IMMUNOLOGICAL PROFILE IN CONGENITAL HEART DISEASE

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ABSTRACT

Fifty children with established congenital heart disease (CUD) were surveyed for the immune profile. Ventricular septal defect (VSD) was the commonest lesion (56%) followed by Tetralogy of Fallot (ToF; 16%), atrial septal defect (ASD; 8%), patent ductus arteriosus (PDA; 4%), transposition of great arteries (TGA; 4%), aortic stenosis (AS; 4%), and pulmonic stenosis (PS), tricuspid atresia (TA), single ventricle with pulmonic stenosis (SV with PS) and dextrocardia with ToF (2% each). Immunoglobulins (IgG, IgA and IgM) were estimated. IgG and IgA levels were significantly reduced in all children with congenital heart disease, whereas IgM levels were increased in cyanotic but unaffected in the acyanotic group. Complement C_3 and C_4 levels were reduced in all, more so in cyanotics. T-helper cells were decreased and T-suppressor cells were increased in all groups with congenital heart disease as compared to controls. B-cell percentage was increased in cyanotics but not affected in the acyanotics.

Key words: *Congenital heart disease, Immunoglobulins, Serum complements.*

Children with congenital heart disease (CHD) are more susceptible to infections especially of the respiratory tract. The association between CHD and immuno-deficiency was first recognized in patients with DiGeorge Syndrome(l). Abnormalities in the T-cell rossette percentage and response to phytohemaglutinins have been seen in CHD(2). Reduction in total T-ccll percentage and helper T-cells, immunoglobulins (IgG and IgA) and complement C_3 and C_4 have also been observed in conotruncal anomalies(3). The recognition of immunodeficiency is likely to help in the management of infections with antimicrobial therapy(4). The present study was thus conducted to evaluate the immunological status in children with congenital heart disease.

Material and Methods

Fifty children with congenital heart disease as diagnosed on history, physical examination, chest roentgenogram, electrocardiogram and 2-D with colour flow doppler echocardiography were randomly selected alongwith twenty age and sex matched healthy controls. Patients and controls with infections other than that of respiratory tract were excluded. The patients with congenital heart disease were studied under two main groups: *(i)* Group A: Cyanotic congenital heart (n = 13); Tetralogy of Fallot (ToF) (n = 8) dextrocardia with ToF (n = l),

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complete transposition of great arteries (TGA) (n=2), tricuspid atresia (n = l), single ventricle with pulmonic stenosis (SV with PS; n = l); *(ii)* Group B: Acyanotic congenital heart disease (n = 37); ventricular septal defect (VSD; n=28), atrial septal defect (ASD; n = 4), patent ductus arteriosus (PDA; n = 2), aortic stenosis (AS; n = 2), and pulmonic stenosis (PS; n = 1). Since, the immunological alterations could be due to cyanosis or due to congenital developmental anomalies, conotruncal anomalies were reported out of the group with cyanotic CHDs and subgrouped under Group-C. Similarly, the immunological alterations could be due to the effect of L→ R shunt so patients with L → R shunt were separated out of the acyanotic group and studied under Group-D.

The following immunological investigations were performed: (i) Serum iummunological levels (IgG, IgM and IgA) by single radial immunodiffusion technique of Mancini *et al.(5)* using tripartigen plates from Hoechst India; *(ii)* Serum complement levels (C_3 and C_4) by single radial immunodiffusion technique of Mancini *et al.(5)* Using tripartigen plates from Hoechst India; and *(iii)* T-cell rossettes were studied for total T-cells and B-cells percentage along with percentage of helper and suppressor T-cells. Ouantitation of lymphocyte by immune peroxidase staining was done as described in the manual of DAKO Corporation, USA titled 'Hand Book of Immunoperoxidase staining' (Bourne, 1983).

Results

Age and Sex Distribution

Thirty-nine of 50 children were of less than 5 years age with 26 males and 13 females (M : F : : 2 : 1). Eleven of 50 children were above 5 years age with 6 males and 5 females (M : F : : 1.2 : 1).

Incidence of Respiratory Infections

Children with CHD had suffered 3.68 ± 2.21 episodes of respiratory infections per year which is comparable to that in the control group (4.18 ± 1.87, $p>0.1$). The annual incidence of respiratory infections in the acyanotic group was 4.94 + 2.54 which is significantly higher than that in the cyanotic group (2.41 ± 1.89, $p<0.01$). The annual incidence of respiratory infections was significantly higher in the group with L → R shunt (5.08 ± 2.55) when compared with the group with conotruncal anomalies (2.41 ± 1.89, $p<0.001$).

Immunological Profile (Tables I & II)

Serum IgG levels were considerably decreased in Group A ($p<0.01$), Group B ($p<0.01$), conotruncal anomalies ($p<0.01$) and to a lesser extent in Group C ($p<0.04$) as compared to the controls.

Serum IgA levels were also significantly lowerifttthe Group A ($p<0.001$); Group B ($p< 0.002$); Group C ($p<0.001$) and Group D ($p< 0.001$) as compared to the controls. However, the levels of IgM were higher only in the cyanotics ($p<0.05$) and the conotruncal group ($p< 0.048$) while the levels were comparable in the acyanotic group including those with L → R shunts with that of the controls.

Serum levels of both complement C_3 and C_4 were significantly lower in all the groups with CHD when compared with the control group. The lower levels were statistically highly significant in the group with conotruncal anomalies and in the cyanotic group when compared with the control ($p< 0.001$). Although the levels of C_4 in both the acyanotic group and the group with L → R shunt and the levels of C_3 in the

TABLE I—*Immunological Profile in the Study Group (Cyanotic and Acyanotic) and Control Group*

Parameter	Cyanotic Group A (n=13) Mean ± SD	Acyanotic Group B (n=37) Mean ± SD	Control Group (n=20) Mean ± SD	P value
IgG (mg/dl)	966.0767± 634.3233	984.4717± 621.3933	1211.6650± 288.3908	<0.01 (A&B)
IgA (mg/dl)	110.7770± 41.2334	108.8927± 51.3894	178.1117± 43.0669	<0.001 (A&B)
IgM (mg/dl)	291.8362± 105.9095	195.5276± 72.8409	164.5236± 42.3755	<0.05 (A) NS (B)
C_3 (IU/ml)	113.5111± 16.930	121.0501± 35.2266	137.2801± 27.8047	<0.001 (A) <0.05 (B)
C_4 (IU/ml)	91.227± 26.438	121.4141± 46.9921	142.2894 33.5640	<0.001 (A) <0.05 (B)
% T-cells	70.71± 2.44	71.75± 3.69	74.05± 3.58	<0.05 (A) <0.052 (B)
% T_4-cells	39.58± 2.41	38.23± 4.42	46.61± 3.55	<0.001 (A&B)
% T_8-cells	33.58± 2.36	34.15± 3.22	27.45± 1.60	<0.001 (A&B)
% B-cells	28.28± 2.44	27.48± 5.21	29.95± 3.51	<0.05 (A) NS (B)

A = Cyanotic group; B = Acyanotic group; NS = Not significant.

acyanotic group were also significantly lower when compared with the control group they did not reach statistically significant values (p=0.05).

The total T-cell percentage was significantly reduced in Group A and Group C (p<0.05), in comparison to controls. Although they were also reduced in Group B and in Group D in comparison to controls, the difference was not statistically significant (p>0.5). T-helper cells were reduced in all the groups as compared to controls and the difference was highly significant (p<0.001). The percentage of T-suppressor cells was higher in all the groups as compared to the controls (p<0.001).

It is interesting to note that total T-cells and T-helper cells were reduced in all the cases of CHD surveyed, whereas T-suppressor cells were significantly increased in the same patients as compared to controls.

The B-cells percentage was significantly higher (p<0.05) in Group A and Group C; while the percentage in Group B and Group D though higher than that in the controls was statistically not significant. So, in the whole the B-cell percentages were not significantly increased in the total study group.

Discussion

Children with CHD are more susceptible to infections especially of the respira-

TABLE II–*Immunological Profile in the Study (Conotruncal and Shunt) Group and Control Group*

Parameter	Conotruncal Group C (n=12) Mean ± SD	L → R shunt Group D (n=34) Mean ± SD	Control Group (n=20) Mean ± SD	P value
IgG (mg/dl)	954.8801± 589.3140	1042.0967± 638.02333	1211.6650± 288.3908	<0.01 (C) 0.04 (D)
IgA (mg/dl)	111.4103± 41.0446	116.8824± 55.9052	178.1117± 43.0669	<0.001 (C&D)
IgM (mg/dl)	296.4383± 99.5990	199.5862± 74.7666	164.5236± 42.3755	<0.048 (C) NS (D)
C_3 (IU/ml)	118.0711± 18.0121	122.4333± 34.8310	137.2801± 27.8047	<0.001 (C) <0.05 (D)
C_4 (IU/ml)	94.4733± 24.0510	118.780± 45.9570	142.2894 33.5640	<0.006 (C) <0.05 (D)
% T-cells	76.65± 3.20	71.89± 2.28	74.05± 3.58	<0.05 (C) <0.06 (D)
% T_4-cells	38.26± 4.55	38.20± 4.19	46.61± 3.55	<0.001 (C&D)
% T_8-cells	33.106± 2.61	32.03± 3.07	27.45± 1.60	<0.001 (C&D)
% B-cells	28.36± 4.60	27.32± 4.60	25.95± 3.51	<0.05 (C) NS (D)

C = Conotruncal group; D = Shunt lesion; NS = Not significant.

tory tract, endocardium and brain for which traditionally hemodynamic and mechanical factors have been considered responsible(6). Immunodeficiency in association with CHD was first recognized in Di-George Syndrome(l). Later, deficiency of lymphocytes was observed in conotruncal anoma4ies(3). Ventricular septal defect was the commonest lesion in the present study. Ferencz *et al.(7)* reported ventricular septal defect to be the commonest lesion after reviewing seven major studies from North America and Europe. The annual incidence of respiratory tract infections was significantly higher in acyanotic group (4.95 ± 2.5) compared to cyanotic group (2.42 ± 1.9; p<0.01) and was even more so in L → R shunt group (5.1 ± 2.6) in comparison to group with conotruncal anomalies (2.42 ± 1.9).

A significant decrease in the levels of IgG and IgA (p<0.01) seen in this study is consistent with the observations of Radford *et al.* (3). igM levels were increased in cyanotic and conotruncal group (p<0.05) whereas the levels were comparable to controls in acyanotic and L → R shunt group. Radford *et al.* did not report different IgM levels in any type of CHD in comparison to the adult controls(4). This discrepancy can be attributed to incipient infections in our patients during the study as IgM is the

first immunoglogulin to rise after any infection (first episode).

The humoral deficiency is expected in 5% of populaHon(8). A significant decrease in the C_3 and C_4 complement levels ($p< 0.001$) in all patients of CHD was observed in our study and this is comparable to the report by Radford *et al.(4). A* significant decrease in total T-cells ($p<0.05$), helper T-cells ($p< 0.001$) and increase in the suppressor T-cells ($p< 0.001$) was observed in cyanotic group as- also a significant decrease in the total T-cells ($p<0.05$), increase in suppressor T-cells ($p< 0.001$) and also of the B-cells ($p<0.05$) in Group C. In patients with acyanotic CHD (Group B) a decrease in the helper T-cells ($p< 0.001$) was observed while the total T-cells and B-cells percentage was comparable with that of the controls.

In cases with left to right shunt lesions (Group D), the total T-cell percentage was similar to controls ($p<0.06$). T-helper cells were reduced in this group ($p< 0.001$) whereas T-suppressor cells were significantly increased ($p< 0.001$) as compared to controls. B-cells were again similar to controls. On comparing our observations with those of Radford *et al. (Table III),* a similar trend in IgG, IgA, C_3, C_4, total T-cells and B-cells percentage was observed. It has been observed that the opposite trend exists between T-helper and T-suppressor cells as well as in total T-cells and B-cells in an immunological process(9,10). This trend was consistent in our patients with T-suppressor cells. However, for B-cells, this trend was present in cyanotic congenital heart disease who also showed increased levels of IgM which can be explained by incipient infection.

The above observations suggest that children with CHD may have altered immune response in general with evidence of attenuation of cells mediated immune response in special cases which may predispos£-these children to infections: the management of these infections may be more

TABLE III–*Comparison of Immunological Profile in Congenital Heart Disease Patients with Other Study*

Parameter	Radford *et al.* (1986)		Present study	
	Conotruncal	Shunt	Conotruncal	Shunt
IgG (mg/dl)	Decreased	Decreased	Decreased	Decreased
IgA (mg/dl)	Decreased	Decreased	Decreased	Decreased
IgM (mg/dl)	NS	NS	Increased	NS
C_3 (IU/ml)	Decreased	Decreased	Decreased	Decreased
C_4 (IU/ml)	Decreased	Decreased	Decreased	Decreased
Total T-cells (%)	Decreased	NS	Decreased	NS
T-helper cells (%)	Decreased	NS	Decreased	Decreased
T-suppressor cells (%)	NS	NS	Increased	Increased
B-cells (%)	Increased	NS	Increased	NS

NS = Not significant; Decreased = Decreased significantly; Increased = Increased significantly

difficult than in children who are immunocompetent. However, the number of children studied is relatively small and the conclusions drawn from the above study may not be directly applicable to the children with CHD in general. Thus, a more comprehensive study with large number of subjects and analysis of functional reactivity of these cells needs to be undertaken for further evaluation of the immune status of these children.

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