45,X/46,XY mosaicism and Oculo-Auriculo-Vertebral Spectrum following an IVF pregnancy: a report and a discussion of their interrelationships

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Abstract The aetiology of Oculo-Auriculo-Vertebral Spectrum (OAVS) is unknown. We report a case following a prenatal diagnosis of 45,X/46,XY mosaicism in a pregnancy achieved by In-Vitro Fertilization (IVF) and describe evidence for the interrelationships of these phenomena and multiple births. This report extends the phenotypes associated with prenatally diagnosed 45,X/46,XY mosaicism and supports the association of OAVS and IVF.

Keywords OAVS · Mosaicism · Assisted reproduction techniques · Multiple births

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Introduction

Prenatally diagnosed 45,X/46,XY mosaicism has been detected in between 0.7 and 2.8 per 10,000 amniocenteses (Bardardottir et al. 1990) [2] and in a neonatal screening study the incidence was 1 in 15,000 (Nielsen and Wohler, 1990) [35]. In contrast to cases diagnosed postnatally, the majority of individuals are phenotypically normal and male (Chang et al. 1990 [5]; Hsu, 1989 [26]), the remainder have a variety of anomalies. However, no case of Oculo-Auriculo-Vertebral Spectrum (OAVS) has been reported.

The term Oculo-Auriculo-Vertebral ‘dysplasia’ was first suggested to describe patients with combinations of abnormalities including microtia, ocular abnormalities, mandibular hypoplasia and skeletal defects (Gorlin et al. 1963) [20]. The phenotype predominantly involves first and second branchial arch derivatives and is highly variable. ‘Goldenhar syndrome’ is often attached to variants of OAVS with ocular and vertebral abnormalities (Boles et al. 1987). The cause of OAVS is unclear. Proposals have included: vascular disruptions, (Poswillo, 1973) [39]

abnormal neural crest migration; (Lammer et al. 1985 [30]) monogenic inheritance; (Liu et al. 2004; Cohen, 1971 [9]; Poswillo, 1973; Stoll et al. 1998 [45]) chromosome disorders; (Lammer et al. 1985; Hathout et al. 1998 [23]) overripeness ovopathy; (Jongbloet, 1987 [28]) maternal drug exposure; (Gorlin RJ et al. 1990 [19]; Lessick et al. 1991 [33]) and multifactorial inheritance (Poswillo, 1973). Causal heterogeneity seems likely.

In this report the first case of OAVS following prenatally diagnosed 45,X/46,XY mosaicism is described and interrelationships between OAVS, multiple births and 45,X/46,XY mosaicism are explored.

Case report

The proband was born to non-consanguineous parents of Australian-English heritage. Maternal and paternal ages were 33 and 38 respectively. The pregnancy was achieved via Intracytoplasmic Sperm Injection (ICSI). There was no maternal illness or teratogen exposure during the pregnancy. Folic acid 0.5 mg daily was taken from the 6th to the

12th week of pregnancy; there was no other licit or illicit drug use. There was vaginal bleeding at 9 weeks of pregnancy. The proband’s mother had no significant medical history. The proband’s father had testicular cancer, treated 8 years prior to conception, with platinum based chemotherapy and a peripheral blood stem cell transplant. There was no other significant family medical history. The couple had two well children, a 7-year-old conceived by unassisted means and a 4-year-old conceived through ICSI. First Trimester screening, at 13 weeks, demonstrated an increased Nuchal Translucency (NT) of 2.4 mm, subsequent chorionic villus sampling demonstrated 45,X/46,XY mosaicism, with 62% of cells having a 45,XY karyotype. Ultrasound performed at 14 weeks did not show any associated abnormalities and male genitalia were seen. NT was not commented upon in the report. Amniocentesis, to investigate the possibility of confined placental mosaicism, was declined due to parental concern of miscarriage. An ultrasound scan at 19 weeks did not show any anatomical abnormalities and the genitalia were reported as normal male. The

proband was born at 36 weeks gestation by spontaneous vaginal delivery, with a birth weight of 2720 g (50th percentile), length of 47 cm (50th percentile) and head circumference of 34 cm (50th percentile). He was reviewed at 3 days of age. Observed anomalies included: left microtia and limbal dermoid; right preauricular skin tags; a tongue that was bifurcated in its anterior third, with the portion to the left of the bifurcation being smaller than the right and the remaining tongue being tethered to the floor of the mouth and a small mandible. Genitalia were normal male and both testes were palpable in the scrotum. Skeletal survey revealed 13 ribs on the right, spinal abnormalities including hemivertebrae from T5–T7 and the lower cervical region and an upper thoracic scoliosis. Cranial ultrasound revealed a cavum septum pellucidum. Cardiac ultrasound, performed at day 3, demonstrated a patent foramen ovale. Abdominal and renal ultrasounds were normal. On day 4 Fluorescent insitu hybridisation on 500 interphase nuclei confirmed 45,X/46,XY mosaicism, with 95.2% and 4.8% of metaphases having 46,XY and 45,X karyotypes respectively. On review at 9 weeks of age: no further anomalies were found, however in view of back-arching with feeding a coordination swallow was performed and demonstrated silent aspiration. At 3 months of age the preauricular skin tags were excised and the bifid and tethered tongue was repaired. On review at 8 ½ months corrected age gross motor development was within normal limits and weight was 7.6 kg (less than the 25th centile) with a head circumference of 42.5 cm (less than the 50th centile). There were no new anomalies detected on examination.

Discussion

Supporting evidence for an association between MZ twinning and 45,X/46XY mosaicism includes: (1) A number of pairs of MZ twins in which one or both twins had 45,X/46,XY mosaicism have been reported (reviewed in Costa et al. 1998) [11]. Notably, in the majority of these cases the females had manifestations of Turner syndrome, and MZ twinning is more frequent in families of patients with Turner syndrome (Boles et al. 1987). (2) The report of MZ twinning in a sibship with 45,X/46XY mosaicism (Gantt et al. 1980) [17]. (3) A report of chimeric MZ twins

with a 45,X/46,XY karyotype (Gonsoulin et al. 1990) [18]. They had a 46,XY/45,X karyotype on foetal blood sampling and discordant tissue karyotypes (46,XY and 45,X). This discordance was attributed to chimerism arising from admixture of foetal blood between their circulations via vascular anastomoses. Some individuals with 45,X/46,XY karyotypes may be chimeras.

Supporting evidence for a relationship between OAVS and multiple pregnancies includes: (1) Reports of OAVS in multiple pregnancies. Both discordant (more than 30 pairs), (Bock, 1951 [6]; Boles et al. 1987; Berthelon and Cremer, 1968 [4]; Cordier et al. 1970 [10]; Papp et al. 1974 [37]; Schinzel et al. 1979 [42]; Setzer et al. 1981 [43]; Ebbesen and Petersen, 1982 [13]) and concordant MZ twins, (terHaar, 1972) [47]) as well as discordant dizygotic twins have been reported (Grabb, 1965 [21]; Heimann, 1968 [24]). Furthermore, OAVS has been reported in triplet infants (Yovich et al. 1985; Ferraris et al. 1999; Roesch et al. 2001 [40]). (2) Findings of epidemiologic studies. In a case-control series multiple gestations were almost 10 times more common among cases than controls (Lawson et al. 2002 [31]). Additionally, in a case series the number of twin pregnancies amongst cases, and amongst family members of cases was greater than the background twinning rate for that population (Werler et al. 2004) [48]. (3) The excess of malformations, including OAVS, in MZ twins. This has led to the consideration of a common cause for both malformations and MZ twinning (Schinzel et al. 1979) [4]. Associations of spontaneous foetal loss and OAVS. Multiple pregnancies may constitute greater than 12% of all natural conceptions, of which about 2% survive to term as twins and about 12% result in single births (Boklage, 1990) [7]. Most twins are lost very early in pregnancy and at least two thirds of twins evident at 10 weeks of gestation are singleton by the time of birth (Levi, 1976 [34]). Theoretically, the remaining singletons are at risk for structural congenital anomalies, including OAVS that are more frequent in twins. Therefore, singletons born with these anomalies may have started out as MZ twins (Hall, 2003) [22]. In this context, it is noteworthy that OAVS has been reported in a child whose monozygotic twin died in utero (Parisi et al. 1983) [38] and bleeding during the first trimester, as occurred in this case, has been associated with singletons affected with OAVS or microtia

(which may be a minimal manifestation of OAVS) (Parisi et al. 1983). In one of these pregnancies the first prenatal scan revealed a twin pregnancy. Furthermore, women who had experienced a previous spontaneous abortion had an approximately 70% increased risk of OAVS (Lawson et al. 2002). Mechanistically, given shared placental circulations of MZ twins, vascular disturbance, such as transient haemodynamic inequalities, embolic phenomena or haemostatic defects, may render the twin more liable to dysmorphic development (Boles et al. 1987) [8]. Therefore, one twin might manifest OAVS and the other be phenotypically normal or one twin might abort and the other manifest OAVS.

An additional aetiological consideration in this case is IVF. Specifically, as IVF has been associated with an increased risk of MZ twinning (Edwards et al. 1986; [14] Sills et al. 2000 [44]). Suggested mechanisms of MZ twinning in IVF include overripeness ovopathy and zona pellucida abnormalities. Overripeness ovopathy refers to the concept that ‘delay of either fertilization or ovulation ...[results in a]... continuum of reproductive casualties’ including dysplasias of one or more developmental fields (Jongbloet, 1987). Overripeness ovopathy has been suggested as a cause for OAVS in the setting of ‘high risk conceptions’ including IVF (Jongbloet, 1987). It is also noteworthy that of Jongbloet’s criteria for overripeness ovopathy those that are or may be met by the current case include: accompaniment of non-specific chromosomal aberrations, accompaniment of gonadal dysgenesis (as found in a proportion of cases with 45,X/46,XY mosaicism) and association with high-risk reproduction, including IVF. ICSI has been proposed to promote MZ twinning by disruption of the zona pellucida, by intentional holes (Alikani et al. 1994) [1] that predisposes to cleavage of the inner cell mass (Sills et al. 2000). A further postulated cause of MZ twinning, that may be relevant in this case, is that discordant cells within the blastocyst, arising from processes including chromosomal anomaly (which might include 45,X/46,XY mosaicism), mutation or differential imprinting may recognise each other as immunologically foreign resulting in inner cell mass separation (James, 2002 [27]; Hall, 2003). IVF has been postulated to disrupt imprinting (Cox et al. 2002) [12] and whilst there is no known imprinting disruption in OAVS, there is evidence for epigenetic disturbances of the BAPX1 gene

in this condition (Fischer et al. 2006) [16]. Interestingly, individuals with Beckwith-Wiedemann syndrome, which has been reported in discordant twins (Leonard et al. 1996 [32]; Orstavik et al. 1995 [36]), has been described on multiple occasions with IVF, and in the majority of these instances an imprinting defect has been demonstrated (Sutcliffe et al. 2006) [46]. It is also noteworthy that OAVS has been reported in a pregnancy achieved by ICSI, (Roesch et al. 2001) and that IVF is common to all reported cases of OAVS in triplets (Yovich et al. 1985 [49]; Ferraris et al. 1999 [15]; Roesch et al. 2001).

Possible sequences of events in this case are as follows: mitotic loss of a Y chromosome in a 46,XY conceptus, which preceded, and perhaps evoked, the process of MZ twinning, resulted in an 45,X/46,XY mosaic conceptus. Splitting of the mosaic conceptus produced twins with differing distributions of 45,X and 46,XY lineages. One of the twins, presumably the one with the higher percentage of cells arising from the X lineage, aborted, manifesting as first trimester bleeding and resulting in a phenotypically male ‘singleton’ with a 45,X/46,XY karyotype. Another possibility is that the twinning event and the mitotic loss of the Y chromosome coincided. In this scenario twins each with non-mosaic 45,X and 46,XY karyotypes would have been produced, subsequently admixture of foetal blood cells via placental anastomoses and loss of the 45,X twin resulted in a phenotypically normal male ‘singleton’ with a 45,X/46,XY blood karyotype. Alternatively, subsequent to the twinning process one of a pair of initially XY twins developed 45,X/46,XY mosaicism, secondary to mitotic loss of the Y chromosome; the other twin retaining a 46,XY karyotype. Passage of blood cells with a 45,X/46,XY karyotype, via shared placental vascular connections, produced chimerism and subsequently the 46,XY twin aborted. This seems the least likely sequence as it invokes preferential abortion of a karyotypically normal twin. The absence of mosaicism in tissues other than blood could support the latter proposition but could not exclude mosaicism. At the time of writing postnatal karyotyping of tissues other than blood had not been performed. Therefore, one or a combination of oocyte overripeness (driven by ovarian stimulation), ICSI and chromosomal anomaly (45,X/46,XY mosaicism) may have contributed to the twinning process, if it did occur, in this case and may have caused or predisposed to the development of OAVS.

A male preponderance has been observed in OAVS (Werler et al. 2004; Rollnick et al.

1987[41]) and microtia. Additionally, prenatally diagnosed 45,X/46,XY mosaicism is usually associated with a male phenotype (Bennun et al. 1985) [3] (Hsu, 1989). Therefore, if some cases of OAVS were associated with 45,X/46,XY mosaicism, this might contribute to the preponderance of males with this condition. Furthermore, as there may be selection against the chromosomally abnormal line in lymphocytes, (Kingston et al. 1993 [29]; Horn et al. 1995 [25]) it is possible that blood karyotyping may not detect 45,X/46,XY mosaicism postnatally. Therefore, it may go undetected either in the setting of OAVS or microtia.

Conclusion

This case reports OAVS in the context of prenatally diagnosed 45,X/46,XY mosaicism. It extends the spectrum of possible outcomes of this entity and is a further report of OAVS in an assisted reproduction pregnancy. Finally, overlapping features of OAVS, MZ twinning and 45,X/46,XY mosaicism suggests relationships between these phenomena.

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