Importance of Ear and Face Abnormalities in Cat Eye Syndrome – A Prenatal and Postnatal Report

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ABSTRACT

Cat Eye Syndrome is a rare disorder of chromosome 22 characterized by tetrasomy of the region that spans the chromosome 22p arm and part of 22q11 which is a cat eye syndrome chromosome. Cat eye syndrome exhibits phenotypic variability which may overlap with that of cleft-auroculo-vertebral spectrum and Townes-Brocks syndrome. Features typical of cat eye syndrome include coloboma, auricular malformations, heart and renal anomalies. We report a case of cat eye syndrome, suspected prenatally on ultrasound findings of the ear abnormality and confirmed by cytogenetic analysis of the amniotic fluid. In addition, we report two cases of cat eye syndrome detected postnatally who presented with features such as preauricular tags, anorectal malformation and cardiac defects. It is important to distinguish between the above three features as all of these have different risks. However when phenotypically similar clinical conditions are observed, cytogenetic investigation can confirm cat eye syndrome from the others. It is imperative to evaluate the fetus for cat eye syndrome when a fetus presents with ear and/or cardiac abnormalities during the anomaly scan. During prenatal diagnosis evaluation of ear and fetal face abnormalities can give us an important clue for the underlying genetic or chromosomal syndromes. However, in the postnatal cases, early diagnosis of cat eye syndrome can help the clinical team to provide best management for the individual patient, thereby improving the prognosis.

Keywords: Cat eye syndrome, Tetrasomy 22, CES, Trisomy 22, Ear and face abnormalities.

Abbreviations: CES - Cat Eye Syndrome; FISH - Fluorescence in situ Hybridization

1. Introduction

Cat eye syndrome (CES) is associated with a supernumerary bisatellited marker chromosome which is derived from duplicated regions of 22pter-22q11.2. The distal boundary of the CES critical region (D22S36) is proximal to that of DiGeorge syndrome, a contiguous-gene-deletion syndrome of 22q11.2 [1].

It is proposed that the term cat eye syndrome should be applied only to cases with trisomy or tetrasomy of chromosome 22 not more than 22pter to q11 and without additional duplication or deletion of another autosomal segment. Less than the above region the terms “partial trisomy 22 syndrome” and “trisomy 22 syndrome” can be used instead [2].

Godinho et al. [3] has stated that, a partial tetrasomy of chromosome 22 is a rare multiple congenital anomaly syndrome that is more commonly known as cat-eye syndrome. It is caused by the duplication of a 2-million base region of chromosome 22 (22pter - q11.2). The phenotype is extremely variable and its clinical characteristics include a combination of craniofacial, cardiac, renal, gastrointestinal and genito-urinary defects.

Unlike other conditions, i.e. the invdup (15), bisatellited dicentric marker, the CES phenotype does not appear to correlate with the size of the marker chromosome. However, additional cases are necessary to be able to draw more specific genotype-phenotype correlations and to determine the outcome of patients with CES, especially when this rare condition is diagnosed in prenatal age [4].

Several observations like (1) The absence of any report in living subjects of trisomy 22 arising from an inherited Robertsonian translocation; (2) The recurrent abortions in carriers of Robertsonian translocations involving chromosome 22; and (3) The existence of a syndrome, showing the same clinical features as trisomy 22 questions the existence of a trisomy 22. However, several attempts have been made to map this chromosome to correlate the genotype-phenotype of CES [5].
1.1 Clinical and ultrasound features of CES
The general clinical features of CES include preauricular pit/tag, cardiac defect (Total anomalous pulmonary venous return), anal atresia, micrognathia, renal agenesis, hypertelorism and down slanting palpebral fissure.

Karcaaltincaba [6] ascribed that the CES is usually characterised by anal atresia, ocular coloboma, preauricular tags or sinuses, congenital heart defects, urinary tract anomalies, and mental and physical retardation.

Volpe et al. [7] stresses the importance of ultrasound examination and states that the facial evaluation is an integral part of the fetal ultrasound examination during pregnancy, whether in a screening setting or during targeted analysis. The use of 3D and 4D ultrasound imaging allows easier and more rapid diagnosis, and a more precise evaluation of the facial features.

An analysis of published report revealed that, of the 57 reported cases, only 21 showed the complete form and 11 had a normal karyotype [8].

Godinho et al., [3] have reported partial tetrasomy of chromosome 22 in a Brazilian family where the three siblings were affected monozygotic twin boys and their younger brother. All three were born to healthy nonconsanguineous parents. The phenotype examination of all three found to have strabismus, primary telecanthus, bilateral coloboma iris and low-set ears with posterior rotation of the pinnae. Partial tetrasomy of chromosome 22 was confirmed by fluorescent in situ hybridization.

In view of such possible anomalies, we report here CES cases detected prenatally and postnatally.

2. Materials and Methods
A written consent was obtained from the expected mother/couple/parents of the respective case and then a detailed study was done, which included, the recording of patient’s history, detailed pedigree analysis on the pre-designed sheets, followed by the sample collection, inoculation and cytogenetic study.

Case 1 (a prenatal case) - About 20 ml of amniotic fluid collected from pregnant mother at 22 weeks of gestation in a sterile condition was spun at 800 rpm for 10 min to get the cell pellet. The culture was set up in 2 sterile flasks with the different combination of amniomax C-100 basal medium (GIBCO BRL) and F-10 nutrient medium (HAM) - (GIBCO BRL). The flasks were incubated at 37 ºC and regularly checked for the colonies and media changes were given. When sufficient colonies with doublets were seen, the cells were harvested and slides were prepared and GTG banded for chromosomal study.

Case 2 and 3 (postnatal cases) - Around 8 ml of peripheral blood was drawn and the culture was set up in a vial containing 5ml of RPMI-1640 media (Rosewell Park Memorial Ins) (GIBCO BRL) and Phytohemagglutinin (PHA). After 72 hrs of incubation at 37 ºC, cells were harvested and slides were prepared and GTG banded with Giemsa stain for the analysis of chromosomes.

3. Results
3.1 Clinical Data
3.1.1 Prenatal Case (Case 1)
Case History
The first trimester scan was normal at 12 weeks on a 32 year pregnant lady who had a history of two abortions (fig.1). However, a 2D anomaly scan at 22 weeks of gestational age showed that the fetus had retrognathia, preauricular tag (fig. 2. A & B) and cardiac defect. Cytogenetic analysis of GTG banded metaphases from PHA stimulated leucocyte culture revealed 47,XX,idic(22)(q11) in all the 20 metaphases. The presence of a supernumerary bisatellite chromosome was confirmed by C banding and AgNOR staining method (fig. 2.C). Fluorescence in situ hybridization (FISH) analysis showed no signals on supernumerary bisatellite chromosome using the TUPLE 1 probe (Abbott Molecular Inc, USA) for the DiGeorge syndrome critical region (22q11). Thus the origin of supernumerary bisatellite chromosome (fig. 2. D) was presumed to be of chromosome 22 which correlated with earlier published reports and ultrasound findings. The absence of hybridization signals with the TUPLE-1 probe indicated that the CES in our case was probably of type I with both break points located proximal to TUPLE 1 region. The parental karyotype was normal which confirmed that the cytogenetic abnormality was de nova. However, the parents opted for termination of pregnancy.

Fig 1: Pedigree

Fig 2.
(A) Ultrasound scan showing micrognathia and pre-auricular ear tag
(B) 4D image of the fetus showing a marked hypoplasia of both ears along with retrognathia and abnormal ear
(C) C banded spread showing isodicentric chromosome 22
(D) FISH picture showing isodicentric chromosome 22
3.1.2 Postnatal Case (Case 2 & 3)

Case 2

Case History

Cytogenetic analysis of GTG banded metaphases from peripheral blood culture of a 5 year old female child with various facial, cardiac and limb abnormalities (Table 1) revealed a karyotype of 47,XX,idic(22)(q11.2) (fig. 3) in all the analysed 25 metaphases spread.

Fig 3: Karyotype showing 47,XX,idic(22)(q11.2)

3.1.3 Case 3

Case History

Cytogenetic analysis of GTG banded metaphases from peripheral blood culture of a 6 months old female baby with facial, anal and limb abnormalities, revealed a mosaic of 47,XX,+del(22)(q13.1)(46%)/47,XX,idic(22q)(54%) i.e. a mosaic of partial trisomy 22 and tetrasomy 22 (fig. 4&5) and the FISH study showed three signals for TUPLE 1 at 22q11.2 region. The control probe ARSA showed two signals (only on normal chromosome 22 and not on abnormal chromosome 22) at 22q13.3 region confirming partial trisomy 22 i.e. + del(22)(q13.1).

Multidisciplinary approach to the management of CES and the importance of prenatal anomaly scan during future pregnancies in both the postnatal cases were explained to the parents.

4. Discussion

The cat eye syndrome is considered as a rare chromosomal disease and is phenotypically quite variable. Studies have shown that the main abnormalities found in CES are preauricular skin tags/pits and imperforate anus. Iris coloboma is an important feature of the syndrome [8]. Congenital heart defect with the atrial septal defect were the most observed one. Uncommon features included the hemifacial microsomia associated to microtia, besides biliary atresia.

The phenotype observed in the CES is very variable and may overlap with that of oculo-auriculo-vertebral spectrum. Despite the good prognosis usually presented by the individuals, it is important that all patients with this syndrome should be evaluated as early as possible for presence of heart, biliary and anorectal malformations. This would avoid the complications and death [9].

The variable phenotype in the CES was observed by Schwendemann et al. [10] in his study of cases with fetal trisomy 22. Schwendemann et al., [10] identified the characteristic sonographic findings of fetal trisomy 22 by performing a retrospective review. In the study all cases of chromosomal mosaicism were excluded, as there were first-trimester losses. Only cases with the indications of gestational age and sonographically detected fetal anomalies, advanced maternal age or abnormal ultrasound findings, oligohydramnios, intrauterine growth restriction and increased nuchal thickness were analyzed, of which nine cases had fetal trisomy 22.

In one of our findings - case 1, scanned at 22 wks of gestation on a 32 year old lady, showed a U/S finding of micrognathia with a marked hypoplasia of both ears with preauricular tags (fig. 2. A & B). The fetal echocardiography showed slight discrepancy in the cardiac ventricles. It revealed a karyotype of 47,XX,idic(22)(q11). With respect to the fact that in cat eye syndrome the phenotype is extremely variable, [11] the above case showed at least 2 of the reported features of CES, apart from which it also showed micrognathia/retrorgnathia (table.1). However, the other features of CES like iris coloboma and few other subtle features could not be compared as the U/S finding in the present case was in relation to 22 wks of gestation.
Table 1: Comparative Features of Cat Eye Syndrome in Prenatal and Postnatal Cases

<table>
<thead>
<tr>
<th>Features</th>
<th>Postnatal Cases</th>
<th>Prenatal Case</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Case 1</td>
<td>Case 2</td>
</tr>
<tr>
<td>Maternal age</td>
<td>32 years</td>
<td>1.8kg</td>
</tr>
<tr>
<td>Gestational age</td>
<td>12 &amp; 22 weeks</td>
<td>5 yrs</td>
</tr>
<tr>
<td>Sex</td>
<td>Female</td>
<td>Female</td>
</tr>
<tr>
<td>Birth weight</td>
<td>1.8kg</td>
<td>1.8kg</td>
</tr>
<tr>
<td>Age</td>
<td>5 yrs</td>
<td>5 yrs</td>
</tr>
<tr>
<td>Face</td>
<td>Triangular</td>
<td>Long, matured for age</td>
</tr>
<tr>
<td>Eyes</td>
<td>-</td>
<td>Telecanthus</td>
</tr>
<tr>
<td>Nose</td>
<td>Anteverted nostril, prominent</td>
<td>Bilateral low set and malformed, bilateral preauricular tags*, sensorineural deafness</td>
</tr>
<tr>
<td>Ears</td>
<td>Preauricular tags*</td>
<td>-</td>
</tr>
<tr>
<td>Mouth</td>
<td>Micrognathia #</td>
<td>Upper lip has a cut</td>
</tr>
<tr>
<td>Heart</td>
<td>congenital heart defect</td>
<td>TAPVC, PS with ASD</td>
</tr>
<tr>
<td>Genitalia</td>
<td>-</td>
<td>Imperforate anus</td>
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<tr>
<td>Upper limbs</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Lower limbs</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Preauricular skin tags*, Micrognathia #</td>
<td></td>
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</tbody>
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5. Conclusion
The prenatal case with the ultrasound marker of micrognathia and preauricular tag detected in the second trimester scan which revealed a karyotype of 47,XX, idic(22)(q11), stresses the importance of mid trimester anomaly scan and the importance of fetal face evaluation. The evaluation of the fetal face and particularly ‘ear’ is an important aspect of the mid trimester anomaly scan during pregnancy which give some important clues for either a syndromic or nonsyndromic. Thus ear and fetal face abnormalities should not be ignored as they can give us a clue for the underlying genetic or chromosomal syndromes.

The postnatal case shows the variable phenotypic expressivity of CES and explains how the early diagnosis of CES can help the clinical team to provide best management for the individual patient, hence improving the prognosis.

This study also shows us the importance of multidisciplinary approach to the management of CES, the importance of ear and fetal face abnormalities during anomaly scan and prenatal diagnosis and the importance of karyotyping to rule out differential diagnosis and counseling.

6. References