A FURTHER PRENATAL DIAGNOSIS OF MOSAIC TETRASOMY 12p BY IN SITU HYBRIDIZATION

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SUMMARY *: A further case of mosaic tetrasomy 12p detected prenatally is reported. The 38-year-old mother in her third pregnancy was referred to our center at 15 weeks of gestation because of advanced maternal age. Amniocentesis was performed and the culture yielded a 46,XX/47,XX,+ i(12p) ? karyotype. The fetus was suspected to have Pallister-Killian Syndrome. The diagnosis was confirmed by FISH analysis. An ultrasound examination showed the fetus to have a diaphragmatic hernia.*

The pregnancy was terminated with the consent of the family. The fetus showed multiple congenital abnormalities including a large and coarse face, frontal bossing, high frontal hairline, hypertelorism, wide-flat nasal bridge, small, upturned nose, full cheeks, large mouth, short mandible, short neck with excess nuchal skin, and low set ears. Fetal skin fibroblast cultures confirmed the cytogenetic diagnosis of tetrasomy 12p whereas the fetal blood yielded only normal karyotype. Karyotypes of the parents were also normal. Autopsy findings of the fetus confirmed the diagnosis of congenital diaphragmatic hernia.

Key Words: *Abnormalities-Multiple, Chromosome Aberrations, Chromosome Abnormalities, Chromosomes-Human-Pair 12, In Situ Hybridization, Diaphragmatic Hernia.*

INTRODUCTION

Patients presenting with Pallister-Killian (P-K) syndrome often present with severe hypotonia, macrocephaly, prominent forehead, hypertelorism, coarse and flat facies, upslanting palpebral fissures, depressed nasal bridge, long philtrum, wide mouth, prognathism, omphalocele, diaphragmatic hernia, joint laxity, and severe motor and mental retardation (1-3). The syndrome first described by Pallister et al. is consistent mostly with mosaic i(12p) in cultured fibroblasts, and is unique in the sense that it is often associated with a normal karyotype in peripheral blood lymphocytes (2-6). Several cases with prenatal cytogenetic diagnosis, but few confirmed with FISH analysis, have been reported (2, 7-12).

Here we report a further prenatal diagnosis of Pallister-Killian syndrome confirmed by in situ hybridization.

CASE REPORT

The 38-year-old mother underwent amniocentesis at 15 weeks of gestation of her third pregnancy because of advanced maternal age. Karyotyping yielded the presence of an extra chromosome in a mosaic state. GTG-banding suggested that the extra chromosome could be an isochromosome 12p (Fig. 1). In situ hybridization

Fig - 1 : Partial karyotype by GTG-banding showing i(12p)

with a chromosome 12-specific DNA probe confirmed that the marker originated from chromosome 12 (Fig. 2). The data allowed us to identify the extra chromosome as i(12p) and the case as a Pallister-Killian syndrome. A levél II ultrasound examination performed at this stage showed the fetus to have diaphragmatic hernia.

The pregnancy was terminated with the consent of the family. The fetus weighed 280 g and the head circumference was 178 mm. She showed multiple congenital abnormalities including a large and coarse face, frontal bossing, high frontal hairline, hypertelorism, wide and flat nasal bridge, small nose, full cheeks, large mouth, short mandible, short neck with excess nuchal skin and low set ears (Fig. 3). Autopsy findings of the fetus confirmed the diagnosis of congenital diaphragmatic hernia.

Fetal blood and skin were sampled for cytogenetic study. A 46,XX karyotype was found in peripheral blood lymphocytes whereas metaphases from fibroblast cultures yielded mosaic tetrasomy 12p. Cytogenetic studies of the parents were normal.

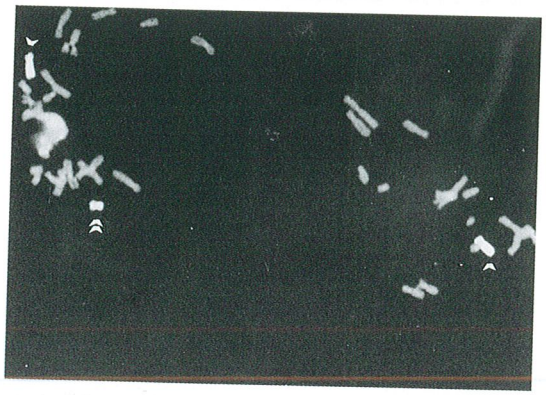

Fig - 2 : In situ hybridization of a metaphase spread showing a flourescent signal on the isochromosome 12 and the two normal 12 chromosomes (arrows).

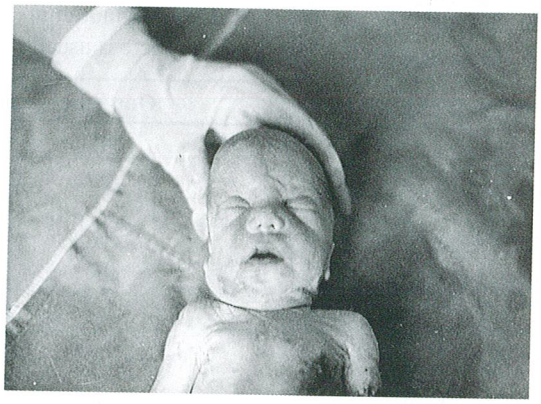

Fig - 3 : Fetus with Pallister-Killian syndrome.

DISCUSSION

Tetrasomy 12p is the most frequent autosomal tetrasomy in humans. It generally represents as a mosaic state in tissue cultures but is frequently undetectable by standard cytogenetic analysis of peripheral blood. This characteristic might have allowed most of the P-K cases to be diagnosed have not prenatally, because cardiocentesis is generally indicated based on an ultrasound abnormality. Fortunately, advanced maternal age indication followed by an amniocentesis allowed the present case to be diagnosed prenatally.

Tetrasomy 12p has been reported several times as tetrasomy 21q (12-14). This is mostly because the identification of the extra chromosome has often been based on GTG-banding pattern, which makes it difficult to distinguish between isochromosome 12p and duplication 21q. Previous to in situ hybridization studies, i(12p) has been confirmed by LDH-B gene dosage effect (7). Recently FISH has been a useful technique for the

rapid detection of i(12p) in Pallister-Killian patients (8, 12, 15-17). Interpretation of the extra chromosome in the present report yielded no difficulty because of the obvious pattern of the GTG-banding; however precise identification was based on in situ hybridization.

Phenotypically Pallister-Killian syndrome presents with a wide range of severity (Table 1). There is hypotonia from birth and severe to profound motor and mental retardation from early infancy. The majority of infants develop a seizure disorder. Many are bedridden and almost will never talk. Some clinical alterations occur during life. Little is known about the fetal phenotype. Sonographic fetal examinations may reveal either non-specific abnormalities, such as polyhidramnios, or no anomalies at all (2, 8, 12). There is usually no growth retardation. Infrequently, diaphragmatic hernia and omphalocele may be noticed. Most of the malformations are identified at autopsy. No detectable ultrasound abnormality was reported in our case during the routine examination, most possibly because it was performed at an early stage of the pregnancy. However, a congenital diaphragmatic hernia was noticed when the ultrasound examination was repeated at 20 week of gestation after the cytogenetic diagnosis of P-K syndrome was established. Autopsy findings of the fetus confirmed the diagnosis of the diaphragmatic hernia and showed that the fetus presented most of the features of P-K syndrome found in infancy or newborn (Table 1). Similarity between our case and that of McLean et al. with regard to fetal morphology is striking.

Clinical Features	Our Case
Hypotonia	NK
Prominent Forehead	+
Flat Occiput	+
Sparse Hair	NK
A Large and Coarse Face	+
Hypertelorism	+
Large Mouth	+
Full Cheeks	+
Small Chin	+
Long Philtrum	+
Cleft Lip and Palate	(-)
Upturned Nose	+
Small Malformed Ears	+
Short Neck	+
Excess Nuchal Skin	+
Congenital Heart Disease	(-)
Omphalocele	(-)
Imperforated Anus	(-)
Undescended Testis	F
Short and Malformed Extremities	(-)
Renal Anomalies	(-)
Pigmentary Dysplasia of the Skin	NK
Diaphragmatic Hernia	+

NK: Not Known F: Female Fetus

Table 1 : Clinical features of Pallister-Killian syndrome.

Approximately 10 to 15 % of reported patients with mosaic isochromosome 12p have diaphragmatic hernia. To evaluate a fetus with diaphragmatic hernia, either amniocentesis or for rapid karyotyping, cordocentesis is recommended. As fibroblasts seem to be more accurate than fetal lymphocytes in defining the true fetal chromosomal status, we insist on performing cytogenetic studies from amniocytes when diaphragmatic hernia is detected prenatally. Postnatally, when clinical phenotype suggests a chromosome abnormality, chromosome analysis on long term cultures (skin fibroblasts) should be performed, rather than lymphocytes, if the latter proves to be chromosomally normal.

The mechanism giving rise to the mosaicism in P-K syndrome remains unexplained. There seems to be no correlation between the severity of the phenotype and the degree of mosaicism. The case reported by Shivashankar et al. did not present as a mosaic and seemed to be less malformed than those reported as mosaics (8).

The presence of i(12p) cells in amniocyte cultures allows prenatal diagnosis of the condition; however prenatally diagnosed cases are rare and often follow amniocentesis for advanced maternal age.

Matenal age for reported cases of Pallister-Killian syndrome is significantly higher than the general population and similar to maternal age in cases of Down syndrome (9, 18). Few cases have been reported in which amniocentesis established the prenatal diagnosis after ultrasound

identification of a fetal diaphragmatic defect (3, 14). Altough a carefully detailed ultrasound examination contributes a lot to the prenatal diagnosis of P-K syndrome, it seems that maternal age is still the most efficient access. We suggest advanced maternal age to stand as an essential indication for the prenatal diagnosis of P-K syndrome, if not for other chromosomal abnormalities.

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