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Case Report: Opitz C Syndrome with a Rare Chromosomal Abnormality

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ABSTRACT Opitz Trigonocephaly C syndrome (OTCS) or Opitz C Syndrome or C syndrome is a congenital malformation syndrome characterized by trigonocephaly, mental retardation and several other dysmorphic features. Commonly reported chromosomal abnormalities associated with trigonocephaly include 3q-, 7p-, 9p-, 11q-, and trisomy 13q. The present case report describes a patient with derivative 7, due to an unbalanced translocation t(7;13)(p22;q21), with a clinical phenotype of OTCS. To the best of researchers' knowledge, this is the second published case report on Opitz Trigonocephaly C syndrome with similar chromosomal abnormality from India.

INTRODUCTION

Individuals with trigonocephaly, (a striking feature in Opitz Trigonocephaly C syndrome) have a keel-shaped forehead with wide biparietal diameter, resulting in a triangular shape of the head. It results from premature closure of the metopic sutures and usually occurs sporadically. Trigonocephaly can be syndromic or non-syndromic.

Opitz Trigonocephaly C syndrome (OTCS) (OMIM C SYNDROME #211750) McKusick (1998), is a congenital malformation syndrome characterized by trigonocephaly, mental retardation, hypotonia, variable cardiac defects, redundant skin, and dysmorphic facial features, including upslanted palpebral fissures, epicanthal folds, depressed nasal bridge, and low-set, posteriorly rotated ears (Chinen et al. 2006).

Opitz et al. (1969) had first described a brother and sister with a multiple malformation syndrome including trigonocephaly. Since then, around 60 cases of OTCS with similar phenotypes have been described. Commonly reported chromosomal abnormalities in trigonocephaly include 3q-, 7p-, 9p-, 11q-, trisomy 13q and duplication of chromosome 20q11.2. (de Grouchy et al. 1984; Borgaonkar et al. 1997; Avila et al. 2013).

In this case report, researchers present a case of OTCS with an unbalanced translocation between chromosome 7 and 13, resulting in partial trisomy of chromosome 13q and no apparent loss of genetic material in chromosome 7.

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CASE REPORT

A 5 month old male child (proband) born of an Indian couple from West Bengal was referred to Kokilaben Hospital for congenital heart defect and was re-referred to us post operation for craniofacial dysmorphic features. He was a second baby, born at full term by caesarian section in view of previous LSCS to non-consanguineous parents. Chief complaints of parents were that the child had feeding problems, breathing difficulties and poor developmental milestones. At 3 months of age, on evaluation for murmur, child was diagnosed to have acyanotic congenital heart disease. Presence of dysmorphic features and trigonocephaly prompted an MRI brain at 3 months of age at Kolkata. MRI showed trigonocephaly and compression of both frontal lobes.

Clinically the child was stable, had polydactyly, craniosynostsosis. dysmorphic facial features, trigonocephaly, posterior rotated low-set ears, upslanting palpebral fissures and frontal bossing (Fig 1). Head circumference was 40cm. ECHO showed a large doubly committed ventricular septal defect with bidirectional shunting (mainly left to right shunt on oxygen). Mild Tri-

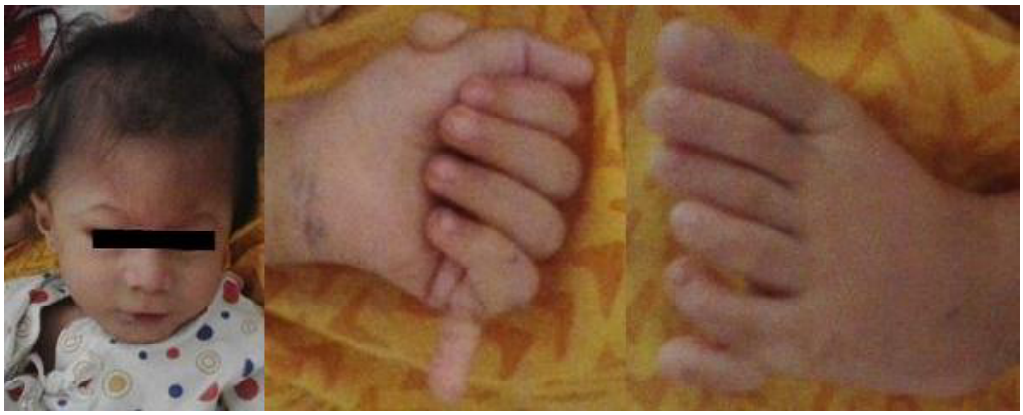

Fig. 1. Photograph of face and limbs of the proband showing trigonocephaly and polydactyly revealing 7 digits in hand and 6 digits in feet

cuspid regurgitation was seen. There was severe coarctation of aorta with total arch gradient of 20mmHg. The biventricular function appeared to be normal.

Ultrasound abdomen showed normal visceral ascitis. Visualized portion of the pancreas was normal in size, shape and echotexture. No calcification / duct dilatation was evident. No focal mass lesion was seen. No peri pancreatic collection was seen.

Spleen was normal in size, contour and echotexture. No focal abnormality was seen in the splenic parenchyma. Splenic vein was not dilated. Both kidneys were normal in size, shape and echotexture. No calculus or hydronephrosis was seen. Cortico – medullary differentiation was intact and cortical thickness is within normal limit on either side. Right kidney measured 5.1 x 1.9 cm and left kidney measured 4.3 x 2.4 cm.

Cytogenetic Analysis

Chromosome analysis, carried out on Trypsin treated Giemsa banded (GTG) slides, revealed a karyotype 46,XY,der(7)t(7;13)(p22;q21) (Fig. 2) in proband essentially resulting in partial trisomy for chromosome 13q and no apparent loss of genetic material in chromosome 7. His parents and sibling were also investigated for chromosome abnormalities and to check the carrier sta-

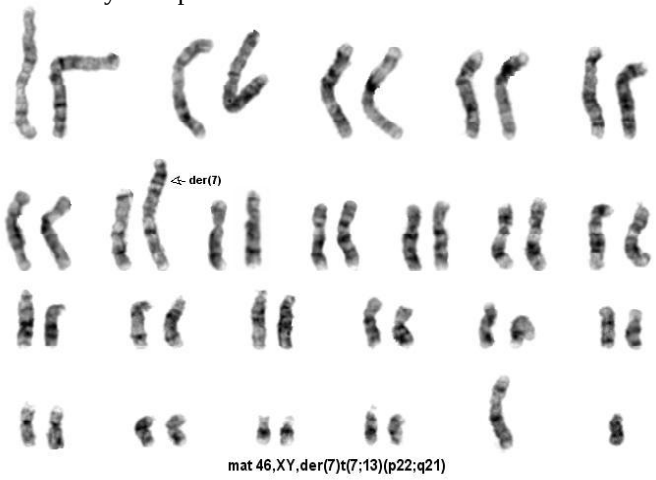

Fig. 2. G-banded Karyotype of the proband showing derivative 7showing t(7;13)(p22;q21) resulting in partial trisomy 13q

tus in parents and for presence of same or different chromosome abnormalities in the brother, who was a suspected case of autism. On analysis, father and brother were found to have an apparently normal male karyotype. Abnormality in the patient was apparently inherited from the mother whose karyotype 46,XX,t(7;13)(p22;q21) (Fig. 3) revealed that she was a balanced carrier of the derivative chromosome, essentially making the proband's final karyotype to be 46,XY,der(7)t(7;13)(p22;q21)mat (Fig. 2).

No monosomy for chromosome 13, 18, 21, X and Y was observed when aneuploidy FISH was performed to rule out Trisomy 13 /18 as a rapid screening procedure. This could be due to the fact the probes for chromosome 13 and 18 were LSI and centromere specific and were localized outside the aberration region.

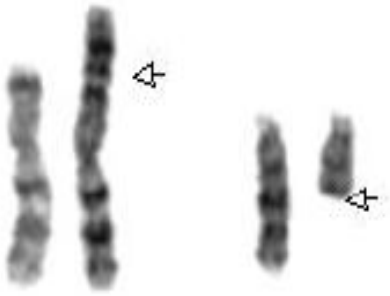

Fig. 3. Partial G-banded karyotype of the mother showing balanced reciprocal translocation 46,XX,t(7;13)(p22;q21)

DISCUSSION

Opitz Trigonocephaly C syndrome is a rare genetic disorder. Less than 60 cases have been reported from all over the world mostly as single case reports (Travan et al. 2011). There are still fewer reports from India, this one probably being the second one after the published case report on free Partial Trisomy 13 by Phadke et al. (2004).

Opitz Trigonocephaly C syndrome, first described by Opitz in 1969, is characterized by trigonocephaly, palpebral fissures, short neck, typical facial appearance, low set ears, central nervous system and visceral anomalies. Presence of normal chromosomes in most patients, unaffected parents with multi affected offsprings, the equal sex ratio of affected individuals, and consanguineous matings support the autosomal recessive inheritance (Rabah et al. 2008). The possibility of dominant inheritance or germline mosaicism is suggested by sporadic presence in many patients, with the recurrence risk being estimated at 10% (Sargent et al. 1985; Opitz et al. 2006). These findings suggest the genetically heterogeneous inheritance of the OTCS.

The clinical features present in proband were polydactyly, dysmorphic facial features, trigonocephaly, posterior rotated low-set ears, upslanting palpebral fissures and frontal bossing. These findings are typical to clinical features of OTCS. Cardiac defects present in most of the OTCS cases were also present in this case. The present child had unbalanced reciprocal translocation t(7;13)(p22; q21) resulting in partial trisomy 13q and no apparent loss of genetic material in chromosome 7.

Interphase FISH analysis had not revealed trisomy for chromosome 13 as the LSI 13 probe region lied outside the trisomic region.

Data from previously reported case study by Phadke et al. (2004) had reported a child with free partial trisomy for chromosome 13q (dup 13q22) and clinical findings similar to our case except for the absence of cardiac defects but unilateral renal agenesis in their proband where as our patient had co-arctation of aorta and no renal anomalies. The full spectrum of features of OTCS has been reported by Antley et al. (1981). The features in the proband reported here fit closely with those described previously (Sargent et al. 1985).

Cases similar to phenotypes of OTCS has also been reported in association with several chromosomal anomalies, including del(3q) and del(7p) (De Grouchy and Turleau 1984); del(13q) (Cohen and MacLean 2000); del(11q) or Jacobsen syndrome (Lewanda et al. 1995; Pivnick et al. 1996; Leegte et al. 1999), and del (9p) syndrome (Christ et al. 1999).

Chinen et al. (2006) described a patient with a severe Opitz Trigonocephaly C Syndrome phenotype and balanced reciprocal translocation t(3;18)(q13.13;q12.1). They reported tirgnocephaly, up slant palpebral fissures, macrocephaly, hypotelorism, high-arched palate, thick and irregular alveolar ridges and hypotonia.

This study is probably the second report of partial trisomy 13, resulting in derivative chromosome 7, formed due to translocation between chromosome 7 and 13. This derivative chromo-

some has been inherited from mother who is a carrier for the balanced translocation for chromosome 7p and 13q.

First one, being a case report from Turkey, published by Percin et al. (2000). In this paper, author had presented a case report of 6 year old girl with trigonocephaly, high forehead, large and low-set ears, a hemangioma on the middle of the forehead. The patient was observed to have a 2/6 systolic murmur in the mesocardiac and aortic loci upon auscultation. Neurological examination revealed severe mental retardation and that her deep tendon reflexes were hypoactive.

Cytogenetically, her karyotype has breakpoints different from the ones reported in the present report. Her Karyotype being 46,XX, der (7) t (7;13) (p22; q31). As obvious, region involved in trisomy is much smaller in comparison to the one reported in the present proband. Like the present case, she has also inherited this chromosome from her mother.

Sargent et al. (1985) presented 12 cases of trigonocephaly of which 6 were associated with other malformations and 6 with isolated skull anomaly. Survival is poor in presence of complex trigonocehaly. Parents cannot be advised early death in anticipation as there are cases which have been reported to survive even till adulthood.

In the present case report proband had mild phenotype with developmental delay, acynotic CHD and normal visceral situs. But as, surgical closure of VSD has been performed on this child and he was symptomatically better. His parents were also contemplating surgery for his craniofacial anamoly.

As a preventive measure genetic counseling has been offered to the parents and prenatal diagnosis by karyotyping in subsequent pregnancies has been advised to prevent birth of affected babies in future.

CONCLUSION

In conclusion, detection of wide varieties of chromosomal abnormalities, reported in cases observed from all over the world implies that Opitz Trigonocephaly C Syndrome is a multifactorial genetic disorder and that multiple genes are involved in manifestation of these clinical phenotypes and studying them using newer techniques like array CGH or next gene sequencing will help reveal the complex mechanism of genes involved behind these genetically heterogeneous disorders.

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