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Extracardiac defects in children with congenital heart disease

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SUMMARY Extracardiac defects were found in 66 (13%) of 513 Nigerian children with congenital heart disease. As a group these 66 children were significantly younger than the remaining 447 children who had congenital heart disease without extracardiac defects. Of the extracardiac defects, 27 per cent occurred in the musculoskeletal system, 23 per cent in the gastrointestinal tract, and 7·5 per cent in the central nervous system. In addition, 15 (23%) and eight (12%) of the 66 children had congenital rubella and Down's syndrome, respectively. With the exception of the well-recognised association between Down's syndrome and endocardial cushion defect, and between congenital rubella syndrome and persistent ductus arteriosus no extracardiac defects appeared to be predictably associated with any specific form of congenital heart disease. The extracardiac defects caused the death of 12 per cent of the patients in the newborn period; and 17 (52%) of 33 surviving patients have mental retardation.

Extracardiac defects should be carefully looked for in children with congenital heart disease because early detection and treatment of the non-cardiac defects could improve the overall prognosis. Where facilities for cardiac surgery are limited priority for corrective surgery should be given to patients who have no mental handicaps since they are more likely to derive maximum benefits from the expensive surgical procedures.

Since most types of congenital heart disease are now amenable to surgery (Aberdeen, 1975; Morris and McNamara, 1975), it is essential that any child with congenital heart disease should be completely evaluated, noting in particular congenital extracardiac defects which may adversely affect the prognosis. Such an evaluation demands, among other things, a knowledge of the incidence and clinical significance of extracardiac defects in children with congenital heart disease. However, previous reports on the subject (Abbott, 1927; Okada *et al.*, 1968; Blankson and Christian, 1975) have given divergent estimates of the incidence of extracardiac defects in such children, and very little attempt has been made to assess the significance of such non-cardiac defects. The present study was therefore undertaken with a view to determine the incidence, distribution pattern, and clinical significance of extracardial defects in Nigerian children with congenital heart disease.

Subjects and methods

Between 1965 and 1978, 513 children with congenital heart disease were studied at the University College Hospital, Ibadan. Of these children, 66 had associated extracardiac defects and they formed the subjects of the present study. In 47 of these 66 patients the diagnosis of congenital heart disease was based on clinical and angiocardiographic findings while the extracardiac defects were diagnosed on the basis of characteristic clinical and radiological features. The clinical diagnoses were confirmed by chromosome studies in appropriate cases. The mental development of the patients was assessed by comparing their levels of psychomotor development, social intercourse, speech acquisition, and learning aptitude with those of healthy subjects attending the children's welfare clinic in our hospital. A patient was judged to be mentally retarded if he was subnormal by three or four of the indices that we employed. However no developmental assessment was attempted in patients aged less than one year because we have found that such assessments are often inaccurate in young infants. In the remaining 19 patients both congenital heart disease and extracardiac defects were confirmed at necropsy (Antia, 1974).

For the purposes of this study congenital rubella syndrome and Down's syndrome were classified as single defects.

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Table 1 *Age distribution of patients with congenital heart disease and associated non-cardiac defects*

Age	*No. of patients*	*Per cent*
Birth to 1 month	12	18
1 month to 1 year	21	32
1 to 5 years	14	21
Above 5 years	19	29
Total	66	100

Results

INCIDENCE OF EXTRACARDIAC DEFECTS

The age groups of the 66 patients with extracardiac defects are shown in Table 1: 50 per cent of them were aged 1 year and less. As a group they were also significantly younger (mean age $\pm$SEM = 15 $\pm$0·29 months) than the other 447 patients (mean age $\pm$SEM = 35 $\pm$0·28 months) who had congenital heart disease without associated extracardiac defects ($t = 3{\cdot}9$; $P < 0{\cdot}01$). There was no significant difference in the sex distribution of the 66 patients, their male to female ratio being 1 to 1·3. The overall incidence of extracardiac defects in all 513 patients with congenital heart disease was 13 per cent (Table 2). However the incidence was lower (10%) in the clinical compared with the necropsy series (35%). Multiple extracardiac defects were encountered in 13 patients, but the average number of defects per patient was 1·2.

ASSOCIATION PATTERNS OF EXTRACARDIAC DEFECTS

If all the extracardiac defects are considered as a group 17 per cent of them occurred in association with complex cardiac lesions like transposition of the great arteries, tricuspid atresia, and endocardial cushion defect; 15 per cent and 13 per cent occurred in association with ventricular septal defect and persistent ductus arteriosus, respectively (Table 2). Isolated pulmonary stenosis and Fallot's tetralogy were associated with the least number of extracardiac defects. These differences were, however, not statistically significant ($P > 0{\cdot}05$).

Three of the eight patients with Down's syndrome had endocardial cushion defects as evidenced by a combination of ventricular septal defects and congenital mitral regurgitation (Table 3). The remaining five patients had auscultatory signs of uncomplicated ventricular septal defects. However their mean electrical QRS axes ranged between 270° and 330°; it is, therefore, reasonable to conclude that they too had endocardial cushion defects (Rudolph, 1974). Thus the incidence of Down's syndrome in patients with endocardial cushion defects (80%) was significantly higher than the 12 per cent incidence of Down's syndrome in the entire study ($\chi^2 = 20{\cdot}2$; $P < 0{\cdot}001$). Similarly, 10 (77%) of the 13 patients with persistent ductus arterious had associated congenital rubella syndrome; this incidence was significantly higher than the 23 per cent incidence of congenital rubella syndrome in the entire study ($\chi^2 = 14{\cdot}8$; $P < 0{\cdot}001$). All four patients with ostium secundum type of atrial septal defect had musculoskeletal defects, but the number of patients was too small for statistical evaluation. Though over 50 per cent of the gastrointestinal defects occurred in patients with ventricular septal defect the association did not achieve statistical significance ($P > 0{\cdot}05$).

TYPES OF EXTRACARDIAC DEFECT

Musculoskeletal defects were the commonest and accounted for 27 per cent of all extracardiac defects (Table 4). The spectrum ranged from single defects like syndactyly and cleft palate (two cases of each) to multiple defects as in Edwards', Ellis-van Creveld, Holt-Oram, Noonan's, and Turner's syndromes (one case of each). Of the patients, 23 per cent had defects in the gastrointestinal tract. These included umbilical and inguinal hernias (seven cases), tracheo-oesophageal fistula (four

Table 2 *Prevalence of extracardiac defects in children with congenital heart disease*

Type of coronary heart disease	*Clinical series*		*Necropsy series*		*Both series combined*	
	No. of patients	*Centile with extracardiac defects*	*No. of patients*	*Centile with extracardiac defects*	*No. of patients*	*Centile with extracardiac defects*
Ventricular septal defect	135	11	9	67	144	15
Persistent ductus arteriosus	96	12	6	33	102	13
Atrial septal defect	40	10	4	0	44	9
Pulmonary stenosis	47	8·5	3	0	50	9
Fallot's tetralogy	48	2	12	33	60	9
Miscellaneous complex lesions (triscuspid atresia; transposition of great arteries; endocardiac cushion defect, etc)	92	13	21	33	113	17
All defects	458	10	55	35	513	13

Table 3 *Prevalence of extracardiac defects in each form of congenital heart disease*

	Congenital heart disease					
	Ventricular septal defect	*Persistent ductus arteriosus*	*Atrial septal defect*	*Endocardiac cushion defect*	*Others*	*Total*
Extracardiac defects						
Gastrointestinal defect	8	1	—	—	6	15
Down's syndrome	—	—	—	8	—	8
Congenital rubella syndrome	5	10	—	—	—	15
Musculoskeletal defects	5	—	4	2	7	18
Others	3	2	—	—	5	10
Total	21	13	4	10	18	66

cases), duodenal atresia (two cases), and one case each of imperforate anus and omphalocele. Fifteen patients had congenital rubella syndrome, eight had Down's syndrome, and three others had spina bifida. There were two cases of renal cysts and one case each of bifid uterus and posterior urethral valve.

CLINICAL SIGNIFICANCE OF EXTRACARDIAC DEFECTS

Non-cardiac defects appeared to have been the immediate or major cause of death in eight (12%) of the 66 patients; and all the deaths occurred in the newborn period. Seven of these eight patients had gastrointestinal defects (Table 5). Of the three patients with tracheo-oesophageal fistula, two died during surgical correction of the defect. The third patient presented in hospital on the second day of life with cyanosis and clinical and radiographic features of tracheo-oesophageal fistula and aspiration pneumonia. This patient died a few hours after admission; necropsy confirmed the clinical diagnosis and also disclosed a coexisting transposition of the great arteries. Two patients with duodenal atresia and another with imperforate anus and gall-bladder atresia died of severe fluid and electrolyte disturbance, while the baby with omphalocele succumbed to a coliform septicaemia. The eighth patient, a 5-day-old baby, had persistence of the fetal circulatory pattern with pulmonary hypertension, right-to-left ductal shunt, and fatal hypoxaemia. Necropsy subsequently disclosed a hypoplastic right lung with the ipsilateral pulmonary veins draining into the inferior vena cava.

The mental development of 33 of the surviving patients was assessed: 17 of them (52%) were mentally retarded, including eight patients with Down's syndrome, seven with congenital rubella syndrome, and two other patients whose neurological features did not fit into any recognised syndrome.

Table 4 *Pattern of extracardiac defects*

Type of defects	*No. of patients*	*Centile*
Musculoskeletal*	18	27
Gastrointestinal	15	23
Rubella syndrome	15	23
Down's syndrome	8	12
Neurological*	5	7·5
Urogenital	4	6
Pulmonary hypoplasia	1	1·5
Total	66	100

*Excluding patients with Down's and congenital rubella syndromes.

Discussion

The reported incidence of extracardiac defects in children with congenital heart disease varies from 11 to 44 per cent and, with one exception (Emerit *et al.*, 1967), the lowest incidence rates have been recorded in clinical (Lamy *et al.*, 1957) and the highest in necropsy studies (Wallgren *et al.*, 1978). The highest incidence in necropsy studies, which is also confirmed by our data, may be partly because necropsies are likely to disclose minor organ defects (for example bifid uterus, single renal cyst) which could easily be missed in clinical studies. Furthermore some extracardiac defects may cause death in the newborn period or early infancy. Such defects would therefore be more prevalent in necropsy studies which invariably include a large number of infants (Wallgren *et al.*, 1978). But despite the

Table 5 *Fatal extracardiac defects in 8 patients*

Extracardiac defect	*Cardiac lesion*
Tracheo-oesophageal fistula	Ventricular septal defect
Tracheo-oesophageal fistula	Fallot's tetralogy
Tracheo-oesophageal fistula	Transposition of great arteries
Duodenal atresia	Ventricular septal defect
Duodenal atresia	Persistent ductus arteriosus
Omphalocele	Transposition of great arteries
Imperforate anus, gall-bladder atresia	Ventricular septal defect
Hypoplastic right lung	Persistent ductus arteriosus, partial anomalous pulmonary venous drainage

Table 6 *Comparison of incidence of some congenital extracardiac defects in general population (Gupta, 1969) and in children with congenital heart disease*

	Incidence (%)	
Defects	*General population*	*Present study*
Gastrointestinal		
Inguinal hernia	0·16	1·0
Imperforate anus	0·03	0·2
Omphalocele	0·03	0·2
Duodenal or ileal atresia	0·02	0·4
Gall-bladder atresia	0·02	0·2
Tracheo-oesophageal fistula	0	0·8
Musculoskeletal		
Defects of long bones	0·10	2·8
Cleft lip and palate	0·08	0·4
Syndactyly	0·04	0·4
Central nervous system		
Spina bifida	0·07	0·6
Other defects	2·45	6·0
Overall incidence	3·0%	13·0%

($X^2 = 107$, $P < 0.001$)

probability that clinical studies underestimate the prevalence of extracardiac defects in children with congenital heart disease the incidence rates so determined are still considerably higher than the general incidence of birth defects which has been estimated at between 1 and 7 per cent (McIntosh *et al.*, 1954; Harris, 1974). Table 6, which includes data obtained by Gupta (1969) in a study of 4,220 consecutive deliveries at a general hospital in Ibadan, clearly shows the excess of extracardiac defects in children with congenital heart disease. Indeed Kenna *et al.* (1975) have estimated the incidence of associated defects in children with congenital heart disease at about 10 times the chance expectation. This excess of extracardiac defects may be explained on the basis of a clustering of defects produced by the action of a pluripotent teratogen on a susceptible fetus.

About half the extracardiac defects in our patients occurred in the musculoskeletal and gastrointestinal systems. This preponderance of skeletal and gastrointestinal defects, which has also been noted by other workers (Macmahon *et al.*, 1953; Wood *et al.*, 1969), is probably because the structural development of the cardiovascular, gastrointestinal, and musculoskeletal systems occurs concurrently between the third and eighth weeks of fetal life (Arey, 1974). Therefore any teratogen acting on one of these three systems at that vulnerable period could affect the other two. Our data suggests, however, that in a majority of cases the teratogens have no predilection for any specific tissues. Thus, with the exception of the well-recognised association between congenital rubella and persistent ductus arteriosus (Campbell, 1961) and between Down's syndrome and septal defects (Berg *et al.*, 1960; Park *et al.*, 1977) no extracardiac defect appears to be predictably associated with any specific congenital heart disease. Similar findings have also been reported by Menashe *et al.* (1967), and Wallgren *et al.* (1978).

In the technically developed countries with abundant health facilities mental retardation is not a contraindication to cardiac surgery, and open-heart operations are performed even on patients with Down's syndrome (Esplugas *et al.*, 1976). With the background of limited financial and health resources in many developing countries, however, a cost/benefit analysis would show that even where the facilities exist priority for cardivascular surgery should be given to patients who have no major mental or other handicaps and can thus derive maximum benefits from such expensive procedures.

Death may result from metabolic derangements caused by extracardiac defects, or during surgical treatment of such defects. Less frequently extracardiac defects may aggravate haemodynamic derangements initiated by congenital heart disease. For instance pulmonary hypoplasia, which may be isolated as in one of our patients, or associated with a diaphragmatic hernia (Dibbins and Wiener, 1974; Dibbins, 1976) may exacerbate the normal pulmonary hypertension of the newborn, perpetuate the fetal circulatory pattern, and precipitate cardiac failure. In the present series death was attributable to extracardiac defect in 12 per cent of the patients, and higher figures have indeed been reported from other centres (Kenna *et al.*, 1975; Wallgren *et al.*, 1978). This mortality is considerable, and it emphasises the need for a thorough evaluation of any child with congenital heart disease since early detection and treatment of these non-cardiac defects could improve the prognosis.

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