Introduction

Fetal cystic hygroma (CH) is the most frequent fetal neck pathology prenatally diagnosed. It is defined as fluid-filled cystic lesions, septated, and located mostly at the neck. It can as well appear in the axilla, mediastinum, groin, and retroperitoneum. It appears between the 9th and 16th week of pregnancy.[1,2] The incidence has been reported to be 1/6000 live births.[3,4] Fetal CH is reported to be associated with karyotype abnormality in almost 60%–80% of cases. Aneuploidies such as trisomy 21, trisomy 13, or monosomy X appear to be the most common chromosome abnormalities. The prognosis of CH is poor; most of the pregnancies with CH cannot reach to term, but end up with spontaneous abortion creating an incidence of 1/750 among fetal losses. In some instances, the fetal karyotype is normal. However, there is a syndromic clinical presentation, namely, Noonan syndrome (NS), achondroplasia, lethal multiple pterygium syndrome, Fryns syndrome, Apert syndrome, Pena-Shokeir syndrome, Cornelia de-Lange syndrome, and fetal alcohol syndrome; or it may simply be associated with isolated congenital heart diseases.[5-9] Reports from different countries refer to similar chromosomal involvement and similar outcomes in fetal CH. Studies from Turkey are few and include a relatively limited number of patients.[10,11] We believe more data are needed to serve for genetic counseling of families in Turkey.

Objective: Genetic burden, fetal malformations, and fetal outcomes of 93 fetuses with cystic hygroma (CH) are reported from a single center in Turkey. Patients and Methods: Pregnancies, having a diagnosis of fetal CH, detected between January 2010 and October 2016, were included in the study except fetuses having increased nuchal translucency. Fetal age/gender, maternal age, the age of pregnancy, types of fetal malformations, karyotype, and outcomes were evaluated. Results: The average gestational age was 16.2 weeks. Nearly 47% of the pregnancies had multiple congenital anomalies, of which 58% had a chromosomal anomaly. Chromosomal anomaly rate was 68.2% in patients with hydrops fetalis. Aneuploidies were major chromosomal defects. All trisomies were of regular type except one with Robertsonian translocation (46, XY, +13, rob[13;14](q10;q10)). Seventy-four percentage pregnancies were terminated due to either fetal/karyotype anomaly. Conclusion: Characteristics of fetal CH were similar in different ethnic backgrounds. Aneuploidy is the dominant chromosomal constitution of fetal CH. Little information was known about the genes involved. Gene dosage effect implies that fetal CH is a complex genetic situation involving multiple genes interactions. For proper genetic counseling, each fetus with CH should be karyotyped, and fetal ultrasound examination should be performed. In the case of normal chromosome set, application of aCGH should be considered.

Keywords: Fetal cystic hygroma, genes, karyotype, outcome

Access this article online

Quick Response Code:
Website: www.jmuonline.org
DOI: 10.4103/JMU.JMU_114_18

Address for correspondence: Dr. Huri Sema Aymelek, Department of Medical Genetics, Ondokuz Mayis University Medical Faculty, Samsun, Turkey.
E-mail: semaymelek@hotmail.com

How to cite this article: Aymelek HS, Oğur G, Tosun M, Abur Ü, Altundağ E, Çelik H, et al. Genetic burden and outcome of cystic hygromas detected antenatally: Results of 93 pregnancies from a single center in the northern region of Turkey. J Med Ultrasound 2019;27:181-6.
This study aimed to evaluate the spectrum of karyotype abnormalities and neonatal outcome of 93 fetuses with CH from a single center in the Northern region of Turkey.

**Patients and Methods**

The study covered the period between January 2010 and October 2016. All pregnant women with fetal CH referred to our genetic department were included in the study. The diagnosis of fetal CH was made by repeated fetal ultrasound examinations [Figures 1-3]. The basic criteria for the description of CH were the occurrence of increased fetal nuchal translucency with excess fluid and one or more septations with an intact skull and spinal column. Fetuses with only nuchal translucency, but absent septations were not included in this study. Couples were routinely offered fetal karyotyping and genetic counseling after CH diagnosis.

Karyotypes were obtained from either amniotic cells or chorionic villi samplings (CVS) by standard procedures. For amniocentesis, along term culture method and for CVS, 24 h incubation method using BIO-AMF culture medium was applied.12 For amniocentesis, a long-term culture method and for CVS, both 24 h incubation and a long-term method were applied using BIO-AMF culture medium.12 After the preparation, chromosomes were GTG banded and analyzed under the optical microscope Olympus BX-51, linked to an automated imaging system (The CytoVision® Version 7.2 Image Analysis and Capture System is a rapid metaphase finder, image acquisition and computer aided chromosome analysis system).

Apart from CH, any other fetal abnormalities associated were recorded, including hydrops fetalis. Fetal hydrops was defined as an excess of subcutaneous fluid in >1 fetal area, including thorax and peritoneal cavity. An autopsy was routinely offered to these couples. Pregnancy outcomes were recorded as elective termination, miscarriage, intrauterine death (stillbirth), live birth, and neonatal death. Clinical data were obtained from patients’ medical records.

In brief, other evaluated parameters were fetal age and gender, maternal age, the age of pregnancy, fetal ultrasound findings, types of fetal malformations, fetal karyotypes, and fetal outcome.

**Results**

During the study period, 3805 pregnancies were tested for fetal karyotype for reasons mainly of fetal ultrasound anomaly, advanced maternal age or high-risk triple screening test. Ninety-three out of 3805 pregnancies were recorded as fetal CH (2.5%). The average gestational age at referral to our genetic center was 16.2 weeks (range 12–23 weeks), and only 16% of pregnancies were in the first trimester. None of the 93 mothers had a previous history of CH in their medical history.

The gender of the fetus was determined by karyotype. There were 48 female and 45 male fetuses. The range of maternal age was between 16 (only one patient) and 50 years. The median maternal age was 29 ± 6.5 and was slightly lower than the age of general pregnancy population (32 ± 6.5). The median maternal age for isolated CH pregnancies was 29.5 ± 7, and for ACH (CH with other anomalies), it was 27.6 ± 5.9.

Forty-nine cases out of 93 fetal CH were isolated (ICH), and hence, no associated congenital abnormalities were detected.
Aymelek, et al.: Fetal cystic hygroma

Forty-four fetal CH were associated with other sonographic anomalies (ACH). Thus, the study population presented multiple congenital anomalies (MCA) in almost half (47.3%) of the patient population. Twenty-two patients presented with associated hydrops fetalis.

Overall, the most common additional congenital anomaly was cardiac malformations (27.5%) followed by anomalies of extremities, brain, gastrointestinal system, and renal anomaly. Two fetuses presented with the single umbilical artery. One fetus was diagnosed with a probable “craniofrontonasal dysplasia.” Types of anomalies observed in the study group are shown in Table 1.

Out of 93 patients, 54 (58%) presented with chromosomal abnormality and 39 (42%) fetuses presented normal karyotype. Overall, there were 26 Down syndrome (48%), 16 Turner syndrome (30%), seven trisomy 18 (13%), and three trisomy 13 (5.5%). One patient showed double trisomy (48, XXY, inv[9][p11q12], +21; klinefelter syndrome, and trisomy 21) [Figure 4]. One of them yielded regular 47, XXY. All trisomies were of regular type except one with Robertsonian translocation (46, XY, +13, rob[13;14] [q10;q10]). For ICH group, 31 (63%) out of 49 patients and for ACH group, 23 (52%) out of 44 patients showed karyotype abnormality. Fifteen (68.2%) out of 22 patients with CH + hydrops presented karyotype abnormality. Distribution of the relevant chromosome abnormalities is shown in Table 2.

In the study population (93 cases of CH), Down syndrome was the most common aneuploidy followed by monosomy X, trisomy 18, and trisomy 13. Thirty-nine out of 93 fetuses showed no chromosomal abnormality, and for 18 out of the 39, no structural abnormalities were observed in addition to normal karyotype.

69 out of 93 (74%) pregnancies were terminated due to either fetal abnormality or karyotype anomaly or both. Forty-seven out of 69 (68%) terminations were due to chromosomal abnormality. 22 (31.8%) patients with normal karyotype were terminated due to MCA (14) or ICH (8). There were eight (8.6%) miscarriages, of which three were with hydrops and one was ACH presenting intracardiac hyperechogenic intensity. The rest four cases presented isolated CH with no karyotype anomaly. 12 pregnancies (13%) were able to reach the term. We do not have any information about the outcome of four pregnancies. Table 3 summarizes the outcome of fetuses within the study group.

Elective termination of pregnancies covered mostly (68%) CH with abnormal karyotype. 22 out of 39 fetuses with normal karyotype were also terminated. The outcome of fetuses with karyotype anomalies and with a normal karyotype is documented in Tables 4 and 5. Overall, survival with normal pediatric outcome was confirmed in only 3% of cases.

### Discussion

CHs are vascular-lymphatic malformations. They arise from the failure of the lymphatic system to communicate with the venous system in the neck. The lymphatic system begins to develop at the 6th week, approximately 2 weeks after the...
development of the recognizable primitive cardiovascular system. In the 8th week of gestation, six lymphatic sacs are identified in the developing embryo. Finally, the lymphatic sacs communicate with the venous system. Ultrasonographic diagnosis of CH is usually obtained in the first trimester and the lesion can appear in septated or nonseptated forms.13

More than 80% of pregnancies affected by CH will result in an abnormal outcome, including chromosomal abnormalities, genetic syndromes, structural anomalies, spontaneous abortion, fetal loss, or neonatal death.8 Most cases of chromosome anomalies are aneuploidies such as Turner syndrome, Down syndrome, Klinefelter syndrome, and trisomy 18 and 13.13 Similar to the literature data, this study shows a high rate of aneuploidy among fetuses with CH. The incidence of abnormal karyotype in our series (58%) is relatively higher than many previous reports8,9,14 but similar to some others.15,16 Few reports were with higher rates.17,18 Trisomy 21, monosomy X, trisomy 18, and trisomy 13 observed as the main aneuploidies. Moreover, one patient showed double trisomy (48, XXY, inv[9][p11q12], +21, Klinefelter syndrome and trisomy 21). To the best of our knowledge, this is the first double trisomy reported in fetal CH. Another fetus showed one regular 47, XXY and one was with a Robertsonian translocation type trisomy 13 (46, XY, +13, rob[13;14]), the only structural abnormality seen in our series.

Aneuploidy is defined as a karyotype that results in an unbalanced genome with different copy numbers of chromosomes. Studies of aneuploidy across several species have shown that aneuploidy is frequently lethal early in the development and that those karyotypes that are not lethal usually have substantial developmental defects. There seems to be also altered gene expression levels and altered metabolism in aneuploid cells.19-21 Deviation from a balanced genome by either gain or loss of entire chromosomes is generally tolerated poorly in all eukaryotic systems studied to date.21 Loss of genetic information due to monosomies is less well-tolerated than the gain of genetic information due to trisomies. Autosomal monosomies are inviable in humans. However, aneuploidies of the sex chromosomes in humans are viable. Turner syndrome (monosomy X) is the only whole chromosomal monosomy viable in humans.20

In spite of all the information given up to date, there is still limited information about the biological impact of aneuploidy during the embryonic development of fetal CH or about the genes involved in CH. Garabedian et al., reported a prenatally detected CH which was subsequently identified to have haploinsufficiency of the FOXF1 and FOXC2 genes via array comparative genomic hybridization (aCGH).22 Fox genes are involved in patterning early embryonic mesoderm. The region encoding for the FOX gene cluster is in 16q24.1 and deletions of this region have been associated with multiple structural anomalies, including cardiopulmonary anomalies.

### Table 3: Outcome of fetuses with cystic hygroma

| Outcome                  | Total number of fetuses with CH 93 (%) |
|--------------------------|----------------------------------------|
| Termination              | 69 (74%)                               |
| Karyotype anomaly        | 47 (47/69, 68%)                        |
| Normal karyotype         | 22 (22/69, 31%)                        |
| Missed abortion          | 8 (8, 6%)                              |
| Reached to term          | 12 (14%)                               |
| Neonatal death           | 4 (4%)                                 |

### Table 4: Outcome in 93 fetal cystic hygroma with relevance to abnormal karyotype

| Number of patients | Percentage | Outcome |
|--------------------|------------|---------|
| CH with chromosome aberrations | 54/93 (58) | 47 termination |
| Trisomy 21         | 26/54 (50) | 23 termination |
| 45, X (Turner syndrome) | 16/54 (29) | 12 termination |
| Trisomy 18         | 7/54 (13)  | 7 termination |
| Trisomy 13         | 3/54 (5.5) | 3 termination |
| Other              | 2/54       | Termination |

### Table 5: Outcome of fetuses with normal karyotypes (n=39)

| Number of patients (normal karyotypes) |
|----------------------------------------|
| Termination                           | 22 |
| ICH                                    | 8  |
| ACH                                    | 14 |
| Missed abortion                       | 5  |
| Reached to term                       | 9  |
| Neonatal death                        | 4  |
| Liveborn (3 healthy, 1 frontonasal dysplasia, 1 congenital heart disease) | 5   |
| No data                               | 3  |

ICH: Isolated cystic hygroma, ACH: CH and other anomalies
and congenital alveolar capillary dysplasia with misalignment of the pulmonary veins.\cite{22,23}

NS is one of the leading causes of CH. Approximately, 50% of NS cases are caused by mutations in the PTPN11 gene.\cite{24} Molecular studies suggest that vascular endothelial growth factor C and its receptors may play an important role in the development of CHs.\cite{25}

Due to possible gene dosage effect of aneuploidies, we suggest that the development of some fetal CH is under the control of >1 gene. This oligogenic or multigenic situation is similar to the pattern seen in complex genetic disorders. Because of seldom autosomal monosomic impact, the gene dose influence ought to be in the range of overdosage of autosomal genes. Both cumulative effects and individual genes seem to be responsible for the complex phenotype of the disease. It is also possible that new diagnostic approaches such as microarray-based comparative genomic hybridization (aCGH) can help to the identification of new CH genes by means of identifications of both genomic gains or losses.

Several nonchromosomal disorders, including NS, Fryns syndrome, multiple pterygium syndrome, and achondroplasia, are also associated with an increased incidence of CH. They are clues for major gene involvement in disease development. Intrauterine alcohol exposure and viral infections have also been associated with the development of CH.\cite{26} One can assume that more genes associated with CH will be discovered in time.

Retrospective studies suggest that CH is associated with poor prognosis. CH often causes fetal death. A study by Lajeunesse et al. involving 69 fetuses with CH diagnosed in the first trimester suggested that the presence of hydrops fetalis, ultrasonographic abnormalities or both were predictors of a poor outcome as well as karyotype abnormalities.\cite{27} Even in euploid pregnancies with CH, there is high mortality with associated abnormalities. A study by Sanhal et al. similarly found that fetuses with septated CH had poor perinatal outcomes.\cite{11}

In this study, 74% of all pregnancies were terminated due to either fetal abnormality or karyotype anomaly or both. Most of the fetuses (68%) presenting an aberrated chromosome were electively terminated by family consent. There were eight (8.6%) miscarriages. Nearly 50% of these miscarriages were due to severe hydrops fetalis, one was with ACH, and three revealed normal karyotype with isolated CH.

Although a few patients with fetal CH could show complete spontaneous resolution. These pregnancies present often in late pregnancy and are mostly those with normal chromosomes. The fetus is unlikely to have a chromosomal abnormality if the CH goes away by week 20. In the present study, 13% of pregnancies were able to reach the term. The mean age of pregnancy for these cases in the present study was 16 weeks. The normal pediatric outcome was confirmed in only 3% of fetal CH cases. In these cases, cysts in the neck disappeared by ultrasound on follow-up of pregnancy, and there was no need to intervene after delivery.

Even in euploid pregnancies with CH, there is high mortality with associated abnormalities. In the present study within the group of CH with normal karyotype, similar poor outcome was achieved; 69% of CH fetuses with a normal karyotype were terminated due to either ICH or ACH. When spontaneous abortions and neonatal death were considered, the rate of fetal loss in this series reached up to 79%. It should be kept in mind that CH associated with a normal karyotype can also be inherited as an autosomal recessive trait. No recurrence of CH was obtained in our series.

**Conclusion**

CH is a clear indication for prenatal diagnosis and genetic counseling. We suggest to follow-up pregnancies with CH by periodic ultrasound examinations for resolution of the CH and/or development of other anomalies, including hydrops and to karyotype each fetus with fetal CH. In case of a normal fetal chromosome set, if there have associated anomalies, chromosomal array, or next-generation sequencing may help discover subtle chromosomal anomalies or genetic syndromes and understanding the genetic contribution to disease.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

**References**

1. Chen M, Lee CP, Lin SM, Lam YH, Tang RY, Tse HY, et al. Cystic hygroma detected in the first trimester scan in Hong Kong. J Matern Fetal Neonatal Med 2014;27:342-5.

2. Chervenak FA, Isaacson G, Blakemore KJ, Breg WR, Hobbins JC, Berkowitz RL, et al. Fetal cystic hygroma. Cause and natural history. N Engl J Med 1983;309:822-5.

3. Tamrideri HA, Ertan AK, Hendrik HJ, Remberger K, Schmidt W. Outcome of cystic hygroma in fetuses with normal karyotypes depends on associated findings. Eur J Obstet Gynecol Reprod Biol 2005;118:40-6.

4. Noia G, Pellegrino M, Masini L, Visconti D, Manzoni C, Chiaradia G, et al. Fetal cystic hygroma: The importance of natural history. Eur J Obstet Gynecol Reprod Biol 2013;170:407-13.

5. Molina FS, Avgidou K, Kagan KO, Poggi S, Nicolaides KH. Cystic hygromas, nuchal edema, and nuchal translucency at 11-14 weeks of gestation. Obstet Gynecol 2006;107:678-83.

6. Achiron R, Haggess J, Grisaru D, Goldman B, Lipitz S, Yagel S, et al. Noonan syndrome: A cryptic condition in early gestation. Am J Med Genet 2000;92:159-65.

7. Hösl IM, Tercanli S, Rehder H, Holzgreve W. Cystic hygroma as an early first-trimester ultrasound marker for recurrent Fryns’ syndrome. Ultrasound Obstet Gynecol 1997;10:422-4.

8. Graeslin O, Demiaux E, Alanio E, Gaillard D, Vitry F, Quecues C, et al. Characteristics and outcome of fetal cystic hygroma diagnosed in the first trimester. Acta Obstet Gynecol Scand 2007;86:1442-6.

9. Malone FD, Ball RH, Nyberg DA, Comstock CH, Saade GR, Berkowitz RL, et al. First-trimester septated cystic hygroma: Prevalence, natural history, and pediatric outcome. Obstet Gynecol 2005;106:288-94.

10. Gedikbasi A, Oztarhan K, Aslan G, Demirali O, Akyol A, Sargin A, et al. Multidisciplinary approach in cystic hygroma: Prenatal diagnosis, outcome, and postnatal follow up. Pediatr Int 2009;51:670-7.
11. Sanhul CY, Mendilcioglu I, Ozekinci M, Yakut S, Merdun Z, Simsek M, et al. Prenatal management, pregnancy and pediatric outcomes in fetuses with septated cystic hygroma. Braz J Med Biol Res 2014;47:799-803.
12. Rooney DE. Human Cytogenetics: A Practical Approach. 3rd ed. Oxford: Oxford University Press; 2001.
13. Beke A, Joó JG, Csaba A, Lázár L, Bán Z, Papp C, et al. Incidence of chromosomal abnormalities in the presence of fetal subcutaneous oedema, such as nuchal oedema, cystic hygroma and non-immune hydrops. Fetal Diagn Ther 2009;25:83-92.
14. Ducarme G, Graesslin O, Alanio E, Bige V, Gaillard D, Gabriel R. Increased nuchal translucency and cystic hygroma in the first trimester: Prenatal diagnosis and neonatal outcome. Gynecol Obstet Fertil 2005;33:750-4.
15. Rosati P, Guariglia L. Prognostic value of ultrasound findings of fetal cystic hygroma detected in early pregnancy by transvaginal sonography. Ultrasound Obstet Gynecol 2000;16:245-50.
16. Tanriverdi HA, Hendrik HJ, Ertan AK, Axt R, Schmidt W. Hygroma colli cysticum: Prenatal diagnosis and prognosis. Am J Perinatol 2001;18:415-20.
17. Bronshtein M, Bar-Hava I, Blumenfeld I, Bejar J, Toder V, Blumenfeld Z, et al. The difference between septated and nonseptated nuchal cystic hygroma in the early second trimester. Obstet Gynecol 1993;81:683-7.
18. Nadel A, Bromley B, Benacerraf BR. Nuchal thickening or cystic hygromas in first- and early second-trimester fetuses: Prognosis and outcome. Obstet Gynecol 1993;82:43-8.
19. Siegel JJ, Amon A. New insights into the troubles of aneuploidy. Annu Rev Cell Dev Biol 2012;28:189-214.
20. Torres EM, Williams BR, Amon A. Aneuploidy: Cells losing their balance. Genetics 2008;179:737-46.
21. Griffiths AJ, Gelbart WM, Miller JH, Lewontin RC. Modern Genetic Analysis. New York: W.H. Freeman and Co.; 1999. p. 675.
22. Garabedian MJ, Wallerstein D, Medina N, Byrne J, Wallerstein RJ. Prenatal diagnosis of cystic hygroma related to a deletion of 16q24.1 with haploinsufficiency of FOXI1 and FOXC2 genes. Case Rep Genet 2012;2012:490408.
23. Stankiewicz P, Sen P, Bhatt SS, Storer M, Xia Z, Bejani BA, et al. Genomic and genetic deletions of the FOX gene cluster on 16q24.1 and inactivating mutations of FOXI1 cause alveolar capillary dysplasia and other malformations. Am J Hum Genet 2009;84:780-91.
24. Croonen EA, Nillesen WM, Stuurman KE, Oudehijs G, van de Laar IM, Martens L, et al. Prenatal diagnostic testing of the Noonan syndrome genes in fetuses with abnormal ultrasound findings. Eur J Hum Genet 2013;21:936-42.
25. Nayak S, Dash SP, Khatua M. Cystic hygroma: An enigma. IOSR J Dent Med Sci 2015;14:2279-861.
26. Edwards MJ, Graham JM Jr. Posterior nuchal cystic hygroma. Clin Perinatol 1990;17:611-40.
27. Lajeunesse C, Stadler A, Trombert B, Varlet MN, Patural H, Prieur F, et al. [First-trimester cystic hygroma: prenatal diagnosis and fetal outcome]. J Gynecol Obstet Biol Reprod (Paris) 2014;43:455-62.