Two Cases of Emanuel Syndrome in a UK District General Hospital

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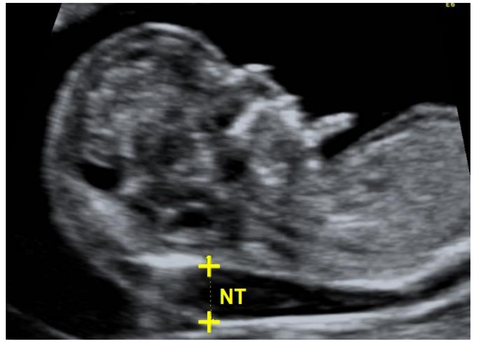
Background:

An unbalanced translocation between chromosomes 11 and 22 is described as Emanuel syndrome. It was first described in 1980 by Beverly S. Emanuel and Elaine H. Zackai. It manifests with distinct phenotypic characteristics including severe intellectual disability, microcephaly, failure to thrive, ear abnormalities, palatal defects, micrognathia, kidney anomalies, congenital heart defects and genital abnormalities in males. Mortality rate is high, with most deaths occurring in the first few months of life. The most common chromosomal abnormality is a supernumerary derivative chromosome 22 [der(22)]. More rarely, the chromosomal imbalance consists of a balanced (11;22) translocation carrier as well as the supernumerary derivative chromosome. There are individuals with Emanuel syndrome currently living who are into their 30s. Information on the average lifespan of an individual with Emanuel syndrome is not available but it really depends on a number of things, most important being the severity of any birth defects. We discuss 2 cases of Emanuel syndrome, presenting differently. These cases presented before the recent advances in next generation sequencing (NGS) and the discovery of cellfree fetal DNA (cfDNA), non-invasive prenatal testing (NIPT). The new technology has brought profound changes to detect common autosomal aneuploidies and genetic conditions early in pregnancy using a maternal plasma test and this is likely to be the way forward for diagnosing of Emanuel Syndrome antenatally. Antenatal utrasound and MRI will help to assist with diagnosing the structural defects.



Case 1

A 22 year-old G1P0+0 presented to maternity triage at 37+5weeks, Bulgaria the night before. She spoke little English. There was no information about previous antenatal care. There was no fetal heart present and a 2.5kg stillborn baby was delivered later that day. Autopsy was declined, but fetal karyotype confirmed a male result consistent with Emanuel Syndrome. There was a gain of the sub-telomeric region of chromosome 11q and of the subcentromeric region of 22q, likely to represent an additional derivative of chromosome 22 from a translocation between chromosome 11 and chromosome 22. Maternal testing showed a balanced reciprocal translocation between long arms of chromosome 11 and 22 with break points at 11q 23 and 22q 11 with a future risk of chromosomally unbalanced conceptions leading to an abnormal fetus. She was referred for genetic counselling.

Case 2

A 43 year old G3P2+0 booked with a dating scan at 12+1 weeks showing severe scalp and anterior abdominal wall oedema with a nuchal translucency of 6.5mm. Individual risk of trisomy 21 on combined test was 1:5. Chorionic villus sampling was performed. The initial QF-PCR was normal but microarray showed a male fetus with trisomy 22 (arr [1-21]x2, [22]x3, [XY]x1) consistent with Emanuel syndrome. Multiple scan abnormalities were picked up including small for gestational age, complex cardiac anomalies, a small cerebellum, Dandy Walker variant, cleft lip and palate and possible tracho-oesophageal fistula. The couple were counselled about significant risk of intra-uterine or neonatal death and likelihood of severe learning difficulty and need for multiple surgeries. They remained committed to the pregnancy despite poor prognosis. After discussion with neonatal palliative care consultant a plan was made for comfort care. She attended at 40+12 in spontaneous labour and a live male infant weighing 2085g was delivered.

Postnatal echo showed AVSD and pulmonary valve atresia. Craniofacial abnormalities included bilateral cleft of hard and soft palates, microcephaly with overriding sutures, low set ears, micro-opthalmia of the right eye and cat-eye on the left. There was congenital trachea-oesophageal fistula without atresia, imperforate anus and ambiguous genitalia. Musculoskeletal problems included bilateral rocker-bottom feet, right sided talipes and possible fixed flexion joint deformities. He had reduced tone globally and newborn reflexes were absent. He became hyponatraemic and developed renal failure. He received comfort care until he died at 22 days of age.

Discussion

Emanuel syndrome is a rare chromosomal disorder which manifests with distinct phenotypic characteristics including intellectual disability, microcephaly, ear abnormalities, palatal defects, micrognathia, kidney anomalies, congenital heart defects and genital abnormalities in males. There is a high mortality rate. The most common chromosomal abnormality is a supernumerary derivative chromosome 22 [der(22)]. Prenatal diagnosis is unusual because ultrasound findings lack specificity (Carter et al. 2009). Detection of ultrasound abnormalities should alert obstetricians to perform cytogenetic testing for definitive diagnosis. Ideally, more specific non-invasive pre-natal screening markers for Emanuel syndrome could facilitate early diagnosis. Walfisch et al. (2012) suggest that increased nuchal translucency and low pregnancy-associated plasma protein A (PAPP-A) could be associated with Emanuel syndrome, however PAPP-A in our second case was not exceptionally low (0.70MoM). Recent research (Luo et at 2020) has shown NIPT could effectively identify Emanuel syndrome, which may indicate risks of a parent being a balanced rearrangement carrier. The followed confirmation test for positive sample is necessary and ensures the accuracy of the diagnosis. This was not available to our patients but availability should be discussed with the local laboratory.

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