Bone disease in infants and children with hepatobiliary disease

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Kobayashi, A., Kawai, S., Utsunomiya, T., and Ohbe, Y. (1974). Archives of Disease in Childhood, 49, 641. Bone disease in infants and children with hepatobiliary disease. Radiological studies of bone were performed in infants and children with hepatobiliary disease. Rickets was found in 23 out of 39 patients (59%) with surgically unrepaired biliary atresia, in 4 out of 15 (27%) with surgically repaired biliary atresia, in 11 out of 21 (52%) with neonatal hepatitis, and in 2 out of 4 (50%) with intrahepatic cholestasis. Osteoporosis was found in 23 out of 39 (59%) with unrepaired biliary atresia, in 3 out of 15 (20%) with repaired biliary atresia, in 5 out of 21 (24%) with neonatal hepatitis, and in 1 out of 4 (25%) with intrahepatic cholestasis. 2 girls with Byler disease and 1 infant with choledochal cyst showed no radiological evidence of bone disease.

In unrepaired biliary atresia comparative studies of biochemical data in the groups with and without bone disease showed the following. Serum calcium levels were reduced in the patients with bone disease compared with those in the group without it. Serum magnesium levels were markedly reduced in the groups with and without bone disease. The product of serum calcium and phosphorus was reduced in the group with osteoporosis compared with that in the group without it. The raised levels of serum alkaline phosphatase were unrelated to the presence or absence of bone disease.

Bone disease has been described in association with chronic liver disease in adults (Atkinson, Nordin, and Sherlock, 1956; Kehayoglou et al., 1968). Atkinson et al. (1956) reported 22 adult patients with obstructive jaundice, in 6 of whom a diagnosis of osteomalacia was made. However, there have been conspicuously few reports on this subject in infants and children (Teng et al., 1961; Yu, Walker-Smith, and Burnard, 1971).

This paper describes the incidence of bone disease in infants and children with hepatobiliary disease, the age of onset, and comparative biochemical studies between the groups with and without bone disease.

Materials and methods
The subjects were 54 infants with biliary atresia, 15 of whom were successfully repaired by hepatic porto-jejunostomy and had no jaundice (Kobayashi et al., 1973), 21 infants with neonatal hepatitis, 4 infants and children with intrahepatic cholestasis, 2 girls with Byler disease (Kobayashi et al., 1975), and 1 infant with choledochal cyst.

All patients with biliary atresia had laparotomy and the diagnosis was confirmed. Diagnosis of neonatal hepatitis was on clinical and laboratory grounds, excluding other diseases causing obstructive jaundice during infancy. Of 4 patients with intrahepatic cholestasis, 3 had so-called intrahepatic biliary atresia shown by laparotomy and histological studies. The other had intrahepatic cholestasis of unknown aetiology. These 4 patients complained of severe pruritus, and 2 of 3 patients with intrahepatic biliary atresia had developed xanthoma. Diagnosis of Byler disease was on clinical and laboratory grounds (Clayton et al., 1969), based on jaundice with intermittent exacerbations, severe pruritus, hepatosplenomegaly, dwarfing, mental retardation, raised serum alkaline phosphatase levels, normal or low serum cholesterol values, hypoprothrombinaemia, and biliary cirrhosis.

The state of the skeleton was assessed in each case by x-rays of both wrist joints. X-rays were made 1 to 6 times for each case with variable intervals. A diagnosis of rickets was made by the rarefaction and irregular
fraying of the provisional zone of calcification. Cupping of the distal end of the ulna was not considered significant because it is observed in some nonrachitic infants. A diagnosis of osteoporosis was made on radiological grounds based on the thin cortex of the radius and reduced bone density.

In unrepaired biliary atresia comparative studies of biochemical data were performed in 2 groups. The data in the group with bone disease were determined when bone disease was detected on x-rays, and in the group without it at the latest examination of normal x-rays.

Serum alkaline phosphatase levels were measured by the method of Kind and King (1954). Serum calcium was determined by a modification of the method of Connerty and Briggs (1966) using the metal complexing dye orthocresolphthalein complexone, and magnesium by the method of Schachter (1961) using a spectrofluorometer. Serum phosphorus was determined by a modification of the method of Fiske and Subbarow (1925). In some cases of biliary atresia the heat stability of serum alkaline phosphatase was studied by the method of Posen, Neale, and Clubb (1965).

**Results**

Incidence of rickets and osteoporosis in hepatobiliary disease (Fig. 1 and 2). Rickets was found in 23 out of 39 patients (59%) with surgically unrepaired biliary atresia. The lesion was observed in 4 out of 15 (27%) with surgically repaired biliary atresia. Osteoporosis was diagnosed in 23 out of 39 patients (59%) with surgically unrepaired biliary atresia, and in 3 out of 15 (20%) with surgically repaired biliary atresia. Of 39 patients with biliary atresia, 17 had both rickets and osteoporosis.

Exact age of onset of these bone diseases was obscure in most cases because the diseases developed insidiously and because x-rays were not made at regular intervals. In our series of biliary atresia the age at which rickets developed ranged from 1 to 4 months, and that of osteoporosis 1 to 5 months.

In neonatal hepatitis the incidence of rickets was the same as in unrepaired biliary atresia. It

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**FIG. 1.** Radiological studies of bone in 54 patients with biliary atresia.
appeared in 11 of 21 cases (52%). The lesions, however, disappeared in most cases by the age of 6 months. Osteoporosis, on the other hand, developed in 5 of 21 (24%), and these 5 infants with osteoporosis also showed the signs of rickets.

Of 4 cases of intrahepatic cholestasis, 2 showed the radiological evidence of rickets and 1 showed osteoporosis. 2 girls with Byler disease and 1 infant with choledochal cyst had no radiological signs of bone disease.

**Comparative studies of biochemical data in the group with and without bone disease in un repaired biliary atresia** (Table and Fig. 3). Serum alkaline phosphatase levels were high in most cases of biliary atresia and were higher in those with rickets and/or osteoporosis than in those without these lesions. However, the difference was not significant. In some cases of biliary atresia with and without rickets the heat stability of alkaline phosphatase was evaluated to assess these high values (Fig. 3). The results showed that the greater contribution of liver alkaline phosphatase was responsible for these high values.

The mean concentration of serum calcium in the patients with rickets was 4·40 mEq/l. (SD 0·42, no. = 15) with a range of 3·7 to 5·0. In the group without rickets the value was 4·76 mEq/l. (SD 0·51, no. = 16) with a range of 4·0 to 5·4, and the difference between these 2 groups was significant (P < 0·05). The same relation was present between serum levels of calcium in the patients with and without osteoporosis (mean 4·37 mEq/l., SD 0·49, no. = 14, and range 3·7 to 5·4 in the patients with osteoporosis; mean 4·70 mEq/l., SD 0·43, no. = 19, and range 4·0 to 5·4 in those without osteoporosis; P < 0·05).

In biliary atresia serum magnesium levels were conspicuously reduced below the normal range. The degree of reduction was greater than that of...
serum calcium, especially in the patients with bone disease. The mean value was 1·39 mEq/l. (SD 0·27, no. = 12) with a range of 0·9 to 1·8 in the patients with rickets, and 1·53 mEq/l. (SD 0·19, no. = 10) with a range of 1·2 to 1·8 in those without the lesion. The difference was, however, not significant between these 2 groups. The mean value was 1·41 mEq/l. (SD 0·26, no. = 10) with a range of 0·9 to 1·8 in the patients with osteoporosis, and 1·56 mEq/l. (SD 0·22, no. = 13) with a range of 1·1 to 1·8 in those without osteoporosis. The difference between these was also not significant.

The mean value of the product of serum calcium and phosphorus concentrations was 21·7 mg/100 ml (SD 9·7, no. = 15) in the patients with rickets, and 27·7 (SD 8·4, no. = 15) in those without the lesion. The difference was not significant between these groups. The value was, however, significantly reduced in the patients with osteoporosis compared with those without the lesion. The mean value was 19·8 (SD 10·6, no. = 13) in the patients with osteoporosis, and 28·0 (SD 8·5, no. = 17) in those without the lesion.

**Discussion**

The present study showed a high incidence of bone disease in hepatobiliary disease in infancy and childhood. In biliary atresia, in which bile flows into the gut was completely absent, more than half the patients studied had bone disease. The incidence of rickets was 60%, the same as that of osteoporosis. Rickets developed about 3 months of age—a little earlier than the osteoporosis. In surgically repaired biliary atresia the incidence of bone disease was conspicuously decreased, and the lesions were rarely seen after the age of 12 months. In most of these cases the lesions were associated with ascending cholangitis after surgery (Kobayashi et al., 1973). In neonatal hepatitis rickets was observed in half of the patients and cured spontaneously by the age of 6 months. On the other hand, osteoporosis was seen only in 25% of cases of this disease. All patients with osteoporosis also had the radiological signs of rickets. This low incidence of osteoporosis compared with that of rickets in neonatal hepatitis was due to the fact that neonatal hepatitis had a favourable clinical course on follow-up and was cured in most cases by the age of 6 months. In intrahepatic cholestasis the patients showed the same incidence of bone disease as in neonatal hepatitis. In one case of choledochal cyst no bone disease was seen. In Byler disease 2 patients had no rickets or osteoporosis, but had knock knees.

The reported incidence of bone disease in hepatobiliary disease in infancy and childhood is variable. In the report of Bastis-Maounis, Matsaniotis, and Maounis (1973) 3 out of 7 patients with biliary...
Bone disease in infants and children with hepatobiliary disease

LE without bone disease in unrepaired biliary atresia

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atresia showed radiological evidence of rickets, and 7 out of 11 with neonatal hepatitis. In the paper entitled 'Rickets: a common complication of neonatal hepatitis' by Yu et al. (1971), 4 out of 30 infants with the disease had rickets. There has been, however, meagre information available on the incidence of osteoporosis in hepatobiliary disease in childhood except for the report by Teng et al. (1961).

The pathogenesis of bone disease in hepatobiliary disease has been poorly understood. Bile is important for the intestinal absorption of calcium and magnesium because it is necessary for the absorption of vitamin D (Schachter, Finkelstein, and Kowarski, 1964), which enhances the absorption of both elements. Bone disease may be attributable to the malabsorption of these elements in hepatobiliary disease in which bile flow into the intestines is deficient or absent (Kobayashi et al., 1974). Furthermore, vitamin D that is absorbed from the gastrointestinal tract via the lymphatics and is transported from there to the liver in the chylomicron of the plasma may be hydroxylated in the liver to a more potent metabolite, 25-hydroxycholecalciferol (25-HCC) (Lund and DeLuca, 1966; Ponchon, Kennan, and DeLuca, 1969), which is thought to be converted to more active forms, 1,25- or 21,25-dihydroxycholecalciferol (1,25- or 21,25-DHCC) in the kidneys (Fraser and Kodicek, 1970). Since the initial step of transformation of vitamin D to its active form may take place in the liver, there may be a failure to metabolize the vitamin adequately, and there is some evidence that this may occur in hepatic cirrhosis (Ponchon and DeLuca, 1969). Yu et al. (1971) postulated that rickets associated with neonatal hepatitis was due to the impairment of the hepatic conversion of vitamin D to its biologically active form.

Conditions which are accompanied with intra- and extrahepatic cholestasis may cause biliary cirrhosis. These disorders include congenital biliary atresia, protracted neonatal hepatitis, Byler disease, etc. Among these, surgically unrepaired biliary atresia is rapidly progressive and patients who survive over 12 months show advanced biliary cirrhosis. The cirrhotic patients show severe impairment of liver function and a systemic deficit of protein. This protein deficit may be an important aetiological factor of osteoporosis in liver disease since osteoporosis is widely considered to be a disorder of the protein matrix of bone (Cooke, 1955).

In neonatal hepatitis, fewer patients had osteoporosis than rickets, whereas in biliary atresia the incidence of osteoporosis was the same as that of rickets. These observations accord better with the fact that deficient or absent bile flow into the gut is observed in both diseases, though biliary cirrhosis is a common feature of biliary atresia but not of neonatal hepatitis.

In biliary atresia serum concentrations of calcium were significantly reduced in the patients with bone disease compared with those without it. Serum magnesium levels were conspicuously reduced in the groups with and without bone disease, and there was no significant difference in serum levels between these 2 groups. The reduction of the product of serum calcium and phosphorus was significant in the group with osteoporosis compared with that in the group without the lesion, but not significant for rickets. The serum levels of alkaline phosphatase were unrelated to the presence or absence of bone disease. Its raised levels were of hepatic origin, shown by a heat inactivation procedure. This observation was not in accord with that of Bastis-Maounis et al. (1973), who reported that the high values of serum alkaline phosphatase in association with hepatic disease in infants reflected, at least in part, a secondary vitamin D deficiency.

Out of 6 cases of unrepaired biliary atresia that had no signs of rickets over the age of 12 months, 2 had received vitamin D 30,000 IU weekly intramuscularly. Kobayashi et al. (1974) showed that in biliary atresia oral vitamin D had little, if any, effect on the absorption of calcium and magnesium, though the vitamin moderately increased absorption.
when given intramuscularly. It is reasonable to conclude from these studies that vitamin D should be given intramuscularly to reduce the incidence and severity of rickets in this disorder. In neonatal hepatitis oral vitamin D supplement in a dosage of 2000 IU daily was recommended by some workers (Danks, 1965; Yu et al., 1971), but we found that rickets was spontaneously cured by the age of 6 months in this condition.

REFERENCES

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