Kabuki syndrome-like features in monzygotic twin boys with a pseudodicentric chromosome 13

Sally A Lynch, Kathryn A Ashcroft, Simon Zwolinski, Connie Clarke, John Burn

Abstract
We present monzygotic twin boys with features of Kabuki syndrome. The twins were discordant for cleft palate and coarctation of the aorta. The occurrence of Kabuki syndrome in monzygotic twins has not been previously reported and reinforces the belief that this condition has a genetic basis. Chromosomal analysis on the boys showed a pseudodicentric chromosome 13 with an inactive centromere and satellite stalks at 13q12.1: 46,XY,psudodicentric dic(13)(13pter→13q12.11::13p12→13q11.00::13q12.11→13qter). Their phenotypically normal mother appears to carry the same pseudodicentric chromosome 13.


The twins were born at 31 weeks' gestation. This was the mother's third pregnancy by this partner. There was no parental consanguinity. The first pregnancy resulted in a 12 week miscarriage and the second pregnancy resulted in the birth of a normal boy. She had three other pregnancies by another partner all of which resulted in liveborn normal male children. This pregnancy was complicated by a threatened miscarriage at 5 weeks. Amniocentesis was performed on both fetuses because of maternal age and was reported as being normal. An antenatal ultrasound had shown a pericardial effusion and ascites in twin 1 (suggestive of a twin to twin transfusion) and an echogenic area over the liver in twin 2. At 29 weeks' gestation the mother was admitted to hospital because of loss of liquor. An emergency section was performed at 31 weeks because of decreased fetal heart rates. The twins were noted to be hypotonic at birth and were admitted to the special care baby unit.

Case reports

Case 1
Twin 1 weighed 1531 g at birth (3rd centile) and OFC was 26 cm (<3rd centile). Apgar scores were 6 at one minute and 9 at five minutes. A twin to twin transfusion had occurred resulting in polycythaemia in this twin. He was ventilated for three days. He remained in ICU for 10 weeks where he was noted to be hypotonic. Tube feeding was instigated because of failure to thrive. Dysmorphic facial features noted at birth including upward slanting palpebral fissures, large protruding ears, retrognathia, and a high arched palate. He had a coarctation of the aorta with an aberrant right subclavian artery. This was repaired at 6 months of age. Global developmental delay was noted at an early age.

At 14 months of age, his height (68 cm), weight (5.6 kg), and head circumference (43 cm) were all below the 3rd centile. Dysmorphic features noted at this stage included upward slanting palpebral fissures, prominent eyes, arched eyebrows, hypertelorism, large ears, a small carp shaped mouth with a smooth philtrum, and a thin upper lip (figs 1 and 2). A high arched palate with retrognathia was also noted. He had fifth finger clinodactyly with fetal pads (fig 3). Other dysmorphic features included broad big toes and a sacral dimple. Developmental milestones were significantly delayed, he was unable to sit up or roll over, and he had no speech.

Case 2
Twin 2 weighed 1313 g at birth (3rd centile) and OFC was 25.5 cm (<3rd centile). Apgar scores were 7 at one minute and 9 at five minutes. He was not noted to have any problems at birth. He was noted to be hypotonic at birth and was not ventilated. He remained in the NICU for 8 weeks where he was noted to be hypotonic. Tube feeding was instigated because of failure to thrive. He had dysmorphic facial features noted at birth including upward slanting palpebral fissures, large protruding ears, retrognathia, and a high arched palate. He had a coarctation of the aorta with an aberrant right subclavian artery. This was repaired at 6 months of age. Global developmental delay was noted at an early age.

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Figure 1 Twin 1 showing upward slanting palpebral fissures, hypertelorism, and large ears.
scores were 2 at one minute and 8 at 5 minutes. He was ventilated for three days. A cleft of the soft palate was noted at birth, which was repaired at 7 months of age. Other dysmorphic features noted at birth included a wide nasal bridge, upward slanting palpebral fissures, prominent epicanthic folds, retrognathia, and cryptorchidism. His development was noted to be delayed at an early stage.

On examination aged 16 months, his height (68 cm), weight (6 kg), and head circumference (42 cm) were all below the 3rd centile. There was gross plagiocephaly on the left side. Other dysmorphic features included upward slanting palpebral fissures, arched eyebrows, hypertelorism, large ears, fifth figure clinodactyly with fetal pads, and cryptorchidism (figs 4 and 5). Chronic failure to thrive and recurrent infections led to repeated hospital admissions. He was unable to sit up and had no speech at 13 months of age. At the age of 15 months, he was admitted with a history of chronic con-
stipation, abdominal distension, and vomiting. A cholangiogram showed narrowing of the common bile duct owing to a moderately large retroperitoneal cyst which was also compressing the pylorus and duodenum. Surgery was performed to drain the cyst which contained bile. He developed klebsiella septicaemia which resulted in his death aged 16 months.

INVESTIGATIONS

A necropsy report on case 2 concluded that the cause of death was shock lung secondary to klebsiella septicaemia. Dysmorphic cardiac features noted at necropsy included a bicuspid aortic valve and a retro-oesophageal right subclavian artery which arose from the descending thoracic aorta. Two well circumscribed areas of entervation (approximately 50 mm in diameter) were noted in the diaphragm.

A skeletal survey was performed on both twins. Skull x ray of case 1 showed that the cranium was narrow in anteroposterior direction with an abnormally steeply sloping anterior cranial fossa. The coronal and lambdoid sutures appeared patent. No spinal abnormalities were seen. In the pelvis, lateral subluxation of both hips was present and the femoral capital epiphyses were incompletely covered by the acetabular roofs. There was a valgus deformity of the upper femora. Skull x ray of case 2 showed evidence of microcephaly with left plagiocephaly. Lumbar spine x ray showed evidence of slight scoliosis in the thoracolumbar region. A CT scan on twin 2 showed the plagiocephaly on the left side and a hypoplastic left anterior fossa.

PCR analysis using 12 poly(CA) repeats with an average heterozygosity of 75% confirmed monoygosity in the twins.

CYTOGENETICS

Peripheral blood lymphocytes were cultured by standard methods. GTG staining showed a structurally altered chromosome 13 in both twins and the mother (fig 6). Fluorescence in situ hybridisation was used to confirm a second but inactive centromere using 13/21 alpha satellite probe (Oncor). This finding was supported by C banding (figs 7 and 8). Silver nitrate staining showed the two unequal NOR/satellite stalk regions (fig 9), one in the short arm, the other proximal to the inactive centromere in the long arm. Secondary association, with other acrocentric chromosomes was observed (fig 10).

Chromosomal integrity was tested using All Human Telomere probe (Oncor) and indicated the conservation of a telomeric sequence at the end of the pseudodicentric short arm.

The most simple explanation of the pseudodicentric chromosome is the insertion of chromosome 13 centromere and satellite stalks at 13q12.11: 46,XY,psu dic(13)(13pter→13q12.11::13p12→13q11.00::13q12.11→13 qter). However, there is a slight possibility that the second centromere is derived from chromosome 21.

Unfortunately maternal grandparents were not available and the exact nature of the inserted material is unknown. The disparity of the two NOR/satellite stalk regions in the pseudodicentric 13 suggest inter- rather than intra-chromosomal insertion.

A cell line from twin 1 has been established at the European Collection of Animal and Cell Cultures under reference number AG0800.

Discussion

Kabuki syndrome was first described in Japan by Niikawa et al in 1981. The aetiology remains unknown. Most cases have been sporadic, although autosomal dominant inheritance has been suggested in one family.2 The apparent sporadic nature of the condition could be explained by a de novo chromosomal deletion or point mutation.

The classical features of Kabuki syndrome include postnatal growth retardation and mental retardation.1,3 The facial features are very specific and include long palpebral fissures with lower palpebral eversion, arching of the eyebrows, prominent ears, and micrognathia. Other features include the presence of fifth figure clinodactyly, fetal pads, and x ray abnormalities. Our patients had many features consistent with the diagnosis of Kabuki syndrome (table).

The presence of such an unusual chromosomal anomaly in the twins cannot be ignored despite its inheritance from a phenotypically normal mother. It is possible that a submicroscopic rearrangement/deletion has occurred. Alternatively, imprinting may play a role, although there is no evidence of imprinting in this region on chromosome 13.56 A third possibility is that a recessive gene has been exposed on the paternal chromosome 13.

Many abnormalities of chromosome 13 have been reported. We reviewed published cases...
Comparison of clinical and radiological features of cases 1 and 2 and 62 published cases of Kabuki make up syndrome

<table>
<thead>
<tr>
<th>Abnormalities</th>
<th>Case 1</th>
<th>Case 2</th>
<th>16 published cases</th>
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</thead>
<tbody>
<tr>
<td>Long palpebral fissures</td>
<td>+</td>
<td>+</td>
<td>16/16</td>
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<tr>
<td>Lower palpebral eversion</td>
<td>+</td>
<td>+</td>
<td>15/16</td>
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<tr>
<td>Postnatal growth retardation</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Arched eyebrows</td>
<td>+</td>
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<tr>
<td>Prominent ears</td>
<td>+</td>
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<td>Malformed ears</td>
<td>+</td>
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<td>13/16</td>
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<tr>
<td>Finger pads</td>
<td>+</td>
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<td>15/16</td>
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<td>Cleft palate</td>
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<tr>
<td>Recurrent infections</td>
<td>+</td>
<td>+</td>
<td>10/16</td>
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<tr>
<td>Micrognathia</td>
<td>+</td>
<td>+</td>
<td>10/16</td>
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<tr>
<td>Hypoplasia</td>
<td>+</td>
<td>-</td>
<td>7/15</td>
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<tr>
<td>Strabismus</td>
<td>-</td>
<td>-</td>
<td>5/15</td>
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<tr>
<td>Dislocation of hip</td>
<td>+</td>
<td>-</td>
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<tr>
<td>Heart defect</td>
<td>+</td>
<td>-</td>
<td>5/15</td>
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<tr>
<td>Seizures</td>
<td>-</td>
<td>-</td>
<td>5/16</td>
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<tr>
<td>Cryptorchidism</td>
<td>+</td>
<td>+</td>
<td>6/9</td>
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<tr>
<td>Eversion of diaphragm</td>
<td>-</td>
<td>+</td>
<td>1/16</td>
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<tr>
<td>Microcephaly</td>
<td>+</td>
<td>+</td>
<td>7/16</td>
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</table>

The phenotype associated with duplication in this region has some features in common with Kabuki syndrome. Dysmorphic features in common include hypertelorism, cryptorchidism, clindactyly, cleft palate, and heart defects. Their facial features were not reminiscent of the classical Kabuki face.

The presence of the Kabuki syndrome-like features in monozygotic twins is suggestive of a genetic basis for the disease. Chromosomal locations suggested in the past include 6q, 12q, X, and Yp. To these is added 13q12.11. For the present, this family may provide a unique insight into the pathogenesis of this disorder. Further work in the region of 13q12.11 using molecular probes may clarify the situation.

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