This communication presents the first case of complete trisomy 19q, prenatally detected by ultrasound investigation.

Real-time high-resolution ultrasound examination was performed at 19 weeks of gestation. After termination of the pregnancy, autopsy investigation was done. GTG-banding, fluorescence in situ hybridization m-(FISH) analysis, and FISH analysis with a 19q subtelomeric specific probe were used for identification of the fetal karyotype. Sonographic examination revealed an enlarged cisterna magna, cerebellar hypoplasia and aplasia of the inferior part of the vermis, combined and bilateral kidney malformations, significant nuchal fold, absence of fetal nasal bones, and intracardial calcifications. Autopsy confirmed ultrasound findings, but also revealed situs viscerum inversus of the lungs. Fetal karyotype was defined as: 46,XY,der(21) t(19;21)(q11;p13)mat. Our ultrasound and autopsy findings will certainly contribute to better knowledge of phenotype characterization of this rare chromosomal disorder. Copyright © 2007 John Wiley & Sons, Ltd.

KEY WORDS: trisomy 19; prenatal diagnosis; multiple malformations

INTRODUCTION

Unbalanced karyotypes due to reciprocal translocation or rearrangement of 19q chromosome are a rare aneusomy. To our knowledge, only ten cases with no concomitant monosomy have been reported so far. All of them were, in fact, partial trisomies that resulted from unbalanced translocation, familiar or de novo, or from pure duplication (Lange and Alfi, 1976; Rivas et al., 1985; Boyd et al., 1992; Valerio et al., 1993; Cotter et al., 1997; Bhat et al., 2000; Tercanli et al., 2000; Qorri et al., 2002; Rombout et al., 2004). Some authors have stated that it could be a recognizable syndrome (Lange and Alfi, 1976; Rivas et al., 1985; Bhat et al., 2000; Tercanli et al., 2000; Rombout et al., 2004) associated with the phenotype that usually includes low birth weight, growth and psychomotor retardation, short neck with redundant skin fold, microcephaly, facial dysmorphism (flat nasal bridge, small nose, short philtrum, down turned mouth, abnormal ears), clinodactyly, heart malformations, and anomalies of the genitourinary tract and/or gastrointestinal system (Rombout et al., 2004).

Moreover, only three of the reported cases were prenatally diagnosed. They arose de novo owing to a duplication in two cases (Cotter et al., 1997; Tercanli et al., 2000) and to a translocation involving chromosome 22 (Rombout et al., 2004) in the third case. We present another prenatally diagnosed case of trisomy 19q, resulting from maternal translocation (19;21)(q11;p13). In contrast to other reported cases, this is the first report of complete trisomy of 19q chromosome.

CASE REPORT

A 25-year-old primigravida was referred to routine ultrasound examination at 19 weeks of gestation. The woman and her husband were healthy, non-consanguineous, and had no family history of congenital malformations. Real-time sonography revealed multiple malformations and because of extremely poor prognosis, the parents decided, after counselling, to terminate the pregnancy.

Ultrasound findings

The fetal biometry agreed with 19 weeks of gestation (biparietal diameter (BPD) 4.4 mm, femur 2.6 mm, abdominal circumference 16.5 mm). Fetal heart rate was normal (145 bpm). Placenta was anterior and amniotic fluid volume was normal. All three umbilical cord vessels were present. However, we found a number of fetal structural abnormalities: increased nuchal fold (13 mm), absence of nasal bones, dilated cisterna magna, agenesia of the inferior part of the cerebellar vermis (keyhole sign), cerebellar hypoplasia (transverse cerebellar diameter (TCD) 16 mm), partially multi-cystic and hydronephrotic left kidney (grade IV) with dilated ureter and mild hydronephrosis of the right kidney (Figures 1 and 2), and intracardial calcifications (two in the left ventricle). Fetal movements were decreased. Umbilical artery velocimetry was normal. RI: 0.71.

Autopsy findings

Termination of pregnancy at 19 weeks’ gestation revealed a male fetus, weighing 400 g, with crown/heel...
Figure 1—A transverse scan of fetal head showing the cystic appearance of the fourth ventricle and cisterna magna. Cerebellar hemispheres due to hypoplasia of the inferior portion of the vermis are clearly separated. Nuchal skin is markedly edematous (8.5 mm)

Figure 2—A longitudinal sonographic scan of fetal abdomen demonstrating extremely enlarged intrarenal urinary collecting system of the left kidney length 22 cm. External examination showed a flat nose, low-set ears, and a short neck with redundant skin fold.

On internal examination, the lungs appeared normal on gross inspection, but the left lung presented characteristics of the right lung and vice versa. No heart malformations were detected. Renal fusion of the upper poles produced the horseshoe kidney. The left kidney was enlarged, showing a marked dilatation of the renal pelvis, calyceal system, and ureter, blunting of renal papillae, and parenchymal thinning. Stenosis occurred at the vesicoureteric junction. The central nervous system showed moderate cystic dilatation of the fourth ventricle.

Cytogenetic analysis

Cytogenetic analysis was performed by long-term cultures on fetal tissue. Unbalanced karyotype with additional chromosomal material on the short arm of chromosome 21 was detected (Figure 3). Chromosome analysis of the parents’ lymphocytes (GTG-banding) showed a maternal balanced translocation between a chromosome 19q and 21p, 46,XX,t(19;21)(q11;p13). The father’s karyotype was normal, 46,XY. In order to confirm translocation, m-FISH analysis was performed on maternal metaphase chromosomes (Figure 4). A subtelomeric specific probe for 19q (Visys) was further used for identification of the translocation (Figure 5).
Table 1—Ultrasound and autopsy findings in prenatally diagnosed cases of trisomy 19q

<table>
<thead>
<tr>
<th></th>
<th>Cotter et al.</th>
<th>Rombout et al.</th>
<th>Tercanli et al.</th>
<th>Present case</th>
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<tbody>
<tr>
<td>Gestational age</td>
<td>10 weeks</td>
<td>12 weeks</td>
<td>20 + 4 weeks</td>
<td>19 weeks</td>
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<tr>
<td>Karyotype</td>
<td>46,XYdir dup(19) (q13.2;q13.4) de novo</td>
<td>46,XX,der(22)t(19;22) (q13.3;p13) de novo</td>
<td>46,XY,dup(19) (q13.1;qter) de novo</td>
<td>46,XY,der(21)(19;21) (q11;p13) mat</td>
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<td>Findings</td>
<td>ultrasound</td>
<td>autopsy</td>
<td>ultrasound</td>
<td>autopsy</td>
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<td>General</td>
<td>cystic hygroma</td>
<td>abnormal nuchal translucency</td>
<td>short neck, microretrognatia, flat nose, low set ears, slightly enlarged interorbital space</td>
<td>nuchal oedema, mild hydrops fetalis with ascites, oligohydramnion</td>
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<td></td>
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<td>Anomalies of</td>
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<td>central nervous system</td>
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<td>Heart</td>
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<td>malformations</td>
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<td></td>
<td>ventricular septal defect, atriotic pulmonary artery, hypoplastic right heart</td>
<td>ventricular septal defect, aortic coarctation, aortic stenosis, anomaly of the aortic arch, abnormal four-chamber view</td>
<td>ventricular septal defect, aortic coarctation, continuous fusion of the left pulmonary artery with aortic arch, absent right pulmonary artery</td>
<td>dilated cisterna magna, aplasia of vermis cerebelli intracranial calcifications (two left)</td>
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<td>Anomalies of</td>
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<td>urinary tract</td>
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<td>bilateral pyelo-calical dilatation without obstructive lesion, cystic renal dysplasia (three bigger cysts), absence of other kidney, on detectable urine bladder</td>
<td>cystic renal dysplasia (three bigger cysts), renal fusion, hydrenephrosis, bilateral absence of ureters</td>
<td>hydrenephrosis of left kidney (IV) and mild hydrenephrosis of the right kidney, dilated left ureter</td>
<td>pyelo-calical dilatation on the left kidney, stenosis at the vesicoureteric junction, horseshoe kidney</td>
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<td>Other anomalies</td>
<td>bilatera clinodactyly</td>
<td>rocker bottom feet</td>
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On the basis of this result, the fetal karyotype was interpreted as: 46,XY,der(21)(19;21)(q11;p13)mat.

DISCUSSION

The present case is the first report of complete trisomy 19q, prenatally detected by a real-time high-resolution ultrasound investigation at 19 weeks of gestation. Sonographic examination revealed enlarged cisterna magna, cerebellar hypoplasia and aplasia of the inferior part of the vermis, combined and bilateral kidney malformations, significant nuchal fold and scalp edema, absence of fetal nasal bones, and intracardial calcifications (Table 1).

A comparison of all prenatally detected trisomies 19q indicates that the report of Tercanli et al. is the most comparable with our case, because of well-described second-trimester ultrasound findings and the fact that they described the largest trisomic segment of the long arm of chromosome 19, distal of 19q13.1 (Table 1). Urinary tract abnormalities were found in both cases. Observed multi-cystic dysplastic kidney disease could be associated with some changes of USF2 gene, located at the 19q13.1 band (Groenen et al., 1996). Disruption of the USF2 gene may cause multicystic renal dysplasia with pelviureteric obstruction, and massive hydronephrosis. In contrast to other reported cases of trisomy 19q, we observed significant CNS anomalies (Table 1), which could be associated with Dandy–Walker complex, or more precisely, to the Dandy–Walker variant (Barkovich et al., 1989). It is worth mentioning that similar brain anomalies have been reported in patients with fructin-related protein (FKRP) gene mutations, mapped to chromosome 19q13.3 (FKRP [OMIM 606,596]; Brockington et al., 2001). These gene mutations account for a wide spectrum of patients with congenital muscular dystrophy associated with brain malformations (Quijano-Roy et al., 2006) including congenital muscular dystrophy type 1C (Louhichi et al., 2004), muscle-eye-brain disease, and Walker–Warburg syndrome (Beltman-Valero de Bernabe et al., 2004). In the present case, neither a real-time high-resolution ultrasound examination, as performed by a fetal echography specialist, nor fetal autopsy revealed any heart malformations. At present, the lack of heart anomaly seems an isolated finding since heart irregularities have been the most common anomalies associated with trisomy 19q (Lange and Alfi, 1976; Rivas et al., 1985; Boyd et al., 1992; Valerio et al., 1993; Bhat et al., 2000; Tercanli et al., 2000; Rombout et al., 2004).

Our autopsy findings also detected situs viscerum inversus of the lungs. Lung anomalies (bilateral right lung) were previously described only by Lange and Alfi (1976). They reported unbalanced translocation (19;22)(q13;p13) with the most severe clinical findings of all reported trisomies 19q, which could indicate the largest duplication. Since high-resolution banding was not available in 1976, the exact size of the trisomic segment was not established and we could not compare their results with ours.

According to the literature, trisomy 19q was reported as a recognizable syndrome (Jablonski, www.nlm.nih.gov/mesh/jablonski/syndromes/syndrome198.htm).

However, phenotype variability associated with trisomy 19q still comprises a problem in syndromal characterization. The present case pointed out some new observations, for example, a possible association with Dandy–Walker variants and therefore raises questions about common clinical features of the mentioned syndrome. Our ultrasound and autopsy findings will certainly contribute to a better knowledge of phenotype characterization of this rare chromosomal disorder.

REFERENCES


