Pallister-Killian syndrome: additional manifestations of cleft palate and sacral appendage

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Abstract

We report a case of Pallister-Killian syndrome in a 28 week gestation infant. In addition to the characteristic phenotype, this patient had a cleft palate, diaphragmatic hernia, sacral appendage, and imperforate anus. The lymphocyte karyotype showed 96% 46,XX/4% 47,XX+i(12p) and the fibroblast karyotype 47,XX,+marker (presumed i(12p)). Fibroblast cytogenetic studies should be considered in all cases of diaphragmatic hernia associated with other malformations.

Since the first report by Pallister, over 30 cases of isochromosome 12p mosaicism have been described and the characteristic phenotype defined of a coarse face, flat, broad nasal bridge, hypertelorism, sparse scalp hair, short neck, limb abnormalities, irregular pigmentation, and developmental delay.¹⁻⁵ There have been two reports^{6,7} in addition to our case of neonatal deaths in the syndrome with the malformations forming a consistent pattern of diaphragmatic hernia (3/3) and anorectal abnormalities (2/3). In addition, a case therapeutically aborted had a diaphragmatic hernia incompatible with life.⁷

We report a further case of isochromosome 12p mosaicism with a diaphragmatic hernia, imperforate anus, cleft palate, and a sacral appendage.

Case report

The parents of the patient were in good health and unrelated. The mother was aged 24 and the father 26 at the time of delivery. The pregnancy was complicated by polyhydramnios and vaginal spotting at 8 weeks. There was no medication taken, she had an occasional

drink containing alcohol, and 5 to 6 cigarettes per day. Prenatal vitamins were taken once daily. Labour was premature and delivery occurred at 28 weeks. The Apgar scores were 2 at one and five minutes and the infant was transferred to the Neonatal Intensive Care Nursery. A chest x ray showed a left diaphragmatic hernia with bowel in the left of the chest and the heart displaced to the right.

The head circumference (OFC) was 27 cm (75th centile), length 38 cm (75th centile), and weight 1430 g (90th centile). The ears were small and low set. There was hypertelorism (inner canthal distance 1.8 cm) and a broad, flat nasal bridge. A midline ridge was present in the maxillary ridge anteriorly (fig 1). The palate had a small posterior cleft. The neck was short with increased posterior neck skin and webbing. Both nipples were hypoplastic and inverted with an internipple distance of 5.4 cm (about +2 SD). The anus was absent with a sacral appendage of 1.5 cm present (fig 2). There was decreased range of movement at the elbows and hips. The hands were square with lymphoedema of the fingers. The thumbs were proximal and held in an adducted position. Oedema was also marked over the thighs.

There was a simian crease on the right hand. The infant died at 3 hours of age from pulmonary

Figure 1 Facial appearance.

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Details of cases with Pallister-Killian syndrome and diaphragmatic hernia.

	Neonatal lethal			Terminations	
	Case 1, Warburton <i>et al</i> ⁷	Present case	Pauli <i>et al</i> ⁶	Lopes <i>et al</i> , ⁹ Wyatt ¹⁰	Case 3, Warburton <i>et al</i> ⁷
Blood karyotype	Not done	Mosaicism 4% abnormal	Mosaicism 10% abnormal	Mosaicism 14% abnormal	
Skin karyotype	Mosaicism 90% abnormal	47,XX,i(12p) 100%		Mosaicism 96% abnormal	
Other karyotype			Gonad 100% abnormal	Amniocytes first 100% abnormal, second mosaicism	Amniocytes- mosaicism CVS-46,XX
Diaphragmatic hernia	Left side	Left side	Left side	Massive	Large
Anorectal anomalies	—	Imperforate anus, sacral appendage	Imperforate anus	—	—
Cleft lip/palate or cleft palate	—	Cleft palate	Cleft lip and palate	—	—

hypoplasia. Necropsy confirmed the pulmonary hypoplasia and showed a blindly ending sigmoid colon and small foci of calcification in the pituitary.

CYTOGENETIC STUDIES

Chromosome analysis was performed on blood and skin. The blood showed a mosaic picture with 48/50 cells 46,XX and 2/50 cells 47,XX,+iso(12p) (fig 3) while the skin fibroblast (passage number 4) karyotype was 15/15 47,XX, +marker. Parental karyotypes were normal.

Figure 2 Sacral appendage.

Discussion

This patient has cleft palate and a sacral appendage as additional manifestations of isochromosome 12p mosaicism and substantiates the association with imperforate anus and diaphragmatic hernia. Details of the four published cases and our case are summarised in the table. The finding of a percentage of cells in the blood with isochromosome 12p is common with diaphragmatic hernia (3/5) and rare if diaphragmatic hernia is not present.³ There are two possible explanations for this; either the more widespread presence of mosaic tissue disrupts the development of the diaphragm or cases with early neonatal death only have fibroblast karyotypes if the lymphocytes show mosaicism. The usual approach to neonates with lethal multiple congenital malformations is to take blood and skin for karyotyping. If the lymphocyte karyotype is normal then an additional fibroblast karyotype is rarely done. It is therefore possible that the cases with isochromosome 12p only in fibroblasts would be missed. This is important as there is overlap in the features of Fryns syndrome and cases of Pallister-Killian syndrome with diaphragmatic hernia. The major features of Fryns syndrome are diaphragmatic hernia, coarse face with a broad, flat nasal bridge, cleft lip/palate, hirsutism, and distal limb abnormalities. Less frequent features include short neck, corneal clouding, narrow thorax, hypoplastic nipples, excess neck skin, genital abnormalities, cystic renal dysplasia, and central nervous system malformations.⁸ The features which may distinguish the two conditions are corneal clouding in Fryns syndrome and sparse scalp hair in Pallister-Killian syndrome. As neither of these features is invariably present, we suggest that infants with diaphragmatic hernia and other malformations should have skin fibroblast karyotype analysis to avoid confusion with

Figure 3 Karyotype 47,XX,+iso(12p).

Fryns syndrome. This is important in counselling, as the recurrence risk for Pallister-Killian is negligible but for Fryns syndrome it is 25%.

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