Pediatr Cardiol 9:95–101, 1988

Pediatric Cardiology

Spectrum of Di George Syndrome in Patients with Truncus Arteriosus: Expanded Di George Syndrome

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SUMMARY. **A study of 26 patients with truncus arteriosus showed a high prevalence of facial dysmorphism, aortic arch abnormalities, extracardiac malformations, and significant prenatal risk factors. There was little evidence of parathyroid or thymic abnormalities. However, there was laboratory evidence of immune deficiency, especially T-helper lymphocytes, and clinical evidence of predilection to infection. These findings suggest that patients with truncus arteriosus belong to the spectrum of the Di George syndrome.**

KEY WORDS: **Truncus arteriosus — Di George syndrome — Immunodeficiency — Prenatal risk factors**

Persistence of a single arterial vessel at the base of the heart, giving origin to systemic pulmonary and coronary arteries, is known as truncus arteriosus (TA) [4, 33, 34]. This cardiac malformation is often a feature of the Di George syndrome [10, 38]. We recently observed that TA patients share other features of the Di George syndrome (DGS), including facial dysmorphism, T-cell immune deficiency and predilection to infection [30, 31], and postulated that those patients belong to the spectrum of DGS.

Although TA is an uncommon cardiac malformation, it is worthy of study because of potential benefits from a clearer understanding of the nature and pathogenesis of congenital cardiac malformations. This study reports 26 cases of TA and its relationship to DGS as regards cardiovascular, parathyroid, thymic, and facial defects. Since the etiology and pathogenesis of DGS are unclear, we also surveyed our patients for prenatal risk factors to determine possible teratogenic insults.

Materials and Methods

A total of 26 consecutive cases of TA admitted to the prince Charles Hospital between 1977 and 1986 were included. Five patients were male and 21 were female. The diagnosis was established by echocardiography, angiography, and surgery. Detailed information was obtained on pregnancy and prenatal risk factors. Clinical photographs were taken whenever possible, and records were kept of significant infections. Autopsy data provided additional information on the thymus and parathyroid glands.

Immunological studies were performed with standard techniques, as previously described [31]. Briefly, total T-lymphocytes, helper, and suppressor T-cell subsets, and B cells were quantified by OKT3, OKT4, OKT8, and B1 monoclonal antibodies. Serum immunoglobulins were estimated by the laser-rate nephelometry technique.

A group of 19 children with minor cardiac anomalies were also recruited into the study to provide data for comparison of immune function, infections and prenatal risk factors. There were ten male and nine female patients. They ranged in age from seven months to 14 years, with a mean of 3.9 years. The cardiac lesions consisted of pulmonary stenosis (ten cases), persistent ductus arteriosus (three cases), atrial septal defect (two cases), aortic stenosis (two cases), and coarctation of the aorta (two cases). Additional controls for immunological studies consisted of 67 healthy young adults. Except for early infancy, T-cell subpopulations are not age dependent [28, 31].

Student's *t*-test and the chi-square test, whichever was appropriate, were used for statistical analysis of the data.

Results

Cardiovascular Abnormalities

Of the 26 patients with TA, 14 (54%) had other cardiovascular anomalies (Table 1). The most common

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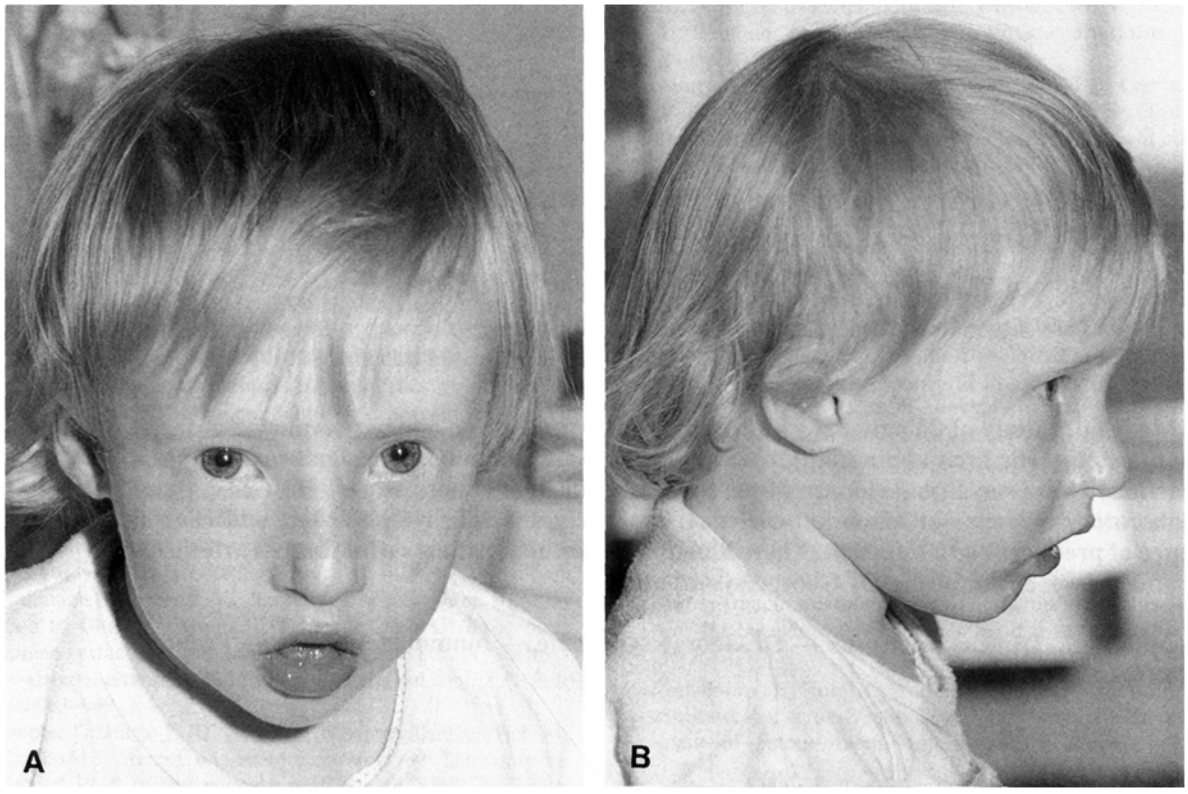

Fig. 1. Frontal **(A)** and lateral **(B)** views of 2-year-old child with truncus arteriosus, absent right pulmonary artery, right aortic arch, and aberrant left subclavian artery. Face shows hypertelorism, low-set ears, short philtrum, a small "fish-like" mouth, and micrognathia.

Table 1. Associated cardiovascular anomalies in 14 of 26 patients with truncus arteriosus

Arch anomalies	
Right aortic arch[a]	5
Interrupted aortic arch[a]	2
Aberrant subclavian artery[a]	2
Double aortic arch	1
Two brachiocephalic vessels	1
Other features	
Absence of one pulmonary artery	4
Truncal valve stenosis	3

[a] Frequently seen in Di George syndrome.

of these were aortic arch abnormalities, which are also frequent in DGS [25, 38].

Facial Dysmorphism

Dysmorphic features were noted in 23 (88%) of 26 patients with TA. The range of facial dysmorphism is listed in Table 2. It will be observed that there is a high frequency of features concordant with DGS [6, 10], including hypertelorism, low-set ears, short philtrum, and micrognathia (Figs. 1 and 2).

Table 2. Facial characteristics of 26 patients with truncus arteriosus[a]

Ocular hypertelorism[b]	17
Low-set ears[b]	14
Micrognathia[b]	9
Small "fish-like" mouth[b]	8
Short philtrum[b]	5
Down-slanting palpebral fissures[b]	4
Short palpebral fissures	3
Deformed or absent pinnae[b]	3
Cleft palate[b]	2
Cleft lip[b]	1
High arched palate[b]	1
Malformed nose	1
Bilateral cataracts	1

[a] Dysmorphic features were present in 23 (88%) of 26 patients.
[b] Features described in Di George syndrome.

Noncardiac Malformations

Extracardiac congenital malformations occurred in 11 (42%) of 26 patients and are listed in Table 3. These defects were mainly confined to the limbs, kidneys, and intestines. Some of these features have been previously noted in DGS [6, 10, 38].

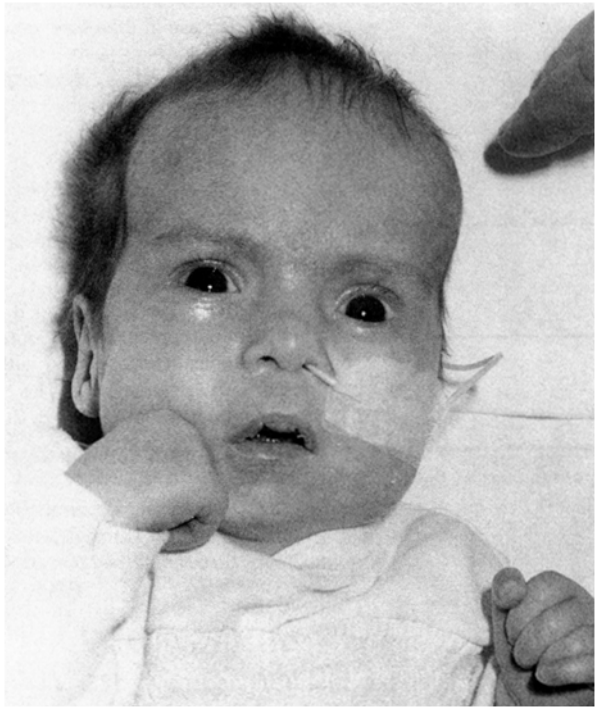

Fig. 2. Infant of 4 months with truncus arteriosus. She has hypertelorism, low-set ears, micrognathia, and a small mouth.

Table 3. Extracardiac congenital malformations present in 11 (42%) of 26 patients with truncus arteriosus

Talipes equinovarus	3
Congenital dislocated hips	2
Inguinal hernia	2
Abnormal digits[a]	2
Hydronephrosis and hydroureter[a]	1
Malrotation of the gut[a]	1
Neurological deficit	1
Multiple bony exostoses	1
Hypoplasia of right pelvis and femur with absent tibia	1

[a] Features previously described in Di George syndrome.

Table 4. Serum immunoglobulin deficiencies in children with truncus arteriosus and with minor cardiac anomalies

Immunoglobulin deficiency[a]	Truncus arteriosus	Minor cardiac anomalies
Normal	5	16
Low IgG only	0	3
Low IgA only	2	0
Low IgG and IgA	1	0

[a] Immunoglobulin deficiency, defined as more than 2 SD below age-matched controls [6, 14], was found in three (37.5%) of TA and three (15.8%) of 19 minor cardiac anomaly patients. The difference was statistically significant (chi square = 13.8, $df = 1$, $p < 0.01$).

Thymus and Immunological Abnormalities

Autopsies were performed on 14 of the 18 patients who died. The mean age at death was 3.5 months. Thymus glands were atrophic in two and absent in one (after histological search of the neck). No information on the thymus was recorded in another three.

Eight patients were available for immunological studies. They ranged in age from two months to four years at the time of the study, with a mean of 1.7 years. Total T-cell percentages of these patients were significantly depressed compared with adult controls ($t = 3.46$, $p < 0.001$) and children with minor cardiac anomalies ($t = 2.26$, $p < 0.05$), with values of mean percentage ± 2 standard deviations (SD) of 58.3 ± 15.3, 73.7 ± 10.7, and 73.2 ± 7.9, respectively (Fig. 3). By contrast, there was no significant difference between adults and children with minor cardiac anomalies ($t = 0.61$, $p > 0.1$), which supports previous findings that T-cell percentages were not age dependent [28, 31].

Additional studies (Fig. 4) suggest that the significant decrease in total T cells of patients with TA is the result of a reduction in the T-helper-cell subset. Thus, T-helper-cell percentages in TA patients were 37.5 ± 11.3 compared with 48.8 ± 9.0 in adult controls ($t = 2.66$, $p < 0.05$), and 44.5 ± 12.0 in children with minor cardiac anomalies ($t = 2.06$, $p = 0.06$). By contrast, T-suppressor cells were less depressed than in the other two groups.

Immunoglobulin deficiency is defined as values less than 2 SD below age-matched control values [36]. The results (Table 4) show that three (37.5%) of eight children with TA have immunoglobulin deficiency, compared with three (15.8%) of 19 children with minor cardiac anomalies. The prevalences of immunoglobulin deficiency in the two groups of children were significantly different from each other (chi square = 13.8, $df = 1$, $p < 0.01$).

Parathyroids and Serum Calcium

Of the three patients in whom a histological search of the neck was made at autopsy, one had no parathyroid glands. No patient had symptomatic hypocalcemia. The earliest measured serum calcium in 17 patients ranged from 1.63 to 2.42 mmol/liter. One infant was treated with calcium gluconate and calcitrol, when the serum calcium fell to 1.56 mmol/liter on day 8 of life.

Infectious Complications

Documented infections, mainly of the respiratory tract, occurred in 16 (61.5%) of 26 patients with TA

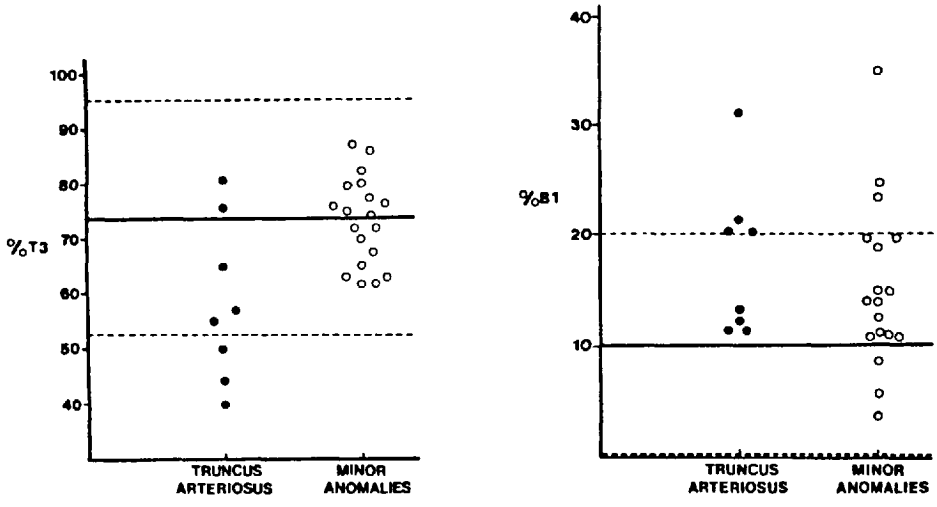

Fig. 3. Total T cell (T3) and B cell (B1) percentages in patients with truncus arteriosus and with minor cardiac anomalies. The parallel lines denote mean ± 2 SD of 67 adult controls.

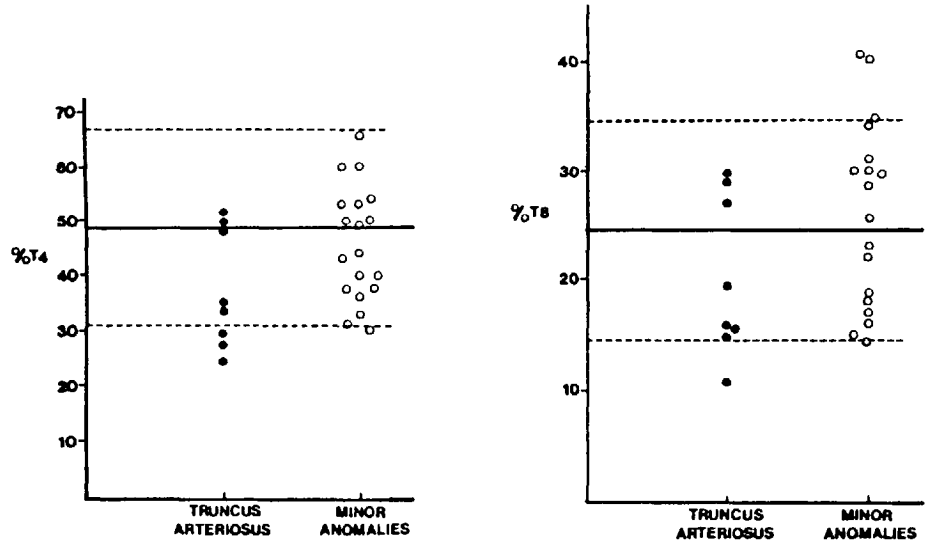

Fig. 4. T-helper (T_4) and T-suppressor (T_8) lymphocytes in patients with truncus arteriosus and minor anomalies. The parallel lines denote mean ± 2 SD of 67 adult controls.

(Table 5). By contrast, only four (21.0%) of 19 patients with minor cardiac anomalies experienced significant infections. Thus, TA patients have a significantly greater propensity toward infections (chi square = 7.25, $df = 1$, $p < 0.01$).

Prenatal Risk Factors

The nature of the teratogenic insult in congenital heart disease is usually unknown, but it has been estimated that ~10% of such pregnancies may have identifiable prenatal risk factors [27]. In our patients with TA, significant prenatal risk factors, excluding prematurity, were present in 11 (42.3%) of 26. These are listed in Table 6. They include maternal conditions such as diabetes mellitus, first-trimester pyrexia, and alcohol abuse, and fetal factors such as chromosomal abnormalities.

To exclude possible local environmental bias, a search of prenatal risk factors in children with the minor cardiac anomalies was made. The results show that only one of 19 cases had a potential risk factor—maternal neurofibromatosis. Thus, TA patients have a significantly higher prevalence of prenatal risk factors (chi square = 7.76, $df = 1$, $p < 0.01$).

Discussion

Di George originally described infants with congenital absence of the thymus and parathyroid glands who presented with hypocalcemic seizures, severe infections, and deficient cell-mediated immunity [8, 9]. It was later found that such infants commonly died of cardiovascular defects, of which aortic arch and conotruncal anomalies were predominant [6,

Table 5. Infectious complications in children with truncus arteriosus and with minor cardiac anomalies

Infections	Truncus	Minor cardiac anomalies
Pneumonia	9	1
Recurrent respiratory infections	5	1
Bacterial endocarditis	1	0
Staphylococcal septicemia	1	0
Gastroenteritis	1	0
Meningitis	0	1
Pertussis	0	1
Conjunctivitis	4	0
Otitis media	2	0
Tonsillitis	2	0
Persistent oral thrush	2	0

Infectious complications were documented in 16 (61.5%) of 26 TA and four (21.0%) of 19 minor cardiac anomaly patients. This difference was statistically significant (chi square = 7.25, $df = 1$, $p < 0.01$).

Table 6. Prenatal factors in children with truncus and with minor cardiac anomalies

Prenatal risk factors	Truncus arteriosus	Minor cardiac anomalies
Maternal diabetes mellitus	3	0
Febrile illness in 1st trimester	3	0
Syphilis	1	0
Alcohol abuse	1	0
Hyperthyroidism (on high-dose neomercazole)	1	0
Maternal neurofibromatosis	0	1
Chromosomal abnormality		
Partial trisomy 4_q	1	0
Banding abnormality of 8	1	0
Intrauterine growth retardation	3	0
Prematurity	7	1

Excluding prematurity, at least one factor was present in 11 (42.3%) of 26 TA patients, but only one (5.3%) of 19 minor cardiac anomaly patients. These differences were statistically significant (chi square = 7.76, $df = 1$, $p < 0.01$).

10, 11, 25]. Another frequent association is facial dysmorphism, including hypertelorism, down-slanting palpebral fissures, low-set ears, short philtrum of the lip, micrognathia, and small "fish-like" mouth [12, 19, 40]. It was also recognized that DGS is a spectral disease, with wide variations in clinical and immunological manifestations [2, 5, 6, 21, 22].

This study of 26 patients with TA documents a high concordance of defects commonly seen in DGS. Thus, cardiovascular malformations are seen in more than 90% of DGS, and these are usually aortic arch abnormalities, persistent TA, or both [6, 10, 11, 38]. Similarly, our TA patients have aortic arch abnormalities of the type seen in DGS. Other reports of TA patients also have an association with right-sided or interrupted aortic arches [4, 33, 38].

Our TA patients also have a high frequency of facial dysmorphism similar to that described in DGS, and extend our earlier observations in a smaller group of patients [30]. Of some interest to this discussion is the description by Japanese workers of another entity termed "conotruncal anomaly face" affecting 5%–10% of children with tetralogy of Fallot and, to a lesser extent, those with defects such as double-outlet right ventricle, transposition of the great vessels, and TA [15, 34]. Facial dysmorphism in these patients includes hypertelorism, small palpebral fissures, bloated eyelids, small mouth, nasal voice, and deformed earlobes. A *forme fruste* relationship to DGS has been postulated [15, 34].

Further support for our hypothesis that TA belongs to the spectrum of DGS comes from immunological studies that demonstrate significant depression of T-lymphocytes in patients with TA. Although autopsy studies show the presence of thymus and parathyroid glands in most of our TA patients, and hypocalcemia was not observed in any of our TA patients, these findings do not invalidate our conclusions, because DGS is known to be heterogeneous in this regard [2, 5, 21, 22]. It is pertinent to note here that T-cell deficiency has also been reported in the "conotruncal anomaly face" discussed earlier [34], and by Kiel et al. [17] in a small group of infants with congenital heart lesions commonly seen in DGS.

Little is known about the pathogenesis of DGS, but embryological studies [26] indicate that elements of the third and fourth pharyngeal pouches, and the first and fourth branchial arches, are involved because these structures give rise to the thymus and parathyroid glands and the face and conotruncus, respectively. The timing of the teratogenic insult is placed at between weeks 4 and 7 of gestation when damage to these developing structures is likely to result in this particular constellation of malformations. Harvey et al. [13] postulated that there is early localized damage in the embryo related to the proximity of the aortic arch and the third and fourth pharyngeal pouches, and Robinson [32] proposed that altered aortic blood flow in connection with the cardiac defect results in poor perfusion of the developing thymus and parathyroids. More recent theories [3, 18, 38] have related the various abnormalities to defective embryological contribution from the neural crest.

The etiology of DGS is also unclear, but it is likely to be multifactorial. In support of this reasoning is our finding of a high prevalence of a wide variety of prenatal risk factors, ranging from chro-

mosomal abnormalities to maternal alcohol abuse. Others [7, 16, 37] have noticed features of DGS in defects of chromosome 8 or 22, and it is obvious interest to us that one of our TA patients also has a defect of chromosome 8. While there are reports of familial DGS [29, 35] and its occurrence in twins [24], most cases of DGS are sporadic. Environmental teratogens may be an important factor in DGS, as indicated by reports of features of DGS in patients with the fetal alcohol syndrome [1, 14] and retinoic acid embryopathy [20]. Taken together, these findings indicate that genetic or environmental factors can interfere with morphogenesis to produce a range of related deformities peculiar to the spectrum of DGS.

Since fatal graft-versus-host reactions have been observed with blood transfusions in patients with Di George syndrome, it is recommended that irradiated blood be used in these children [2, 23].

Acknowledgment. This work was supported in part by a grant from the Queensland Institute of Cardiovascular Research.

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