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Kabuki patients with CHDs: outcomes after cardiac surgery

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Abstract

Objective: This study aims to examine the surgical outcome of Kabuki syndrome patients after neonatal congenital heart surgery. *Methods:* This was a single-centre retrospective study of Kabuki syndrome patients undergoing neonatal congenital heart surgery from 2018 to 2023. Primary outcome was survival to discharge after index surgery. Secondary outcomes were morbidities and complications. Survival and hospital length of stay were compared to neonates with non-Kabuki genetic anomalies undergoing congenital heart surgery in the same time period. *Results:* A total of seven patients were reviewed. All Kabuki syndrome patients had left-sided lesions including three with hypoplastic left heart syndrome, three with aortic stenosis and/or aortic arch hypoplasia, and one with an isolated coarctation of aorta. Hospital survival was 5/7 (71% compared to 88% for neonates with non-Kabuki genetic anomalies). To date, four remain alive, including one with hypoplastic left heart syndrome. A higher percentage of Kabuki syndrome patients had unplanned interventions (43% vs 15% in non-Kabuki), abnormal brain imaging (29% vs 5%), and bacteremia (29% vs 9%). Median total ventilator days for Kabuki patients were also longer (16 days vs 6 days in non-Kabuki) as was hospital length of stay (66 days vs 41 days). *Conclusions:* Despite survival to discharge after index operation, Kabuki syndrome patients with single ventricle physiology remain at high risk of mortality and morbidity after cardiac surgery. However, they may be discharged without ventilator dependency and survive to toddler years.

Introduction

Kabuki syndrome is a rare genetic disorder that affects 1 in 32,000 live births.[1] It is characterised by hypotonia, developmental delay, intellectual disability, and distinct dysmorphic features. Through molecular genetic testing, 70% of Kabuki syndrome patients also carry a pathogenic variant in the KMT2D or KDM6A gene.[2] Kabuki syndrome may affect multiple organ systems, including musculoskeletal abnormalities, renal malformations (renal dysplasia, hypoplasia), gastrointestinal abnormalities (malrotation, anal atresia), immunologic deficiencies, and congenital heart disease(CHD).

The prevalence of CHD in Kabuki syndrome patients varies, though reported rates have been as high as 55–80%.[3,4,5] Left-sided lesions, including coarctation of the aorta, account for almost half of the cardiac defects in this population.[6,7,8,9] Additional common cardiac defects include atrial and ventricular septal anomalies.[6,9,10] These lesions commonly require surgical correction, ranging from surgeries for simple lesions to staged palliation for complex defects.[10] Kabuki syndrome patients with complex CHD are often considered at high risk for poor surgical outcomes, which impacts decisions for surgical candidacy.

While there have been studies examining the post-cardiac surgery outcomes of patients with other genetic conditions,[11,12,13,14] few studies have examined the post-cardiac surgery outcomes in Kabuki syndrome patients. One retrospective study examined the post-operative course of 15 Kabuki syndrome patients who underwent cardiac surgery with varying degrees of complexity.[6] These patients experienced a prolonged hospital course and increased complications, but no increase in post-op mortality (94% survival rate at 6 years) compared to patients without genetic anomalies. The main complications examined were infection, glycemic disturbance, pleural effusion, and pericardial effusion. Other reports of post-cardiac surgery outcomes in Kabuki syndrome patients are primarily individual case studies that detail the course of surgical intervention but do not provide an aggregate understanding of surgical risk.[15,16,17]

We seek to contribute to the few studies that have examined outcomes in Kabuki syndrome patients after cardiac surgery and to broaden the outcomes that are considered. Improved

understanding of surgical outcomes will aid in better identifying appropriate candidates for surgical intervention.

Materials and methods

Overview

This was a single-centre retrospective study of Kabuki syndrome patients undergoing neonatal surgery for CHD from January 2018 to September 2023 at a tertiary referral centre. Patients were identified through our local Pediatric Cardiac Critical Care Consortium (PC^4) database and electronic medical record. No patient was denied surgery for Kabuki syndrome alone. Inclusion criteria were any patients with diagnosis of Kabuki syndrome who had undergone neonatal cardiac surgery. Diagnosis of Kabuki syndrome in all patients was confirmed by postnatal genetic testing. The outcomes of Kabuki syndrome patients were compared to the neonates with chromosomal abnormalities other than Kabuki syndrome who underwent cardiac surgery within the same time period in our centre. All chromosomal abnormalities were identified via genetic testing. The University of California San Francisco Institutional Review Board approved this study.

Data collection

We collected basic demographics, including sex, race, ethnicity, gestational age, age at surgery, and birth weight. We then examined each patient's baseline function across several organ systems (cardiac, respiratory, renal, gastrointestinal, neurologic, haematologic, and endocrine). Our post-operative primary outcomes were survival to discharge after index surgery and survival to date (as of September 2024). Secondary outcomes were hospital length of stay, post-operative complications, and comorbidities. This included cardiac complications (cardiac arrest, extracorporeal mechanical support (extracorporeal circulatory life support), unplanned re-interventions), respiratory support, renal failure requiring dialysis, infection, neurological complications, and gastrointestinal support (feeding tube at discharge). Where available, these variables were compared between Kabuki patients, patients with non-Kabuki genetic anomalies, and all neonates undergoing surgery for CHD during the same time period.

For the purposes of this study, neonates at time of operation were extended to 33 days to include all suitable candidates. Infection included necrotising enterocolitis (modified Bell's staging criteria II or III), bacteremia (positive blood culture), urinary tract infection (positive urine culture), and pneumonia/tracheitis (positive respiratory, tracheal, bronchial lavage culture). Neurological complications included seizure (clinical or electroencephalogram evidence of epileptiform activity) and abnormal brain imaging (intraventricular haemorrhage or stroke as seen in head ultrasound or MRI).

Results

We identified seven patients with Kabuki syndrome who underwent cardiac surgery from January 2018 to September 2023. The majority of the patients were male (86%) and identified as Caucasian (43%), Asian (14%), or other/undisclosed (43%). Besides cardiac defects, preoperative structural renal (43%) and neurological anomalies (29%) were common (Table 1).

All patients had left-sided lesions, including three with hypoplastic left heart syndrome (HLHS), three with aortic stenosis and/or aortic arch hypoplasia, and one with isolated coarctation of aorta. Accordingly, the three patients with HLHS underwent staged palliation. The index operation was Norwood with right ventricle to pulmonary artery conduit for two patients and hybrid for one patient. The three with aortic stenosis/arch hypoplasia underwent aortic arch repair, and the one patient with isolated coarctation underwent coarctation repair. The age at index operation was 17 to 33 days for HLHS and 3 to 30 days for arch repair.

Preoperatively, one patient had systolic dysfunction on echocardiogram. Comorbid organ dysfunction included non-invasive ventilation ($n = 5$), mechanical ventilation ($n = 1$), structural renal abnormalities ($n = 3$), neurologic abnormalities on imaging ($n = 2$), and coagulation disorder ($n = 1$). Notably, none had preoperative gastrointestinal dysfunction or renal dysfunction (i.e. acute kidney injury or chronic kidney disease) (see Table 1).

Postoperatively, 71% of patients with Kabuki syndrome survived to discharge, compared to 89% among neonates with other chromosomal abnormalities and 94% among neonates without known chromosomal abnormalities undergoing surgery for CHD. Four of five patients who survived to discharge remain alive, including one with HLHS. Three of the cohort survived until 3 years of age. Cardiac complications were present in a subset of Kabuki syndrome patients (one cardiac arrest, one extracorporeal circulatory life support, and three patients with unplanned re-interventions). Ventricular hypertrophy was found in all mortalities. For extracardiac morbidities, two patients developed pulmonary hypertension including one mortality. None required dialysis. All five surviving patients were discharged home with a gastrostomy or nasogastric tube.

Overall, a higher percentage of Kabuki syndrome patients experienced complications compared to patients with non-Kabuki chromosomal abnormalities. Most significantly, higher percentage of patients had unplanned re-interventions (43% versus 15% in non-Kabuki syndrome chromosomal abnormalities), abnormal brain imaging (29% versus 5%), and bacteremia (29% versus 9%) (Table 2). Median total ventilator days (16 days versus 6 days) and hospital length of stay (66 days versus 41 days) were both longer than in Kabuki syndrome patients than in non-Kabuki syndrome chromosomal abnormalities patients.

There were 97 patients with non-Kabuki chromosomal abnormalities including 14 patients with 22q11.2 deletion and 10 patients with Trisomy 21. No Trisomy 13 or 18 patients underwent neonatal cardiac surgery during the study period. The most common neonatal operation in non-Kabuki genetic anomaly patients was coarctation of aorta repair (20%). Norwood palliation was the second most common operation (13%), followed by Truncus arteriosus repair (10%).

Among the fourteen 22q11.2 deletion syndrome patients, four underwent interrupted aortic arch repair, four Truncus arteriosus repair, and two Yasui operation (See Supplemental Table 1 for details). Overall survival to discharge was 86% in 22q11.2 deletion syndrome neonates after cardiac surgery.

Out of the ten Trisomy 21 patients, six patients underwent coarctation of aorta repair while two had atrioventricular (AV) canal repair (Supplemental Table 1). There was no inpatient mortality among Trisomy 21 patients.

Discussion

Kabuki syndrome patients with cardiac defects usually present with left-sided lesions. Their outcomes can be stratified based on the complexity of cardiac lesions as well as extracardiac anomalies and

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Table 1. Demographics and preoperative factors

Sex	
Male	86%
Female	14%
Race	
White	43%
Black/African American	0%
American Indian or Alaska Native	0%
Asian	14%
Native Hawaiian/Pacific Islander	0%
Other or declined	43%
Ethnicity	
Hispanic/Latino	57%
Age	
Gestational age, weeks (median, range)	37 4/7 (34 1/7-39 2/7)
Age at surgery, days (median, range)	17 (3-33)
Weight	
Birth weight, kg (median, range)	2.7 (2.1-3.2)
Extracardiac anomalies	
Gastrointestinal	0%
Renal	43%
Neurological	29%
Cardiac function	
Preoperative mechanical circulatory support	0%
Shock at time of surgery	0%
Systolic dysfunction on echocardiogram	14%
Hypertrophic cardiomyopathy on echocardiogram	0%
Respiratory function	
Mechanical ventilation	14%
Highest level of non-invasive ventilation: CPAP	57%
Highest level of non-invasive ventilation: HFNC	14%
Renal function	
Acute kidney injury	0%
Structural abnormalities on imaging	42%
Gastrointestinal function	
NEC (higher than modified Bell stage 2)	0%
Gastrointestinal malformation requiring operation	0%
Gastrostomy tube prior to cardiac surgery	0%
Neurologic function	
Abnormalities on imaging (including stroke and IVH)	28%
Electrographical seizure	0%
Haematologic function	
Coagulation disorder	14%
Endocrine function	
Hypothyroidism	0%

Abbreviations: IVH (intraventicular haemorrhage).

preoperative risk factors. These factors should be weighed in the discussion for their surgical candidacy. While Kabuki syndrome patients have lower survival-to-discharge than counterpart cardiac patients with non-Kabuki syndrome genetic abnormalities, we found a significant portion (71%) of Kabuki syndrome patients survive the index operation. Three-quarters of our two-ventricle Kabuki syndrome patients in our cohort survived to discharge and to date. Two-thirds of our single ventricle Kabuki syndrome patients survived to discharge. Two underwent the bidirectional Glenn procedure, including one demise three years after bidirectional Glenn with hypertrophic cardiomyopathy, worsening heart and renal failure. Surgical intervention is associated with long-term survival in two-ventricle physiology, but likely yields only short-term survival in single-ventricle population with Kabuki syndrome. This result aligns with other reports where single ventricle Kabuki syndrome patients have successfully undergone Stage 1 palliation or bidirectional Glenn procedure with subsequent demise prior to reaching Fontan palliation. Therefore, the surgical candidacy of single ventricle Kabuki syndrome patients should be discussed within the context of surgical palliation where the patients may live beyond neonatal period and be discharged home but likely with limited life expectancy.

The two patients who did not survive to discharge did not have significant preoperative differences compared to the population who survived. Their underlying cardiac lesions also varied in complexity. One patient had an aortic stenosis, while the other had HLHS with aortic stenosis, mitral stenosis, and a ventricular septal defect. The former underwent an aortic arch repair, while the latter underwent single ventricle stage 1 palliation. Interestingly, all mortalities from Kabuki syndrome patients had ventricular hypertrophy on echocardiogram. However, baseline comorbidities and underlying cardiac function did not necessarily correlate with likelihood of overall survival in this small cohort. Further study with large patient numbers would help determine the predictor variables for survival.

Complications after surgery are common in Kabuki syndrome patients, including the need for unplanned re-interventions and end-organ complications (e.g. acute kidney injury, abnormal brain imaging, bacteremia, urinary tract infection, and pneumonia). All of our surviving patients were discharged home with feeding tube, which is consistent with feeding difficulty in Kabuki syndrome patients with or without cardiac involvement. Interestingly, our patients did not develop long-term ventilator dependency or chronic kidney disease. Improved understanding of these long-term comorbid risks of surgical intervention in Kabuki syndrome patients will help in making a more informed decision.

The primary limitation of our study is the small sample size. Our cohort was limited to a single institution, yielding a small sample size that was not powered for statistical significance. We compared Kabuki syndrome neonates with other chromosomal anomalies patients for clinically meaningful comparison. However, this came with a caveat that the pattern of cardiac lesions differed from Kabuki population to other chromosomal anomalies, as exemplified by only 13% of non-Kabuki genetic anomaly patients undergoing Norwood palliation. Also, we had expected a higher percentage of Trisomy 21 patients to have AV canal; we speculate that the majority of AV canal patients might have been repaired past the neonatal period, hence not captured in our neonatal surgical population. Further multi-institutional studies will be helpful to determine patient characteristics in evaluating surgical candidacy.

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Table 2. Post-surgical outcomes following neonatal surgery

Primary outcome	Kabuki (7)	Non-Kabuki genetic anomalies (97)		
		All non-Kabuki genetic anomalies (97)	22q11 (14)	T21 (10)
Survival to discharge from the index operation	71%	89%	86%	100%
Survival to date	57%	81%	79%	90%
Secondary outcomes				
Cardiac arrest	14%	6%	7%	0%
Mechanical circulatory support	14%	9%	14%	0%
Unplanned re-interventions	43%	15%	14%	0%
Length of stay after index surgery (median)	66	41	52	35
Total ventilator days (median)	16	6	7	2
Renal failure requiring dialysis	0%	2%	7%	0%
Discharge home with feeding tube or gastrostomy tube	71%	59%	29%	80%
Abnormal brain imaging (change from preop imaging)	29%	5%	7%	0%
Seizure	14%	3%	14%	0%
Infection				
Bacteraemia	29%	9%	14%	0%
Pneumonia	0%	0%	0%	0%
Surgical site infection	0%	0%	0%	0%
Urinary tract infection	14%	4%	7%	0%
Necrotising enterocolitis	0%	6%	7%	0%

Abbreviations: 22q11 (22q11.2 deletion syndrome); T21 (Trisomy 21 syndrome).

Conclusion

Kabuki syndrome patients with two-ventricle physiology seem to benefit from improved survival after neonatal cardiac surgical intervention. Kabuki syndrome patients with single ventricle physiology remain at high risk of mortality and morbidity after cardiac surgical intervention, although they may be discharged home without ventilator dependency and survive to toddler years. The development of ventricular hypertrophy is a marker for poor outcomes.

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