Clinical Report

Opitz “C” Trigenocephaly-Like Syndrome in a Patient With Terminal Deletion of 2p and Partial Duplication of 17q

Márta Czákó,¹ Mariluce Riegel,² Éva Morava,³ Katalin Bajnóczky,⁴ and György Kosztolányi^{1,3*}

¹MTA-PTE Clinical Genetics Research Group, Pécs, Hungary

²Institute of Medical Genetics, University of Zurich, Switzerland

³Department of Medical Genetics and Child Development, University of Pécs, Hungary

⁴Genetics Laboratory, County Hospital Győr, Hungary

A boy with trigonocephaly, cleft palate, multiple minor anomalies, flexion deformities of elbows, cryptorchidism, and severe muscular hypotonia had an unbalanced karyotype with duplication of the distal 17q and deletion of the tip of 2p. This was derived from a reciprocal translocation in the father, 46,XY,t(2;17)(p25;q24). The proband had some findings observed in patients with distal dup(17q), while trigonocephaly not found in these patients may be associated with the terminal deletion of 2p including the locus of *SOX11* gene. It is proposed that the major clinical findings of this patient are consistent with the phenotype characteristic of the Opitz “C” trigonocephaly syndrome. © 2004 Wiley-Liss, Inc.

KEY WORDS: Opitz syndrome; subtelomeric deletion of 2p; partial duplication of 17q; *SOX11* gene locus

INTRODUCTION

Opitz “C” trigonocephaly is a rare syndrome with considerable clinical variability [Lalatta et al., 1990; Glickstein et al., 1995]. Characteristic craniofacial anomalies including a narrow forehead with prominent metopic suture, hypo- or hypertelorism, and cleft palate are associated with multiple organ anomalies, severe muscle hypotonia, and flexion deformities of upper limbs [Opitz et al., 1969]. The underlying defect of this syndrome is not known. Trigenocephaly, the most significant finding in Opitz “C” phenotype, has been observed in various chromosome aberrations [Sargent et al., 1985; Azimi et al., 2003], and genetic heterogeneity has been suggested in Opitz “C” as well. It was postulated that the disorder may represent a defect in the mineralocorticoid receptor, in association with a cytogenetically undetectable microdeletion on chromosome 4 [De Koster et al., 1990]. Duplication of 3p was recently identified by subtelomeric FISH probes in a patient with apparent “C” trigonocephaly syndrome [McGaughan et al., 2000]. Here, we report on a patient with a terminal deletion of 2p and partial duplication of 17q with clinical findings consistent with the Opitz “C” trigonocephaly syndrome.

CLINICAL REPORT

The patient was born at 38 gestational weeks by cesarean section to apparently healthy parents (maternal age at birth was 20 years, the father was 30 years old). No consanguinity was reported in the family. A paternal cousin, who died at the age of 2 years, had a Turner-like phenotype with short stature, webbed neck, aortic stenosis, and mental retardation. No chromosome examination was done. Her healthy mother, who is the first cousin of the patient's father was unavailable for genetic examination.

The patient's birth weight was 3,800 g (90th centile), length 52 cm (75th centile), and head circumference (OFC) 34 cm (25th centile). He required neonatal intensive care due to asphyxia. Cranial ultrasound examination showed signs of a mild subependymal bleed. Craniofacial anomalies, ambiguous genitalia, and severe muscular hypotonia were noted immediately. When examined at the age of 4 years (Fig. 1), he had trigonocephaly a flat temporal region and maxillary hypoplasia on the right, hypertelorism, upslanting palpebral fissures with epicanthal folds, convergent strabismus, a full base of the nose, cleft palate, posteriorly angulated low-set ears, short and webbed neck, low hairline, low set thumbs, wide gap between the thumb and the second finger on both side, a single palmar crease on the right palm, loose joints, flexion deformities of elbows, cryptorchidism, micropenis, and a mild form of epispadias (dorsal aspect of the prepuce is defective with dorsally shifted urethral meatus). Neurologic examination detected profound generalized muscular hypotonia, and decreased deep tendon reflexes. He did not react to visual or auditory stimuli.

Cranial MRI found an 8 mm-wide hypodense lesion in the left temporal region. EEG demonstrated age-appropriate activity. Renal ultrasonography showed hypoplasia of both kidneys and an accessory spleen. The echocardiogram showed an ASD. Fundi were normal with abnormal evoked potentials suggesting a severe brain lesion. Auditory potentials were abnormal on both sides at 70 Hz. Results of routine laboratory tests including ions, proteins, aminoacids, cholesterol, demonstrated no significant alterations.

Presently, at the age of 8 years, the patient has profound growth and psychomotor retardation; his length, weight, and OFC are below the 3rd centile, and his IQ is <20 (non-verbal Wechsler test). He is unable to roll over or lift his head, he has no speech, and he does not recognize his parents.

CYTOGENETIC FINDINGS

Metaphase chromosome preparations were obtained from PHA-stimulated lymphocyte cultures from the patient and both parents according to standard procedures. Conventional GTG-banding was performed at a 400–600 band level according to standard protocols, suggesting an alteration (not clearly identifiable, most probably a tiny deletion) of the short arm of

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*Correspondence to: György Kosztolányi, Department of Medical Genetics and Child Development, University of Pécs, József u.7 H-7623 Pécs, Hungary.

E-mail: gyorgy.kosztolanyi@aok.pte.hu

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Fig. 1. Frontal (a) and side (b) view of the patient at the age of 4 years. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

one chromosome 2 in the patient. Cytogenetic analyses in the parents showed normal karyotype in the mother, while the alteration detected in the patient was also found in the father.

Fluorescence in situ hybridization studies were performed in the father using chromosome 2 library probe (Vysis[®]) according to the manufacturer's instructions and showed that the terminal region of 2p was translocated to the terminal region of 17q (identified by the use of DAPI reverse banding [Riegel et al., 2001]). FISH with telomeric probes for chromosome 2 and 17 (Vysis[®]) confirmed a reciprocal translocation (Fig. 2a,b). Studies with these probes in the patient showed a deletion of the short arm of chromosome 2 with partial trisomy of the long arm of chromosome 17. According to these findings we defined the following karyotype: 46,XY,der(2)t(2;17)(p25;q24)pat.

DISCUSSION

Partial trisomy 17q has been observed in patients with psychomotor retardation, minor anomalies, skin and hair anomalies, cryptorchidism, deafness, and heart malformations [Caine et al., 1989; Butt et al., 1993]. Interstitial deletion of the short arm of chromosome 2 has been reported in mental retardation syndromes associated with holoprosencephaly [Münke et al., 1988], and with eye anomalies and Hirschsprung disease [Webb et al., 1988]. However, according to our knowledge, deletion of the terminal region of the short arm of chromosome 2 has not been described yet. Trigenocephaly, joint anomalies, profound muscular hypotonia, and genital anomalies in this patient, not observed previously in dup(17q)

Fig. 2. Metaphases from the father of the patient. FISH with subtelomeric probes for chromosome 17 (short arm green, long arm red) (a) and telomeric probes for chromosome 2 (short arm green, long arm red) (b) showing the balanced translocation of chromosome 2p and 17q. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

patients, may be due to the terminal short arm deletion on chromosome 2. It is interesting to note that human *SOX11* gene encoding a transcription factor, thought to play important role in the developing nervous system, was mapped to chromosome region 2p25.3 [Azuma et al., 1999]. The lack of hypercholesterolemia supports the cytogenetic finding of the breakpoint at 2p24.

We propose that the characteristic phenotype in this unbalanced chromosomal syndrome is compatible with Opitz "C" trigonocephaly syndrome. Syndromic trigonocephaly is causally heterogeneous. Cases were observed in association with various chromosomal anomalies including aneuploidy of segments at 3p, 3q, 11q, and 13q chromosome regions [Azimi et al., 2003]. According to our knowledge, no patients with syndromic trigonocephaly including Opitz "C" syndrome have been reported with rearrangements involving 2p or 17q.

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REFERENCES

- Azimi C, Kennedy SJ, Chitayat D, Chakraborty P, Clarke JTR, Forrest C, Teebi AS. 2003. Clinical and genetic aspects of trigonocephaly: A study of 25 cases. *Am J Med Genet* 117:127–135.
- Azuma T, Ao S, Saito Y, Yano K, Seki N, Wakao H, Masuho Y, Muramatsu M. 1999. Human *SOX11*, an upregulated gene during the neural differentiation, has a long 3' untranslated region. *DNA Res* 6:357–360.
- Butt AM, Mehta D, Goodeva JA, Flinter FA. 1993. Probably de novo 17q duplication (q11.2 → q21.1): A newly recognised chromosomal syndrome in a child with Klinefelter's syndrome. *J Med Genet* 30:436–437.
- Caine A, Knapton DM, Mueller RF, Congdon PJ, Haigh D. 1989. Duplication of distal 17q from a maternal translocation: An additional case with some unique features. *J Med Genet* 26:577–589.
- De Koster J, Legius E, de Zegher F, Devlieger H, Fryns JP, Eggermont E. 1990. Opitz C syndrome and pseudohypoadosteronism. *Am J Med Genet* 37:457–459.
- Glickstein J, Karasik J, Caride DG, Marion RW. 1995. "C" trigonocephaly syndrome: Report of a child with agenesis of the corpus callosum and tetralogy of Fallot, and review. *Am J Med Genet* 56:215–218.
- Lalatta F, Clerici Bagozzi D, Salmoiraghi MG, Tagliabue P, Tischer C, Zollino M, Di Rocco C, Neri G, Opitz JM. 1990. "C" trigonocephaly syndrome: Clinical variability and possibility of surgical treatment. *Am J Med Genet* 37:451–456.
- McGaughran J, Aftimos S, Oei P. 2000. Trisomy of 3pter in a patient with apparent C (trigonocephaly) syndrome. *Am J Med Genet* 94:311–315.
- Münke M, Emanuel BS, Zackai EH. 1988. Holoprosencephaly: Association with interstitial deletion of 2p and review of the cytogenetic literature. *Am J Med Genet* 30:929–938.
- Opitz JM, Johnson RC, McCreadie SR, Smith DW. 1969. The C syndrome of multiple congenital anomalies. *Birth Defects Orig Art Ser* 5(2):161–166.
- Riegel M, Baumer A, Jamar M, Delbecq H, Herens C, Verloes A, Schinzel A. 2001. Submicroscopic terminal deletions and duplications in retarded patients with unclassified malformation syndromes. *Hum Genet* 109:286–294.
- Sargent C, Burn J, Baraitser M, Pembrey ME. 1985. Trigonocephaly and the Opitz C syndrome. *J Med Genet* 22:39–45.
- Webb GC, Keith CG, Campbell NT. 1988. Concurrent de novo interstitial deletion of band 2p22 and reciprocal translocation (3;7)(p21;q22). 1988. *J Med Genet* 25:125–127.