Familial Intrahepatic Cholestasis:
An Update

CAROLINE A. RIELY, M.D.

Assistant Professor of Medicine and Pediatrics
Yale University School of Medicine,
New Haven, Connecticut

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Familial intrahepatic cholestasis is a confusing group of syndromes. Four forms are defined and discussed in detail ("arteriohepatic dysplasia," the Byler syndrome, the THCA syndrome, and Norwegian cholestasis). A comparison of the distinguishing characteristics of these syndromes demonstrates that they share many features, including areflexia, retinal degeneration, and paucity of the intrahepatic bile ducts on biopsy. Alternatively, some traits appear to be specific for a single syndrome: posterior embryotoxon and bony anomalies for arteriohepatic dysplasia, the presence of an abnormal bile acid for the THCA syndrome, and giant cell transformation for Norwegian cholestasis. These syndromes, although rare, merit complete evaluation because, as nature's experiments in bile formation, they represent models of cholestasis and may provide clues to the understanding both of other forms of cholestasis of unknown etiology and of the normal mechanisms of bile formation.

INTRODUCTION

Confusion Abounds

Cholestasis is a state of decreased hepatic bile formation, sometimes associated with elevation in the serum bilirubin but always accompanied by an elevation in serum bile acids [1]. Intrahepatic cholestasis has no extrahepatic, obstructive cause. The term "intrahepatic cholestasis of childhood" has been used to describe patients with prolonged cholestasis in whom no extrahepatic obstruction or atresia is found [2]. Broad definitions such as this include a bewildering variety of patients who demonstrate confusing differences in prognosis and response to therapy. Further confusion arises when this group of patients is subdivided into disparate syndromes which have been only incompletely characterized. This subdivision is still further complicated by the fact that within each syndrome there exists a wide clinical spectrum.

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The first step toward understanding these patients is to define clearly individual syndromes. Such definitions should be detailed in order to provide the best possible structure on which to base the diagnosis. On the other hand, these definitions must also be flexible in order to include the wide clinical spectrum which can occur. Diagnostic criteria which are too exacting only add to the confusion.

When such workable definitions of each syndrome have been established and generally agreed upon, then these rare patients can be accurately compared from institution to institution. Characteristics which are found in multiple, divergent syndromes can then be presumed to be secondary, not of pathogenic significance. Alternatively, characteristics unique to any one syndrome can be supposed to be indicative of pathogenic mechanisms.

As will be seen, many of these cholestatic conditions in childhood are probably of genetic etiology. As such, each presumably represents an "experiment in nature" on the mechanisms of bile formation. Although the production of bile by the liver is surely one of the body's most important tasks, its basic physiology is still very poorly understood [3]. Therefore, each patient with familial intrahepatic cholestasis, no matter how rare, deserves full evaluation, in hopes that a better understanding of nature's "mistakes" will lead to understanding normality.

This paper will review four different types of familial intrahepatic cholestasis. Two types have been studied extensively here at Yale [4,5]. The data presented will include that available in the literature but will be biased toward the Yale experience. The other two have not been studied here but have been clearly described in the literature.

**What's in a Name**

A word about nomenclature is warranted. A disease cannot be adequately described until its etiology is known. Pneumococcal pneumonia is a much more informative name than chronic active hepatitis. All the syndromes discussed herein are of unknown etiology. It seems preferable, therefore, as McKusick suggests [6], to abandon attempts at adequate nomenclature until the specific defects are identified. Instead we will use eponyms or abbreviated (and clearly incomplete) descriptions as names.

**THE SYNDROMES**

"**Arteriohepatic Dysplasia**"

Patients with this condition were probably in the group described by Ahrens et al. in 1951 [7]. Watson and Miller gave this syndrome the name arteriohepatic dysplasia in 1973 [8]. Alagille and co-workers further described these patients, and the syndrome is occasionally given Alagille's name [9]. Because Watson and Miller were the first to report in English one of the major extrahepatic manifestations of this syndrome, we will use the name arteriohepatic dysplasia, recognizing that it is inadequate as a full description and has no pathogenic significance.

This syndrome is associated with cholestasis and usually jaundice in the neonatal period (refer to Table I). Laboratory tests reveal hyperbilirubinemia, although this is not invariable, hypercholesterolemia with a Type II hyperlipoproteinemia, and elevated alkaline phosphatase, SGOT, and 5' nucleotidase. The serum bile acids are moderately elevated but there are no abnormal bile acids present. The jaundice clears in childhood, usually by age four, but milder cholestasis, as demonstrated by elevated bile acids, alkaline phosphatase, and 5' nucleotidase, persists. In the adult, despite normal bilirubin values, the BSP (sulfobromophthalein) Tm is markedly diminished [4].
### TABLE 1
Characteristics of Four Forms of Familial Intrahepatic Cholestasis

| Pattern of Cholestasis | Arteriohepatic Dysplasia | The Byler Syndrome | The THCA Syndrome | Norwegian Cholestasis |
|------------------------|--------------------------|--------------------|-------------------|----------------------|
| Onset                  | Neonate                  | 1–12 mo.           | Neonate           | Neonate              |
| Jaundice               | Clears                   | Persistent         | May clear         | In episodic attacks  |
| Alkaline phosphatase   | (nl < 75) 178–209        | 293–440            | ↑                  | ↑                    |
| 5' Nucleotidase        | (nl < 10) 36–98          | 15–28              | –                 | –                    |
| SGOT                   | (nl < 35) 158–201        | 96–140             | ↑                  | –                    |
| Cholesterol mg/dl      | 199–364                  | 134–141            | Normal            | ↑During attacks      |
| Bile acids             | (nl < 4 μg/ml) 25–56     | 87–130             | ↓ Cholate         | ↑During attacks      |
|                       |                          |                    | ↑ THCA            |                      |
| BSP Tm                 | 0.16, 2.3                | ↓↓                 |                   | –                    |
|                       |                          |                    |                   | –                    |
| Response to phenobarbital | 0                  | +                  | 0                 | –                    |
| Other Organ Involvement|                          |                    |                   |                      |
| Heart                  | PPS, +                   | Normal             | Normal            | –                    |
| Bones                  | Anomalies                | Rickets            | –                 | –                    |
| Kidneys                | ↑ Uric acid              | Normal             | –                 | –                    |
|                       | ↓ Creatinine clearance   |                    |                   |                      |
| Extremities            | Short fingers            | Clubbing           | Clubbing          | Leg edema            |
|                       |                          |                    |                   | –                    |
| Neuro                  | Areflexia                | Areflexia          | –                 | Areflexia            |
| Eye                    | Posterior embryotoxon    | K-F rings, late    | Retinal degradation| –                    |
|                       | Retinal degeneration     |                    |                   |                      |
| Liver biopsy           |                          |                    |                   |                      |
| Bile ducts             | ↓↓                       | May be↑            | ↑ or prolif.      |                      |
| Cholestasis            | +                        | +                  | +                 | +                    |
| Giant cells            | 0                        | 0                  | 0                 | +                    |
| Cirrhosis              | 0                        | +, late            | +                 | Possibly             |
| Presumed inheritance   | Autosomal dominant       | Autosomal recessive| Autosomal recessive| Autosomal recessive  |
| Outcome                | Benign                   | Death in childhood or adolescence | Death by age 2 | Benign (?) |

Key to table: ↓ = decreased, ↑ = increased, 0 = reported to be absent, + = reported to be present, – = not reported.

The remarkable feature of this syndrome is the multitude of associated anomalies in other organs. The face is typically abnormal, with a broad forehead, small maxillary region, and pointed chin [10]. The heart is involved, with markedly attenuated peripheral pulmonary arteries plus a variety of other possible anomalies [11]. There are characteristic anomalies of the bones, including butterfly vertebrae [9], a pointed anterior process of C1, shortened ulna, and decreased interpedicular distances in the lumbar spine. The hands are small with foreshortened fingers. The eyes are involved, with anterior chamber anomalies such as posterior embryotoxon. In addition, some patients have choroidal degeneration with a variable degree of...
retinal involvement. Renal function may be impaired, with hyperuricemia and decreased creatinine clearance. The patients are often areflexic and may have minimal cerebral dysfunction.

The liver biopsy demonstrates cholestasis and a marked paucity of intrahepatic bile ducts. There is no progression to cirrhosis and the outcome appears to be benign. The cholestasis does not improve on phenobarbital therapy, either in the infant or the adult [12]. Transmission from one generation to the next in two instances [4,13] suggests that this syndrome is inherited as an autosomal dominant. Watson and Miller [8] reported a wide variability in clinical expression, as found in other dominantly inherited syndromes.

*The Byler Syndrome*

A more progressive form of intrahepatic cholestasis was reported in 1965 in an inbred Amish family named Byler [14]. Excellent descriptions of similarly affected families have been published from points as divergent as Japan [15] and France [16], as well as from Yale [5]. In this syndrome, the first symptom is often neonatal malabsorption, followed within the first year of life by jaundice (refer to Table 1). As in arteriohepatic dysplasia, the liver function tests reflect cholestasis. As a rule, the cholesterol is normal or low. Initially, the jaundice may come in attacks, precipitated by intercurrent infections, but by childhood it is persistent. Serum bile acid levels are high. Previous reports of elevated levels of lithocholate in the serum [17] have not been substantiated and the bile acid pattern may be normal. The BSP Tm is markedly decreased (less than 1 mg/min) [18].

Other organs are less commonly involved in this syndrome. The rickets frequently observed [5,18] is presumably secondary to severe malabsorption of Vitamin D. The patients may be severely retarded, both mentally and physically [18]. Kayser-Fleischer rings have been observed in the Byler syndrome after many years of cholestasis [19]. The patients also are areflexic and clubbing of the digits [18] is prominent. The liver biopsy may show a relative paucity of intrahepatic bile ducts initially [5], but later cirrhosis develops [18,19]. Phenobarbital therapy lowers the serum bilirubin and decreases the pruritus, although it does not change the serum bile acid levels [12,20]. The occurrence of this syndrome in sibships suggests inheritance as an autosomal recessive [5,16,18]. Abnormalities of BSP transport in the fathers of two cases [18] suggested that this test could be used to successfully demonstrate heterozygotes but subsequent studies of another family have not confirmed this [21]. The prognosis is for death to occur in childhood or adolescence.

*The THCA Syndrome*

In 1975 Hanson et al. reported two siblings affected with a rapidly progressive form of intrahepatic cholestasis which was associated with high levels of 3α,7α,12α-trihydroxy-5β-cholestan-26-oic acid (THCA) in serum and bile [22]. Jaundice appears in the neonatal period in the THCA syndrome (Table 1). The bilirubin and alkaline phosphatase are elevated but the cholesterol is normal. Total serum bile acids are elevated but the cholic acid level is low, with instead a peak which migrates late in the usual gas chromatographic analysis and is identical to THCA. In one case jaundice improved coincident with cholestyramine therapy [22,23].

Involvement of other organs is not prominent. Growth retardation is present. Retinal degeneration was described in one case [23]. Rickets has been reported. The liver biopsy demonstrates paucity of the intrahepatic bile ducts, with progression to
cirrhosis [22]. Phenobarbital has not been effective. The occurrence in sibships suggests autosomal recessive inheritance [22,23], although a defect in presumed heterozygotes has not been detected. Death has occurred by age two in the patients reported thus far [22,23].

Norwegian Cholestasis

In 1968 Aagenaes et al. [24] reported a series of patients with intrahepatic cholestasis from Norway. The patients reported by Sharp and Krivit in 1971 [25] with a similar syndrome were also of Norwegian extraction.

Jaundice occurs in the neonatal period (Table 1). It clears in early childhood but recurs intermittently throughout life, not necessarily in response to insults such as infection or pregnancy. During attacks, the liver function tests are compatible with cholestasis (elevated bilirubin, alkaline phosphatase, cholesterol, and triglycerides). The serum bile acids are elevated but the pattern is normal [10,25].

The most striking finding in this syndrome is profound lymphedema of the legs which begins either in childhood or before puberty. Although the jaundice clears between attacks, the lymphedema is persistent. The patients have growth retardation during attacks, but there is catch up growth and adults are of normal height. Rickets may be present after prolonged cholestasis and attendant malabsorption. Areflexia has been reported in this syndrome.

Liver biopsy may demonstrate either a paucity of intrahepatic bile ducts or some degree of ductular proliferation. The striking biopsy finding in infants with this syndrome is pronounced giant cell transformation of the hepatocytes [26]. Cirrhosis has been reported in adults with the syndrome. The results of phenobarbital therapy have not been reported. The occurrence of the syndrome in sibships suggests autosomal recessive inheritance, although again an abnormality has not been detected in presumed heterozygotes. Since the introduction of Vitamin K therapy these patients no longer die of hemorrhage in infancy and may live normal life spans, although cirrhosis has been reported in some.

Others

Limiting this discussion to these four syndromes excludes several others which might have been included. There exist at least two other types of familial liver diseases of unknown etiology which present in infancy [27,28]. In these syndromes cholestasis is not prominent, so they were not discussed. There are two other well-recognized syndromes of intrahepatic cholestasis: benign recurrent cholestasis [29] and intrahepatic cholestasis of pregnancy [30]. Because these syndromes usually, although not invariably, present after puberty and because they are not generally considered familial—although familial instances have been reported—these were also excluded from this discussion.

DIFFERENTIAL DIAGNOSIS

The four syndromes under consideration are compared in Table 1. Two are benign in outcome (arteriohepatic dysplasia and Norwegian cholestasis) and two progress to death (the Byler and THCA syndromes). The age of onset of these syndromes is usually the neonatal period, although the Byler syndrome may not present until as late as age 12 months. All four syndromes demonstrate chemical cholestasis, with elevation in serum bile acids and alkaline phosphatase. Hyperbilirubinemia is usual although not invariable. Of interest is the contrast observed between the SGOT and
5' nucleotidase in the cases here at Yale. The Byler syndrome patients have more severe hepatocellular disease (progressing to cirrhosis) and more severe cholestasis but have lower SGOT's and 5' nucleotidases than patients with arteriohepatic dysplasia. The serum cholesterol is also helpful differentially: in the "benign" syndromes it is high, whereas in the more progressive syndromes it is normal or low. BSP infusion studies have been used in a variety of clinical situations to assess the capacity of the liver to excrete BSP [31], an organic anion which is metabolized in a fashion similar to bilirubin. A nonspecific decrease in the BSP Tm can be seen in a variety of liver diseases and very low levels are found in the Dubin-Johnson syndrome [32]. Values in this low range are also seen in arteriohepatic dysplasia and in the Byler syndrome. The BSP Tm can also be moderately low in benign recurrent cholestasis, although it returns toward normal between attacks [33].

By definition, the serum bile acids are elevated in all of these cholestatic syndromes. The only specific abnormality is in the THCA syndrome, where the total cholate level is low and instead there is an elevated THCA level. THCA is a major bile acid in alligators and a precursor of cholic acid in humans. Abnormal precursor bile acids, both THCA and DHCA, are also seen in patients with Zellweger's syndrome (the cerebro-hepato-renal syndrome), a disease of multiple anomalies, including infantile cirrhosis [34,35].

Multiple organ involvement can be seen in several of the familial intrahepatic cholestatic syndromes, although this is the particular hallmark of arteriohepatic dysplasia. In this condition, posterior embryotoxon has been seen in all patients and may be quite specific for this disease. Variable degrees of choroidal sclerosis and retinal degeneration are found, and it is interesting that retinal involvement is also reported in one patient with the THCA syndrome. K-F rings have been reported late in the course of the Byler syndrome but are in no way specific for this disease. Absent or markedly decreased reflexes have been reported in three of the four syndromes discussed. Finally, examination of the extremities in these syndromes can be very rewarding. Patients with both of the "progressive" conditions (Byler and THCA) have clubbing, whereas patients with arteriohepatic dysplasia have small hands with foreshortened fingers and patients with Norwegian cholestasis have lymphedema.

Improvement in cholestasis during phenobarbital therapy has been reported both in adults and children [36]. The hyperbilirubinemia of the Crigler-Najjar syndrome can be successfully treated with this drug, which delineates two distinct subgroups, one which responds to phenobarbital with a decrease in serum bilirubin, and one which does not [37]. Phenobarbital was initially felt to be useful in the treatment of familial intrahepatic cholestasis [38,39,40], although it is clear that not all patients respond [39]. We have demonstrated a decrease in serum bilirubin on phenobarbital in patients with the Byler syndrome. No change was seen in the patient with the milder condition, arteriohepatic dysplasia [12], and none reported in the THCA syndrome [22].

The liver biopsy may be very helpful in the diagnosis of these syndromes [41], but only when taken in the clinical context. Table 1 shows that a paucity of intrahepatic bile ducts (Fig. 1) may be found in any of the syndromes under discussion, but this is a nonspecific finding and should not be used as the sole diagnostic criteria for any syndrome. Thirteen children with paucity or absence of the intrahepatic bile ducts have been evaluated at Yale in the past 30 years (Table 2). The most common cause of this finding was arteriohepatic dysplasia, with extrahepatic atresia the second most common cause. Several of these patients had syndromes which did not readily fall into any specific syndrome.
FIG. 1. Portal triad from a patient with arteriohepatic dysplasia. A large vein is seen, as well as several smaller arterioles. No duct is present. This appearance could be found in any of the four conditions discussed.

DISCUSSION

An analysis of Table 1 demonstrates that several of the characteristics of these syndromes occur in more than one syndrome. It would seem safe to assume, therefore, that these characteristics are nonspecific and are in some way secondary to the underlying disorder. For instance, it is not surprising that clubbing of the extremities has been reported in the two more progressive syndromes, as this finding is common in cirrhosis. Similarly, a decrease in the BSP Tm has been reported in many forms of liver disease and is found both in arteriohepatic dysplasia and in the Byler syndrome. As discussed above, a decrease or absence of the intrahepatic bile ducts is nonspecific. It would be of interest to speculate that perhaps this decrease in bile ducts is secondary to the cholestasis, the decreased hepatic bile formation. It is unlikely to be the cause of the cholestasis as it is quite nonspecific for any one syndrome.

The table reveals two new associations with infantile liver disease and/or cholestasis. The first is hypo or areflexia, a finding in three out of the four syndromes. This association has previously been reported in children with unclassified progressive liver disease [42] but its etiology is obscure. The second new association is that of retinal degeneration, a finding observed in some of our patients with arteriohepatic

| TABLE 2 |
| Paucity of Intrahepatic bile ducts on biopsy. |
| Presumed clinical diagnosis in all children seen at Yale with this finding, 1948-1978. |

| Diagnosis                      | Count |
|-------------------------------|-------|
| Arteriohepatic Dysplasia      | 5     |
| The Byler Syndrome            | 2     |
| Extrahepatic Obstruction      | 3     |
| Other (?) Diagnosis           | 3     |
| **Total**                     | **13**|
dysplasia and in one patient with the THCA syndrome. The etiology of this finding is also unknown but it appears to be nonspecific.

Table 1 also demonstrates that few characteristics are specific or pathognomonic for any one syndrome. Bony anomalies and posterior embryotoxon have been found only in arteriohepatic dysplasia, not in the Byler syndrome, and have not been reported to occur in either of the other two syndromes. A specific abnormality in serum and bile acids has been demonstrated only in the THCA syndrome [22]. This abnormal bile acid is not present in arteriohepatic dysplasia or in the Byler syndrome, both of which show elevated levels of cholic acid in serum, unlike findings in the THCA syndrome. Giant cell transformation of the liver is seen only in Norwegian cholestasis. This finding occurs in other types of neonatal jaundice, but not in any of the other forms of familial intrahepatic cholestasis. These characteristics which are specific for only one syndrome may perhaps provide clues to understanding the underlying pathogenesis.

Speculation

It now seems clear that all four syndromes under discussion have a genetic etiology. The pathogenic mechanism underlying each syndrome remains an enigma, however. It is tempting to speculate that these are all diseases of bile formation and that a better understanding of the pathogenesis of these syndromes will lead to a better understanding of the normal mechanisms of bile formation.

Based on the foregoing discussion, some speculations can be made about the pathogenesis of each of these syndromes. Arteriohepatic dysplasia is clearly a multi-organ disease. This catholic organ involvement suggests a defect in connective tissue and one might suppose that a generalized defect in microfilament function could result in a decrease in bile formation [43] as well as other organ involvement. The Byler syndrome is restricted to the liver, and seems to represent a severe, generalized defect in hepatic excretory function, perhaps involving some as yet undefined common excretory enzyme. The THCA syndrome is characterized by the presence of an abnormal bile acid in serum and bile. It is presumed that this syndrome represents an inborn error of bile acid metabolism, with a block in the major biosynthetic pathway to cholic acid at the cleavage of the cholesterol side chain [44]. It is unclear why this defect results in liver disease but one might postulate that the abnormal C27 bile acid is in some way toxic to the liver, perhaps to the canalicular membrane. Lithocholic acid, a normally occurring secondary bile acid, causes cholestasis when infused into animals [45]. Feeding this bile acid to pregnant rats results in a cholestatic syndrome in the infant and it has been suggested that this cholestasis is secondary to a decrease in Na⁺,K⁺-ATPase activity in the liver plasma membranes [46]. Such a model is interesting and may be related to the THCA syndrome. Norwegian cholestasis is characterized by lymphedema of the legs and one author has suggested that the hepatic abnormality may also be secondary to abnormal lymph.

These kinds of speculation can be further extended to other types of cholestatic syndromes, for instance benign recurrent cholestasis, intrahepatic cholestasis of pregnancy, and perhaps even primary biliary cirrhosis. It is possible that information gained from study of the familial intrahepatic cholestatic syndromes may be of use in understanding and treating these other types of cholestasis of unknown etiology.

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