Emanuel syndrome with unique cardiac defects: a case series

Emanuel syndrome is a rare condition resulting from the presence of an extra chromosome composed of pieces of chromosomes 11 and 22. The clinical presentation varies – the main features of the syndrome include cleft palate, ear anomalies, heart defects, genital anomalies, hypotonia and mental retardation. This report describes two cases of Emanuel syndrome in infants with antenatal diagnoses of congenital heart defects. Extra cardiac features in this case series include microcephaly, hypotonia, cleft palate and necrotising enterocolitis.

Adnan Zafar
BSc, MBBS, MRCPCH
Neonatology Registrar
James Cook University Hospital, Middlesbrough
adnan157@doctors.org.uk

Milind Chaudari
MBBS, MD, MRCP
Consultant Cardiologist
Freeman Hospital, Newcastle

David Crossland
MBBS, MRCPCH
Consultant Cardiologist
Freeman Hospital, Newcastle

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Key points

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1. Emanuel syndrome results from an unbalanced translocation between chromosomes 11 and 22.
2. Infants with Emanuel syndrome have a very varied clinical presentation.
3. This case series considers antenatal diagnosis of cardiac defects and subsequent postnatal syndromic diagnosis.
4. Diagnosis of Emanuel syndrome has a profound impact on a baby's prognosis and future management.

Emanuel syndrome is caused by the presence of an extra chromosome, which is made up of the top and middle parts of chromosome 22 and the bottom part of chromosome 11. The extra chromosome is inherited from one of the parents. The carrier parent has the usual number of chromosomes however, chromosome 11 and 22 have switched pieces with no loss or gain of genes – a balanced translocation.

In 2004 members of the online parent support group, Chromosome 22 Central[1], successfully lobbied to have Emanuel syndrome added as an entry in the Online Mendelian Inheritance in Man (OMIM) database. Prior to this, there was concern among parents about the disparate names given to their children's condition, which impeded their ability to find support, eg supernumerary derivative 22 syndrome, partial 11q trisomy, derivative 11;22 syndrome and partial trisomy 11;22. 'Emanuel syndrome' was suggested by the parent group in recognition of Dr Beverly Emanuel's cytogenetic work and her molecular characterisation of the chromosomal breakpoints.

Heart defects are reported in 57% of cases of Emanuel syndrome with the three most common defects being atrial septal defect, ventricular septal defect and patent ductus arteriosus[2,3]. Also reported are coarctation of the aorta, pulmonary stenosis and total anomalous pulmonary venous return[4]. Rare cardiac defects include tetralogy of Fallot, truncus arteriosus, transposition of the great arteries and tricuspid atresia. Cardiac surgery is required in 30% of those cases with heart malformations[2].

Other conditions associated with Emanuel syndrome include cleft palate, genitourinary tract malformations, intestinal atresias and craniofacial dysmorphism. There is significant variability in the facial appearance of individuals with Emanuel syndrome. The most common facial features observed include hooded eyelids, deep-set eyes, upslanting palpebral fissure, facial asymmetry and ear anomalies.

Developmental delay is common and can be significant in infancy[2]. The most frequent anomalies consistent with developmental delay include defects affecting the midline, such as Dandy-Walker malformation; hypoplasia of the corpus callosum, pons and cerebellar vermis; dilatation of the third and fourth ventricles and trigonocephaly[5]. Microcephaly was reported in only 23% of subjects in one study, while another study stated that 100% of individuals with Emanuel syndrome had microcephaly[6].

Failure to thrive is a common problem in the neonatal period and into childhood[2]. In neonates, poor feeding due to hypotonia and the presence of cardiac and gastrointestinal malformations are the most likely cause. Aside from feeding issues, which are ongoing in childhood, recurrent infections may be partly responsible for failure to thrive as these children get older.

Emanuel syndrome is rare – only about 200 cases have been reported in the literature. Chromosome 22 Central is aware of approximately 500 cases worldwide but it is presumed that there are more cases, especially in non-English speaking countries[1]. The infant mortality

rate in Emanuel syndrome is unknown, yet follow-up has shown some long-term survival in affected children. A poor prognosis is mostly due to central nervous system problems, however current literature provides limited information on outcomes beyond the first few years of life.

Clinical presentation

The two unrelated cases reported in this article presented within a six-month period in the same hospital in the north east of England, between September 2012 and March 2013. The infants were noted to have dysmorphic features at birth. In both cases, a genetic team was consulted and chromosome testing revealed an extra chromosome containing material from chromosomes 11 and 22.

Case 1

A female Caucasian infant was born at term with a birth weight of 2.8kg. Her antenatal diagnosis was pulmonary atresia with an intact ventricular septum. This was confirmed by a postnatal echocardiogram, which revealed a bipartite right ventricle (RV), good sized pulmonary artery and confluent branch pulmonary arteries. There was no antegrade flow across the pulmonary valve. A chest X-ray showed a normal sized heart and normal looking lung fields. On examination, the infant was noted to have dysmorphic features that included ear tags, skin tags, a small chin and microcephaly. This prompted the genetic testing that revealed Emanuel syndrome. The infant was also noted to have mild hypotonia and talipes of the feet but no genital anomalies. An ophthalmological assessment revealed a small eye (microphthalmia). The infant developed mild renal failure early in the course of her stay at the cardiac intensive care unit; however a renal ultrasound scan showed structurally normal kidneys.

The infant has undergone the first stage of palliative cardiac surgical correction, ie pulmonary valvotomy. Follow-up showed a borderline result with still no antegrade flow across the pulmonary valve and moderate tricuspid regurgitation on an echocardiogram. The most recent echocardiogram showed a deterioration in terms of a smaller RV in line with morphological monopartite ventricle. A univentricular repair is planned for sometime in the future (the Fontan procedure) but in the meantime the infant has been diagnosed with necrotising enterocolitis and has undergone surgical treatment for this.

The infant's parents have received genetic counselling with genetic testing, which showed that the mother is a carrier of a balanced translocation between chromosomes 11 and 22.

Case 2

The second case, a male infant of south east Asian origin born at 37 weeks' gestation by induction of labour due to fetal distress, had an antenatal diagnosis of interruption of the aortic arch. A postnatal echocardiogram revealed mitral hypoplasia, a small left ventricle, aortic hypoplasia and hypoplastic arch. The diagnosis of hypoplastic left heart syndrome came as a shock to the parents who expected a better prognosis in light of the antenatal diagnosis.

The infant was born in a stable condition and a chest X-ray showed a normal sized heart and hyperaemic lung fields. Shortly after birth he was started on alprostadil to maintain ductus arteriosus patency. On examination he was noted to have a small chin, a cleft palate and growth restriction. There were signs of acute kidney injury yet an abdominal ultrasound scan was normal. Due to excessive pulmonary flow the infant underwent pulmonary artery band insertion. He was started on continuous positive airway pressure (CPAP) to facilitate systemic circulation by negative intrathoracic pressure.

The genetic team was consulted and genetic testing revealed Emanuel syndrome. The parents had a detailed discussion with a geneticist, a cardiologist and cardiac surgeon. The different options were described, ie univentricular heart repair (palliative repair) with follow-up or withdrawal of care. The parents decided on a palliative care pathway. The child was sent home on palliation at three weeks of age and died within 24 hours.

Discussion and conclusion

Emanuel syndrome is a very rare condition with only a few case reports published. It is extremely unusual for two unrelated cases to present at the same hospital within a six-month period. There have been no reports of infants born with antenatal diagnosis of cardiac defects and subsequent postnatal syndromic diagnosis, as described here. According to one study, abnormalities detected by ultrasound during pregnancy were only reported in 16% of cases[2], which is surprising given the high rate of congenital anomalies seen in this syndrome.

Congenital heart defects have been reported in the literature, ranging from mild to severe, but there appear to be no data on the long-term prognosis for children with severe cardiac defects requiring palliative correction, as presented in this report.

Diagnosis has a profound impact on prognosis and future management. Although there are no clear cut mortality data for these children, a poor prognosis for this syndrome resulted in one family in this report deciding on a palliative care pathway.

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