Prenatal diagnosis of the Wolf-Hirschhorn syndrome

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Wolf-Hirschhorn syndrome (WHS) is caused by a deletion of the short arm on chromosome 4 and is characterized by multiple congenital abnormalities, growth and mental retardation. In this case report, we performed amniocentesis for the chromosome analysis on a 25-year-old pregnant woman at 16 weeks of gestation whom we suspected of Edward's syndrome by the triple test of maternal serum and ultrasonography. The result of analysis revealed a karyotype of the fetus with 46,XY,del(4)(p15) by trypsin Giemsa's banding technique. With the result, we were able to diagnose the fetus as having WHS. As such, after therapeutic termination of the pregnancy, we confirmed WHS through the sampling of tissue by both trypsin Giemsa's banding and fluorescence in situ hybridization (FISH) method. To determine the origin of the WHS, we further tested the karyotypes of the parents. As parental karyotypes were found to be normal, we determined the case of the fetal WHS to be de novo.

Keywords: Wolf-Hirschhorn syndrome (WHS), prenatal diagnosis, triple test, chromosome 4p deletion

INTRODUCTION

The Wolf-Hirschhorn syndrome was first discovered by Wolf *et al.* (1965) and Hirschhorn *et al.* (1965) to be associated with deletion of the short arm on chromosome 4. It is characterized by intrauterine growth retardation, profound psychomotor retardation, characteristic facial dysmorphism, and several midline fusion defects including midline scalp defects, hypertelorism, cleft lip or palate, agenesis of the corpus callosum, cardiac septal defects, and hypospadias (Johnson *et al.*, 1976; Lurie *et al.*, 1980; Wilson *et al.*, 1981).

Generally prenatal diagnosis of WHS is rarely made, especially as major malformations associated with WHS are often missed clinically. Rather, WHS is more often diagnosed after fetal karyotyping for those with indications of abnormal malformations such as intrauterine growth retardation with or without associated anomalies (Verloes *et al.*, 1991; Tachdjian *et al.*, 1992).

In this report, we present a case of WHS which was first detected by the triple test of maternal serum and ultrasonography, then referred to genetic laboratory for confirmation through the karyotyping,

CASE REPORT

A 25-year-old, without family history of any disease, was referred for the triple test of maternal serum at the 15th week of gestation. The result of triple test was screen positive for Edward syndrome. So, we performed amniocentesis for fetal karyotyping at 16th week of gestation. The result of trypsin Giemsa banding revealed a karyotype with 46,XY,del(4)(p15) (Fig. 1). The pregnancy continued to 21 weeks of gestation and further examination was made using ultrasonography, which revealed fetal nuchal thickness, intrauterine growth retardation and diaphragmatic hernia (Fig. 2). With the results of karyotype and ultrasonogaphy, selective abortion was carried out in week 22 of gestation, after which the tissue was used for final confirmation of the WHS with FISH, which showed concordance with previous conventional karyotyping (Fig. 3). To confirm the origin of WHS, we performed parental chromosome analysis to determine whether parents were reciprocal

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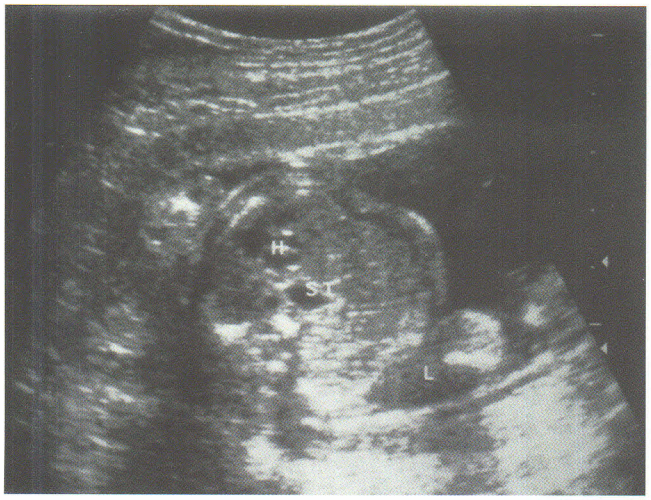

Fig. 1. Sonography of the fetus at the 21th week of gestation showing diaphragmatic hernia (H:heart, ST: stomach, L: upper limb).

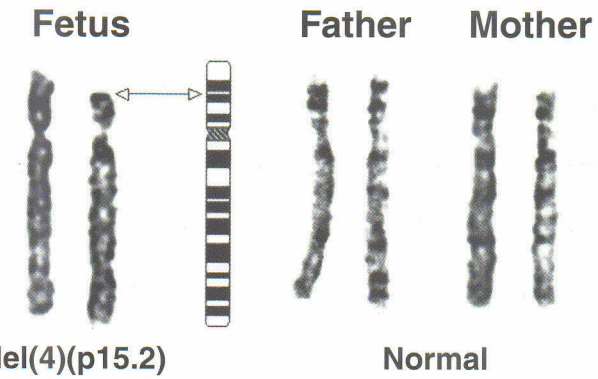

Fig. 2. Fetal karyotyping was deletion of the short arm of chromosome 4 (arrow). Parental karyotyping were normal.

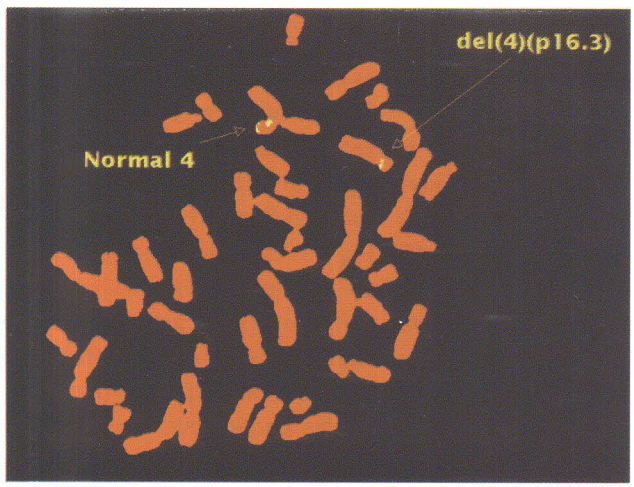

Fig. 3. A metaphase spread of the apparently terminal deletion patient showing D4S96 probe to only one chromosome 4 short arm (arrow). A chromosome 4 control probe D4S174 was used for identification.

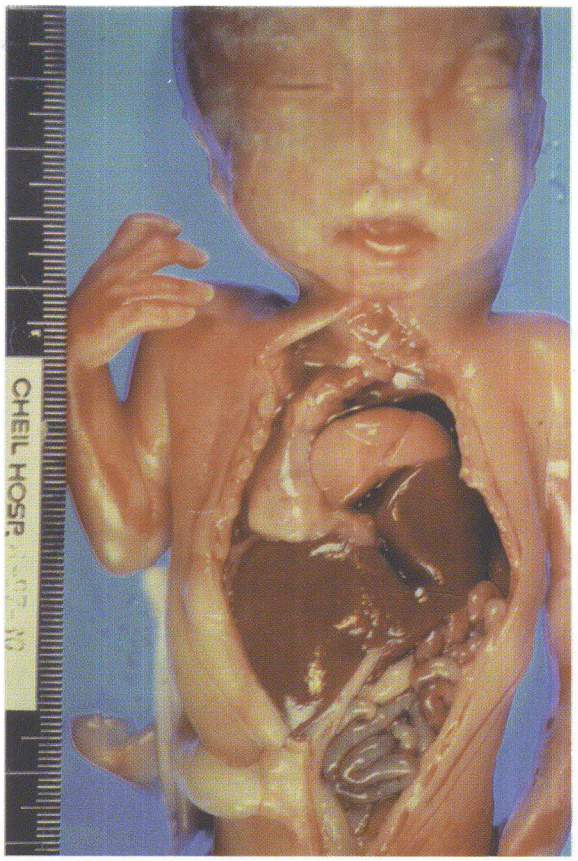

Fig. 4. Note cleft palate, low set ear, hypertelorism, diaphragmatic hernia, hypoplasia.

translocation carrier or not. The autopsy result obtained showed the same result of amniocytes (Fig. 3). The result of autopsy showed intrauterine growth retardation, bilateral pulmonary hypoplasia, cleft palate, low set ear, hypertelorism, nuchal fold thickening, diaphragmatic hernia which are common characteristizations of patient of WHS (Fig. 4).

DISCUSSION

As it is known, the prenatal karyotyping by amniocentesis and chorionic villi sampling in the general pregnant women, who don't have the family history of disease or the routine indications, has been applied when abnormal physical findings were found through triple test of maternal serum and ultasonography.

According to several reports, serum AFP concentrations were found to be abnormally low for women bearing fetus with chromosome abnormalities such as Down's, Edward's and Patau's syndromes. Kim *et al.* (1995) reported the 4p-syndrome associated with low AFP concentration. This

case showed also low AFP concentration and Edward's syndrome was suspected in triple test.

Intrauterine growth retardation (IUGR) have been found very often as a major characteristics in WHS by routine ultrasonography (Tachdjian *et al.*, 1992; Eiben *et al.*, 1988; Verloes *et al.*, 1991; Vinals *et al.*, 1994). This severe growth retardation has always been emphasized in infants and children with WHS, and does not improve with survival. In our study, IUGR was also diagnosed through routine ultrasonography. In addition, diaphragmatic hernia and fetal nuchal thickness were found. The typical pattern of WHS includes 'Greek helmet' dysmorphism which has cardiac visceral malformations, and mental retardation (Verloes *et al.*, 1991). The classical craniofacial dysmorphism ('Greek helmet') included a long straight nose, micrognathia and dolichocephaly, major hypertelorism and large ears. However, the craniofacial abnormalities have not yet been described in fetuses (Tachdjian *et al.*, 1992) because of the limitation of ultrasonoraphy, and craniofacial abnormalities can not be detected easily in the fetuses during pregnancy.

As a result, the typical craniofacial dysmorphisms are mostly found during autopsy or after birth. Since WHS (4p- syndrome; 4p monosomy) was described in 1965, more than 120 cases have been reported in newborn babies, children, and adults (Lazjuk *et al.*, 1980; de Grouchy and Turleau, 1982).

Currently, the frequency of WHS is 1 out of 50,000 live births. Among them, about 87% of the cases are *de novo* deletions, the remanding 13% are due to translocations of the parental chromosome (Johnson *et al.*, 1976; Lurie *et al.*, 1980). Cytogenetic studies of the patients with classical WHS suggest that the critical deleted segment is within 4p 16.3 (Tranebjerg *et al.*, 1984; Altherr *et al.*, 1991). However the size of the 4p deletion does not usually influence the phenotype (Leonard and Huret, 1988).

In this case, the breakpoint of the segment was 4p15, deleted from the region of 4p15 to the terminal region of the short arm, which was not difficult. However, some patients with the clinical manifestation of 4p- syndrome do not show any apparent cytogenetic abnormalities in chromosome 4 (Dallapiccola *et al.*, 1993). In these cases where microdeletion is suspected, fluorescence in situ hybridization (FISH) or Southern blot can be applied as useful method for the detection of the microdeletion. Our case was refered to us after fetal abnormalities were detected by triple test and ultrasonography, in normal pregnant woman without family history. For this case, we applied the chromosome analysis and FISH for the prenatal diagnosis of WHS.

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