Obstructive Jaundice in Early Infancy

AETIOLOGICAL, CLINICAL AND PROGNOSTIC ASPECTS

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SUMMARY

The aetiology of obstructive jaundice, as encountered in 113 Black and 17 White infants, as well as the clinical manifestations and prognosis, are discussed, together with a review of the literature. The commonest causes in Black infants were syphilitic hepatitis (28 patients), neonatal hepatitis (27), extrahepatic billary atresia (20), veno-occlusive disease (8) and sepsis (6). Of the 17 White infants 12 suffered from neonatal hepatitis, 4 from the 'inspissated bile syndrome' following blood group incompatibility, while only 1 had extrahepatic biliary atresia. The clinical features of these entities as well as the difficulty of distinguishing between neonatal hepatitis and biliary atresia are discussed. The importance of establishing the cause of obstructive jaundice as soon as possible is stressed, because specific treatment is available in the case of some of the entities, especially syphilis, sepsis and urinary infection.

Obstructive jaundice in infancy is a serious disorder. Fifty-two of the 113 Black infants died while still in hospital or soon after discharge, and it was obvious that at least another 20 would die of cirrhosis at a later stage, the expected mortality, therefore, being at least 64%.

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In previous publications[1,2] we discussed some aspects of prolonged obstructive jaundice in young infants. Since that time, however, the number of infants in our series has increased considerably and we considered it worth while to re-examine some aspects of the problem. The present article is concerned with aetiological, clinical and prognostic aspects.

The different entities encountered in a total of 130 patients (113 Black and 17 White infants) admitted to the H. F. Verwoerd Hospital over the past 7 years are set out in Tables I and II. The diagnostic procedures, which will be discussed in detail in a later article, included in most instances the clinical course, laboratory tests for specific disease entities (including urinary examination for infection, reducing substances and cytomegalic inclusion bodies), serological tests for syphilis (on both infant and mother) and toxoplasmosis, liver function tests, liver scanning and histological examination of the liver specimens obtained by needle and/or wedge biopsy, or at post-mortem examination.

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TABLE I. CAUSES OF OBSTRUCTIVE JAUNDICE IN BLACK INFANTS

Diagnosis	Number of patients
Syphilitic hepatitis	28
Neonatal hepatitis	27
Extrahepatic biliary atresia	20
Veno-occlusive disease	8
Septicaemia	6
Cirrhosis (aetiology unknown)	3
Hepatofibrosis	2
'Inspissated bile syndrome' (due to blood group incompatibility)	2
Urinary tract infection	1
Cardiac failure	1
Cause not established	15
Total	113

TABLE II. CAUSES OF OBSTRUCTIVE JAUNDICE IN WHITE INFANTS

Diagnosis	Number of patients
Neonatal hepatitis	12
'Inspissated bile syndrome' (due to blood group incompatibility)	4
Extrahepatic biliary atresia	1
Total	17

During the past few years attempts were made to isolate viruses (cytomegalovirus and rubella virus) from urine, and enteroviruses from faeces. A few serological tests for rubella antibodies and hepatitis-associated antigen and antibody were also done.

AETIOLOGY

The commonest causes of obstructive jaundice were neonatal hepatitis, syphilitic hepatitis and extrahepatic biliary atresia. A considerable number of infants suffering from veno-occlusive disease, sepsis and the 'inspissated bile syndrome' following blood group incompatibility were also encountered.

Syphilitic Hepatitis

Syphilitic hepatitis was the commonest cause of obstructive jaundice in Black infants. Serological tests for syphilis were positive in all 28 infants and also in 20 of 21 mothers who were available. The infant whose mother had negative tests, however, showed typical syphilitic bone lesions on radiological examination.

As the histological interpretation of biopsy specimens of the infants was difficult,[3] it is not impossible that the obstructive jaundice in a few cases could in fact have been due to neonatal hepatitis rather than syphilitic hepatitis.

Neonatal (Giant Cell) Hepatitis

A diagnosis of neonatal hepatitis was made in 38 patients (26 Black and 12 White infants). It is well established that neonatal hepatitis is not a single entity, but may be caused by several infections, especially viral, and can also be the result of certain non-infective factors.

Cytomegalovirus infection seems to be an important cause of neonatal hepatitis.[4] In the present series, however, no cytomegalic inclusion bodies were detected in the 23 urine specimens examined. Attempts to isolate the virus from 8 urine specimens of 7 patients with neonatal hepatitis also failed.

Serum hepatitis virus infection (hepatitis type B; Australia antigen hepatitis; hepatitis-associated antigen infection; MS-2 virus infection). Although neonatal hepatitis can be caused by the serum hepatitis virus,[5] it seems to be an uncommon cause.[6,7] Hepatitis-associated antigen (HAA) can be transmitted from a mother to her newborn baby. This applies to clinically affected mothers as well as, in rare instances, HAA carriers.[5-8] Although transplacental transmission of HAA *in utero* can occur,[5] this mode of infection seems to be very rare.[6,7] There is conclusive evidence that transmission, should it occur, takes place either during delivery by oral contamination with blood or faeces of the mother, or soon after birth during maternal care of the infant.[5,6,8] Transmission of the antigen via mother's milk also seems possible, but in the limited number of studies carried out no antigen was detected in the milk of HAA-positive women.[6,7]

With few exceptions, evidence of infection (appearance of HAA in the blood) in infants of HAA-positive women developed 2 - 3 months after birth. This is compatible with transmission at parturition. Most of these HAA-positive infants were either asymptomatic or showed evidence of subclinical hepatitis.[5,6,9] However, clinical hepatitis, which may be fatal, can occur in these infants.[8]

It seems unlikely that HAA was an important aetiological factor in our patients with neonatal hepatitis. The majority of our patients developed jaundice soon after birth which is, as mentioned earlier, exceptional in patients with hepatitis due to HAA. No hepatitis-associated antigen and antibody were detected in the sera of 9 of our patients tested. These tests, however, were done soon after admission and were not repeated.

Infectious hepatitis virus infection (hepatitis type A; MS-1 virus infection): There is difference of opinion whether neonatal hepatitis can be caused by the virus of infectious hepatitis.[10] In a recent survey, however, epidemic hepatitis-associated antigen (EHAA; Milan antigen) was detected in the serum of 6 of 11 infants with neonatal hepatitis tested.[11] This seems to indicate that the virus of infectious hepatitis was the responsible agent in these patients.

Rubella virus infection: Rubella virus infection, acquired *in utero*, is a well-established cause of neonatal hepatitis.[10] The sera of 9 patients with neonatal hepatitis were tested for the presence of rubella antibody by means of the haemagglutination inhibition test. Evidence of rubella (raised titre and isolation of the virus from urine) was obtained in 1 infant.

Other viral infections: Both Coxsackie B and herpes simplex virus can cause severe hepatitis in the newborn. Giant cell formation in the liver, however, is rarely, if ever, a feature in infants suffering from these infections.[10]

Toxoplasmosis: The clinical and histological features of neonatal hepatitis, including giant cell formation, can also be caused by the protozoan parasite, *Toxoplasma gondii*.[12] In the present series, serological tests on the sera of 27 patients with neonatal hepatitis were all negative.

Genetic Causes

It seems certain that neonatal hepatitis is not invariably the result of infection.[10,11] Genetic factors, which may be either familial or sporadic, seem to be of aetiological importance in some cases. Both neonatal hepatitis and biliary atresia may be associated with the trisomy 17 - 18 syndrome.[13]

Recently several cases of neonatal hepatitis have been described in infants with deficiency of alpha-1-antitrypsin in the serum.[11,14] This substance inhibits various proteolytic enzymes, including trypsin. Liver involvement seems to be frequent in homozygous-deficient children ('Pi type ZZ').[14] Liver damage does not seem to be caused by excessive proteolytic activity in the liver. It has been found, in fact, that these livers contain excessive amounts of alpha-1-antitrypsin which is structurally different from the normal substance.[14] It has been suggested that this condition is a storage disease, the excessive amounts of inhibitor interfering with cellular processes or with intracellular proteolytic enzymes.[14]

Extrahepatic Biliary Atresia

Twenty-one patients (20 Black and 1 White) were regarded as cases of extrahepatic biliary atresia. No patients with intrahepatic biliary atresia were encountered.

Biliary atresia is usually attributed to faulty embryogenesis. It has recently been suggested, however, that it may be an acquired lesion, biliary atresia and neonatal hepatitis representing different stages of a single disease caused by an infective agent.[15] There is suggestive evidence

that both biliary atresia and neonatal hepatitis can be caused by rubella, cytomegalovirus and hepatitis-associated antigen.[16-18] In one infant reported biliary atresia apparently followed ascending cholangitis due to prenatal *Listeria monocytogenes* infection.[19] As mentioned earlier, both neonatal hepatitis and biliary atresia were observed in several infants suffering from the trisomy 17 - 18 syndrome.[13] In addition, mothers who suffered from hepatitis during pregnancy had children with biliary atresia. Extrahepatic ducts can later also open up in spite of finding atresia at operation.[15] The possibility also exists that extrahepatic biliary atresia may be caused by amphetamine ingestion by the mother during pregnancy.[20]

Veno-occlusive Disease

Veno-occlusive disease was the fourth commonest cause of obstructive jaundice in Black infants in the present series. Four of the 8 infants were less than 2 months of age when symptoms developed. As an onset of jaundice after the age of a few weeks or even months is sometimes observed in infants with either neonatal hepatitis or biliary atresia, it is advisable to include veno-occlusive disease in the differential diagnosis of obstructive jaundice in young Black infants.

There seems to be little doubt that veno-occlusive disease in South Africa is caused by the intake of parts of *Senecio* plants which contain pyrrolizidine alkaloids which are hepatotoxins.[21] The mode of ingestion of senecio alkaloids by these 8 infants could not be established. The possibility exists that witch-doctors' medicines may contain these alkaloids. A history of a visit to a witch-doctor, however, was obtained from the mother of only 1 of the infants.

More than 300 species of *Senecio* are found in South Africa. In an extensive survey carried out by Rose[21] in the Eastern Cape, the following points were established: these plants are used by Blacks as a spinach and as a remedy for several ailments, especially as purgatives and in enemas; it is even given to babies as a purgative and an enema, as well as to babies being weaned.

As the pyrrolizidine alkaloids are soluble, transplacental transfer of toxin affecting the fetal liver seems to be a distinct possibility.

Sepsis

Sepsis was considered the cause of obstructive jaundice in 6 of the Black infants but was not encountered in White infants. Septicaemia should always be considered in the differential diagnosis of jaundice in newborns and young infants, since the infection is amenable to treatment.[22]

It has now become well-established that jaundice, often of the obstructive type, apparently due to an associated toxic hepatitis, can be caused by urinary infection in infants.[23] Since symptoms apart from jaundice can either be absent or non-specific, the nature of the disease may not be recognised.[23,24] If urinary infection is not recognised the infection may readily progress to septicaemia.[24] One of our patients suffered from urinary infection due to *E. coli*.

'Inspissated Bile Syndrome'

It is generally accepted that the so-called 'inspissated bile syndrome', due to the presence of viscid bile in the bile ducts, is a rare cause of obstructive jaundice in infancy and that most of the reported patients were in fact suffering from neonatal hepatitis.[12] Many of the reported cases followed haemolysis due to Rh or ABO incompatibility. The obstructive jaundice of 6 of our patients (4 Black and 2 White infants) were the result of blood group incompatibility. After performing exchange transfusions the serum levels of conjugated bilirubin decreased, but this was accompanied by a gradual increase in the levels of conjugated bilirubin. This was later followed by a gradual decrease, normal values being reached (except in 1 of the infants who died) after 2 - 4 weeks. It is accepted that the inspissated bile syndrome associated with erythroblastosis is due to impairment of the excretory mechanism for conjugated bilirubin in the liver cells.[25,26]

Miscellaneous Causes

Other causes of obstructive jaundice encountered in the series were cirrhosis of unknown aetiology (3 patients), hepatofibrosis (2 patients) and cardiac failure in an infant with a ventricular septal defect.

Obstructive Jaundice of Unknown Origin

In a relatively large number (15) of Black infants a definite diagnosis could not be established. One of the reasons was that 10 of these infants were in poor condition on admission and died within a few days. The mothers of 3 other patients who probably had biliary atresia, refused consent for laparotomy, while the mothers of 2 patients removed their babies from hospital while the investigations were still in progress.

Other Causes

There are many other causes of obstructive jaundice in infants which were not encountered in the present series.[3] These conditions, which are rare, include the following: intrahepatic biliary atresia, choledochal cyst, galactosaemia, fructosaemia, toxoplasmosis, chlorpromazine medication, the Dubin-Johnson and Rotor syndromes and hypoplasia of the bile ducts. Several forms of hereditary and idiopathic intrahepatic cholestasis have also been described in recent years.[27,28]

CLINICAL ASPECTS

It is agreed that the differentiation on clinical grounds between extrahepatic biliary atresia and neonatal hepatitis is usually possible.

It is often stated that growth retardation is more pronounced in infants with neonatal hepatitis than in those with biliary atresia.[15,29] This was not the case in the present series, a small mass being a feature in the infants of both groups. In fact, the percentage of Black infants with biliary atresia whose mass fell below the 3rd Boston percentile (83%) was considerably higher than those who suffered from neonatal hepatitis (56%).

Hepatomegaly was almost invariably present in patients with both biliary atresia and neonatal hepatitis. Splenomegaly was present in 61% of infants with biliary atresia and in 51% of patients with neonatal hepatitis.

The only clinical sign which was of some diagnostic value was the colour of the stools. Although acholic stools may be passed by infants with either condition, the passing of yellow stools suggests incomplete obstruction and favours the diagnosis of neonatal hepatitis. It should be kept in mind, however, that patients with biliary atresia can produce yellow stools due to contamination of stools by bile-rich urine.[1] In the present series a history of acholic stools was obtained in 86% of patients with atresia, the corresponding percentage in the patients with neonatal hepatitis being 15%. It is obvious, therefore, that the colour of the stools can be of great diagnostic value.

The urine of infants with both biliary atresia and neonatal hepatitis almost invariably contained bilirubin. Urobilinogen was found in the urine of only 2 patients with biliary atresia and 1 with neonatal hepatitis.

The time of onset of jaundice is of no help in distinguishing between biliary atresia and neonatal hepatitis.[1,15,29] In the majority of infants with both conditions jaundice was noticed within a few days after birth, although in several infants in both groups it was not detected until several weeks after birth.

In 11 of 28 infants with syphilitic hepatitis the diagnosis was suspected on clinical grounds, while the clinical manifestations were indistinguishable from those of neonatal hepatitis or biliary atresia in the remainder. The commonest features were snuffles, epistaxis, and skin eruptions and desquamation. Three patients had oedema, and ascites was present in another. With 1 exception, all patients had hepatomegaly, while splenomegaly was present in 24 (86%) of the patients. Anaemia, usually severe, and often accompanied by leucocytosis and the presence of immature white cells and nucleated red cells in the blood smears, was found in 16 of 24 patients on whom blood counts were done.

Although a definite diagnosis of veno-occlusive disease on clinical grounds is not possible, several features are suggestive. As in the series of Freiman *et al.*,[30] abdominal distension was a presenting feature in all the infants, and all but 1 had ascites. A hard liver was palpable in 7 patients, while splenomegaly was present in 4. In our area abdominal distension of sudden onset, the presence of ascites and an enlarged, hard liver in a Black infant beyond the age of about 2 months, are suggestive of veno-occlusive disease.

Jaundice may be the only abnormal finding in young infants with septicaemia, and signs of toxicity and fever may be absent. For this reason bacterial infection should be considered as a possible cause of jaundice in young infants even if the baby appears to be quite well. Urinary examination and blood culture should therefore always be done in young infants with jaundice.[22] Lumbar puncture may also be indicated in some patients and blood counts should also be done, although anaemia and leucocytosis are often absent.[22]

In the present series all 6 patients were seriously ill and showed overt signs of septicaemia, including neonatal meningitis (2 patients), multiple subcutaneous abscesses (3 patients), purpura, osteitis and septic arthritis. The organisms isolated from blood or pus, or both, were staphylococci (2 patients), *E. coli* and *Aerobacter aerogenes*. No organism was isolated from the other 2 patients, but they had obvious signs of septicaemia, including neonatal meningitis and purpura.

One of our patients had urinary infection due to *E. coli*. This patient had marasmus and severe anaemia. The intravenous pyelogram and voiding cystogram were normal and the patient recovered completely after the institution of antibiotic treatment. As mentioned earlier, jaundiced infants with urinary infection may appear quite well.[23,24]

The diagnosis of the 'inspissated bile syndrome' due to blood group incompatibility presents little difficulty. Initially these patients show manifestations of haemolytic disease, including elevation of unconjugated bilirubin in the serum. The jaundice gradually becomes obstructive and may persist for several weeks.

The 3 patients with cirrhosis had, in addition to jaundice, a large, hard liver, and distended veins on the abdomen. Two had ascites. The clinical features of the 2 patients who suffered from hepatofibrosis were indistinguishable from those of neonatal hepatitis and biliary atresia.

DIAGNOSIS

The aetiology of obstructive jaundice in young infants is established, apart from the history, clinical manifestations, course and special tests to exclude certain specific entities (e.g. septicaemia, syphilis, toxoplasmosis, galactosaemia and viral infections), by liver function tests, liver scanning, needle biopsy and sometimes surgical biopsy and operative cholangiography.[1]

PROGNOSIS

Obstructive jaundice is a serious condition, particularly in Black infants. Fifty-two (46%) infants died in hospital or soon after discharge. It seemed most likely that at least another 20 infants (including 5 with biliary atresia and 2 with cirrhosis), who showed no improvement while in hospital, would eventually die from cirrhosis. The expected mortality rate, therefore, was about 64%, and even this figure may be too low, since some of those who apparently recovered could develop cirrhosis later.

Of the White infants only the patient with biliary atresia died in hospital while another developed severe cirrhosis following neonatal hepatitis. The other 15 patients

seemed to recover completely, but long-term follow-up was not possible.

Eleven of the 28 Black infants with syphilitic hepatitis died in hospital. Another 3 apparently failed to respond to penicillin therapy and still showed signs of severe liver damage, including jaundice, when discharged.

Five of the 27 Black infants with neonatal hepatitis died in hospital, while an additional 5 failed to improve over a period from 6 weeks to 3 months and probably developed cirrhosis. The combined incidence of death and cirrhosis was 37%. It is of interest that none of the White infants died in the acute stage, and only one developed cirrhosis. However, as cirrhosis may develop after many months and even years, the actual percentage will be higher. In the series reported by Thaler and Gellis,[31] 20% of infants with neonatal hepatitis died during the acute stage of the disease. Among 26 patients on whom exploratory laparotomy was done to exclude biliary atresia, about 60% developed cirrhosis, the corresponding percentage for 36 infants not operated on being about 20%. The adverse effect of laparotomy under general anaesthesia on the prognosis (mortality and development of cirrhosis) of infants with neonatal hepatitis has also been documented.[31,32,34]

In the present series none of the infants who died with neonatal hepatitis had undergone surgery. Laparotomy was performed on 2 of the 5 Black infants who subsequently showed evidence of cirrhosis. However, operation was performed because these 2 patients did not improve over a lengthy period and was done to exclude the possibility of an erroneous diagnosis. One explanation for the subsequent development of cirrhosis after laparotomy is that it is usually done on infants who have not improved and are possibly due to develop cirrhosis in any case.

The prognosis of patients with extrahepatic biliary atresia is very poor since only about 5 - 10% patients have surgically remediable lesions.[32,34] In addition, the results of surgical repair are disappointing and cure can probably be expected in only about one-quarter of those treated.[33] None of the patients in the present series was saved by surgery. Two patients had operable lesions, 1 of whom (atresia of common bile duct) died of bronchopneumonia 5 days after cholecystoduodenostomy was carried out. The other patient was admitted in a severe marasmic state and died soon after admission, the nature of the lesion (patent hepatic ducts; atresia of the common bile duct and cystic duct) being established at postmortem examination.

There is a great variation in the mortality rate of infants with jaundice due to septicaemia in different series, the figures varying from 20 - 60% in earlier reports[35] to none in a more recent report.[22] This difference could be due to more awareness of sepsis as a cause of neonatal jaundice, better recognition of the non-specific nature of the clinical manifestations and improvements in antibiotic therapy. In the present series of 6 patients, all were seriously ill, and 3 died. In earlier series several deaths were reported in jaundiced infants with urinary infection, but none occurred in more recent series. The reasons for this decline are probably identical to those mentioned in the case of septicaemia. The patient in the present series recovered completely.

In general the prognosis of infants with 'inspissated bile syndrome' due to erythroblastosis is good and spontaneous recovery is the rule. According to Reiquam *et al.*,[26] however, the mortality rate of erythroblastotic infants whose serum conjugated bilirubin levels exceed 1 mg/100 ml is considerably higher than that of infants with lower levels. In the present series 5 of the 6 infants with this syndrome recovered spontaneously, although the serum levels of conjugated bilirubin were exceptionally high (maximum levels: 11,4; 16,6; 20,8; 23,2; and 7,9 mg/100 ml, respectively). The 6th patient, a Black infant, had shown manifestations of kernicterus on admission and died after about 2 weeks. On admission the total serum bilirubin was 50 mg/100 ml, the conjugated fraction being 26 mg/100 ml.

The prognosis of patients with irreversible cirrhosis is very poor, as surgical procedures for the relief of portal hypertension in children under the age of 4 years are usually unsuccessful.[36]

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