(*Bharat Medical Journal* (1970): (2), 2, 130)

Cirrhosis of Liver

Shantilal C. Sheth and **Tibrewala, N.S.**

SUMMARY

Cirrhosis of liver – an interesting clinical condition that baffles our aims of diagnosis – is the end-result of not one cause but of many processes. Here is a study based on 59 cases of early, intermediate and late cirrhosis which becomes an interesting part of the continuing search to find out and thoroughly understand the real cause so that the medical profession can go ahead to eradicate the disease.

INTRODUCTION

The main problem in the field of liver disorders that confronts the medical profession in India today, especially in paediatric practice, and probably baffles us all is the cirrhosis of liver. We may try to seek approaches to the understanding of this problem that would help to solve it some day.

Liver disorders present different features in different age groups. In the newborn there is a deficiency of certain enzymes that facilitate the proper transport of serum bilirubin through the liver. This may lead to a mild or severe form of neonatal jaundice. The factors of under nutrition, poor hygienic conditions, low economic status and some doubtful traditional practices contribute materially to ill health in childhood. Out of all conditions affecting the infant the outstanding one is known as "Infantile Cirrhosis of Liver" or so-called "Indian Childhood cirrhosis". Dr. Sen described it 77 years ago and its aetiology is still not established or understood. Enlargement of the liver is often found in a large number of children not suffering from cirrhosis of liver.

Haemolytic diseases like Rh. or blood ABO group incompatibility, congenital haemolytic anaemias, various infections, poor nutrition and viral hepatitis may be contributory. Maternal ill health or infections during pregnancy, infantile allergy due to various factors, low-grade infections, toxic action of drugs administered during the neonatal period and early infancy, protozoal infections in infancy and various other factors may be contributory. No satisfactory correlation can be shown either between the clinical condition seen in patients with this disorder or between these and the findings obtained from the numerous laboratory tests available for determining the abnormal liver function, including biopsy studies. Though more accurate knowledge is available today, the correlation between the structure and functions of the liver remains undefined.

Once the diagnosis has been established, the modern methods of therapy seem to offer poor chances. To cure this disease has become a challenge to the medical profession. No substance is known to convert interstitial tissue into a parenchymatous one, and so once the disease has developed and progressed, search for its cure is futile. All that could be hoped for is to get functionally the best out of the remaining healthy or less affected liver parenchymatous cells.

The disease is met with mostly between the age of six months and three years, with a maximum incidence between one and three years. Fifty nine cases showing cirrhosis of liver clinically in its various stages were selected for study, and the clinical diagnosis was made and later confirmed in the majority of the cases both biochemically and histopathologically. In this series 3 per cent were observed at the age of six months, 17 per cent at one year and 73 per cent between one and two years, 14 per cent between two and three years and 3 per cent at subsequent age groups.

The dietetic history of the children varied from breast milk without supplements to artificial feeding and in older infants food such as rice, dal, chappatis, vegetables with a little milk and no fruits or extra proteins. The history of inadequate feeding after the stoppage of breast feed or feeding with a high carbohydrate diet with too little milk or high fat or low carbohydrate diet or marked loss of weight six months after weaning, was quite common. Dr. Radhakrishna Rao in Bombay found cirrhosis of liver more common in vegetarian families at the weaning time, when the child was weaned from mother's milk and put on protein-free cereal diet. Disturbance of nutrition with or without signs of vitamin deficiency was present in 90% cases. We have come across families where consecutive children suffered from typical cirrhosis of liver. So also the incidence of cirrhosis has been recorded in three sets of identical twins by Dr. Sarma. It is possible that hereditary, familial and genetic factors may be responsible to some extent for this condition. We have seen groups of either male or female children alone affected in a given family, with the other sex completely escaping the disease. Anticipation of this disease in cases with family history has been found in this series in five cases. Experimentally high-fat and low-protein diet produced fatty changes in the liver in dogs. In Jamaica (West Indies) fatty changes in the liver were found more frequently in the areas where cirrhosis of liver was more common. Vitamin B-1 and its relation to choline deficiency, and Vitamin C and its relation to the adrenal cortex, may have some bearing. Though dietetic factors may be contributory, it does not explain all the cases of infantile cirrhosis of liver. Himsworth and Glynn brought forward that dietetic injury also produced independently an insidiously developing diffuse hepatic cirrhosis, besides acute massive necrosis and its sequelae of post-necrotic scarring and nodular hyperplasia. They showed that acute massive necrosis was related to a protein, especially cysteine, deficiency and to tocopherol deficiency, and post-necrotic scarring and nodular hyperplasia to fatty infiltration of liver due to a low protein and high-fat diet. The lesion could be prevented by giving amino acids containing sulphydryl groups, viz methionine and cysteine. Trowel *et al* found that in kwashiorkor a starchy diet deficient in proteins led to fatty liver, but the follow-up studies have not shown the development of cirrhosis of liver. Cirrhosis seems to be the result of a variety of factors causing repeated or continued liver damage singly or in combination with various drugs, chemicals, bacteria, viruses, protozoa, toxic agents and dietary deficiency with probably a hereditary or family background.

MATERIAL AND METHODS

Fifty nine cases were divided into early, intermediate and late cirrhosis. Thirty eight cases were treated on the usual lines, and 21 were treated in addition with Liv.52, an indigenous medicine compound. One to two tablets three times a day for over a period of six weeks to six months were administered.

In the first series, 68 per cent expired, 15 per cent were partially relieved but not cured and the disease continued to progress slowly, and 17 per cent could not be treated.

In the second series, six out of 21 patients were in the early stage of cirrhosis, five in the intermediate stage and 10 in the last stage. In the early and intermediate group anorexia, nausea, fever, constipation, jaundice, ascites, oedema and abdominal distension were relieved in most of the cases, but the advanced group of 10 cases did not show any response and expired. The improved group showed returning of liver function to normal as evidenced by increase in total proteins and improvement in serum alkaline phosphatase. Cephalin cholesterol and thymol turbidity tests showed no marked improvement. The liver decreased in size and there was some change in its consistency. When the patient showed improvement in symptoms and liver function tests, there was no change in the size and consistency of the liver. Functional improvement was not noteworthy though histopathological changes did not revert completely to normal. Histopathological changes showed a definite decrease in fibrosis and a change in the architecture of the liver, indicating

improvement in some cases. Seven patients showed partial improvement with return of appetite, clearance of ascites and oedema and complete freedom of movement.

EFFECT OF Liv.52

The study was carried out to find out the protective effect of Liv.52 against liver damage resulting from varying doses of carbon tetrachloride. Studies on the serum albumin, serum proteins, serum bilirubin, serum transaminase activity (using a pyruvate standard) and the effect on the histopathology of the liver were carried out. In this study mice were selected as test animals; varying doses of carbon tetrachloride were used and the effects of liver damage at varying intervals of 24 hours, five days or three or more weeks noted. In all, eight experiments were carried out using 28 groups of ten mice each. Liv.52 in doses of 1000, 200 and 300 mg per kilo of body weight was used. A suitable dose of carbon tetrachloride was found which would produce a suitable degree of central lobular necrosis. For this gingely oil solution of carbon tetrachloride was used. The required dose was contained in 0.1 cc of the solution. The study was carried out in each experiment with a proper control group.

In the first experiment, four groups of 10 mice were used. The results seemed to indicate that a single dose of 0.50 cc/100 gm of body weight would be suitable for future experiments.

In the second experiment, four groups of 10 mice each were used. The results indicated that the dose of 0.40 cc/100 gm was negligible.

In the third experiment, four groups of 10 mice each were used. The dose of 0.4 cc/100 gm of body weight was chosen as suitable for future experiments. By this a clear correlation was noticed between the degree of central lobular necrosis and the content of glycogen in the liver. Serum protein picture was often not numerically related to the extent of the morphological damage.

In the fourth experiment, four groups of ten mice were used. Results showed that while Liv.52 in the doses used in this experiment did not produce any demonstrable protection against central lobular necrosis by carbon tetrachloride, it had prevented the deglycogenation of the peripheral part of the lobule and had stimulated the same part of the liver lobule to synthesise serum albumin. All the three groups receiving Liv.52 showed a more normal albumin globulin ratio mainly due to the rise in the absolute concentration of albumin fraction.

In the fifth experiment, four groups of ten mice were used. The results were almost like the previous experiment.

In the sixth experiment, four groups of mice were used. All the animals were sacrificed at the end of the seven weeks and tissues examined as in the previous experiment. Serum protein in the control group was very disturbed. The results showed that though Liv.52, in the doses used here, did not prevent central lobular necrosis by carbon tetrachloride poisoning, it did somehow stimulate the remainder of the liver lobule to greater biochemical activity.

In the seventh experiment, tests for acute toxicity were carried out. Two groups of ten mice each were used. At no time did any of the animals show any distress, none died and at autopsy examination of the organs nothing suggesting damage was discovered.

NOT SIGNIFICANT

By way of summary we can say that in experiments 4, 5 and 6 we have been able to show quite considerable biochemical protection but no significant protection against central lobular necrosis. The pathologist's reports all indicate that there was no reduction in the extent of the area of the

central part of the lobules which shows necrosis, but the remaining liver parenchyma definitely showed less deglycogenation in those animals which had been receiving the drug for 15 days prior to the dose of carbon tetrachloride. We have seen that the maximum protective action was exerted by the dose of 200 mg per kilo of body weight. In just the same way we have seen that there was less reduction in the serum albumin concentration in those animals which had been pre-treated with the drug. A daily dose of 200 mg per kg. to mice gave almost complete protection against the fall in serum albumin obtained with a dose of 0.05 cc of carbon tetrachloride per 100 gm. of body weight given on the fifteenth day. In no dose level were we able to show any alteration in the degree of fatty infiltration of the liver, neither were we able to detect significant difference in the levels of serum transaminase. The whole picture in fact adds up to the fact that the drug has not protected cells of the central part of the liver lobule against damage, but rather has protected and stimulated the more peripheral parenchymatous cells to greater biochemical activity. Experiments 7 and 8 show that it has no acute or chronic toxicity.

Mathur from Bhopal has reported clincial response to the drug. Rule and Sathe from Poona have reported good response. S.R. Captain and A.H. Syed, veterinary surgeons, in "Clinical Studies on Liv.52 in Race Horses," have shown that Liv.52 protected the animal against the harmful effects of opiates and equine jaundice, azoturia colic and hepatotoxic drugs. Joglekar and Chitele and Balwani have made a comparative study of promethazine, Chlorpromazine and Liv.52 against the effects of carbon tetrachloride in mice. For 21 days the study was undertaken on 50 female mice. Histopathological examination revealed that Liv.52 could effectively prevent the liver damage and offer significantly protection. Jal Patel and N.L. Sadre have, through histopathological studies and bromsulphalein elimination tests, shown that Liv.52 has marked protective action on the liver against hepatotoxic agents.

Sule and Sathe have reported clinical improvement in an enlarged liver. Liver function tests showed special improvement and returned to normal and the patient enjoyed good health even after discontinuing Liv.52.

G.R. Murkibhavi and U.K. Sheth have reported that 26 cases of jaundice in dogs were treated orally with Liv.52 and that 12 cases recovered completely against the 100 per cent mortality during the last three years.

CONCLUSION

Cirrhosis of liver is a very interesting clinical condition baffling our aims in diagnosis. It is an end-result of the many processes which could bring about a change in the structure of the liver. The causes are many. The liver structure in the process is altered and modified by various processes.

This study is an interesting one and yet the search for the cause of cirrhosis of liver will have to go on till finally the real cause is found out and thoroughly understood so that the medical profession can go ahead to eradicate it. Perhaps the studies from veterinary and allied sciences may be contributory and of great value.

REFERENCES

1. Achar, S.T. (1955); "Childhood Hepatic Cirrhosis in India", Ind. J. Child. Hlth., 6: 291.

2. Amin, B.M. (1958); Cirrhosis of Liver, Proceedings of Bombay Medical Congress, page 54.

3. Captain, R.M. (1959); Personal Communication of research reports.

4. Coelho, G. (1952); Cirrhosis of the Liver in Children", Ind. J. Child Hlth., 1: 455.

5. Douglas, B.E. and Snell, A.M. (1950); “Portal Cirrhosis”, Gastroventacology, 15: 407.

6. Higginson, J., Grobelar, B.G. and Walker, A.R.D. (1957); “Hepatic Fibrosis and Cirrhosis in Man in Relation to Malnutrition, Amer. J. Path., 33: 29.

7. Himsworth, H.P. and Glynn, L.E. (1944); “Toxipathic and Trophopathic Hepatitis”, Lancet, 1: 457.

8. Himsworth, H.P. (1950); “The Liver and its Diseases”, Blackwell Scientific Publications.

9. Howard, R. and Watson, C.J. (1947); Arch. Intern. Med., 1: 80. (quoted by Higginson).

10. Kinare, S.C., and Purandare, N.M. (1958); “Portal Cirrhosis of Liver, an Autopsy Study of 250 Cases”, J. Post-Grad. Med., 4: 28.

11. Laennec, R.T.H. (1826); “R.T.H. (1826); “Traits de L’Auscultation”, J.S. Clause, Paris, 28: 196. (Quoted by Himsworth).

12. Merchant S.M. (1952); “Infantile Cirrhosis of Liver”, Ind. J. Child Hlth., 1: 53.

13. Mathur, P.S. (1957); “Some Clinical Observations on the Use of Liv.52 (an indigenous drug) in Cases of Cirrhosis of Liver in Children”, Current Medical Practice, 2: 107.

14. Murkibhavi, G.R. and Sheth, U.K (1957); “Treatment of Jaundice in Dogs with an Indigenous Drug. Liv.52”, Ind. Vet. Jour. 34: 276.

15. Northover, Basil J. (1959); Personal communication of research study, Vellore.

16. Parekh, J.G. (1958); “Cirrhosis of Liver”, proceedings of XVI Bombay Medical Congress P.37.

17. Patex, A.J. (1956); “Diseases of Liver”, J.B. Lippincott Co., P.449.

18. Patex, A.J. Jr., Post, J., Ratnoff, O.D., Mankin, M. and Hillman, R.W. (1948); “Diet Treatment of Cirrhosis of Liver”, J. Amer. Med. Ass., 138, 543.

19. Patrao, S. (1957); “Observations on Liv.52”, J. Ind. Med. Prof., 8: 1878.

20. Radhakrishna Rao (1935-36); “Histopathology of Liver in Infantile Biliary Cirrhosis”. J. Ind. Med. Res., 23: 69.

21. Ratnoff, O.D., Patek, A.J. (1942); “the Natural History of Laennec’s Cirrhosis of the Liver — Analysis of 337 Cases,” Medicine, 21; 207.

22. Sarma, A.V.S., (1952); Quoted by Merchant, Ind. J. Child Hlth., 1: 53.

23. Sarma, A.V.S. (1955); Quoted by Sheth. J. Ind. Med. Prof., 1: 463. Oxford.

24. Shah, M.J. and Shah, P.M. (1958); Cirrhosis of Liver, Proceedings of XVI Bombay Medical Congress, P. 49.

25. Sheth, Shantilal C. (1955); “Cirrhosis of Liver in Children”, J. Ind. Med. Prof., 1: 463.

26. Sheth, Shantilal, C., and Warerkar, U.R. (1959); “Liver in Malnutrition”, Ind. J. Child Hlth., 8: 468.

27. Sherlock, S., (1952); “Diseases of Liver and Biliary System”, Blackwell Scientific Publications Oxford, P. 303.

28. Sule, C.R. Sathe, P.M., Koshy, M.C., Deshpande, M.S. (1956); “Ascites due to Liver Deficiency Treated with an Indigenous Drug”, Indian Practit., 4: 357.

29. Sule, C.R. and Sathe, P.M. (1957); Liv.52 in the “Treatment of Ascites”, Current Medical Practice, 1: 42.

30. Trowell, H.C., Davies, J.N.P. and Dean, R.A.F. (1954); Kwashiorkor, Edward Arnold, London.

31. Vyas, K.J. (1958); “Treatment of Infantile Cirrhosis with an Indigenous Preparation”, Ind. Practit., 1: 107.

32. Wahi, P.N., Tandon, M.D. and Arora, M.M. (1954); “Correlative Studies of Structural and Functional Alterations of the Liver”, Ind. J. Med. Sci., 8, 458.

33. Welchselbaum, T.E. (1935); Quart J. Exp. Physiol., 25: 363. (Quoted by Himsworth).