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

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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

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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...
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 death 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 neurodevelopmental-
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 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.
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 required calcium or vitamin D supplementation to maintain normocalcemia. Serum PTH levels increase with age in healthy subjects, independent of the level of 25-hydroxyvitamin 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 (TOF), 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 22q11.2 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 middle 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, although echocardiography had been performed (46). Interestingly, these anomalies of the aortic arch were detected during CT performed six months after the diagnosis of 22q11.2 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.

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-hydroxyvitamin 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 (TOF), 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 22q11.2 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.

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### 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/ hyperparathyroidism, Age at diagnosis, y | Cardiac vascular anomalies/ Age at diagnosis, y | Psychiatric disorders/ Age at diagnosis, y | Neurodevelopmental disturbance | Dysmorphic face | Other features |
|----------|-----------|--------------|--------------------------------------------------------------------------------|------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|------------------|----------------|----------------|
| 1        | 15        | 21/F         | severe distress                                                                 | epilepsy, depression | ND                                           | ND                                           | schizophrenia/20                             | ID, LD             | ND              |                  |
| 2        | 20        | 21/M         | irritability, increased psychomotor activity, etc.                              | ND                | VSD/6                                         | -                                            | mania/16                                     | ID                | +               |                  |
| 3        | 21        | 22/F         | psychosis                                                                       | -                 | TOF/3.5                                       | 22                                           | psychosis/22                                 | ID, LD            | +               | CSP, CV          |
| 4        | 22        | 23/M         | confusion (hypocalcemia and psychosis)                                          | ND                | 23                                           | -                                            | -                                            | ID                |                  |                  |
| 5        | 23        | 24/F         | profound mental retardation and autism                                          | ND                | 24                                           | RAA/24                                       | -                                            | ID, autism         | +               | cleft palate     |
| 6        | 24        | 24/F         | delusion                                                                        | ND                | -                                            | 25                                           | -                                            | ID                | ND              |                  |
| 7        | 25        | 24/F         | seizure (hypocalcemia)                                                          | -                 | 24                                           | -                                            | -                                            | ID, ND            |                  |                  |
| 8        | 11        | 25/F         | seizure (hypocalcemia)                                                          | -                 | 25                                           | -                                            | -                                            | ID                | ND              |                  |
| 9        | 26        | 25/F         | seizure (hypocalcemia)                                                          | -                 | 26                                           | -                                            | -                                            | ID, ND            | +               | cleft palate     |
| 10       | 27        | 26/M         | carpopedal spasm (hypocalcemia)                                                | -                 | 27                                           | -                                            | -                                            | ID                | +               | conductive deafness |
| 11       | 28        | 27/F         | tetanic spasms (hypocalcemia)                                                  | -                 | 27                                           | ND                                           | -                                            | ND                |                  |                  |
| 12       | 29        | 29/F         | faint gas and muscle pain (hypocalcemia)                                       | -                 | 29                                           | ASD, RAA                                     | ND                                           | ND                |                  |                  |
| 13       | 30        | 29/F         | numbness of hands and feet (hypocalcemia)                                       | -                 | 27                                           | ND                                           | -                                            | LD, ND            |                  |                  |
| 14       | 31        | 29/F         | cognitive disorder                                                              | -                 | VSD                                          | ND                                           | -                                            | -                |                  |                  |
| 15       | 32        | 30/M         | operation for cataracts                                                         | idiopathic hypoparathyroidism | 16                                           | RAA/30                                       | ND                                           | ID                |                  |                  |
| 16       | 33        | 30/F         | syncope and seizures (hypocalcemia)                                             | ND                | TOF with PA/30                                | ND                                           | ND                                           | +                 |                  |                  |
| 17       | 34        | 31/F         | delirious/schizophrenia                                                         | -                 | 31                                           | TOF/6                                        | schizophrenia/31                             | ID                | +               | CSP, CV          |
| 18       | 35        | 31/F         | katatonic excitement                                                            | -                 | -                                            | -                                            | -                                            | -                |                  |                  |
| 19       | 36        | 32/M         | hallucination (schizophrenia)                                                  | -                 | 15                                           | -                                            | schizophrenia/32                             | ID                | +               | bila uv, CSP     |
| 20       | 37        | 32/M         | management of hypocalcemia                                                      | -                 | -                                            | -                                            | LD                                           | +               |                  |                  |
| 21       | 38        | 32/F         | malaise, etc. (FE and asymptomatic hypocalcemia)                               | persisting VSD    | 32                                           | VSD                                          | -                                            | ID, LD            | +               |                  |
| 22       | 39        | 32/F         | chest pain (hypocalcemia)                                                       | -                 | 32                                           | TOF                                         | -                                            | ID, LD            | +               | thrombocytopenia, reduced T-cells |
| 23       | 40        | 32/F         | seizure (hypocalcemia)                                                          | Hashimoto's thyroiditis | 32                                          | VSD/8 months                                 | -                                            | -                |                  |                  |
| 24       | 41        | 32/F         | dyspnea (sleep apnoea syndrome)                                                 | hypocalcemia, schlorophenia | 23                                          | -                                            | schlorophenia/30                             | ND                |                  |                  |
| 25       | 42        | 32/F         | cerebellar ataxia (cerebellar atrophy)                                          | neurodegenerative disorder | -                                             | ND                                           | -                                            | ID                |                  | cleft palate, bila uvula |
| 26       | 43        | 32/F         | consciousness disturbance (hypocalcemia)                                        | -                 | 36                                           | TOF/5                                        | -                                            | LD                |                  |                  |
| 27       | 44        | 32/F         | confusion, agitation, and tiredness (hypocalcemia)                             | -                 | 38                                           | TA with PHT                                   | psychotic                                    | ND                |                  | cleft palate     |
| 28       | 45        | 32/F         | seizure (hypocalcemia)                                                          | -                 | 39                                           | -                                            | anxiety disorder/31                          | ID, LD            | +               | nephroscleion     |
| 29       | 46        | 32/F         | seizure (hypocalcemia)                                                          | -                 | 40                                           | -                                            | -                                            | -                |                  |                  |
| 30       | 47        | 32/F         | seizure (hypocalcemia)                                                          | -                 | 42                                           | -                                            | -                                            | ID                |                  | cleft palate, restless polychondritis |
| 31       | 48        | 32/F         | seizure (hypocalcemia)                                                          | -                 | 43                                           | -                                            | -                                            | ID                |                  |                  |
| 32       | 49        | 32/F         | seizure (hypocalcemia)                                                          | -                 | 43                                           | VSD                                          | -                                            | +                |                  |                  |
| 33       | 50        | 32/F         | diabetes, etc. (asymptomatic hypocalcemia)                                     | -                 | 43                                           | -                                            | -                                            | +                |                  |                  |
| 34       | 51        | 32/F         | weakness and involuntary movement (hypocalcemia)                               | -                 | 47                                           | -                                            | -                                            | ID                |                  |                  |
| 35       | 52        | 32/F         | cervical lymphedema/ (asymptomatic hypocalcemia)                               | -                 | 47                                           | -                                            | -                                            | ID                |                  |                  |
| 36       | 53        | 32/F         | dementia and ataxic features                                                   | -                 | 52                                           | -                                            | -                                            | +                |                  |                  |
| 37       | 54        | 32/F         | widening of mediastinum (high-positioned RAA)                                  | -                 | 51                                           | RAA, ALSA, KD/54                             | -                                            | ID                |                  |                  |
| 38       | 55        | 32/F         | bronchitis, sinusitis (asymptomatic hypocalcemia)                              | -                 | 59                                           | RAA, ALSA, KD/59                             | -                                            | ID                |                  |                  |
| 39       | 56        | 32/F         | adolelting of the aorta (aortic root anomaly)                                  | HTN               | -                                             | RAA/9, ALSA/59                                | -                                            | ND                |                  |                  |
| 40       | 57        | 32/F         | dyspnea (heart failure due to hypocalcemia)                                    | -                 | 64                                           | -                                            | -                                            | ID                |                  |                  |
| 41       | 58        | 32/F         | angina, HTN                                                                     | -                 | 34                                           | -                                            | -                                            | ID, LD            | +               | 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, CS: cavo pulmonary venous connection, 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.
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-threatening 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).

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