Type and frequency of cardiac defects in embryofetal alcohol syndrome

Report of 16 cases

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Within a period of 3 years, 56 infants and children with embryofetal alcohol syndrome have been detected and examined for heart defects. All children were from mothers who had been addicted to alcohol even during pregnancy and they showed a typical pattern of malformations, as described by Lemoine et al. (1968) and Jones et al. (1973).

In 16 cases cardiovascular malformations were confirmed by heart catheterisation or pathological examination. The overall incidence of heart defects in this syndrome was 29 per cent. The incidence rises to nearly 50 per cent in the more severe types of this syndrome. Atrial septal defects were found to be the most common heart defect (10 out of 16 cases); ventricular septal defects and other variable malformations occurred less frequently.

The high incidence of heart defects indicates that alcoholism during pregnancy has to be considered as a serious and preventable cause of congenital heart disease.

Previous clinical studies on the embryofetal alcohol syndrome resulting from severe maternal alcoholism in pregnancy indicate that alcohol is a teratogenic agent. Alcoholism during pregnancy may produce multiple malformations including heart defects in the offspring. We owe it to Lemoine *et al.* (1968) in Nantes, France, and Jones *et al.* (1973, 1974) in the USA for recognising a typical pattern of malformations in this syndrome, which is characterised by the following basic features: prenatal and postnatal growth retardation; retardation of mental, psychomotor, and motor development; craniofacial dysplasia, particularly microcephaly, short palpebral fissures, ptosis of the upper lids, epicanthic folds, upturned nostrils ('nez court en trompettes'), and mandibular hypoplasia (Fig. 1A and B). Other malformations are frequently found, such as heart defects, abnormalities of the limbs or genitals, dermatoglyphs, etc. The malformations vary in individuals in number and in severity.

The prevalence and types of cardiac defects in the embryofetal alcohol syndrome are still matters of controversy. On the basis of our first reports of 8 confirmed cases, atrial septal defect was thought to

be the most frequent abnormality (Löser *et al.*, 1975, 1976). On the basis of other reports, however, the most frequent defect seemed to be ventricular septal defect. Little information is available concerning the frequency of cardiovascular malformations in this syndrome. Since an increase in the number of alcohol-consuming women of child-bearing age is to be expected in all industrial countries, the question of cardiovascular malformations in the embryofetal alcohol syndrome is important both prophylactically and therapeutically.

Subjects and methods

Following our first reports of heart diseases in embryofetal alcohol syndrome (Löser *et al.*, 1975), we were able to detect in our clinic a total of 16 infants and children with congenital heart disease in 56 cases with the syndrome (Bierich *et al.*, 1976; Majewski *et al.*, 1976). The observation spanned a 3-year period. In all these 56 cases the heart was examined clinically and chest radiographs and electrocardiograms were obtained. If reasonably certain indications of cardiac defect were present, heart catheterisation and angiocardiology were performed.

All patients were children of mothers who had

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Fig. 1 (A) and (B) Typical facies of children with embryofetal alcohol syndrome. The narrow palpebral fissures, the upturned nostrils, the hypoplasia of the mandible, and the vermilion border of the upper lip are noteworthy.

drunk excessive amounts of alcohol for several years, even during pregnancy. An estimate of the alcohol intake was obtained from case histories and expressed as grams of ethanol per day. In addition, data concerning alcohol-related diseases, duration of pregnancy, birthweights, and gestational ages were collected. Children of mothers who were only occasional drinkers were not included. The minimal alcohol consumption admitted by the mothers ranged from 75 to 350 g/day. As is typical with alcoholics, the actual amounts must be assumed to be higher and, therefore, could not be established precisely. Additional drug intake was noted in as far as it was admitted.

Because of the broad spectrum of symptoms in this syndrome, the 56 cases of embryofetal alcohol syndrome have been divided into three groups according to the occurrence and severity of mental, neurological, and physical abnormalities (Majewski *et al.*, 1976).

Grade 1 (20 cases): oligosymptomatic cases with only slight expression of morphological features. Except for reduced body weight and microcephaly these children showed no manifestations typical of the syndrome. Abnormal development in utero was

in some cases less important than postnatal growth retardation which usually persisted into later childhood. Motor development was moderately delayed in most cases. Mental age did not seem to differ from that of normal subjects.

Grade 2 (19 cases): moderately affected cases. The craniofacial dysmorphism was not striking, but sufficiently pronounced to be apparent to those with some experience in its recognition. In this group there were no neurological manifestations, except for hyperexcitability and hypotonia of the muscles. Mental and physical development were moderately delayed.

Grade 3 (17 cases): severely affected cases with all or nearly all the typical abnormalities. All cases showed pronounced craniofacial changes: microcephaly, epicanthic folds, ptosis, upturned nostrils, thin vermilion border of the upper lip, and mandibular hypoplasia. Physical, motor, and mental development were seriously delayed in all cases.

Results

The historical data and catheterisation results in our 16 cases are summarised in Tables 1 and 2. They

comprise 7 girls and 9 boys between the ages of 1 month and 6 years. Except for cases 13 and 14 the birthweights were below 2500 g, and the data in Table 1 show that these children were premature and/or small for dates at birth. The overall incidence of heart defects in embryofetal alcohol syndrome was 29 per cent. There was a tendency for the more severely affected to have a higher incidence of heart defects: thus cardiovascular malformations occurred in 1 of 20 cases with grade 1 changes, 5 of 19 cases with grade 2 changes, and 10 of 17 cases with grade 3 changes. If the mildly affected cases of grade 1 are

excluded, heart defects were present in 15 of 36 children (42%).

Atrial septal defects were found in 10 cases. In one of these distinct displacement of the heart to the left and hypoplastic left pulmonary arteries were shown. In one case of atrial septal defect, catheterisation was not justified during life because of respiratory problems and internal hydrocephalus. The heart is shown in Fig. 2. At histological examination of both ventricles no abnormal structure of the muscle fibres or other signs of cardiomyopathy were found. In all cases additional left-sided defects were

Table 1 Birthweights, gestational ages, and history of maternal alcohol abuse

Case No.	Birthweight	Gestational age (wk)	Duration of abuse before birth (y)	Minimum amounts of alcohol in pregnancy (g/day)	B=beer W=wine S=spirit	Further indications of maternal alcoholism
1	1600	39	5	?	S	Withdrawal treatment; fatty liver (histol.)
2	1970	40	4	?	S	Diffuse fatty liver (histol.); barmaid; tremulous states
3	1970	35	6	190	S	—
4	1790	32	6	150	B	{ Delirium tremens; generalised convulsions (children of same mother)
5	2410	36	4	300	B	
6	2080	41	14	125	B, S, W	Tremulous states in 4th month of gestation; fatty liver
7	2110	32	10	100	W, B	Withdrawal treatment: delirium tremens
8	2280	41	7	190	W, S, B	—
9	2000	35	11	350	S	Several suicidal attempts
10	2290	40	2	75	S, B	2 withdrawal treatments without success
11	2000	40	7	250	S, S	Mother died from hepatic coma 1 y after delivery
12	1380	32	2-3	100	S, B	Barmaid, divorce because of drinking
13	3300	40	11	300	W	2 withdrawal treatments; delirium tremens; alcohol damage of liver; epilepsy for 11 y; drugs in pregnancy: 3 × 0.1 g phenytoin/day
14	2950	40	4	250	B, S	Delirium tremens (2); drunk during delivery
15	2420	36	3	125	S, B, W	Withdrawal treatment; damage of liver; drugs in pregn.: up to 10 tabl. Thomapyrin®/day (=2.5 g aspirin + 2.0 g phenacetin)
16	1810	36	5	240	B, S	Withdrawal treatment; diffuse fatty liver (histol.); tremulous states

Table 2 Embryofetal alcohol syndrome: results of catheterisation

Case No.	Sex	Age* y mth	Diagnosis	Shunt	Qp/Qs	Pulmonary hypertension	Notes
1	M	7	ASD II	L-R	1.3	0	
2	F	2	ASD II	L-R	1.7	0	Died; mild suprav. pulm. stenosis
3	M	2	ASD II	L-R	2.3	0	
4	M	6	ASD II	L-R	2.1	0	
5	F	7	ASD II	L-R	1.1	0	Displacement of the heart to the left; hypoplast. left pulm. art.
6	F	3	ASD II	L-R	2.4	0	
7	F	9	ASD II	L-R	—	—	Died; heart section; int. hydroceph.
8	F	8	ASD II	L-R	1.9	0	
9	M	6	ASD II	L-R	2.2	0	
10	M	3	Aplasia right PA	0	1.0	0	Collateral arteries to right lung
11	F	4	Mild IHSS	0	1.0	0	
12	M	4	VSD	L-R	1.3	++	Right aortic arch
13	F	2	VSD	L-R	1.8	0	
14	M	1	AV—canal	L-R	—	+	
15	M	1	Infund. PS, VSD	R-L	0.5	0	Died; hypoxic spells
16	M	1	ASD II	L-R	1.7	0	

*At time of catheterisation; + = mild, ++ = moderate; Qp/Qs = pulmonary to systemic flow ratio; PS = pulmonary stenosis.

excluded by angiocardiology. Electrocardiograms showed no evidence of left axis deviation.

An isolated ventricular septal defect was found in 2 cases, one of which had a right-sided aortic arch and pulmonary hypertension (Fig. 3).

In other isolated cases, variable defects were found. In one case aplasia of the right pulmonary artery was established (Fig. 4), which was also confirmed by lung perfusion scintigraphy. In one case a mild obstruction of the left ventricular outflow tract was found. One case of atrioventricular canal, and one case of infundibular pulmonary stenosis and ventricular septal defect with pronounced cyanosis were also shown.

Two infants died from extracardiac causes (cases 2 and 7), at the ages of 5 and 9 months. One infant died in the course of hypoxic spells and respiratory troubles at the age of 4 months (case 15).

The catheterisation and electrocardiographic data gave no reliable signs of cardiomyopathy in any subject.

Discussion

The frequent appearance of cardiac defects in the embryofetal alcohol syndrome can now be regarded

as established. No exact data regarding the frequency of cardiac defects in children from alcoholic mothers are available. There are several reasons for this:

(1) The degree of severity and the expression of

Fig. 3 Case 12. Angiogram after injection into the left ventricle. Filling of the right ventricle and the pulmonary artery. Right-sided aortic arch.

Fig. 2 Case 7. Portion of the heart. The arrow indicates a large atrial septal defect (secundum type).

Fig. 4 Case 10. Angiogram showing absence of the right pulmonary artery.

manifestations varied in our observations and also in other published studies. They range from mild ('formes frustes') to severe cases (grade 1-3, Majewski *et al.*, 1976). This depends more on the drinking pattern and the individual tolerance than on the absolute quantity of alcohol consumed (Majewski *et al.*, 1976). The question remains whether infants with only a slight expression of symptoms should be included in the embryofetal alcohol syndrome.

(2) In many currently reported cases of embryofetal alcohol syndrome, the diagnosis of heart defect is based only on clinical findings (see Table 3). It has been suggested that heart defects can be expected in nearly 50 per cent of all cases (Jones *et al.*, 1973; Löser *et al.*, 1975). This percentage, however, seems to be too high if the cases of mild degree are included. But if only the cases of grades 2 and 3 are considered the percentage rises to 42 per cent, and in severe degrees to more than 50 per cent (9 of 16). A definitive statement concerning the frequency of heart defects will be possible only when more extensive material is available and investigated.

The influence of concurrent drug intake did not appear to be significant in our study.

In contrast to the currently available reports, particularly that of Jones *et al.* (1973), the most frequent malformation of the heart is atrial septal defect and not ventricular septal defect. An atrial septal defect was diagnosed in 10 out of 16 cases, an isolated ventricular septal defect in 2 cases. According to the reported clinical observations (Table 3), ventricular septal defect was often suspected, but the typical sharp harsh murmur was seldom described. Noonan (1976) recently presented a paper on 3 cases with embryofetal alcohol syndrome and heart defects. Two of these had tetralogy of Fallot.

Based on experimental studies, particularly the chick embryo and mouse embryo (Sandor, 1968; Chernoff, 1976), it has been confirmed that ethyl-alcohol affects embryonic development, produces a high mortality rate, and alters early growth as well as differentiation and morphogenesis in cardiac development. Sandor and Elias (1968) described a lack of circulation in beating embryonic hearts after

Table 3 Summary of published cases of embryofetal alcohol syndrome with cardiac defects

Author	Case No.	Sex	Age y m	Heart defect	Heart catheter.	Notes
Jones <i>et al.</i> (1973)	1	F	1	VSD suspected	φ	Spontan. closure
	2	F	11	ASD	+	Heart failure
	3	F	4 3	VSD suspected	?	Spontan. closure suspected
	4	F	3 9	PDA suspected	?	—
Jones and Smith (1973)	8	M	2 6	VSD suspected	φ	Spontan. closure suspected
	1	M	Newborn	VSD suspected	φ	—
	2	F	Newborn	VSD	φ	Died; pathol. examination
	3	F	7	VSD suspected	φ	—
Palmer <i>et al.</i> (1974)	2	F	1 9	VSD suspected	φ	Twins
	3	F	1 9	?	φ	(systolic murmur)
Saule (1974)	1	F	Newborn	VSD suspected	φ	—
Manzke and Grosse (1975)	4	M	6	Defect suspected	φ	—
	7	M	9	Mitr. stenosis	+	Infrahepat. stenosis IVC
Reinhold <i>et al.</i> (1975)	2	F	4	VSD suspected	φ	—
Löser <i>et al.</i> (1975)	1	M	7	ASD	+	Died, 5th mth
	2	F	2	ASD	+	
	3	M	2	ASD	+	
	4	M	1 6	ASD	+	
	5	F	7	ASD	+	
	10	M	3 4	Aplasia r. PA	+	
	11	F	4 3	Mild IHSS	+	
	12	M	4 5	VSD, r. ao. arch	+	
Mulvihill <i>et al.</i> (1976)	2	M	1	PAST suspected	φ	—
Noonan (1976)	1	?	4	T/F	+	—
	2	?	6	T/F	+	—
	3	?	17	VSD, PDA	+	—

Abbreviations: ao., aortic; ASD, atrial septal defect; IHSS, idiopathic hypertrophic subaortic stenosis; IVC, inferior vena cava; PA, pulmonary artery; PAST, pulmonary artery stenosis; PDA, persistent ductus arteriosus; T/F, tetralogy of Fallot; VSD, ventricular septal defect. φ, catheterisation not performed.

exposure to alcohol. Chernoff (1976) noted a higher rate of heart defects on the eighteenth day of gestation in developing mice during exposure to alcohol. The type of defects in the heart and great vessels were, however, not elaborated.

The cardiovascular malformations produced by thalidomide during pregnancy represent a comparable embryotoxic effect on the developing heart (Khera, 1976). Congenital heart disease was found in approximately 19 per cent of the children affected by thalidomide embryopathy (Keck *et al.*, 1971). As with thalidomide embryopathy, the critical period for toxic injury to the developing heart is assumed to be between the fourth and sixth week of gestation. It is expected that the spectrum of cardiovascular defects in embryofetal alcohol syndrome is more extensive than has been known up to now.

Previous investigations indicate that it is the ethanol itself and not its metabolites, such as acetaldehyde, that is responsible for the direct damage to the embryo, since alcohol is able to cross the placental barrier readily. Moreover, it is known that alcohol metabolism is deficient in chronic alcoholics and also in the human fetal liver. The concentration of alcohol dehydrogenase in the human fetal liver is extremely low (Pikkarainen and Riih, 1967) and ethanol clearance is reduced (Seppl *et al.*, 1971), which enhances the toxic influence.

It is surprising that widespread alcoholism during pregnancy has not been recognised earlier as a cause of congenital heart disease, since many women as well as men have been addicted to alcohol for generations.

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