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Research Article

Kabuki-Make-Up Syndrome with Multiple Congenital Heart Defects

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Abstract

We report a one-and-half year old child with Kabuki syndrome and had multiple congenital heart defects – ventricular septal defect, patent ductus arteriosus, bicuspid aortic valve, coarctation of aorta with reversal of shunt from right ventricle to left ventricle suggesting Eisenmenger's physiology.

Keywords: Eisenmenger's physiology; genetic; reversal of shunt; rare.

Introduction

Kabuki Make up Syndrome(KMS) is a very rare genetic disorder with a prevalence of 1 in 32000 live births in Japanese

population.¹ KMS has five cardinal manifestations which includes characteristic facial features, skeletal abnormalities, dermatoglyphic abnormalities, mild to moderate mental retardation and postnatal growth insufficiency.² Recently some atypical features like chronic and/or severe diarrhea, diaphragmatic defects, pseudarthrosis of the clavicles, vitiligo, and persistent hypoglycemia, severe autoimmune thrombocytopenia, cerebellar vermis atrophy, and myopathic features have also been described.^{3,4} KMS has an autosomal dominant inheritance with sporadic mutations. MLL2 gene is the most common gene involved, recently point mutations in the KDM6A gene has also been reported in association with KMS.^{5,6}

Various congenital heart defects like single ventricle with common atrium, ventricular septal defect, atrial septal defect,

tetralogy of Fallot , coarctation of aorta , patent ductus arteriosus, aneurysm of aorta , transposition of great vessels , right bundle branch block, and “parachute” mitral valve, coarctation of aorta, bicuspid aortic valve have been described in KMS since 1980s. The association of congenital heart defects with KMS has been well established, though combination of heart defects in association with this syndrome has been rarely reported. Here we describe a one and half year old Indian (non-Japanese) female child with KMS who had multiple congenital heart defects and ultimately developed Eisenmenger's physiology.

Case Report

One-and-half year old Indian (non-Japanese) female child presented with feeding and breathing difficulties since two

months of age. The child was the first child of non-consanguineous parents delivered at home, with no antenatal, natal or post natal complications. The child weighed normally at birth but was floppy (hypotonic) since birth according to the parents. The child was first brought to medical attention at two months of age with infrequent follow-up visits.

The past history was significant for several episodes of respiratory tract infections not associated with cyanosis since two months of age, which according to the parents has improved in the past few months. There was no history suggestive of malabsorption syndrome, seizures, storage disorders, defects of metabolism and chronic infections.

Her weight (6 kg) and her length (67 cm) were less than 3rd percentile for age according to World Health Organization(WHO) growth charts. Her head circumference was 42 cm which was less than 3 Standard deviation for age according to World Health Organization (WHO) growth charts; as well her weight for length was between 1 Standard deviation and 2 Standard deviation for age. Thus the child had failure to thrive, severe stunting and microcephaly. On examination, the child had characteristic facial features (Figure 1) – interrupted eyebrows, long palpebral fissure, depressed nasal bridge, low set ears, high arched cleft palate, short fifth digit with clinodactyly and finger pads, hypotonia, overlapping of toes and rocker bottom feet. The child is unusually sociable with a happy disposition and had delayed milestones in all domains.



Figure 1 : Clinical Photograph of the child showing a) characteristic facial features : interrupted eyebrows, long palpebral fissure, depressed nasal bridge, low set ears; b) short fifth digit with clinodactyly; c) overlapping of toes and rocker bottom feet

The child had central cyanosis, precordial bulge with a grade II, soft and short systolic murmur heard maximum in the lower left parasternal area and had features of pulmonary hypertension—palpable and loud P2, parasternal heave, ejection systolic murmur in the pulmonary area. Her saturation (SaO_2) was 57%. Arterial blood gas showed a partial pressure of oxygen of 37 mm Hg, partial pressure of carbon-di-oxide of 33 mm Hg and a pH of 7.364. Chest x-ray showed borderline cardiomegaly (Cardio thoracic ratio 0.6) with dilated proximal pulmonary arteries and prominent right cardiac silhouette. Electrocardiogram showed the right axis deviation with marked right ventricular hypertrophy and peaked P waves. Echocardiography revealed muscular ventricular septal defect of 4 mm with right to left shunt (Figure 2) and hypertrophied right ventricle with an enlarged right atrium. Aortic valve was bicuspid with a pressure

gradient of 9 mm Hg, and the arch of aorta was narrow at the origin of left subclavian artery. Echocardiography was suggestive of Eisenmenger's physiology. The child also had a patent ductus arteriosus which was ligated

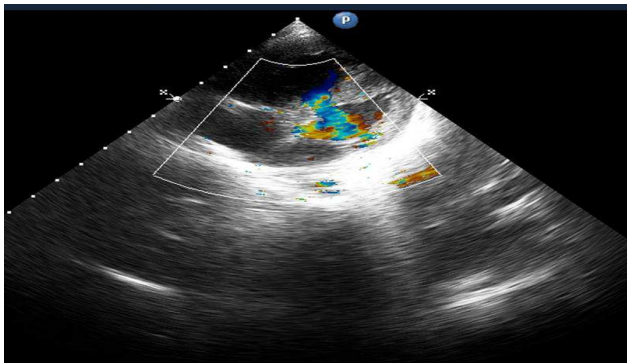


Figure 2: Echocardiographic picture showing the shunting of blood from right ventricle to left ventricle – reversal of shunt (Eisenmenger's physiology).

Skeletal survey revealed spina bifida at T9 and T11 with butterfly vertebra at T10 and T11 and mild scoliosis with concavity toward right. Ultrasonography of abdomen was normal. Karyotyping done on peripheral lymphocytes was normal.

Discussion

Kabuki Make up Syndrome is a multiple congenital anomaly syndrome which was first described in the Japanese population in 1981.^{7,8} Some major, minor and behavioral features have been described with this syndrome.⁹ Major features consists of characteristic facies (100%), long palpebral fissures(99%), abnormal dermatoglyphics(96%), short nasal septum (92%), persistent finger pads(89%), malformed ears(87%), arched eyebrows(85%), Intelligent quotient<80(84%), depressed nasal

tip (83%), short 5th digit (79%), joint laxity(74%), high arched palate(72%), abnormal dentition(68%), hypotonia(68%), short stature (55%)and ptosis(50%). Minor features include cardiovascular abnormality(42%), cleft lip/palate(35%), scoliosis(35%),deformed vertebrae or rib(32%), kidney and urinary tract malformation (28%) , premature thelarche (28%), hearing loss(27%), lower lip pits(27%), cryptorchidism (24%), preauricular pits(22%), hip dislocation(18%) and seizures(17%). Behavioral features include having a happy disposition(87%), liking routine(74%), unusually sociable(50%) and engaged in minimal interaction with others (30%).⁹ The index child had 7 major(characteristic facies, long palpebral fissures, persistent finger pads, arched eyebrows, short fifth digit, hypotonia, short stature) 4 minor(cardiovascular abnormality, cleft palate, scoliosis, deformed vertebrae) and 2 behavioral features(happy

disposition, unusually sociable) mentioned above.

Various congenital heart defects have been described in this syndrome since 1980s. Cardiovascular anomalies has been described in 31-58% of patients with Kabuki syndrome in various studies most of which had described isolated heart defects^{10,11}. Particularly the incidence of cardiovascular anomalies seems to be lower in the Japanese population with one review of 62 Kabuki patients reporting an incidence of 31%.² While the incidence of cardiovascular anomalies in non Japanese population has been reported from 58-83%.^{12,13,14} Hughes et al (1994), in their study of 20 patients with Kabuki syndrome had an estimated incidence of cardiovascular anomalies of 30% in which 25% had more than one documented cardiac malformation which, in all cases, included an aortic coarctation.¹⁰

Although more than about 100 cases of cardiac defects in Kabuki syndrome have been described, combined defects have rarely been described. Hughes et al. 1994, described a combination of coarctation with ventricular septal defect, patent ductus arteriosus and bicuspid aortic valve in 5 of their patients.¹⁰ But the recent extensive study and review by Digilio et al. 2001, did not reveal any such combined anomalies.¹¹ Almost all the 60 cases in their study and 70 cases reviewed by them had isolated heart defects. Recently, coarctation of aorta with non obstructing anomalous left pulmonary artery branch (aLPA) from right pulmonary artery (RPA) has been reported in a neonate with Kabuki syndrome.¹⁷ Another novel case with Kabuki syndrome diagnosed with hypoplastic left heart syndrome, and right-sided partial anomalous pulmonary venous drainage to the inferior vena cava has been reported.¹⁶ The authors chose to report this

patient as she had multiple congenital heart defects namely, bicuspid aortic valve, coarctation, ventricular septal defect and patent ductus arteriosus and as the child also developed pulmonary hypertension with reversal of shunt with the ratio of pulmonary flow to systemic flow greater than 1 at a very early age, which has not been reported till date. Although Kabuki syndrome is said to be not associated with serious complications with a good prognosis to adulthood, children with multiple congenital heart defects like ours can have a catastrophic outcome at an early age. This could have been prevented by early diagnosis and appropriate surgical management of the congenital heart defects.

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