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Biliary Dysgenesis and Congenital Cardiovascular Malformation Association

A Czeizel

Department of Human Genetics and Teratology — WHO Collaborating Centre for Community Control of Hereditary Diseases, National Institute of Hygiene Budapest, Hungary

In a population-based unselected registry material involving 1038 unidentified multiple congenital abnormalities there were 20 cases with a combination of biliary dysgenesis and congenital cardiovascular malformations. One subgroup contained 7 cases where the above combination was associated with other major congenital abnormalities. Another subgroup contained 13 cases with this combination of congenital anomalies. The family study detected two sib-occurrences. One of them was a typical manifestation of Alagille syndrome. There are probably some other characteristic combinations of these two types of congenital anomaly, e.g. ventricular septal defect and extrahepatic biliary taresia. This group of congenital anomaly combinations of heterogeneous origin has been named biliary dysgenesis — congenital cardiovascular malformation association.

The occurrence of two or more different developmental morphogenetic abnormalities (MCAs) [17] are of importance from public health aspects. The birth prevalence of registered MCAs was 4.0 per 1000 total births in Hungary in the period 1973—1982 [20]. The proportion of MCAs was about 10% within all recorded cases affected by congenital abnormalities (CAs). Rates of stillbirth and infant death in MCAs were 8.7% and 23.8%, respectively, and these figures are 10 and 9 times higher than the Hungarian population figures in the study period.

In Hungary 7049 index patients with MCA born between 1973 and 1982 were notified to the Hungarian Congenital Malformation Registry. Only 29% notified MCA cases were specified as CA syndromes or CA associations. (Additionally, 60% of the identified cases had Down syndrome). Hundreds if not thousands of MCA-entities remained undelineated [65], thus it is not possible to estimate the prognosis and recurrence risks. There are two main possibilities to decrease the proportion of unidentified MCAs. On the one hand we have to do our best to increase the expertise of clinicians in the identification of recognizable MCA-entities. On the other hand it is necessary to create new opportunities for syndromologists to delineate further MCA-entities. In order to achieve the latter, we have introduced a *registry approach* for the evaluation of unidentified MCAs.This approach has several steps as follows:

TABLE I

Cases of combination of congenital cardiovascular malformations and biliary dysgene

Case number (sex)°	CCM	BD	Other CAs
41 (F)	Ventricular septal defect (VSD)	EHBA	(Haemangioma)
70 (F)	Patent ductus arteriosus (+ foramen ovale apertum)	IHBA+EHBA, biliary cirrhosis	—
160 (M)	Ventricular septal defect (+patent) ductus arteriosus	EHBA	(Undescended testes)
171 (M)*	Truncus communis (+atrial septal+ventricular septal defect)	Hypoplasia of gallbladder	Intestinal atresia (pyloric) +caecum mobile+stricture of ureterovesical orifice +hydroureter+hydronephrosis, bilateral
251 (F)	Stenosis of pulmonary artery	IHBA	(Shortened distal phalanges: brachymesophalangia) Growth and mental retardation
268 (F)	Ventricular septal defect	EHBA	—
303 (F)	CCM ("complex")	EHBA	(Malrotation of kidney)
357 (M)	Atrial septal defect, type I and ventricular septal defect	EHBA	Atresia of bowel
376 (F)	Atrial septal defect, +dystopia of pulmonary veins	Aplasia of gallbladder	Cleft palate+syndactyly, right toes III—IV+hypoplasia of kidneys caecum mobile+fusion of left III—IV ribs
424 (M)	Stenosis of pulmonary artery	IHBA	—
434 (F)	Ventricular septal defect	EHBA	—
454 (M)*	Common atrioventricular canal+ventricular septal defect+valvular anomalies	Hypoplasia of gallbladder	Split hand, left+Meckelís diverticulum+hypoplasia of penis+undescended right testis supernumerary vertebra (thor. V—VI)
493 (F)	Tetralogy of Fallot	Aplasia of gallbladder	Diaphagmatic defect, left (+hypoplasia of lung)
595 (F)	Ventricular septal defect	EHBA	—
875 (M)	Dextroposition of aorta	Aplasia of gallbladder	Hypoplasia of lung+ Auricular deformation
888 (F)	Patent ductus arteriosus	IHBA+EHBA, biliary cirrhosis	(Congenital inguinal hernias)
919 (M)	Ventricular septal defect	IHBA	—
967 (F)	Ventricular septal defect	IHBA+EHBA	—
1008 (M)	Stenosis of pulmonary artery	IHBA, biliary cirrhosis	(Splenomegaly)
1180 (M)*	Ventricular septal defect+dextraposition of aorta	Cholangio-vascular dysplasia of liver Pseudocirrhosis	Congenital hydrocephalus with agenesis of corpus callosum

M = male
F = female
x = unidentified MCAs

EHBA = extrahepatic biliary atresia
IHBA = intrahepatic biliary atresia

Birth weight (g)	Gestational week	Outcome (day)	Number of sibs	Comment	Diagnosis
2950	39	ID (58)	2	One brother had bilateral congenital inguinal hernias	VSD+EHBA s
2400	39	ID (78)	4	One sister is affected by same syndrome (Case number 251)	Alagille s
1540	36	ID (4)	2	Clomide ingestion during pregnancy	VSD+EHBA s
3100	38	ID (2)	2	—	Random combination or CCM+EHBA+Visceral atresia-stenosis s?
3200	40	Living (9 year)	3	One sister is affected by same syndrome (Case number 70)	Alagille s
3050	36	ID (118)	4	One brother is affected by Alagille syndrome	VSD+EHBA s or Alagille s
2840	40	ID (180)	1	—	CCM+EHBA s
2000	38	ID (2)	2	—	CCM+EHBA+Visceral atresia-stenosis s?
1600		ID (12)	2	One stillborn sib had congenital hydrocephalus another liveborn has dyscrania with mental and somatic retardation	Random combination
2200	33	ID (69)	2		Alagille s
2950	37	ID (2)	2	Myasthenia gravis in mother	VSD+EHBA s
2750		ID (17)		One sib has atrial septal defect	Random combination
2700	36	ID (0)	2	—	Random combination
2000	40	ID (34)	2	Contraceptive pill use in first and second months of pregnancy	VSD+EHBA s
1600	30	ID (2)	2	—	Random combination or Acilia s (?)
3130	36	ID (115)	2	Contraceptive pill use immediately before conception; congenital inguinal hernias in father	Alagille s (?)
2600	39	ID (145)	2	Down syndrome in one female sib	VSD+EHBA s
3400	40	Living (4 years)	1	Atrial septal defect type II in father	Alagille s (?)
3250	40	ID (31)	2	Contraceptive pill in first month of pregnancy. One sib died owing to encephalocele	Alagille s
3100	40	ID (3)	2	Five miscarriages	Random combination

ID = infant death

Registry-diagnosis in some well-defined CA-entities [16].

A *nationwide follow-up* study unidentified multimalformed cases by the help of Multiple Congenital Abnormality Examination Centres [15, 21].

These two efforts eventually resulted in a 50% proportion of identified MCA entities.

A *family study* was organised to attempt the identification of MCA entities in 1982—1983. It helped us to decrease the proportion of unidentified MCA entities to one-third. Science 1980 this type of evaluation has been performed continuously through the computerised data-base of the Case-Control Surveillance System of Congenital Anomalies [16].

We are at the beginning of utilizing the *computer system* of Winter and Baraister [91] in the diagnosis of unidentified MCA entities on the basis of their component CAs.

We have established a *diagnostic centre* in a paediatric hospital for the detailed examination of unidentified multimalformed babies and their sib(s).

As mentioned above, in 1982—1983 a family study was organised to evaluate 50% of unidentified multimalformed patients born between 1973 and 1980 and recorded in the Hungarian Congenital Malformation Registry. A total of 1038 MCAs were evaluated and among them 20 index patients had a combination of *b*iliary *d*ysgenesis (BD) and *c*ongenital *c*ardiovascular *m*alformations (CCM), corresponding to the Alagille syndrome. Our population-based material seemed to be adequate to evaluate the spectrum of the component CAs of this syndrome and perharps a wider group of BD-CCM association.

Material and Methods

A specially designed post-paid questionnaire with an explanatory letter was mailed to the mothers of 1 384 index patients having at least 2 CAs and recorded in the Hungarian Congenital Malformation Registry. We asked these mothers to send us all medical documents connected with their pregnancies and their children's CAs. 109 letters (7.9%) were returned by the post office as undeliverable. When there was no response, we asked district nurses to visit and to obtain data on these families. However, 166 women (12.0%) refused to respond. Only those questionnaires were evaluated in which every question concerning CAs of sibs was completed. Sibs in good health were not examined personally. Lethal CAs of index patients and sibs were checked on the basis of medical documentation including autopsy records. (In Hungary autopsy is obligatory for all dead infants.) Sixty-three cases were excluded owing to misdiagnosis or to nosological diagnosis achieved before the study. Thus, our study sample finally involved 1038 index patients with unidentified MCA.

Results

The combination of BD, i.e. CAs of gall-bladder, bile ducts and liver and CCMs was found in 20 index patients (Table I). This surprisingly high number of the cases represented 1.9% of the study sample and indicated a predisposition of these two CA groups to

run together. The syntrophy index (66, 65) of the concurrence of BD and CCM was calculated on the basis of the recorded birth prevalence of BD (0.3 per 1000) and CCM (70 per 1000) in the study population of 527 640 livebirths. The observed figure of 20 exceeded significantly the expected one of 11.

The cases were separated into two subgroups.

The first subgroup included seven index patients (171, 357, 376, 454, 493, 875 and 1180) with several other major CAs. The male : female ratio was 5 : 2. All index patients died within the first three weeks of life and of these, 5 cases in the first three days of life. All of them had different patterns of CAs besides BD and CCMs, i.e. they may have been random combinations or some undelineated or unidentified syndromes (Table I). Of six cases, five had very severe complex CCMs. The exceptional case 875 had only dextroposition of the aorta but other CAs were not severe, and the classification of this index patient was not unequivocal between two subgroups. It was, however, remarkable that out of 7 cases, 6 had aplasia or hypoplasia of the gallbladder. Aplasia of the external biliary duct and gallbladder were recorded in one case; it was classified as *extrahepatic biliary atresia* (EHBA). In another case only cholangovascular dysplasia with pseudocirrhosis was recorded but it may have also been the consequence of biliary dysgenesis.

The second subgroup involved 13 cases affected only by BD and CCM sometimes associated with minor anomalies, which are shown in brackets. The proportion of this subgroup was 1.3% of the study sample. Two

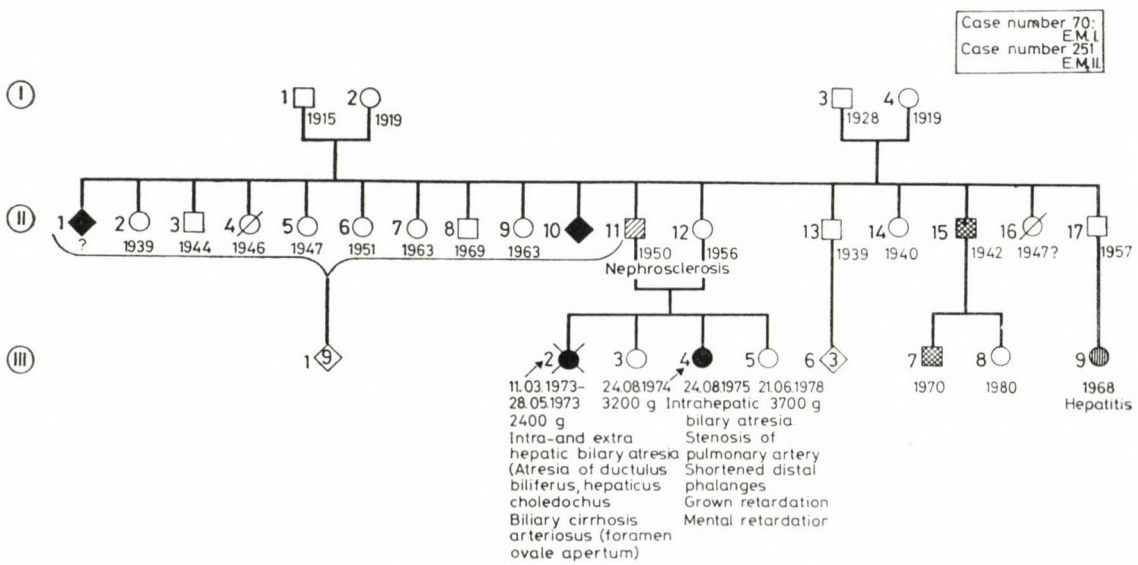

FIG. 1. Familial cluster of Alagille syndrome

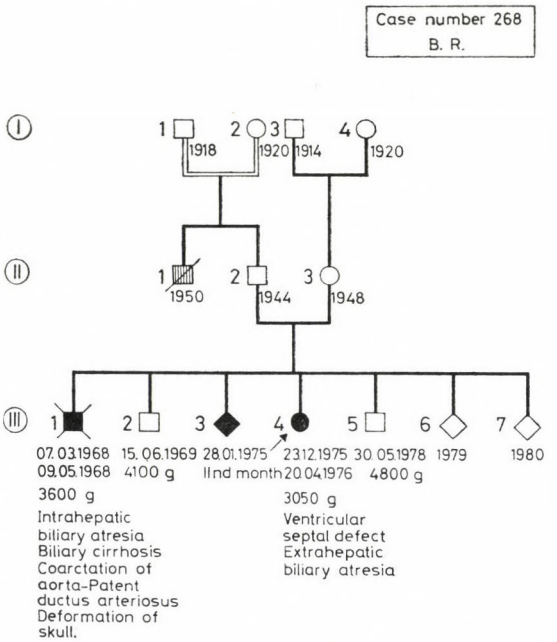

FIG. 2. Sib-occurrence of Alagille syndrome and ventricular septal defect — extrahepatic biliary atresia

of the subjects were sibs, and another female index patient had a sib-occurrence, but this brother was not an index patient because he was born in 1968. The male : female ratio was 5 : 8. Out of 13, 11 died. Both *intra*hepatic *b*iliary *a*tresia (IHBA) (three cases) and EHBA (seven cases) were found. Three cases had both IHBA and EHBA.

The point is that EHBA had a predominance in this subgroup. The majority of CCMs was ventricular septal defect, it occurred in seven cases, but in one case it was associated with patent ductus arteriosus. The latter condition was diagnosed in an infant who died on the 4th day of life and this type of CCM may be physiological at this time. All but one ventricular septal defect was combined with extrahepatic biliary atresia and in one case with IHBA and EHBA. Thus the conbination of ventricular septal defect and EHBA. seemed to be characteristic of this subgroup. Pulmonary stenosis was diagnosed in three cases, all of them combined with IHBA. Out of the remaining three cases, two had patent ductus arteriosus, one of them was a concurrence with foramen ovale apertum. In the last case the "complex" CCM was not specified.

The family study detected two affected sib-pairs. Case 70 had IHBA+ +EHBA and patent ductus arteriosus and died at about 11 weeks of her life (Fig. 1). Her sister had a similar combination of BD and CCM, though

CCM is a survivor at 9 years of age. The brachymesophalangia, i.e. shortened distal phalanges, furthermore growth and mental retardation corresponded to the well-known symptoms of Alagille's syndrome. Their parents seemed to be healthy. Another index patient (Case 268) had also an affected sib (Fig. 2). The index patient had EHBA and ventricular septal defect while her brother was affected by IHBA and complex CCM. Both sibs died between 2 and 6 months of their life.

Discussion

BD involves a wide spectrum of clinical diseases that previously were classified as neonatal hepatitis, biliary hypoplasia, ductular hypoplasia, EHBA and IHBA. Recently all of these variants of BD have been considered due to a single acquired disease process.

EHBA is defined as partial or total absence of permeable bile ducts between the hepatic porta and the duodenum. The normal extrahepatic biliary duct is partially or totally replaced by fibrous remnants which have neither lumen nor epithelium. This macroscopic and microscopic situation excludes extrahepatic biliary hypoplasia where the extrahepatic biliary duct is present and permeable but due to intrahepatic cholestasis bile flow is interrupted [8] .The extent and rate of bile duct destruction vary greatly from case to case. The gallbladder may be absent or present. In 20% of cases with EHBA gallbladder and cystic duct are present and permeable but lack connection with the intrahepatic biliary ducts. EHBA is often associated with IHBA and always with more or less precocious biliary cirrhosis. It is wort-hwhile separating the EHBA with discontinuity of bile duct ("correctable") and EHBA without discontinuity of bile duct ("noncorrectable"), though the Kasai hepatoportoenterostomy operation resulted in a considerable improvement in the life expectancy in the latter subgroup too.

Infants with BD are not jaundiced at birth because of maternal clearance of bilirubin via the placenta. Jaundice usually occurs after the 2nd or 3rd day of life. The point is that jaundice in an infant of more than 2 weeks of age associated with yellow urine or acholic stools indicates potentially serious BD. The inflammatory destruction of the extrahepatic bile ducts and the sclerosing process which extends to the intralobular ducts is rapidly followed by biliary type cirrhosis. The mean age of mortality is 11 months in untreated cases. The survival rate is only 2% at the age of 4 years [52]. The incidence of EHBA is estimated as 0.5—1.0 per 10,000 livebirths [8, 52, 70, 71, 80]. EHBA is the most frequent cause of extrahepatic cholestatis in infants. There is a 4 to 5 fold increased incidence in populations of the Pacific and Indian ocean areas [8].

Fessy et al (1985) presented characteristics in the diagnosis of 143 infants with suspected biliary ob-

struction. 69 patients had surgically confirmed extrahepatic diseases and 74 had intrahepatic disorders. A disproportionate number of infants with intrahepatic disease were boys (65% versus 52%; $p = 0.013$), low birth weight (35% versus 11%; $p = 0.001$) or had siblings with liver disease (13% versus 2%; $p = 0.017$). Thus these two groups of biliary obstruction in infancy may be different in origin. According to the most accepted embryological view, the proximal liver anlage or entodermal outgrowth forms the extrahepatic bile duct system and all the hepatic ducts in the liver whose course lies between the lobules (interlobular bile ducts of the portal septa). The smaller, intralobular bile ducts which connect the bile canaculi to these interlobular ducts are formed with the liver cells from the mesodermal liver anlage. These structures, also called perilobular bile ducts of canals of Hering, differentiate from the liver-cell cords [60].

Landing [46] proposed the concept of "infantile obstructive cholangiopathy". This hypothesis suggests that neonatal hepatitis, biliary atresia and choledochal cyst are different pathological responses to a variety of single insults to the fetal biliary tract. The insults would be modified by the genetic and metabolic background of the host. The process is dynamic, allowing for the progression of neonatal hepatitis to biliary atresia. Overlapping histological findings in these conditions tended to support this concept. The presence of inflammatory cells, the occurrence of giant cells and the lack of recovery of Listeria monocytogenes or parasitas successive pregnancies an unconfirmed finding, [11] has led to the assumption that some viral agent was responsible for EHBA. Thus, though biliary atresia was originally thought to be a developmental defect, microscopical examination of the bile ducts revealed postnatal process of infections [93]. Still, virus isolation and serologic studies have usually been negative except occasional cases associated with schemes based on developmental approaches (Clark, 1986) have led to the definition of five basic groups of CCMs.

I. Cell migration abnormalities, such as truncus communis, transposition of great arteries, tetralogy of Fallot, ventricular septal defect type I (i.e. supracristal).

II. Flow lesions as atrial septal defect type II, ventricular septal defect type II, hypoplastic left heart, bicuspid aortic valve, valve stenosis, pulmonary valve stenosis, patent ductus arteriosus, coarctation of aorta, pulmonary atresia.

III. Cell death such as Ebstein anomaly or ventricular septal defect type IV (i.e. muscular).

IV. Extracellular matrix abnormalities such as endocardial cushion defect, ventricular septal defect type III.

V. Targeted growth defects as total anomalous pulmonary return.

The combination of CCM and BD, more precisely EHBA was published first by Sweet [85] who described three cases in one family; two of the three had right ventricular hypertrophy,

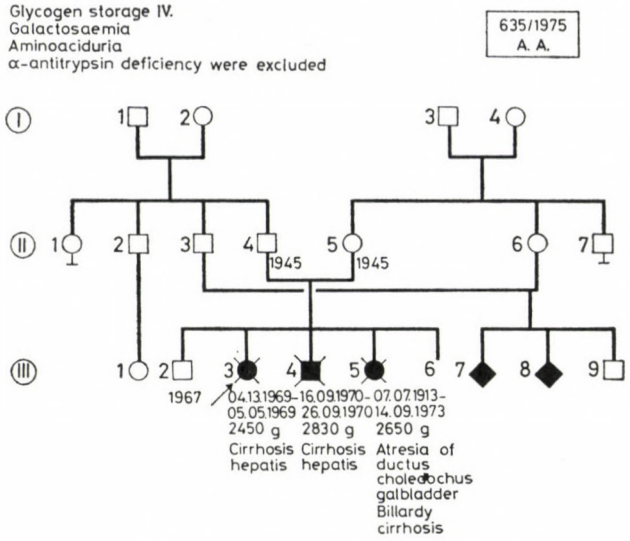

FIG. 3. Familial cluster of biliary atresia-liver cirrhosis of autosomal recessive origin. Cases from Hungarian Congenital Malformation Registry

one with ventricular septal defect and patent ductus arteriosus. Krauss [43] reported 5 sibships in which two or more sibs were affected by EHBA; renal and cardiac CAs were also found in these cases. Porter et al [69] and Millard [55] also found families in which cytomegalovirus [39, 47] (Fig. 3) and rubella [83]. Recently, Morecki and coworkers [56, 57, 58] have found some evidence of the causal role of reovirus type 3 infection in the pathogenesis of biliary atresia. Serologic observations using an indirect immunfluorescent-antibody technique namely showed that 17 out of 26 patients (65%) under one year of age with biliary atresia had antibodies to Reo type 3 as compared with only 7 of 48 age-matched controls (14.6%). Some authors [27] were hesitant to accept this finding because they could not detect any difference in biliary atresia, neonatal hepatitis and control groups. Nevertheless, later Morec et al [58] confirmed their previous results in a much larger material and in cases with neonatal obstructive cholangiopathy [32] and by immune cytochemical and ultrastructural methods [57] they were able to detect reovirus type 3 in the hepatic porta of an infant with EHBA. In addition, experimental infection with Reo-3 of weanling mice resulted in acute hepatobiliary inflammation which evolved into a chronic icteric disease with obliterative inflammation of the extrahepatic bile ducts resembling EHBA [9, 67]. A common observation in both murine and human disease was the failure to identify Reo-3 during the icteric phase either by viral isolation or electron microscopy. It has been suggested that this stage of disease may due to defective viral parti-

cles which lack the genetic material necessary for replication but continue to produce some viral coded proteins [9]. Recently, Waever et al [89] have indicated an association of EHBA and neonatal Epstein—Barr virus infection acquired in utero. In view of the association of hepatitis with Epstein—Barr virus in later life [42], this infection seemed to be responsible for the development of bile duct obstruction. The intrauterine viral infection theory was confirmed by two epidemiological studies. Danks et al [23] noted time-space clusters of cases with EHBA in Australia while Strickland and Shannon [84] analysed 30 EHBA cases in northern Texas between 1972 and 1980 and found a preponderance of affected infants from rural counties and during the fall. Thus, environmental factors may be important in the aetiology of EHBA. Still, intrauterine viral infections in twin pregnancies rarely show discordance of the disease in the twins regardless of zygosity. In spite of this observation, except in one case no twins concordant for EHBA were reported [61, 85, 90], and the four twin-pairs were dizygotic. The exceptional report of biliary atresia in both of twins of unknown zygosity appeared in the Russian literature [40]. Thus, it is difficult to exclude other aetiological hypotheses.

EHBA was found in experimental animals after surgical ligation during the few weeks around the middle of pregnancy, of either the extrahepatic bile duct or the branch of the hepatic artery supplying the biliary tree [36, 59, 68, 82]. The work of Pickett and Briggs [68] and of Spitz [82] suggested that the mechanism of EHBA was an occlusion of the arterial supply of the biliary tree. Thus, biliary atresia would have the same mechanism as that demonstrated for intestinal atresia [10]. This common cause may explain the combination of visceral, mainly intestinal atresia and BD [30]. EHBA was found in fetal alcohol syndrome, too [26, 64]. The possibility of a genetic background in the origin of EHBA was also raised on the basis of family clusters which indicated an autosomal recessive inheritance [37, 78, 91] (Fig. 4).

CCM constitutes a major problem of CAs because of its common occurrence, the birth prevalence being 7—10 per 1000, and high mortality. The aetiology of CCMs is heterogeneous, but only a small proportion is attributable to chromosomal, Mendelian or teratogenic factors. Although the familial cluster of CCMs has long been recognized, low heretibility was indicated by both twin and family studies [19]. More recently, classification multiple sibs and/or parents appeared to have BD-CCM combination.

Arteriohepatic dysplasia, i.e., the combination of pulmonary arterial stenosis, neonatal liver disease, skeletal anomalies, odd facial appearance and its familial occurrence caused by autosomal dominant inheritance was described by Watson and Miller [88] and the syndrome of intrahepatic biliary dysgenesis (IHBD) and CCM by Greenwood et al [34]. Review of their autopsy material between 1923 and

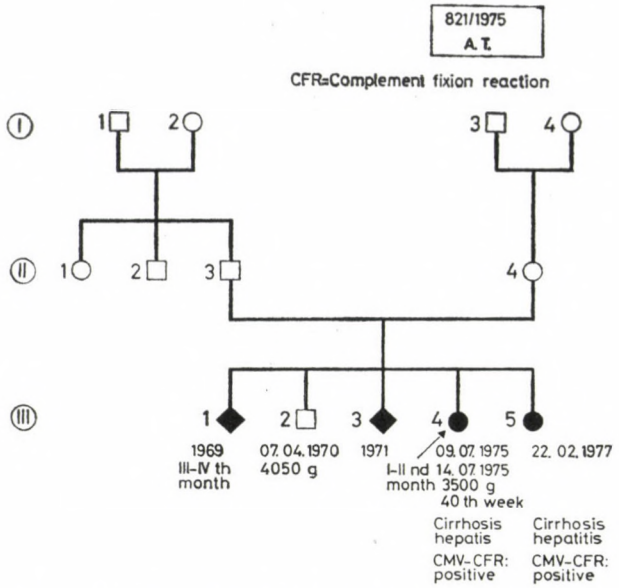

FIG. 4. Sib-occurrence of biliary atresia-liver cirrhosis. The cause was cytomegalovirus infection based on serological methods

1973, i.e., during 50 years revealed four patients with IHBD and CCM; patent ductus arteriosus and peripheral pulmonary stenosis were present in two, patent ductus arteriosus in one and patent ductus arteriosus, peripheral pulmonary stenosis, pulmonary atresia and ventricular septal defect in one case. None of the necropsied patients with extrahepatic biliary dysgenesis had CCM. CCM was diagnosed in eight additional living patients with IHBD. Six exhibited clinical and laboratory findings of peripheral pulmonary stenosis (one documented at cardiac catheterization and subsequently operated upon for associated ventricular and atrial septal defect) and in two the auscultatory findings were compatible with the diagnosis of peripheral pulmonary hypertension but could not be verified. The point is that peripheral pulmonary stenosis with or without other CCMs was present in 9 patients and isolated patent ductus arteriosus in one. In their opinion mainly vascular and not intracardiac structures were predominantly involved. Two of the patients were sibs, one of whom died and also had cystic disease of the kidneys and hemivertebras. At the same time, *Alagille* [2, 3, 4, 5, 6] delineated a syndrome of

(i) *unusual facies* (broad forehead, frontal bossing, deeply set eyes with mongoloid slant, ocular hypertelorism, flattened malar eminence, long straight nose with prominent nasal bridge and a pointed mandible); these facial features may not be evident at birth. Recently, the importance of *ocular anomalies* have been pointed out, namely bilateral ocular posterior

embryotoxon: prominence of Schwalbe's line [72, 80], pigmentary retinopathy, Axenfeld anomaly, strabismus, band keratopathy, anomalous optic disks, choroidal folds, unilateral ectopic pupil [75, 71].

(ii) *Heart lesions* mostly peripheral pulmonary stenosis (isolated in 55% and with other CCMs in 45% of cases) but tetralogy of Fallot, coarctation of the aorta, ventricular and atrial septal defect, patent ductus arteriosus have also been reported [24].

(iii) *CAs of bones* fusion of ribs, shortened distal phalanges, failure of anterior vertebral arch fusion, so-called butterfly vertebrae [76].

(iv) *Life-long cholestasis* presumably intrahepatic in origin, probably secondary to some unidentified defect of bile formation. The common bile duct is hypoplastic but patent and there are few bile ducts in the portal areas, but ductular proliferation has occasionally preceded ductular paucity i.e. it is a ductular hypoplasia [32].

The failure of development of interlobular ducts is the most attractive hypothesis, since a reduced number of bile ducts is consistently seen in very young infants [63].

Involvement of extrahepatic ducts was found in 10 of 54 cases [63]. Thus, liver disease is mostly benign, without progression to cirrhosis which only occurred in 3 of these cases and was intrahepatic cholestasis [76], e.g. intrahepatic cholestasis (21330), fetal intrahepatic choleastasis — Byler disease (21160), cholestasis with lymphoedema (21490) [53].

(v) *Hyperlipidaemia* after 6 months of age with xanthomata which responded to cholestyramine treatment with 16-year survival [29].

(vi) *Suboptimal physical, intellectual and sexual development* (hypogonadism). Some authors also demonstrated *kidney diseases* like renal dysplasia, renal artery stenosis, progressive renal failure caused by severe tubulointerstitial nephropathy or renal hypertension in this syndrome [38, 45].

The aetiology of Alagille's syndrome was explained by autosomal dominant origin with very variable expression on the basis of some families [1, 4, 35, 45, 48, 49, 76, 80].

Kocoshis et al [41], however, described a patient with pulmonary valvular atresia, overriding aorta and ventricular septal defect (pseudotruncus arteriosus), "wizened" facies and butterfly vertebrae associated with EHBA. Zukin et al [93] published three cases with EHBA associated with cyanotic heart disease. Previously only four well-described patients were reported who had both cyanotic CCMs and EHBA [31, 44, 50, 54]. Gorelick et al [33] observed three patients with CAs of the biliary tract which included an overall decrease in the number of intrahepatic ducts, attenuation of the intra- and extrahepatic biliary tract and focal regions of dilatation of the intrahepatic ducts. Thus, one could speculate that perhaps both the intra- and extrahepatic attenuation or atresia are secondary to a primary defect in bile formation which in the neonate leads to atrophy of the bile ducts [22]. Furthermore, these biliary tree ab-

TABLE II

Component CAs of some atypical combinations of BD-CCM

Author	Sex	CCM	EHBA	Other CAs
Krovitz 1960	F	Total anomalous pulmonary venous drainage	+	Talipes equinovarus
McLoughlin—Shauklin 1967	M	Transposition of great arteries and total anomalous pulmonary venous drainage	+	Accessory spleens and unilateral glomerular dysplasia
Freedeom—Gerald, 1973	F	Tricuspid atresia and total anomalous pulmonary venous drainage	(accessory hepatic tissue)	Coloboma, anal atresia, cleft palate, polysplenia, annular pancreas
Lilly—Chandra, 1974	M	Total anomalous pulmonary drainage, mitral atresia, hypoplastic aortic arch, ventricular septal defect, preductal coarctation of aorta and hypoplastic left ventricle	+	Gastrointestinal malformation, oesophageal atresia with tracheoesophageal fistula, vertebral CAs, right renal agenesis, polysplenia and pulmonary levoisomerism
Zukin et al, 1981	F	Tetralogy of Fallot	+	—
	M	Transposition of great arteries	+	—
	F	Tetralogy of Fallot, mirror-image dextrocardia	+	Situs inversus
Kocoshis et al, 1981	M	Pulmonary valvular atresia overriding aorta, ventricular septal defect (pseudotruncus arteriosus)	+	"Wizened" facies, Butterfly vertebrae
Mueller et al, 1984	M	Ventricular septal defect and pulmonary stenosis	+ (+IHBA)	Hypoplastic right kidney
	F	Nodular dysplasia mitral and tricuspid valves	+	Narrow distal interpedicular distance
	F	Aortic stenosis, pulmonary stenosis, and obstructive cardiomyopathy	+ (+IHBA)	Trilobed left lung, four-lobed right lung

normalities may be just one more finding in a multiorgan disease, since there is a great variety of phenotypic manifestation of BD-CCM combinations [63]. These cases provide evidence that EHBA may also accompany the other findings of arteriohepatic dysplasia. Some atypical cases are summarized in Table II.

There are some well-described associations of polysplenia syndrome, situs inversus and EHBA [13, 25, 51, 87]. These cases suggest that they may be the result of a common pathological process, and the morphologically defective cilia might be responsible for their relation at the cellular level. The point is that within the combinations of BD and CCM several nosological entities have to be differentiated (Fig. 5).

It is a reasonable supposition that IHBA prefers to associate with CAs of great vessels, i.e. pulmonary stenosis and patent ductus arteriosus, while EHBA is mainly associated with cardiac CAs.

The most important conclusions are as follows:

The existence of Alagille syndrome involving IHBA and CCM, mainly pulmonary stenosis, was confirmed both in the literature and in our material. There were at least four cases in our study sample. The sib-occurrences seemed, however, to indicate an autosomal recessive origin, as has been assumed also by Mücke [62], instead of the autosomal dominant inheritance and penetrance may also support this.

Probably there is another syndrome which involves EHBA and CCM mainly ventricular septal defect. The sib-occurence in our study sample indicated an autosomal recessive inheritance, confirming previous findings [85, 43, 63].

Our study sample involved mainly lethal cases; this, however, might have been the consequence of a selection bias due to the obligatory autopsy and complete ascertainment in dead infants.

There are some other characteristic combinations of BD, CCM and other CAs, e.g. the combination of visceral (e.g. bowel) atresia and polysplenia. Thus I suggest the term *biliary dysgenesis-cardiovascular CA-association* for the group of these MCA-entities of heterogenous origin. The association of biliary atresia with CCMs strongly suggests a common aetiology

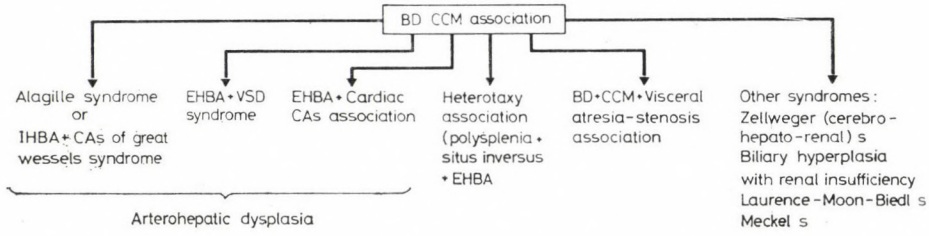

FIG. 5. The suggested structure of BD (biliary dysgenesis) — CCM (congenital cardiovascular malformation) association

of the biliary and cardio-vascular developmental disturbances. On the one hand the possible role of intrauterine infection should be considered. On the other hand, the genetic background has been proven in some syndromes within this CA-association.

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A Czeizel MD
Gyáli út 2
1966 Budapest, Hungary