

First Clinical Case report of a Libyan Girl with Kabuki Syndrome and Literature review

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Abstract

Kabuki syndrome is a rare autosomal disorder, diagnosed by presence of dysmorphic facies, mental retardation, short stature, skeletal and visceral abnormalities and cardiac anomalies. It is caused by a mutation in the KMT2D gene also known as MLL2 and in fewer cases due to mutations in the KDM6A gene. We report on the first description of a 2-year-old Libyan girl with Kabuki syndrome with typical facial features, skeletal abnormalities (fingertip foetal pads, brachydactyly, clinodactyly of the little finger, single simian crease, and abnormal lower limbs), cardiac anomalies, biliary atresia, single kidney and developmental dysplasia of the hips DDH. The patient also suffered from recurrent infections which has been noted in KS patients. The patient so far has shown normal neurological and behavioural development, but still has high liver enzymes.

Key words: Kabuki syndrome, Coarctation of the aorta, Biliary atresia, Advanced paternal age.

Introduction:

Kabuki syndrome KS (also known as Kabuki-makeup syndrome or Niikawa-Kuroki syndrome) is a rare genetic disorder first described in Japan in 1981¹. It is estimated to occur at a rate of 1 / 32000 births in the Japanese population; it has also been reported in other populations including Northern European, Brazilian, Filipino, Vietnamese, Arab, East Indian,

Chinese, Mexican, African, Australian and New Zealand³. The Kabuki-makeup name was given because its characteristic facial features resembled the makeup of actors in Kabuki – traditional Japanese theatre -⁴. It is characterized by distinct dysmorphic facial features associated with mild to moderate developmental delay, postnatal growth retardation, skeletal abnormalities

(deformed spinal column with or without sagittal cleft vertebrae and brachydactyly), dermatoglyphic abnormalities and less frequently visceral abnormalities (involving heart, kidneys, and gastrointestinal system), precocious puberty, and susceptibility to infections⁴. The specific facial features include elongated palpebral fissures with eversion of the lateral margins of the lower lids, wide set eyes, arched eyebrows with sparseness in the lateral one-third, broad and depressed nasal tip, prominent ears, and a cleft or high arched palate⁵⁶. KS is an autosomal dominant disorder that arises *de novo* in the majority of cases⁷. Most of KS cases are caused by mutations in the lysine methyltransferase 2D (*KMT2D*) gene, also

Case report

A 3-day old girl presented to our neonatal department with history of poor feeding, reduced activity and jaundice. She is the product of full term normal spontaneous vaginal delivery with meconium stained liquor, with a birth weight of 3.6 kg. Born to a non-consanguineous couple, a 43 years old mother and 60 years old father. On examination, she was lethargic, icteric and had facial dysmorphic features as shown in figure 1, long palpebral fissures, everted

known as *MLL2*, while 5-8% of cases are caused by mutations in the lysine demethylase 6A (*KDM6A*) gene. In approximately 30% of individuals with a clinical diagnosis of KS, the genetic cause remains unknown. Both *KMT2D* and *KDM6A* encode proteins that belong to the histone modification machinery. Defective *KMT2D* or *KDM6A* activity leads to imbalances in the histone marks on downstream target genes, resulting in errors in differentiation during embryonic development⁸.

Here we describe a case of a Libyan girl with KS associated with coarctation of the aorta and biliary atresia. This is the first Libyan KS patient - as far as we know - to be reported in literature.

lower eyelids, orbital hypertelorism, long and curved eyelashes, high-arching eyebrows with sparse hair in the lateral one third, depressed and broad nasal bridge, flat nasal tip, large anteverted ears. Examination of upper and lower limbs showed fingertip foetal pads, brachydactyly, clinodactyly of the little finger, single simian crease, and abnormal lower limbs.



Figure 1 Typical patient abnormality (A) dysmorphic facies (arched eyebrows, long palpebral fissures, long eyelashes, epicanthus, depressed nasal tip), (B) large ears, (C) brachydactyly of feet, (D) short fifth digit with clinodactyly, (E) fingertip pads, (F) single palmar crease.

Other positive findings on examination were as follow: Pericardial examination revealed an ejection systolic murmur at upper left sternal border, weak femoral pulses. Blood pressure in the upper limb above 97th centile (128/80mmHg). Hip examination showed a clunk of the left hip joint. The liver function test showed a high total serum bilirubin of 14.5mg/dl with 6mg/dl direct bilirubin. The septic screen showed a growth of *E. coli* in urine culture and she received a course of cefotaxime and amikacin. The serum bilirubin level declined for a while but was still persistent at 2weeks of age and the skin was yellow greenish in colour. Total serum bilirubin was 14mg/dl of which mainly was direct bilirubin 10mg/dl. Liver enzymes were

high ALT(SGPT) 150IU/l, AST(SGOT) 320U/l. Abdominal ultrasonography showed that liver is normal in size and shape, homogenous in echogenicity without focal lesions, no intrahepatic biliary dilatation. Cystic lesion in liver segment VII about 1.5x2 cm. No stones or acute inflammatory signs in the gallbladder. CBC and PV with normal calibre about 0.5 cm and 1.2 cm. spleen is normal in size, homogenous in echogenicity without focal lesions. Normal pancreatic echogenicity without focal lesions. Enlarged left kidney with no dilation of PCS, normal cortical echogenicity without focal lesions nor stones. Urinary bladder is full and no clear free fluid collection in pelvic cavity. No

lymph nodes enlargement in para-aortic nor mesenteric regions. Conclusion of U/S biliary atresia with cholydocal cyst, compensatory big left kidney with no dilatation of PCS. At 32-days of age an MRI of abdomen and pelvis with MRCP technique, axial T1, T2 weighted images, coronal T1, T2 weighted images post contrast study done, finding evidence of well-defined cystic lesion in gallbladder region with ill-defined biliary radicals. Normal signal intensity of liver. No masses or focal regions. Normal size, parenchyma thickness, and signal intensity of left kidney, with no hydronephrosis nor masses. Normal appearance of pancreas, adrenals, scanned portion of the aorta and IVC. No ascites nor intraabdominal collection. Conclusion of a well-defined cystic lesion at gallbladder region with ill-definition of biliary radicals with ill-definition of CBC suggestive of biliary atresia with a solitary ectopic left kidney. At 39-days of age MRCP technique SSFSEE sequence in axial and coronal section with reconstructed images done and reported secular cystic dilatation

communicated with cystic duct. Normal shape and calibre of the CBC and intrahepatic biliary ducts with no evidence of intraluminal filling defect. Normal both hepatic duct origin and morphology. Normal calibre of the pancreatic duct (Wirsung duct), with no pancreatic duct accessories. Normal appearance of the gallbladder with no evidence of filling defect. Conclusion of secular cystic dilatation communicated with cystic duct. At 42-days of age a porto-enterostomy with end to side small bowel anastomosis (Kasai operation) done and early cirrhotic liver changes seen. Microscopic examination of the resected part showed that section from gallbladder examines reveals columnar epithelial lining with underlying lamina propria and muscularis propria, show no significant abnormality, attached cystic mass shows cyst lined with columnar epithelial cells with ulcerated area of granulation tissue formation, mild inflammation and thick fibrous tissue of the underlying stroma. No evidence of atypical cells.



Figure 2CT scan angiography showing coarctation of the aorta

Echocardiogram revealed situs solitus, A.V-V.A concordance, small partially closed VSD, severe coarctation of the aorta, severe left ventricular hypertrophy, interventricular septum diameter 9mm, left ventricular LVID d15mm. EF80%, pulmonary pressure gradient 35 mm HG with diastolic runoff, normal pulmonary artery. Colour Doppler ultrasound show no sign of renal artery stenosis. She was put on antihypertensive agents (Inderal, Captopril), ursodeoxycholic acid. CT scan angiography of the aorta showed severe hypoplasia or narrowing of the segment within junction between aortic arch and descending aorta distal to the origin of the left subclavian artery. The narrowing segment measured 2.9mm in length and 3.3mm in transverse diameter. The

diameter of the descending thoracic aorta measures 10mm distal to stenosis. Small pre-stenosis patent ductus arteriosus between aorta and main pulmonary arteries. Normal origin of ascending aorta with no stenosis and measures 11mm. Normal origin and calibre of the main pulmonary trunk. Left pulmonary artery normal size with no evidence of intraluminal thrombosis. Normal drainage of pulmonary veins into left atrium with no venous anomalies. Normal drainage of IVC, SVC into the right atrium. Repair of the coarctation was done at age of 5 months, and after which the antihypertensive drugs were gradually stopped successfully.

Ultrasonography of hip joints showed developmental hip dysplasia of the left hip joint.

Cerebral magnetic resonance of the brain was normal. Other skeletal radiographic survey was normal. Micturating cystourethrogram was normal. Thyroid function test was normal.

At 3 months of age she developed cholangitis. She also had recurrent

Discussion

KS is a rare congenital disease characterized by distinctive dysmorphic facial features and mental disability. Its incidence rate has been previously described to be approximately 1 in 32,000 individuals; however, this rate may be underestimated due to missed diagnosis. KS is generally diagnosed clinically based on the combination of five main criteria, postnatal growth retardation, development of mental disability, typical facial features, skeletal anomalies, and foetal fingertip pads⁹. Our study describes a case of a young Libyan girl with KS, characterized by typical facial appearance, including long palpebral fissures, everted lower eyelids, long and curved eyelashes, high arching eyebrows with sparse hair in lateral one third, broad depressed nasal bridge with flat nasal tip, and large ears,

infections in form of pneumonia, acute otitis media and recurrent urinary tract infections.

Now she is a 2-year-old thriving normally, with normal physical and neurological development. Her last liver function test shows an elevated liver enzymes, AST (SGOT) 155U/l, ALT (SGPT) 132 U/l, total bilirubin 0.4 mg/dl, direct 0.3 mg/dl, indirect 0.1 mg/dl, GGT 206 U/l and ALP 420 U/l.

and skeletal anomalies, referring to brachydactyly, clinodactyly and foetal fingertip pads, and visceral anomalies, with single left kidney, heart anomalies and coarctation of the aorta, and biliary atresia. She also showed recurrent respiratory tract infections and recurrent urinary tract infections.

Congenital heart defects CHDs are relatively common in KS, mostly coarctation of the aorta and left sided anomalies^{10, 11}. In a study by Digilio et al. where they analysed cardiac characteristics and differences in sex prevalence of specific CHDs in a series of patients with KS and literature review, among 60 patients, CHD was diagnosed in 35 (58%). Coarctation of the aorta (CoA) (23%), atrial septal defects (ASD) (20%), and

ventricular septal defects (VSD) (17%) where the most frequent CHDs in those patients and in previous reports from literature ¹². Digilio et al. also categorized the CHDs associated with KS into: (1) left-sided obstruction as coarctation of the aorta (22.8%), aortic stenosis (5.7%); (2) septal defects: ventricular septal defects (17.1%), secundum atrial septal defects (20%); (3) right-sided obstructions: pulmonary stenosis (2.8%); (4) extracellular matrix defects: atrioventricular canal (5.7%); (5) outflow/conotruncal defects: tetralogy of Fallot (11.4%), double outlet right ventricle (2.8%), d-transposition of the great arteries with intact ventricular septum (2.8%); (6) targeted growth defects: partial anomalous pulmonary venous return (5.7%); and (7) cell death defects: Ebstein's anomaly (2.8%) ^{13, 14}. Our case had a small partially closed ventricular septal defect and a severe condition of coarctation of the aorta which was corrected surgically at age of 5 months.

Biliary atresia (BA) is an inflammatory cholangiopathy of infancy characterized by progressive fibrosclerosis and obliteration of intrahepatic and extrahepatic bile ducts ¹⁵. It is presented clinically in neonatal period by direct or conjugated hyperbilirubinemia, pale stools, dark urine, hepatosplenomegaly and progressive

hepatic failure, and is the most common cause of neonatal jaundice, representing approximately 25 – 30 % of cases ¹⁶. Biliary atresia has been reported in some rare genetic syndromes including Alagille syndrome, Progressive familial intrahepatic cholestasis type 6, Crigler-Najjar syndrome, Kabuki syndrome, and others. According to this association conducted a whole exome sequencing to detect for rare genetic disorders in 20 infants with biliary atresia who underwent hepatic portoenterostomy (Kasai's operation) and found an association in one case with the mutated gene *MLL2*¹⁷, which has been suggested as a major cause of KS ¹⁸. Masui et al. reported a case of a male baby diagnosed with biliary atresia at age 4 days and after running a whole-exome sequencing on DNA from his parents a mutation was identified in *KDM6A* which lead to the hypothesis of *KDM6A*'s association with hepatic malformation through its association with notch signalling pathways, and as a gene mutation in *KDM6A* has been identified in some cases of KS, we can argue of an association between KS and biliary atresia ¹⁹. The patient still has slightly elevated liver enzymes as was mentioned previously in the report and as is known that despite the Kasai portoenterostomy, the destructive bile duct injury progresses leading to

biliary cirrhosis in the majority of children¹⁶ and as such there will need to be constant followup and management for our patient in the future.

In addition to positive findings mentioned above, the parents advanced age and more specifically the advanced paternal age around 60 years at time of conception was to be taken into notice. The association between an advanced paternal age and a syndrome supports its genetic or epigenetic etiology and advanced paternal age association has been shown to be present in certain types of mutations²⁰. In a study by Armstrong et al. in which paternal age, cytogenetic abnormalities, and familial cases and their association with KS has been discussed and additionally explored syndromes with overlapping features has found that observed KS births are

underrepresented in young fathers and overrepresented in older fathers and the data has suggested that KS may be related to mutations associated with paternal aging²¹. As so, the advanced paternal age in our case may be used as a supporting evidence for this association.

An increased incidence of infections has been reported in KS, including otitis media and upper airway tract infections. Decreased IgA and IgG levels were observed in 79% and 42% of KS patients, respectively and severe immunodeficiency with hypogammaglobinaemia has been reported in several patients²²⁻²⁴. Our patient has suffered from recurrent acute otitis media, urinary tract infections and pneumonia in addition to the acute cholangitis which she had at age 3 months.

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