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Congenital heart defects in Kabuki syndrome

Shi-Min Yuan

The First Hospital of Putian, Teaching Hospital, Fujian Medical University, Putian, Fujian Province, China

Abstract

Background: *Kabuki syndrome (KS) is an entity of multiple congenital malformations with mental retardation with undetermined etiology. Congenital heart defects are one of the clinical manifestations of KS with insufficient elucidations.*

Methods: *Literature of congenital heart defects associated with KS was comprehensively retrieved, collected and reviewed. The clinical features of the congenital heart defects in the patients with KS were summarized.*

Results: *Congenital heart defects were one of the clinical manifestations of KS with 90.6% of the patients being diagnosed prenatally or at an early age. Left-sided obstructions/aortic dilation and septal defects were the first two types of anomalies, accounting up to 46.1% and 32.9%, respectively. The most common congenital heart defects were coarctation of the aorta, and atrial and ventricular septal defects. Fifteen (19.7%) patients received surgical repair of congenital heart defects at a mean age of 0.8 ± 1.3 years.*

Conclusions: *Congenital heart defects are one of the clinical manifestations of KS with 90.6% of the patients being diagnosed prenatally or at an early age. About 20% of the patients warranted surgical repair of the heart defects. Patients with KS require close follow-up in terms of their etiology, clinical presentations and long-term prognosis.* (Cardiol J 2013; 20, 2: 121–124)

Key words: cardiac surgical procedures, congenital heart defects, Kabuki syndrome

Introduction

Kabuki syndrome (KS) was firstly reported in 1981 by Niikawa et al. [1] and Kuroki et al. [2]. It is an entity of multiple congenital malformations with mental retardation with undetermined etiology, characterized by typical facial features (elongated palpebral fissures with eversion of the lateral third of the lower eyelid; arched and broad eyebrows; short columella with depressed nasal tip; large, prominent, or cupped ears), minor skeletal anomalies, persistence of fetal fingertip pads, mild to moderate intellectual disability, and postnatal growth deficiency [3, 4]. In 1988, Niikawa et al. [5] proposed 5 diagnostic criteria for KS: peculiar facies (in 100% of all patients), skeletal anomalies (92%), dermatoglyphic anomalies (93%), medium to moderate mental retardation (92%), and short stature (83%). In clinical practice, the diagnosis of KS is often made based on laterally sparse arched eyebrows, long palpebral fissures, eversion of the lower eyelid, depressed nasal tip, down-turned corners of the mouth, and prominent ears with preauricular pits [6]. Most patients had postnatal growth retardation, and all had developmental delay and hypotonia. Feeding difficulties, with or without cleft palate, were common [7]. Ewart-Toland et al. [6] reported a girl with KS had an autoimmune

Address for correspondence: Prof. Shi-Min Yuan, The First Hospital of Putian, Teaching Hospital, Fujian Medical University, 389 Longdejing Street, Chengxiang District, Putian 351100, Fujian Province, China, tel: 0086 594 6923117, e-mail: shi_min_yuan@yahoo.com

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disease IgA deficiency manifesting with Hashimoto thyroiditis and vitiligo. There have been more than 300 cases of KS reported in the literature [8]. Since 1994, the cardiovascular sequelae of KS, namely the syndrome-associated congenital heart defects, were continuously found, and the clinical importance of the diagnosis and treatment strategies of the cardiovascular problems of KS became more and more emphasized. So far, there has been scanty report on cardiovascular aspects of KS in terms of the contemporary surgical strategies. Therefore, it is necessary to make a comprehensive review on the congenital heart defects of this syndrome to discuss the modern treatment approaches.

Methods

Literature of KS was comprehensively retrieved, collected and reviewed from MEDLINE database (1994-present). Search terms included "Kabuki syndrome" and "congenital heart defect". The clinical features of the congenital heart defects that were associated with KS were summarized.

Results

Totally 76 cases of KS were reported to be associated with congenital heart defects by 19 reports [6, 7, 9–25]. Of them, the gender was expressed in 37 patients including 17 males and 20 females with a male-to-female ratio of 0.85:1. The patients' age at initial diagnosis varied: 4 (12.5%) were diagnosed antenatally, 11 (34.4%) patients were diagnosed when they were a newborn, 14 (43.8%) patients were younger than 18 years and 3 (9.4%) patients were equal to or older than 18 years, aging from 8 weeks to 33 years old for these 17 patients. Their mean age was 4.7 ± 8.0 years (n = 28) and their median age was 0.54 years by excluding the 4 antenatally diagnosed cases.

The classification of the congenital heart defects according to Digilio et al. [12] were listed in Table 1. Left-sided obstructions/aortic dilation and septal defects were the first 2 types of anomalies, accounting up to 46.1% and 32.9%, respectively. The most common congenital heart defects were coarctation of the aorta (22/76, 28.9%), atrial septal defect (13/76, 17.1%) and ventricular septal defect (13/76, 17.1%).

Fifteen patients received surgical repair of congenital heart defects including atrial septal defect plus pulmonary stenosis in 1, coarctation of the aorta in 9, and hypoplastic left heart syndrome in 5 patients, respectively. The age at the initial operation averaged 0.8 ± 1.3 years (range, 2 days – 4 years; median, 10 weeks; n = 10). Stage 2 of the palliation of hypoplastic left heart syndrome was described in 3 patients who underwent a Glenn shunt in 2 patients at the age of 6 months and 6.5 months, and a Fontan procedure in 1 patient at the age of 3 years.

Table 1. The classifications of the congenital heart defects associated with Kabuki syndrome.

Left-sided obstructions/aortic dilation	35 (46.1)
Aortic dilation	1 (1.3)
Aortic stenosis	2 (2.6)
Coarctation	13 (17.1)
Coarctation + anomalous pulmonary artery branch	1 (1.3)
Coarctation + ASD	1 (1.3)
Coarctation + ASD + PDA	1 (1.3)
Coarctation + BAV	1 (1.3)
Coarctation + BAV + VSD	1 (1.3)
Coarctation + BAV + VSD + PDA	1 (1.3)
Coarctation + VSD	1 (1.3)
Coarctation + VSD + PDA	1 (1.3)
Coarctation + PDA	1 (1.3)
HLHS	8 (10.5)
HLHS + mitral stenosis + PAPVR + PDA	1 (1.3)
HLHS + VSD	1 (1.3)
Right-sided obstructions	1 (1.3)
PS	1 (1.3)
Septal defects	25 (32.9)
ASD	9 (11.8)
ASD + PAPVR	1 (1.3)
ASD + PS	2 (2.6)
ASD + VSD	1 (1.3)
VSD	11 (14.5)
VSD + PDA	1 (1.3)
Extracellular matrix defects	3 (3.9)
AVSD	2 (2.6)
AVSD + PS	1 (1.3)
Outflow/conotruncal defects	9 (11.8)
DORV	1 (1.3)
Double aortic arch + LSVC	1 (1.3)
d-TGA/IVS	1 (1.3)
TGA	1 (1.3)
TOF	5 (6.6)
Targeted growth defects	2 (2.6)
PAPVR	2 (2.6)
Cell death defects	1 (1.3)
Ebstein's anomaly	1 (1.3)

ASD — atrial septal defect; AVSD — atrioventricular septal defect; BAV — bicuspid aortic valve; HLHS — hypoplastic left heart syndrome; IVS — intact ventricular septum; LSVC — left superior vena cava; PAPVR — partial anomalous pulmonary venous return; PDA — patent ductus arteriosus; PS — pulmonary stenosis; TGA — transposition of the great arteries; TOF — tetralogy of Fallot; VSD — ventricular septal defect

Discussion

Congenital heart disease is commonly associated with KS, with a reported incidence of 30–55% in large series. The spectrum of associated cardiac defects varied. Left-sided obstructive lesions, in particular coarctation of the aorta, were reported to be associated with KS in up to 25% patients [26].

Digilio et al. [12] reported congenital heart defects was present in 35 (58%) of their 60 patients with KS. Of them, aortic coarctation (23%), atrial septal defect (20%), and ventricular septal defect (17%) were the most frequent congenital heart defects. Male preponderance in patients with KS and coarctation supports the hypothesis that genes located on the X chromosome may be involved in determining KS in some patients. In another report, Digilio et al. [24] described further congenital heart defect, which was shown in 71 of 121 (59%) of KS patients and left-sided obstructions in 27 of 71 (38%) patients with congenital heart defect. Hypoplastic left heart syndrome was diagnosed in 5 patients, corresponding to 4.1% (5 of 121) of the patient group, 7% (5 of 71) of patients with congenital heart defect, and 19% (5 of 27) of patients with left-sided obstructions. Three patients with hypoplastic left heart were males, and 2 were females, and 1 of the females was with perimembranous subaortic ventricular septal defect [24]. Bhat et al. [25] reported a wide variety of cardiac malformations (31–58%) seen in this syndrome, the most common of them being aortic coarctation (29%). Of greater interest, Digilio et al. [12] categorized the congenital heart defects associated with KS into 7: (1) left-sided obstructions: aortic coarctation 8 (22.8%), aortic stenosis 2 (5.7%); (2) septal defects: ventricular septal defects 6 (17.1%), secundum atrial septal defects 7 (20%); (3) right-sided obstructions: pulmonary stenosis 1 (2.8%); (4) extracellular matrix defects: atrioventricular canal, complete 2 (5.7%); (5) outflow/conotruncal defects: tetralogy of Fallot 4 (11.4%), double outlet right ventricle 1 (2.8%), d-transposition of the great arteries with intact ventricular septum 1 (2.8%); (6) targeted growth defects: partial anomalous pulmonary venous return 2 (5.7%); and (7) cell death defects: Ebstein's anomaly 1 (2.8%).

The majority of the cardiac defects have been isolated shunt lesions such as atrial and ventricular septal defects and patent ductus arteriosus. There has been a prevalence of cases with left-sided obstructive lesions and coarctation of the aorta, leading some to hypothesize an overlap between KS and Turner syndrome [23].

The genetic studies of KS have been conducted towards pertinent gene mutations. The screening of 110 families with KS showed MLL2 mutations in 81/110 (74%) of families. KS may have novel nonsense or frameshift mutations predictive of haploinsufficiency. The clinical characteristics of MLL2 mutation-positive cases did not differ significantly from MLL2 mutation-negative cases with the exception that renal anomalies were more common in MLL2 mutation-positive cases [27]. MLL2 carriers obviously showed more frequently a typical facial gestalt (17/19) compared with non-carriers (9/15) [28]. GJA1, NKX2.5, ZIC3, and ISL1 seemed to be involved in nonsyndromic congenital heart defects [12]. It has been evidenced that 8p22–p23.1 duplication may not be a common mechanism for KS [29].

The clinical features and diagnostic criteria have been described as above-mentioned. For the diagnosis of congenital heart defects associated with KS, the clinical manifestations provide with important diagnostic evidences. Besides, medical images including echocardiography [19, 25], computed tomography [22] and angiography [25] are important means for the diagnosis of congenital heart defects that may reach a definite diagnosis. Standard chromosomal analysis might also be helpful [18].

With the development of various closure devices, percutaneous atrial septal defect closure can be accomplished interventionally in selected patients [30]. Mini-thoracotomy, min-sternotomy and video-assisted thoracoscopy have also been utilized as minimally invasive surgical techniques in the repair of simple congenital heart defects and other heart operations [31]. The surgical treatment of the congenital heart defects in KS, may start early in even neonates. Stenting of the arterial duct along with restricting pulmonary blood flow has been utilized in many centers to avoid cardiopulmonary bypass in the neonatal cases [32]. Simpler heart defects including coarctation of the aorta, aortic stenosis, atrial and ventricular septal defects, atrioventricular canal and Ebstein's anomaly can be repaired with minimally invasive/robotic assisted surgery [33–35]. As a result, minimal traumas, less postoperative pain, shorter postoperative stay and better cosmetic results lead to satisfactory outcomes. For complex congenital heart defects, patients with hypoplastic left heart syndrome may receive staged palliative and physiological radical operations as usual; and those with tetralogy of Fallot, double outlet right ventricle, d-transposition of the great arteries with intact ventricular septum

and partial anomalous pulmonary venous return should undergo conventional heart operations [12].

Nevertheless, the long-term prognosis of the patients with KS is still uncertain [36]. Continued clinical observations with medical treatment are mandatory for such patients.

Conclusions

Congenital heart defects were one of the clinical manifestations of KS with 90.6% of the patients being diagnosed prenatally or at an early age. Coarctation of the aorta, and atrial septal defect and ventricular septal defect are the congenital heart defects most commonly seen in KS. About 20% of the patients with congenital heart defects may warrant a surgical correction, while the simpler congenital heart defects may benefit from the minimally invasive/robotically assisted surgical techniques with fewer traumas. Patients with KS require close follow-up in terms of their etiology, clinical presentations and long-term prognosis.

Conflict of interest: none declared

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