

Cystic hygroma: a single-centre experience

INTRODUCTION

Cystic hygroma (CH) is a congenital anomaly of the lymphatic system, which is characterised by abnormal fluid accumulation with single septum or multiseptated appearance.^[1] CH was first described by Redenbacher in 1828, and its incidence is approximately one out of 1,000–6,000 at birth, and one out of 750 leads to spontaneous abortion.^[2–4] The lymphatic system starts developing at the end of the fifth week of gestation,^[1] and the malformation develops at the end of the sixth week of gestation.^[2] CH may be temporary if an alternative path of drainage develops or if the jugular veins and jugular lymphatic sacs could form a connection.

Major congenital anomalies, aneuploidies, genetic syndromes and developmental disorders are found in the aetiopathogenesis of CH. The prognosis is often considered poor.^[5] The most common numerical chromosomal abnormalities diagnosed in conjunction with CH in the first trimester include both trisomies 18 and 21 and Turner syndrome.^[1] When the karyotype results are normal, microarray analysis should be offered. In some cases, copy number variants (CNVs) can be detected.

Ultrasound-based prenatal diagnosis of CH is based on the demonstration of bilateral, symmetrical/asymmetrical and/or septate/aseptic cystic structure in the foetal back or neck.^[6]

In this study, we aim to describe our experiences with CH in a single centre and determine the association between diagnosis of CH and perinatal outcome.

METHODS

Study population

In this retrospective study, all fetuses diagnosed with CH based on first-trimester prenatal ultrasound at Gazi University Hospital in Ankara, which is a tertiary referral centre, were included. The local ethics committee approved the study (decision no. 168; 24074710-07, 24.02.2020). Data from January 2013 to December 2017 of cases that were diagnosed as CH based on first-trimester sonography were retrospectively reviewed. CH was diagnosed using a standardised first-trimester sonographic examination (at 11–13 weeks and 6 days of gestation) by an experienced foetal-medicine specialist using either a Voluson E8 or a E10 ultrasound machine (GE Healthcare, Milwaukee, WI, USA). Genetic counselling and prenatal invasive diagnostic procedures to obtain foetal karyotypes (chorionic villus sampling for all) were offered to all patients. If the pregnancy was continued, an expert perinatologist performed foetal echocardiography and detailed second-trimester sonographic

anomaly screening between 18 and 22 weeks of pregnancy. Demographic characteristics and karyotype results of the pregnant women were obtained from the database of our hospital and correlated with obstetric results. Foetuses with CH with pleural effusion or foetal hydrops were also included in the study. A hypoechoic space that runs along the length of the foetal ridge behind the foetal neck was defined as CH by our centre. As shown in Figure 1, CH was differentiated from nuchal oedema by the presence of the nuchal ligament (midline septum). The cases were evaluated in terms of maternal age, gestational week at CH diagnosis, karyotype result, associated foetal abnormality and perinatal outcomes. If a live newborn with no abnormalities was detected during the neonatal or childhood period, the result was defined as normal.

Genetic analysis

Genetic testing was performed by the Department of Medical Genetics, Gazi University, and the DNA probe vendor for these studies was Cytocell. Fluorescence *in situ* hybridisation (FISH) analyses from cells was done via direct harvest of trophoblasts using a unique sequence DNA probe for chromosome 21 and hybridisation for chromosomes 13, 18, X and Y.

Karyotyping was performed by the Department of Medical Genetics, Gazi University. *In situ* cultures from enzymatic dissociated mesenchymal cells were obtained to investigate numerical and structural chromosome abnormalities.

The Department of Medical Genetics, Gazi University, performed the microarray analysis using SurePrint G3 ISCA V2 comparative genomic hybridisation (CGH) 8x60K array CGH kit (Agilent Technologies, Santa Clara, CA, USA) with the DNA obtained from cultured cells. This process involved whole-genome CGH-based copy number analysis targeting

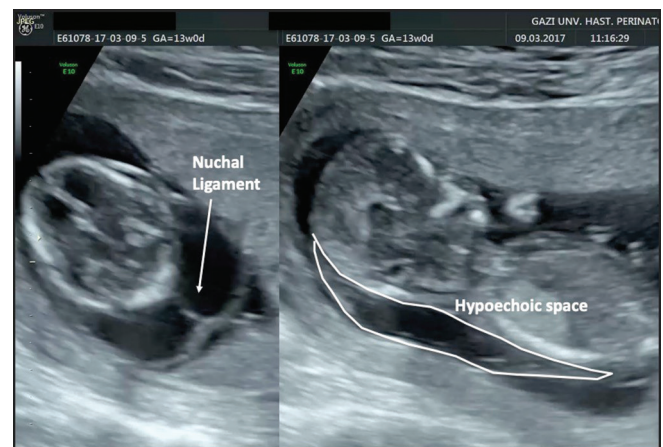


Figure 1: Sonographs show the transverse and sagittal views of fetuses with cystic hygroma.

500 kb resolution. CNVs were reported based on the size of the abnormality and the presence of Online Mendelian Inheritance in Man (OMIM) genes in the region. CNVs were classified as one of the following five groups according to the scientific literature and databases available at the time of the report: pathogenic, likely pathogenic, variant of unknown clinical significance, likely benign or benign.

Statistical analysis

Statistical analysis was performed using Microsoft Excel for Mac 2011 version 14.6.1 (Microsoft Inc, Redmond, WA, USA) and IBM SPSS Statistics version 21.0 (IBM Corp, Armonk, NY, USA). Descriptive statistics were presented as means $\pm$ standard deviations, median (minimum–maximum) values and percentages.

RESULTS

A total of 64 pregnancies were included in the study. The median maternal age at birth was 32 years, and 19 (29.6%) patients were >35 years old. Median nuchal translucency was 4.5 mm (minimum: 3.20, maximum: 10.00, range: 6.80, interquartile range [IQR]: 2.69). Karyotype results were available for all patients. Twenty-three patients (36%) had abnormal karyotypes (monosomy X: 7, trisomy 21: 6, trisomy 13: 4, trisomy 18: 3, triploidy: 1, translocation: 1, inversion–duplication: 1), which were diagnosed using the conventional karyotype analyses [Figure 2]. CGH arrays were obtained for nine patients and we found one abnormal result — 18p deletion, partial 8p duplication — 46,XX,der(18)(18qter→18p11.1::8p22→8pter). All patients with chromosomal abnormalities chose pregnancy termination after learning the results. Of the 40 patients who continued the pregnancy after receiving normal karyotype results, 16 (25%, 16/64) patients had a foetal abnormality and all these 16 pregnancies were then terminated after diagnoses. Skeletal anomalies ($n = 4$), foetal hydrops ($n = 3$), cardiac, thoracic and

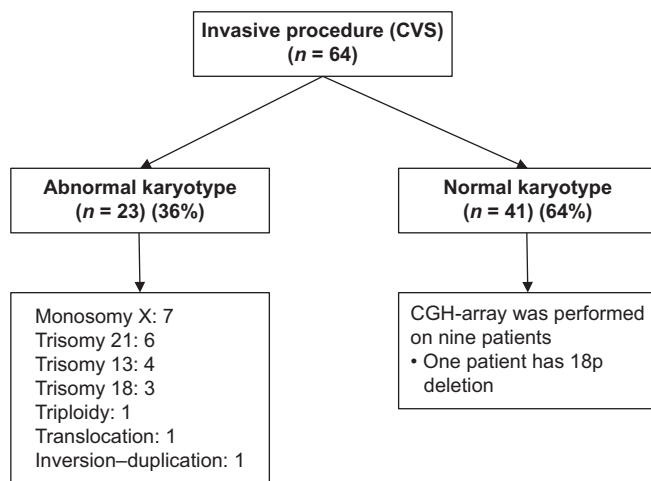


Figure 2: Diagram shows the genetic results of all patients. CGH: comparative genomic hybridisation, CVS: chorionic villus sampling

multiple anomalies ($n = 3$, 2 and 2, respectively), abdominal wall defects ($n = 1$) and cranial anomaly ($n = 1$) formed the group of observed anomalies [Figure 3]. Of the 37.5% (24/64) of patients who had isolated CH only, 21.0% (5/24) had spontaneous intrauterine death, while the other 79.0% (19/24) of patients had normal pregnancy outcomes and neonatal/childbirth follow-ups, except one patient who needed surgery because of a neck CH. Postnatal median follow-up time was 30 (12–72) months in this study.

DISCUSSION

This study evaluated the characteristics and outcomes of pregnancies diagnosed with CH in the first trimester in a single tertiary centre. In this study, we aimed to compare our data to the data in the literature. A diagnosis of CH during pregnancy is related to poor perinatal outcomes. The most important outcome in our study was that 29.6% (19/64) of patients with CH had normal pregnancy outcomes and neonatal follow-ups, except one patient who needed surgery because of neck CH. The second important outcome was a chromosomal abnormality rate of 37.5%.

The outcomes of CH are related to the time of CH onset. If we detect CH in the first trimester, a worse outcome is expected than if CH is detected later in pregnancy.^[1] In the literature, the overall rate of normal neonatal outcome was between 7% and 29%. In our study, the normal outcome rate was 29.6%. During antenatal counselling, it is important to point out this normal neonatal outcome rate, as patients with a diagnosis of CH during pregnancy may have the option of having a healthy child after careful evaluation.

Malone *et al.*^[7] reported a strong association between CH and aneuploidy (51%). In this study, we found that an abnormal karyotype was present in 37.5% of all cases as compared to 35%–66% in the literature [Table 1].^[1,2,6–13] In our study, we found a higher prevalence of monosomy X than trisomy 21. This finding is similar to that of Schreurs *et al.*,^[1] but differs from those of Scholl and Chasen^[10] and Malone *et al.*^[7] In the

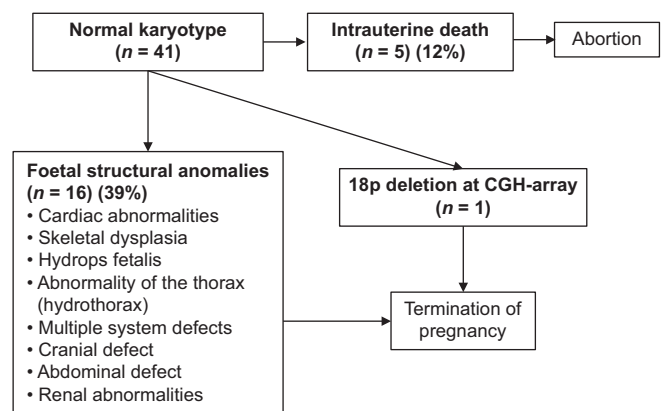


Figure 3: Diagram shows the outcomes of foetuses with normal karyotype.

Table 1. Comparison of our study with studies in the literature.

Study	Chromosomal abnormality rate (%)	Structural abnormalities in euploid foetus (%)	Overall live birth (%)	Overall normal neonatal outcome (%)
Published studies ^[1,2,7-10]	43–66	12–56	9–27	7–19
National data ^[6,11-13]	35–61	7–39	8–24	8–29
Current study	37.5	39	29.6	29.6

literature, cardiac anomalies are the most frequently associated major congenital anomalies in cases with normal karyotype.^[1] However, in our study, the most frequent anomaly was skeletal, followed by cardiac anomaly. If foetal hydrops develops, the prognosis is poor, despite the absence of other structural anomalies. In our study, all the patients with foetal hydrops and normal-karyotype fetuses selected pregnancy termination.

As shown in previous studies, intrauterine regression of CH could be associated with more favourable outcomes.^[2] Noia *et al.*^[2] demonstrated that intrauterine regression of CH occurred in 36% of these cases and CH disappeared completely in 77% of these cases. According to a recent study, 20% of the affected fetuses showed disappearance of an enlarged nuchal translucency before 14 weeks of gestation.^[14]

Scholl and Chasen^[10] categorised patients with foetal CH by measuring the crown–rump length (CRL) for the abnormal outcomes. They reported that CH was detected when the CRL was <45 mm. In these cases, they detected lower rates of chromosomal abnormalities (43.4% vs. 73%) and a higher proportion of normal birth outcomes compared to those detected later in the first trimester (25% vs. 11%).^[10] In our study, the CRL of all the fetuses were >45 mm when diagnosed with CH.

Microarray analysis was used from the end of 2016 in our study. Grande *et al.*^[15] reported that the use of a genomic microarray provided a 5.0% incremental yield in CNV detection in fetuses with increased nuchal translucency and normal karyotype. A multicentre French study demonstrated that with an isolated increase in nuchal translucency, the diagnostic yield was 2.7% in the study cohort.^[16] In our study, we found only one abnormal result with a microarray (11%, 1/9). As the microarray is a new technology, our patient sample size did not provide a large enough size to comment on the accuracy of this technology.

Our study has several limitations. First, it examined only a small sample in a retrospective cohort study. The lack of a standard definition and interobserver variability may affect the rate of CH diagnosis. Microarray analysis was only available from the end of 2016, and thus it was not used during the entire study period.

In the presence of any foetal anomaly comorbid with CH, the prognosis can be evaluated as poor, and only one out of three patients with CH shows a convincing result. The incidence of

chromosomal abnormalities is very high. A microarray may be helpful for foetal pathological chromosomal abnormality diagnoses, which cannot be diagnosed with conventional karyotype analysis. Normal karyotypes, normal array results and resolution of CH yield a better prognosis. After diagnosis, microarray and cytogenetic analyses and foetal structural evaluation have an important role in treatment selection. If no structural anomalies were detected in the first and second trimesters and the genetic analysis is normal, a good foetal outcome may be attainable, as seen in our study (19/64, 29.6%).

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Conflicts of interest

There are no conflicts of interest.

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