Cirrhosis of the Liver Simulating Congenital Cyanotic Heart Disease*

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During the last 25 years, 20 patients with cirrhosis of liver with severe cyanosis and gross clubbing simulating congenital cyanotic heart disease were subjected to cardiac catheterization and angiography, splenography, liver function tests, and liver biopsy. No portopulmonary fistulas could be demonstrated. The cyanosis and clubbing were secondary to right to left intrapulmonary shunting across multiple tiny pulmonary arteriovenous fistulas. In 15 cases, selective pulmonary angiography revealed discrete arteriovenous fistulas. In five cases, the angiogram did not reveal any convincing evidence of pulmonary arteriovenous fistulas. In two of these five cases, peripheral vein contrast echocardiography demonstrated right to left intrapulmonary shunting and seems a sensitive investigation. Open lung biopsy in one case showed evidence of pulmonary arteriovenous fistulas.

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Central cyanosis in cirrhosis of liver was first described by Fluckiger1 in 1884, and subsequently, there have been a few stray reports describing desaturation of arterial blood in this condition. In 1966, Hansoti and Shah4 described a rare but distinct clinical entity in seven cases of cirrhosis of liver who presented with dyspnea, intense cyanosis, and gross clubbing that simulated congenital cyanotic heart disease.

During the last 25 years, one of us (R.C.H.) investigated 20 such patients who were referred as cases of congenital cyanotic heart disease. Nonavailability of any concise report on this distinct clinical entity prompted us to review clinical, investigative, and other features of these cases.

PATIENTS AND METHODS

The study includes 20 patients with cirrhosis of liver who had severe cyanosis and gross clubbing simulating congenital cyanotic heart disease seen by one of us (R.C.H.) between 1962 and 1987. All the patients had biopsy-proven cirrhosis of liver.

A detailed clinical history was obtained in every case with special reference to duration of cyanosis, clubbing, dyspnea and other symptoms, as well as history of antecedent jaundice, alcoholism, umbilical sepsis, hematemesis, and protein or caloric malnutrition. A complete clinical examination was performed in every case.

Routine investigations consisting of hematocrit, chest roentgenogram, a 13-lead electrocardiogram, barium examination of the esophagus, liver function tests, and spectrographic examination of the blood were performed in all patients. A needle biopsy specimen of the liver was obtained in 19 patients and an open biopsy in one. An open lung biopsy of the right lower lobe was performed in one case. Every patient was subjected to right heart catheterization, selective right ventricular and main pulmonary artery angiography. Selective right and left lower lobe pulmonary arteriography was performed in cases where main pulmonary artery injections were nondiagnostic. In ten patients, additional left heart catheterization, left ventriculography, and aortography were performed. The angiography was performed on AOT changer at the rate of four films per second during the years 1962 to 1975, whereas subsequently, both cineangiography as well as AOT changer were used. Transpulmonary splenography was performed in 12 cases with plates covering the chest and abdomen to look for any evidence of portopulmonary fistulas.

In two cases investigated recently, cross-sectional echocardiography and peripheral vein contrast studies were performed using a phased-array sector scanner to specifically look for any dropouts in interatrial or interventricular septum and to demonstrate any evidence of right-to-left shunting at atrial, ventricular, or intrapulmonary level.

RESULTS

The results of cardiac catheterization, angiography, and biopsy are shown in Table 1 and Figures 1 to 6. Eleven of the patients were men. All patients were between seven and 21 years of age. All of them showed severe cyanosis, gross clubbing, and grade 2-3 effort intolerance of one to six years' duration. Eight patients complained of a lump in the abdomen, and one complained of soft swelling on the right forearm, swelling of wrists and ankles, and exhibited wing flap tremors. There was history of hematemesis in one. There was no history of alcoholism, protein malnutrition, or umbilical sepsis in any case.

Every patient had severe cyanosis, gross clubbing, warm hands, wide pulse pressure, a grade 2/6 ejection systolic murmur at the pulmonary area, and a normally split second heart sound with normal aortic and pulmonary components. The spleen was palpably enlarged. The liver was palpable one to three finger breadths below the costal margin in 18 cases. One patient had marked swelling of the ankles and wrists due to osteoarthropathy. He also had a hemangiomma on the lateral aspect of the upper part of the right forearm. He exhibited marked wing flap tremor of the outstretched hands, but there was no Kayser-Fleischer

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ring nor any other neurologic abnormality. Three patients showed arterial spiders and telangietasia on the chest, back, and arms. One of these three patients showed a caput medusae and another a few engorged veins on the abdomen.

There was polycythemia in 18. Spectroscopic examination of blood revealed no abnormality. The liver function test results were slightly abnormal in 17 patients. The serum globulin was raised in 17. In five patients in whom plasma electrophoresis was performed, the rise was largely due to gamma-globulin. Sulfobromophthalein (Bromsulfalein) retention was increased and flocculation tests were positive in 15.

Barium swallow demonstrated esophageal varices in eight cases. Histologic examination of needle biopsy specimens of liver in 19 cases and open biopsy in one case revealed portal cirrhosis of the liver.

Intrasplenic pressure was measured in 12 cases.
where portal splenography was performed and was raised in all patients. Portopulmonary fistulas could not be demonstrated on portosplenography in any patient. In five cases, the portal vein could not be visualized and a few large collaterals were seen to open into the inferior vena cava. In the remaining cases, portal vein was seen and the intrahepatic pattern was distorted.

Chest x-ray films showed mild cardiomegaly with somewhat increased pulmonary vascularity in 13 cases and were normal in the remaining patients. The electrocardiogram was within normal limits in 16, and showed nonspecific ST-T changes in four. Table 1 shows the intracardiac pressures to be normal in all. There was marked desaturation of the femoral arterial blood in all, which could not be restored to normal by inhalation of 100 percent oxygen for ten minutes. Pulmonary venous samples were obtained in six and were found to be markedly desaturated. Selective right ventriculography, pulmonary angiography, left ventriculography, aortography, and right superior pulmonary vein angiography revealed no evidence of shunt at atrial, ventricular, or aortopulmonary level in any case. Selective pulmonary angiography revealed two patterns of pulmonary vasculature. The pulmonary vasculature appeared blotchy on main pulmonary angiography (Fig 2) and showed multiple small pulmonary arteriovenous fistulas on selective left or right lower lobe angiography (Fig 3) in 15 cases (type A). In five cases, the pattern of pulmonary vasculature appeared indistinguishable from normal (Fig 4) and no convincing evidence of arteriovenous fistulas could be demonstrated (type B). Peripheral vein contrast studies demonstrated passage of contrast material in the left atrium and left ventricle four to five cycles after its appearance in the right heart chambers (Fig 5). The contrast studies thus suggested right to left intrapulmonary shunting through pulmonary arteriovenous fistulas too small to be observed on selective main pulmonary artery or lobar angiography. Open lung biopsy performed in one patient showed a collection of arterial spaces filled with blood and crowded in certain areas. These probably represent pulmonary arteriovenous fistulas (Fig 6).

**DISCUSSION**

Our group in 1966 reported seven patients suffering from cirrhosis of liver who showed severe cyanosis and gross clubbing and closely simulated congenital cyanotic heart disease. It was shown conclusively that cyanosis was secondary to intrapulmonary shunting through multiple tiny pulmonary arteriovenous fistulas. While with the advent of cross-sectional echocardiography it is easy to exclude an intracardiac cause of severe cyanosis, cirrhosis of liver with multiple tiny arteriovenous fistulas is not easy to suspect unless one knows about the clinical features of this entity.

Some workers have reported a minor degree of arterial desaturation in cirrhosis of liver. The reported cases were not like the ones seen by us and did not simulate congenital cyanotic heart disease. It is surprising that there have been no previous or subsequent reports in the literature on cirrhosis of liver simulating cyanotic heart disease. There is no mention even of the specific entity in currently available major textbooks dealing with internal medicine, pediatrics, pediatric cardiology, and liver diseases. This condition, though rare, is certainly prevalent in this part of the world, and 20 cases have been investigated by us during 1962 to 1987.

The predominant occurrence of this condition in a younger age group and the invariable presence of an ejection systolic murmur at the pulmonic area make
Peripheral vein contrast echocardiography studies in a case (group B) showing passage of contrast material in the left atrium and left ventricle four to five cycles after its appearance in the right heart chambers. Abbreviations: RV, right ventricle; RA, right atrium; LV, left ventricle; LA, left atrium.

The resemblance to congenital cyanotic heart disease complete. Cardiomegaly, when present, enhances the suspicion of cyanotic heart disease. However, a normally split second heart sound with normal aortic and pulmonary components, normal electrocardiogram, and almost normal cardiac shadow on chest x-ray film would not indicate congenital cyanotic heart disease. The systolic murmur was almost certainly due to hyperkinetic circulation. Hepatic and splenic enlargement are usual and point to the liver pathology. Portal collateral vessels and evidence of hepatic failure when present are helpful for the diagnosis of cirrhosis of the liver. One patient had marked osteoarthropathy of ankles and wrists. Such osteoarthropathy in cirrhosis of liver was observed by Hijmans Van den Bergh.7 Liver function tests usually show some impairment, but may be normal as in three cases. The liver biopsy specimen demonstrated portal cirrhosis in all.

The cause of desaturation of the arterial blood in cirrhosis has been investigated by some workers.8 The postulated mechanisms include portopulmonary venous shunting, shift of oxyhemoglobin dissociation curve, pulmonary diffusion defect, ventilation perfusion defect, and intrapulmonary shunting. The presence of anastomosis between portal and pulmonary veins via mediastinal veins has been demonstrated in some patients with cirrhosis of the liver.8,10 It appears unlikely that this mechanism contributes significantly to arterial desaturation since the quantity of blood flow through the portopulmonary shunts is small10 and since the portal venous blood has a relatively high
oxygen saturation. We could not demonstrate any portopulmonary fistulas in our cases where splenogram was performed with film covering lungs, liver, and spleen.

A rightward shift in the oxygen dissociation curve in cirrhosis has been suggested as a cause of arterial desaturation.\textsuperscript{11} Subsequent studies,\textsuperscript{2,3} however, indicate that the magnitude of the shift is inadequate to explain the level of arterial desaturation frequently encountered. This factor does not appear to be important in causing deep cyanosis. Pulmonary diffusion defect\textsuperscript{4} and ventilation/perfusion mismatch\textsuperscript{4} have been postulated as possible mechanisms for arterial desaturation in cirrhosis. In our patients, femoral arterial and pulmonary venous samples showed marked desaturation and could not be restored to normal by administration of 100 percent oxygen for ten minutes. This excludes uneven ventilation and diffusion defect as a possible mechanism for cyanosis in these patients.

Our study conclusively demonstrates that, at least in our cases, pulmonary arteriovenous fistulas are the cause of deep cyanosis. In 15 cases, the pulmonary angiography demonstrated pulmonary arteriovenous fistulas. In these cases, the pulmonary vasculature appeared blotchy on main pulmonary angiography and showed presence of multiple tiny pulmonary arteriovenous fistulas on selective lobar angiography. The angiographic findings conclusively proved that cyanosis in these cases was due to intrapulmonary shunting through arteriovenous fistulas. In the remaining five cases, the pulmonary vasculature appeared indistinguishable from normal and no convincing angiographic evidence of pulmonary arteriovenous fistulas was demonstrated. It is quite likely that even in these cases, the cause of right to left shunt is in the lungs in the form of fistulas too small to be demonstrated on pulmonary angiography. In one of his two cases, Hales\textsuperscript{12} demonstrated pulmonary arteriovenous fistulas on postmortem injection of pulmonary vessels which could not be detected on pulmonary angiography or histology. Peripheral vein contrast echocardiography\textsuperscript{13,14} has been used to localize and quantitate intrapulmonary shunts. Normally, the echocardiographic contrast is completely eliminated in transit through the pulmonary capillary bed. In the presence of pulmonary arteriovenous fistulas, the contrast is transmitted directly into the pulmonary vein and appears in the left heart. In two of our cases from group B where peripheral vein contrast echocardiography was performed, the contrast material appeared in the right heart, and within four to five cycles, appeared in the left heart. The sequential appearance of contrast material in the right and left heart chambers confirmed right to left intrapulmonary shunting between pulmonary arteries and veins through pulmonary arteriovenous fistulas too small to be detected on pulmonary angiography. Our observations suggest that contrast echocardiography is more sensitive than angiography for detection of intrapulmonary shunts.

Several unanswered questions emerge from this study. The etiologic origin of these pulmonary arteriovenous fistulas is uncertain, and though they could be congenital, the relatively short history suggests an acquired etiology. It is interesting to note that normal lungs appear to have nonfunctional precapillary potential communications between the pulmonary arteries and veins.\textsuperscript{15} In patients with cirrhosis, however, it is not clear whether there is opening of preexisting channels that are normally nonfunctional or completely new channels are formed. Vascular malformations such as arterial spiders and telangiectasia are known to develop in cirrhosis.\textsuperscript{16} The angioma on the right forearm and left leg in one of our patients was acquired. How cirrhosis of the liver causes these malformations is uncertain. The predilection of these pulmonary arteriovenous fistulas to occur in younger patients also remains to be explained. The cause of cirrhosis in these patients is uncertain.

Our study indicates that cirrhosis of liver with cyanosis and clubbing is a distinct clinical entity. Our observations indicate that contrast echocardiography is a valuable noninvasive tool in the diagnosis of this entity.

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