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Clinical characteristics and immunological status of patients with 22q11.2 deletion syndrome in Northern Thailand

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Abstract

Background: 22q11.2 deletion syndrome is one of the most prevalent microdeletion syndromes in humans. The syndrome is characterized by extensive phenotypic variability.

Objective: to investigate the clinical characteristics, immunological features, and intellectual status of 22q11.2 deletion syndrome patients at Chiang Mai University Hospital, Thailand.

Method: Patients who had a confirmed diagnosis of 22q11.2 deletion syndrome by fluorescent in situ hybridization (FISH) were enrolled. Data collated and evaluated included that pertaining to history, physical examination, laboratory testing including T-cell, immunoglobulin, calcium, thyroid and parathyroid levels in the blood, cardiac and urological imaging, and intellectual status.

Results: We identified 34 patients diagnosed with 22q11.2 deletion syndrome; 18 (53%) were female. The median age of patients was 18.5 months (IQR; 1.5-35.8). Ninety-one percent of patients had characteristic facial features; 94% had a congenital heart defect with tetralogy of Fallot being the most frequent (72%); 88% had hypocalcemia, and 35% had genitourinary tract abnormalities. Recurrence of 22q11.2 deletion syndrome in the family was detected in 18% of cases. Twenty-eight patients (82%) were found to have a low number or percentage of T-cells. Five patients (15%) had low immunoglobulin levels. Intellectual disability (IQ/DQ scores < 70) were found in 20 out of 25 patients who were evaluated (80%), whereas the other five (20%) performed at a level of borderline intellectual function.

Conclusion: Tetralogy of Fallot, hypocalcemia, immunologic defect, and cognitive impairment were common in our 22q11.2 deletion syndrome study group. We recommend that all affected patients have a multi-system evaluation by a comprehensive care team.

Key words: 22q11 deletion syndrome, DiGeorge syndrome, congenital heart disease, T-cell defect, intellectual disability

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Introduction

22q11.2 deletion syndrome (22q11.2 DS) is the most common microdeletion syndrome in humans.[1] It occurs as a result of a set of losses in the long arm (q) of chromosome 22.[2] The syndrome has been previously described as DiGeorge syndrome, velocardiofacial syndrome, conotruncal anomaly face syndrome, Cayler syndrome, CHARGE association and in a subset with autosomal dominant Opitz G/BBB syndrome.[3,4] Fluorescence in situ Hybridization (FISH) is the most commonly used diagnostic test for this deletion.[2,5]

An estimated prevalence of 22q11.2 DS has been given as between 1 in 4,000 to 1 in 7,092 live births in two different studies.[1,6] Most cases (approximately 90%) resulted from de novo mutations, the remainder inherited the chromosome 22 with deletion at the q11.2 arm from one of their parents in an autosomal dominant pattern.[2,7,8] 22q11.2 DS patients have a high variability of clinical manifestations, and common features, including conotruncal congenital heart defect, immunodeficiency, characteristic facial features, palatal defects,

developmental and/or learning disabilities, hypocalcemia, hypoparathyroidism, and hypothyroidism. Other abnormalities may be associated but are less common. These include renal anomalies, hearing loss, growth retardation, psychiatric disorders, feeding and swallowing problems. The practical guidelines for managing patients with 22q11.2 DS propose strategies for the recognition, evaluation, surveillance, and management of the associated morbidities.[3,9] They recommend that all affected individuals have periodic comprehensive evaluations.[9] The data regarding the 22q11.2 DS patients in northern Thailand are limited. The objective of this study was to describe the clinical characteristics, immunological features, and intellectual status of patients who were diagnosed with 22q11.2 DS at Chiang Mai University (CMU) Hospital. It was aimed to help early identification and intervention of the disease, which is under recognized by physicians.

Materials and Methods

A hospital-based, cross-sectional study was performed at CMU Hospital. CMU Hospital is the largest teaching hospital in the northern part of Thailand with 1,400 beds. It serves as a tertiary care-referral medical center for more than 11 million inhabitants in the northern region. Electronic medical records from 2004–2018 were reviewed. Sixty patients with a 22q11.2 DS diagnosis, verified by FISH, were identified. Most of these cases were diagnosed by the Pediatric Cardiology Clinic. Out of these 60, 34 patients (57%) were enrolled onto the study, 24 patients were lost to follow-up and 2 were deceased due to cardiac problems.

The study was conducted from January 2017 to December 2018. The electronic medical records of patients' data were reviewed. The clinical history interview and physical examination had been performed, including growth and development, family history, facial malformation, congenital heart diseases, history of hypocalcemia, urological imaging, feeding difficulties, infection, and vaccination. Thymus abnormalities were diagnosed by reviewing the patient chest computer tomography (CT) and as noted by the surgeons during the cardiac surgery. All of these 34 participants were invited for further evaluation of their intellectual status and laboratory tests.

Genetic testing

A deletion of chromosome 22q11.2 was determined by FISH, using Vysys LSI TUPLE1 SpectrumOrange/LSI ARSA SpectrumGreen probes which hybridize to the band 22q11.2, loci D22s553, D22S609 and D22S942 (LSI DiGeorge/VCFS, TUPLE1-HIRA locus SpectrumOrange, Abbott®) and to the band 22q13 (LSI ASRA SpectrumGreen, Abbott®). In each FISH assay at least 20 metaphases were analyzed.

Intellectual Testing

Intellectual status was assessed and analyzed by a developmental-behavioral pediatrician and a licensed clinical psychologist. In this study, we have divided the patients into four categories based on age, four assessment tools being used for evaluation of intellectuel quotient (IQ). Bayley scales of infant and toddler development third edition (Bayley-III), Stanford-Binet Intelligence Scales, Wechsler Intelligence Scale for Children (WISC)-fourth edition, and Wechsler Adult Intelligence Scale (WAIS) -fourth edition were administered to children at birth-3 years, aged 3-7 years, 7-17 years, and > 17 years, respectively. The psychiatric diagnosis was also recorded. An IQ score less than 70 (2 S.D. below the mean) was recorded as within the intellectual disability range and an IQ score of between 70 and 84 was considered to have borderline intelligence (1 to 2 S.D. below the mean).[10]

Laboratory Testing

Laboratory test results evaluated included complete blood count (CBC), CD3+, CD4+ and CD8+ lymphocyte sub-populations, immunoglobulin levels (IgG, IgA, IgM, IgE), serum calcium and phosphate level, thyroid hormone measurements (thyroid-stimulating hormone (TSH) and free T4), and parathyroid hormone (PTH) level. The lymphopenia and low immunoglobulin levels were defined as low total lymphocyte and immunoglobulin levels after comparison with normal 95% confidence limits by age. Absolute counts and percentages of CD3+, CD4+ and CD8+ were low with the values below the 10th percentile by age.[11,12] Hypocalcemia (corrected by total calcium, based on the serum albumin level), hypophosphatemia, hypothyroid and hypoparathyroid were the values below the 10th percentile below the median by age.[13]

Statistical Analysis

The Statistical Package for the Social Science (SPSS), version 23.0 for windows was used for all statistical analysis. A descriptive analysis was used for characterization of the study population. Continuous variables and categorical variables were expressed as median, interquartile range (IQR) and percentage or ratio as appropriate.

Written informed consent was obtained from all parents and/or patients. Ethical approval for the study was obtained from the Research Ethics Committee at the Faculty of Medicine, Chiang Mai University (PED-2560-04587).

Results

The study included 34 patients with genetically confirmed 22q11 DS. Of these, 16 (47.0%) were male. The clinical characteristics are presented in **Table 1**. The median age of patients in this study was 51 months (IQR; 28.3-99.0). Most of the patients first presented with clinical symptoms during the newborn period. The median age at the time of diagnosis was 18.5 months (IQR; 1.5-35.8). The median duration from time of onset to time of diagnosis was 11.5 months (IQR; 1.0-28.3). The age at onset, age at diagnosis, and criteria for diagnosis varied considerably with regard to different types of major symptoms. Eighteen percent had confirmed familial occurrence of the deletion, two of these were siblings.

Table 1. History and Clinical Characteristics (n = 34)

Clinical Characteristics	n (%)
Gender: Male	16 (47.0)
Median Age (Months (IQR))	51 (28.3-99.0)
Median Age of Diagnosis (Months (IQR))	18.5 (1.5-35.8)

Table 1. (Continued)

Clinical Characteristics	n (%)
Median Age of Onset (Months (IQR))	0 (0-3)
Parental history of 22q11.2 DS	
Confirmed 22q11 Deletion	6 (17.6)
Facial Malformation	7 (20.6)
Facial dysmorphic features:	
Typical Facial Malformation	31 (91.2)
Cleft Lip	1 (2.9)
Cleft Palate	2 (5.9)
Cleft Lip and Palate	2 (5.9)
Hearing Test (n = 13): Abnormal	2 (15.4)
History of Cardiac Surgery	27 (79.4)
Urogenital Imaging (n = 17)	
Urinary Tract Malformations:	6 (35.3)
Renal Parenchymal Disease	3 (17.6)
Single Kidney	1 (5.9)
Medullary Nephrocalcinosis	1 (5.9)
Hypospadias	1 (5.9)
Presence of Thymus (n = 21)	
Normal	15 (71.4)
Absence or Ectopic	6 (28.6)
History of Recurrent Infection:	17 (50)
Recurrent Pneumonia	27 (79.4)
Acute Otitis Media	9 (26.5)
Chronic Otitis Media	6 (17.6)
Septicemia	3 (8.8)
History of Vaccine Adverse Reactions	1 (2.9)

A total of 31 patients (91.2%) had typical facial malformations. These included narrowing a palpebral fissure, hypertelorism, widened nasal dorsum, hypoplastic nasal alae, nasal voice, short philtrum, micrognathia, and malar flattening. One patient had cleft lip (2.9%) and two had cleft palate (5.9%). The both cleft lip and palate were only found in two patients (5.9%). Histories of feeding difficulties and reflux were reported in 17.6% and 26.5% of patients, respectively. Thirteen patients had data pertinent to a hearing examination and abnormal hearing was observed in two patients (15.4%). The levels were mild and moderate to severe hearing loss. Of the patients who had undergone urogenital tract imaging, malformations, specifically renal parenchymal disease, absent kidney, medullary nephrocalcinosis and hypospadias presented in six patients (35.2%). Congenital heart disease was the most common presenting symptom in these patients. The majority of these had been referred to CMU Hospital for cardiac evaluation and treatment. Two patients had been diagnosed prenatally. Interestingly, there was a single patient who first presented with hypocalcemic tetany at 12 years of age.

Congenital cardiovascular anomalies were confirmed in 32 patients (94%). The details of cardiovascular findings are in **Table 2**. Tetralogy of Fallot was the most common cardiac defect, found in 24 patients (72%), followed by ventricular septal defect (12%), interrupted aortic arch type B (6%), atrial septal defect (3%) and patent ductus arteriosus (3%). These primary anomalies were frequently associated with right sided aortic arch (45%), aberrant subclavian artery (30%) and major aortopulmonary collateral arteries (MAPCAs) (30%). One patient had vascular anomalies without heart abnormalities which was aberrant subclavian artery.

From review of the electronic medical records, 22 patients (64.7%) had a history of hypocalcemia and median age of resolution was 48 months (IQR; 31.3-70.5). Of six patients who had hypoparathyroid hormone levels (17.6%), all of them experienced hypocalcemia. Six patients (17.6%) had primary hypothyroidism and a single patient (2.9%) had primary hyperthyroidism.

Table 2. Cardiovascular Findings (n = 33)

Type of cardiovascular anomalies	n (%)	Associated lesions; n (%)						
		RAA	Double aortic arch	ASCA	Bilateral SVC	LSVC	MAPCAs	Subpulmonic VSD
Congenital heart disease#	32 (94)							
Tetralogy of Fallot and variants								
TOF/PS*	14 (42)	7 (21)	-	5 (15)	3 (9)	1 (3)	3 (9)	3 (9)
TOF/PA*	10 (30)	6 (18)	-	3 (9)	-	-	7 (21)	-
Interrupted aortic arch type B*	2 (6)	-	-	1 (3)	-	-	-	-
Ventricular septal defect*	4 (12)	1 (3)	1 (3)	1 (3)	-	-	-	-
Atrial septal defect*	1 (3)	-	-	-	-	-	-	-
Patent ductus arteriosus*	1 (3)	1 (3)	-	-	-	-	-	-

Table 2. (Continued)

Type of cardiovascular anomalies	n (%)	Associated lesions; n (%)						
		RAA	Double aortic arch	ASCA	Bilateral SVC	LSVC	MAPCAs	Subpulmonic VSD
Vascular anomalies								
Aberrant subclavian artery#	-	-	-	1 (3)	-	-	-	-
No congenital heart disease#	2(6)							

* Percentage among children with 22q11.2 deletion and cardiovascular findings (n = 33)
# Percentage among all children with 22q11.2 deletion (n = 34)
RAA = right sided aortic arch; ASCA = aberrant Subclavian artery; SVC = superior vena cava; LSVC = left superior vena cava; MAPCAs = major aorto-pulmonary collateral arteries; VSD = ventricular septal defect; TOF = tetralogy of Fallot; PS = pulmonary stenosis; PA = pulmonary atresia

Table 3. Immunologic and Laboratory Profiles (n = 34)

Parameters	n (%)
Abnormal Thyroid Function:	7 (20.5)
Hypothyroidism	6 (17.6)
Hyperthyroidism	1 (2.9)
Hypoparathyroidism	6 (17.6)
Hypocalcemia	
Current	8 (23.5)
Resolved	22 (64.7)
Median Age of Resolution (Months (IQR))	48 (31.3-70.5)
Immunologic Parameters:	
Low White Blood Cell Count	0 (0)
Low Absolute Lymphocyte Count	4 (11.8)
T Cell Defect	28 (82.4)
Low CD3	18 (52.9)
Low CD4	22 (64.7)
Low CD8	5 (14.7)
Low Immunoglobulin	5 (14.5)
Low IgG	1 (2.9)
Low IgM	5 (14.7)
Low IgA	2 (5.9)
Low IgE	1 (2.9)

All of our patients were evaluated for immunologic status. Low serum immunoglobulin levels were found in five patients (14.5%). One of these (2.9%) had panhypogammaglobulinemia, one had low a IgA and IgM level, and the other three patients had an isolated low IgM level. Lymphopenia, compared to normal value by age was observed in 11.8% of patients. According to lymphocyte-subset enumerations by flow-cytometry, 28 (82.4%) had T-cell defects. Low absolute counts or percentages of CD3+, CD4+ and CD8+ in this study were demonstrated in 18 (52.9%), 22 (64.7%), and five patients (14.7%), respectively. None of the patients required intravenous immunoglobulin replacement therapy. One of immunologic deficiency patients received oral antibiotic prophylaxis due to a very low T-cell count. No evidence of autoimmune disease was found. The immunologic and hormonal laboratory profiles are shown in **Table 3**. Evaluation of the thymus was possible in 21 patients by either CT scan or during a surgical procedure. Six out of 21 (17.6%) had a non-visualized or hypoplastic thymus.

Recurrent infections affected 17 patients (50%). Recurrent pneumonia, defined as more than two episodes in one year or more than three episodes of pneumonia during a lifetime was noted as the most common infection which was reported in 27 patients (79.4%). Other infections recorded were acute otitis media in nine patients (26.5%), chronic otitis media in six patients (17.6%) and septicemia in three patients (8.8%). The pathogenic organism which was isolated from one patient with septicemia was *Staphylococcus aureus*. All of the patients in this study had received the live attenuated vaccine BCG and the mumps-measles-rubella vaccine without any complications. A vaccine adverse event was reported in a patient who had febrile seizure following the diphtheria-tetanus-pertussis vaccine. This reaction was considered to be unrelated to the immune status. There was no statistical association between immunologic profiles and the history of recurrent infection or vaccine adverse reactions observed (data not shown).

Twenty-five patients (74%) were included in the formal intellectual analyses (**Table 4**). Median age at evaluation was 57 months (IQR; 36.0-129.8). The median full scale IQ (FSIQ) of all evaluated patients was 58 months and ranged from 51 to 62. Patients age under three years were evaluated using Bayley-III and patients aged 3-7 years were evaluated using the Stanford-Binet Intelligence scales; these had a median FSIQ of 75.0 (IQR; 63.8-78.8) and 56.0 (IQR; 51.5-61.5) respectively. Patients aged 7-17 years were evaluated with WISC-IV and the median FSIQ was 57.5, ranging from 55.0 to 58.0. Their mean verbal IQ (VIQ) was 51.5 (IQR; 49.3-56.0). Patients older than 17 years tested with WAIS-IV had a median FSIQ of 48.5 with a range of 48.0-49.5, and a VIQ median of 52 (IQR; 52.0-52.5). Out of 25 patients, 20 (80%) were considered to have intellectual disability according to previous mentioned definitions, another five (20%) were considered to have borderline intelligence (FSIQ 70-84). From analysis of factors which might affect the IQ score, there was no statistical difference between the group with the presence of a major

Table 4. Intellectual Status (n = 25)

Intellectual Status	n (%)
Median Age of Evaluation (Months (IQR))	57 (36-129.8)
Median Full-Scale IQ/DQ Level (IQR)	58 (51-62)
-1 to -2 S.D.	5 (20)
Less than -2 S.D.	20 (80)

cardiovascular diseases and the group who had minor cardiovascular diseases. The median FSIQ score was 57.5 (IQR; 51.0-65.3) and 58.0 (IQR; 49.0-60.0), respectively. One patient was diagnosed with psychosis at age 21 years.

Discussion

This report shows the clinical features of patients with 22q11.2 DS in Northern Thailand. There was no gender preference. Although, individuals in this population first presented with their symptoms during the newborn period, the age of genetic diagnosis was delayed until the median age of 18 months. The majority were referred to CMU Hospital because of congenital heart disease problems. Tetralogy of Fallot was the most common cardiac finding. Thirty patients (88%) had hypocalcemia. Of the patients who underwent after intellectual evaluation, all had developmental delay or intellectual impairment. The findings confirm that 22q11.2 DS involves multiple systems, and has a wide phenotypic spectrum.

The 22q11.2 DS is a haplosufficiency disorder, the chance of an affected parent having an affected offspring is approximately 50%.[7] However, the majority of cases of 22q11.2 DS are spontaneous or de novo mutations. Peer review shows that only 10% is inherited from affected parents,[1-3] in line with our finding that 18% had a history of parents with confirmed chromosomal deletions. However, the actual proportions of inherited chromosomal deletions may be higher than the report because 22q11.2 deletions were not evaluated in all of participants' families. The use of the FISH technique using a probe for the 22q11.2 chromosome region is considered to be the gold standard for detecting this microdeletion.[5,14] It is the most widespread method and allows the detection of the proximal and common deletion in > 90% of 22q11.2 DS patients.[5,15] Nevertheless, a negative FISH result does not exclude 22q11.2 DS, since minor or atypical deletions may occur. Currently, a chromosomal microarray is useful in FISH-negative, clinically suspected patients.[1,5] Several genes have been considered as being the major contributors of the 22q11.2 DS phenotype. These include *TBX1*, *HIRA*, *UFD1L*, and *CRKL* which are associated with cardiac and palatal abnormalities.[15] Due to the use of the FISH technique, we were unable to identify the specific genes and patients with an atypical deletion may have been missed.

A previous study established that conotruncal heart defects such as truncus arteriosus, tetralogy of Fallot, and interrupted aortic arch are the most typical cardiac malformations associated with 22q11 DS.[16] Because CMU Hospital is the referral tertiary care hospital for congenital complex heart disease surgery in Northern Thailand, the prevalence of conotruncal heart defects in our patients was higher than previous reports.[3,14,16,17] The proportion of tetralogy of Fallot in conotruncal heart defects in this study was 72%, which was higher than previous reports from North-eastern Thailand (56%) and Korea (63%),[14,18] and much higher than the report from Western countries which reported the percentage of tetralogy of Fallot cases as being between 13 and 43%.[16,19] It does however suggest that tetralogy of Fallot could be more common in Asian than Caucasian patients with 22q11.2 DS.[14]

The clinical features associated with 22q11.2 DS are very broad, and the causal heterogeneity also leads to confusion.[3,19] Hypocalcemia caused by hypoparathyroidism is one of the common presentations. It may arise at any age, especially after puberty.[9] Eighty-eight percent of patients in this study experienced a lifetime history of hypocalcemia which is comparable to a large study of adults,[20] but higher than most of the previous reports.[3,9] Seven percent showed abnormal serum thyroid hormone. Hypo- and hyperthyroidism was seen in previous studies.[3,9] The mechanisms involved are not entirely clear and it is unknown whether they caused by either autoimmune or developmental mechanisms.[1]

Immunodeficiency results from dysmorphogenesis of the third and fourth pharyngeal pouches during early embryogenesis, leading to hypoplasia or aplasia of the thymus and parathyroid glands, which are responsible for making T cell lymphocytes. The lymphopenia is related to a quantitative decrease in functional thymic mass. The spectrum of immune defects is broad but most often includes decreased CD3+, CD4+ and CD8+ T lymphocytes, and mildly impaired cellular immunity.[21-23] There were conflicting results of the correlation between immune status and phenotypic characteristics.[1,3,9] Suksawat et al. showed that the patients with hypocalcemia had increased odds ratio of CD4 lymphopenia.[17] We did not find such correlation between immune status and heart disease, palate anomalies, hormonal function test, or hypocalcemia. In this study, all our patients with thymus abnormalities had low absolute counts or percentages of T cells. Twelve percent of our patients had a low absolute lymphocyte count and 82% had low absolute counts or percentages of T cell number, which was higher than a previous report concerning Thai patients that 61% had decreased CD4+ T cells and 52% and 45% had low CD3+ T cells and CD8+ T cells.[17] These findings suggest that patients with a normal absolute lymphocyte count may have a low T cell count, thus immunologic evaluation with lymphocyte sub-population enumeration by flow-cytometry should be performed in all cases.[1,3] In cases of 22q11.2 DS, B cell function and immunoglobulin levels are usually normal, but in 50% of patients these can be low in the first year of life as result of abnormal thymic migration. Transient diminished IgG level, selective IgM deficiency, or selective IgA deficiency have been reported.[21,22] B-cell defects can be found in as high an incidence as 42% of cases in one study.[24] However only 15% of our patients had a low immunoglobulin level which agrees with a previous report from Bangkok by Suksawat et al. who reported 14% of patients with 22q11.2 DS had abnormal immunoglobulin levels, with improvement shown at 1.4 years of age.[17] In addition, selective IgA deficiency, which is the common B-cell defect cited in the other reports have not been observed in our population.[24] The immune defects improve with age, and most of the patients have normal numbers

of functional T lymphocytes when older.[9,17,25] However, an unpredictable clinical course, and the T-cell numbers may not be predictive of infection.[9,26] Fewer than one percent of 22q11.2 DS having severe T-cell deficiency with severe combined immunodeficiency disease (SCID) as a result of complete thymic aplasia, a condition requiring bone marrow or thymic tissue transplantation.[21] These are the reasons why early diagnosis is important to ensure the provision of proper management and improve outcomes. From previous studies, one of the common presentations is recurrent infection, the majority being sinopulmonary including recurrent pneumonia and otitis media, others were gastrointestinal tract and skin infection.[3] We did not find any severe immunodeficiency in our 22q11.2 DS population, most of them only experiencing relatively trivial infections. Only one patient had a history of severe septicemia.

Live vaccines do not pose a risk to most patients with 22q11.2 DS, but they should not be administered in patients with severe immunodeficiency.[1,3] No adverse reactions due to live vaccine were documented in our population because they did not have severely depleted T-cell numbers (the lowest CD3, CD4, and CD8 lymphocyte numbers were 545, 350, and 292 /cu.mm., respectively). The low incidence of severe immunodeficiency and severe infection may be due to lack of recognition and under-diagnosis in patients who arrived with a severe life-threatening condition and died without genetic investigation.

Cognitive impairment, learning disorders, intellectual disabilities, speech and language deficits, behavior, mood and psychiatric disorders have been reported as being prevalent in cases of 22q11.2 DS.[1,3,9] Previous reports have shown that 22q11 DS have intellectual abilities ranging from borderline intelligence to mild learning disability.[25,27] The results from this study showed a replication of lowered FSIQ as seen in previous studies.[27,28] Also, categories showed a discrepancy between VIQ and FSIQ, but in the 7-17 year-old group the FSIQ favored the verbal IQ, which was opposite in the > 17 years-old group in which the verbal IQ was a higher score than in the FSIQ. There was no statistical association between cardiovascular disease and intellectual status in our patients. The median FSIQ of patients > 17 years-old group was lower than the younger age group which could reflect under-diagnosis and previous inappropriate intervention. These results were limited by small sample sizes. All our patients had a history of globally delayed development reflected in 80% of intellectual disability (FSIQ < 70) so lack of early intervention could be implied. Congenital heart disease is also known to affect cognitive performance and neurological development. However, there was no statistical difference in intellectual status between the groups where there was major cardiovascular disease and the group who had minor cardiovascular disease. A psychotic problem was reported in one of our adult patients but this would not be statistically relevant despite psychiatric issues being increasingly highlighted as the experience with adult increases.[9] Approximately 25% of adults with 22q11.2 DS have schizophrenia.[29,30]

As this study was cross-sectional in design, there were major limitations due to no longitudinally followed data of immunologic, hormonal, and intellectual evaluation of patients. Throughout the lifespan of the 22q11.2 DS, new syndrome related conditions may present, immunologic and hormonal conditions are improving with age, and psychological problems may start later in adult life.[3,9] There is a selection bias because only the patients with a suspected clinical phenotype were evaluated by FISH and most of the patients were selected from a pediatric cardiology clinic. Hence, the identification of the true prevalence of 22q11.2 DS and the clinical difference between 22q11.2 deletion detected and undetected patients are not able to be statistically substantiated. Further prospective longitudinal studies in more diverse communities are required for more accurate data on 22q11.2 DS patients in our region.

In conclusion, we demonstrated a wide range of clinical phenotypes of 22q11 DS patients in Northern Thailand. In all individuals with suspected associated symptoms of cardiac defects, abnormal face, thymic hypoplasia, cleft palate, or hypocalcemia, genetic tests for 22q11 deletion syndrome should be held without delay in order to confirm the diagnosis and to facilitate genetic counseling. Early diagnosis and intervention are critical to the minimizing morbidity and improving the quality of life. In the context of the multi-system nature of 22q11.2 DS, we recommend that all affected individuals be evaluated periodically by a comprehensive multidisciplinary care team.

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