INTERNAL MEDICINE

□ CASE REPORT □

An Adult Case of Chromosome 22q11.2 Deletion Syndrome Associated with a High-positioned Right Aortic Arch

Yoichi Hoshino, Moriya Machida, Shun-ichi Shimano and Teizo Taya

Abstract

Chromosome 22q11.2 deletion syndrome (22q11.2 DS) has a very wide phenotypic spectrum that includes dysmorphic features, cardiac anomalies, and hypocalcemia arising from hypoparathyroidism. We herein describe an adult case of 22q11.2 DS with associated hypoparathyroidism and anomalies of the aortic arch. Because the patient had been diagnosed with primary hypoparathyroidism at another hospital, a diagnosis of 22q11.2 DS had been overlooked. A chest X-ray examination revealed widening of the mediastinum caused by a high-positioned right aortic arch, and we subsequently confirmed a diagnosis of 22q11.2 DS using fluorescence *in situ* hybridization. Because primary hypoparathyroidism is a rare disorder, physicians should be aware of the variable phenotypic features of 22q11.2 DS.

Key words: chromosome 22q11.2 deletion syndrome, high-positioned right aortic arch, aberrant left subclavian artery, Kommerell's diverticulum, anomalous subaortic left brachiocephalic vein, hypoparathyroidism

(Intern Med 56: 865-872, 2017)
(DOI: 10.2169/internalmedicine.56.7558)

Introduction

Chromosome 22q11.2 deletion syndrome (22q11.2 DS) is a congenital anomaly arising from a hemizygous microdeletion on the long arm of chromosome 22. The syndrome has an incidence of 1 in 4,000 to 10,000 children (1). Over 35 genes are present within the commonly deleted region of chromosome 22q11.2 (2). Because these genes regulate the development of the cardiac outflow tract, thymus, parathyroid, facial structure, and brain mesoderm, patients with this syndrome can demonstrate various phenotypic features, including cardiac anomalies; immune deficiency; velopharyngeal insufficiency with or without palatal defects; hypocalcemia; developmental delay; behavioral and psychiatric disorders; renal, dental, structural, central nervous system, spinal, and ophthalmic anomalies; and hearing loss (1, 2). In particular, cardiovascular anomalies are present in 80% of patients with 22q11.2 DS (3). However, because of unrecognized combinations of various clinical phenotypic features, the diagnosis of 22q11.2 DS can be missed until adulthood (1). Previous studies have described patients with 22q11.2 DS being followed as patients with idiopathic hypoparathyroidism, epilepsy, or schizophrenia until adulthood despite the presence of other typical phenotypic features (4-16).

We herein report the findings of a 54-year-old man that was diagnosed with 22q11.2 DS. The patient had been treated for primary hypoparathyroidism for three years at another hospital's outpatient clinic. We detected widening of the mediastinum because of a high-positioned right aortic arch (RAA) on chest X-ray. The combination of hypoparathyroidism and isolated anomalies of the aortic arch and its branches suggested a diagnosis of 22q11.2 DS. We also review an additional 43 reported cases of 22q11.2 DS that were first diagnosed during adulthood and discuss the clinical characteristics of these cases.

Case Report

A 54-year-old man was referred to our hospital for follow-up treatment for primary hypoparathyroidism. He had no history of neck injury or surgery. He had been diagnosed with primary hypoparathyroidism at another hospital three

Department of Internal Medicine, Keiaido Hospital, Japan
Received for publication April 12, 2016; Accepted for publication August 16, 2016
Correspondence to Dr. Yoichi Hoshino, fwgi9866@nifty.com

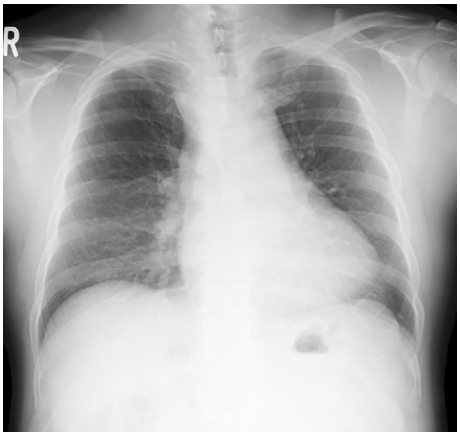

Figure 1. Chest X-ray findings. The widened superior mediastinum is visible on chest X-ray.

years prior and was being treated with vitamin D and calcium supplementation. His physical findings were as follows: height, 160 cm; weight, 65 kg; blood pressure, 130/80 mmHg; and pulse rate, 75 beats per minute. Chest and abdominal examinations revealed no abnormal findings. Chest X-ray showed widening of the mediastinum, suggesting an anterior mediastinal tumor or a thoracic aortic aneurysm (Fig. 1). Contrast-enhanced computed tomography (CT) revealed that the top of the RAA reached the upper border of the manubrium sterni (not the cervical aorta); furthermore, an aberrant left subclavian artery (ALSA) originating at Kommerell's diverticulum (KD) and an anomalous subaortic left brachiocephalic vein (ASLBV) were also observed (Fig. 2A and C-F). KD had compressed the esophagus and trachea posteriorly (Fig. 2B). No abnormal electrocardiogram or echocardiogram findings were observed.

The combination of hypoparathyroidism and aortic arch anomalies suggested a diagnosis of 22q11.2 DS. Consequently, we reevaluated whether or not the patient had other features of 22q11.2 DS. His family members showed no signs of 22q11.2 DS, and he was unmarried. He attended a special supported education school from the age of 7 to 15 years. He had graduated from a part-time high school and had become a garbage man. He had had a part-time job once a month for 10 years. He did not have a history of attention deficit or psychiatric disorders. We used the Mini-Mental State Examination-Japanese (MMSE-J) scale (Nihon Bunka Kagakushya Co., Ltd.), which is significantly correlated with the Intellectual Quotient of the Wechsler Adult Intelligence Scale (17), to evaluate his intelligence. His MMSE-J score was 21/30, which corresponds to a mild intellectual disability. His face exhibited mildly dysmorphic features, with a narrow nasal ridge and a broad nasal root. Laboratory tests revealed lymphocytopenia (739/μL), mild hypocalcemia (8.3 mg/dL), and a low level of serum parathyroid hormone (PTH) (<50 pg/mL; normal range, 68-110 pg/mL). His thyroid function was normal. Because of a strong clinical suspicion that the patient had 22q11.2 DS, we performed a chromosome analysis using fluorescence *in situ* hybridization (FISH) to confirm a diagnosis. The FISH analysis detected a hemizygous deletion of the chromosome 22q11.2 region (Fig. 3). The patient has remained stable without experiencing dysphagia as a result of KD for 5 years.

Discussion

The present case was diagnosed with 22q11.2 DS at 54 years of age. In a large European cohort study of 558 patients with 22q11.2 DS, 11% of the cohort (n=67) had been diagnosed at an age of 18 years or older (18). A previous review indicated that parents who were diagnosed after the diagnosis of an affected offspring accounted for 60% of all adults with 22q11.2 DS (≥18 years), whereas 40% of affected adults were identified by means other than familial transmission (19). Compared with the parents of affected offspring, adult cases identified by means other than familial transmission exhibited higher rates of congenital heart disease (56% vs. 15%) and psychiatric disorders (64% vs. 17%) but similar rates of learning disability or mental retardation (98% vs. 91%) and facial anomalies (98% vs. 100%) (19). However, the reason why these adults with 22q11.2 DS were only diagnosed during adulthood or had been overlooked until adulthood remains unclear.

To verify the clinical events that occurred at the time of the first diagnosis of 22q11.2 DS in adult patients (≥20 years) with 22q11.2 DS, we reviewed the available case reports in two databases: PubMed and Ichu-shi Web (version 5). The following adult cases were excluded: 1) cases identified as a result of transmission to an affected offspring or as siblings of affected siblings, 2) cases confirmed by genetic screening for psychiatric disorders, and 3) cases with uncertain diagnostic events. The clinical characteristics of 44 cases, including the present case, are listed in Table (4-16, 20-48). The median age at the time of the first diagnosis of 22q11.2 DS was 32 years (range, 20-71 years). More than half of the patients were diagnosed before 40 years of age (29/44, 69%). A minority of cases were diagnosed after 50 years of age (7/44, 16%). The clinical events at the time of the first diagnosis of 22q11.2 DS were mainly hypocalcemia/hypoparathyroidism (21/44, 48%) or psychiatric disorders (11/44, 25%). Prior to the confirmation of their diagnoses, most of the patients had been followed for hypocalcemia/hypoparathyroidism (8/44, 36%), epilepsy (6/44, 14%), or a psychiatric disorder (6/44, 14%). However, 15 cases (34%) had not exhibited any remarkable diseases prior to the diagnosis. The frequencies of the major phenotypic features of 22q11.2 DS were as follows: hypocalcemia/hypoparathyroidism, 36/44 (82%); cardiovascular anomalies, 23/44 (52%); psychiatric disorders, 16/44 (36%); neurodevelopmental disorders such as intellectual disabilities, autism, attention deficit/hyperactivity disorder, or learning disability, 32/44 (73%); and dysmorphic facial features, 37/44 (84%). Although most of the adult cases with 22q11.2 DS, including the present case, exhibited neurodevelopmen-

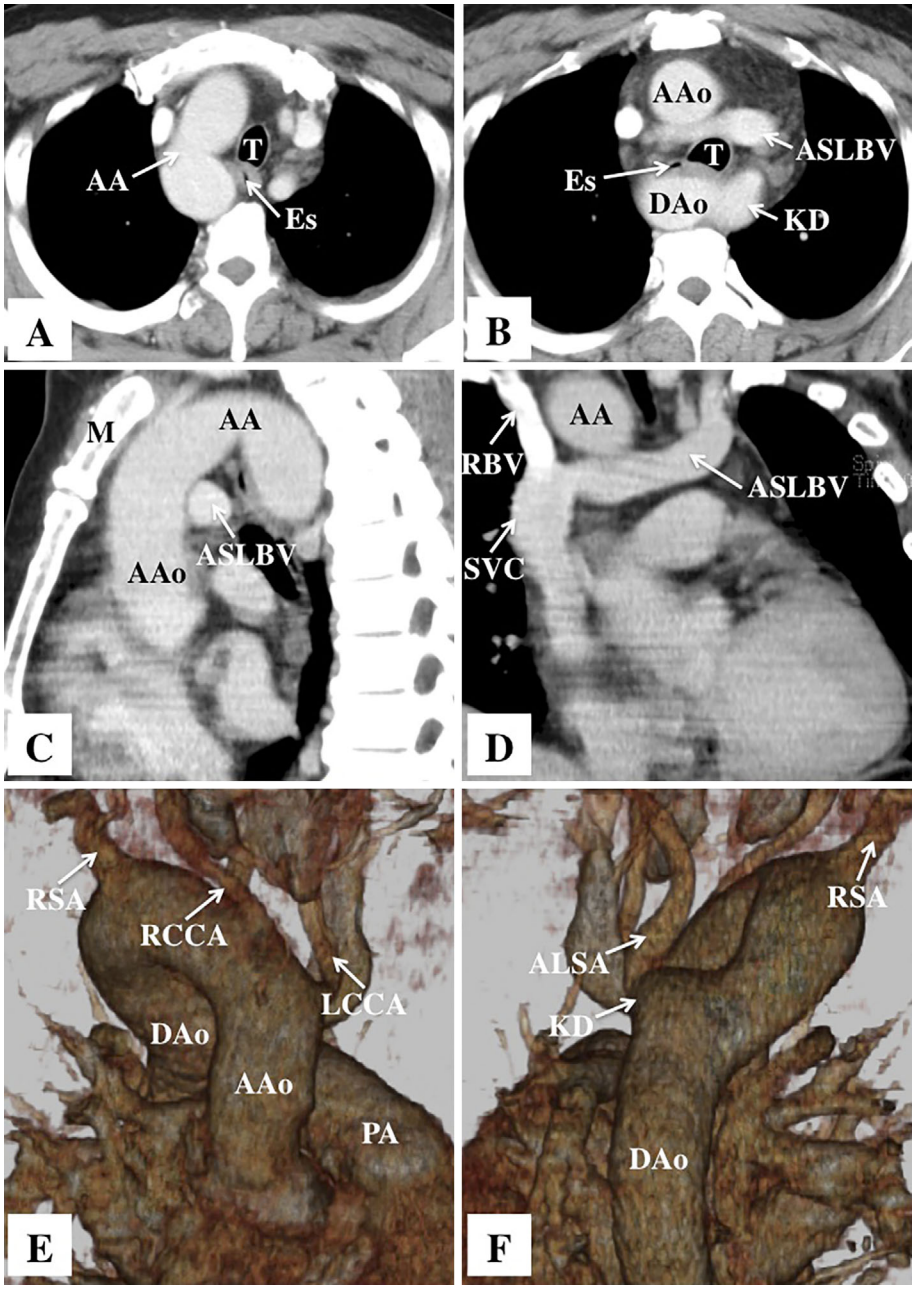

Figure 2. **Axial views (A and B), multi-planar reconstruction views (C and D), and three-dimensional views (E and F) obtained using contrast-enhanced thoracic computed tomography. A: The aortic arch is right-sided. B: The trachea and esophagus are surrounded by both the descending aorta and Kommerell's diverticulum. An anomalous subaortic left brachiocephalic vein passes anterior to the trachea. C: A sagittal view of the thorax shows that the top of the aortic arch reaches the superior border of the manubrium sterni. D: A coronal view of the thorax shows that the anomalous subaortic left brachiocephalic vein passes under the aortic arch and joins the right brachiocephalic vein. E: An anterior view of the right aortic arch shows the left common carotid artery arising as the first branch of the aorta, followed by the right common carotid and right subclavian artery. F: A posterior view of the right aortic arch shows an aberrant left subclavian artery arising from Kommerell's diverticulum. AA: aortic arch, T: trachea, Es: esophagus, AAo: ascending aorta, DAo: descending aorta, ASLBV: anomalous subaortic left brachiocephalic vein, KD: Kommerell's diverticulum, M: manubrium sterni, RBV: right brachiocephalic vein, SVC: superior vena cava, RSA: right subclavian artery, RCCA: right common carotid artery, LCCA: left common carotid artery, mPA: main pulmonary artery, ALSA: aberrant left subclavian artery**

tal disorders or dysmorphic facial features, these findings were not recognized as phenotypic features of 22q11.2 DS. 22q11.2 DS had clearly been overlooked in 21 cases (48%), including the present case, at the time of the first

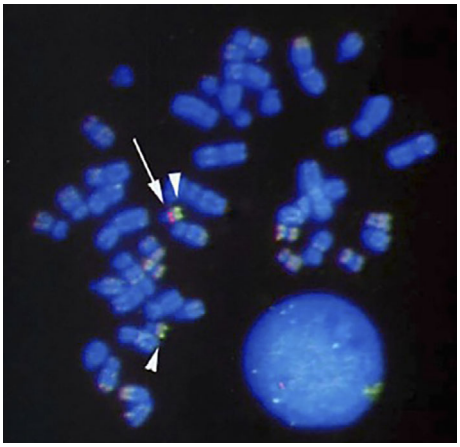

Figure 3. Fluorescence *in situ* hybridization (FISH). A FISH analysis using a TUPLE1 (22q11.2) probe (red, white arrow) and an ARSA (22q11.3) probe (green, white arrow head) is shown. The ARSA probe was used as a control and shows hybridization signals on chromosome 22. The absence of a red signal (TUPLE1 probe) on one chromosome 22 indicates a hemizygous deletion of a locus at 22q11.2.

medical examination leading to a diagnosis of 22q11.2 DS, since these 21 subjects had been previously diagnosed with hypocalcemia/hypothyroidism, cardiovascular anomalies, or psychiatric disorders (4-11, 14, 16, 20, 21, 28, 33, 34, 36, 37, 39, 40, 48).

The present case had been followed for primary hypoparathyroidism. Hypoparathyroidism is an uncommon endocrinological disorder, defined as hypocalcemia caused by a PTH deficiency (49). In adults, anterior neck surgery is the most common cause of hypoparathyroidism, accounting for approximately 75% of all such patients (50). Other etiologies of hypoparathyroidism include autoimmune or genetic disorders (49, 50). Genetic forms of hypoparathyroidism may occur as part of syndromic disorders or as a non-syndromic solitary endocrinopathy (50). 22q11.2 DS is included among the syndromic forms of hypoparathyroidism (51). In our literature review (Table), 48% of the cases had been diagnosed with 22q11.2 DS after the detection of hypocalcemia/hypoparathyroidism. In contrast, 18% of the cases, including the present case, had been overlooked for 3 to 37 years since the initial detection of hypocalcemia/hypoparathyroidism (4-10). Thus, determining the etiology of adult hypocalcemia/hypoparathyroidism is quite important.

In the present case, late-onset hypocalcemia/hypothyroidism during adulthood caused a delay in the diagnosis of 22q11.2 DS. A previous study demonstrated that more than half of the first documented hypocalcemic episodes in patients with 22q11.2 DS occurred after the age of 17 years (51). In our literature review (Table), most of the patients (32/44, 73%), including the present case, developed hypocalcemia/hypoparathyroidism during adulthood (≥20 years). Although the etiology of late onset hypocalcemia/hypoparathyroidism is unclear, we speculate that two main reasons may exit. First, some patients may have subclinical hypocalcemia. Patients can remain symptom-free if hypocalcemia develops slowly (52). In our review (Table), 5 cases had asymptomatic hypocalcemia at the time of their 22q11.2 DS diagnosis (14, 35, 43, 44, 46). Second, some patients have an inadequate parathyroid function manifesting as a reduced PTH reserve (53). These patients are usually normocalcemic but cannot release an adequate amount of PTH to correct hypocalcemia occurring in response to stressors (birth, operations, or illness) (53). The presently reported patient usually required calcium and vitamin D supplementation to maintain normocalcemia. Serum PTH levels increase with age in healthy subjects, independent of the level of 25-hydrooxyvitamin D, ionized calcium, and phosphate and the renal function (54). We speculated that patients who are diagnosed during adulthood become unable to release an adequate amount of PTH as they age and might begin to require calcium or vitamin D supplementation to maintain normocalcemia.

Our patient had anomalies of the aortic arch and its branches, characterized by a high-positioned RAA, ALSA, KD, and ASLBV. In patients with 22q11.2 DS, the most common congenital cardiac defects are conotruncal anomalies, including tetralogy of Fallot (TF), TF with pulmonary atresia, and truncus arteriosus (3). Anomalies of the aortic arch and its branches are often identified with or without intracardiac anomalies, such as a cervical or high-positioned aortic arch, RAA, aberrant subclavian artery, KD, and vascular ring (55). Isolated anomalies of the aortic arch and its branches with a normal heart have been found in 5-24% of patients with 22q11.2 DS (55, 56). In our reviewed cases (Table), the most frequent types of intracardiac anomalies and anomalies of aortic arches were tetralogy of Fallot (TOF) (n=8) and RAA (n=4), respectively. Isolated anomalies of the aortic arch were seen in four cases, including the present case (7, 24, 46). Similar to the present case, RAA with ALSA and KD was identified in one case (46). In this previously reported patient, RAA with ALSA and KD had been overlooked at the time of the diagnosis of 22q11.2 DS, although echocardiography had been performed (46). Interestingly, these anomalies of the aortic arch were detected during CT performed six months after the diagnosis of 22q 11.2 DS because of the development of pneumonia (46). These facts suggest that anomalies of the aortic arch are more likely to be overlooked than intracardiac anomalies at the time of the diagnosis of 22q11.2 DS.

RAA can usually be easily recognized on chest X-ray. In the present patient, however, we were unable to determine the laterality of the aortic arch based on the chest X-ray findings because of the mediastinal widening caused by the high-positioned RAA. The upper border of the aortic arch is usually at the midlevel of the manubrium sterni (57). In the present case, however, the upper border was as high as the superior border of the manubrium sterni. A cervical or high-positioned aortic arch appears at a higher level than normal and results from a persistent third arch instead of a fourth arch or an abnormal elongation of the fourth aortic

Table. **Review of 44 Cases of Chromosome 22q11.2 Deletion Syndrome Diagnosed during Adulthood.**

Case No.	Reference	Age*, y/ Sex	Clinical events at the time of the first diagnosis of 22q11.2 deletion syndrome	Initial diagnosis#	Hypocalcemia/ hypoparathyroidism, Age at diagnosis, y	Cardiovascular anomalies/ Age at diagnosis, y	Psychiatric disorders/ Age at diagnosis, y	Neuro-developmental disturbance	Dysmorphic face	Other features
1	15	21/F	severe distress	epilepsy, depression	ND	ND	schizoactive disorder/20	ID, LD	ND	
2	20	21/M	irritability, increased psycomotor activity, etc.	ND	ND	VSD/6	mania/16	ID	+	
3	21	22/F	psychosis	-	22	TOF/3.5	psychosis/22	ID, LD	+	CSP, CV
4	22	23/M	confusion (hypocalcemia and psychosis)	-	23	ND	psychosis/23	ID	+	
5	23	24/F	profound mental retardation and autism	autism	ND	-	-	ID, autism	+	cleft palate
6	24	24/F	delusion	-	24	RAA/24	schizoprenia-like symptoms/24	ID	+	Graves disease
7	25	24/F	seizure (hypocalcemia)	-	24	-	ND	LD	ND	
8	11	25/F	seizure (hypocalcemia)	epilepsy	25	TOF/1	ND	ID	+	
9	26	25/F	seizure (hypocalcemia)	-	25	-	ND	ID	+	
10	27	26/M	carpopedal spasm (hypocalcemia)	-	26	-	ND	ID	+	conductive deafness
11	28	27/F	tetanic spasms (hypocalcemia)	-	27	ND	ND	ND	ND	postpartum
12	29	29/F	fatigue and muscle pain (hypocalcemia)	viral myalgia, fibromyalgia	29	ASD, RAA	ND	ND	+	cleft palate, IgA deficiency
13	30	29/F	numbness of hands and feet (hypocalcemia)	-	27	-	ND	LD	+	transient neonatal hypocalcemia
14	31	29/F	cognitive disorder	-	ND	VSD	ND	-	ND	cleft palate
15	7	30/M	operation for cataracts	idiopathic hypoparathyroidism	16	RAA/30	ND	ID	+	lymphocytopenia, asthma
16	32	30/F	syncope and seizure (hypocalcemia)	ND	30	TOF with PA/30	ND	ND	+	aneurysm of pulmonary artery
17	33	31/F	delusion(schizophrenia)	-	31	TOF/3 months	schizophrenia/31	ID	+	CSP, CV
18	34	32/M	katatonic excitement	-	ND	TOF/6	schizophrenia/32	ID	+	cleft palate
19	4	32/M	hallucination (schizophrenia)	idiopathic hypoparathyroidism	15	-	schizophrenia/32	ID	+	bifida uvula, CSP
20	16	32/M	large cavum septi pellucidi	schizophrenia	ND	VSD	schizophrenia/16	ID	+	cleft palate
21	8	32/M	management of hypocalcemia	hypocalcemia	14	-	ND	LD	+	
22	35	32/F	malaise etc. (IE and asymptomatic hypocalcemia)	persisting VSD	32	ASD, VSD	ND	LD	+	cleft palate
23	36	32/F	chest pain (hypocalcemia)	post PVR	32	TOF	-	ID, LD	+	thrombocytopenia, reduced T-cells
24	37	32/F	seizure (hypocalcemia)	Hashimoto's thyroiditis	32	VSD/8 months	-	-	+	lymphocytopenia
25	10	33/M	dyspnea (sleep apnea syndrome)	hypocalcemia, schizophrenia	23	-	schizophrenia/30	ND	+	Graves disease, obesity, cleft palate
26	38	34/M	cerebellar ataxia (cerebellar atrophy)	neurodegenerative disorder	+	ASD/8	ND	ID	+	cleft palate, bifida uvula
27	39	36/F	consciousness disturbance (hypocalcemia)	DM, Hashimoto's thyroiditis	36	TOF/5	-	LD	+	
28	40	38/F	confusion, agitation, and tiredness (hypocalcemia)	PHT	38	TA with PHT	psychosis	ND	ND	cleft palate
29	41	39/M	seizure (hypocalcemia)	anxiety disorder, CKD	39	-	anxiety disorder/31	ID, LD	+	nephrosclerosis
30	42	40/M	seizure (hypocalcemia)	-	40	-	-	-	+	
31	9	40/M	seizure (hypocalcemia)	epilepsy, hypocalcemia	29	-	ND	ID	+	spina bifida, myelomenigocele
32	12	40/M	seizure (hypocalcemia)	epilepsy	40	-	ND	ID	+	asthma
33	5	40/F	psychosis	idiopathic hypoparathyroidism	20	TOF/8 months	schizophrenia-like psychosis/40	ID	+	
34	43	42/F	scleritis, cough (asymptomatic hypocalcemia)	-	42	-	ND	ND	-	cleft palate, relapsing polychondritis
35	13	43/F	seizure (hypocalcemia)	epilepsy	43	-	-	LD	+	
36	14	43/F	diarrhea, etc. (asymptomatic hypocalcemia)	epilepsy, depression	43	VSD	depression	-	+	absent kidney
37	44	47/F	weakness and involuntary movement (hypocalcemia)	-	47	-	ND	LD	+	hypothyroidism
38	25	52/F	cervical lymphadenopathy (asymptomatc hypocalcemia)	PDA	52	PDA	ND	-	+	
39	45	52/M	dementia and austic features	psychotic illness	ND	ND	psychiatric problem/34	ID	ND	
40	our case	54/M	widening of mediastinum (high-positioned RAA)	primary hypoparathyroidism	51	RAA, ALSA, KD/54	-	ID	+	lymphocytopenia
41	46	59/M	bronchitis, sinusitis (asymptomatic hypocalcemia)	-	59	RAA, ALSA, KD/59	ND	+	+	bifida uvla, sensory deafness
42	47	59/M	unfolding of the aorta (aortic root aneurysm)	HTN	-	VSD/9, ARSA/59	ND	ND	+	
43	48	64/F	dyspnea (heart failure due to hypocalcemia)	asthma, HTN	64	-	ND	ID	+	asthma
44	6	71/M	anxious-depressive syndrome, cerebral dysrhythmia	idiopathic hypoparathyroidism	34	-	anxious-depressive syndrome/71	ID	+	parkinsonism

* Age at the time of the first diagnosis of 22q11.2 deletion syndrome.
# Initial diagnosis before a diagnosis of 22q11.2 deletion syndrome was confirmed.
ALSA: aberrant left subclavian artery, ARSA: aberrant right subclavian artery, ASD: atrial septal defect, CKD: chronic kidney disease, CSP: cavum septi pellucida, CV: cavum vergae, DM: diabetes mellitus, HTN: hypertension, ID: intelligence disorder, IE: infective endocarditis, IgA: immunoglobulin A, KD: Kommerell's diverticulum, LD: learning disability, ND: not described, PA: pulmonary atresia, PDA: patent ductus arteriosus, PHT: pulmonary hypertension, PVR: pulmonary valve replacement, RAA: right aortic arch, TA: truncus arteriosus, TOF: tetralogy of Fallot, VSD: ventricular septal defect

Intern Med 56: 865-872, 2017 DOI: 10.2169/internalmedicine.56.7558

arch (55). The aortic arch in the present case can be referred to as a high-positioned aortic arch because the cervical aorta is specifically defined as the location of the aortic arch in the neck (58).

RAA is divided into the following three types: RAA with ALSA, RAA with mirror-image branching of the major arteries, and RAA with the isolation of the left subclavian artery from the aortic arch (59). The present case had RAA with ALSA. This type of anomaly results from the interruption of the left arch between the left carotid and left subclavian arteries (59). As a result, the left common carotid artery arises as the first branch of the aorta, followed by the right common carotid, right subclavian, and left subclavian arteries (59).

KD, which is a diverticular outpouching of the aortic arch, is classified into the following three types: KD in left aortic arch (LAA) with aberrant right subclavian artery (ARSA), KD in RAA with ALSA, or KD at the aortoductal junction (60). KD in LAA with ARSA is a remnant of the primitive right dorsal aorta (60). ARSA arises from KD, passes behind the esophagus, and causes symptoms of esophageal compression (dysphagia lusoria) (60). ARSA arising from KD was first described by Kommerell in 1936 based on radiographic examinations (61). The present case had KD in RAA with ALSA. This type of KD represents the remnant of the primitive distal LAA. The ALSA, arising from KD, passes obliquely upward, behind the esophagus, and toward the left arm and can cause symptoms of tracheal or esophageal compression (60). The development of KD can cause aneurysms (62). Aneurysms of KD associated with rupture or dissection are a life-threating complication (62). Therefore, careful attention to new-onset dyspnea and dysphagia or KD enlargement is required.

ASLBV is strongly associated with conotruncal cardiac or aortic arch anomalies, such as TF, cervical aorta, RAA, and 22q11.2 DS (63). Although ASLBV is a rare systemic venous anomaly, ASLBV was an important clinical feature of 22q11.2 DS in this patient. The pathogenesis of ASLBV has not been clarified. Aortic arch anomalies may prevent the normal development of the ventral precardinal anastomosis (63). As a result, abnormal connections between two precardinal veins may develop into ASLBV (63).

The long-term outcome of adult patients with 22q11.2 DS is uncertain. One study of 102 adults with 22q11.2 DS reported that the rates of survival to 40 and 50 years of age were 89.9% and 73.9%, respectively (64). The median age at death was 41.5 years (range, 18.1-68.6 years) (64). The most common cause of death is sudden or unexpected death, which is usually unrelated to major cardiac anomalies or schizophrenia (64). Because our patient has survived to more than 50 years of age, the possible development of conditions other than hypocalcemia and aortic anomalies will require careful monitoring.

In conclusion, we present a case of 22q11.2 DS that was first diagnosed during adulthood. The patient had unusual chest X-ray findings caused by isolated anomalies of the aortic arch and its branches. Although these anomalies are usually clinically asymptomatic, they are important clinical manifestations of chromosomal disorders. Physicians should pay attention to the presence of multisystem syndromes in patients with primary hypoparathyroidism.

The authors state that they have no Conflict of Interest (COI).

References

1. Bassett AS, McDonald-McGinn DM, Devriendt K, et al. Practical guidelines for managing patients with 22q11.2 deletion syndrome. J Pediatr **159**: 332-339, 2011.
2. McDonald-McGinn DM, Sullivan KE. Chromosome 22q11.2 deletion syndrome (DiGeorge syndrome/velocardiofacial syndrome). Medicine **90**: 1-18, 2011.
3. Momma K. Cardiovascular anomalies associated with chromosome 22q11.2 deletion syndrome. Am J Cardiol **105**: 1617-1624, 2010.
4. Chow LY, Waye MM, Garcia-Barcelo M, Chiu HFK, Fung KP, Lee CY. Velo-cardio-facial syndrome, schizophrenia and deletion at chromosome 22q11. J Intellect Disabil Res **42**: 184-188, 1998.
5. Tastuzawa Y, Sekinaka K, Suda T, et al. An interictal schizophrenia-like psychosis in an adult patient with 22q11.2 deletion syndrome. Epilepsy Behav Case Rep **3**: 36-38, 2015.
6. Passeri E, Figerio M, Valaperta R, Costa E, Ambrosi B, Corbetta S. Adult onset hypoparathyroidism in apatient with psychiatric illness: a 71 years delayed diagnosis of DiGeorge syndrome. J Endocrinol Invest **33**: 852-853, 2010.
7. Hirotani A, Morimoto S, Koh E, Ogihara T. Partial DiGeorge syndrome at the age of thirty-four. Intern Med **33**: 418-421, 1994.
8. Maalouf NM, Sakhashayar K, Odvina CV. A case of chromosome 22q11 deletion syndrome diagnosed in a 32-year-old man with hypoparatyroidism. J Clin Endocrinol Metab **89**: 4817-4820, 2004.
9. Kinoshita H, Kokudo T, Ide T, et al. A patient with DiGeorge syndrome with spina bifida and sacral myelomeningocele, who developed both hypocalcemia-induced seizure and epilepsy. Seizure **19**: 303-305, 2010.
10. Kondo N, Yuasa H. 22q11.2 deficiency syndrome associated with congestive heart failure and sleep apnea syndrome. Nagoya Shiritsu Byoin Kiyo **31**: 5-7, 2008 (in Japanese).
11. Nagata K. An adult case of 22q11.2 deletion syndrome diagnosed by adult onset hypocalcemia (author's translation). Horumon to Rinsho **52** (suppl winter): 84-87, 2004 (in Japanese).
12. Cao Z, Yu R, Dun K, Burke J, Caplin N, Greenaway T. 22q11.2 deletion presenting with severe hypocalcaemia, seizure and basal ganglia calcification in an adult man. Intern Med J **41**: 63-66, 2011.
13. van den Berg K, Diderich K, Poddighe P, Berghout A. Symptomatic hypoparathyroidism based on a 22q11 deletion first diagnosed in a 43-year-old woman. Neth J Med **67**: 102-104, 2009.
14. van Vliet EI, van Ouwerkerk BM. Hypocalcaemia as presenting symptom of velocardiofacial syndrome. Neth J Med **67**: 105-106, 2009.
15. EI Tahir MO, Kerr M, Jones RG. Two cases of generalized seizures and the velocardiofacial syndrome — a clinically significant association? J Intellect Disabil Res **48**: 695-698, 2004.
16. Vataja R, Elomaa E. Midline brain anomalies and schizophrenia in people with CATCH 22 syndrome. Br J Psychiatry **172**: 518-520, 1988.
17. Folestein MF, Folestein SE, McHugh PR. "Mini-Mental State." A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res **12**: 189-198, 1975.
18. Ryan AK, Goodship JA, Wilson DI, et al. Spectrum of clinical features associated with interstitial chromosome 22q11 deletions: a

European collaborative study. J Med Genet **34**: 798-804, 1997.
19. Cohen E, Chow EWC, Weksberg R, Bassett AS. Phenotype of adults with the 22q11 deletion syndrome: a review. Am J Med Genet **86**: 359-365, 1999.
20. Praharaj SK, Sarkar S, Sinha VK. Velocardiofacial syndrome presenting as chronic mania. Psychiatry Clin Neurolsci **64**: 666, 2010.
21. Sieberer M, Haltenhof H, Haubitz B, Pabst B, Miller K, Garlipp P. Basal ganglia calcification and psychosis in 22q11.2 deletion syndrome. Eur Psychiatry **20**: 567-569, 2005.
22. Thomas ZS. Psychosis, electrolyte imbalance, and velocardiofacial syndrome. Psychosomatics **44**: 348-350, 2003.
23. Kozma C. On cognitive variability in velocardiofacial syndrome: profound mental retardation and autism. Am J Med Genet **81**: 269-270, 1998.
24. Monya C, Ujike H, Wake Y, Okahisa Y, Kuroda S. A case of 22q11.2 deletion syndrome with schizophrenia-like symptoms. Seishin Igaku (Clinical Psychiatry) **46**: 187-190, 2004 (in Japanese).
25. Kar PS, Ogoe B, Poole R, Meeking D. Di-George syndrome presenting with hypocalcemia in adulthood: two case reports and a review. J Clin Pathol **58**: 655-657, 2005.
26. Aljabri KS, Bebb RM. DiGeorge's syndrome presenting as hypocalcemia in an adult. Ann Saudi Med **25**: 173-174, 2005.
27. Korpaisarn S, Trachoo O, Sriphrapradang C. Chromosome 22q11.2 deletion syndrome presenting as adult onset hypoparathyroidism: clues to diagnosis from dysmorphic facial features. Case Rep Endocrinol, in press.
28. Saeed A, Khan M, Irwin S, Fraser A. Sarcoidosis presenting with severe hypocalcaemia. Ir J Med Sci **180**: 575-577, 2011.
29. van den Bosch MA, Wittebol S, vanDijk H, Kramer MH. Hypocalcemic tetany as an early sign of DiGeorge syndrome in an adult woman. Am J Med **112**: 161-162, 2002.
30. Johnston PC, Donnelly DK, Morrison PJ, Hunter SJ. DiGeorge syndrome presenting as late onset hypocalcaemia in adulthood. Ulster Med J **77**: 201-202, 2008.
31. Hida S, Nakajima M, Ishigaki S, Kawamura M. Neuroimaging findings of a 29-year-old woman with 22q11.2 deletion presenting with cognitive deterioration. Brain and Nerve **63**: 1294-1295, 2011 (in Japanese).
32. Kinoshita O, Mizoue T, Kusama A, et al. Pulmonary arterial aneurysm with CATCH 22 syndrome - a case report. Angiology **52**: 789-791, 2001.
33. Akihisa T, Kasai K, Onai H, Onai F. Large cavum septi pellucidi and Vergae in a case of 22q11.2 syndrome with schizophrenia. Seishin Igaku (Clinical Psychiatry) **47**: 399-403, 2005 (in Japanese).
34. Matsunaga Y, Kitanishi K, Ushijima S, Takao A. A case of conotruncal anomaly face syndrome with schizophrenia. Seishin Igaku (Clinical Psychiatry) **39**: 539-541, 1997 (in Japanese).
35. McCusker LA, Jenkins NP, Hancock JE. Hypocalcaemia in a patient with congenital heart disease. J R Soc Med **100**: 51-53, 2007.
36. Shea YF, Lee CH, Gill H, et al. Delayed diagnosis of 22q11.2 deletion syndrome in an adult Chinese lady. Chin Med J (Engl) **125**: 2945-2947, 2012.
37. Sasaki Y, Obara H, Shimabukuro A. A 32-year-old woman diagnosed with 22q11.2 deletion syndrome and complicated by hypothyroidism. Gen Med **15**: 72-75, 2014.
38. Lynch DR, McDonald-McGinn DM, Zackai EH, et al. Cerebellar atrophy in a patient with velocardiofacial syndrome. J Med Genet **32**: 561-563, 1995.
39. Nakada Y, Terui K, Kageyama K, et al. An adult case of 22q11.2 deletion syndrome diagnosed in a 36-year-old woman with hypocalcemia caused by hypoparathyroidism and Hashimoto's thyroiditis. Intern Med **52**: 1365-1368, 2013.
40. Buchanan LM, Hargreaves A, Warwick MM. Velocardiofacial syndrome or DiGeorge's anomaly. Lancet **358**: 420, 2001.
41. Furuya K, Sasaki Y, Takauchi T, Urita Y. Characteristics of 22q11.2 deletion syndrome undiagnosed until adulthood: an example suggesting the importance of psychiatric manifestations. BMJ Case Rep, in press.
42. Tonelli AR, Kosuri K, Wei S, Chick D. Seizures as the first manifestation of chromosome 22q11.2 deletion syndrome in a 40-year old man: a case report. J Med Case Rep **1**: 167, 2007.
43. Himeno R, Fujita K, Kawakita S. A case of 22q11.2 deletion syndrome associated with relapsing polychondritis and autoimmune thyroid disease (author's translation). Horumon to Rinsho **56** (suppl spring): 97-103, 2008 (in Japanese).
44. Novoselsky C, Codish S, Manor E, Khait K, Sukenik S. DiGeorge syndrome presenting as hypocalcemia in an adult woman. IMAJ **6**: 562-563, 2004.
45. Evers LJM, Vermaak MP, Engelen JJM, Curfs LMG. The velocardiofacial syndrome in older age: dementia and autistic features. Genet Couns **17**: 333-340, 2006.
46. Trombetti A, Bottani A, George F, Rizzoli R. Hypoparathyroidism associated with aneurysm of the left subclavian artery (Kommerell's diverticulum) in an adult patient with chromosome 22q11.2 deletion. J Bone Miner Res **16**: 1926-1928, 2001.
47. King C. Undiagnosed DiGeorge syndrome presenting in middle age with an aortic root aneurysm and chronic dissection. BMJ Case Rep, in press.
48. Shoji T, Yamagami T, Nishizawa K, et al. 22q11.2 deficiency syndrome diagnosed with congestive heart failure. Nihon Naikagakkai Zasshi **97**: 2785-2787, 2008 (in Japanese).
49. Bilezikian JP, Kahn A, Potts JT Jr, et al. Hypoparathyroidism in the adult: epidemiology, diagnosis, pathophysiology, target organ involvement, treatment, and challenges for future research. J Bone Miner Res **26**: 2317-2337, 2011.
50. Clarke BL, Brown EM, Collins MT, et al. Epidemiology and diagnosis of hypoparathyroidism. J Clin Endocrinol Metab **101**: 2284-2299, 2016.
51. Cheung EN, George SR, Costain GA, et al. Prevalence of hypocalcemia and its associated features in 22q11.2 deletion syndrome. Clin Endocrinol (Oxf) **81**: 190-196, 2014.
52. Cooper MS. Diagnosis and management of hypocalcemia. BMJ **336**: 1298-1302, 2008.
53. Kapadia CR, Kim YE, McDonald-McGinn DM, et al. Parathyroid hormone reserve in 22q11.2 deletion syndrome. Genet Med **10**: 224-228, 2008.
54. Carrivick SJ, Walsh JP, Brown SJ, et al. Brief report: Does PTH increase with age, independent of 25-hydroxyvitamin D, phosphate, renal function, and ionized calcium. J Clin Endoclinol Metab **100**: 2131-2134, 2015.
55. Momma K, Matsuoka R, Takao A. Aortic arch anomalies associated with chromosome 22q11 deletion (CATCH 22). Pediatr Cardiol **20**: 97-102, 1999.
56. McElhinney DB, Clark BJ III, Weinberg PM, et al. Association of chromosome 22q11 deletion with isolated anomalies of aortic arch laterality and branching. JACC **37**: 2114-2115, 2001.
57. Drake RL, Wayne Vogl A, Mitchell ADM. Gray's anatomy for students. 3rd ed. Churchill Livingstone, Philadelphia, 2015: 211-222.
58. Shuford WH, Sybers RG, Milledge RD, Brinsfield D. The cervical aortic arch. Am J Roentgenol Radium Ther Nucl Med **116**: 519-527, 1972.
59. Shuford WH, Sybers RG, Edwards FK. The three type of right aortic arch. Am J Roentgenol Radium Ther Nucl Med **109**: 67-74, 1970.
60. van Son JA, Konstantinov IE, Burckhard F. Kommerell and Kommerell's diverticulum. Tex Heart Inst J **29**: 109-112, 2002.
61. Kommerell B. Verlagerung des Ösophagus durch eine abnorm verlaufende Ateria subclavia dextra (Atreria lusoria). Fortschr Geb

Roentgenstrahlen **54**: 590-595, 1936 (in German).

62. Cinà CS, Althani H, Pasenau J, et al. Kommerell's diverticulum and right-side aortic arch: A cohort study and review of the literature. J Vasc Surg **39**: 131-139, 2004.

63. Nagashima M, Shikata F, Okayama T, et al. Anomalous subaortic left brachiocephalic vein in surgical cases and literature review. Clin Anat **23**: 950-955, 2010.

64. Bassett AS, Chow EW, Husted J, et al. Premature death in adults with 22q11.2 deletion syndrome. J Med Genet **46**: 324-330, 2009.