# First trimester diagnosis of 13q-syndrome associated with increased fetal nuchal translucency thickness. Clinical findings and systematic review

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**Summary**

13q-syndrome is a rare chromosomal disorder caused by partial deletion of the long arm of chromosome 13 with variable phenotypic presentation. Further sonographic features involve fetal growth restriction, bradycardia, encephalocele, facial dysmorphism and upper extremity deformity. We report a case of 13q-syndrome presenting as increased nuchal translucency diagnosed by chromosome studies and confirmed by array comparative genomic hybridization (CGH) analysis in the first trimester of pregnancy. Pregnancy was terminated at 14 weeks' gestation. The parents did not give consent for a postmortem examination. Furthermore we performed a systematic review of the international literature on previous cases of 13q-syndrome diagnosed prenatally. Our case emphasizes the importance of a detailed 11-14 week ultrasound assessment in diagnosing fetal chromosomal aberrations in combination with the modern aspects of array CGH, thus providing more precise and rapid prenatal diagnosis.

*Key words:* 13q deletion; Nuchal translucency; Prenatal diagnosis, Comparative genomic hybridization.

## Introduction

Partial deletion of the long arm of chromosome 13, also known as 13q-syndrome, is an exceedingly rare chromosomal aberration which is related to mental and growth retardation and various congenital malformations [1]. Clinical features include moderate to severe developmental delay, growth retardation, craniofacial dysmorphism (microcephaly, hypertelorism, broad nasal bridge, micrognathia), hand and foot anomalies (hypoplastic or absent thumbs), hypoplastic kidneys, and ambiguous genitalia. Central nervous system anomalies such as neural tube defects, holoprosencephaly and agenesis of the corpus callosum, and malignant neoplasms like retinoblastoma have also been reported [2, 3]. Herein we report a case of 13q deletion diagnosed prenatally together with a systematic review of the literature.

## Case Report

A 24-year-old Caucasian woman, gravida 1, para 0, with no remarkable previous obstetric or family history, presented in the first trimester of pregnancy. An ultrasound (US) examination at 13 weeks of gestation revealed an increased nuchal translucency (NT) of 3.4 mm. The adjusted risk for trisomy 21 was one in 29 whereas the adjusted risk for trisomy 18 and 13 was one in 131. Although the woman was sure about the first day of her last menstrual period and had had regular cycles, fetal crown-rump length (CRL) was 49.6 mm showing an obvious discrepancy between fetal size and gestational age, suggesting early fetal growth restriction. Fetal heart rate was measured as 140 beats per minute (below the fifth percentile for the gestational age). A midsagital view of the face revealed a dysmorphic appearance (micrognathia, distinctive flat profile); additionally, a small parietal encephalocele was documented.

Assessment of fetal extremities showed fixed arms with lack of elbow extension and suspicion of bilateral clinodactyly. Genetic counseling was performed and the parents opted for invasive prenatal diagnosis by chorionic villus sampling (CVS). Fetal DNA was extracted and a multiplex quantitative fluorescent polymerase chain reaction (QF-PCR) analysis was performed. The QF-PCR products were analyzed by capillary electrophoresis on an ABI 3130 automated DNA sequencer. All short tandem repeat markers for chromosomes 18, 21 and X were observed in a normal diallelic pattern. The three markers used for chromosome 13 were monoallelic (D13S634, D13S631, D13S258) and were unusually lower in peak height and peak area compared to the other markers thus indicating a possible monosomy.

The QF–PCR report for chromosome 13 was given as inconclusive. The chorionic villi were then cultured and GTG banding (300-400 bands) of chromosomes revealed a deletion of chromosome 13 in two different cultures [fetal karyotype: 46,XX,del (13)(q22.2qter)].

Further analysis by array-CGH1 confirmed the diagnosis revealing a deletion of about 40 MB of the distal long arm of chromosome 13 [del(13)(q22.2qter)] with the proximal breakpoint between 74,497 MB (last normal oligonucleotide) and 74,620 MB (first deleted oligonucleotide). The last oligonucleotide present in the array at the 13q position, 114,077 MB was deleted (Figure 1). Both parents had normal karyotype.

Based on US findings and cytogenetic analysis the prenatal diagnosis of 13q-syndrome was established. After genetic counseling, termination of pregnancy was carried out at 14 weeks. Autopsy was not performed due to lack of parental consent.

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Table 1. — *Clinical characteristics of the studies with prenatal diagnosis of 13q deletion.*

| Author (year) | Country | Maternal age | Gravidity Parity | Ultrasound features (wks) | Invasive testing | Cytogenetic analysis karyotype-outcome | Gender-pathology report |
|---|---|---|---|---|---|---|---|
| Santolaya *et al.* [13] 1993 | USA | 18 | G1PO | 18 weeks - Holoprosencephaly bilateral talipes, hydrocephalus | Amniocentesis | Giemsa banding 46 XY,del(13) IUD | Male - Hydrocephalus, bilateral talipes, atrial septal defect |
| Chen *et al.* [7] 1996 | Taiwan | 28 | G3P2 | 27 weeks - IUGR cardiomegaly microcephaly, encephalocoele | Amniocentesis | Giemsa banding 46,XX,del(13) (pter+q21:) Termination | Male - Microcephaly, encephalocoele, micropthalmia, hypertelorism, micrognathia |
| Lam *et al.* [8] 1998 | Hong Kong | 37 | NS | 12 weeks - Exencephaly abnormal fetal cranium | NP - material analysed after curetage | Giemsa banding of placental tissues 46,XX,13q Termination | Post-mortem examination not possible |
| Rodriguez *et al.* [18] 1999 | Spain | NS | G6P3 * | 2nd pregnancy US features NS | CVS | FISH-46-XX, -13,+der(13) | Female - Oligodactyly |
| | | | | 6th pregnancy US features NS | CVS | Termination FISH-46-XX, -13,+der(13) Termination | Male - Oligodactyly |
| Guttierez *et al.* [14] 2001 | Chile | 29 | G3P0 | 32 weeks - IUGR polyhydramnios holoprosencephaly micrognathia unilateral talipes | Cordocentesis | Giemsa banding 46,XY,del(13) (q22 →qter) IUD in 33 wks | Male - Holoprosencephaly micropthalmia, micrognathia, unilateral clubfoot, agenesis of thumbs, ambiguous genitalia |
| Widschwendter *et al.* [19] 2002 | Austria | 27 | G1PO | 24 weeks - Asymmetric IUGR - encephalocele retrognathia hypoplastic thumbs unilateral hydronephrosis | Amniocentesis Cordocentesis | Rapid-FISH Culture-fetal lymphocytes 46,XY/46,XY,del(13) (q13.3) Termination | Male - Meningoencephalocele microcephaly, micropthalmia, hydronephrosis, hypoplastic thumbs, syndactyly |
| McCormack *et al.* [15] 2002 | USA | 30 | G3P1 | NS-IUGR | Amniocentesis | Giemsa banding 46,XY,der(13) t(1;13)(q43;q21) Infant died 22 h PP | Male - Microcephaly, holoprosenecephaly, aplasia of organs |
| Chen *et al.* [9] 2005 | Taiwan | 28 | G2P1 | 17 weeks - Holoprosencephaly premaxillary agenesis hypoplastic left heart hexadactyly | Amniocentesis | FISH 46,XX,der(8)t(8;13) (p23.3;q22)de novo Termination | Female - Holoprosencephaly, premaxillary agenesis, hexadactyly |
| Alanay *et al.* [10] 2005 | Turkey | 27 | G1PO | 21 weeks - IUGR DWM-limb deformities | Amniocentesis | Giemsa banding 46,XYdel(13) (q14→qter) Premature labor and death | Male - Absence of fetal vermis DWM, corpus callosum agenesis, renal agenesis lobe anomaly |
| Gul *et al.* [11] 2005 | Turkey | NS | NS | 25 weeks - IUGR microcephaly, micropthalmia, oligodactyly, DWM | Cordocentesis | FISH - 46 XY del (13) (13q31.2 /q32.13qter) Termination | Male - IUGR, DWM, microcephaly, micropthalmia, oligodactyly |
| Araujo *et al.* [16] 2006 | Brazil | 22 | G3P1 | 23 weeks - IUGR-fusion of the lateral ventricles, agenesia of left kidney, hypertelorism | Amniocentesis Cordocentesis | Giemsa banding Giemsa banding 46, XX, del (13) (pter-31:) IUD in 27 weeks | Female - Pathology, findings consistent, with US findings |
| Hindryckx *et al.* [20] 2008 | Belgium | 41 | G8P3 | 13 weeks - Increased NT 16 weeks - Encephalocele DWM | CVS | FISH-CGH-Array Deletion 13q31.1 to 13q33.1 Termination | NS - DWM, parietal encephalocele, agenesis of corpus callosum, renal dysplasia |
| Miyake *et al.* [12] 2008 | Japan | 35 | G3P2 | 25 weeks - Duodenal atresia polyhydramnios | Amniocentesis | Giemsa banding 46,XX,del(13) (q21.1q22.3) * Fetus was delivered alive however died at 9 months PP | Female - Multiple cord lacerations, Pathology NS |
| Cain *et al.* [17] 2008 | USA | 30 | G8P2 | 10 weeks - Cystic hygroma 16 weeks - Encephalocele VSD, orbital hypoplasia | CVS | FISH-CGH-Array 46,XX,der(13)t(2; 13)(p25.1;q32)pat Termination | Female - Pathology, findings consistent with US findings |
| Current case 2009 | Greece | 33 | G2P1 | 13 weeks - Increased NT encephalocele, clinodactyly, facial dysmorphism | CVS | FISH-CGH-Array 46,XX,del(13)(q22.2qter) Termination | Male - Post-mortem examination not performed |

NS: Not stated, NP: Not performed, CVS: Chorion Villus Sampling, DWM: Dandy Walker Malformation, FISH: Fluorescent in situ hybridization, CGH: Comparative genomic hybridization, IUGR: Intrauterine Growth Retardation, IUD: Intrauterine death, VSD: Ventriculoseptal Defect.

## Discussion

We report a case of 13q-syndrome diagnosed in the first trimester of pregnancy manifesting with increased NT. Increased NT in the first trimester can be associated with numerous chromosomal abnormalities, fetal structural defects, congenital heart defects, and genetic syndromes [4, 5]. It can also be a variant of normal, documented by spontaneous resolution as the pregnancy advances beyond the first trimester [6]. The clinical characteristics of 13q syndrome have been known since 1963 [3]. Up to now approximately 100 cases have been reported and most of them were diagnosed in individuals with mental retardation associated with several congenital anomalies [1]. However in the international literature there are few cases diagnosed prenatally.

We performed a search of Medline (1950-March 2010) electronic database. The MesH (Medical subject Headings) we used were the following: 'prenatal diagnosis','13 q deletion','13 q syndrome'. We included in the review only studies associated with in utero prenatal diagnosis of 13q syndrome. Studies that reported clinical diagnosis of 13q syndrome post partum and during early and late childhood were excluded from the review. The articles were all written in the English language and published during the time period of July 1993 to September 2008. The clinical characteristics of the selected studies are summarized in Table 1.

A total of 15 patients, including our case were enrolled in the review. Six studies derived from Asia [7-12] five studies were reported from America [13-17], and three studies were from Europe [18-20] The median maternal age was 29.61 years with a range of 18-41 years (standard deviation = 6.03). Median maternal gravidity was 3 (standard deviation = 2.4). Median weeks of diagnosis was 18 with a range of 12-32 weeks [13-17]. With regard to the aspect of prenatal invasive diagnosis, amniocentesis was the most common procedure performed in eight cases (53.3%) [7, 9, 10, 12, 13, 15, 16, 19]; CVS in five cases (33.3%) [17, 18, 20], cordocentesis in four cases (26.6%) [11, 14, 16, 19]. IUGR (intrauterine growth retardation) was the most common US feature notified in eight cases (53.3%) [7, 10, 11, 14-16] including our case as well.

The most common structural abnormality reported was encephalocoele, present in five cases (33.3%) [7, 17, 19, 20], followed by holoprosencephaly in four cases (26.6%) [13-15, 19].

In three cases (20%) of 13q deletion we observed a combination with Dandy-Walker malformation [10, 11, 20]. Multiple limb deformities were visualized, most often localized on the hands, and in six cases (40%) these were anomalies such as syndactyly, oligodactyly, agenesis of thumbs and other morphological abnormalities [9-11, 17, 19].

Cytogenetic diagnosis with FISH (fluorescent in situ hybridization) was confirmed in eight patients [9, 11, 17-20] and CGH array was utilized in three cases [17, 20], including our patient.

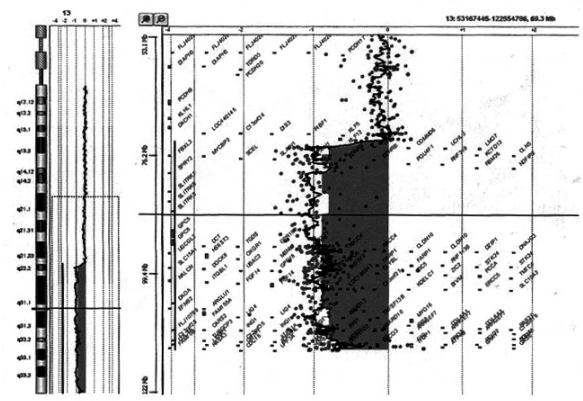

Figure 1. — Array-CGH profile of chromosome 13 showing a terminal deletion. To the left, the whole chromosome 13 view. To the right, the enlarged view of the rearrangement as provided by Agilent CGH Analytics 3.5.14. The proximal deletion breakpoint was between 74.497 MB (last normal oligo) and 74.640 (first deleted oligo). The last oligonucleotide present in the array at position 114.077 was deleted. The overall size of the deletion was about 40 MB.

Termination occurred in ten pregnancies (66.6%) [7-9, 11, 17-20] and IUD (intrauterine death) in three pregnancies (20%) [13, 14, 16]; three neonates (20%) expired after delivery [10, 12, 15]. Nine fetuses had male gender and five had female gender.

Brown *et al*. [1] suggested a new classification in which the individuals with deletion of the chromosome 13 long arm should be subdivided in three groups according to the location of the deletion. Individuals with distal deletions would be the most severely affected, while those with proximal deletions would have fewer major anomalies. The first group would include those with proximal deletion, generally not reaching band 32q, presenting mild to moderate mental retardation, varied dysmorphism and growth restriction. The second group would include those with distal deletion reaching band 32q, with a larger number of major anomalies such as severe microcephaly, occipital encephalocele, holoprosencephaly, lack of the thumbs or other anomalies of the distal limbs, severe microphthalmia, coloboma, malformations of the genitourinary and gastrointestinal tract and severe mental retardation with growth restriction. The third group would include those with a more distal deletion reaching bands 33 and 34q, with severe mental retardation but not with major anomalies and usually without growth restriction. The authors suggested that there is a critical area on band 32q that contains a gene or genes which are essential for brain, finger and other organ development.

In our case the most remarkable finding was the early detection of increased NT in the first trimester scan in association with IUGR, encephalocele, clinodactyly and facial dysmorphism. Three studies achieved early prenatal diagnosis, the first by Lam *et al*. [8], the second by

Hindryckx *et al*. [20] and the last by Cain *et al*. [17]. Our findings are consistent with those of Hindryckx *et al*. [20], where the fetus exhibited increased NT at 13 weeks of gestation.

Identification of small unbalanced translocations is one of the most difficult tasks in prenatal cytogenetics. It often requires parental karyotyping to search for a familial translocation, but frequently the unbalanced rearrangement will be a de novo event or a key family member will not be available for karyotyping. Until now, FISH has been the method of choice for uncovering these translocations. Probes are selected based on the phenotype, or in some cases, an analysis of all the subtelomeric regions is necessary. The process is time-consuming, expensive and not always successful. For these reasons array CGH appears to be an attractive alternative to traditional FISH, providing information on copy number changes at subtelomere regions and loci known to be involved in genetic disease in one, rapid assay [17].

Our case emphasizes the importance of a detailed 11-14 week US assessment in diagnosing fetal chromosomal aberrations, adding a further type of structural chromosomal abnormality diagnosed in the first trimester of pregnancy presenting with increased NT. CGH-array is a modern and precise diagnostic tool which will complement and enhance current methods of detecting chromosomal imbalances prenatally.

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