Clinical features and mental development of a child with a prenatally identified 45,XX,der(5)t(5;18)(p15;q11.2),-18 karyotype

R Gordon Hutcheon, Aparna Mallik, Meira Shaham

Abstract

We present the clinical features and growth and development of a child with a 45,XX,der(5)t(5;18)(p15;q11.2),-18 karyotype. She had microcephaly, prominent, posteriorly rotated ears, short palpebral fissures with an upward slant, a wide nasal bridge, a thin upper lip, and a short neck. In addition, she had complex congenital heart disease. Although there has been delay in growth and development, she has shown progress in both areas.

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Prenatal diagnostic testing provides information that can be used to predict potential problems for an affected child. The situation becomes more complex, however, when a fetus is found to have an anomaly that has not been described previously. In this report we will discuss the clinical features of a child born after amniocentesis showed a 45,XX,der(5)t(5;18)(p15;q11.2),-18 karyotype.

Case report

Our patient was the product of a 37 week pregnancy to a 39 year old, G3 P1 Ab1 woman. Amniocentesis, offered at about 16 weeks' gestation because of advanced maternal age, had been declined. However, an ultrasound study performed at 23 weeks' gestation identified a single umbilical artery and a possible cardiac anomaly. A subsequent fetal echocardiogram confirmed the presence of tetralogy of Fallot. With this additional information the family elected to have an amniocentesis for fetal chromosome analysis.

Analysis of amniocytes showed a 45,XX,der(5)t(5;18)(p15;q11.2),-18 fetal karyotype (fig 1). Acetylcholinesterase electrophoresis of amniotic fluid showed a normal banding pattern. Subsequent testing of the parents showed normal karyotypes.

The infant was born by normal spontaneous vaginal delivery. She weighed 2275 g (2nd–25th centile for 37 weeks' gestation), was 43 cm long (just below the 2nd centile for 37 weeks' gestation), and had a head circumference of 30.5 cm (2nd centile for 37 weeks' gestation). Her craniofacial appearance was notable for prominent, posteriorly rotated ears, a right preauricular dimple, a left preauricular skin tag, upward slanting palpebral fissures, a wide nasal bridge, a thin upper lip, and a short neck (fig 2). Her chest was symmetrical with widely

Figure 1 Partial karyotype of amniocytes, showing 45,XX,der(5)t(5;18)(p15;q11.2),-18 karyotype.

spaced, hypoplastic nipples. She had a weak, cat-like cry. A grade III/VI systolic murmur was heard.

Karyotype analysis on peripheral blood lymphocytes confirmed the chromosome abnormalities noted at amniocentesis. An echocardiogram identified tetralogy of Fallot, pulmonary atresia, and a patent ductus arteriosus.

The infant initially required supplemental oxygen and this was continued for eight days. She was started on prostaglandin E1 therapy to maintain the patency of the ductus. This medication was discontinued at 5 days of age and the ductus remained open. The infant began to take formula by mouth. She remained stable and was discharged home at 12 days of age. The infant's course was characterised by heart failure and respiratory distress. At 7 months of age she had a Blalock-Taussig shunt created and she showed marked improvement in her general health following the procedure. She continued to grow in weight and length although remaining below the 5th centile. For example, at 27 months her weight was at the 50th centile for 7 months and her length was at the 50th centile for 12 months. Her head circumference showed an abnormal deceleration of growth, such that at 27 months the head size was at the 50th centile for 4 months.

The infant had her initial formal developmental evaluation at 7 weeks of age. At that time, her developmental skills were at a level between 0 and 4 weeks. Brief visual fixation could be elicited in her line of vision and facial grimacing was noted in response to loud bell ringing. She kept her head turned to the right side. In supine and in sitting positions her back was kept rounded. When brought from supine to sitting position by pulling on her arms there was a head lag. When she was held in ventral

Section of Genetics,
Department of
Pediatrics, St Joseph's
Hospital and Medical
Center, 703 Main
Street, Paterson, New
Jersey 07503, USA
R G Hutcheon

Section of Child
Development,
Department of
Pediatrics, St Joseph's
Hospital and Medical
Center, Paterson, New
Jersey, USA
A Mallik

Genzyme Genetics, 100
Corporate Drive,
Yonkers, New York,
USA
M Shaham

Correspondence to:
Dr Hutcheon.

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Figure 2 Front (A) and side (B) views of patient showing prominent ears, left preauricular skin tag, short, upward slanting palpebral fissures, wide nasal bridge, thin upper lip, and short neck.

suspension she did not lift her head or legs. A mild diffuse hypotonia was noted with normal deep tendon responses.

The infant attended an Early Intervention Programme where she received stimulation therapy. This, in conjunction with the loving and nurturing home environment provided by her parents, sister, and extended family, has helped her make limited but definite developmental gains (table 1). At 27 months of age she was able to engage in midline hand playing, reach out to grasp objects, sit independently, roll in both directions, assume a creeping position when prone, make vowel and consonant sounds, imitate sounds by others, respond to her name, and play social games like peek-a-boo. Although her developmental progress has been very slow, it has been continuous. The child has shown no loss or regression of her skills.

Table 1 Summary of patient's developmental progress from birth until the age of 27 months

Developmental skills	Age					
	7 wk	21 wk	46 wk	64 wk (16 mth)	88 wk (22 mth)	108 wk (27 mth)
Adaptive (weeks)	0-4	8-12	16	16-20	20-24	24-28
Fine motor (weeks)	0-4	8	16	16-20	20	20-24
Gross motor (weeks)	0-4	8-12	16-20	16-24	24-28	24-32
Language (weeks)	0-4	8	16	20-24	28	28-32
Social (weeks)	0-4	8	16	24	28	24-32

Table 2 Summary of clinical features of 5p-, 18p-, and our patient with a 45, XX, der(5)t(5;18)(p15q;11.2), -18 karyotype

	5p-	18p-	Patient
Growth failure	+	+	+
Developmental delay	+	+	+
Congenital heart disease	+	+	+
Cat-like cry	+	-	+
Microcephaly	+	+	+
Rounded facies	+	-	-
Broad nasal bridge	+	+	+
Hypertelorism	+	+	-
Ptosis	-	+	-
Slant of palpebral fissures	Down	Horizontal	Up
Epicanthic folds	+	+	+
Low set, dysplastic ears	+	-	+
Micrognathia	+	-	+

Discussion

Prenatal diagnostic testing identified a fetus with a 45,XX,der(5)t(5;18)(p15;q11.2), -18 karyotype. Her physical features and subsequent course are characteristic of both cri du chat (5p-) syndrome and of 18p- syndrome.

The cri du chat syndrome was initially described by Lejeune in 1963 and has well defined clinical features. Affected subjects have a characteristic weak, high pitched cry that sounds like the mewling of a kitten. Although there is not a single physical feature that characterises the syndrome, the frequent associated findings include microcephaly, rounded facies, hypertelorism, broad nasal bridge, epicanthic folds, downward slanting palpebral fissures, low set, dysplastic ears, micrognathia, and transverse palmar creases. Congenital heart disease, including tetralogy of Fallot, has been described.¹ Although severe developmental delay is often present, especially when a chromosome translocation is involved, some affected subjects benefit from an early intervention programme and have been found ultimately to attain the psychomotor and social level of a 5-6 year old child.² Major features of the syndrome have been mapped: speech delay to distal 5p15.3, cat-like cry to proximal 5p15.3, and childhood facial dysmorphism to proximal 5p15.2.^{3,4}

Monosomy 18p is characterised by severe developmental delay, short stature, microcephaly, round facies, flat nasal bridge, epicanthic folds, ptosis, and hypertelorism.⁵ Although congenital heart disease in affected subjects is usually a ventriculoseptal defect, one infant has been reported with a 45,X,t(Y;18)(q12;q11.2) karyotype who had the clinical features of 18p- syndrome and tetralogy of Fallot.⁶ The critical segment for the 18p- syndrome appears to be from 18pter to 18p11.21.⁷

Table 2 compares the features found in cri du chat syndrome and 18p- syndrome with those of our patient. The patient shows features of both disorders. Her growth and microcephaly

could be predicted based on a knowledge of the two conditions. Developmental delay is also an expected feature but it is notable that our patient has shown no regression of skills and is quite interactive.

We have discussed the clinical features of a child who has a chromosome translocation that has not been previously described. She shows that when a prenatal karyotype indicates abnormalities which could involve two different syndromes, there is value in considering the features of each when providing genetic counselling. She also shows that the complex karyotype may result in unexpected findings as well. This makes prenatal and postnatal management decisions more difficult.

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