

Double Partial Monosomies (10p- and Xp-) in a Female Baby with Choanal Atresia

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Chromosomal abnormalities involving double partial monosomies are very rare. A female infant with non-mosaic monosomy 10p13→10pter along with monosomy Xp11.4→Xpter which arose de novo is described. The clinical manifestations of this patient included microcephaly, mild synophrys, short and down-slanted palpebral fissures, ptosis of the left eye, long eyelashes, a depressed nasal bridge, dysplastic ears, micrognathia, a short neck, sensorineural hearing impairment, and severe growth retardation. Left choanal atresia and laryngomalacia were detected by flexible fibroscopy. No signs of hypoparathyroidism or defective cellular immunity could be found. Fluorescence in situ hybridization (FISH) with whole-chromosome painting probes for chromosomes 10 and X was performed, which excluded the possibility of cryptic translocations of the involved chromosome segments. No submicroscopic chromosome 22q11 deletion could be found by FISH. Thus this very rare coexistence of double independent partial monosomies was confirmed. There are no previous reports of such concurrent double partial monosomies. (*Chang Gung Med J* 2002;25:260-5)

Key words: monosomy, chromosome 10, chromosome X, choanal atresia.

Partial monosomy of the short arm of chromosome 10 is rarely observed. A possible partial 10p monosomy was first described by Elliott et al. in 1970.⁽¹⁾ Partial monosomy 10p, due to a de novo deletion of the terminal part of the short arm, was first described in 1975.⁽²⁾ Later reports have shown a breakpoint at 10p13 in most cases.⁽²⁻⁴⁾ The clinical manifestations include psychomotor retardation, growth failure, frontal bossing, ear anomalies, down-slanted palpebral fissures, microcephaly, congenital heart disease, urinary tract anomalies, hypoplastic olfactory bulbs, neurosensory hearing loss, and overlapping features with DiGeorge anomaly.⁽¹⁻⁵⁾ Partial deletion of Xp in 1 of the 2 X chromosomes in females may result in Turner syndrome,⁽⁶⁾ or other phenotypes (e.g., microphthalmia with linear skin

defects syndrome). A partial deletion of 10p or Xp may arise de novo or as the result of parental balanced translocations involving a segment of the short arm of chromosome 10 or X.^(4,6-8) However, as far as is known, the concurrence of double monosomies--del(10p) and del(Xp)-- in the same individual has not been reported. We report on a female patient with multiple malformations, especially choanal atresia, who was proven to be a victim of this hitherto unreported double partial monosomies.

CASE REPORT

This female baby is the second child born at term by normal vaginal delivery to her healthy non-consanguineous parents (mother aged 33 years,

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father aged 35 years). The pregnancy was uncomplicated, but symmetrical intrauterine growth retardation with a birth weight of 1600 g and a small head circumference of 31 cm was noted at birth. There is no history of intrauterine fetal death, spontaneous abortion, or early infant death in her family. She was transferred to our hospital because of tachypnea and poor feeding with easy choking for more than 1 month after birth. Physical examination revealed short and down-slanting palpebral fissures, ptosis of the left eye, long eyelashes, mild synophrys, slightly low-set crumpled ears, a depressed nasal bridge, a shallow philtrum, micrognathia (Fig. 1), a high-arched palate, a short neck, and bilateral single palmar creases. She had central hypotonia but hypertonicity of the lower extremities. There was no cardiac murmur or shortening of the fourth finger. The genitalia had a normal morphology for a female baby. Due to tachypnea during feeding and the inability to smoothly insert a nasogastric tube into the left nostril, left choanal atresia or stenosis was suspected. This anomaly was later confirmed by flexible fibroscopy and computed tomography scan of the upper airway. In addition, inspiratory stridor was noted, and laryngomalacia was also proven by



Fig. 1 The patient at 2 months old.

fibroscopy. Chest films were normal. Echocardiography showed that the heart was structurally normal except for a persistent left superior vena cava and a prominent coronary sinus. Renal sonography revealed no hydronephrosis or polycystic kidney. Fundus examination showed no coloboma nor hypoplasia of the retina or choroid. While the CHARGE association was a possibility, her condition was rather a result of the chromosomal abnormalities. On a hemogram, the blood chemistry and sugar levels were all within normal limits. Levels of serum parathyroid hormone, calcium, and phosphate were all normal. The lymphocyte subset revealed 96% lymphocytes (56% T cells, 34% B cells, and 6% NK cells). T cells included 38% CD4+ (34% naive cells and 4% memory T cells) and 18% CD3+8+. So the lymphocyte count and number and ratio of helper (CD4) to suppressor (CD8) subsets were normal.

A chromosome study revealed 46,X, del(10)(qter→p13:), del(X)(qter→p11.4:) in 100 cells counted in both peripheral blood and skin fibroblasts from the patient (Fig. 2). An X-inactivation study by 5-bromodeoxyuridine replication analysis on peripheral blood showed non-random X-inactivation over the deleted X. A chromosome study of her mother revealed 46,XX, while her father was 46,XY. Whole-chromosome painting studies by fluorescence in situ hybridization (FISH) with the COATASOME 10 and X probes (Oncor, Gaithersburg, MD, USA) detected no cryptic translocations involving either

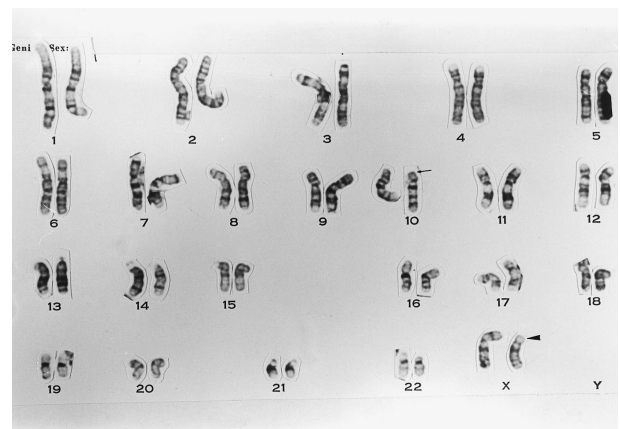


Fig. 2 Karyotype of this patient showing a terminal deletion of 10p with the breakpoint at p13 (arrow) and 1 X chromosome deleted from Xp11.4 (arrowhead) to Xpter.

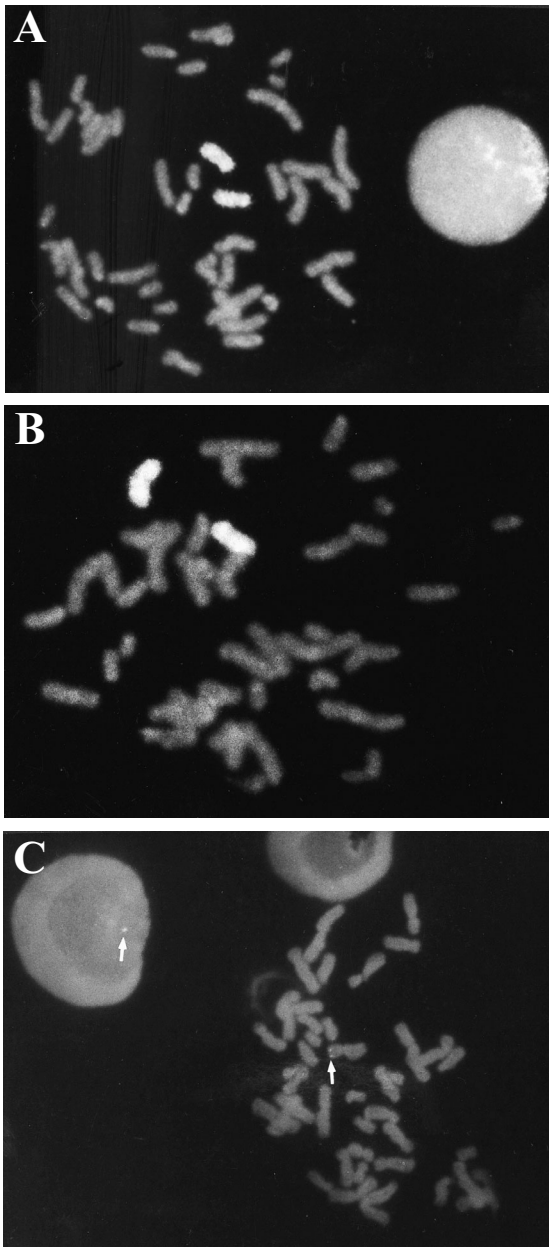


Fig. 3 FISH studies revealing no cryptic translocations involving 10p(A) or Xp(B) by using painting probes for chromosomes 10 and X. Only 1 signal (arrow) is shown over the intact chromosome 10 homologue (C) by using the 10p telomere probe.

chromosome X or 10 (Fig. 3A, B). The use of the D22S75 DiGeorge chromosome region (DGCR) probe also showed the intact status of the DGCR

over 22q11.2. FISH with all human telomeres and telomere-specific 10p DNA probes (Fig. 3C) showed that both terminal deletions were present in the child. At the age of 1 year, a round face developed in addition to the previous dysmorphism. Developmental delay with marked hypotonia persisted despite a rehabilitation program. Brainstem auditory evoked potentials showed bilateral sensorineural hearing loss. The body weight and length and head circumference were still below the third centile of the Chinese female controls to the present (4 years old).

DISCUSSION

It is amazing that this patient is still alive even with non-mosaic, non-translocated double partial monosomies involving large portions of chromosomes 10 and X. Indeed, conventional and molecular cytogenetics proved this possibility. No cryptic balanced translocations involving chromosomes 10 or X could be found by FISH studies. In Table 1, we compare the major clinical features of this patient with previously published findings for monosomy 10p^(4,5) and monosomy Xp,⁽⁹⁾ respectively. This patient had overt growth failure, which is common to both syndromes. Other features such as psychomotor retardation, ear and eye anomalies, a high-arched palate, a depressed nasal bridge, micrognathia, and a short neck are more or less similar to those of monosomy 10p, but differ from those of the CHARGE association, DiGeorge anomaly, and Turner syndrome. Our case, showing the coexistence of 2 independent de novo deletions, revealed a different phenotype (e.g., choanal atresia) from what would be expected by simply combining the features found in both monosomies.

Most cases of choanal atresia (CA) or stenosis are sporadic. About 20%-50% of CA cases are associated with other congenital malformations (e.g., Antley-Bixler syndrome, Apert syndrome, CHARGE association, Coffin-Sirin syndrome, Klippel-Feil syndrome, Pallister-Hall syndrome, and Treacher Collins syndrome).⁽¹⁰⁾ Several chromosomal abnormalities have also been reported with CA,⁽¹¹⁻¹³⁾ including trisomy 18, deletions (4q and 9p), and trisomies (6p and 7q). However, CA has not previously been described with 10p monosomy or Xp monosomy. CA in this case could be due to the uncovering of

Table 1. Comparison of Clinical Symptoms in Patients with Partial Monosomy 10p, Partial Monosomy Xp, and This Case

Phenotype	10p-(4,5) (N=27)	Xp-(9) (N=52)	This case
Psychomotor retardation	100%	13%	+
Growth retardation	96%	88%	+
Ear anomalies	85%	12%	+
Down-slanted palpebral fissures	74%	i-	+
Micrognathia	74%	6%	+
Depressed nasal bridge	67%	i-	+
Frontal bossing	67%	i-	i-
Congenital heart disease	56%	2%	i
Epicanthal folds	56%	2%	i-
Eye/eyelid anomaly	52%	8%	+
Short neck	52%	38%	+
Urinary tract anomaly	42%	8%	i-
High-arched palate	41%	6%	+
Hypertelorism	41%	i-	i-
Wide-spaced nipples	41%	88%	i-
Small for date	41%	i-	+
Umbilical hernia	33%	i-	i-
Abnormal philtrum	30%	i-	+
Features of DiGeorge anomaly	30%	i-	i-
Hypoplastic olfactory bulbs	11%	i-	i-
Sensorineural hearing loss	7%	i-	+
Cubitus valgus	i-	25%	i-
Low hairline	i-	19%	i-
Shield chest	i-	35%	i-
Shortening of the 4 th metacarpal	i-	29%	i-
Choanal atresia	i-	i-	+

recessiveness due to the deletions,⁽¹⁴⁾ or may even be a consequence of the double 10p and Xp monosomies. The deletion may have uncovered a recessive mutation present in the non-deleted chromosome 10, or an interaction between the dominant genes on 10p or Xp and other genes determining the existence of CA.

Due to the effects and consequences of excessive gene loss, victims of double partial monosomies are often not viable. For example, 38% of patients with 10p- die before 1 year.⁽⁴⁾ The most common cause of death may be the effects of DiGeorge anomaly. The features of DiGeorge anomaly were not present in this patient, and only a persistent prominent coronary sinus in the left superior vena cava was shown by echocardiography. However, this female baby was born at term without major abnormalities,

such as cardiac, renal, or immunological abnormalities, except for severe psychomotor retardation. Since both the Xp and 10p deletions have a broad spectrum of phenotypic manifestations, the milder phenotype and good intrauterine survival in our case may have been due to 1 of the following mechanisms: 1) a better prognosis of the partial 10p deletion without DiGeorge anomaly compared with other autosomal monosomies, 2) a skewed inactivation of the structurally abnormal X chromosome from somatic selection,⁽¹⁵⁾ or 3) recessive genes unmasked by the deletion having only a mild effect on the phenotype. The deletion or mutation of some recessive genes (such as putative genes for CA) in 10p would not create a fatal effect.

REFERENCES

- Elliott D, Thomas GH, Condron CJ, Khuri N, Richardson F. C-group chromosome abnormality (?10p-). Occurrence in a child with multiple malformations. *Am J Dis Child* 1970;119:72-3.
- Shokeir MHK, Ray M, Hamerton JL, Bauder F, O'Brien H. Deletion of the short arm of chromosome no. 10. *J Med Genet* 1975;12:99-113.
- Koenig R, Kessel E, Schoenberger W. Partial monosomy 10p syndrome. *Ann Génét* 1985;28:173-176.
- Hon E, Chapman C, Gunn TR. Family with partial monosomy 10p and trisomy 10p. *Am J Med Genet* 1995;56:136-40.
- Hsu HL, Hsiao PH, Hou JW, Tsai WY, Wang TR. Partial DiGeorge anomaly associated with 10p deletion. *J Formos Med Assoc* 1997;96:996-9.
- Zinn AR, Page DC, Fisher EMC. Turner syndrome: the case of the missing sex chromosome. *Trend Genet* 1993; 9:90-3.
- Prieto F, Badia L, Moreno JA, Barbere P, Asensi F. 10p-syndrome associated with multiple chromosomal abnormalities. *Hum Genet* 1978;45:229-35.
- Lai MMR, Sriven PN, Ball C, Berry AC. Simultaneous partial monosomy 10p and trisomy 5q in a case of hypoparathyroidism. *J Med Genet* 1992;29:586-8.
- Therman E, Susman B. The similarity of phenotypic effects caused by Xp and Xq deletions in the human female: a hypothesis. *Hum Genet* 1990;85:175-83.
- Richardson MA, Osguthorpe JD. Surgical management of choanal atresia. *Laryngoscope* 1988;98:915-8.
- Clementi M, Tenconi R, Turolla L, Silvan C, Bortotto L, Artifoni L. Apparent CHARGE association and chromosome anomaly: chance or contiguous gene syndrome. *Am J Med Genet* 1991;41:246-50.
- Shashi V, Golden WL, Fryburg JS. Choanal atresia in a patient with the deletion (9p) syndrome. *Am J Med Genet*

- 1994;49:88-90.
13. Lee WT, Hou JW, Tsou Yau KI, Wang TR. Trisomy 18 in a patient with CHARGE association. *J Formos Med Assoc* 1995;94:60-2.
 14. Gershoni-Baruch R. Choanal atresia: evidence for autosomal recessive inheritance. *Am J Med Genet* 1992;44:754-6.
 15. Belmont JW. Genetic control of X inactivation and processes leading to X-inactivation skewing. *Am J Hum Genet* 1996;58:1101-8.

第十號及X染色體短臂缺損之雙重部分型單體症的 後鼻孔閉鎖女嬰

侯家瑋

在同一細胞中出現兩個不同染色體缺損是相當罕見的，有一女嬰同時帶有非拼湊型，新突變的第十號及X染色體短臂缺損。症狀包括小頭症，輕度一字眉，短且外斜的眼瞼裂，眼瞼下垂，長睫毛，扁鼻樑，耳畸形，小下巴，短頸，神經性聽障，及嚴重的生長遲緩。她同時也被發現有喉頭軟化及左後鼻孔閉鎖症，但並沒有副甲狀腺機能低下或胸腺細胞免疫障礙之情況。以螢光性原位雜交法排除其它染色體異常或細微染色體轉位的可能。其臨床表徵除了部分與第十號染色體或X染色體短臂缺損有關外，後鼻孔閉鎖及其它未被報告症狀可能是兩個不同染色體缺損間基因交互作用的結果。(長庚醫誌 2002;25:260-5)

關鍵字：單體症，第十號染色體，X染色體，後鼻孔閉鎖。