Tetralogy of Fallot with Complete DiGeorge Syndrome: Report of a Case and a Review of the Literature

Daisuke Kobayashi, MD, Salaam Sallaam, MD, and Richard A. Humes, MD

Section of Pediatric Cardiology, Children's Hospital of Michigan, Carman and Ann Adams Department of Pediatrics, Wayne State University School of Medicine, Detroit, Mich, USA

ABSTRACT

Complete DiGeorge syndrome (CDGS) has a severe T-cell immunodeficiency and is fatal without thymus or bone marrow transplantation. Associated congenital heart disease (CHD) further complicates the clinical management. We report an infant with tetralogy of Fallot, confluent and hypoplastic pulmonary arteries, right aortic arch, and aberrant left subclavian artery. He was athymic with no CD3+ T cells. CDGS was diagnosed with 22q11.2 deletion. The patient underwent central aortopulmonary shunt at 12 days of age. The patient died at 5 weeks of age awaiting thymus transplantation. We performed a review of the literature regarding CDGS and CHD. We found 43 cases including conotruncal defects (20) and nonconotruncal defects (23). The overall mortality rate was 67%. Among 30 cases undergoing transplantation (bone marrow 16 and thymus 12, bone marrow + thymus 2), the mortality rate was 53%. The patients with conotruncal defects were more likely to die before transplantation (45% vs. 16%, $P = .04$). The main cause of death was infection before and after transplantation. We conclude that children with CDGS and CHD have a high mortality. Bone marrow and thymus transplantation can improve the survival, but the overall management of these high risk patients remains challenging.

Key Words. Tetralogy of Fallot; Complete DiGeorge Syndrome; Congenital Heart Disease; Thymus Transplantation; Bone Marrow Transplantation

Introduction

Complete DiGeorge syndrome (CDGS) is an extremely rare and profound T-cell immunodeficiency disease with a poor prognosis.[1] Recently, thymus and bone marrow transplantation has been reported as a treatment option for CDGS.[2,3] About half of the cases with CDGS have congenital heart disease (CHD) requiring surgery.[3] Children with both CDGS and CHD remain at high risk and their clinical management is challenging. We report an infant with tetralogy of Fallot (TOF), who was also diagnosed as CDGS. We reviewed the literature regarding CDGS and CHD.

Case Report

A term infant with a prenatal diagnosis of TOF was born with a birth weight of 2.9 kg to a 35-year-old mother who has history of repaired TOF and a heterozygous Factor V Leiden deficiency. Apgar score was 8 at 5 minutes. He was started on prostaglandin E1 infusion at birth. He had a dysmorphic face characterized by low set and anteriorly rotated ears, ocular hypertelorism, as well as bilateral inguinal hernia. Echocardiogram confirmed the prenatal diagnosis of TOF with a hypoplastic pulmonary valve, but the anatomy of pulmonary arteries was unclear. A cardiac catheterization was performed at 3 days of age. There were confluent and hypoplastic pulmonary arteries, a right aortic arch and aberrant left subclavian artery with two small collateral arteries arising from the aberrant left subclavian artery to the branch pulmonary arteries (Figure 1). There was no evidence of a patent ductus arteriosus. Prostaglandin E1 was discontinued.

The 22q11.2 deletion was detected by fluorescence in situ hybridization. Immunology consultation was made because of lymphopenia (0.9×10^9/L). Flow cytometry revealed 0% CD3+ T cells, 60% CD19+ B cells (0.54×10^9/L), and 25% natural killer (NK) cells (0.225×10^9/L). Immunoglobulin G, A, and M were 660, <7, and 8 mg/dL, respectively. Serum calcium was 6.5 mg/dL with intact parathyroid hormone (PTH) <1 IU/mL, which was consistent with hypocalcemia second-

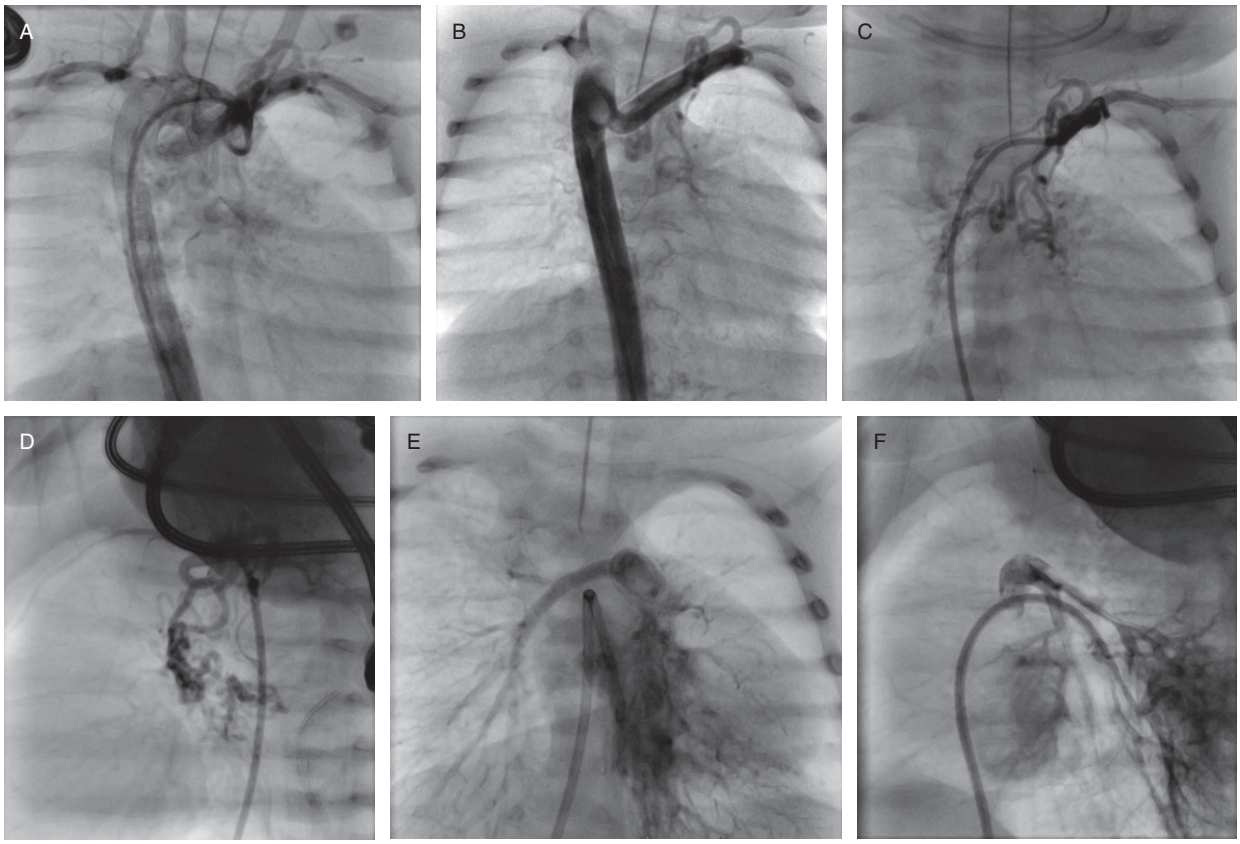

Figure 1. Angiographic images at 3 days old. The 4-Fr pigtail catheter is in the ascending aorta (A) and descending aorta (B) in the AP view. There is a right aortic arch with an aberrant left subclavian artery arising from descending aorta. Note no patent ductus arteriosus or coarctation of the aorta. Two small collateral arteries arise from the aberrant left subclavian artery to branch pulmonary arteries. Selective injection in the aberrant left subclavian artery shows collateral arteries connecting to each pulmonary artery branch respectively in AP (C) and lateral (D) view. Left lower pulmonary vein wedge injection shows the confluent and hypoplastic pulmonary arteries in AP (E) and lateral (F) view.

ary to hypoparathyroidism. The diagnosis of CDGS was made. He was kept in a negative pressure isolation room and started on antibiotic prophylaxis with sulfamethoxazole–trimethoprim. His persistent hypocalcemia was controlled with oral calcium supplements and calcitriol. One dose of intravenous immunoglobulin (IVIG was given at 3 weeks of age. He was referred to an outside institution for possible thymus transplantation. Surgical systemic-pulmonary shunt was pursued to establish more reliable source of pulmonary blood flow because of persistent systemic desaturation, before the transfer for thymus transplantation.

At 12 days of age, he underwent a 4-mm central aortopulmonary shunt. The pathology of tissue in the thymus area was reactive lymph nodes with no thymus tissue present. Intraoperative inspection discovered unique coronary artery anatomy. A large branch from the right coronary artery coursed right along the annulus and then inserted into the left anterior descending artery. It appeared that a single left anterior descending artery was fed by two different branches. Electrocardiographic ischemic change was noted with transient occlusion of this accessory branch. This unique anatomy would preclude the future use of a transannular patch. The postoperative course was complicated with a sternal wound dehiscence and postpericardiotomy syndrome which was treated with steroids. He was going to be discharged with scheduled thymus transplantation. He developed acute respiratory distress after an episode of emesis at 4 weeks of age. Chest radiograph showed right lower lobe opacity. Vancomycin and cefepime were started for suspected aspiration pneumonia. Seven days later, he suddenly developed cardiopulmonary failure and expired.

Autopsy was obtained with his parental consent. The central aortopulmonary shunt was patent.

The interstitial fibrosis and early myocyte damage with contraction bands suggested recent and remote episodes of ischemia. No evidence of pneumonia was noted with mild to moderate intimal fibrosis of small pulmonary arteries. Postmortem lung and blood cultures grew mixed *Enterococcus faecium* and *Psuedomonas fluorescens*, felt to be due to postmortem contamination.

Discussion

DiGeorge syndrome is a clinically heterogeneous disease, characterized by cardiovascular defects, thymus, parathyroid, and craniofacial anomalies, and is caused by developmental defects in the third pharyngeal pouch and fourth pharyngeal arch.[4] Most cases of DiGeorge syndrome are caused by chromosome band 22q11.2 deletion.[5] A chromodomain-helicase-DNA-binding protein 7 (CHD7) mutation has been recently reported in patients with CDGS.[6] Thymus defects occur in ~80% of patients with DiGeorge syndrome, leading to varying degrees of cellular immunodeficiency.[1] CDGS describes a rare subset of children with the clinical features of DiGeorge syndrome and severe T-cell immunodeficiency, which is fatal without intervention within the first 2 years of life.[1] Our patient had TOF, 22q.11.2 deletion, and no detectable $CD3^+$ T cell, consistent with CDGS. Intraoperative inspection revealed no thymus.

The incidence of TOF, including TOF with pulmonary atresia, is present in 10–21% of patients with 22q11.2 deletion.[5] The study of 545 patients with 22q11.2 deletion showed the presence of TOF in 17%, pulmonary atresia/ventricular septal defect in 10%, ventricular septal defect in 14%, interrupted aortic arch in 14%, and truncus arteriosus in 9%.[7] Our patient had right aortic arch, confluent and hypoplastic pulmonary arteries, collateral arteries from the aberrant left subclavian artery to branch pulmonary arteries, without a patent ductus arteriosus. There was a unique coronary artery anomaly which would preclude the use of a transannular patch. Two small collateral arteries arose from the aberrant left subclavian artery. A central aortopulmonary shunt was elected because a modified Blalock–Taussig shunt was deemed not suitable for hypoplastic branch pulmonary arteries.

Thymus transplantation and bone marrow transplantation for CDGS are promising immune reconstitution therapies with reasonable outcomes.[2,3,8,9] Janda et al. reported 17 patients with CDGS who underwent transplantation of hematopoietic cells.[2] The overall survival rate was 41% with a median follow-up of 5.8 years. Among 12 of 17 patients having CHD, nine patients (75%) died after transplantation. Markert et al. reported 54 patients with CDGS who were enrolled in protocols for thymus transplantation.[3] Among 44 patients undergoing thymus transplantation, 33 (75%) survived with a median follow-up of 3 years and 10 months. Thirty-one (57%) of 54 subjects had CHD requiring surgery. Seventeen subjects had conotruncal defects including eight with TOF. Although the survival of patients with CHD was not reported, authors mentioned that infants with CDGS continued to die of cardiac complications and infections.

We performed a review of the literature regarding CDGS with CHD.[1–3,6,8,10–19] We included cases in which a detailed CHD diagnosis is available with severe immunodeficiency consistent with CDGS. A total of 43 cases (including ours) were reported and can be categorized into two groups: (1) conotruncal defects, n = 20; and (2) nonconotruncal defects, n = 23 (Table 1). The conotruncal defects group consisted of TOF 11, truncus arteriosus 4, interrupted aortic arch 2, double outlet right ventricle and interrupted aortic arch 1, truncus arteriosus and interrupted aortic arch 1, and nonspecified 1. The nonconotruncal defects group consisted of the combination of the following diagnoses: ventricular septal defect, atrial septal defect, atrioventricular septal defect, patent foramen ovale, coarctation of aorta, right aortic arch, aberrant subclavian artery, and aortic arch anomaly. With the median age of 14 months (range, 5 weeks to 24 years) at the last follow-up, the overall mortality was 67% (28/42). No patients survived without transplantation. The mortality rate was comparable between the conotruncal and nonconotruncal group (75% vs. 64%, $P = .514$). The major cause of deaths was infection in the whole group before and after transplantation. The 22q11.2 deletion and CHD7 gene mutation were documented in 44% and 14%. Findings consistent with CHARGE syndrome were seen in 30%. The cardiac repair was performed in 64% (18/28). Transplantation was performed in 70% (30/43) at a median age of 107 days (range, 33 days to 13 months). The type of transplantation included bone marrow 16, thymus 12, and bone marrow + thymus 2. In the patients undergoing transplantation (n = 30), the mortality rate was 53% at the median follow-up duration after the first transplantation of 17 months (range, 107 days to 24 years). In the conotruncal group (n = 20), 11

Table 1. Summary of 43 Cases of Complete DiGeorge Syndrome with Congenital Heart Disease

	Diagnosis					Cardiac Repair		Transplantation		Follow up				
Pt	Cardiac Diagnosis	Conotruncal Anomaly	22q11.2 Deletion	CHD7	CHARGE	Yes/No	Type	Age	Type	Duration after 1st Transplant	Age	Death/Alive	Detail	Ref
1	TOF	Yes	Yes		No			6 mo	BMT	79 mo	85 mo	Alive	Alive well	2
2	VSD, ASD, PDA	No	No	Yes	Yes			3 mo	BMT	144 mo	147 mo	Alive	Developmental delay	2,12
3	PDA, RAA, PFO	No	No		Yes	Yes	PDA ligation	6 mo	BMT	48 mo	54 mo	Alive	Alive, developmental delay, feeding difficulty	2,14
4	Conotruncal defect	Yes						7 wk	BMT	88 wk	102 wk	Alive		16
5	PS, VSD	No	Yes		No	Yes		29 wk	BMT	23 y	24 y	Alive	Doing well	8,18
6	ASD, AA anomaly	No			No	Yes		5 mo	BMT	20 y	20 y	Alive	Doing well	8
7	Large ASD and minor AA anomaly	No				Yes	ASD repair (17 mo after BMT)	5 mo	BMT	21 y	21 y	Alive		8,19
8	PDA	No	No		No	No		90 d	Thymus	9 y	9 y	Alive	In fourth grade, doing well. free of infection	1,3,10
9	PDA, PS, left SVC, dilated coronary sinus	No	No		Yes	No		63 d	Thymus	3.3 y	3.5 y	Alive	Severe developmental delay, tube feeding, free of infection	3,10
10	TOF, VSD, small PV, RAA	Yes	Yes		No	Yes	TOF repair (15 mo after Thymus)	33 d	Thymus	26 mo	27 mo	Alive	Doing well, speech delay, free of infection	3,10
11	IAA type B, PDA, VSD, small LVOT, PFO, aberrant R SCA	Yes	Yes		No	Yes	IAA repair	133 d	Thymus	17 mo	22 mo	Alive	Doing well, slight developmental delay, on Bactrim, IVIG, free of infection	3,10
12	Aberrant R SCA, PFO	No	Yes		No	No		75 d	Thymus	15 mo	17 mo	Alive	Doing well, slight developmental delay, on IVIG, free of infection	3,10
13	PDA, ASD	No	No		Yes	Yes	PDA ligation	53 d	Thymus	16 mo	18 mo	Alive	Doing well, mod developmental delay, on IVIG, free of infection	3,10
14	TA	Yes	No		No	Yes	TA repair	82 d	Thymus	9 mo	12 mo	Alive	Doing well, on IVIG, free of infection, tube/oral feeding	3,10
15	TOF, absent PV	Yes	Yes		No			13, 19 mo	BMT	12 mo	25 mo	Death	Sudden death at home (cause unknown)	2,13
16	TOF	Yes	Yes		No			3 mo	BMT	3 mo	6 mo	Death	Died of CMV PNA	2

17	AVSD	No	No	No		5 mo	BMT	2 mo	7 mo	Death	Died of circulatory failure during cardiac surgery	[2]
18	PDA	No	No	Yes	Yes	6 mo	BMT	4 mo	10 mo	Death	Died of respiratory failure	[2,12]
19	TOF	Yes	No	Yes	Yes	3 mo	BMT	5 mo	8 mo	Death	Died of circulatory failure	[2]
20	ASD, PDA, L pulm vein stenosis	No	No	Yes	Yes	4 mo	BMT	6 mo	10 mo	Death	Died of parainfluenza PNA associated with recurrent GER	[2,12]
21	PDA, PFO	No	No		Yes	7 mo	BMT	8 mo	15 mo	Death	Died of PNA, chronic GVHD	[2]
22	Aberrant L SCA	No	No	Yes	Yes	3 mo	BMT	14 mo	17 mo	Death	Died of acute renal failure, intractable hyperkalemia, LV dysfunction after open lung Bx	[2,15]
23	TOF	Yes	Yes		No	3 mo	BMT	11 mo	14 mo	Death	Died of pulmonary hemorrhage after 2nd cardiac surgery	[2]
24	PDA	No	No		Yes	96 d	Thymus	66 d	162 d	Death	Died of IVH/sepsis	[1,3,10]
25	Aortic narrowing, Aberrant CS	No	Yes		No	51 d	Thymus	130 d	181 d	Death	Died of sepsis/respiratory failure	[3,10]
26	ASD, PDA, RAA	No	Yes		No	127 d	Thymus	45 d	172 d	Death	Died of CMV sepsis/multiorgan failure	[3,10]
27	AVSD, absent R SVC, L SVC to CS	No	No		Yes	67 d	Thymus	132 d	199 d	Death	Died of sepsis	[3,10]
28	TOF, VSD, PDA, hypoplastic PA	Yes	Yes		No	107 d	Thymus	0 d	107 d	Death	Died of hemorrhage due to Ca accretion in IVC that ruptured, during fundoplication due to bleeding at transplantation	[10]
29	TOF	Yes				202, 262 d	Thymus BMT	75 d	279 d	Death	Died of PNA	[1]
30	VSD, RAA, Anomalous L PA	No	Yes			7, 16, 21, 26 mo	BMT ×4 Thymus	7 mo	35 mo	Death	Died of sepsis	[1]
31	CoA, VSD, PDA, BAV, aberrant R SCA	No	Yes		No	Yes	CoA repair, PAB, PDA ligation	No	No		Death	Death of sepsis while waiting transplant	[10]

Table 1. *Continued*

	Diagnosis					Cardiac Repair		Transplantation		Follow up				
Pt	Cardiac Diagnosis	Conotruncal Anomaly	22q11.2 Deletion	CHD7	CHARGE	Yes/No	Type	Age	Type	Duration after 1st Transplant	Age	Death/Alive	Detail	Ref
32	DORV, IAA, PDA, AS, VSD, ASD	Yes	Yes		No	Yes	IAA repair	No	No			Death	Death of sepsis while awaiting transplantation	10
33	TOF, PDA, severe PA with VSD	Yes	Yes		No	Yes	mBTS	No	No			Death	Death of cardiac arrest while awaiting transplantation	10
34	IAA type B, large VSD, hypoplastic & small AV and AsAo, subaortic stenosis	Yes	Yes		No	Yes	Modified Norwood type procedure	No	No			Death	Death of sepsis, patient not surgical candidate	10
35	TA	Yes				No		No	No			Death		11
36	TOF	Yes				No		No	No			Death		11
37	TA	Yes				No		No	No			Death		11
38	Aberrant R SCA, stenotic L SCA, PDA, VSD	No						No	No		90 d	Death	Died of aspiration	1
39	TA type IA, IAA, ASD, VSD	Yes	Yes			Yes		No	No		85 d	Death	Died of sepsis	1,17
40	TA, IAA, ASD, VSD	Yes	Yes			Yes		No	No		5 mo	Death	Died of pulmonary hemorrhage	1
41	RAA, ASD	No	No		Yes	No		No	No		6 mo	Death	Died of aspiration	1
42	ASD, VSD, PDA	No	No	Yes	Yes	Yes		NA	NA			NA		6
43	TOF, hypoplastic PA, RAA, aberrant LSCA	Yes	Yes			Yes	Central aortopulmonary shunt	No	No		5 wk	Death	Died of sepsis	Our case

AA, aortic arch; ASD, atrial septal defect; AsAo, ascending aorta; AV, aortic valve; AVSD, atrioventricular septal defect; BAV, bicuspid aortic valve; BMT, bone marrow transplantation; Bx, biopsy; CHD7, chromodomain-helicase-DNA-binding protein 7 gene mutation; CMV, cytomegalovirus; CoA, coarctation of aorta; CS, coronary sinus; DORV, double outlet right ventricle; GER, gastroesophageal reflux; IAA, interrupted aortic arch; IVH, intraventricular hemorrhage; LVOT, left ventricular outflow tract; mod, moderate; mBTS, modified Blalock–Taussig shunt; PA, pulmonary artery; PAB, pulmonary artery banding; PDA, patent ductus arteriosus; PFO, patent foramen ovale; PNA, pneumonia; PS, pulmonary stenosis; Pt, patient; Pulm, pulmonary; PV, pulmonary valve; R, right; RAA, right aortic arch; SCA, subclavian artery; SVC, superior vena cava; TA, truncus arteriosus; Thymus, thymus transplantation; TOF, tetralogy of Fallot; VSD, ventricular septal defect.

underwent transplantation and six died later. In nine patients who died before transplantation, six underwent palliative or definitive cardiac repair. In the nonconotruncal group (n = 23), 19 underwent transplantation and three died afterward. The patients with conotruncal defects were more likely to die before transplantation (45% vs. 16%, P = .04). Among 14 patients who survived after transplantation, eight (57%) had a significant morbidity such as developmental delay, speech delay, and/or pharyngeal and gastrointestinal problems. The timing between transplantation and cardiac repair can not be assessed because of limited reported data. This review of the literature suggests that children with both significant CHD and CDGS remain at high risk for morbidity and mortality, even after bone marrow or thymus transplantation. Although the survival rate after transplantation is lower in children with CDS and CHD as compared to those without CHD, about half of children may survive if their CHD can be treated adequately with successful transplantation.

Conclusion

We report a rare case of CDGS and TOF. Unfortunately, the infant expired after a central aortopulmonary shunt while awaiting thymus transplantation. Review of the literature suggests that children with CDGS and CHD have a high mortality and morbidity. Conotruncal defects have a high mortality before transplantation. Bone marrow and thymus transplantation can improve the survival, but the overall management of these high risk patients remains challenging.

Author Contribution

D.K. is the first author who participated in the concept/design and wrote the manuscript. S.S. participated in collecting data and drafted the manuscript. R.A.H. is a senior author and critically edited and approved the manuscript.

Corresponding Author: Salaam Sallaam, MD, Section of Pediatric Cardiology, Children's Hospital of Michigan, Carman and Ann Adams Department of Pediatrics, Wayne State University School of Medicine, 3901 Beaubien Blvd, Detroit, MI 48201-2119, USA. Tel: +1(313)745-5481; Fax: +1(313)993-0894; E-mail: SSallaam@dmc.org

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