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Factors in the Aetiology of Congenital Malformations of the Heart in Nigeria

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Summary

Antia AU. Factors in the Aetiology of Congenital Malformations of the Heart in Nigeria. *Nigerian Journal of Paediatrics* **1984; 11:71.** A number of factors, including birthrank of affected children, maternal age, haemoglobin genotype, established hereditary syndromes, maternal rubella infection, drug or herbal concoction ingestion during pregnancy and abnormal chromosomes, were studied for their possible aetiological relationship with congenital malformations of the heart (CMH) in 260 children. Significant relationship was found in respect of birthrank and between haemoglobin genotype and PDA. While there was a significant difference between the maternal age of children with CMH and controls from a rural area of Nigeria (Igbo-Ora), no such difference existed between the maternal age of children with CMH and other controls born at the University College Hospital (UCH), Ibadan. There was no relationship between the genotype and the other major malformations. Of the hereditary syndromes, a case each of Ellis-van Creveld and Holt-Oram was encountered. There were nine patients with PDA and features consistent with congenital rubella syndrome. Twelve cases of Down's syndrome and heart malformations occurred in the series. Although 27% of the mothers admitted taking herbal concoctions during the pregnancy, a cause-effect relationship between the malformations and the concoctions could not be established.

Introduction

CONGENITAL malformations of the heart occur throughout the world. The incidence of the malformations in Nigeria has been reported to be 3.3 per thousand of all births[1] and 3.9 per thousand among South African black school children.[2] Kenna, Smithells and Fielding[3] have reported that in Britain, the malformations occur in about 6.5 per thousand live births. Based on a review of a number of studies, Ellison [4] has estimated the incidence to be 9 per thousand live births. In most developing parts of the world where preventable diseases overwhelm, little attention is being given to the problems of congenital malformations of the heart. Prevention or control of congenital

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malformations in general and of the heart in particular, can only be achieved through knowledge of the various causative factors. The purpose of the present study was therefore, to search for possible aetiologic factors among children with congenital malformations of the heart.

Materials and Methods

The subjects comprised 260 children, aged between birth and 12 years, with proven congenital malformations of the heart. Factors which were studied for possible aetiological relationship with the malformations included birthrank of the subjects, maternal age, haemoglobin electrophoresis (Hb genotype), established hereditary syndromes, maternal rubella infection, drug or herbal ingestion during pregnancy and abnormal chromosomes. Statistical analysis was carried out, using the chi-square (X^2) test.

Results

Birthrank

Reliable birthrank was obtained in 130 of the 260 patients. The birthrank of these 130 patients was compared to that of the controls, consisting of 1902 births at the University College Hospital (UCH), Ibadan, and 3076 births at Igbo-Ora, a rural community some 112.7 kilometres (70miles) north of Ibadan. Fig 1 shows that there is a marked difference between the third birthrank of children with congenital malformations of the heart and that of the controls from the UCH and Igbo-Ora. On statistical analysis (Table 1), this difference was found to be significant ($p<0.001$ and $p<0.05$, respectively).

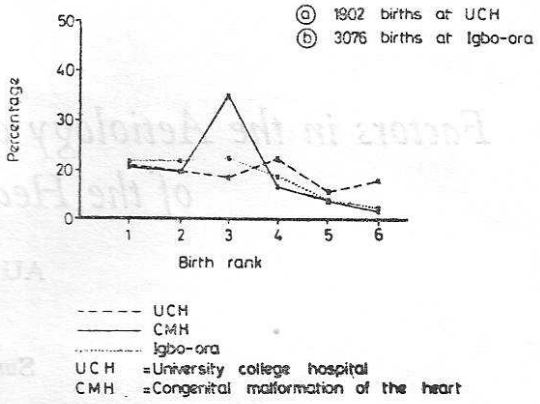

Fig. 1 Birthrank of 130 children with congenital malformations of the heart and that of (a) 1902 births at the University College Hospital (b) 3076 births at Igbo-Ora. Note the difference between the 3rd birthrank of children with heart malformations and the controls.

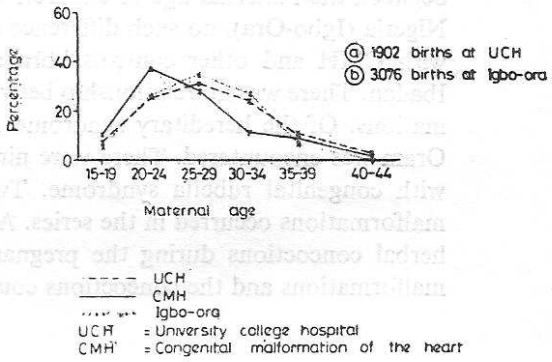

Fig. 2 Maternal age at birth, of 61 children with congenital malformations of the heart and that of (a) 1902 births at the University College Hospital (b) 3076 births at Igbo-Ora

Maternal Ages

Accurate maternal age at the time of birth of each patient was obtained from 61 mothers excluding 12 others who had children with Down's syndrome. Forty-one patients (67.2%)were born ot mothers, aged between 20 and 29 years (Fig. 2). Using as controls, the maternal age of the 1902 births from the UCH and that of the 3076 births from Igbo-Ora (Table II), there was no significant difference between the maternal age of the patients and that of the controls from the UCH ($p>0.05$), but a significant difference ($p<0.05$) existed between the subjects and controls from Igbo-Ora.

TABLE I

Birthrank of 130 Children with CMH and that of 1902 Births in UCH and 3076 Births at Igbo-Ora

Birthrank	No. of Subjects			% of Total		
	CMH	UCH	Igbo-Ora	CMH	UCH	Igbo-Ora
1	27	402	713	20.7	21.1	23.2
2	24	374	716	18.5	19.7	23.3
3	46	332	749	35.4	17.5	24.3
4	15	290	497	11.5	15.2	16.1
5	10	217	221	7.7	11.4	7.2
6	4	287	180	3.1	15.1	5.9
7	4	–	–	3.1	–	–
Total	130	1902	3076	100.0	100.0	100.0

CMH vs 1902 births at UCH
$X^2 = 36.88$; $p < 0.001$
CMH vs 3076 births at Igbo-Ora
$X^2 = 11.27$; $p < 0.05$
UCH = University College Hospital
CMH = Congenital malformations of the heart

TABLE II

Maternal Age at Birth of 61 Children with CMH and that at birth of 1902 Children at UCH and 3076 Children at Igbo-Ora

Maternal Age (years)	No. of Subjects			% of Total		
	CMH	UCH	Igbo-Ora	CMH	UCH	Igbo-Ora
15–19	6	120	125	9.8	6.3	4.1
20–24	23	479	801	37.8	25.2	26.0
25–29	18	586	1047	29.5	30.8	34.0
30–34	7	469	823	11.5	24.7	26.8
35–39	6	202	222	9.8	10.6	7.2
40–44	1	46	58	1.6	2.4	1.9
Total	61	1902	3076	100.0	100.0	100.0

CHM vs UCH
$X^2 = 9.22$; $p > 0.05$
CMH vs Igbo-Ora
$X^2 = 14.09$; $p < 0.05$
UCH = University College Hospital
CMH = Congenital malformations of the heart

Hb genotype

The genotype was determined in 179 of the 260 patients. Table III summarizes the distribution of the genotype in the 179 cases compared to the distribution among 3,000 blood donors. It will be noted that there was no significant difference ($P > 0.05$) between the distribution among the patients and the general population of the blood donors. Tables IV–VIII show the genotype distribution among 47 children with ventricular septal defect (VSD), 33 with persistent ductus arteriosus (PDA), 29 with atrial septal defect (ASD), 25 with pulmonary stenosis (PS) and 25 others with Fallot's tetrad (FT) compared to the distribution among 3,000 blood donors. There was a significant association ($p < 0.025$) between the genotype and PDA, but not between it and the other major malformations and the genotypes (VSD, $p > 0.05$; ASD, $p > 0.5$; PS $p > 0.1$; FT, $p > 0.5$).

TABLE III

Hb Genotype Distribution among 179 Children with CMH and that among 3,000 Blood Donors

Genotype	No. of Patients	% of Total		
		Observed	Expected	
AA	126	70.4	66.0	
AS	36	20.1	25.6	
AC	11	6.1	5.8	
SS	6	3.4	1.7	2.6
SC	–	–	0.8	
CC	–	–	0.1	
Total	179	100.0	100.0	

CMH = Congenital malformations of the heart
$X^2 = 5.04$; $p > 0.05$

TABLE IV

Hb Genotype Distribution in 46 Children with VSD and that among 3,000 Blood Donors

Genotype	No. of Patients	% of Total		
		Observed	Expected	
AA	31	66.0	66.0	
AS	9	19.1	25.6	
AC	4	8.5	5.8	
SS	3	6.4	1.7	2.6
SC	–	–	0.8	
CC	–	–	0.1	
Total	47	100.0	100.0	

VSD = Ventricular septal defect
X^2 = 7.00; $p > 0.05$

TABLE V

Hb Genotype Distribution in 33 Children with PDA and that in 3,000 Blood Donors

Genotype	No. of Patients	% of Total		
		Observed	Expected	
AA	24	72.7	66.0	
AS	5	15.2	25.6	
AC	1	3.0	5.8	
SS	3	9.1	1.7	2.6
SC	–	–	0.8	
CC	–	–	0.1	
Total	33	100.0	100.0	

PDA = Persistent ductus arteriosus
X^2 = 11.96; $p < 0.025$

TABLE VI

Hb Genotype Distribution in 29 Children with ASD and that in 3,000 Blood Donors

Genotype	No. of Patients	% of Total		
		Observed	Expected	
AA	19	65.5	66.0	
AS	9	31.0	25.6	
AC	1	3.5	5.8	
SS	–	–	1.7	2.6
SC	–	–	0.8	
CC	–	–	0.1	
Total	29	100.0	100.0	

ASD = Atrial septal defect
X^2 = 0.57; $p > 0.5$

TABLE VII

Hb Genotype Distribution in 25 Children with Pulmonary Stenosis and that in 3,000 Blood Donors

Genotype	No. of Patients	% of Total		
		Observed	Expected	
AA	18	72.0	66.0	
AS	4	16.0	25.6	
AC	3	12.0	5.8	
SS	–	–	1.7	2.6
SC	–	–	0.8	
CC	–	–	0.1	
Total	25	100.0	100.0	

X^2 = 1.41; $p > 0.1$

TABLE VIII

Hb Genotype Distribution in 25 Children with Fallot's Tetrad compared with that in 3,000 Blood Donors

Genotype	No. of Cases	% of Total		
		Observed	Expected	
AA	18	72.0	66.0	
AS	5	20.0	25.6	
AC	2	8.0	5.8	
SS	–	–	1.7	2.6
SC	–	–	0.8	
CC	–	–	0.1	
Total	25	100.0	100.0	

X^2 = 0.61; $p > 0.5$

Hereditary syndromes

A case each, of Ellis-van Creveld and Holt-Oram syndromes was encountered in the series. The patient with Ellis-van Creveld syndrome (Fig 3a & 3b) had ASD as well as all the other features of the syndrome. A family study of this patient revealed no congenital malformations in any other member of the family. By contrast, the family study of the propositus with Holt-Oram syndrome revealed several congenital skeletal and cardiovascular malformations as reported earlier.[5] The propositus, a 6-year old boy (Fig 4), had skeletal malformations including pectus excavatum and ASD; the mother had pectus excavatum only, while the maternal grandfather (Fig 5) had complete heart block, presumed to be of congenital origin, as well as pectus excavatum and other skeletal malformations. The maternal aunt (Fig 6) also had skeletal malformations and ASD.

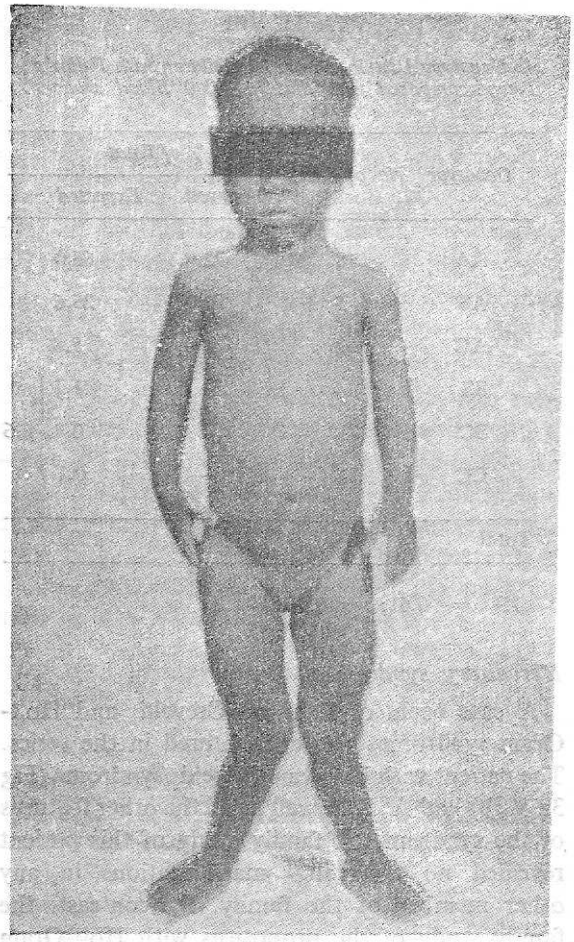

Fig 3a A photograph of (a) a 4-year old girl with Ellis-van Creveld syndrome and atrial septal defect. Note the short stature, large head and marked knock-knee. She also had dystrophic nails and polydactyly, the extra digits having been amputated at birth (3b).

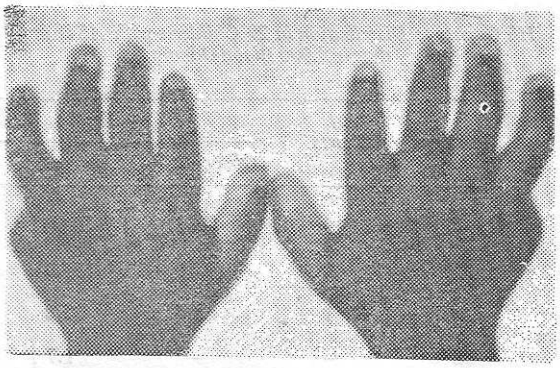

Fig 3b

Malformations in siblings

In the present series, VSD occurred in a pair of twins and PDA in two other siblings, one of whom had HbSS.

Maternal rubella infection

There were 41 patients with PDA and nine of these had associated microphthalmos, congenital cataract, mental retardation and microcephaly, features which are consistent with congenital rubella syndrome. Three of the mothers gave a history of rashes and mild fever lasting for few days during the first six weeks of pregnancy. The exact month of birth was obtained in 32 of the 41 patients and of these 32 patients, 12 (37.5%) were born between September and November, thus suggesting that the maternal infection with rubella virus possibly occurred between January and March during the period of the study.

Drug or herbal ingestion

Reliable information was obtained from 112 mothers about the use of drugs or local herbal concoctions during the pregnancy of the patients. Eighty-two (73%) of the 112 mothers denied taking anything during the pregnancy; 30 (27%) admitted taking herbal concoctions prepared by herbalists. Eleven of the 30 mothers claimed they took the same preparation during all previous pregnancies.

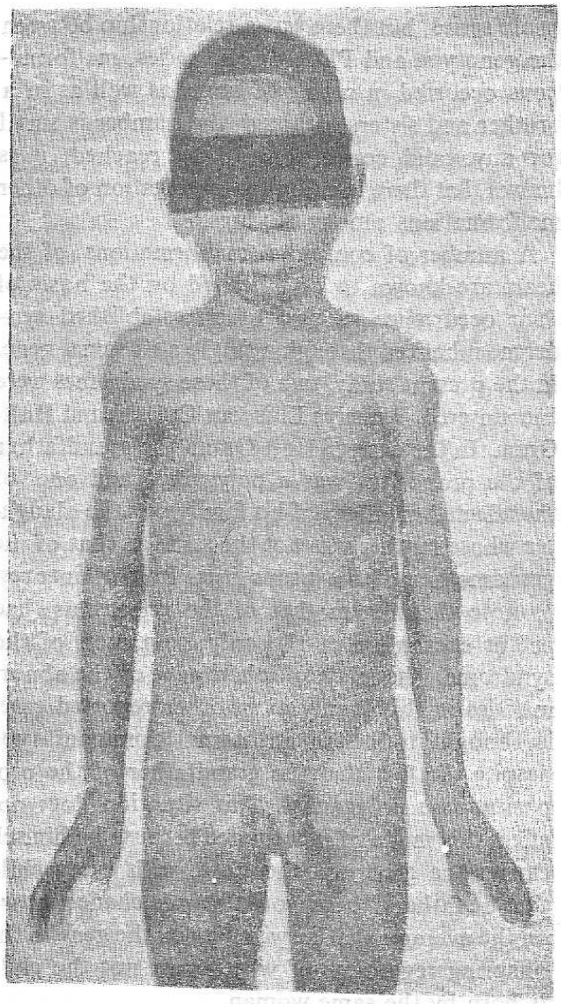

Fig 4 A photograph of a 6-year old boy (propositus) with Holt-Oram syndrome and atrial septal defect. Note the finger-like thumbs.

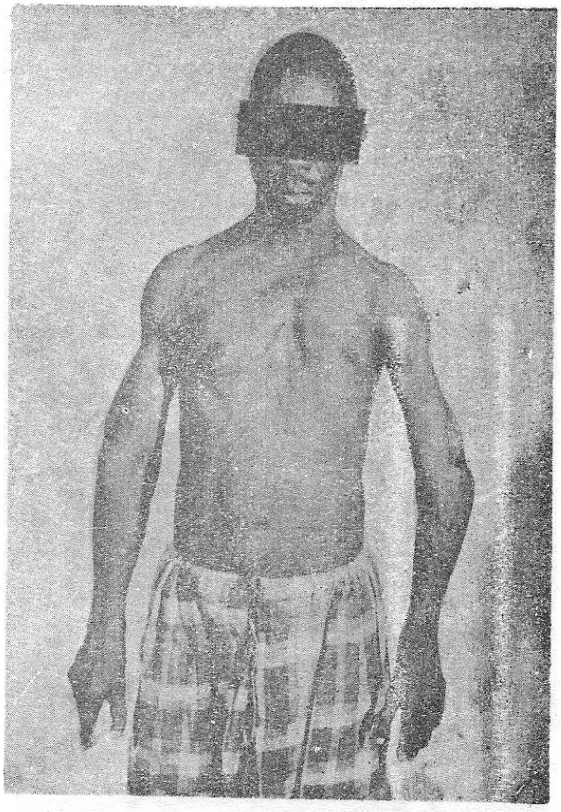

Fig 5 A photograph of the maternal grandfather of the propositus (Fig 4) He had malformed thumbs, pectus excavatum and complete congenital heart block.

Abnormal chromosomes

Twelve patients in the series were cases of Down's syndrome; no cases with other abnormal chromosomes were encountered.

Discussion

The aetiology of congenital malformations of the heart is largely unknown, but from the available evidence, there are broadly environmental and genetic causes of the malformations.[6–9] In a majority of the cases however, no clear-cut aetiological factors have been established. In the present study, there was evidence that birthrank of the child was a significant factor in the aetiology of the malformations. By contrast, Campbell[9] has stated that birthrank is not a significant factor. Advanced maternal age is a well established factor in Down's syndrome which is known to be associated with a high incidence of the malformations. However, after exclusion of Down's syndrome from his study, Campbell[10] showed that VSD and Fallot's tetrad were often associated with older mothers. The present series revealed significant association between the malformation

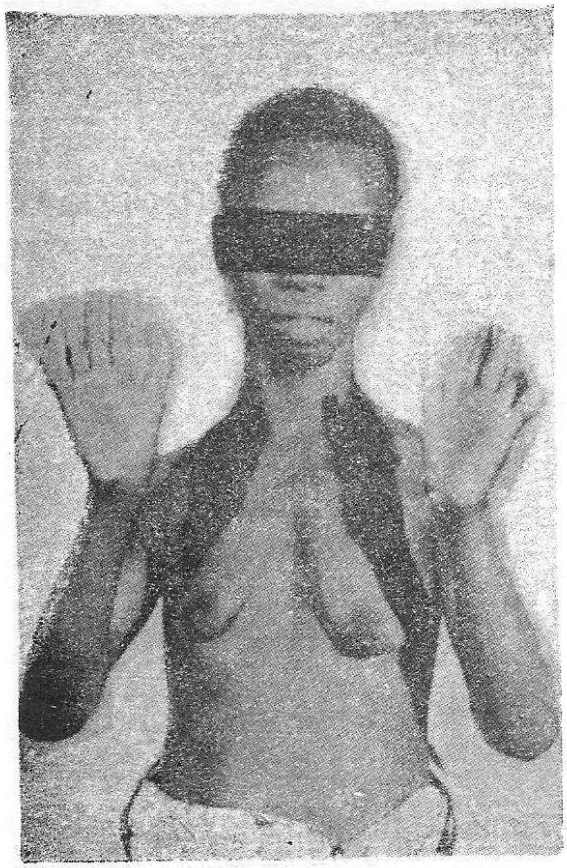

Fig 6 *A photograph of the maternal aunt of the propositus (Fig 4) Note the malformed thumbs. She also had an atrial septal defect.*

and maternal age of those from Igbo Ora. It should be noted that mothers attending the UCH constitute a highly selected population and this may explain the difference in the significance level between the UCH mothers and those from Igbo-Ora. Lamy, de Grouchy and Schweisgnth[11] found no association between maternal age and the malformations, but they and Penrose[12] have however, maintained that it is the paternal maternal age difference which is of genetic significance in the aetiology of the malformations.

An analysis of the distribution of haemoglobin genotype, an inheritable blood disorder, revealed no significant causative relationship with the entire series, but there was a relationship between the genotype and PDA. In the series, malformations occurred in a pair of twins as well as in a brother and sister. Although the number is small for any valid conclusions to be reached, it is known that there is a familial aggregation of other malformations among siblings.[13]

A number of congenital malformations of the heart are known to be inherited on the basis of their occurrence as part of an established syndrome inherited through a single autosomal gene. In the present study, two of these syndromes were encountered, namely: Ellis van Creveld and Holt-Oram. In the case of Holt-Oram, the grandfather of the propositus was a polygamist and one of the affected members of his family was the daughter whose mother was not the same as that of the grandmother of the propositus. It is of interest to note that the mother of the propositus had pectus excavatum as the only expression of the syndrome. The mode of inheritance of the abnormalities in this family as in other reported cases is thought to be an autosomal dominant type despite the fact that the grandfather of the propositus is a polygamist. This situation does not affect this mode of inheritance because he himself carries the gene and therefore, with every child that he fathers, there would be one chance in two on the average, that he will pass on the gene to the offspring regardless of whether or not the child is born by the same woman.

There were nine cases of congenital rubella syndrome and of these, three of the mothers gave a history suggestive of rubella infection during the first trimester of pregnancy. Recently, there has been evidence of high levels of rubella virus antibodies in Nigerian women of child-bearing age, thus confirming that rubella virus infection commonly occurs in Nigeria. Until 1964, it was thought that Downs' syndrome did not occur in African children.[14] However, in the present study, 12 cases of the syndrome were encountered.

The cause-and-effect relationship between drugs or herbal concoctions and human malformations is extremely difficult to establish except perhaps,

for thalidomide[15] and excess vitamin D ingestion.[16] In the present study, 27% of the mothers admitted to having taken some herbal concoctions prepared by traditional healers. Although it is possible that some of these concoctions contained teratogenic substances, proof of this possibility was difficult to establish, but may perhaps, be obtained if, like the thalidomide tragedy, there is an epidemic of congenital malformations of the heart among pregnant women who, during pregnancy took a particular concoction prepared by the same herbalist.

Acknowledgements

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