Case Report

New Case of Non-Mosaic Tetrasomy 9p in a Severely Polymalformed Newborn Girl

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Received 13 May 2003; Accepted 27 August 2003

BACKGROUND: The phenotypic expression of an additional chromosome 9 causes a very broad clinical spectrum of anomalies. The prognosis for infants with non-mosaic tetrasomy 9p is poor, and they usually die at a very early age. **CASE:** In this article we present a new case of complete tetrasomy 9p in a newborn girl with multiple dysmorphologic features. Cytogenetic studies were carried out by CBG, GTG, and QFQ chromosome bandings, as well as by fluorescence in situ hybridization (FISH). The cytogenetic findings for the newborn girl showed an extra chromosome interpreted as an isochromosome 9p. The karyotype was characterized as 47,XX,+mar.ish i(9)(p10)(wcp9+). The parental chromosomes were normal. **CONCLUSIONS:** The karyotype and clinical features of the newborn girl (e.g., typical craniofacial dysmorphism, severe skeletal anomalies, and visceral and genito-urinary malformations), compared with cases reported in the literature, give additional support to a clinical definition of this chromosomal syndrome. *Birth Defects Research (Part A) 67:985–988 , 2003.*

Key words: non-mosaic tetrasomy 9p; multiple congenital anomalies; advanced maternal age

INTRODUCTION

Tetrasomy 9p is an uncommon chromosomal syndrome, which was first described by Ghymers et al. (1973). A review of the literature shows variability of expression, ranging from stillborn babies to survivors with malformations and developmental delay. Mosaicism for an extra isochromosome 9p has been suggested may determine an increased survival, despite both mosaic and non-mosaic patients surviving beyond infancy (Tonk 1997).

In this work we present a new case of non-mosaic tetrasomy 9p, in a newborn girl who showed a pattern of dysmorphic clinical features. The case was investigated by both banding studies and fluorescence in situ hybridization (FISH).

CASE REPORT

The proposita, a baby girl (Fig. 1), was born in May 2000 after a 36-week gestation. The baby was the 10th child born to a gravida 9, para 9 mother (G9, P9, A0). The mother was 44 years old and the father was 45 at the time of her birth. The parents were nonconsaguineous, and the family history was negative for abortions and genetic abnormalities.

The mother denied having any prenatal exposure to drugs, but she admitted using supposedly abortive herbal teas during the first three months of gestation. She also denied smoking during pregnancy. She reported that she felt few fetal movements, but had received no prenatal care. The baby was delivered vaginally with the help of forceps (because of a breech presentation). The newborn was asphyxiated at the moment of her birth, and she had an Apgar score of 4 at 1 min, 7 at 5 min, and 8 at 10 min. The baby was small for her gestational age (weight = 1.865 gm, length = 40 cm [both values below the third percentile], and head circumference = 32.5 cm [~60th centile]). The newborn baby was transferred to the neonatal emergency unit, where she was nursed in an incubator.

The newborn presented significant dysmorphologic features, including an abnormally shaped cranium, with an extensive lesion on the right side of the scalp; widely open sagittal sutures and anterior fontanelle; and symmetric enlargement of the ventricular system, as revealed by ultrasound (US). Hydrocephaly was suspected. Other features included small, deep-set eyes with short palpebral

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DOI: 10.1002/bdra.10126

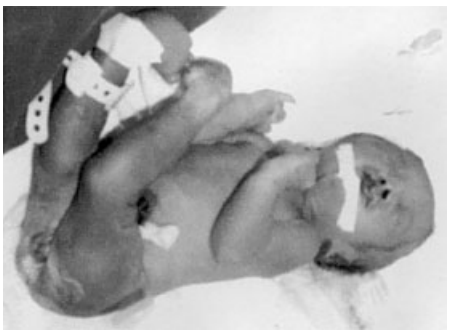

Figure 1. Overall appearance of newborn girl with multiple severe malformations at eight days after birth.

fissures; telecanthus; facial asymmetry; a beaked nose; cleft lip and high ogival palate; micrognathia; malformed, low-set ears; and a webbed neck. Cardiac auscultation revealed a heart murmur. The genitalia were female, with hypoplastic labia and a large, penis-like clitoris. The hands were held in a clenched position with flexed and overlapping fingers and transverse palmar creases. The nails were hypodysplastic. Skeletal anomalies included brachydactyly, clinodactyly of the fifth finger, dislocated knees, severe rotation of the hip, and very small rocker-bottom and club feet.

The newborn's general health condition became progressively more serious, and she was hypoactive, icteric, and tachdyspneic. She died 19 days after birth, in spite of all the medical procedures that were performed. The parents did not allow an autopsy.

CYTOGENETIC STUDIES

Metaphase spreads were obtained by standard peripheral blood culture procedures. Chromosome studies were performed by GTG and QFQ bandings at a resolution of 550 band level, and by CBG banding. In addition, FISH was performed, with specific whole chromosome painting probes according to standard protocols.

The banded karyotype of the newborn girl showed an extra chromosome, which was interpreted as an isochromosome 9p (Fig. 2A). This finding was consistent in all 30 cells that were analyzed. The extra chromosome showed a symmetric banding pattern with only one positive C band and an absence of heterochromatic segment 9q, which suggests that this chromosome is formed only by the short arms and centromere(s) of chromosome 9. FISH experiments using a chromosome 9 WCP probe (Vysis®, Downers Grove, IL) showed an absence of rearrangements with another chromosome, and painted both normal chromosomes 9 and the der(9) completely (Fig. 2B). The proband's karyotype was characterized according to the ISCN (1995) as 47,XX, +mar.ish i(9) (p10)(wcp9+). Additional molecular investigations with 9p markers to exclude trisomy $9q^-$ syndrome could not be done because the child died before more blood samples could be obtained. The parents' chromosomes were normal.

CONCLUSIONS

Several hypotheses have been proposed to explain tetrasomy 9p. Rutten et al. (1974) suggested a meiosis I disturbance, with nondisjunction and rearrangement in two of the four chromatides of a bivalent 9, resulting in the formation of an isochromosome 9p. Molecular cytogenetic investigations in families with a proband carrier of an additional autosomal isochromosome frequently reveal a maternal origin, starting with meiosis II nondisjunction followed by rearrangements (isochromosome formation), with duplication of the short arm and loss of the acentric long arm at the subsequent mitosis (Dutly et al., 1998).

Most studies of tetrasomy 9p carriers employ conventional cytogenetics and banding techniques, which reveal a dicentric additional chromosome in most cases. However, previous molecular studies using a chromosome 9 classic satellite probe (Petit et al., 1998) showed that an error in the division of centromere 9 by means of a double-break event could result in the formation of a monocentric isochromosome. Our proband CBG banding showed only one centromere and therefore, presumably, a monocentric isochromosome. In support of this hypothesis, Dutly et al. (1998) observed that maternal age at delivery can be a further indication that meiotic nondisjunction may be the first step in the formation of an isochromosome, as probably happened in the present case.

Our patient died in the first month of life, a survival period that is consistent with most reported cases of non-mosaic tetrasomy 9p (Schaefer et al, 1991; Shapiro et al, 1985; Wisniewski et al, 1978). The prognosis for survival has been related to the presence of mosaicism, and only four cases of complete tetrasomy carriers living longer than 1 year have been reported (Abe et al., 1977; Garcia-Cruz et al., 1982; Tonk, 1997; Dutly et al., 1998). However, it is possible that those three cases involved undetected mosaicism, since not all authors analysed two different tissue types.

A comparison of our patient's clinical findings with the 10 other cases of non-mosaic tetrasomy 9p reviewed by Tonk (1997), and the three patients followed by Dutly et al. (1998) gives further support to the existence of a specific clinical phenotype resulting from that chromosomal disturbance (Table 1). Findings of hydrocephalus were also reported by Cavalcanti et al. (1987) and Schaefer et al. (1991) in studies of complete tetrasomy 9p cases. Accord-

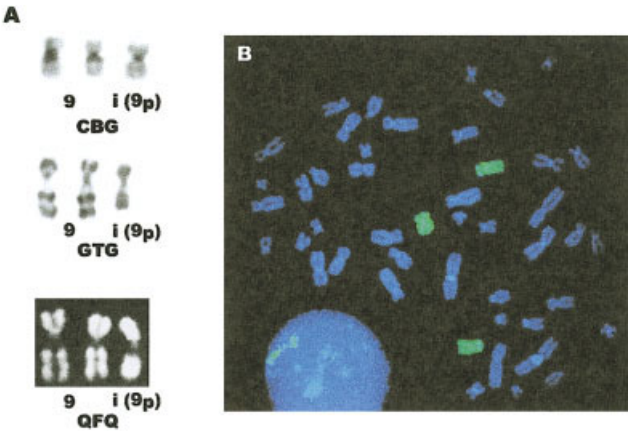

Figure 2. Patient's partial metaphase, showing 9 and i(9p) chromosomes, obtained from different techniques (**A**); positive hybridization (wcp9) to both those 9 chromosomes (**B**).

Table 1
Comparative Clinical Findings and Survival Data of i(9p) Nonmosaic Cases*

	References										Dutly et al. (1998)				
Clinical features	Abe et al. (1977)	Cavalcanti et al. (1987)	Garcia-Cruz et al. (1982)	Jalal et al. (1991)	Leichtman et al. (1996)	Moedjono et al. (1980)	Schaefer et al. (1991)	Shapiro et al. (1985)	Wisniewski et al. (1978)	Tonk (1997)	Patient 4	Patient 5	Patient 6	Present case	Total
Sex	M	M	F	M	F	M	M	F	M	F	M	M	F	F	6F/8M
Age	3y	4d	13y9m	Birth	5d	4d	Prenatal	Birth	Birth	4m	17 2/7w	33 6/7w	21y	15d	
Survival		63d		2m	6w	2m	Several h	9d	Several h	3y				19d	
Mental retardation	+		+		+					+			+		5/5
Growth retardation			+	+	+		+	+	+	+	+	+	+	+	11/11
Hypotonia	+	+			+	+		+	+	+				+	8/8
Microcrephaly		+	+	+	–	–		+	+	+				–	7/10
Hydrocephaly/macrocephaly		+	+	+			+			–				+	5/6
Open suture/wide fontanelle	+	+		+	+	+	+	+		+	+			+	10/10
Hyperteleorism/telecanthus	+	+	+	+	+	+	+	+	+	–		+	+	+	12/13
Antimongoloid slant					+					–		+	+		3/4
Enophthalmos/ microphthalmos		–	+							+				+	3/4
Epicanthus	+	+	+				+	+		+				+	7/7
Strabismus/myopia	+		+							+					3/3
Bulbous/beaked nose	+	+	+	+	+		+		+	+			+	+	10/10
Downturned corners of the mouth	+	+	+		+		+			+			+		7/7
Retromicrognathia	+	+			+	+	+			–				+	6/7
Cleft palate/lip or abnormal palate	+	+	+	+		+	+	+	+	+	+	+		+	12/12
Ear malformation/ malposition	+	+	+	+	+	+	+	+	+	+	+	+	+	+	14/14
Short neck		+	+	+	+		+			+				+	7/7
Redundant skin		+			+		+			–				+	4/5
Wide-spaced nipples			+							+					2/2
Congenital heart disease	+	+	–	+	+	–		+	+	+	+	–		+	9/12
Genital abnormality/ cryptochidism	+	+	+	+	+	+	+	+	+	+				+	11/11
Renal anomalies	–	+	–				+	–		+		–			3/7
Sacral dimple or pits						+		+		+					3/3
Skeletal anomalies/joint dislocation(s)		+	+	+	+	+	+	+	+	+	+	+	+	+	13/13
Dysplastic nails or hypoplastic distal digits	+	+	+	+	+	+	+	+	+	+		+	–	+	12/13
Transverse palnar creases	+	+		+		+	+	+		+		+	–	+	9/10
Clinodacylyl			+		+					+				+	4/4
Maternal age	35	27	27	29	22	19	Not advanced	35	33	Young	31	35	31	44	
Paternal age	38	33	31	29	20	14	Not advanced	46	35		32	37	30	45	

*Blank space indicates that this particular feature has not been mentioned by the author. –, negative findings; +, positive findings; d, days; w, week; m, month; y, year.

ing to Schaefer et al. (1991), abnormalities found in more than 80% of the cases studied included early death in non-mosaic cases, psychomotor retardation in long-term survivors with mosaicism, hypotonia, open cranial sutures/wide fontanelles, and characteristic facial anomalies, such as a bulbous beaked nose, hypertelorism, cleft lip and palate, and malformed/malpositioned ears. Additional findings included cryptorchidism, renal and/or genital anomalies, skeletal anomalies, deep sacral dimple, dysplastic nails, and redundant skin. Most of these features were observed in the case reported herein.

It should be stressed that there is considerable phenotypic variation in tetrasomy 9p, a chomosomal disturbance that can present clinical features similar to those found in trisomy 9. Fryns (1998) analyzed 13 patients who presented a typical trisomy 9p phenotype, and concluded that trisomy 9 and tetrasomy 9p fit together into a single, clinically recognizable chromosomal syndrome.

Leichtman et al. (1996) compared clinical findings in trisomy and tetrasomy 9p and found considerable major phenotypic overlap; however, compared to trisomy, tetrasomy has a lower survival prognosis and a more severe phenotype. According to Schinzel (2001), patients with mosaicism for an extra isochromosome 9p have a distinctly milder phenotype than patients without mosaicism. Wilson et al. (1985) also reported more severe and random defects with complete trisomy 9 or tetrasomy 9p, which suggests that an extreme excess of genetic material increases developmental variability.

The present study provides evidence that non-mosaic patients with an extra isochromosome 9p have a specific pattern of congenital malformations with several abnormalities, including typical craniofacial dysmorphism, severe skeletal anomalies, and visceral and genito-urinary malformations. By reporting this new case, the authors believe they can contribute to a better understanding of tetrasomy 9p, and thereby assist in the early diagnosis of this syndrome in severely malformed newborns.

ACKNOWLEDGMENTS

The authors thank the patient's parents for giving permission for this publication; Sonia Moura Costa, M.Sc., for helping with the translation; and Prof. A. Schinzel, Zurich, for a critical review of the manuscript.

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