Neonatal hepatitis syndrome and alpha-1-antitrypsin deficiency:

An epidemiological study in south-east England

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Summary

A prospective epidemiological study of the Neonatal Hepatitis Syndrome in S.E. England showed Alpha-1-Antitrypsin Deficiency (Pi ZZ) to be present in seven out of fifty-two patients. Data are considered from these seven patients, and from a further six cases from outside this area. The nature of acute illness, pathological changes on early liver biopsy, and short-term prognosis show considerable variability, but in general the hepatitis is more severe in patients with Alpha-1-A.T. deficiency than in those in whom no aetiological factor was found.

The following clinical features were observed in thirteen children who presented with the Neonatal Hepatitis Syndrome and a genetic deficiency of alpha-1-antitrypsin. The relative frequency of the deficiency in infants with the Neonatal Hepatitis Syndrome will be indicated and the variable clinical and pathological course of hepatitis, particularly in the first year of life will be observed. Some aspects of these cases will be compared with patients who did not show the deficiency.

The data were obtained as a result of a prospective ongoing survey started at King’s College Hospital in January 1971 to try and determine the aetiological importance of infections, genetic and other possible harmful environmental factors. All cases are recorded in a central register and long-term follow up is proposed.

The study was limited initially to a circumscribed geographical area of the South-East Metropolitan Hospital Board, which extends from Central London to the South-East coast of England. With the help of all the paediatricians in the area we have been able to study all cases of the Neonatal Hepatitis Syndrome in the region. Paediatricians from outside this area have also kindly allowed us to include their patients in the survey, and from these three patients will be included in whom the diagnosis of alpha-1-antitrypsin deficiency was made long after neonatal hepatitis was diagnosed.

For the purpose of this study we have defined the Neonatal Hepatitis Syndrome as a disorder starting in the first 4 months of life and characterized by the presence of conjugated hyperbilirubinaemia with features of hepatocellular damage, such as raised serum transaminases, and often bilirubinuria, pale stools and hepatosplenomegaly. By appropriate tests all the known causes of the syndrome were systematically sought. Details were also obtained of the pregnancy, delivery and perinatal period, as well as of illness in the parents, siblings, and other family members.

Table 1 refers to patients from the South-East Metropolitan Hospital Board area alone, during the period of January 1971 to September 1973. Fifty-two cases have been observed so far, seven of these showed biliary atresia, and seven showed alpha-1-antitrypsin deficiency. The estimated frequency of neonatal hepatitis syndrome in this population is therefore about 1 in 2000 live births, while that of

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<tr>
<th>Table 1. Neonatal hepatitis survey: South-East Metropolitan Regional Hospital Board area, January 1971–September 1973</th>
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<tr>
<td><strong>Total population</strong></td>
</tr>
<tr>
<td><strong>Births per annum (estimated)</strong></td>
</tr>
<tr>
<td><strong>Total no. of cases of N.H. syndrome</strong></td>
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<tr>
<td><strong>Alpha-1-antitrypsin deficiency</strong></td>
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<tr>
<td><strong>Biliary atresia</strong></td>
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<tr>
<td><strong>Estimated incidence of neonatal hepatitis syndrome</strong></td>
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<tr>
<td><strong>Frequency of alpha-1-antitrypsin deficiency and N.H. syndrome</strong></td>
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alpha-1-antitrypsin deficiency and neonatal hepatitis is about 1 in 14,000 live births. We do not, unfortunately, have data on the frequency of alpha-1-antitrypsin deficiency in this population, but would surmise that it may be near the figure of 1 in 3460 as reported by Dr P. J. L. Cook. If we assume this as being the true frequency of the Pi ZZ phenotype, it becomes necessary to explain why only some of these infants develop hepatitis in the newborn period.

Our early experience caused us to infer that hepatitis B antigen could be such a trigger factor (Porter et al., 1972); as three out of the original five cases described had the antigen in their sera, while the parents of these children also showed a high incidence of either antigen or antibody in their sera. In these children the hepatitis B antigen was found only transiently, although the antigen or antibody or both have persisted in some of the parents. In the subsequent eight cases, however, only one child was found to have the antigen, and that by radioimmunoassay only. Not all cases were investigated in the acute phase however, and it would appear therefore, that the hepatitis B antigen, whilst being a possibly important factor, is not an invariable one in this series of patients.

Table 2 shows the possible aetiological or associated factors that have been observed by us in a total of 100 cases of Neonatal Hepatitis Syndrome by September 1973. Twenty-one cases not shown in this table had biliary atresia at laparotomy. Note that in nearly 50% of these cases, no aetiological or associated factor could be identified, in spite of the fact that this was a prospective study and all diagnostic tests were performed during the acute illness in most instances. The clinical features associated with each of these factors will not be described. Although two neonates were exposed to hepatotoxins, namely, halothane and lincomycin, their role as aetiological agents is by no means clear. Indeed, the difficulty in ascribing the disease to any of these causes is well illustrated by the history of one of these infants whose hepatitis was associated with eosinophilia and raised antimitochondrial antibodies after 3 exposures to halothane; this suggested a halothane injury at the time. However, the finding of a gallstone in the same infant at the age of 18 months, made this conclusion much less certain. In the genetic group, one child had galactosaemia, two were found to have cystic fibrosis, but thirteen showed alpha-1-antitrypsin deficiency, these children constitute the rest of this paper.

All of our thirteen patients presented with jaundice, pale stools and dark urine, starting within the first 4 weeks of life, except for one child whose jaundice was not noticed until the sixtieth day. The maximum recorded bilirubins ranged from 2 mg% to 16 mg% and in all these patients jaundice cleared during a period ranging from 2 weeks to 6 months, and was accompanied by raised serum aspartate transaminases and alkaline phosphatase. Apart from the findings of hepatitis B antigen already mentioned, no other similar aetiological factor was detectable during the acute period of the illness.

Earlier reports in the literature have stated that the outlook for children with hepatitis and alpha-1-antitrypsin deficiency is uniformly bleak with features of cirrhosis appearing in the first and second decade of life (Sharp et al., 1969; Sharp, 1971). Since these reports have been based on studies in patients who already had cirrhosis, we wondered if this was necessarily so in patients who had only a mild illness in the neonatal period.

Of the thirteen patients in our series, four have developed cirrhosis and its complications by the age of 1 year, and two of these have died. The remaining nine, however, are clinically well and thriving.

The range of maximum recorded abnormality of liver function tests in twelve of the thirteen patients shown in Fig. 1 reflects the variability of the acute hepatitis among these patients. It is noteworthy that the maximal abnormal results were found in the four infants who have developed cirrhosis and its complications by the age of 1 year. For the sake of convenience, the severely affected four patients will be referred to as group A, and the remaining nine as group B.

Are the complications of cirrhosis inevitable in patients in group B? As the ages of all our patients ranged from 7 months to 6½ years (mean—27·8 months), the period of follow-up is too short to answer this important question. We felt that it was of interest to look at the course of the acute illness and the pathological changes in the liver in the first 6 months of life to see if a different pattern of response was evident.

The variable nature of the course of the disease is illustrated in Table 3, where it is seen that the age at onset of jaundice was less (range 2–10 days) and the
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Table 3. Alpha-1-antitrypsin deficiency and neonatal hepatitis syndrome

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<tr>
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<th>Group A</th>
<th>Group B</th>
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<tr>
<td>No. of patients</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Age of onset (days)</td>
<td>4.7±1.9</td>
<td>18.4±6.0</td>
</tr>
<tr>
<td>Mean ± S.E.M.</td>
<td>P&lt;0.1</td>
<td></td>
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<tr>
<td>Duration of Jaundice (months)</td>
<td>5.2±0.5</td>
<td>2.4±0.4</td>
</tr>
<tr>
<td>Mean ± S.E.M.</td>
<td>P&lt;0.05</td>
<td></td>
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<tr>
<td>Biopsy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Fibrosis</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>2</td>
<td>1</td>
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Clinical course of their illness. Note that of the nine children who were mildly affected, four have already got fibrosis on biopsy and one further child has cirrhosis. There is therefore considerable variability in the pathological changes seen on liver biopsies and even among the group that is mildly affected, irreversible changes may have occurred.

What then is the prognosis in those infants who on liver biopsy have features of hepatitis only, for instance, as opposed to those with rather more advanced changes? The liver biopsy of one such patient on haematoxylin and eosin stained section (Fig. 2) shows periportal inflammatory cell infiltrate and giant cell formation, features which are commonly recognized in neonatal hepatitis. Eighteen months later, however, a repeat biopsy (Fig. 3) shows definite evidence of excess fibrous tissue around the portal tract. This child, who is now 3½

![Fig. 1. Maximum recorded levels of S. bilirubin, aspartate transaminase (S.G.O.T.) and alkaline phosphatase in patients with N.H. syndrome and alpha-1-antitrypsin deficiency. The triangles (▲) indicate patients who developed cirrhosis and its complications by the age of 1 year. The interrupted line is the upper limit of normal for each parameter.](http://pmj.bmj.com/)

![Fig. 2. Needle biopsy specimen of liver at 3 months from a patient in group B showing inflammatory cells around the portal tracts and giant cell formation (Haematoxylin and Eosin preparation).](http://pmj.bmj.com/)
years old, is clinically well and thriving, although he
continues to show mild elevation of serum aspartate
transaminases and alkaline phosphatase in his liver
function tests.

Indeed, of all the six infants that were tested from
this group of nine, similar continuing abnormalities
in liver function tests are detectable on follow-up
study. Thus, in spite of their relative wellbeing, one
is still unsure of the ultimate outcome of their con-
dition.

The duration of follow-up of cases of Neonatal
Hepatitis Syndrome in whom no aetiological factor
was identified, i.e. the 'unclassified' group—is too
short to comment on their ultimate outcome. Never-
theless, it is noteworthy that of forty-eight such
cases observed so far, only six show evidence of
fibrosis or cirrhosis on early liver biopsy, as opposed
to eight out of the thirteen with alpha-1-antitrypsin
deficiency. There has been only one death due to liver
disease out of this 'unclassified' group. Thus the
prognosis for patients with the Neonatal Hepatitis
Syndrome and Pi ZZ phenotype does appear to be
worse than for patients who have normal alpha-1-
antitrypsin.

Conclusion

Our observations of the Neonatal Hepatitis Syn-
drome and alpha-1-antitrypsin deficiency, show that:

(1) in a circumscribed area that was studied the
frequency of alpha-1-antitrypsin deficiency is similar
to that of biliary atresia;

(2) hepatitis B antigen or antibody is a possible
'trigger' factor in the Pi ZZ phenotype who develops
hepatitis in the newborn period;

(3) the disease among these subjects has a variable
course, but long-term studies are clearly necessary in
order to determine whether cirrhosis is the inevitable
outcome;

(4) prognosis appears to be worse among these
children when compared to those with neonatal
hepatitis who do not have the deficiency.

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study could not have been possible.

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Conclusion

Our observations of the Neonatal Hepatitis Syn-
drome and alpha-1-antitrypsin deficiency, show that:
Dr Chastell of Thanet asked, 'Have you treated these children in any way whatsoever, either dietary or drug wise?' Dr Cottrall replied that the four children in group A, all of whom had evidence of continuing liver disease, had been treated with a variety of agents. Three had had phenobarbitone, three had corticosteroids, one had had both corticosteroids and Azathioprine, one had prolonged course of Cholestyramine. Dietary supplements of vitamins and medium chain triglycerides were also given. We have no clear evidence that any of these agents modified the serum alpha-1-antitrypsin concentrations, nor affected the course of the disease. Dr Peter Scheurr asked if PAS positive globules were always to be seen in the biopsies of the infants with neonatal hepatitis and whether this observation could be used for diagnosis. Dr Cottrall answered that diagnosis in our cases was based on the serum alpha-1-antitrypsin phenotype but in some liver biopsies in which PAS positive material had been looked for it had been found. Dr Marshall of London asked whether hepatitis B antigenaemia was persistent and whether PAS positive granules had been found in those patients who had pulmonary disease. Dr Cottrall replied that the post mortem lung examination in one case who had died did not show PAS positive granular material. Hepatitis B antigen had been found in three of the first five patients by either immunoelectrophoresis or complement fixation test. The sixth child was positive to hepatitis B antigen on radioimmunoassay only. In all these instances the antigenaemia had been transient. In some patients antibody has been examined for by complement fixation tests and radioimmunoassay, but none found.

Dr Glasgow of Belfast reporting on eleven patients with alpha-1-antitrypsin deficiency and liver disease seen in Toronto while working with Dr Sass-Korstak, stated that his experience had been very similar to Dr Cottrall's. Two of the eleven patients had died, 50% of the remainder were very well and 50% ill. The ill patients with more advanced liver disease had more abnormal liver function tests initially and some of the children in fact had persistent mild hyperbilirubinaemia.

**General discussion on alpha-1-antitrypsin deficiency**

Much of the discussion during this period centred around the difficulties of defining liver disease in infants. Dr Douglas, Glasgow, stressed the importance of trying to differentiate between parenchymal disease, duct disease, or portal tract disease. The term 'hepatitis' clearly means different things to different people. Dr Emery took the view that the word 'hepatitis' was completely outmoded except where there is knowledge of an infectious agent. Professor Zuckerman reminded the audience of the World Health Organization definition, 'Viral hepatitis is acute inflammation of the liver caused by two immunologically distinct agents referred to as virus A, which causes type A hepatitis, or infectious hepatitis, and virus B which causes serum hepatitis or hepatitis B'. This does not include inflammation of the liver caused by other known viruses such as yellow fever, cytomegalovirus, or EB virus. He took the view that hepatitis was acute inflammation of the liver and nothing else, the lesion in hepatitis being one of inflammation. Dr Emery, commenting on this stated that often one does not see the ordinary signs of hepatitis.

Dr Eddleston commented that some of the liver disease in children we were talking about was clearly caused by viral hepatitis but much of it was ill-defined, but one had to adopt definitions which were workable, for example some of the children had already developed cirrhosis, some had jaundice which was due to hepatocellular disfunction, in others cholestasis appeared to be the predominant abnormality. If one were to use such terms one could make a start to classifying these conditions and defining groups of some homogeneity with uniform response to treatment X or Y. It was certainly not good enough to talk about hepatitis without characterizing the condition further.
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