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Congenital Structural Abnormalities in Biliary Atresia: Evidence for Etiopathogenic Heterogeneity and Therapeutic Implications

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ABSTRACT. Silveira, T. R., Salzano, F. M., Howard, E. R. and Mowat, A. P. (Departments of Pediatrics and Genetics, Federal University of Rio Grande do Sul, Porto Alegre, Brazil, and Departments of Surgery and Child Health, King's College Hospital, London, UK). Congenital structural abnormalities in biliary atresia: Evidence for etiopathogenic heterogeneity and therapeutic implications. Acta Paediatr Scand 80: 1192, 1991.

The clinical, surgical, laboratory and histological data of 237 children with extrahepatic biliary atresia were reviewed. Forty-seven patients (20%) had associated congenital anomalies, and of these, 28 had cardiovascular, 22 digestive and 19 splenic malformations. Of the 19 patients with splenic malformations, 13 showed the polysplenia syndrome and two had asplenia. Chromosome studies were performed in eight children, six having associated anomalies, and two of them showed karyotype abnormalities (46,XX,del 18 p- and 49,XXXXY). These observations indicated that biliary atresia could be subdivided into four distinct etiopathogenic subgroups, three involving a congenital form that could arise through a malformation, a disruption or a chromosome abnormality, and the remaining to agents active in the perinatal period (the acquired form). The surgical outcome in 171 patients operated on by an experienced surgeon was not influenced by the presence of anomalies but by the timing of surgery. Seventy-one percent of 24 patients operated on by 8 weeks of age were jaundice-free as opposed to only 34% of those who had later surgery ($p<0.01$) *Key words: biliary atresia, neonatal jaundice, congenital malformations, surgery of biliary atresia.*

Extrahepatic biliary atresia (EHBA) is the result of a process of unknown aetiology which leads to the complete obstruction or disappearance of part or all of the extrahepatic bile ducts in young infants. The frequency has been estimated to be 0.5–1.0 per 10000 live births (1). From the pathological view, it is interesting that it can occur as an isolated lesion or in conjunction with several congenital anomalies. Questions unanswered are (*a*) whether these two groups should be considered as distinct nosologic entities, particularly those associated with splenic malformations; and (*b*) how could these associations be explained ontogenetically? The present communication is concerned with these problems. We also wish to document the type and frequency of anomalies observed in a large consecutive series of patients investigated in a relatively short period, to assess how these anomalies influence diagnosis and outcome with current surgical management. A previous analysis was made about several epidemiological aspects of this series (2).

PATIENTS AND METHODS

The clinical, surgical, laboratory and histological data of 237 consecutive cases of EHBA seen at King's College Hospital, London from 1973 to 1985 were retrospectively reviewed. All cases had been documented in a standardised fashion, using a specially designed form for

neonatal hepatitis syndrome (3). Laparotomy and surgical correction of biliary atresia had been performed by one surgeon (E. R. H.) in 171 cases. The remainder were referred after initial surgery for consideration of surgical revision or possible liver transplantation. The follow-up ranged from 5 months to 12 years (mean: three years). The outcome was assessed by absence of jaundice (serum bilirubin > 20 μmol/l). A complete autopsy was performed in 29 of the 94 patients deceased. Standard G-band chromosome analysis was carried out in 8 patients.

One hundred and fourteen of the patients were males and 123 females; 203 were Caucasians of North European origin (United Kingdom 178; Greece 14; Spain 3; Malta 2; France 2; Portugal 2; Italy 2) and 34 of other origin (Asia 16; Middle East 9; Africa 5; West India 4).

RESULTS

Forty-seven (20% of the children) had significant associated anomalies (Tables 1 and 2). In these 47 patients 60% had cardiovascular, 47% digestive, and 40% splenic abnormalities. A total of 113 anomalies were identified, 47 of which involved the heart or major intraabdominal vessels, 12 having a preduodenal portal vein. Among digestive anomalies, 16 had intestinal malrotation and 9 abdominal situs inversus.

Additional data about patients with splenic malformations are given in Table 3. Of the 13 with polysplenia syndrome nine had preduodenal portal vein, and seven intestinal malrotation. No other preferential combination of characteristics was found, almost all children presenting a unique pattern of malformation. For instance, in the 6 patients with 3 associated anomalies only 2 exhibited the same subset (patients H. W. and P. S.).

Chromosome studies were abnormal in 2 of 8 children of European origin, 6 of whom had anomalies. Deletion of the short arm of chromosome 18 (46, XX, del 18 p-) was found in a child with multiple malformations, intestinal malrotation and preduodenal portal vein, while a 49,XXXXY karyotype was found in a child with multiple malformations including dysplastic ears, bilateral clinodactyly, small penis and ventricular septal defect. The age of their mothers at the time of birth of the children was 36 years, and that of their fathers 36 and 31, respectively.

Of the 171 infants operated on by one surgeon, 50 of 140 (36%) of those with isolated EHBA became jaundice-free, as compared with 8 of 31 (26%) in patients with associated anomalies; differences in follow-up between the two groups were statistically non-significant. The anomalies in these eight patients were: (*a*) asplenia with situs inversus, intestinal malrotation and Kartagener syndrome; (*b*) polysplenia with situs inversus, absent inferior vena cava and preduodenal portal vein; (*c*) isolated polysplenia; (*d*) Meckel's diverticulum; (*f*) ventricular septal defect; and

Table 1. *Congenital anomalies associated with extrahepatic biliary atresia (frequency per patient) in 47 patients*

System involved	No.	% in affected children
Cardiovascular	28	60
Digestive	22	47
Splenic	19	40
Genitourinary	6	13
Musculoskeletal	4	8
Eye	1	2

Table 2. *Types of congenital anomalies associated with extrahepatic biliary atresia*

Types of anomalies	No. of anomalies	% of anomalies
Cardiovascular	47	42
Pulmonary stenosis	7	
Ventricular septal defect	5	
Patent ductus arteriosus	3	
Atrioventricular septal defect	3	
Atrial septal defect	2	
Dextrocardia	2	
Coarctation of aorta	1	
Oval fossa defect	1	
Right juxtaposition of atrial appendages	1	
Hypoplasia of left heart	1	
Aortic stenosis	1	
Preduodenal portal vein	12	
Inferior vena cava absent	2	
Portal vein absent	2	
Hypoplastic hepatic artery	1	
Double right renal artery	1	
Hepatic artery absent	1	
Anomalous portal vein	1	
Digestive	35	31
Intestinal malrotation	16	
Abdominal situs inversus	9	
Hepatic anatomic abnormality	3	
Annular pancreas	2	
Jejunum atresia	1	
Duodenal stenosis	1	
Pyloric stenosis	1	
Meckel's	1	
Abnormal mesentery	1	
Splenic	19	17
Polysplenia syndrome	13	
Polysplenia	2	
Accessory spleen	2	
Asplenia	2	
Genitourinary	7	6
Double ureter	1	
Congenital hydronephrosis	1	
Congenital hydroureter	1	
Tubular ectasia	1	
Renal cysts	1	
Vesico-ureteric stenosis	1	
Minute penis	1	
Musculoskeletal	4	3
Dysplastic ears	2	
Talipes equinovarus	1	
Cleft lip and palate	1	
Eye	1	<1
Microphthalmia	1	
Total	113	

(*g*) pyloric stenosis. The age at surgery was significantly related to jaundice-free survival, being 71 % in 24 having portoenterostomy by 8 weeks of age, and only 34 % in 147 with later surgery ($p<0.01$).

DISCUSSION

In considering the reported frequency of extrahepatic abnormalities in biliary atresia, it should be remembered that the information will be influenced by the thoroughness with which the patient is evaluated at three levels, (*a*) pre-operative clinical and laboratory investigations including scanning and radiography; (*b*) surgical exploration; and (*c*) postmortem examination. For instance, the first 11 cardiovascular anomalies listed in Table 2 were detected clinically, but the other 7 only at surgery. A further source of bias is that small series may not be representative of the number of patients with other anomalies. In our comparative analysis of the frequency of anomalies associated with EHBA (Table 4) we have therefore considered only reports of 20 or more cases. The percentages of patients with abnormalities (not including the present study) varied from 11 % to 37 % with an average of

Table 3. *Associated congenital anomalies in 19 EHBA patients with splenic malformations*

+: presence; −: absence. Accessory spleen: up to four spleens; Polysplenia: more than four accessory spleens

Patient	Sex	Splenic condition	Preduodenal portal vein	Intestinal malrotation	Abdominal situs inversus	Cardiac malformation	Others
L.D.	F	[a]	−	−	+	−	−
J.S.	F	[a]	+	+	−	−	−
N.M.	F	[a]	+	+	−	−	−
H.W.	F	[a]	+	+	+	−	−
C.W.	M	[a]	+	−	+	−	Absent inferior vena cava
Y.D.	F	[a]	+	+	−	+	−
T.P.	M	[a]	+	+	+	−	Annular pancreas
A.L.	F	[a]	+	−	−	−	Anomalous mesentery
C.B.	M	[a]	+	−	−	+	−
D.K.	M	[a]	−	+	−	−	−
E.W.	F	[a]	−	+	−	−	−
H.C.	F	[a]	−	−	+	+	−
K.W.	F	[a]	+	−	+	+	−
R.T.	F	[b]	−	−	−	−	−
H.S.	F	[b]	−	−	−	−	−
M.A.	F	[c]	−	−	−	−	Hand polydactyly
N.B.	M	[c]	−	−	−	−	−
V.L.	F	[d]	−	+	+	−	Kartagener syndrome
P.S.	M	[d]	+	+	+	−	−

[a] Polysplenia syndrome.
[b] Polysplenia.
[c] Accessory spleen.
[d] Asplenia.

21%, being 26.5% in those with postmortem examination and 16% of those without autopsy. These results are similar to those reported here. If the malformations are classified in four large subgroups, cardiovascular, digestive, splenic and others, the frequency of the present series was also in the range previously reported.

Chandra (13) emphasized that the simultaneous occurrence of EHBA and the polysplenia syndrome may not be a mere coincidence. Indeed, after describing ten cases of the syndrome, half of which with EHBA, he proposed that the biliary pathology should be regarded as a component of the syndrome. We reviewed six series in which this simultaneous occurrence was studied (Table 5). The percentage with the polysplenia syndrome varied from 2% to 29% (average 4%), practically identical with our finding of 5%. In our necropsy cases we identified 2 in 24 (8%). There was a predominance of females both in the reported series (67%) and in the

Table 4. *Frequency of associated anomalies in EHBA patients*

Type of study: 1 = surgical exploration, clinical or autopsy study; 2 = autopsy study

Study	Type of study	No. of patients	Frequency of anomalies (%)
Lilly & Chandra (4)	1	22	27
Dimmick et al. (5)	2	35	26
Choulot et al. (6)	1	178	11
Maksem (7)	2	29	31
Henriksen et al. (8)	1	64	13
Altman (9)	1	83	16
Miyamoto & Kajimoto (10)	2	758	12
Ambrosius-Diener & López-Varela (11)	2	35	37
Saing & Tam (12)	1	45	15
This study	1	237	20
	2	29	24

Table 5. *Polysplenia syndrome and EHBA*

Reference	No. of cases of EHBA	Sex		Polysplenia syndrome		Description of cases: Anomalies					
		M	F	No.	%	Cardiac	Vascular	Situs inversus	Pulmonary	Intestinal malrotation	Others
5	35	1	5	6	17	2	1	3	3	3	1
6	178	4	6	10	6	3	5	6	3	4	3
7	29	2	4	6	21	5	2	1	2	3	4
10	758	5	9	14	2	10	6	6	6	6	0
11	35	2	2	4	11	3	0	1	2	0	4
13	17	1	4	5	29	1	4	3	3	5	4
Total	1 052	15	30	45	4	24	18	20	19	21	16
No. not recorded						5	13	12	18	13	21
Total assessed						40	32	33	27	32	24
% involvement						60	56	61	70	66	67

present study (69%; Table 3). The frequency of recorded anomalies varies in the 6 series, comprising cardiac (60%), vascular (56%), situs inversus (61%) and intestinal malrotation (66%). In our study the percentages were 31%, 69%, 46% and 54%, respectively (cf. Table 3).

Numerical, as well as structural chromosome abnormalities have been described previously in EHBA patients. Among the numerical abnormalities the most frequent is trisomy 18. Alpert et al. (14), studying 19 patients with this trisomy, found extrahepatic biliary atresia in 2 of the 7 with cholestasis; they suggested that an intra-uterine viral infection could be responsible for both the meiotic non-disjunction and the inflammation of the biliary ducts. Trisomy of chromosome 21 (15, 16), as well as Turner's syndrome (17) have been observed less frequently in association with EHBA. Delicado et al. (18) described a family with a translocation, t(10;21)(q22;q22) transmitted through three generations, in which two sisters showed multiple malformations, cystic fibrosis and biliary atresia.

These observations support the hypothesis that EHBA is a heterogeneous entity. The majority have no associated congenital anomalies and presumably are caused by factors acting after organogenesis is complete. Whether these act late in gestation, at birth or postnatally is unknown.

The remaining 20% to 25% have congenital malformations, but this is not a homogeneous sub-group. Three etiopathogenic mechanisms may be involved in this category: chromosome abnormality, presumably acting from conception and accounting for a minority of cases (although these patients have not been systematically studied with modern techniques); disordered organogenesis due to environmental factors acting around 5 weeks gestation, with the polysplenia syndrome being a distinct subset; or disruptive events occurring later in gestation. The latter are associated with such abnormalities as intestinal atresia or cardiovascular anomalies (19). Previous suggestions that EHBA could consist of at least two types of conditions (embryonic or fetal and perinatal) have already been made (20, 21).

Polysplenia syndrome, accounting for 5% of cases in our series and from 2% to 29% in the literature is a relatively homogeneous and intriguing subset. In only one previous case has asplenia been reported in biliary atresia (10). It is noteworthy that our two cases had two or more of the abnormalities comprising the polysplenia syndrome, namely, preduodenal portal vein, intestinal malrotation or abdominal situs inversus. This raises important questions concerning the embryonic processes believed to cause polysplenia syndrome or asplenia. Polysplenia syndrome is considered to occur as a result of a defect in organogenesis at 30 to 40 days gestation, while asplenia occurs as a result of events at 20 to 29 days of gestation (10). Current hypotheses are that the main mechanism underlying these abnormalities in development is an alteration in the laterality process during embryogenesis resulting in an insufficient, defective or absent development of the organs on one side and an excessive development on the other side. In the polysplenia syndrome—in which a bilateral left-sided sequence of development is considered to occur—the right side structures are suppressed resulting in anomalies such as two lobes in both lungs, while the inferior vena cava, gall bladder and extrahepatic biliary system (normally located on the right side) are malformed or absent. On the contrary, in the asplenia syndrome, which is considered to be an example of bilateral right-sided sequence of development, both lungs have three lobes (dextro-isomerism) and the extrahepatic biliary system develops normally. The finding of biliary atresia in association with asplenia and features of the polysplenia syndrome in the two cases we report challenges the above hypothesis.

The acquired form of EHBA could result from an external pathogenic agent, e.g. a virus in a child with genetic susceptibility, possibly related to HLA status (22). Landing et al. (15) suggested that EHBA could be part of a spectrum of infantile cholangiopathy, but this would imply a homogeneity which probably does not exist. In acquired EHBA the sequence of events would be epithelial cell degeneration, inflammatory cell infiltrates, fibrosis, duct stenosis, sclerosis and complete obliteration or destruction of the bile ducts.

The practical implications of these findings can be considered at a diagnostic and therapeutic level. Situs inversus, polysplenia (on ultrasound examination) or malrotation (radiologically demonstrated) are strong pointers to a diagnosis of EHBA likely to be associated with unusual anatomical arrangements near the porta hepatis requiring skilled surgical appraisal. Conversely, the finding of a cardiovascular lesion in 11% of our patients lessens the value of congenital heart lesions, particularly pulmonary stenosis, in distinguishing patients with syndromic paucity of interlobular bile ducts (23) from those with biliary atresia, when liver biopsy findings are inconclusive.

The presence of extrahepatic anomalies might be expected to adversely affect the outcome of surgical management in two ways: delay in undertaking surgery because of the time spent in investigating other abnormalities prior to laparotomy; and technical difficulties at the time of surgery, because of unusual anatomical arrangements at the porta hepatis. The outcome in this series and of that of Hall (24) was no worse in those with anomalies. Two factors may have contributed to this unexpected finding. The infant with anomalies may have come to expert pediatric attention earlier than the infant with isolated biliary atresia, who is typically deceptively well in the first 6 to 8 weeks of age (25). Whatever the etiology or pathogenesis of EHBA, the timing of surgery is critical, and the best results are consistently achieved in infants of less than 8 weeks of age operated on in units with experience of this rare condition (1, 25).

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