

# Diagnostic and counselling dilemmas arising from prenatal sonography with radial ray defects

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## Citation

N Massiah, C Boon, V Bamigboye. *Diagnostic and counselling dilemmas arising from prenatal sonography with radial ray defects*. The Internet Journal of Gynecology and Obstetrics. 2008 Volume 11 Number 2.

## Abstract

Primary infertility led to conception by in vitro fertilisation. Anomaly scan revealed upper limb defects. After termination of pregnancy, post mortem found radial ray defects and facial dysmorphism. Fetal chromosomal analysis, parental karyotyping and genetic studies were normal. Difficulty in this case lay with determining a definitive diagnosis which has implications on recurrence and counselling. Nager syndrome is the closest possible diagnosis. This case shows that it is essential for obstetricians to have good communication and counselling skills. A multidisciplinary team approach is important including the fetomaternal specialist, geneticist and pathologist.

## CASE REPORT

A 33 year old nulliparous woman and her 38 year old partner presented with a history of trying to conceive for 2 years. There was no family history of congenital, chromosomal or genetic conditions. Male factor infertility was identified with a total sperm count of 16 million, 1% motility and normal morphology of 5%. Serum progesterone was low, indicating anovulation. Hysterosalpingography revealed tubal patency. They conceived by intra-cytoplasmic sperm injection (ICSI).

At 7 weeks amenorrhea, ultrasound scan confirmed a 7 weeks size intrauterine pregnancy. Routine antenatal booking blood investigations were normal. They declined to have the serum screening triple test. The 20 week anomaly scan showed an abnormal left thumb, right radial hypoplasia and an absent right thumb. The left thumb was globular in appearance and there were no bones connecting it to the hand. Fetal karyotyping was declined. The couple chose to have a medical termination of pregnancy which was carried out without any complications.

Consent was given for a post mortem to be performed. A female fetus was found with asymmetric growth restriction, facial dysmorphism with malar and mandibular hypoplasia, mild lung hypoplasia, limb malformations consisting of right radial aplasia, absent right thumb, hypoplasia of the left radius, ulna and thumb; and absent first metacarpal. Fetal chromosomal analysis was normal. Parental karyotyping and genetic studies were normal. The couple also had consultations with a clinical geneticist and bereavement

counsellor.

## DISCUSSION

Radial ray defects are not common. The presence of bilateral radial ray defects increases the likelihood of a syndromic diagnosis. Syndromes with this type of upper limb defect are Fanconi's pancytopenia syndrome, Holt-Oram syndrome, Okihiro syndrome, VATERR association and TAR syndrome<sup>1</sup>. The most severe of these syndromes is Fanconi's and was our principle concern after the anomaly scan.

Fanconi pancytopenia syndrome, an autosomal recessive condition was first described in 1927<sup>2</sup>. This syndrome consists of radial hypoplasia, hyperpigmentation and pancytopenia. Fanconi's was ruled out as the diagnosis in our case because the fetal chromosomal analysis was normal. Chromosome breaks are a feature of Fanconi's anemia. The parental genetic screen revealed no abnormalities. Since Fanconi's is inherited in a recessive mendelian pattern, each parent must carry one affected gene<sup>2</sup>. Fanconi anemia has a 1 in 4 or 25% risk.

Holt-Oram syndrome was first reported in 1960 and consists of upper limb defects and cardiovascular anomalies. It is an autosomal dominant condition but with variable penetrance<sup>3</sup>. The upper limb defects may occur with different degrees of severity. The thumbs may be absent, hypoplastic, triphalangeal or bifid. The first metacarpal or radius may be absent or hypoplastic. There may also be defects affecting

the ulna, humerus, clavicle, scapula or sternum. The cardiovascular anomalies may be atrial septal defects, ventricular septal defects, conduction defects or hypoplasia of distal bloodvessels. In our case, although the upper limb defects were present, the post mortem did not reveal any cardiovascular abnormalities.

Okhiro syndrome is caused by a *SALL4* gene mutation on chromosome 20. It is a familial condition but there may be variability within families <sup>4</sup>. The syndrome comprises malformations of the hand and radius in combination with Duane anomaly (congenital disorder of ocular motility). It may present with features such as facial asymmetry, pigmentary disturbance, hearing impairment, external ear malformations, atrial septal defects, renal abnormalities or anal stenosis. In our case we do not know if the child would have developed eye conditions such as those of Okhiro. The only similarity between our case and Okhiro was the upper limb defects. There were no other similar features. In addition, none of the facial dysmorphic features found in our case, are recognised features of Okhiro syndrome.

VATERR Association is not a syndrome. Association describes the phenomenon where some malformations present collectively more frequently than you would expect by chance <sup>5</sup>. The acronym VATERR stands for Vertebral defects, Anal atresia, TE (tracheo-oesophageal) fistula with oesophageal atresia, Radial dysplasia and Renal dysplasia. Cardiac defects, single umbilical artery and growth deficiency have also been reported. Radial dysplasia occurs in 65% of reported cases and include hypoplasia of the thumb or radius, preaxial polydactyly or syndactyly. In our case, there was no evidence of vertebral or renal abnormalities on ultrasound scan. It was not possible to exclude anal atresia or a tracheoesophageal fistula on scan but corrective surgery is possible soon after birth. Children with VATERR association often have ongoing feeding and chest problems but in most cases will need less and less medical intervention as they grow older. Some children do not thrive and have slow development in early infancy. Most of them have normal neurological function and may benefit from intense rehabilitation or surgical care. The only feature of VATERR in our case was the radial dysplasia. At post mortem, the other features of VATERR association were absent and therefore make VATERR unlikely to be the cause.

TAR syndrome comprising radial aplasia and thrombocytopenia was first described in 1956 <sup>6</sup>. It carries an

autosomal recessive inheritance. The defects occur in both upper and lower limbs. There may be bilateral absence of the radius, abnormalities of the ulna such as hypoplasia, bilateral absence or unilateral absence; abnormal humerus, abnormal shoulder joint but the thumbs are always present. Forty percent of the live births reported have died as infants from haemorrhage. TAR syndrome has also been ruled out as the diagnosis, because the fetus did not have lower limb defects, only upper limb defects. The other difference was that TAR syndrome babies always have thumbs. In our case there was an absent right thumb. Most importantly the TAR syndrome babies always have bilateral absence of the radius <sup>7</sup> which was not the presentation in this case.

At post-mortem facial dysmorphism was identified. Holt-Oram syndrome, Okhiro syndrome, VATERR association and TAR syndrome do not have facial dysmorphism as a feature and none of their characteristic features were found at postmortem. Mandibulofacial dysostosis (Treacher Collins syndrome) and maxillofacial dysostosis have facial features close to Nager syndrome but do not have abnormalities of the radius <sup>8</sup>. Miller syndrome and Nager syndrome have both lower limb defects and facial dysmorphism.

Miller syndrome (Post axial acrofacial dysostosis syndrome) has an autosomal recessive inheritance pattern <sup>9</sup>. Craniofacial abnormalities may occur such as malar hypoplasia, vertebral bony cleft, downslanting palpebral fissures, colobomata of eyelids, ectropion, micrognathia, cleft lip or palate. The postaxial deficiencies make it distinct from Nager syndrome. Those affected by Miller syndrome have absent fifth digits of all four limbs. There may also have shortening or incurving of forearms, ulnar and radial hypoplasia and syndactyly. The fetus in this case report had both radial hypoplasia and malar hypoplasia, but the fifth digits of all the four limbs were present. Therefore, this fetus was not affected by Miller syndrome.

Of the syndromes with limb and/or facial defects Nager syndrome is the closest possible diagnosis that fits the clinical presentation of this case. It was first described in 1948 <sup>10</sup>. Nager acrofacial dysostosis syndrome comprises of radial limb hypoplasia, malar hypoplasia and ear defects. It may occur sporadically but autosomal dominant or autosomal recessive inheritance patterns have been reported <sup>11</sup>. The limb defects range from hypoplasia to aplasia of thumb, hypoplasia to aplasia of the radius, proximal radial ulnar synostosis and limitation of elbow extension and short

forearms. The craniofacial defects that may be present include malar hypoplasia, down slanting of palpebral fissures, high nasal bridge, micrognathia, partial to total lower eyelashes, atresia of the external ear canal and cleft palate<sup>12</sup>. Perinatal mortality is 20%<sup>8</sup>. They may develop conductive deafness, problems with articulation but have normal intelligence. They can live to adulthood but may have extensive orthodontic and surgical procedures<sup>13</sup>.

The complexities of this case lay not only in finding the definitive diagnosis. When the abnormality was detected, prior to termination, a differential diagnosis had to be made, the prognosis and quality of life for children affected by the suspected disorders had to be determined and explained to the couple. In addition, this was a childless couple who had gone through the difficult and emotional process of intracytoplasmic sperm injection which would make counselling even more a sensitive issue with the need for great empathy. The couple also had to be counselled on the recurrence of the abnormality in future pregnancies. Since parental chromosome and genetic studies were normal, and there was no family history of similar entities, the likelihood of recurrence was less. But we could not accurately quote a recurrence risk. It is essential for obstetricians to have good communication and counselling skills. A multidisciplinary team approach is important including the fetomaternal specialist, geneticist and pathologist.

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