The fate of children with microdeletion 22q11.2 syndrome and congenital heart defect: clinical course and cardiac outcome

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Abstract: BACKGROUND: This study aimed to evaluate the cardiac outcome for children with microdeletion 22q11.2 and congenital heart defect (CHD). METHODS: A total of 49 consecutive children with 22q11.2 and CHD were retrospectively identified. The CHD consisted of tetralogy of Fallot and variances (n = 22), interrupted aortic arch (n = 10), ventricular septal defect (n = 8), truncus arteriosus (n = 6), and double aortic arch (n = 1). Extracardiac anomalies were present in 46 of 47 children. RESULTS: The median follow-up time was 8.5 years (range, 3 months to 23.5 years). Cardiac surgical repair was performed for 35 children, whereas 5 had palliative surgery, and 9 never underwent cardiac surgery. The median age at repair was 7.5 months (range, 2 days to 5 years). The mean hospital stay was 35 days (range, 7-204 days), and the intensive care unit stay was 15 days (range, 3-194 days). Significant postoperative complications occurred for 26 children (74%), and surgery for extracardiac malformations was required for 21 patients (43%). The overall mortality rate was 22% (11/49), with 1-year survival for 86% and 5-year survival for 80% of the patients. A total of 27 cardiac reinterventions were performed for 16 patients (46%) including 15 reoperations and 12 interventional catheterizations. Residual cardiac findings were present in 25 patients (71%) at the end of the follow-up period. CONCLUSIONS: Children with microdeletion 22q11.2 and CHD are at high risk for mortality and morbidity, as determined by both the severity of the cardiac lesions and the extracardiac anomalies associated with the microdeletion.

DOI: https://doi.org/10.1007/s00246-007-9074-2

Pediatr Cardiol (2008) 29:76–83
DOI 10.1007/s00246-007-9074-2

ORIGINAL ARTICLE

The Fate of Children with Microdeletion 22q11.2 Syndrome and Congenital Heart Defect: Clinical Course and Cardiac Outcome

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Received: 22 January 2007 / Accepted: 3 July 2007 / Published online: 29 September 2007

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Keywords Congenital heart disease · Conotruncal malformations · Genetics · Outcome

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Deletions within chromosome band 22q11.2 are the most common cause of DiGeorge syndrome (OMIM #188400), velocardiofacial syndrome (OMIM #192430), and conotruncal anomaly face syndrome (OMIM #217095) [11, 20]. Microdeletion 22q11.2 is estimated to occur in 10 to 23 per 100,000 live births, mostly as a *de novo* deletion [16, 25]. When the condition is familial, the inheritance pattern is autosomal dominant [26]. The clinical spectrum of the microdeletion 22q11.2 syndrome is wide, ranging from subtle isolated findings to severe multiorgan involvement [4]. Congenital heart disease (CHD) is a major feature of this syndrome, as well as velopharyngeal anomalies, facial dysmorphisms, and learning disabilities [4, 26]. The most common cardiac lesions observed are conotruncal malformations, consisting of tetralogy of Fallot and its variances, interrupted aortic arch type B, and truncus arteriosus communis [13, 14].

The prevalence of 22q11.2 deletions in conotruncal defects and the overall clinical features of this syndrome have been extensively investigated [13, 14, 16, 26].

However, information about long-term follow-up evaluation and outcome of these patients is scarce.

Our study aimed to assess the clinical course and outcome for children with deletion 22q11.2 and CHD, with an emphasis on cardiac outcome.

Materials and Methods

This retrospective cohort study investigated all children with CHD and microdeletion 22q11.2 who received their diagnosis and treatment at our hospital during the past 25 years. The computer database for the division of cardiology and medical genetics was used to identify all patients with microdeletion 22q11.2 and CHD. The clinical records for each patient were analyzed for diagnosis, treatment, clinical course, and outcome, with special attention paid to cardiac findings as well as related diagnostic and therapeutic interventions. Cardiac diagnosis was achieved primarily by echocardiography using generally accepted standard views. A diagnostic cardiac catheterization was performed if echocardiographic information was not complete.

Residual cardiac lesions were defined as significant if the cardiologist performing echocardiography described the lesion as being at least moderate. Lesions described as trivial or mild were not considered relevant.

Genetic Screening

Patients with conotruncal malformations or other CHD associated with typical facial dysmorphisms or extracardiac abnormalities were selected originally for screening of chromosomal anomalies and microdeletion 22q11.2. Thus, genetic testing was indicated on the basis of the CHD for 41 patients and on the basis of extracardial anomalies for 8 patients. These anomalies consisted of facial dysmorphism and rhinolaryngologic findings in five patients, immunodeficiency with recurrent infections in two patients, and hypoparathyroidism in one child.

Fluorescence *in situ* hybridization (FISH) analysis, available in our institution since 1994, was performed using the standard technique previously described [13]. For 18 patients born before 1994, the presence of microdeletion 22q11.2 was suspected and confirmed during follow-up evaluation.

Statistical Analysis

Quantitative data are expressed as mean ± standard deviation or as median and range as appropriate. The data of four children who had a delayed referral for cardiac evaluation and therefore a delayed cardiac diagnosis were not included in the demographic statistics. This study was approved by the Ethics Board of our institution.

Results

Clinical Findings and Genetics

Between July 1978 and June 2003, 49 children with microdeletion 22q11.2 and CHD were identified retrospectively. The median age at cardiac diagnosis was 3 days (range, 0–94 days), and the median weight was 2.9 kg (range, 1.3–4.8 kg). The gender distribution was equal (49% males).

Congenital Heart Disease. The Cardiac Diagnoses are Shown in Table 1.

Aortic arch anomalies were present in 24 patients, including 12 right aortic arches and/or 15 aberrant subclavian arteries. These anomalies represented the most frequent additional cardiac findings.

Ventricular septal defect was associated with additional cardiac lesions in seven of eight patients. These lesions consisted of a right aortic arch in three patients and an atrial septal defect in four patients.

For complete cardiac diagnosis, cardiac catheterization was required in addition to echocardiography for 25 (51%) of the 49 patients. A prenatal cardiac diagnosis was achieved for three fetuses.

Cytogenetics

Parental genetic screening with FISH analysis was performed in 35 (71%) of the 49 cases, demonstrating the presence of a parental deletion in two cases. Thus, a *de novo* deletion 22q11 was found in 33 (94%) of 35 cases.

Extracardiac Anomalies

Extracardiac anomalies, described in all but one patient (Table 2), ranged from isolated craniofacial dysmorphisms to lethal multiple malformations**.** In 13 cases (26%), extracardiac anomalies required invasive diagnostic examinations, including laryngotracheobronchoscopy for 12 children and esophagogastroduodenoscopy for 2 children. Six patients underwent more than one investigation.

Table 1 Diagnosis and surgical repair of congenital heart defect (CHD)[a]

Diagnosis CHD	*n* = 49 *n* (%)
Tetralogy of Fallot	22 (45)
TOF/RVOT obstruction	10
PA/VSD, Fallot type	4
PA/VSD, MAPCAs	7
Absent PV syndrome	1
Interrupted aortic arch type B	10 (20)
Ventricular septal defect	8 (16)
Truncus arteriosus communis	6 (12)
Double outlet right ventricle	2 (4)
Double aortic arch	1 (2)
Surgical repair of CHD	***n* = 35**
Age at total repair: months (range)	7.5 (2 d to 5 y)
Weight: kg (range)	6.6 (2.7–16.5)
Hospitalisation: days (range)	35 (7 d to 7 mo)
ICU stay: days (range)	15 (3 d to 6.5 mo)
Complications of cardiac surgery: *n* (%)	26 (74)

TOF, tetralogy of Fallot; RVOT, right ventricular outflow tract; PA, pulmonary atresia; VSD, ventricular septal defect MAPCAs, major aortopulmonary collaterals; PV, pulmonary valve; ICU, intensive care unit

[a] Continuous data are given as median (range)

Clinical Management

Cardiac surgery was performed for 40 of the 49 patients. The management algorithm is shown in Fig. 1. Repair of CHD was achieved for 35 patients, including 10 repairs after previous surgical palliation. Palliation comprised insertion of a Blalock-Taussig shunt in five children, an aortopulmonary shunt with unifocalization of the pulmonary arteries in three children, and pulmonary artery banding in two children. Repair could not be performed for five palliated patients due to the premature death of three children and anatomic vascular findings precluding repair for two children. In these cases, palliation consisted of a central aortopulmonary shunt in three patients and a right ventricular to pulmonary artery shunt in one patient. Repeated interventions, including a Blalock-Taussig shunt once and a central shunt with unifocalization twice, were performed for the fifth patient.

Cardiac surgery could not be performed in nine cases. Five patients presented with a cardiovascular anatomy not suitable for surgery. Three patients died of major extracardiac malformations or major complications before surgery (Table 3), and another patient showed spontaneous closure of a ventricular septal defect.

Table 2 Extracardiac anomalies and related surgical interventions in 49 children with microdeletion 22q11.2 and congenital heart defect (CHD)

Extracardiac anomalies	*n* (%)
Dysmorphisms and growth	
Facial dysmorphic features	36 (73)
Weight ≤3P	18 (37)
Lenght ≤3P	14 (29)
Immunohematologic findings	
Lymphocytopenia	30 (61)
Thymus aplasia	15 (31)
Thrombocytopenia	7 (14)
Neurologic findings	
Abnormal muscle tone	26 (53)
Abnormal neuroimaging	16 (33)
Seizures	9 (18)
Neurodevelopmental delay	33 (67)
Endocrinologic findings	
Hypocalcemia	21 (43)
With seizures	2 (4)
Rhinolaryngologic findings	
Pharyngeal, laryngeal anomalies	19 (39)
Hearing impairment	11 (22)
Speech deficiency	9 (18)
Renal anomalies	10 (20)
Skeletal anomalies	5 (10)
Ophtalmologic anomalies	2 (4)
Surgical interventions	***n* = 32 (*n*)**
Velopharyngoplasty	8
Herniotomy	7
Diaphragmatic plication	3
Gastrostomy	3
Fundoplication	2
Laparotomy	3
Cricoid splitting	2
Orchidopexy	1
Fasciotomy	1
Cholecystectomy	1
Duodenostomy	1
Corneal transplantation	1
Probing of ductus nasolacrimalis	1

The data concerning cardiac surgical repair are shown in Table 1. Postoperative complications prolonging intensive care unit (ICU) stay to more than 10 days occurred for 24 patients after 26 cardiac operations. Seven patients (14%) required tracheotomy: secondary to tracheobronchial malformations in four patients and because of prolonged ventilatory support in three patients. One child presented

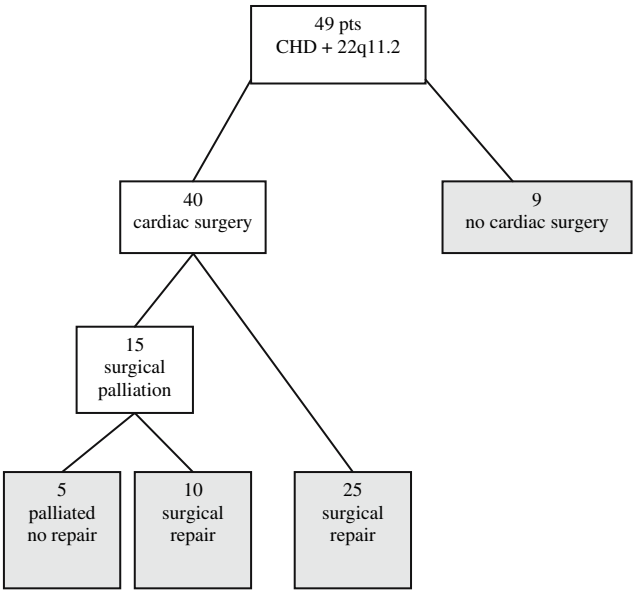

Fig. 1 Clinical management of congenital heart defect (CHD)

with severe gastrointestinal complications involving bowel perforation and necrosis, which required bowel resection and caused a prolonged clinical course in the hospital. The remaining patients experienced more than one postoperative complication, mainly related to heart surgery, including prolonged cardiac low output, arrhythmias, thrombosis, chylothorax, diaphragmatic palsy, pneumonia, renal failure, and sepsis. In all these cases, the cause for a prolonged ICU stay was multifactorial, and one single reason for it retrospectively was not identifiable.

For 21 children (43%), 32 noncardiac surgical interventions were required (Table 2). A total of 25 operations (78%) were related to extracardiac anomalies associated with the microdeletion 22q11.2, and 7 (22%) were related to postoperative complications after cardiac surgery. Laparotomy was required after perioperative iatrogenic intestinal perforation in one patient and because of postoperative intestinal necrosis in another patient (described earlier). Fasciotomy was performed for a girl with postoperative ischemic compartment syndrome in the lower leg. In one patient with a choledocus anomaly, a cholestatic syndrome and pancreatitis developed, requiring cholecystectomy and duodenostomy.

Outcome

The median follow-up time was 4.8 years (range, 2 days to 24 years). The median age of the survivors at the end of the follow-up period was 8.5 years (range, 3 months to 24 years). Follow-up information was complete for 48 of the 49 patients.

Survival

Overall mortality was 22.4% (11 of the 49 patients). The survival rates were 86% for 1-year survival, 80% for 5-year survival, and 78% for 10-year survival (Fig. 2). Higher mortality was observed during the neonatal period (median age, 7 days) and at the midterm follow-up point (median age, 5 years). The cause of death was cardiac related in six children, with three patients dying perioperatively, and not cardiac related in five cases (Table 3). Considering the cardiac diagnosis of the deceased patients, we found mortality rates of 36% for pulmonary atresia and ventricular septal defect, 30% for interrupted aortic arch, and 33% for truncus arteriosus. No patient with tetralogy of Fallot and right ventricular outflow tract obstruction died, and the patient with an isolated ventricular septal defect died of extracardiac causes.

Reinterventions

For 16 (46%) of the 35 patients who underwent total repair, 27 cardiac reinterventions were required (Table 4). Five patients required more than one reintervention**.** Reinterventions consisted of 15 reoperations and 12 interventional catheterizations. The indications for reintervention are summarized in Table 4. The median interval between surgical repair and reintervention was 6 months (range, 18 days to 13 years). Reintervention-free survival was 75% after 1 year, 70% after 2 years, and 64% after 10 years (Fig. 3). At the end of the follow-up period, significant residual cardiac lesions were observed in 27 (71%) of 38 survivors and in 24 (68%) of 35 corrected patients.

Extracardiac Follow-up Assessment

Neurologic abnormalities represented the most frequent extracardiac findings during mid- to long-term follow-up period. Neurodevelopmental delay was described for 32 patients (66%) and abnormal morphologic findings at neuroimaging for 16 patients (33%). Among the hematologic complications, lymphocytopenia (less than 1,000 G/l) and thymus aplasia were of clinical relevance, particularly during the first months of life and in the postoperative period. Thus, a clinically relevant infection occurred during the postoperative period in 18 patients, consisting of sepsis in 9 patients, pneumonia in 7 patients, tracheitis in 4 patients, endocarditis in 2 patients, and meningitis in 1 patient. Eight children experienced more than one infection.

Thrombocytopenia (less than 100,000 G/l), described for eight patients, was the most common abnormal finding

Table 3 Causes of death

Patient	CHD	Extracardiac anomalies	Cause of death	Age at death
1	PA/VSD	Lymphocytopenia, velopharyngeal incompetence, developmental delay, psychiatric disorder	Cardiac cause/perioperative	6 years
2	PA/VSD	Thymic aplasia, thrombocytopenia, blindness (microphthalmia, cataract), severe developmental delay, renal agenesis	Cardiac cause/sudden death	1.8 years
3	PA/VSD	Lymphocytopenia, hypoparathyroidism, renal agenesis	Cardiac cause/perioperative	3 months
4	IAA	Lymphocytopenia	Cardiac cause/perioperative	4 days
5	Truncus arteriosus communis	Dysplastic ears	Cardiac cause before surgery	2 days
6	Truncus arteriosus	Lymphocytopenia, thrombocytopenia, splenomegaly, developmental delay	Immunologic cause	4.9 years
7	VSD	Severe immunologic disorder, pancytopenia, developmental delay, brain malformations, renal agenesis, hydronephrosis	Immunologic cause	2 years
8	Absent PV syndrome	Thymic hypoplasia, tracheobronchomalacia, uvula bifida, brain malformations	Multiple malformations	3 days
9	IAA	Lymphocytopenia, hypoparathyroidism	Cardiac cause/postoperative intracranial bleeding, multiorgan failure	11 days
10	PA/VSD	Hypoparathyroidism	Postoperative sepsis, pulmonary complications, repeated CPR	7 months
11	IAA	Brain and skeletal malformations, microphthalmia and cataract cleft palate	Multiple malformations	1 day

CHD, congenital heart defect; PA, pulmonary atresia; VSD, ventricular septal defect; IAA, interrupted aortic arch; PV, pulmonary valve; CPR, cardiopulmonary reanimation

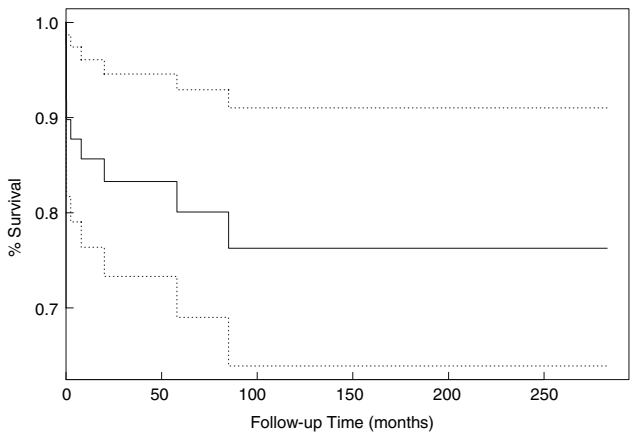

Fig. 2 Survival curve for the 49 patients with microdeletion 22q11.2 and congenital heart defect (CHD)

during midterm follow-up assessment. In one case, an acute severe thrombocytopenia was caused by a toxic shock syndrome associated with pneumonia. One girl required splenectomy as treatment for chronic recurrent thrombocytopenia. In the remaining six cases, thrombocytopenia did not cause any complications, but it was recommended to avoid drugs which could potentially impair platelet function, and to check the platelet count regularly, particularly if surgery was planned.

Table 4 Cardiac reinterventions and residual cardiac lesions at the end of the follow-up period in 35 patients after total repair

Anatomic lesion	Surgery	Interventional catheterization	Residual findings
RVOT	8	3	6
PPS	1	8	8
LVOT	3	—	3
Aortic arch	—	1	1
VSD	3	—	6
Total	15	12	24

RVOT, right ventricular outflow tract; PPS, peripheral pulmonary stenosis; LVOT, left ventricular outflow tract; VSD, ventricular septal defect

Discussion

The prevalence of microdeletion 22q11.2 in CHD pre- and postnatally and the phenotypic features of the syndrome have been reported for pediatric and adult patients [3, 5, 16,

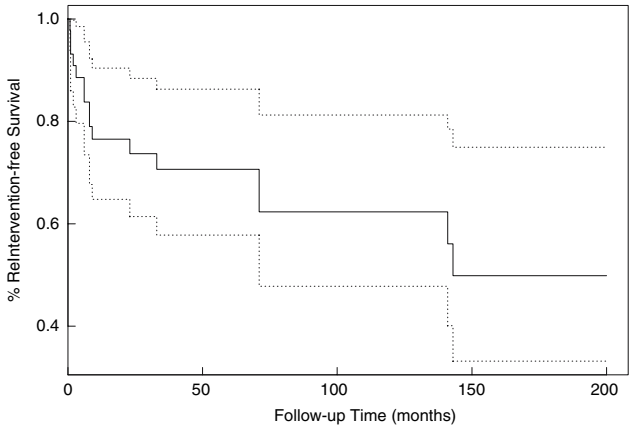

Fig. 3 Reintervention-free survival of 35 patients after surgical repair of congenital heart defect (CHD)

24, 26]. More recently, a few reports have assessed the influence of deletion 22q11.2 on the outcome for patients with a specific cardiac lesion [8, 21, 22].

Our data demonstrate that when microdeletion 22q11.2 and CHD are diagnosed during childhood, the cases are complex, mainly due to the severity of CHD and the additional extracardiac anomalies. Most of these cases required repeated surgery, repeated cardiac surgery, long hospitalization time, additional diagnostic and therapeutic interventions, and most importantly were associated with significant morbidity and mortality. As determined by comparative data on the overall phenotype of children and adults with microdeletion 22q11.2, these subjects certainly represent the most severe end of the spectrum and have a correspondingly poor outcome [24, 26]. Therefore, our results are different from those published for the adult population, who may present with less severe "later recognized" clinical features [3].

The cardiac defects occurring in our cohort were similar to the spectrum described by other groups, with tetralogy of Fallot and its variances, interrupted aortic arch, and truncus arteriosus communis representing the most commonly observed anomalies [13, 14]. Aortic arch anomalies were the most frequent additional cardiac malformations [22]. The mortality rate found for our patients was similar to that reported for surgical repair of interrupted aortic arch (31%) [27], but slightly higher than that described for pulmonary atresia and ventricular septal defect (15–22%) [7, 19] and for truncus arteriosus (13–17%) [6, 28]. It should be noted that studies reporting the outcome of selected conotruncal malformations did not differentiate between patients with and those without the microdeletion 22q11.2, and therefore are not completely comparable with our study [6, 9, 27]. In fact, other authors demonstrated that monosomy of a segment within chromosome band 22q11.2 may represent a significant risk for perioperative death [1, 18].

A typical pulmonary vascular phenotype, consisting of hypoplastic pulmonary arteries and a higher occurrence of major aortopulmonary collaterals, has been described in patients with microdeletion 22q11.2 and tetralogy of Fallot or pulmonary atresia and ventricular septal defect [8, 18]. The anatomy of the pulmonary vessels has been identified as an important risk factor for mortality and for reinterventions in patients undergoing repair of tetralogy of Fallot and its variances [15, 21]. The high rate of reinterventions found in our study confirms these data. Similarly, the presence of associated cardiac anomalies has been demonstrated to be a risk factor for truncus arteriosus repair [6, 15].

The cause of death was cardiac related in only 54% of the cases. Thus, extracardiac anomalies seem to have a crucial influence on morbidity and mortality (Table 2). The prevalence of cases requiring tracheal cannulation was significantly higher among patients with CHD and microdeletion 22q11.2 (14%) than among patients with CHD but no microdeletion 22q11.2 (0.5%). Laryngotracheobronchial malformations, found frequently in children with microdeletion 22q11.2, may explain the need for cannulation and long-term ventilation [29].

Besides the anomalies influencing the perioperative course, neurodevelopmental retardation, learning disabilities, and immunohematologic disease frequently characterized the clinical picture during mid- to long-term follow-up. The retrospective nature of the study did not allow us to evaluate this particular aspect in detail because the importance of neurodevelopmental and social outcome has been recognized only recently and still is a subject of evaluation. Moreover, psychosocial deficits may become more evident during adulthood, when the patients are expected to function more independently in daily life [23]. Another burden for these patients is the risk for developing significant psychological disabilities, with schizophrenia occurring in up to 30% of the adult patients [3, 12, 17].

The presence of a microdeletion 22q11.2 can be suspected prenatally if the fetal ultrasonographic examination shows a conotruncal heart malformation and an absent or hypoplastic thymus [2]. A prenatal cytogenetic examination including FISH analysis then is recommended because the presence of an interstitial deletion may have a major impact on the decision of the parents to continue or terminate the pregnancy [5]. For counseling of the families, the results of our study add important information about the course of the cardiac disease in this group of patients and about the associated extracardiac malformations that may have a major influence on the outcome.

The need for postnatal cytogenetic screening for all patients with conotruncal malformations has been a subject of debate [10, 14]. Because early detection of microdeletion 22q11.2 may enable better risk stratification, allow

adequate management strategies, avoid potential complications, and facilitate counseling of the families, we suggest genetic testing for all newborns with a conotruncal malformation suggesting the presence of a microdeletion or another cardiac defect associated with facial dysmorphisms.

Limitations

The retrospective design of this study based on clinical records as the only available source of data limits the quality of information about the clinical course of the patients. For instance, retrospectively, it was not possible to determine precisely which one of the postoperative complications may have been the real cause for a prolonged ICU stay.

As the combination of CHD and microdeletion 22q11.2 represents a rare condition, we assessed a long period of time, in order to evaluate an adequate number of patients. Thus, during the initial years, some cases less severely affected may have not been correctly identified, and a selection bias may have influenced morbidity and mortality rates. Moreover, the clinical and surgical treatment of such complex CHD has improved during the past decade, potentially leading to better current results.

Finally, during the same period of time, the rarity of the condition did not allow us to create a matched group of patients with the same CHD but no microdeletion 22q11.2 for comparison of outcomes. Thus, comparison of outcomes was based on data reported in the literature [6, 9, 27, 28].

Conclusion

Patients with microdeletion 22q11.2 and CHD present high morbidity and mortality. These are mainly determined by the severity of the CHD. Nevertheless, the presence of the microdeletion and the related extracardiac anomalies contribute to significant morbidity and may influence mortality. Knowledge of the cardiac outcome and the risks for complications related to the microdeletion 22q11.2 syndrome may be crucial for appropriate management of these patients during the perioperative period and for counseling of the families. Careful repeated cardiac and neurodevelopmental evaluation is recommendable during follow-up evaluation.

Acknowledgments We thank all the pediatric cardiologists who referred patients to our institution for their help in collecting the data. We also thank Patrick Hargreaves (IMG) for his review of the manuscript and his helpful suggestions.

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