight (g)	Gross observations	Interstitial (IF) and replacement fibrosis	Intramyocardial small vessel changes	Myocardial inflammation	Other	Myocardial copper content (μg/g)
1	400	Normal	Mild IF (1+)	Medial and intimal hyperplasia	perivascular	hypertrophied myocardial fibers with disorganization	16, 19
2	200	Normal	Mild IF (1+) right ventricle	Marked medial hyperplasia; perivascular fibrosis	perivascular and interstitial	Focal acute ischemia	69, 89
3	400	Normal	Moderate IF (2+)	Marked medial and intimal hyperplasia; perivascular fibrosis	Perivascular and interstitial		228
4	375	Scarred ventricular septum, normal coronary arteries	Mild to severe IF (3+), Focal replacement scars left ventricle	Medial hyperplasia, perivascular fibrosis	Focal, in conduction system	Degeneration fibrosis AV node	13, 14
5	350	Normal	Severe IF (3+) atrium	Medial hyperplasia and perivascular fibrosis, atrium	0	0	1,428, 1,268
6	320	Non-bacterial thrombotic endocarditis, mitral valve and left ventricular cavity, left coronary artery occlusive atherosclerosis	Severe IF (3+)	Medial and intimal hyperplasia.	Interstitial	75–85% occlusion left main coronary artery. Myocardial fiber disorganization. Myxomatous degeneration mitral valve.	138, 148
7	450	Left ventricular hypertrophy	Mild IF (1+)	Focal intimal and medial thickening, perivascular fibrosis	Interstitial	Focal myocardial disorganization	49, 118
8	220	Normal	Moderate IF (1–2+)	Marked vascular sclerosis, perivascular fibrosis	0	Acute contraction band necrosis	21
9	320	Focal diffuse fibrosis	Mild IF (1+)	Perivascular fibrosis	Interstitial	Normal AV node	12.5, 18.8

tachycardia, paroxysmal atrial tachycardia, and unifocal ventricular premature beats, and were the only abnormal electrocardiograms in this series. Case 5, the oldest patient in this group, had a grade II/VI systolic ejection murmur, with no clinical symptomatology.

Pathological Findings

Table 2 summarizes the gross and histological alterations of the 9 cases, and tabulates the myocardial copper content. Table 3 provides the clinical and pathological features of the 3 control cases.

The mean cardiac weight was 337 g, with 5 out of 9 cases greater than 350 g, in the overtly hypertrophied range. Gross abnormalities were not prominent, with the exception of ventricular scarring observed in cases 4 and 9, and non-bacterial thrombotic endocarditis of the mitral valve in case 6. This latter patient also had ventricular mural thrombi, and subtotal occlusion of the left main coronary artery.

Histological alterations were observed in every case. Focal, severe (3+) interstitial fibrosis was noted in 3 cases, while the other 6 cases had mild (1+) to moderate (2+) fibrosis (Figs. 1 and 2). Case 4, with a long history of cardiac arrhythmias, also had focal replacement scars present throughout the left ventricle (Fig. 3), and had fibrosis and degeneration in the atrioventricular node. Every case had varying degrees of intramyocardial small vessel sclerosis and perivascular fibrosis. In several instances (cases 2, 3 and 8) these alterations were severe, leading to significant luminal narrowing (Fig. 4). Myocardial inflammatory cell infiltration, including mast cells, was observed in all but cases 5 and 8 (Fig. 5). Mast cells were often associated with fibrosis in the myocardial interstitium, were seen around blood vessels, and were observed in the section of AV node taken from case 4. Sections from the left main coronary artery of case 6 revealed 75–85% atherosclerotic occlusion (Fig. 6); other vessels from this 15 year old boy were histologically normal. Significant atherosclerosis was not detected in any other patient.

Histochemical preparations stained for copper with rubeanic acid and rhodanine were uniformly negative in all 9 Wilson's disease cases. This was

Table 3. Clinical and pathological features – control cases

Case #	Age	Sex	Diagnosis	Heart Weight (g)	Cardiac Pathology
1	14	F	Chronic active hepatitis, cirrhosis	260	Focal, minimal perivascular fibrosis
2	37	M	Narcotic addict, cirrhosis	340	Mild vascular sclerosis and perivascular fibrosis
3	12	M	Submassive hepatic necrosis, early cirrhosis	290	Focal, mild interstitial fibrosis of right ventricle

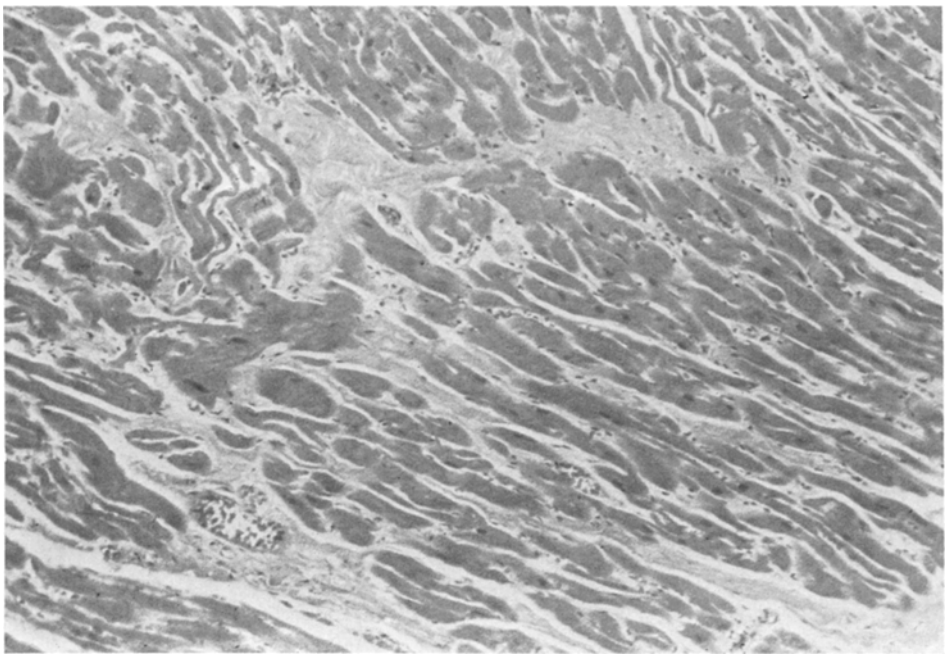

Fig. 1. Moderately severe (2–3+) interstitial fibrosis associated with focal cellular hypertrophy and disorganization is present in this left ventricular section from case 8. Haematoxylin-eosin, ×155

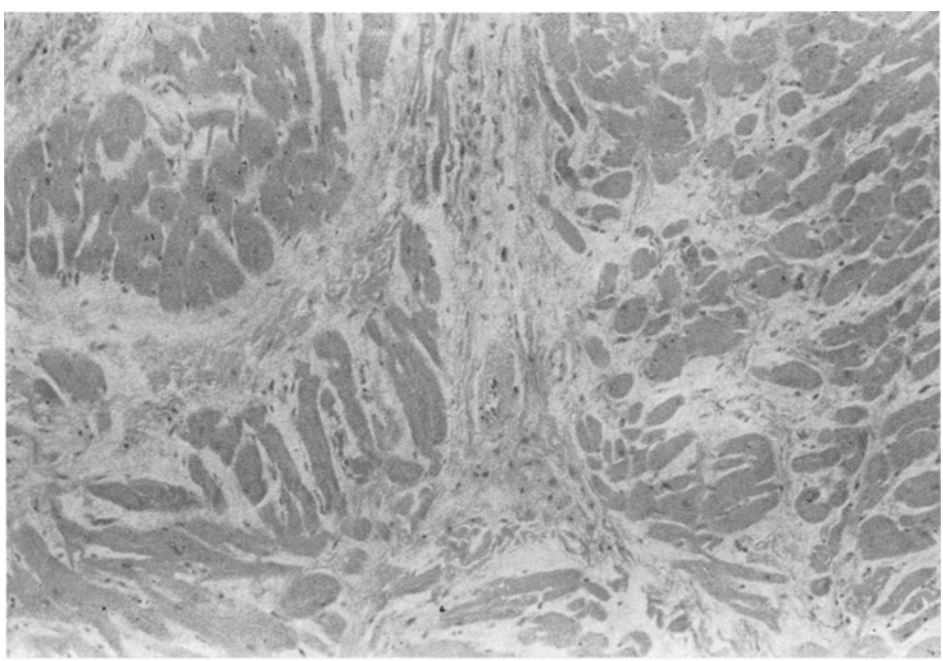

Fig. 2. There is severe (3+) interstitial fibrosis, cellular hypertrophy and mild disorganization in this left ventricular section from case 6. A small artery in the center of the field has a thickened wall, with luminal narrowing. A few mononuclear inflammatory cells are located in the perivascular connective tissue. Haematoxylin-eosin, ×155

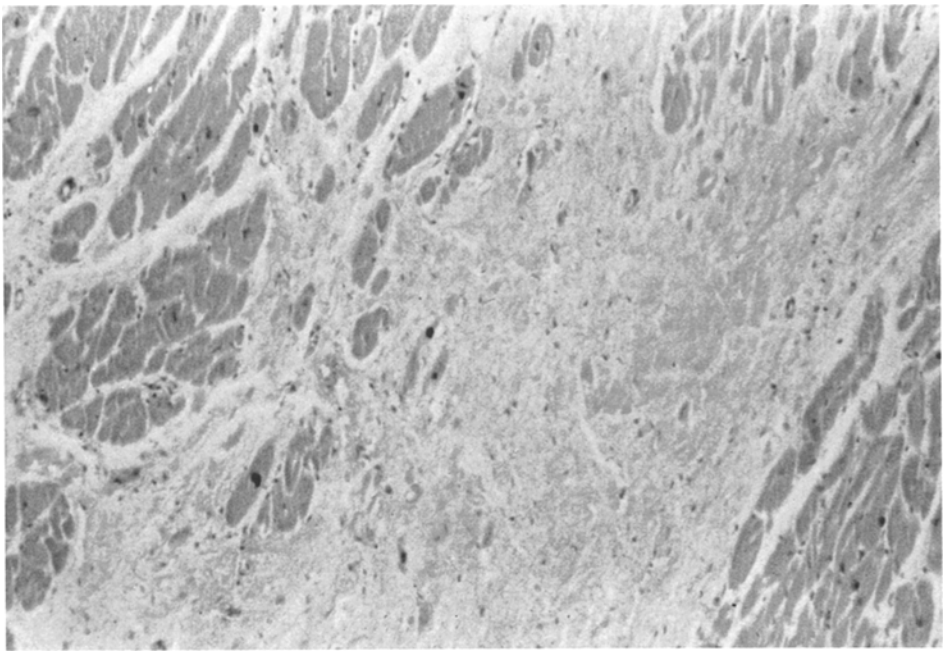

Fig. 3. One of several focal replacement scars from case 4 can be seen in this section of left ventricular subepicardium. In contrast to interstitial fibrosis where connective tissue surrounds viable myocytes, here collagen has been deposited in an area of prior cellular necrosis. Haematoxylin-eosin, × 155

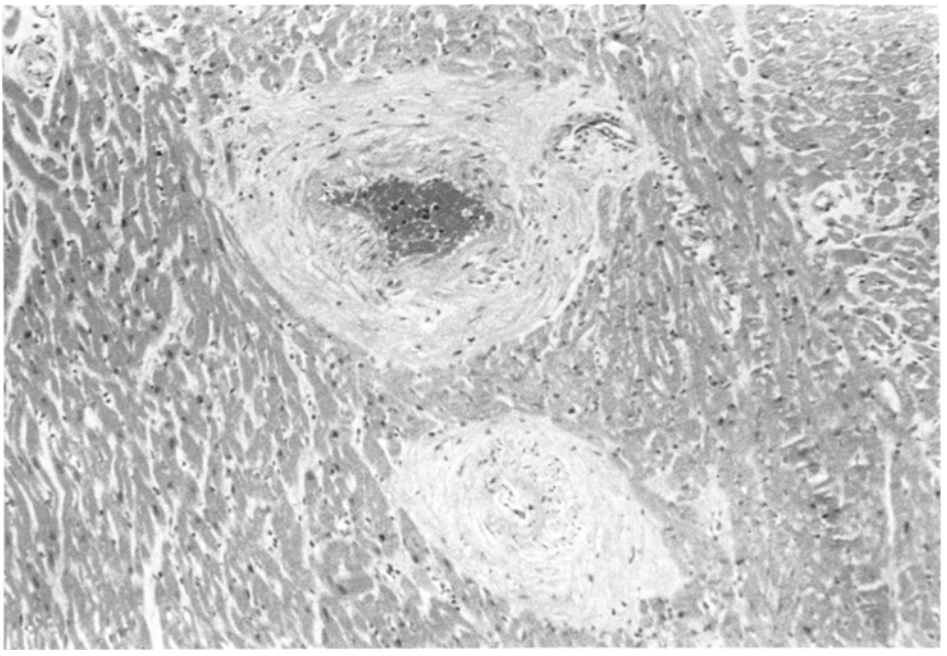

Fig. 4. Two intramyocardial small muscular arteries can be seen in this field from the left ventricle of case 8. Both vessels have increased perivascular connective tissue which encroaches on the surrounding myocardium, and both have sclerotic, thickened walls. The lower vessel has subtotal luminal occusion. Haematoxylin-eosin, × 155

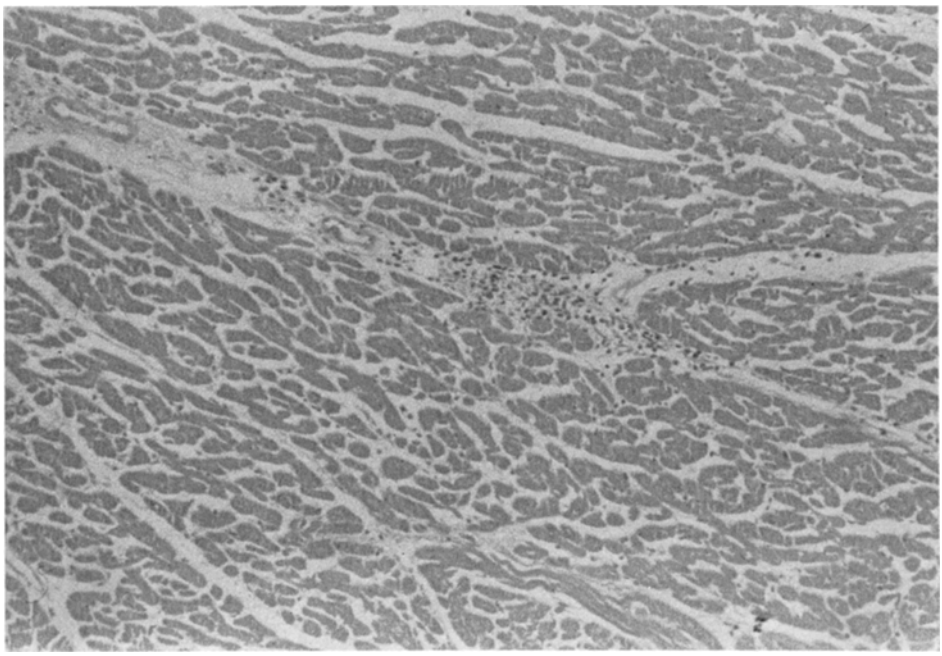

Fig. 5. There is a heavy interstitial, inflammatory cell infiltrate in this left ventricular section from case 3. The infiltrate is composed of histiocytes, lymphocytes, and mast cells. Haematoxylin-eosin, × 70

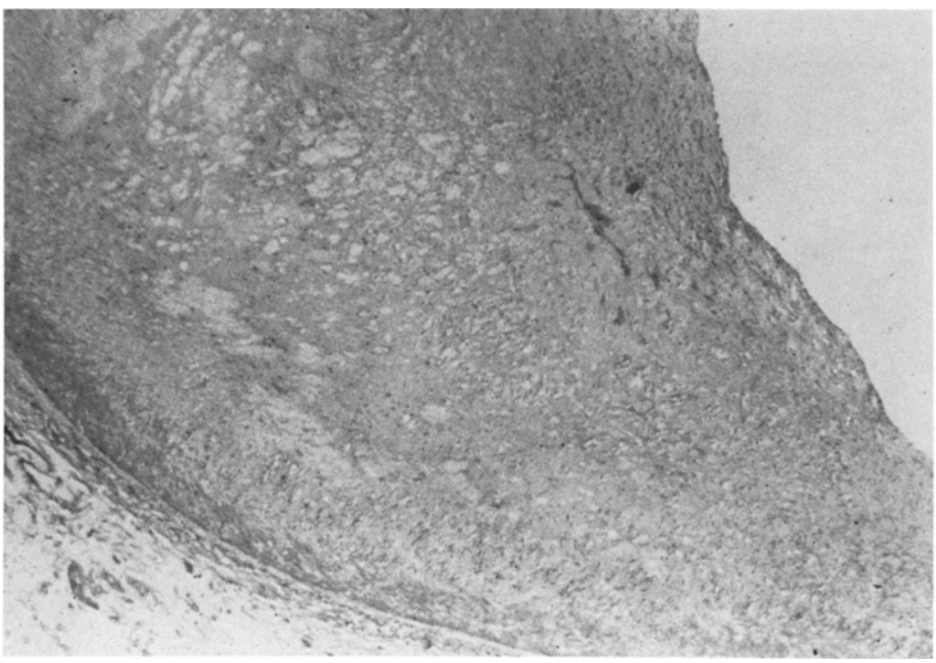

Fig. 6. A portion of the severely atherosclerotic left main coronary artery from case 6, a 15 year old boy. The adventitia is to the lower left, and the lumen is to the upper right. The intimal plaque is composed of collagen, foam cells, and cholesterol clefts, and is otherwise similar to atherosclerotic plaques seen in adults without Wilson's disease. Trichrome stain, × 155

true even in case 5, with approximately 100× normal copper content in the myocardium, analyzed spectrophotometrically. In the 8 other cases copper levels were elevated moderately in 4 (Table 2). In general, we were not able to correlate the degree and extent of myocardial and vascular damage with the copper content determined at autopsy. Case 1, with normal copper content, had only mild histological alterations, while cases 4, 8, and 9, also with normal copper levels, had degenerative lesions ranging from mild to severe.

Myocellular hypertrophy with focal disorganization of the fiber orientation was observed in 2 hearts weighing over 400 g and in the 320 g heart from the 15 year old boy, which probably also represents a significant increase of cardiac weight for this adolescent. It may be that this type of alteration is related to myocardial hypertrophy. Despite increased heart weights, none of these patients had a history of hypertension, nor did any, except case 6, have significant coronary atherosclerosis.

None of the 3 control cases with cirrhosis had abnormal hearts, with the exception of mild, focal interstitial and perivascular fibrosis, and mild vascular sclerosis (Table 3). Analysis of the copper content of the myocardium was not done in any control patient.

Discussion

The major pathological findings in this study of the myocardium in Wilson's disease included the presence of interstitial and replacement myocardial fibrosis, intramyocardial small vessel disease, focal myocarditis and cardiac hypertrophy. In addition, we found AV nodal degeneration in a patient with sudden death, and left main coronary artery occlusive atherosclerosis in a 15 year old boy. These alterations are non-specific, but they are similar to those observed in haemochromatosis (Buja and Roberts 1971; Arnett et al. 1975), as well as in other cardiomyopathies (Roberts and Ferrans 1975; Olsen 1979; Factor et al. 1980). Their existence in a relatively young group of patients without other significant aetiology for the development of heart disease, suggests the possibility of a direct relationship between Wilson's disease and cardiac degeneration.

There are similarities between the cardiomyopathy associated with Wilson's disease and the cardiac alterations seen in haemochromatosis. Both diseases are typified by the presence of hepatic fibrosis, and intracellular storage of copper or iron within lysosomes (Goldfischer and Sternlieb 1968; Koss and Factor 1979; Goldfischer et al. (1980).

Haemochromatosis is often associated with disturbances in cardiac rhythm which may (Vigorita and Hutchins 1979) or may not (Buja and Roberts 1971) correlate directly with the histochemical demonstration of iron in the conduction system. Both cases 4 and 8, with sudden, unexpected deaths presumed to be arrhythmic, suggest that conduction system dysfunction may be significant in Wilson's disease. Copper concentrations were increased in 5 of 9 hearts in which spectrophotometric analysis was carried out, but histochemical staining failed to show where the copper was localized.

A recent report (Kaduk et al. 1980) describing cardiomyopathy in Wilson's disease, suggested that mitochondrial alterations were the consequence of the accumulation of myocardial copper. The published electron micrographs however, showing dense storage material in single membrane bounded structures, without cristae, were more consistent with secondary lysosomes.

Could the non-specific myocardial alterations in Wilson's disease be due to treatment with D-penicillamine, or to the concomitant development of hepatic cirrhosis? Several features of this group lead us to believe neither is the case. First, of our 9 patients, cases 2 and 6 had been treated for only 3 days and less than 2 months, yet both patients had myocardial alterations, including significant coronary artery atherosclerosis (in case 6).

Nor does hepatic cirrhosis appear to play a major role in the genesis of cardiac degeneration in Wilson's disease. Case 4 did not have cirrhosis, yet he had the most severe myocardial alterations of the entire group, and he succumbed from a cardiac cause. Among the 3 control cases with cirrhosis, none had significant myocardial abnormalities. This compares to 6 of 9 Wilson's disease patients with either severe fibrotic changes or marked intramyocardial vascular degeneration. It is possible, however, that the intramyocardial small vessel disease in the Wilson's disease hearts was related to hepatic damage, since we have shown similar vascular lesions in patients with alcoholic liver disease (Factor 1976).

In conclusion, we believe that there are definite morphological abnormalities in the hearts of a number of patients with Wilson's disease. These alterations are non-specific, and in some cases of limited severity; however, in our series cardiac degeneration may have contributed to the death of at least two patients. Prospective study of such patients will be required to define the clinical prevalence and significance of this cardiomyopathy.

Acknowledgement. We would like to thank Drs. Z. Wessely, D. Miller, and A.H. Ropper for allowing us to include their patients in this study. We appreciate the efforts of Ms. Bernice Coltoff-Schiller for histochemistry, Ms. Dinah Wortsmann-Carroll for histology, and Ms. Camilla Davis for secretarial assistance.

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Accepted July 22, 1982