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Tetralogy of Fallot associated with chromosome 22q11.2 deletion in adolescents and young adults

Kazuo Momma, MD[1], Atsuyoshi Takao, MD[1], Rumiko Matsuoka, MD[1], Yasuharu Imai, MD[2], Ayako Muto, MD[3], Makiko Osawa, MD[3], and Mikiko Takayama, MD[4]

Purpose: To clarify the clinical profiles of adolescents and young adults with tetralogy and 22q11.2 deletion, which has recently been identified as a cause of tetralogy of Fallot in about 15% of patients. **Methods:** Thirty-four patients with 22q11.2 deletion and tetralogy of Fallot, with or without pulmonary atresia, including 15 males and 19 females, with their age ranging from 16 to 35 years (mean = 25) were studied. Main outcome measurements include chromosome deletion identified by fluorescence in situ hybridization (FISH) of peripheral blood lymphocytes, medical states assessed with New York Heart Association classification, social activity assessed with Warnes index, IQ assessed by Wechsler test. **Results:** Eighteen of 20 patients with tetralogy and pulmonary stenosis had cardiac repair, and their cardiac conditions were good except one. Of 14 patients with tetralogy with pulmonary atresia, 7 had Rastelli type cardiac repair and were doing well, although 4 of them needed re-operation for conduit stenosis. No cardiac repair was done in the other 7 patients with tetralogy, pulmonary atresia and major collateral arteries because their peripheral pulmonary arteries were too small. In 28 of the 34 patients (82%), overall social activity was limited because of extracardiac diseases, including deafness, club feet, mental retardation, and schizophrenia. The IQ in 17 patients was 59 ± 13 (mean ± SD): range 41 to 79. In two patients, repeated IQ study showed a decrease. Four patients developed schizophrenia. **Conclusion:** Tetralogy with 22q11 deletion can be repaired surgically except in those patients with pulmonary atresia, major collateral arteries, and small peripheral pulmonary arteries. However, most of the adult patients show an inability to function in social life in contrast to most patients with tetralogy but without the deletion, who have a normal social life. Extracardiac diseases, including deafness, club feet, mental retardation, and schizophrenia were major handicaps limiting full social activities in postoperative adolescents and young adults with 22q11.2 deletion and tetralogy. ***Genetics in Medicine*, 2001:3(1):56–60.**

Key Words: *chromosome 22, 22q11.2 deletion, tetralogy of Fallot*

About 15% of patients with tetralogy of Fallot have deletion of chromosome 22q11.2.[1,2] The incidence of deletion is higher in tetralogy of Fallot with pulmonary atresia. About 50% of patients with tetralogy of Fallot, pulmonary atresia, and major aortopulmonary collateral artery show deletion of chromosome 22q11.2.[4] Tetralogy of Fallot with the deletion is usually associated with additional anomalies of the aortic arch, its branches, the pulmonary artery, and the ductus arteriosus.[5–7]. In addition, extracardiac anomalies,[8,9] progressive mental retardation[10,11] and development of psychiatric disease in adolescents[12–16] are additional clinical features of the deletion. Therefore, long-term prognosis of patients with tetralogy and the deletion is an issue to be clarified. To shed further light on this issue, clinical profiles of adolescents and young adults with tetralogy of Fallot and the deletion are reported in this article.

MATERIALS AND METHODS

Thirty-four patients who had 22q11.2 deletion, tetralogy of Fallot with or without pulmonary atresia, over age 16 years were located in our medical records, and comprise in this study. The deletion was confirmed by fluorescence in situ hybridization (FISH) using peripheral lymphocytes and a DNA probe N-25 by Oncor which was specific for the DiGeorge critical region. FISH study was indicated for those cardiac patients with conotruncal anomaly face (Fig. 1).[17] Medical records of these 34 patients were reviewed. Congenital heart diseases were diagnosed by echocardiography, cardiac catheterization and angiocardiography. Diagnoses were confirmed at intracardiac repair in 26 patients. Subtypes of tetralogy of Fallot are as follows: 20 patients with tetralogy of Fallot and pulmonary stenosis,[6] 3 patients with tetralogy of Fallot, pul-

From the [1]Department of Pediatric Cardiology, [2]Pediatric Cardiac Surgery, [3]Pediatrics, and [4]Otolaryngology, Tokyo Women's Medical University, Kawadacho 8-1, Shinjukuku, Tokyo, Japan.

Kazuo Momma, MD, PhD, Department of Pediatric Cardiology, Tokyo Women's Medical University, Kawadacho 8-1, Shinjukuku, Tokyo, Japan.

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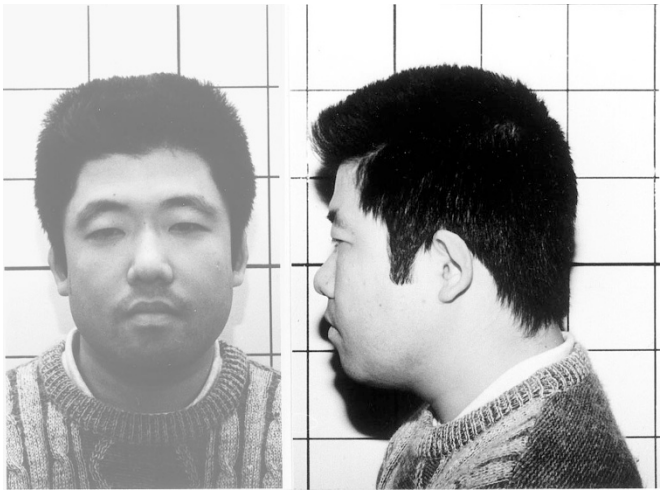

Fig. 1 Conotruncal anomaly face in a young man aged 24 years with complicated tetralogy of Fallot and the deletion (case 16 in Table 1). Conotruncal anomaly face is characterized by small eyelids, a flat nose, a small mouth, and deformed ear lobes.[2,12] Printed with permission of the patient's parents.

monary atresia, patent ductus arteriosus without major aortopulmonary collateral arteries, and 11 patients with tetralogy of Fallot, pulmonary atresia, and major aortopulmonary collateral arteries.[7] Intelligence quotients (IQ) were tested with the Wechsler method in 17 patients,[10] and compared with IQ scores of children aged 4 to 6 years with tetralogy and 22q11.2 deletion. The ability index reported by Warnes and Somerville[18] was used to assess physical and social activities of these patients. In 10 patients whose physical and social activities were not recorded, data were obtained by telephone.

RESULTS

Tetralogy of Fallot

Table 1 shows age, gender, congenital heart defect, intracardiac repair, associated extracardiac anomalies, mental retardation and IQ, psychiatric disease, Warnes index, and New York Heart Association (NYHA) classification of the 34 patients. Results of intracardiac repair and long-term results were fairly good except in one instance. Eighteen of 20 patients with tetralogy of Fallot with pulmonary stenosis (patients 1 to 20 in Table 1) had intracardiac repair. Two patients (#7 and #19) did not have intracardiac repair because of absent left pulmonary artery (#7) and because of hypoplastic right lung (#19). Of 18 patients who had intracardiac repair at age 2 to 8 years, 17 had good cardiac condition without cardiac failure, without significant arrhythmia, without cardiac medication and in NYHA functional Class I. One patient (#17) had severe postoperative pulmonary regurgitation, severe tricuspid regurgitation, congestive failure, multifocal ventricular ectopic beats, and ventricular tachycardia. He was in NYHA Class III to IV, and developed schizophrenia at age 20 years. He died suddenly while playing at home at age 26 years.

Tetralogy of Fallot, pulmonary atresia, and ductus

Three patients had tetralogy of Fallot, pulmonary atresia, patent ductus arteriosus, and normal arborization of the pulmonary arteries (patients 21 to 23 in Table 1). They were operated with the Rastelli procedure. Two patients developed stenosis of the conduit and underwent re-operation for its replacement. The cardiac condition of all 3 patients are good, without cardiac medication and were in NYHA Class I.

Tetralogy of Fallot, pulmonary atresia, and major aortopulmonary collateral arteries

Eleven patients had tetralogy of Fallot, pulmonary atresia, and major aortopulmonary collateral arteries (patients 24 to 34 in Table 1). Four of these 10 patients had a three-stage repair: right and left unifocalization and Rastelli operation.[19] Two developed stenosis of the conduit, which was replaced. Three of these 4 patients have high right ventricular pressure and mild congestive failure and are on cardiac medication. They are in NYHA Class II. Seven patients did not have surgery, because of too small pulmonary arteries, and are in NYHA Class II.

Function index

The function or ability index in our patients was more variable than expected from the cardiac conditions. Normal active life with full-time work or regular student life was found in only 6 patients. Four of these 6 patients were under the age of 20 years and were attending high school and college. Only 2 patients (#20 and #24 in Table 1) worked full-time. Nineteen patients were in Grade 2 of the function index. They worked half-time and usually did simple jobs. Major limiting factors in these 19 patients in Grade 2 included mental retardation in 13, deafness in 4, hypoxemia in 3, club feet in 2, schizophrenia in 2, and depression in 1 patient. Some patients had two major limiting factors, including mental retardation. Five patients could not work and were rated Grade 3 in the ability index. Major limiting factors in these 5 patients included deafness, mental retardation, club feet, schizophrenia, and hypoxemia. Two patients were essentially housebound and grade 4 in ability index. Major factors were congestive heart failure and schizophrenia in one patient (#17 in Table 1, died suddenly) and schizophrenia in the other (#15 in Table 1, with repeated admissions). In total, schizophrenia developed in 4 patients, at ages 15 to 25 years. One patient developed depression at age 20. Deafness in 4 patients was congenital in 2 due to defect of ossicles of middle ear (Table 2). Deafness in the other 2 patients was caused by chronic otitis media. None of these patients was married.

IQ

IQ was assessed with the Wechsler test in 17 patients. IQ in these patients was 59 in mean with standard deviation of 13, and ranged from 41 and 79 (Fig. 2). In the Wechsler test, there were no differences between verbal and performance IQ. IQ test data in childhood was available in 2 of these 17 adults, and showed decline with time (Fig. 2). Mental retardation was diagnosed in an additional 13 patients clinically. Mental state was

Table 1
Adolescents and young adults with 22q11.2 deletion and tetralogy of Fallot

Patient no.	Age (years)	Gender	Additional congenital cardiovascular defect	Surgery (age, years)	New York Heart Association class	Other diseases	IQ & mental retardation	Ability index
Tetralogy of Fallot, pulmonary stenosis								
1	16	Male	Right aortic arch	6	1		Not known	1
2	16	Male	Right aortic arch	5	1		80	1
3	17	Female	Right aortic arch, Patent ductus arteriosus	4	1	Deafness, club feet	54	2
4	17	Male	Persistent left superior vena cava	2	1	Club feet	+	2
5	18	Male	Right aortic arch, isolated left subclavian artery	3	1		Not known	1
6	19	Male	Atrial septal defect	3	1	Deafness	46	2
7	20	Male	Absent left pulmonary artery	−	3		Not known	Not known
8	20	Female	Aortic regurgitation, infundibular septal defect	7	1		+	2
9	21	Male	Atrial septal defect	7	1		+	2
10	21	Female	Right aortic arch, isolated left subclavian artery	6	1	Deafness	61	2
11	21	Female	Persistent left superior vena cava	6	1	Cleft palate	+	2
12	21	Female	Isolation of right subclavian artery	5	1		+	2
13	22	Female	Right aortic arch, aberrant origin of left subclavian artery infundibular septal defect	6	1	Inguinal hernia	+	2
14	24	Female	Persistent left superior vena cava, stenosis of left pulmonary artery	7	1	Scoliosis	+	1
15	25	Female	Right aortic arch	7	1	Thrombocytopenia, schizophrenia	+	4
16	26	Male	Right aortic arch, aberrant origin of left subclavian artery, infundibular septal defect	8	1	Uvula bifida	47	2
17	26	Male	Atrial septal defect, infundibular septal defect, congestive cardiac failure	6	4	Schizophrenia	+	4
18	27	Male	Right aortic arch, pericardial defect	6	1	Cleft palate	70	2
19	29	Female	Right aortic arch	−	2	Lung hypoplasia	78	3
20	35	Male	Right aortic arch	7	1	Schizophrenia	68	3
Tetralogy of Fallot, pulmonary atresia, patent ductus arteriosus								
21	17	Female	Right aortic arch	6	1	Deafness, club foot	54	3
22	21	Female	Right aortic arch	6	1	Inguinal hernia, cleft palate	+	2
23	22	Female	Right aortic arch, Aberrant origin of left subclavian artery	11	1	Cleft palate	+	2
Tetralogy of Fallot, pulmonary atresia, major aortopulmonary collateral artery								
24	16	Female	Aberrant origin of right subclavian artery	8	1	Inguinal hernia	58	2
25	16	Male	Right aortic arch	6	1		+	2
26	16	Female	Right aortic arch	−	2		60	2
27	16	Male		3	1		Not known	1
28	17	Male	Right aortic arch	−	2		51	2
29	18	Female		−	2	Deafness	+	2
30	20	Female	Right aortic arch, aberrant origin of left subclavian artery	−	1	Atresia ani	+	Not known
31	20	Female	Right aortic arch	10	1	Depression	+	3
32	22	Female	Right aortic arch	−	2	Nasopharyngeal insufficiency	+	2
33	30	Female	Right aortic arch	23	1	Epilepsy	53	3
34	35	Female	Right aortic arch	−	2	Schizophrenia	43	2

Table 2
Hearing loss associated with 22q11.2 deletion and tetralogy in adults

Patient no.	Audiometry (dB) Right	Left	Diagnosis	Cause
3	30	65	Bilateral conductive hearing loss	Congenital anomaly of ossicles, diagnosed by X-ray CT of temporal bone
10	Not available		Bilateral conductive hearing loss	Congenital anomaly of ossicles, diagnosed by X-ray CT of temporal bone
29	30	15	Right conductive hearing loss adhesive otitis media	Chronic otitis media, adhesions of ear drum
6	10	25	Left conductive hearing loss	Chronic otitis media perforation of ear drum

dB, decibel; CT, computed tomography.

not known in the remaining four patients. The mean IQ score was 75 ± 15 (mean ± SD) in children aged 4 to 6 years with tetralogy and 22q11.2 deletion (Fig. 2).

Cleft palate

Cleft palate was repaired in five patients. Submucosal cleft palate was frequently present, but its accurate prevalence was not obtained. Velopharyngeal insufficiency and nasal voice were frequent and were noticed in more than 80% of the patients.

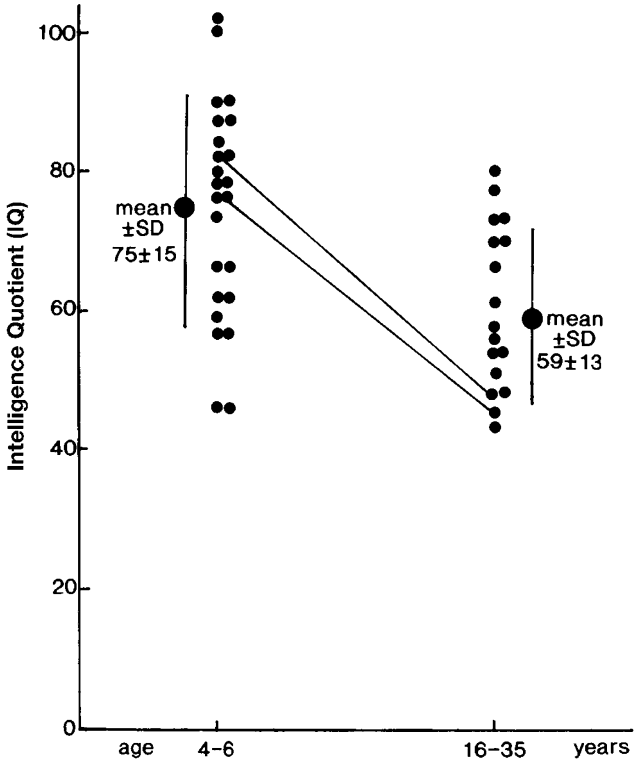

Fig. 2 Change with time of IQ in patients with tetralogy and the deletion. This figure shows the IQ of 17 adult patients in this study. Two patients in this study had a previous IQ test at 4 to 6 years of age, and in both cases, the scores declined with time. For comparison, scores of an additional 22 patients with the deletion aged between 4 to 6 years are shown.

DISCUSSION

Long-term results of surgical repair of tetralogy of Fallot were variable and have improved considerably recently. About 98% of these patients are considered by themselves or their parents to be in NYHA functional Class I after repair.[20] In this study, 18 patients had surgical repair of tetralogy and pulmonary stenosis, and only one had congestive failure (5%). An additional 7 patients with tetralogy and pulmonary atresia had surgical repair with a Rastelli procedure. Although four needed replacement of the conduit, all were NYHA Class I, 7 to 15 years after operation. Although study of surgical results was retrospective rather than prospective, results indicated that tetralogy of Fallot with pulmonary stenosis or atresia associated with deletion of chromosome 22q11 could be repaired with fairly good long-term results, if the peripheral pulmonary arteries are not too hypoplastic.[2]

However, more than 80% of adolescent and young adult patients were limited in their social and working function. Limiting factors were multiple, including mental retardation, schizophrenia, deafness, and club feet.

Generally, associated mental retardation was borderline to moderate. Mean IQ was about 60 in these young adults in this study, while the average IQ of children with the deletion was about 80 at age 4 to 6 years,[10] suggesting the progressive nature of their mental retardation. Examples of progressive mental retardation in del 22q11 have been reported,[12] but the mechanism is not clear. However, magnetic resonance imaging of the brain showed multiple abnormal findings in 80% of patients, including focal or sporadic T2 high density areas in the white matter and cerebral atrophy,[10] suggesting organic abnormalities of the brain as a basis for the mental retardation.

Some patients with the deletion develop psychiatric disorders such as schizophrenia and less commonly mania and depression in adolescence and young adulthood,[12–15] but this is seen only rarely before adolescence.[16] A high frequency up to 60% of these psychiatric diseases in adults with the deletion was reported.[21] Our study suggests that at least 10 to 20% of patients with the deletion develop psychiatric diseases as young adults.

Congenital deafness was the major limiting factor in two young adults. Defective ossicles of the middle ear were diagnosed by x-ray CT. Evidence suggests abnormal function of neural crest cells in early development as the cause of anomalies associated with deletion of chromosome 22q11.2. Ossicles in the middle ear are derived from the neural crest cells,[22] and this associated anomaly is compatible with the hypothesis of neural crest cell dysfunction as a cause of associated congenital anomalies in 22q11.2 deletion. Acquired deafness was related to repeated chronic otitis media and perforation and adhesions of the ear drum.

CONCLUSION

Postoperative cardiac condition was fairly good in tetralogy of Fallot with 22q11.2 deletion except in those patients with pulmonary atresia, major aortopulmonary collateral arteries, and small peripheral pulmonary arteries. However, most of these adult patients have an inability to function in social life in contrast to most patients with tetralogy without the deletion, who have normal social life. Extracardiac diseases, including mental retardation, deafness, club feet, and schizophrenia were major limiting factors for active social life in young adults with postoperative tetralogy of Fallot and the deletion.

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