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Extrahepatic Biliary Atresia and Associated Anomalies: Etiologic Heterogeneity Suggested by Distinctive Patterns of Associations

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Fifty-one cases of extrahepatic biliary atresia (EHBA) with associated anomalies were found in a study of EHBA (251 cases). Analysis of segregation patterns of these anomalies in individual patients suggested the existence of 2 major groups: (1) 15 cases (29.4%) with various combinations of anomalies within the laterality sequence, and (2) 30 cases (58.8%) with one or 2 anomalies mostly involving the cardiac, gastrointestinal, and urinary systems. These latter anomalies did not follow any recognizable pattern. The third group of 6 cases all had intestinal malrotation, some with preduodenal portal vein; these cases show some similarity to the laterality sequence group and may represent a more confined phenotypic result of faulty situs determination.

This previously unattempted classification of patients with EHBA and associated anomalies might enable a more targeted approach towards identification of causes in this heterogeneous disorder. EHBA within the laterality sequence might prove a suitable candidate for a major gene mutation. Teratogenic, infectious and polygenic multifactorial causes might play a more significant role in EHBA associated with "nonsyndromic" organ system anomalies.

KEY WORDS: extrahepatic biliary atresia, laterality sequence, situs inversus, polysplenia, associated anomalies

INTRODUCTION

Congenital extrahepatic biliary atresia (EHBA) constitutes the most common hepatic surgical disorder of infancy [Hendren and Vacanti, 1989] and a major cause of fatal cirrhosis in childhood [Javitt, 1976]. The anatomic hallmark of this disorder entails partial or complete absence of the external bile conduit system, or various combinations of missing, fibrosed, and atretic ductal segments [Kasai, 1977]. Major physiologic consequences are unremitting cholestatic jaundice and a lack of intestinal bile for digestive functions. Invariable intrahepatic manifestations are cholestasis, early disappearance of intrahepatic bile ducts, inflammation, and interlobular portal bile duct proliferation (reduplication) with subsequent fibrosis/cirrhosis. Chronic hepatic failure warrants liver transplantation during infancy for approximately 40% of cases, and in another 15% before adolescence [Wanek et al., 1989].

Controversy continues over the pathogenesis of this disorder. The presence of both chronic and acute inflammatory injury [Chandra and Altman, 1978], and the progressive nature of the process, which may continue even after surgical relief of biliary obstruction [Desmet, 1987], have suggested a postnatal inflammatory cause. The detection of antibody to reovirus type 3 as well as localization of Reo 3 particles in the porta hepatis [Morecki et al., 1984] implicated this virus as a possible, though unsubstantiated, cause in some patients [Morecki and Glaser, 1989].

Stowens [1963] first emphasized the prolonged period of fetal growth and differentiation of the hepatobiliary system, rendering it potentially vulnerable to teratogenic insults throughout the gestational period. He further noted that the wide spectrum of coexisting malformations (25% of his autopsy series of 515 cases) had affected organ systems with diverse periods of organogenesis. Coexistence of EHBA with other anomalies has been widely reported, with an observed incidence of anomalies ranging from 10 to 25% and involving both single and multiple organ systems [Moore, 1953, Krovetz, 1960; Warkany, 1971; Lilly and Karrer, 1985].

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While these observations further supported an early prenatal onset for EHBA, major gene determination has not been documented. Despite several isolated case reports of affected sibs [Nevin et al., 1969; Krauss, 1974; Sommer et al., 1976; Schulte and Lenz, 1978], with one case of consanguinity suggesting recessive inheritance [Lachaux et al., 1988], most published series do not report recurrence of EHBA in sibships. Discordance for EHBA has been noted repeatedly in both monozygotic and dizygotic twins [Morris et al., 1977; Werlin, 1981; Hyams et al., 1985; Moore and Hyman, 1985; Strickland et al., 1985]. Recently, fetal and neonatal animal models have demonstrated that hepatobiliary defects with cholestasis and fibrosis, clinically and histologically identical to human EHBA, can result from various laboratory manipulations including mechanical obstruction of fetal bile ducts [Spitz, 1980], ligation of fetal arteries supplying the extrahepatic ducts [Hashimoto et al., 1983] and chemical exposure in utero [Ogawa et al., 1981]. Clinical support for possible similar mechanisms in humans is derived from the occasional concurrence of EHBA together with intestinal atresia, for which a vascular pathogenesis is hypothesized [McKenzie et al., 1960; de Lorimier et al., 1969; LeCoultre et al., 1983]. Thus, while it is convenient to consider a common cause in an observed phenotype, on the basis of available data this does not seem possible for EHBA. EHBA is probably the end result of different causal and pathogenetic mechanisms operating at different periods in gestation or postnatally [Morris et al., 1977; Chandra, 1974].

This report analyzes 51 cases with EHBA and associated nonhepatobiliary anomalies which occurred among 251 cases ascertained retrospectively in an epidemiologic study [Magee-Maschal, 1990]. The observation of 2 and possibly 3 different patterns of anomalies suggests heterogeneity of EHBA with probable early prenatal onset and provides a basis for further causal research.

MATERIALS AND METHODS

During the 1980s, the first large-scale epidemiologic case control study of EHBA was conducted throughout the continental U.S. to identify possible teratogenic risk factors among suspect environmental and occupational exposures of both mothers and fathers [Magee-Maschal, 1990]. Under the auspices of Dr. John R. Lilly from the University of Colorado, School of Medicine, all study cases were solicited from pediatric surgeon members of the American Academy of Pediatrics, Surgical Subsection. Diagnostic criteria for EHBA cases consisted of visual and contrast media confirmation of absent or atretic external bile ducts, through surgical laparotomy, and pathognomonic liver biopsy. Sixty-seven major pediatric surgical centers provided access to their unselected series of cases, born since January 1, 1982, of whom 267 (52%) participated. Families of more recently diagnosed cases had higher participation rates; other unknown self-selection factors may also have potentially affected the representativeness of the study sample compared with the entire EHBA population.

Group characteristics of the participant cases were as follows: normal birth weight distribution with mean of 3.25 kilograms; sex (M/F) ratio of 0.82; mean gestational length >39 weeks, with no elevation of prematurity over the population frequency; mean age of mothers 27.7 years and of fathers 30.7 years; 97.6% with history of hepatoportoenterostomy surgery, with mean age at diagnosis/initial corrective surgery of 8.6 weeks; extreme rarity of EHBA among sibs (one affected set of sibs among 266 families); discordance in all 9 liveborn (including confirmed monozygotic as well as dizygotic) twin pairs. These characteristics closely reflect those described for the majority of published series [Mowat et al., 1976; Danks et al., 1977; Hays and Kimura, 1981; Henriksen et al., 1981; N.C.H.S., 1989].

Medical history at the time of infantile EHBA diagnosis was obtainable on 251 (94%) of the total eligible cases. This provided a data file on coexisting major and minor anomalies ascertainable during early infancy, by means of ultrasonography and echocardiography when applicable, as well as internal abdominal anomalies evident during abdominal surgery (exploratory laparotomy) which had been performed on all cases. All morphologic groups observed and described herein are from this subgroup of 251 cases for whom coexisting anomaly data were available. Referred infants with final diagnoses of alpha-1 antitrypsin deficiency, Alagille syndrome, and cystic fibrosis were excluded from study, since these genetic cholestatic syndromes may simulate, and be potentially misclassified as, EHBA. Inguinal hernia (unilateral or bilateral) and umbilical hernia, when occurring in EHBA cases lacking other defects, have been excluded as "anomalies."

RESULTS

Out of 251 cases with EHBA, 51 (20.3%) had associated anomalies and have been divided into 3 subgroups. **Group I** (Table I) included 15 cases with various combinations of anomalies, constituting the polyasplenia sequence: cardiovascular malformations, polysplenia, abdominal situs inversus, intestinal malrotation, and anomalies of the portal vein and hepatic artery. Retrospective review of hospital diagnostic admission records provided no information regarding the anatomy of the lungs, bronchi, or their blood supply. This group accounted for 29% of the cases of EHBA with associated anomalies and 6% of the whole EHBA study sample.

Cardiovascular malformations were present in 8 of the 15 cases in Group I (53%): 3 of the 8 had polysplenia (Table I). (Pulmonary arteriovenous fistulae may have been congenital or secondary to hepatic cirrhosis.) Anomalies of the inferior vena cava, including azygos return or "absent IVC," (Inferior Vena Cava) occurred in association with abnormalities of the portal vein or hepatic artery: preduodenal portal vein (PDPV) was present in 3 cases, all with polysplenia.

Polysplenia occurred in 9 cases in Group I and was commonly associated with anomalies of the portal vein and hepatic artery, and with intestinal malrotation. Nine cases had intestinal malrotation (60%), 2 associated with intestinal atresia and one with anomalous mesentery. One case in this group, with polysplenia, visceral situs inversus, and PDPV, reportedly had a cousin with the same pattern of anomalies.

Group II (Table II) included 30 patients in whom

TABLE I. EHBA and Associated Anomalies in the Spectrum of the Laterality Sequence*

Cardiovascular malformation	Polysplenia	Abdominal situs inversus	Intestinal malrotation	Anomalous portal + hepatic vessels	Intestinal obstruction	Other
Left sided IVC		+				
PDA (term)	+		+	PDPV		
VSD, absent IVC		Transverse liver	+	Anomalous course of portal V, anomalous hepatic a		Maternal insulin dependent DM
Right aortic arch, MVP		+	+			Maternal gestational DM
CAVC		+				
Azygos return of IVC	+			Aberrant hepatic a.		
Dextrocardia, common atrium double outlet right single ventricle, L-TGA, severe PS, PLSVC, azygos return of IVC to SVC		+		Hepatic venous drainage direct to atrium		
Multiple diffuse A-V fistulae in pulmonary alveolar level[a]	+	+	+		Multiple jejunal atresiae, apple peel anomaly	Absent small bowel mesentery
		+	+		Duodenal atresia	
	+		+	PDPV		Same anomalies reported in cousin
	+		+			
	+	+	+			
	+			PDPV		
	+		+	Abnormal hepatic a		
	+	+				

* IVC, inferior vena cava; PDA, patent ductus arteriosus; PDPV, preduodenal portal vein; VSD, ventricular septal defect; DM, diabetes mellitus; MVP, mitral valve prolapse; CAVC, complete atrio-ventricular canal; TGA, transposition of great arteries; PS, pulmonic stenosis; PLSVC, persistent left superior vena cava; SVC, superior vena cava; A-V, arterio-venous.
[a]See text.

associated anomalies did not follow any recognizable syndromic pattern or known sequence. This group accounted for 59% of EHBA cases with associated anomalies and 12% of all EHBA cases. Most patients had only one associated defect. The 3 organ systems most commonly involved were the heart (10 cases), kidney and urinary tract (10 cases) and gastrointestinal tract (10 cases). Two patients were each one-of-twins discordant for EHBA. One of the twin pairs (where the case had EHBA and unilateral multicystic dysplastic kidney), showed concordance for Hirschsprung disease which also was reported in a previous sib. The patient with choanal atresia had a sib with the same congenital anomaly. Pulmonic valve anomalies were the most frequent cardiac defect (5/10 cases) and complete AV (atrioventricular) canal was found in 2 cases. Various urinary tract anomalies were found in 10 cases, while Meckel diverticulum accounted for more than two-thirds of the gastrointestinal anomalies. Two patients had atresia of either small or large bowel and one patient had midgut volvulus with no apparent malrotation.

Group III (Table III) consisted of 6 cases (5 of them females) with a pattern of associated anomalies which were not clearly related to either of the previous groups. All had intestinal malrotation, mostly complete, and one had multiple atresias of the small bowel. Three of these 6 cases had PDPV.

Sex distribution among the various subgroups of EHBA and associated anomalies is presented in Table IV. The Male:Female ratio was similar for the general group of EHBA with associated anomalies and for isolated EHBA (0.76 and 0.8, respectively). Variations were observed in the different subgroups with small numbers, but for the malrotation cases both in group III and in the laterality sequence group (I), female excess was noted.

DISCUSSION

The notion that EHBA is heterogeneous is well accepted [Chandra, 1974; Morris et al., 1977; Miyamoto and Kajimoto, 1983, Silveira et al., 1991]. Etiologically, there are probably at least 2 separate groups of EHBA:

TABLE II. EHBA With Associated Organ System (Nonlaterality) Anomalies*

Cardiac (n[a] = 10)	Urinary tract (n = 10)	Gastrointestinal (n = 10)	Central nervous system (n = 1)	Facial (n = 2)	Other (n = 2)
Single organ involvement (n = 25)					
CAVC	Solitary kidney	Partial volvulus	Meningomyelocele	Choanal atresia (familial)	Bilat. clinodactyly absent left 12th rib
CAVC	Solitary kidney	Rectal atresia			
PDA (term)	Right megaloureter	Meckel's diverticulum			
TF, PDA	Hypospadias	Meckel's diverticulum			
VSD	UPJ obstruction	Meckel's diverticulum			
PS	Horseshoe kidney	Meckel's diverticulum			
PS	Right multicystic dysplastic kidney	Meckel's diverticulum			
PA, VSD, Absent pulmonic atresia					
Multi organ involvement (n = 5)					
ASD, PS	Solitary kidney[b]				
	Vesicoureteral reflux	Meckel's diverticulum[b]			
	Persistent urachus	Ileal atresia[b]			
PA, hypoplastic HRV		Midgut volvulus[b]			
				Cleft lip and palate	Abnormal right portal vein, hepatic artery[b]

* CAVC, complete atrioventricular canal; PDA, patent ductus arteriosus; TF, tetralogy of Fallot; VSD, ventricular septal defect; PS, pulmonic stenosis; ASD, atrial septal defect; PA, pulmonic atresia; HRV, hypoplastic right heart; UPJ, uretero-pelvic junction.
[a] Total group cases = 30, some with multiple anomalies.
[b] Case with 2 anomalous organ systems, specified horizontally.

one with a late intrauterine or early neonatal insult of a presumed inflammatory process, and a second group, with associated nonhepatobiliary anomalies, which accounts for at least 15–25% of EHBA cases, for whom an early embryologic insult is hypothesized. Extrapolation from other congenital malformations permits the prediction that this group of early onset EHBA is still heterogeneous. Indeed, a critical examination of patterns of associated anomalies with EHBA, in individual patients, proposes the existence of at least two different major groups: the laterality sequence and the organ system association. A recent confirmation for this proposition has emerged from the study of Silveira et al. [1991] which is comparable to our study both in design and results.

TABLE III. EHBA With Intestinal Malrotation and Intra-Abdominal Vascular Anomalies (n = 6)

Type of malrotation	Vascular anomalies	Other
Partial		
Complete		
Complete		
Complete	PDPV[a]	
Complete	PDPV, anomalous hepatic A	
Complete	PDPV, absent dorsal mesentery	Duodenal atresia; apple peel deformity of small bowel

[a] PDPV, preduodenal portal vein.

The association of EHBA with polysplenia had been noted infrequently [Helwig, 1929; Rumler, 1961; Rodin et al., 1972; Strauss et al., 1972] until 1974 when Chandra and Altman [1978] reported 5 patients with EHBA out of 10 cases with the so called "polysplenia syndrome." This association was later confirmed by a considerable number of reports in the surgical, radiological, and pediatric literature on series of patients with either EHBA or polysplenia (Table V). Also shown in Table V are 6 cases of EHBA within a case control study (The Baltimore-Washington Infant Study or BWIS) of cardiovascular malformations (CVM) [Ferencz, 1990]. Five were ascertained by their CVM and had associated anomalies in the spectrum of the laterality sequence, as did the sixth infant who was in the control group and had a sibling with CVM. The 5 CVM cases with EHBA constituted 0.1% of the total 4,390 CVM cases.

The percentage of EHBA patients with the "polyasplenia" sequence can only be estimated from the literature since ascertainment through splenic anomalies definitely ignores cases with only part of the spectrum.

TABLE IV. Sex Distribution Among the Subgroups of EHBA and Associated Anomalies*

	Laterality sequence (n = 15)			Associated organ system anomalies (n = 30)	Malrotation (n = 6)
Female		9		15	5
Male		6		15	1
M/F		0.7		1	0.2
	Polysplenia (n = 9)	Abdom. situs inversus (n = 9)	Malrotation (n = 9)		
Female	6	4	6		
Male	3	5	3		
M/F	0.5	1.3	0.5		

* M/F EHBA isolated = 0.8; M/F EHBA with associated anomalies = 0.7.

The percentage varies from 4% [Miyamoto and Kajimoto, 1983] to 11–12% [Hall et al., 1986; Abramson et al., 1987] and 17% [Dimmick et al., 1975; Brun et al., 1985]. Pooled literature data on over 1,250 reported cases of EHBA (Table V) shows that about 6% of them had part or most of the polyasplenia spectrum. This percentage is very similar to that found in the study by Silveira et al. [1991] for EHBA and splenic anomalies, and in our study for EHBA cases with associated anomalies included in the spectrum of the laterality sequence or developmental field complex, a term which, as will be discussed later, seems to more appropriately describe the anomalies observed [Opitz, 1985; Toriello et al., 1986]. Though splenic anomalies occur in only a small fraction of the total EHBA population, this subgroup accounts for about 30% of cases with EHBA and associated anomalies in our group. Similar percentages were found in 2 large studies by Miyamoto and Kajimoto [1983]—29%, and Silveira et al. [1991]—40%. Especially interesting is the finding in those two studies of 3 cases of asplenia and EHBA, further supporting the suggestion that polysplenia and asplenia are overlapping manifestations of a primary morphogenetic defect of symmetry determination or lateralization [Opitz, 1985] which might affect, among many other organs, the biliary tree.

There is a twofold advantage in viewing EHBA polysplenia in the broader context of the laterality sequence. First, it provides a categorization for certain "laterality" anomalies associated with EHBA in the absence of polysplenia, since a spectrum is not expected to be always fully manifested. Symmetrical liver and anomalies of the inferior vena cava, for example, are especially liable to occur when the situs is neither completely inverted nor completely normal [Campbell and Deuchar, 1967], and thus should be considered a subtle manifestation of the defect in lateralization. Therefore, EHBA with situs inversus, either overt [Fonkalsrud et al., 1966; Zukin et al., 1981; Ruben et al., 1983] or suggested by symmetrical liver [Campbell and Deuchar, 1967], as well as with vascular anomalies like absent IVC, PDPV, and anomalous hepatic artery [Lilly and Chandra, 1974; Chiba et al., 1987], and abnormal lobation of lungs [Mueller et al., 1984] should all be considered part of the laterality sequence even in the absence of polysplenia. Second, the recognition that such a subgroup of EHBA is part of the laterality determination sequence might provide further insight into its cause. The suggestion that symmetry determination is a developmental field complex has been advanced on the basis of observed causal heterogeneity [Opitz, 1985]. Laterality defects have been reported sporadically, in familial cases documenting autosomal recessive, dominant, and X-linked inheritance [Katcher, 1980; Zlotogora and Elian, 1981; Arnold et al., 1983; Niikawa et al., 1983; de la Monte and Hutchins, 1985; Toriello et al., 1986; Mathias et al., 1987], in aneuploidy [DeCicco et al., 1973; Schinzel, 1984], and in genetic conditions such as the Kartagener [Schidlow et al., 1982] and Meckel [Hsia et al., 1971; Moerman et al., 1982] syndromes. Furthermore, a mouse recessive gene responsible for situs inversus (*iv*) [Hanzlik et al., 1990] has been hypothesized to act through loss of control on the development of the normal sense of bilateral asymmetry, allowing situs to be determined by chance [Layton, 1978], thus further supporting the definition of a laterality developmental field. In an attempt to demonstrate clinically the abnormal asymmetry determination, polysplenia has been generally attributed to bilateral left sidedness and asplenia to bilateral right sidedness [Van Mierop et al., 1972; Rose et al., 1975]. However, in view of the frequent overlap of clinical findings, the broader term of laterality sequence was coined [Arnold et al., 1983]. This terminology seems even more appropriate at present, since the Murine *iv* mutant gene has been recently localized to chromosome 12 [Brueckner et al., 1989; Hanzlik et al., 1990] thus opening new lines of research for a counterpart human gene. If EHBA is viewed as a potential constituent of the spectrum of anomalies resulting from loss of developmental control over the left-right asymmetry, then it is plausible that EHBA within the context of the laterality sequence is genetically controlled, possibly by this putative gene. We have not encountered any reported familial case of EHBA laterality sequence. However, one affected member in the family with X-linked laterality sequence reported by Mathias et al. [1987] did have EHBA. Also, McLoughlin and Shanklin [1967] report on two sibs with what they propose to be "Laurence-Moon-Biedl" syndrome and multiple associated anomalies. One of the sibs had, among other defects, polysplenia, and the other had polysplenia, left isomeric liver, anomalous lobation of lungs, and EHBA. It is also worth noting that in one case within our laterality group, as well as in one of the BWIS cases, there might be a

TABLE V. Literature Review on EHBA and Associated Anomalies in the Spectrum of the Laterality Sequence

Reference	Mode of ascertainment	CVMs	Polysplenia	Abd. situs inversus	Intestinal malrotation	Intraabdominal vascular anomalies	Other
Helwig [1929]	1/2 cases with polysplenia	–	+				
Rumler [1961]	4/21 cases with EHBA	–	+	+	+	Abn. mesentry	
		–	+	+	–	Abn. mesentry	
		–	+	–	–	Abn. mesentry	
		–	–	–	–	Abn. mesentry	Trilobed left lung
McLoughlin and Shanklin [1967]	Case report	TGA, single ventricle, azygos return of IVC, right aortic arch	+	Levoisomeric liver			Omphalocele, diagnosed with LMB Syn[a]
Rodin et al. [1972]	1/3 cases with polysplenia	Interrupted IVC with azygos continuation, complex heterotaxy	+	+			Bilateral bilobed lungs
Strauss et al. [1972]	1/12 EHBA autopsies	Cardiovascular anomalies–unspecified	+	+		Abnormal mesentry	Double pelvis left kidney
Freedom and Gerald [1973]	1 case with EHBA out of 5 cases with the cat eye syn and CHD	TAPVD,[c] tricuspid atresia, hypoplastic IVC with azygos return, common atrium	+	–			"Cat eye" syn. (trisomy or tetrosomy 22pter→q11) incomplete lobation of lungs
Chandra [1974]	5/10 cases with polysplenia	–	+	Levoisomeric liver	+		Bilobed right lung, right hyparterial bronchus
		PLSVC to coronary sinus	+	+	+		Bilobed right lung, right hyparterial bronchus
		Anomalous suprahepatic vena cava and azygos return	+	+	+		Bilobed lung, bilateral hyparterial bronchus
		–	+	+	+		
		DORV, HLV, TAPVD, absent hepatic IVC, hypoplastic right aortic arch	+	–	+	PDPV	Bilobed lungs, right hyparterial bronchus Absent right kidney, TE fistula, abnormal vertebrae
Lilly and Starzl [1974]	3/29 cases with liver transplantation for EHBA	Absent IVC	+		+	PDPV, hepatic a from superior mesenteric a	
		Absent IVC	+	Liver symmetry	+	PDPV, hepatic a from superior mesenteric a	
		Absent IVC			+	PDPV, hepatic a from superior mesenteric a	

Dimmik et al. [1975]	Report of 6 cases of EHBA and polysplenia	–	+	+			
		VSD	+	+			Rt. pulm. symmetry
		–	+		+		
		–	+		+		
		–	+	+			Lt. pulm. symmetry
		CAVC, C/A	+	Hepatic symmetry	+		Lt. pulm. symmetry
Zukin et al. [1981]	1/3 cases with EHBA and cyanotic heart dis.	Mirror image dextrocardia, T/F		+			
Paddock and Arensman [1982]	2/4 cases with the polysplenia syndrome	–	+		+		
		–	–	Levisomeric liver	+		Multiple bowel atresiae, ileal duplication
Teichberg et al. [1982]	Case report	–	+	+	+	PDPV	Abnormal cilia
Miyamoto and Kajimoto [1983]	79 cases of EHBA and associated anomalies[b]	40 cases	27 cases	5 cases	11 cases		7 cases with abnormal lobation of lungs
Ruben et al. [1983]	2 cases with EHBA out of 23 cases with situs inversus	CAVC, PS, PAPVD, absent IVC	+	+		PDPV	3 umbilical vessels
		CAVC, common atrium and ventricle		+	+		Rt. diaphragmatic hernia
Brun et al. [1985]	86 cases of EHBA with ultrasound prior to surgery[b]	Azygos continuation of IVC–1 case; left sided IVC–1 case	10 cases	Situs inversus–1 case; medially located liver–4 cases		PDPV–9 cases	
Ledesma-Medina et al. [1985]	1/19 cases of EHBA with preliver transplantation diagnostic imaging	Interrupted IVC with azygos continuation	+		+		
Hall et al. [1986]	14/114 consecutive patients with Kasai operation for EHBA	2/14 absent IVC		2/14	6/14	3/14 PDPV 3/14 aberrant hepatic artery	
Abramson et al. [1987]	112 cases with EHBA[b]	Interrupted IVC with azygos continuation–number of cases not given	12 cases	10 cases with malrotation and/or situs inversus		4 cases with PDPV	Bilateral bilobed lungs–number of cases not given
Sullivan et al. [1987]	Case report	–	+	+			

(continued)

TABLE V. Literature Review on EHBA and Associated Anomalies in the Spectrum of the Laterality Sequence (Continued)

Reference	Mode of ascertainment	CVMs	Polysplenia	Abd. situs inversus	Intestinal malrotation	Intraabdominal vascular anomalies	Other
Yamagiwa et al. [1988]	Case report	VSD	+			PDPV	
Day et al. [1989]	3/26 cases with EHBA[b]	2 cases with azygos continuation of IVC	2 cases		1 case		Bowel atresia in the case with malrotation
Gershoni et al. [1989]	EHBA in one of 2 sibs with immotile cilia syn.	–	+				Consanguinous parents
Hoffman et al. [1989]	2/31 EHBA cases with liver transplant	Absent prerenal IVC	+		+	PDPV, anomalous origin of hepatic artery	
		Absent prerenal IVC	+				
Woodle et al. [1990]	Case report	Left IVC with hemiazygos continuation	+			Absent portal V	
Silveira et al. [1991]	19 patients with splenic malformations out of 237 consecutive cases of EHBA	5 cases	2 cases with asplenia	8 cases	9 cases	10 cases with PDPV	1 case polydactyly 1 case Kartagener syndrome
Carmi et al. [1991] (BWIS-*Unpublished data*)	6 cases of EHBA in a case control study of congenital cardiovascular malformations (Cases: 4,390 Controls: 3,572)	PLSVC to coronary sinus, complex heterotaxy	+				
		Single ventricle L-TGA, aortic hypoplasia	+	+			
		Dextrocardia, atrial situs inversus		+			
		Dextrocardia, CAVC, PS, hypoplastic right ventricle	+				
		Single atrium, absent IVC PLSVC to coronary sinus	+	+			Jejunal atresia
		–(Control)		+	+		Sib w/congenital CVM

[a] LMB, Laurence-Moon-Biedl.
[b] Segregation of anomalies per patient not given.
[c] Abbreviations as in Tables I–IV and CHD, congenital heart disease; T/PAPVD, total/partial anomalous pulmonary venous drainage; DORV, double outlet right ventricle; HLV, hypoplastic left ventricle; C/A, coarctation of aorta; CVM, cardiovascular malformation.
+ = Present.
– = Absent.

suggestion of familial occurrence. Recognition of rarely occurring similar cases might further support genetic causation of EHBA within the laterality sequence.

The other relatively large subgroup of EHBA (Table II) with associated anomalies presents a heterogeneous group with regard to the type of extrahepatic organs involved, and the actual defects. However, the common denominator is that neither "syndromic" nor other specific patterns could be identified for the various associations. In this respect, this subgroup is comparable to other isolated malformations of organs like heart or kidneys which frequently associate in a nonspecific fashion with other anomalies. It is difficult to comment on the frequency of the association of EHBA with the anomalies found in our study, since none of the literature reviews on EHBA and associated anomalies had used a similar classification. In a study of 7,049 patients with multiple congenital anomalies in Hungary [Czeizel, 1987], 10 cases were found with the combination of CVM and EHBA. Seven of those had VSDs, 2 had PDA, (Patent ductus arteriosus) and one had complex CVM. One case also had malrotation of the kidney and another had atresia of the bowel. It is interesting to note that these types of CVMs are totally different from those of the 5 BWIS cases, who uniformly presented the laterality sequence. VSD was also found to commonly associate with EHBA in Miyamoto and Kajimoto's review [1983]. However, it is not clear whether the cardiac defects were isolated or part of the laterality sequence observed in a considerable number of their patients. Miyamoto and Kajimoto [1983] also report renal and gastrointestinal anomalies in 16% and 23%, respectively, of 79 patients with EHBA and associated anomalies. However, again, the segregation of those anomalies in individual patients is not known and thus these numbers are not comparable to ours.

According to our suggested classification, the organs which are most frequently involved in anomalies associated with EHBA in a "nonsyndromic" fashion are the heart, kidneys, and gastrointestinal tract. While renal anomalies show great variability, 5 out of the 7 upper urinary tract defects do represent components of the RAD syndrome. The gastrointestinal anomalies are rather limited in their repertoire. Isolated Meckel diverticulum accounts for more than 50% of the cases with GI anomalies, while volvulus and atresia of small or large intestine account for the remaining cases. Isolated small bowel atresia with EHBA has been infrequently reported in the past [LeCoultre et al., 1983]. Since an ischemic lesion, occurring in the later stages of pregnancy, has been postulated as the pathogenesis of small bowel atresia [Touloukian, 1978], the coexistence of these anomalies might suggest a rare vascular cause for some cases of EHBA. Two cases of intestinal atresia were also observed in the laterality sequence group. Both were associated with intestinal malrotation; in one of them the multiple jejunal atresias were probably the result of absence of mesenteric vessels. Jejunal and multiple small bowel atresias have been reported in patients with EHBA and other anomalies in the spectrum of the laterality sequence [Poddock and Arensman, 1982; Day et al., 1989]. While polysplenia and situs inversus were not uniformly present, all these patients had malrotation. This observation suggests that although different causes are expected for intestinal atresia associated with EHBA in a "nonsyndromic" fashion versus within the context of the laterality sequence, vascular compromise either primary or secondary to malrotation might play a major pathogenetic role in both.

Six cases (Table III) seemed sufficiently different from the 2 main subgroups of EHBA with associated anomalies to warrant a third subgrouping, yet they bear some similarities to both of these groups. All of these cases had intestinal malrotation with or without anomalies of the portal vein (PDPV), hepatic artery, or mesenteric vessels. While not a common finding with isolated malrotation [Filston and Kirks, 1981], EHBA has been repeatedly observed with PDPV and malrotation within the spectrum of the laterality sequence [Chandra, 1974; Teichberg et al., 1982; Miyamoto and Kajimoto, 1983; Abramson et al., 1987; Yamagiwa et al., 1988]. This anomalous course of the portal vein has also been observed in approximately 40% of patients with situs inversus [Ruben et al., 1983]. Normal development of the portal vein results from the paired vitelline veins which begin to decline by the fifth week of in utero life [Grays and Skandalakis, 1972], subsequent to situs determination, and is apparently dependent upon a normal situs. Normal rotation and fixation of the gut, occurring later at 10–12 weeks of intrauterine life [Moore, 1988], also requires normal situs, and is indeed abnormal in 50–70% of cases with situs inversus [Ruben et al., 1983]. Although this small group of patients with EHBA presents associated anomalies confined to the gastrointestinal tract, these anomalies seem to be embryologically related to one basic pathology in situs determination with subsequent anomalous development of the duodenal vein, intestinal malrotation, mesenteric malfixation, and intestinal atresia probably due to in utero vascular compromise [Filston and Kirks, 1981]. Thus, these cases bear similarity to the laterality sequence group, though they have clinical evidence for neither situs inversus nor polysplenia.

Of further interest is the observed female excess in the laterality sequence group (Table IV). Female predominance has been previously observed for EHBA and the polysplenia syndrome [Silveira et al., 1991] and was confirmed in this study. The overall M:F ratio was found in our study to be similar for isolated EHBA (0.8) and EHBA with associated anomalies (0.7). When further calculated for the various subgroups, this ratio appears much lower for the cases with malrotation. Although these cases cannot account for the general female excess observed in EHBA, they might support similarity between the malrotation and laterality subgroups, since malrotation alone is not reported to be more frequent in females. Along these lines of reasoning, the association of EHBA with malrotation and PDPV can be viewed as some type of "forme fruste" of the laterality developmental field complex, and thus be included with the laterality sequence group. Alternately this association might represent a separate entity, possibly a more con-

fined phenotypic result of a specific abnormality in situs determination coded by a different mutation within the putative *iv* gene.

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