Inverted Duplication of the Distal Short Arm of Chromosome 3 Associated With Lobar Holoprosencephaly and Lumbosacral Meningomyelocele

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A fetus with lobar holoprosencephaly and lumbosacral meningomyelocele associated with duplication of the short arm of chromosome 3 is reported. The anomalies were detected on fetal ultrasound at 20 weeks' gestation and the autopsy findings correlated well with the prenatal findings. The fetal karyotype was 46,XY,der(3)del(3)(p26)dup(3)(p26p21.3). The association of holoprosencephaly with duplication 3p is well known, but to the best of our knowledge this is the first reported association of meningomyelocele with 3p duplication. These findings suggest that a gene or genes with a crucial role in central nervous system development are located on the short arm of chromosome 3.

INTRODUCTION

Neural tube defects are in most cases multifactorial in etiology [Hall et al., 1988]. However, about 5% of neural tube defects (NTD) are the result of a single gene disorder and as many as 6.5% of cases are associated with chromosome abnormalities [Kennedy et al., 1998].

Holoprosencephaly is also an etiologically heterogeneous disorder. About half of the cases are associated with a chromosome abnormality [Croen et al., 1996]. A minimum of 12 holoprosencephaly-associated loci have been proposed as well as specific teratogens acting at the earliest stages of neurulation [Wallis et al., 1999].

We report the prenatal and autopsy findings on a fetus with a de novo duplication and deletion of the short arm of chromosome 3. Prenatal ultrasound performed at 20 weeks' gestation showed multiple abnormalities including cerebral anomalies and lumbosacral meningomyelocele. Postnatal fetal autopsy confirmed the lumbosacral NTD and showed lobar holoprosencephaly as well as tetralogy of Fallot.

Holoprosencephaly is known to be associated with duplication of the short arm of chromosome 3. However, to the best of our knowledge this is the first reported case of NTD associated with holoprosencephaly in duplication 3p. These findings suggest that a gene or genes important in the normal embryological development of the central nervous system are located on the short arm of chromosome 3.

CASE REPORT

A 39-year-old primigravida woman was referred to the Prenatal Diagnosis Program following the detection of lumbosacral meningomyelocele, cerebral ventriculomegaly, and a midline facial cleft on fetal ultrasound performed at 20 weeks' gestation (Fig. 1). Maternal serum screening at 16 weeks' gestation showed an increased risk of open NTD (MSAFP of 92.4
\( \mu g/L \) or 2.44 MOM and a risk of 1:275 for open NTD). The couple decided to terminate the pregnancy and this was performed by an intra-amniotic injection of prostaglandin (PGF2\( \alpha \)). Amniocentesis was performed at the time of the termination at 22 weeks’ gestation for chromosome analysis.

On external examination the 310 g male fetus had marked hypotelorism with a midline cleft lip and palate (Fig. 2). There was no nose. A lumbosacral meningocele was covered by a thin membrane and measured 2 cm in diameter (Fig. 3). Internal examination showed an abnormal heart with tetralogy of Fallot. The pulmonary valve was narrow and bicuspid with infundibular stenosis. The aorta was right-sided and overriding a large ventricular septal defect.

Neuropathological examination revealed lobar holoprosencephaly and arhinencephaly. The septum pellucidum and fornices as well as the corpus callosum were absent. The deep gray matter structures (basal ganglia and thalami) were dysplastic and fused with obliteration of the third ventricle, dysplastic inferior olivary nuclei, mild dysplasia of the midbrain involving the ventral peduncles and dorsal colliculi with hypoplastic interhemispheric fissure and mild anterior focal cortical fusion.

Fetal radiographs showed slight widening of the neural arches from approximately L3 to S1 associated with a soft tissue defect. Several butterfly vertebrae from T5 to T8 as well as a hemivertebra at T4 were present. Nasal bones were not visible radiologically and a maxillary cleft could be seen.

**CYTOGENETIC STUDIES**

Cytogenetic studies performed on amniocytes revealed an abnormal karyotype: 46,XY,der(3)del(3)(p26)dup(3)(p26p21.3) (Fig. 4). Parental karyotypes were normal.

FISH studies were performed using a chromosome 3 painting probe (Oncor, Gaithersburg MD). Positive hybridization was seen along the whole length of both the normal chromosome 3 homolog and the derivative chromosome 3, indicating that the extra material on 3p originated from chromosome 3. Further molecular cytogenetic studies were performed on metaphase cells using a telomeric cosmid clone, B47a2, the most distal probe currently mapped on chromosome 3p (D. Ledbetter and J. Flint, personal communication). In all cells analyzed, positive hybridization was seen only to the normal chromosome 3p and not to the derivative 3p or to any other chromosome, indicating a deletion of this region. In conjunction with the cytogenetic studies, the molecular findings suggest that the derivative chromosome is an inverted duplication of the distal short arm of chromosome 3 with deletion of at least some telomeric sequences in 3p26.

**DISCUSSION**

Inverted duplication in the short or long chromosome arms with a deletion of the segment distal to the duplication has been reported for chromosomes 7 [Stetten...
et al., 1997], 8 [Floridia et al., 1996], and 9 [Teebi et al., 1993]. To the best of our knowledge, inverted duplication 3p with duplication of p21p26 and deletion p26 has been reported only once before [Jenderny et al., 1998].

Weleber et al. [1976] suggested that the mechanism for this type of chromosome abnormality involved a symmetric meiotic recombination between two homologous chromosomes which results in a U-shaped exchange and thus a formation of a dicentric chromosome. A subcentromeric break in anaphase results in duplication and deletion of a segment distal to the duplicated region. Floridia et al. [1996] modified the mechanism as a result of data indicating asymmetric meiotic recombination between the two homologous chromosomes.

The phenotypic manifestations in cases with inverted duplication and distal deletion of chromosome 3p should theoretically be a combination of trisomy 3p21 to 3p26 and deletion of 3p26. Comparison of clinical features of our case with other cases reported in the literature is difficult. With the exception of the case reported by Jenderny et al. [1998], other reported cases with duplication of 3p involve a translocation with another chromosome. Thus, some of the clinical features may be the result of duplication or deletion of another chromosome. Comparison of other cases with deletion of 3p is equally problematic. Most of the reported cases were based on traditional chromosome banding, which implies that most or all of band p26 and perhaps part of band p25 was deleted. Deletion in the inverted duplication cases based on FISH analysis is smaller than would be detected by traditional banding. Although neither NTD nor holoprosencephaly was noted in the patient reported by Jenderny et al. [1998], no details of brain structure were reported.

Duplication of the distal short arm of chromosome 3 (trisomy 3p) was first reported by Rethore et al. [1972] and since then more than 45 patients have been reported in the literature [Schinzel, 1984; Conte et al., 1995]. The most common findings associated with this chromosome abnormality are microcephaly or microbrachycephaly, square-shaped facies with temporal indentation, frontal and parietal bossing, hypertelorism, telecanthus, short and flat nose, full cheeks, large downturned corners of the mouth, cleft lip and palate, micrognathia, abnormal ears, syndactyly of the fingers, as well as cardiac, genitourinary, gastrointestinal, skeletal and brain anomalies, mainly holoprosencephaly as well as arhinencephaly [Van Regemorter et al., 1983; Martin and Steinberg, 1983; Gimelli et al., 1985; Gillerot et al., 1987; Kurtzman et al., 1987]. The prognosis is poor and most patients with dup(3p) die within the first year of life. As in other cases with dup(3p), our patient had a midline facial cleft and absent nasal bones, facial findings frequently associated with the holoprosencephaly field defect [Cohen, 1989].

Deletion of the terminal portion of the short arm of chromosome 3: del(3)(pter→p25) has been reported in at least five patients in detail as well as in another three abstracts [Schinzel, 1984]. All cases were de novo and all of the patients displayed very similar findings, including asymmetry of the skull and facies, low hairline both frontal and nuchal, hypertelorism, synophrys, upslanting palpebral fissures, epicanthic folds, ptosis, strabismus, narrow nose with prominent nasal bridge, long philtrum, small and protruding ears, scoliosis, brachydactyly (fingers and toes), pre- and postnatal growth retardation, and delayed skeletal maturation.
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