Microdeletion of 22q11 (CATCH 22) in children with conotruncal heart defect and extracardiac malformations

Mehmet Alikaşifoğlu, Neslihan Malkoç, Naci Ceviz, Şencan Özme, Şebnem Uludoğan Ergül Tunçbilek

Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey

SUMMARY: Alikaşifoğlu M, Malkoç N, Ceviz N, Özme Ş, Uludoğan Ş, Tunçbilek E. Microdeletion of 22q11 (CATCH 22) in children with conotruncal heart defects and extracardiac malformations. Turk J Pediatr 2000; 42: 215-218.

CATCH 22 is a medical acronym for cardiac defects, abnormal facies, thymic hypoplasia, cleft palate, and hypocalcemia, and a variable deletion on chromosome 22q11. The deletion within the chromosome region of 22q11 may occur in patients with dysmorphologic and cardiological syndromes: DiGeorge syndrome (DGS), velocardiofacial syndrome (VCFS), and conotruncal anomaly face syndrome (CAFS). In this study, using N25 (D22S75) DiGeorge chromosome region probe. fluorescence in situ hybridization (FISH) analyses were performed on 32 patients with congenital heart diseases. Twenty-nine of 32 patients had conotruncal heart disease. A 22q11 deletion was detected in two patients (6.9%) of the 29 patients with conotruncal heart disease. One of our 22qdel (+) patients had unilateral facial nerve palsy. Although it is not a frequent finding, unilateral facial nerve palsy will be included among the symptoms of CATCH 22 syndrome. After careful clinical evaluation of patients with conotruncal cardiac anomalies, only syndromic cases should be screened for this deletion.

Key words: CATCH22 cardiac defects, abnormal facies, thymic hypoplasia.

Despite recent advances in the diagnosis and treatment of children with congenital heart disease, we do not have enough knowledge on the etiology of these defects. One of the most dramatic relationships between genetic and congenital cardiac lesions is the finding of monosomy of a locus on chromosome 22 in patients with aortic arch and conotruncal cardiac defects. Chromosome 22q11 deletions have been demonstrated in patients with a spectrum of cardiac malformations, from severe lesions such as truncus arteriosus and interruption of the aortic arch, to the mildest form of conotruncal defects such as isolated subarterial ventricular septal defect.

Hemizygosity for the human chromosome region 22q11 is associated with a wide range of overlapping phenotypes including DiGeorge syndrome, velocardiofacial (Sprintzen) syndrome and conotruncal anomaly face syndrome (CAFS). The acronym CATCH22 (cardiac anomaly, abnormal facies, thymic hypoplasia, cleft palate, hypocalcemia) has been suggested to decribe the broad clinical spectrum of phenotypes with 22q11 deletions[1-3]. The aim of this study was to estimate the frequency of microdeletion of 22q11 in children with conotruncal heart defects and extracardiac malformations.

Material and Methods

This prospective study was based on 32 patients with cardiac defects who were investigated by the Pediatric Cardiology and Clinical Genetics Units of İhsan Doğramacı Children's Hospital of Hacettepe University Faculty of Medicine. Twenty-nine of the patients had conotruncal heart anomalies. In addition, two patients with tricuspid insufficiency and one patient with atrial septal defect were included in the study because of similarities of extracardiac anomalies.

All patients were evaluated by echocardiography or cardiac catheterization in respect to cardiological problems. A clinical geneticist obtained family history and evaluated dysmorphic features of the patients.

Chromosome preparations were obtained from peripheral blood of each patient and analyses were performed by conventional G banding and fluorescence in situ hybridization (FISH). Two Oncor N25 (D22539) chromosome 22 control probes, both labelled with dioxigen, were used for FISH analysis. Slides were denatured in 70 percent formamide/2xSSC at 70°C for 2 min, dehydrated by passing them for 3 min each into 70, 90, and 100 percent ethanol and air dried. Ten microliters of the combined probe were hybridized in situ to denatured chromosome preparations at 37°C overnight. After post hybridization washing at room temperature, the hybridizing probe was viewed using a detection kit (Oncor). The chromosomes were observed using Nikon E800 fluorescent microscope and Cytovision (ver. 2.1. Applied Imaging).

The serum calcium concentration was investigated in all patients and immunologic studies were performed in one of the FISH-positive patients.

Results

A total of 32 patients were studied. Of these, 15 (46.9%) were female and 17 (53.1%) were male. The youngest patient was 16 days old and oldest was 15 years of age.

Conotruncal cardiac anomalies were as follows: tetralogy of Fallot (19 cases; 65.5%), truncus arteriosus (3 cases; 10.4%), supracristal ventricular septal defect (2 cases; 6.9%), transposition of great arteries (2 cases; 6.9%), pulmonary atresia (2 cases; 6.9%) and vascular ring (1 case, 3.4%).

Tricuspid insufficiency in two patients and atrial septal defect in one were found as cardiac anomalies in an additional three patients.

The most common extracardiac features were prominent nose, squared nasal root, short stature, long slender fingers, micrognathia, mild mental retardation, microcephaly, malar hypoplasia, almond shaped palpebral fissure, minor auricular anomalies, and thin upper lip.

The less frequently observed findings were hypertelorism, undescended testes, cleft palate, retrognathia, and scoliosis.

Serum calcium concentrations were normal in all patients. All karyotypes were normal at the level of 400-600 band (ICSN) using G banding.

Two patients had a segmental monosomy 22q11 that could be detected by FISH analysis (6.3%). One was a 15-month-old girl with tetralogy of Fallot, patent foramen ovale and peripheral pulmonary hypoplasia. Dysmorphic features of this girl were unilateral facial nerve palsy at right side, prominent nose, squared nasal root, almond-shaped palpebral fissure, minor auricular abnormality, hypertelorism, long slender fingers, short stature and hypotonia (Fig. 1). Immunological studies of this patient were evaluated as normal.

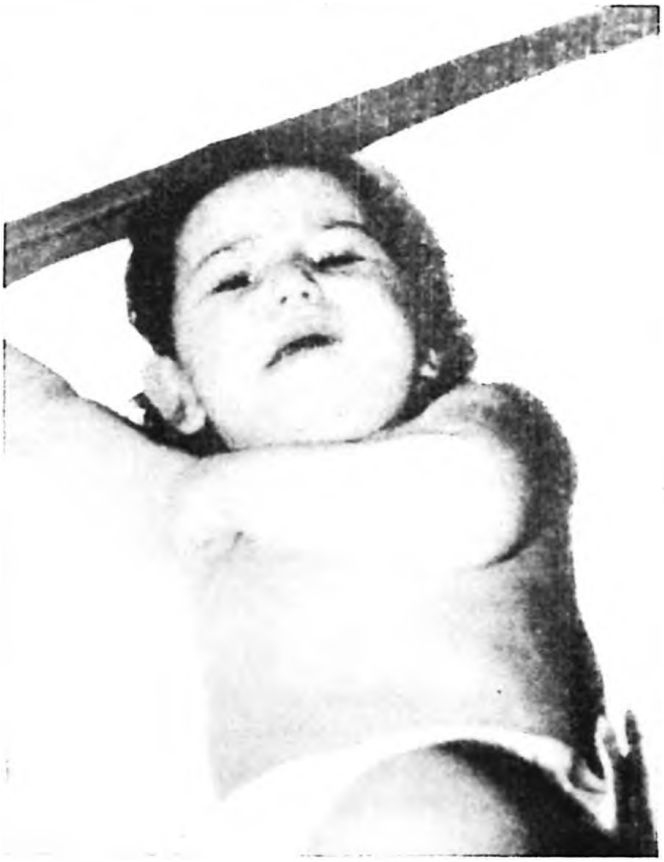

Fig. 1. One patient with segmental monosomy 22q11. Please note unilateral facial nerve palsy.

The second patient was a one-year-old boy with supracristal ventricular septal defect and pulmonary stenosis. Clinical findings of this child showed micrognathia, short neck, camptodactyly of the 5th finger of right hand and the 2nd, 3rd and 4th finger of the left hand, and hypotonia. Immunological investigations were not performed in this patient.

Serum calcium levels of both patients were within normal limits (9.2 and 9.8 mg/dl).

Discussion

Most previous studies revealed a high incidence rate of deletions in 22q11 among patients with

congenital heart defects. It is estimated that deletion of 22q11 may be involved in five percent of all newborns with heart defects, and that it is the single most important cause of heart malformation after Down syndrome[1]. But recent studies have shown that the incidence of deletion in 22q11 is lower than suspected by former investigators. Possibly, the observed frequency of deletions depends on the selection criteria.

We found the frequency of del 22q11 among 32 patients with cardiac defects and dysmorphic features as 6.3 percent. However, if only patients with conotruncal heart defects were evaluated, the incidence would be 6.9 percent.

Different researchers reported different frequencies of 22q del among different conotruncal heart defects and aortic arch anomalies:

Although the number of cases was not enough, the highest incidence of deletion (75%) was found in absent pulmonary valve syndrome by Johnson et al.[5] Interruption of the aortic arch type B (50%) and truncus arteriouss (33%) were also associated with a high frequency of del 22q11[6,7].

One of the highest figures belongs to Goldmuntz et al.[4] They studied 17 non-syndromic patients with one of the three most common conotruncal defects: truncus arteriosus, interruption of the aortic arch and tetralogy of Fallot. Out of these 17 patients, a 22q deletion was found in five (29%). They wrote that the 22q11 deletion-positive patients were mildly dysmorphic but did not have characteristics of a specific syndrome.

Webber et al.[15] stated that 22q11 deletions are important causes of selected malformations of the ventricular outflow tracts and aortic arch, and that they account for about 15-20 percent of cases.

Digilio et al.[8] evaluated 315 children with conotruncal heart defects and 22qdel was found in 11 percent of the patients. All the patients except one presented with one or more extracardiac anomalies, and were therefore considered as syndromic. The authors point out that five patients diagnosed as isolated in the beginning were subsequently included in the group of syndromic cases because of the presence of subtle facial dysmorphism which was previously overlooked.

Takahaski et al.[9] found a submicroscopic deletion in chromosome 22q11 in five out of 64 patients (7.8%) with a conotruncal heart disease.

Devriend et al.'s analysis of 150 patients with conotruncal anomalies found the incidence of del 22q11 to be 12.8 percent. They did not include patients with transposition of great arteries (TGA) in their group, since this is an uncommon heart defect in del 22q11[10].

It is clear from the above-mentioned studies that there are great variations in the reported incidence of CATCH 22 syndrome, even in study groups consisting only syndromic conotruncal heart anomalies, but a major limitation of many studies is the small sample size. These observations suggest the need for establishing the incidence of 22q11 deletions for individual anatomic diagnosis instead of for generic groups such as conotruncal anomalies.

General opinion is that facial appearance involves subtle changes and can easily be misinterpreted in young children. These dysmorphisms may barely be recognizable; a precise phenotypical evaluation is essential to distinguish syndromic from isolated conotruncal anomalies[8,9,13,14]. Different studies showed that non-syndromic conotruncal cardiac anomaly patients are not likely to have a 22q11 deletion[13,8,9,10]. Therefore, it is advisable that children with conotruncal cardiac anomalies should be carefully examined to detect dysmorphic features of DiGeorge, velocardiofacial and conotruncal anomaly face syndromes. After careful clinical evaluation, only syndromic cases should be screened for this deletion.

One of our 22qdel (+) patients had unilateral facial nerve palsy. Unilateral facial nerve palsy was described in a patient with CATCH 22 syndrome without cardiac anomaly, thymic hypoplasia cleft palate or hypocalcemia[12]. Tho the best of our knowledge, our patient is the first case showing unilateral facial nerve palsy in syndromic conotruncal heart anomaly. These observations suggest that although it is not a frequent finding, unilateral facial nerve palsy should be included among the symptoms of CATCH 22 syndrome.

REFERENCES

1. Glover TW. CATCHing a break on 22. Nat Genet 1995; 10: 257-258.
2. Thomas JA, Graham JM. Chromosome 22q11 deletion syndrome: an update and review for the primary pediatrician. Clin Pediatr 1997; 36: 253-266.
3. Wulfsberg EA, Leana-Cox J, Neri G. What's in a name? Chromosome 22q abnormalities and DiGeorge, velocardiofacial and conotruncal anomalies face syndromes. Am J Med Genet 1996; 65: 317-319.

4. Goldmuntz E, Driscoll D, Budarf ML, et al. Microdeletions of chromosomal region 22q11 in patients with congenital conotruncal cardiac defects. J Med Genet 1993; 30: 807-812.
5. Johnson MC, Strauss AW, Dowton B. Deletion within chromosome 22 is common in patients with absent pulmonary valve syndrome. Am J Cardiol 1995; 76: 66-69.
6. Lewin MB, Lindsay EA, Jurecic V. A genetic etiology for interruption of the aortic arch type B. Am J Cardiol 1997; 79: 388-390.
7. Momma K,Ando M, Matsuoka R. Truncus arteriosus communis associated with chromosome 22q11 deletion. J Am Coll Cardiol 1997; 30: 1067-1071.
8. Digilio MC, Marino B, Giannotti A, Dallapiccola B. Chromosome 22q11 microdeletion and isolated conotruncal heart defects. Arch Dis Child 1997; 76: 79-81.
9. Takahaski K, Kido S, Hoshinod K, Ogawa K, Ohask iH, Fukushima Y. Frequency of a 22q11 deletion in patients with conotruncal cardiac malformations: a prospective study. Eur J Pediatr 1995; 154: 878-881.
10. Devriendt K, Eyskens B, Fryns JP. The incidence of a deletion in chromosome 22q11 in sporadic and familial conotruncal heart disease. Eur J Pediatr 1996; 155: 721.
11. Lipson A, Emanual B, Colley P, Fagan K, Driscoll DA. "CATCH 22" sans cardiac anomaly, thymic hypoplasia, cleft palate, and hypocalcemia: CATCH 22. A common result of 22q11 deficiency? J Med Genet 1994; 31: 741.
12. Ehara H, Hara T, Takeshita K. CATCH 22: a possible cause of congenital unilateral facial nerve palsy. Eur J Pediatr 1997; 156: 739.
13. Von Beust G,Bartmus D, Bartels I. CATCH 22-microdeletion 22q11 screening in patients with congenital heart defects. Genetic Counseling 1998; 9: 223-227.
14. Johnson M, Watsonn MS, Strauss AW. Chromosome 22q11 monosomy and the genetic basis of congenital heart disease. J Pediatr 1996; 129: 1-3.
15. Webber SA, Hatchwell E, Barber JC, et al. Importance of 22q11 as a cause of selected malformations of the ventricular outflow tracts and aortic arch: a three-year prospective study. J Pediatr 1996; 129: 26-32.