CLINICOPATHOLOGIC CORRELATIONS

De Subitaneis Mortibus

IV. Coronary Vessels and Conduction System in Homocystinuria

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SUMMARY

Conspicuous abnormalities of the coronary arteries and veins and of the sinus node, atrioventricular (A-V) node and His bundle are described in the heart of a boy dying with congenital homocystinuria. The unproven possibility of transient disturbances of cardiac rhythm or conduction is discussed relative to the pathogenesis of the bouts of unconsciousness with and without convulsions characteristic of the disease. Factual information on the stability or instability of electrical activity of the heart in such patients is particularly needed because of the possibility of treatable aspects of an otherwise seemingly inexorable process.

Additional Indexing Words: Platelet dyscrasia Coronary venous pathology Sinus node A-V node Sudden death

CAREFUL STUDY of rare diseases can be broadly rewarding in clinical medicine. The same may be said of esoteric manifestations of less rare diseases, and within the memory of many of us it was held that "to know all about tuberculosis (or about syphilis) was to know all about medicine." Although its clinical expression as an inborn error of metabolism was first described barely a decade ago, congenital homocystinuria offers many valuable lessons for internists in general and those working with cardiovascular diseases in particular. Distinctive clinical features of patients with this disorder include bouts of unconsciousness with and without convulsions, mental retardation, a duck-like gait, fine and fair hair, malar flush, various musculoskeletal deformities, ectopia lentis (and associated glaucoma), and an unusual form of fatty liver. The inborn error in methionine metabolism results in characteristic elevations of methionine and homocystine in the blood and increased excretion of homocystine in the urine.

While the general clinical features and laboratory abnormalities in congenital homocystinuria are distinctive, there are certain cardiovascular and hematological manifestations which have a special relevance to the pathogenesis of cardiac disease broadly and to its expression in certain events such as syncope and sudden death. Extensive intimal proliferation is found in focal segments of many arteries of patients dying with homocystinuria, and this includes both the cerebral and coronary arteries. Thromboembolic episodes are cardinal features of the clinical picture, and platelet function is abnormal. The purpose of this report will be to consider the coronary disease and platelet abnormalities together and to include from one case an instructive examination of the specialized system of the heart responsible for the generation and conduction of the normal electrical impulse.

Clinical Information

J. R. was a boy who was born with homocystinuria and who died shortly before the age of seven years. Most aspects of his case have been the
subject of two previous reports\textsuperscript{1, 3} He exhibited characteristic clinical features including fair hair, blue eyes, intense malar flush, mental retardation with irritability and generally refractory behavior, bilateral ectopia lentis, bilateral genu valgum and pes cavus, and right-sided spastic hemiplegia.

At the age of fifteen months he had first developed a series of generalized convulsions followed by the appearance of the hemiparesis. There were no abnormal findings in the cerebrospinal fluid, but the electroencephalogram exhibited diffuse abnormalities without consistent focal location. A pneumoencephalogram demonstrated diffuse cerebral atrophy attributed to thrombosis of one of the cerebral venous sinuses.

Both major and minor convulsive seizures occurred sporadically until the last year of his life, when they became more numerous and more severe. His course the last few months was one of progressive deterioration. One day he suddenly developed marked cyanosis, stertorous breathing, and died within 30 minutes.

**Figure 1**

These photomicrographs illustrate the spectrum of sizes of narrowed small coronary arteries. Reference bars indicate the magnification here and in all subsequent illustrations (all Goldner trichrome stain). A, B and C are from left ventricular myocardium.

**Figure 2**

Narrowing of larger coronary arteries is illustrated here from two different branches of the right coronary artery. The intimal proliferative process is similar to that in smaller branches.
Special Necropsy Findings

Previously reported pathological findings included occluding thrombi within the left renal artery and at the bifurcation of the aorta, almost complete infarction of the left kidney, and thrombotic occlusions of the celiac axis and hepatic artery. In the brain there were multiple healed infarctions and atrophy, particularly of the left side; the dura mater was thick and the superior sagittal sinus was extensively obstructed with recanalized fibrous tissue. In general the most impressive lesions were vascular, involving both arteries and veins. To varying degrees these were found in the spleen, pancreas, colon, thyroid, thymus, brain, liver and kidney. Larger vessels such as the celiac axis and iliac arteries were narrowed by the same histopathological process, which was one of intimal proliferation and fibrosis. The wall of the aorta was dilated and thin with focal degeneration and metachromasia in the tunica media.

From the present special subsequent study of the same heart the following was observed. There were intimal proliferative and hyperplastic lesions in coronary arterial branches of all sizes (fig. 1-3). The extent of these varied from minor encroachment on the lumen to its virtual obliteration. Focal fibrosis throughout the myocardium of all four chambers of the heart was commensurate with the scattered focal arterial lesions, although we were not able to relate single arterial lesions with single foci of fibrosis. No large or confluent area of necrosis or fibrosis was present. Venous and venular proliferative lesions were also observed (fig. 4, 5) but did not appear as numerous or as extensive as the arterial ones, although no effort to quantify the relative prevalence was made. In addition to the chronic luminal-narrowing lesions, there were abundant focal arterial and venous thrombi in various stages of organization but composed predominantly of platelets (figs. 3, 4). With pseudo-
pods and cytoplasmic extensions from aggregated platelets, these "activated" forms suggest an ongoing antemortem process.4

Special attention was directed to the blood supply and to the histological appearance of the sinus node, atrioventricular (A-V) node and His bundle. There was no significant narrowing of the main coronary arteries either proximal or distal to the origin of the sinus node artery and A-V node artery, although a number of large branches of the main trunks were markedly narrowed as they coursed over and into the ventricular myocardium (fig. 2). The narrowing process consisted of intimal proliferation and hyperplasia identical to that described in the arteries of many other organs of the body.3,5

The sinus node was well formed and normally located, but its internal structure (which normally contains a dense collagen matrix)6 included excess collagen in the form of focal fibrosis (fig. 6). The lumen of the sinus node artery was intermittently narrowed in its course to and through the sinus node by the typical intimal proliferation. Both the main sinus node artery and numerous branches of it in the crista terminalis contained platelet aggregates (fig. 7).

The A-V node artery contained numerous focal narrowings and the same sort of platelet aggregations as elsewhere in the coronary circulation (fig. 8). The A-V node and the His bundle also exhibited focal fibrosis (fig. 9, 10) similar to that described for the sinus node, and at the point of maximal abnormality in the His bundle approximately one third of its normal mass was replaced by collagen.

Discussion

Congenital homocystinuria is a disease with protean clinical and biochemical features. Two of
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these which deserve special consideration on the basis of findings in the case being reported here are the possible role of electrical instability of the heart in the pathogenesis of some of the characteristic neurologic abnormalities, and the relationship of the platelet dyscrasia to the pathogenesis of the vascular lesions and certain focal ischemic consequences.

There is clearly no dearth of plausible explanations for the typical bouts of unconsciousness with and without convulsions, and for the mental retardation. Either or both may be functional and morphologic abnormalities of the central nervous system itself, or may be the consequence of recurring vascular occlusions (both arterial and venous). On the other hand, syncope with or without convulsions also occurs as the consequence of certain forms of cardiac electrical instability. The successful use of electronic pacemakers to treat these latter disorders has led to a new appreciation of the magnitude of this problem in clinical cardiology. To our knowledge the hypothesis that some of the neurological manifestations of congenital homocystinuria may be attributable to abnormalities in cardiac rhythm or conduction has not previously been reported. A need to test the hypothesis can be best appreciated from the corollary possibility that this may be one feature of the underlying disease susceptible to effective treatment.

In the present case there were distinct histopathological abnormalities both in the sinus node and in the A-V junctional region, on the basis of which one must consider possible periodic malfunction both of impulse formation and of conduction. With the abundance of alternative explanations for syncope and sudden death in this condition, it is understandable that electronic monitoring of cardiac

Figure 7
Arterial branches within the sinus node are shown in more detail here, with platelet stars again identified in B.

Figure 8
Considerable narrowing of the AV node artery is shown here from a point near its origin A and several millimeters downstream, after the artery has entered the node B. At both calibers the artery contains extensive intimal proliferation. In B the arrow indicates sludging of platelets along the lining of the vessel.

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rhythm may have been neglected. One must also anticipate that if such monitoring were conducted, some of the neurological episodes may be found to be wholly or predominantly non-cardiac in nature while others may be associated with preceding or concomitant significant disturbances in electrical stability of the heart. In any event, it is a sufficiently logical and pressing question to merit examination, and if dysrhythmia or heart block is a factor, to consider possible forms of prophylactic therapy.

Two related diseases further illustrate why electrical instability of the heart must be suspected

Figure 9
The posterior margin of the AV node is seen in A, containing the artery shown at higher magnification in Figure 8B. CFB is the central fibrous body. There is excessive focal fat and fibrosis in A, and interlacing of excess collagen within the main body of the AV node in B. Recurring focal ischemia is a plausible basis for these abnormal changes.

Figure 10
Two sections of the His bundle are shown from near its midpoint A and just prior to its bifurcation into branches B. Even at the lower magnification in B it is apparent that a significant portion of the normal cross-sectional area (outlined by arrows) is missing and replaced by collagen.
in congenital homocystinuria. *Thrombotic thrombocytopenic purpura* is characterized by, among other features, thromboembolic episodes, syncopal attacks and multiform neurological disorders, and by a distinct platelet dyscrasia. While there are multiple possible explanations for the neurological problems, it has been documented that acute heart block and destructive lesions in the His bundle occur in thrombotic thrombocytopenic purpura. The several striking similarities between patients with congenital homocystinuria and those with Marfan’s syndrome have been the basis of recurring discussion since the first description of the former disease. In addition to previously reported features shared by both diseases, we may now add the existence of vascular and other structural pathology of the sinus node, A-V node and His bundle. Indeed, the findings in the present case are remarkably similar to ones described in Marfan’s syndrome where the clinical electrocardiographic abnormalities have been documented.

If recurring bouts of significant dysrhythmias or heart block actually do occur in patients with congenital homocystinuria, then their very early recognition in a child’s life may not only be crucial to the effective treatment of fainting and convulsions, but would also deserve consideration in the possible prevention of mental deterioration. While focal thrombotic lesions have been demonstrated in the vessels of the brain, it has been questioned whether this is sufficient explanation for either the clinical neurological problems or for the reported neuropathological findings in the brain. Not only may cardiac rhythm disturbances contribute to focal cerebral ischemic attacks, but transient cessation or marked slowing of the cerebral circulation may secondarily lead to thrombosis there and in other organs, particularly in subjects with manifest abnormalities of platelet function as have been demonstrated in congenital homocystinuria. Furthermore, primary malfunction of the brain can have profound influence on cardiac electrical stability, making the entire process a vicious cycle.

This brings us to a consideration of the pathogenesis of the vascular lesions demonstrated in the heart of the present case. Coronary occlusion and acute myocardial infarction occurred at an early age in four patients of the study by Schimke and his colleagues. Two photomicrographs in their report illustrate marked narrowing of a large coronary artery. However, whereas they remark that smaller coronary branches appear unaltered, in our case the predominant abnormalities were in the smaller coronary arteries, including those supplying the centers of electrical impulse formation and conduction. There is no evidence either of predilection for or sparing of the coronary branches, and the similarity of the coronary lesions to those in vessels of other organs would suggest that whatever the pathogenesis, it is similar throughout the body.

Coexistence of both arterial and venous narrowings and the presence of platelet aggregates both places in the heart would indicate that either transient or more prolonged obstruction of the coronary circulation in patients with congenital homocystinuria may be doubly severe. Furthermore, just as one must consider a train of events relative to the pathogenesis of the neurological events, it is possible that acute changes in the rhythm or conduction of the heart may lead to stasis of the coronary circulation with secondary activation of platelets, compounding of the focal ischemia in the heart and further disruption of the normal electrical stability.

Beginning with the early reports of this inborn error of metabolism, investigators have been concerned with the relationship between the platelet dyscrasia and the pathogenesis of the vascular lesions which is one of the cardinal features of the clinical picture. It has been suggested that platelets deposit on sites of structural defects in vascular lining as is known to occur in many experimental and clinical examples. It has also been suggested that the inborn metabolic error has a direct influence on various components of the vessel wall, based on experimental and histopathological evidence. On the other hand there is equally persuasive evidence that abnormal behavior of platelets may play a key role ab origine in the pathogenesis of arterial disease and of sudden cardiac death. Both in gout and in diabetes mellitus, two other diseases with an inborn error of metabolism, abnormal platelet function has been demonstrated. The fact that patients with either gout or diabetes mellitus or congenital homocystinuria have in common both a platelet dyscrasia and impressively severe coronary disease supports the possibility of an important causal relationship between the two.

References


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