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Prognosis of babies with neonatal hepatitis

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SUMMARY 105 babies with neonatal hepatitis were studied carefully and followed for up to 11½ years. Ascertainment was complete for those with severe and persistent jaundice, but less complete for mild or anicteric cases. Prognosis was found to be poor (40% death or cirrhosis) in babies with persistently acholic stools, but relatively good (<15% death or cirrhosis) in those with jaundice which was less persistent and less obstructive. The presence of second diseases (including α_1-antitrypsin deficiency or a family history of other affected children) seemed to play a part in determining poor prognosis. A distinctive group of babies (22 cases) presented with acute fulminant illness (with or without jaundice) in the neonatal period. Cytomegalovirus infection carried a relatively good prognosis. Guidelines for selection of patients for therapeutic trials are suggested.

Debate has raged for many years about the prognosis of neonatal hepatitis (NNH) and about the factors which may affect the prognosis adversely. Unfortunately very few facts have been available as a basis for this debate. This paper presents some pertinent facts gathered from an 11½-year prospective study including almost all babies with neonatal liver disease born in the State of Victoria in this period.

Materials and methods

Case ascertainment has been described (Danks *et al.*, 1977) and is thought to be nearly complete for severe cases of NNH in Victoria from 1 July 1963 to 31 December 1974. Some mild cases must have escaped detection. A very broad definition of NNH was used (Danks *et al.*, 1977), based upon microscopical changes in the liver (Smith *et al.*, 1977) in 88 patients. 17 babies with particularly typical clinical features were included without biopsy support for the diagnosis. Babies whose symptoms could not be dated to an onset before 4 weeks of age were excluded (14 babies with onset between 5 and 8 weeks were excluded).

Intrahepatic biliary atresia (IHBA) (Longmire, 1964; Alagille *et al.*, 1975) posed problems because it can be distinguished from NNH only by the clinical and pathological course. The outcome of IHBA has been shown for comparison with NNH in Table 1, and the IHBA cases have been included when looking at the effects of surgery upon prognosis. There were 105 babies with NNH and 11 with IHBA in the study.

Follow-up was achieved as part of clinical care in most cases, but a few babies treated by other paediatricians were reviewed at longer intervals. Further biopsies were performed in babies with persisting clinical abnormalities and in babies whose early biopsies showed fibrosis or severe damage. Almost all babies were followed to 1974 or to earlier death. Necropsy was performed in all who died, but one.

Children whose biopsies had never shown significant fibrosis were classed as 'clinically normal' if growth and development were within normal limits and if there were no clinical or biochemical abnormalities. Babies who were healthy but less than 2 years old were regarded as 'too young to assess' the prognosis. All other patients were rebiopsied and classified according to the biopsy result.

The term 'obstructive' is used to describe babies whose stools remained clinically acholic for more than 4 weeks. 'Partially obstructive' indicates passage of stools which were pale but not acholic, or passage of acholic stools for a shorter period of time. Babies whose stools were always normal in colour are described as having 'nonobstructive' jaundice.

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Table 1 *Outcome in babies with IHBA and with NNH (classified by aetiology, by type of jaundice, and according to presence of a second disease)*

			Aetiological categories of NNH									
			Genetic		*Infective*		*No cause found*		*NNH classified according to type of jaundice*			
Outcome	*All NNH*	*IHBA*	*Galactosaemia*	*α_1AT deficiency*	*CMV*	*Other**	*Familial*	*Sporadic*	*Obstructive*	*Partially obstructive*	*Non-obstructive‡*	*NNH with second disease*
Recovered												
Biopsy proven	6	4†	1	0	2	1	1	1	1	3	2	2
Clinical evidence	45	0	3	3	6	1	2	30	3	19	23	12
Persisting disease												
Fibrosis or inflammation	10	1	0	2	3	0	0	5	4	6	0	2
Cirrhosis	5	0	0	2	0	1	1	1	3	1	1	3
Death												
Before 3 m	22	1	1	1	0	5	4	11	0	5	17	10
After 3 m	6	4	0	0	0	0	2	4	5	0	1	5
Lost to follow-up	6	0	0	0	1	0	0	5	1	2	3	0
Too young to assess	5	1	1	0	1	1	0	2	1	3	1	0
Total	105	11	6	8	13	9	10	59	18	39	48	34

*Agents involved were rubella (1 recovered, 1 died), toxoplasmosis (1 died, 1 too young), syphilis (1 recovered), hepatitis B (1 cirrhosis), Coxsackie B_2 (1 died), Coxsackie B_4 (1 died), and parainfluenza type 3 (1 died).
†Biopses in these 4 children showed small portal tracts with no bile ducts and no significant fibrosis.
‡Includes patients with no jaundice.

Results

The outcome of the whole group of patients with NNH and IHBA is shown in the first columns of Table 1. It is immediately apparent that NNH is a serious disease with 30% mortality. The 5 patients with cirrhosis and about half of the 10 with persisting inflammation may eventually die of their disease, bringing the final mortality as high as 40%.

Aetiological factors. It is apparent in Table 1 that the large group of patients in whom no definite aetiological factor was identified contributed heavily to the mortality, and that those families containing several babies with NNH contributed especially heavily. Deaths after 3 months of age were confined to these two categories, which also contributed two-thirds of the early deaths. Most of the remaining early deaths were caused by identified acute viral infections.

The one patient who died of galactosaemia was diagnosed only at necropsy (Oberklaid *et al.*, 1976). Only 1 of the 8 α_1-antitrypsin (α_1AT) deficient babies has died, and 3 seem to have made such good clinical recovery that biopsy was not performed. The sister of one of the patients in this group presented with NNH in 1956 and is now clinically and biochemically normal at 19 years of age, despite a Pi ZZ genotype. Cytomegalovirus (CMV) appeared to carry a relatively good prognosis.

Progression to cirrhosis and later death due to liver failure were seen mainly in familial cases and in those with a proven second disease—α_1AT deficiency in 2, Aagenaes's syndrome in 1, an affected sib in 2 cases (with consanguinity in one family), superadded postnatal CMV infection in 1, Niemann-Pick disease in 1, and polycystic kidneys in another. A second factor was present in 7 of the 13 babies in whom progressive liver disease developed.

Clinical categories. The type of jaundice influenced the outcome greatly. Most of the 22 early deaths occurred in patients with nonobstructive jaundice and in patients who were never jaundiced at all. 14 of these babies died in the first month and most of these presented with an overwhelming systemic illness in which jaundice was a late or insignificant feature. An infective cause was found in some, but no cause was identified in the majority.

Most of the babies with jaundice of a non-obstructive type (or no jaundice) who survived the first month made a complete recovery (20 of 22 babies). One baby died at 4 months of progressive liver disease, cerebral degeneration, and haemolytic anaemia—his parents were first cousins and a sib died of liver failure on the first day of life. Only one baby has developed cirrhosis—an HBsAg positive baby born to a drug addict.

On the other hand, those babies with persistent obstructive jaundice had a very poor prognosis. Only 4 of 16 babies have recovered fully, and an eventual mortality of 60–75% seems likely.

Most of the patients with partially obstructive features made good progress after the newborn period. 3 of the 4 babies who died early had other serious abnormalities (Down's syndrome 2 and multiple major malformations 1), so only 1 death in this category can really be attributed to the liver disease. Eventual mortality in this group seems unlikely to exceed 15%.

Finally, an attempt was made to study the effects of operative diagnostic procedures upon prognosis, especially upon progression to cirrhosis (Table 2).

Table 2 *Influence of operative and diagnostic procedures upon outcome in NNH and IHBA (excluding 6 babies lost to follow-up and 6 too young to assess)*

		Persisting disease		*Death*		
	Recovered (clinical or biospy evidence)	*Fibrosis or inflammation*	*Cirrhosis*	*Early*	*Late*	*Total assessable*
Obstructive						
Needle biopsy (LA)	3	2	2	1	5	13
No biopsy	2	0	0	0	0	2
Cholangiogram and operative biopsy (GA)	4	2	1	0	4	11
Partially obstructive						
Needle biopsy (LA)	9	3	0	1	0	13
No biopsy	3	1	1	1	0	6
Needle biopsy (GA)	11	2	0	2	0	15
Nonobstructive						
Needle biopsy (LA)	11	0	0	0	1	12
No biopsy	10	0	1	17	0	28
Needle biopsy (GA)	4	0	0	0	0	4

LA, GA = local, general anaesthesia.

From 1963 to 1966 babies with obstructive jaundice had operative cholangiography under general anaesthesia, and needle liver biopsy was performed under general anaesthesia in those with less obstructive clinical features. After 1966, needle biopsy using local anaesthesia replaced both procedures and very few operations have been performed on babies with NNH (Danks, 1977). It is apparent that the obstructive cases have done badly whichever procedure was used, and that needle biopsy under general anaesthesia had no harmful effect on babies with partially obstructive jaundice.

Discussion

Neonatal hepatitis is a serious disease. However, it is obvious that it is not one disease (Danks *et al.*, 1977) and it is therefore important to look at the effect of aetiology upon prognosis. It is also vital to consider whether biases of ascertainment may be exaggerating the seriousness of the outcome.

This study has ascertained 100% of babies with severe and prolonged obstructive jaundice in the State of Victoria. Consequently it is possible to say with complete confidence that this form of NNH carries a very serious prognosis. This fact has been recognized before and there has been a tendency to attribute this to operative intervention in the management of these patients (Thaler and Gellis, 1968). The analyses presented in this study appear to refute this suggestion and blame the poor outcome upon the disease itself.

Ascertainment is much more difficult to assess in those patients with NNH who have minimal jaundice or no jaundice. Some patients run a rapidly lethal course in the first few weeks of life. Unfortunately the number of babies in the community who suffer anicteric NNH is unknown and it is therefore impossible to describe the prognosis of this class of disease accurately. Arguments advanced elsewhere (Danks *et al.*, 1977) suggest that mild anicteric NNH is very common. If this is true, acute fulminant lethal illness may not be much more common than in older patients. However, it is important to remember that acute fulminant NNH can present in the newborn period as an illness mimicking septicaemia, without significant jaundice. Some of these patients might possibly survive with intensive supportive therapy, which has been rarely tried in this age group. Our own experience is limited to one published and unsuccessful attempt (Danks, 1974) and 2 recent babies treated with repeated exchange transfusions, one of whom made a complete recovery.

The majority of babies with NNH present at 3 or 4 weeks of age because of persisting jaundice with stools that are paler than normal, but not acholic. The prognosis in this group of patients is good. The most interesting point is that patients in whom multiple possible aetiological factors can be shown seem more likely to progress to chronic liver disease. Second disease processes are remarkably frequent in babies with NNH and may act by rendering some babies unduly susceptible to the effects of some common infective agent or agents (Danks *et al.*, 1977). This hypothesis could be extended to suggest that some second disease processes may also increase the risk of persistent liver damage. The hypothesis is important because treatment of one of the multiple aetiological factors may allow the natural healing processes to deal with the remaining untreatable aetiological factors. Several patients in the series started to recover well and then suffered a second infective illness (CMV 2, tuberculosis 1) after which relentless progression to liver failure ensued.

This line of reasoning leads one to search for any treatable components in the aetiology. Obstructive jaundice is more severe and persistent in NNH than in hepatitis in older patients. A relationship to the different metabolism of bile salts in the newborn may exist and trials of treatments directed to reducing the bile salt levels seem warranted, e.g. with phenobarbitone and/or cholestyramine. Liver copper content can reach very high levels in some of these patients (Reed *et al.*, 1972) and reduction with penicillamine may have a beneficial effect, which may make the difference between progressive disease and healing in some patients.

Whatever methods of treatment are chosen, it is apparent that the group of patients with severe obstructive features would be the best to choose for a therapeutic trial. The prognosis is so bad that a good effect would become obvious even in an uncontrolled study and one could easily justify using forms of treatment which carry some risk of side effects. On the other hand, the spontaneous recovery rate in the less obstructive cases is so good that it would be very difficult to show an effect of any therapy. The rapidly fulminant cases vary so much from one to another that therapy would be extremely difficult to assess. This has been the experience even in adults in whom diagnosis is much easier.

Serum bilirubin levels, serum transaminase levels, growth patterns, and other clinical parameters were examined for prognostic significance and none proved useful. A careful study of the liver biopsies indicated that widening of the portal

tracts with proliferation of bile ducts was a poor prognostic feature (Smith *et al.*, 1977). This finding correlated strongly with the severe obstructive features seen clinically and this combination should warn the clinician to be very guarded regarding prognosis.

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