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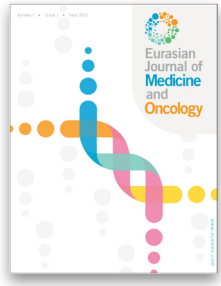

Research Article

Retrospective Evaluation of the Effect of NT Thickness and Septation on Karyotype Anomalies in Cystic Hygroma Patients

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Abstract

Objectives: This study was planned to observe the effect of septation and nuchal translucency (NT) on the outcomes of karyotype analysis in cystic hygroma (CH) patients.

Methods: Between 2010 and 2014, 84 patients who were suspected to have elevated NT thickness (>3 mm) or CH were included in this study and were retrospectively investigated. Patients were evaluated in two different categories that were divided into four groups: 1) those with NT thickness between 3 and 5 mm (n=47), 2) those with NT thickness >5 mm (n=37), 3) those with septation (n=43), and 4) those without septation (n=41).

Results: The rate of aneuploidy was found to be 36.1% in CH patients with NT thickness between 3 and 5 mm, whereas this rate was found to be 56% in CH patients with NT thickness >5 mm. In the statistical comparison of these two groups, NT thickness >5 mm increased the aneuploidy risk, but it was not statistically significant (p=0.232). The aneuploidy rate was found to be 79% in CH patients with septation, whereas it was 9.7% in CH patients without septation. On statistical comparison of CH groups with and without septation, it was observed that CH septation was statistically significant in terms of karyotype anomaly (p=0.021).

Conclusion: As a conclusion, we observed that the NT thickness of over 5 mm was not statistically significant in increasing the aneuploidy risk, whereas the presence of septation increased the risk of aneuploidy statistically significantly. Further studies are required to explain this.

Keywords: Aneuploidy, cystic hygroma, nuchal translucency, perinatal outcomes, septal cyst

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Fetal nuchal cystic hygroma (CH) is a very rare disease. The incidence of CH is between 1/1000 and 1/6000, and it is a rare malformation that occurs in the vascular and lymphatic systems.[1] CH was first defined by Redenbacher in 1828.[2] In CH, the etiology is not clearly understood, but it is known to be not neoplastic.[3] CH is frequently seen in the nape region.[4] However, 5% cases with CH may occur in the axillary, mediastinum, abdomen, and retroperitoneal mesenteric regions.[5] CH usually begins to develop after the sixth week of gestation. It is likely to be diagnosed in the routine ultrasound (USG) examination during the first trimester of pregnancy.[6] However, the ultrasonographic diagnosis of CH is usually made at the end of the first trimester and at the beginning of the second trimester.[7, 8]

It is known that fetal outcomes are poor in the presence of CH.[9] However, when the long-term prognosis of live-

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born babies is examined, the findings are not very positive.[10] When fetuses with CH and those with purely increased nuchal thickness are compared, the outcome is poorer because of high aneuploidy risk in CH patients.[8] Whether or not there is a structural anomaly in CH fetuses, the outcomes are poorer in the presence of chromosomal anomalies.[11] Studies in CH patients have found karyotype anomalies to be approximately 50%–55%.[12, 13] Turner syndrome and Down syndrome have been found to be the most common karyotype abnormalities in different case series in CH cases.[13, 14] In this large-scale case study, aneuploidy was detected in 54% of 729 cases and major congenital anomaly was observed in 28% of patients with normal karyotypes.[15]

In literature, two important parameters, CH septation and nuchal translucency, are mentioned and if they affect the rate of karyotype anomalies and fetal outcomes in CH patients. The first one is whether or not CH is septation and the second one is nuchal thickness.[14, 15]

In this study; we retrospectively analyzed our patients who were referred to our clinic with CH at the first or second trimester of pregnancy and whose CH was detected and karyotype analysis was performed. We evaluated these fetuses separately in terms of NT and septation. We aimed to observe the effect of these two factors on the rate of karyotype anomaly.

Methods

Between 2010 and 2014, 84 patients who were referred to our clinic with either increased nuchal translucency (NT) thickness (>3 mm) or CH suspicion were included in this study. Permission was obtained from the ethics committee for the study. Patients were evaluated in two different categories that were divided into four groups: 1) those with NT thickness between 3 and 5 mm (n=47), 2) those with NT thickness >5 mm (n=37), 3) those with cystic septation (n=43), and 4) those without septation (n=41). Ultrasonographic evaluation was performed using abdominal and vaginal probes with ALOKA 4000 Prosound 5 MHz (Aloka 4000 Prosound, Aloka Co. Ltd., Tokyo, Japan).

Maternal age and gestational weeks were recorded as the demographic data of the patients. For karyotype analysis of patients, amniocentesis for 52 patients, CVS for 26 patients, cordocentesis for four patients, and fetal tissue sampling for two patients were performed.

Pregnancy termination was performed in 53 of 84 patients included in the study. Intrauterine fetal loss was observed in 19 of the remaining patients. During the follow-up, two patients were lost during the postpartum period. The other 10 patients were included in the study did not achieve the results postpartum.

Patients with NT thickness between 3 and 5 mm and those with NT thickness >5 mm were statistically compared in terms of karyotype anomalies. Besides, patients with CH septation and those without septation were statistically compared in terms of karyotype anomalies. In addition, the rates of karyotype anomalies were calculated in patients with cystic septations and patients with NT thickness >5 mm.

Statistical Analysis

Collected data were analyzed using Statistical Package for Social Sciences version 18.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean ± standard deviation (range: minimum–maximum), whereas categorical variables were expressed as numbers or percentages, where appropriate. Paired samples t-test, Chi-square test, and Mann–Whitney U-test were used for the comparisons. Two-tailed P-values <0.05 were accepted to be statistically significant.

Results

The average gestational week of the participating patients was determined to be 16, and the average maternal age was determined to be 27 years. A total of 84 patients underwent karyotype analysis with CH diagnosis. NT thickness was assessed to be >3 mm in all patients who underwent karyotype analysis. Aneuploidy was detected in 38 (45.2%) of the patients included in the study. Of these patients, 18 (47.3%) were detected with Trisomy 21, 14 (36.8%) with Turner syndrome, five (13.1%) with Trisomy 18, and one with Trisomy 22 (Table1).

Table 1. Classification of patients by NT thickness and septate as well as karyotype analysis values

	NT thickness = 3-5 mm (n=47)	NT thickness >5 mm (n=37)	P	Non-septated (n=41)	Septated (n=43)	p
Aneuploidy	17 (36.1%)	21 (56%)	p= 0.232	4 (9.7%)	34 (79%)	p= 0.021
Trisomy 21	11 (64.7%)	7 (33.3%)		1 (25%)	17 (50%)	
Turner	4 (23.5%)	10 (47.6%)		2 (50%)	12 (35%)	
Trisomy 18	2 (11.8%)	3 (14.3%)		0	5 (14.7%)	
Other	0	1 (4.8%)		1 (25%)	0	

NT: Nuchal translucenc.

According to NT thickness, patients were examined in two groups: Those with NT thickness between 3 and 5 mm and those with NT thickness >5 mm. The aneuploidy rate was found to be 36.1% (17/47) in CH patients with NT thickness between 3 and 5 mm, whereas this rate was 56% (21/37) in CH patients with NT thickness >5 mm. In the statistical comparison of these two groups, it was detected that NT thickness >5 mm increased the risk of aneuploidy, but it was not statistically significant (p=0.232). Trisomy 21 (64.7%) was the most frequently detected karyotype anomaly in CH patients with NT thickness between 3 and 5 mm, whereas Turner syndrome (47.6%) was the most common karyotype anomaly in patients with NT thickness >5 mm (Table1).

CH patients were divided into two groups according to presence or absence of septation. The aneuploidy rate was found to be 79% (34/43) in the CH patients with septation and 9.7% (4/41) in the CH patients without septation. In the statistical comparison of the CH groups with and without septation,it was observed that the presence of CH septation was statistically significant in terms of karyotype anomalies (p =0.021). Trisomy 21 (50%) was the most common karyotype anomaly detected in the CH group with septation, whereas Turner syndrome (50%) was the most frequently detected karyotype anomaly in the CH group without septation (Table1).

Discussion

Fetal CH is a congenital malformation of the lymphatic system, which occurs due to obstruction between the lymphatic and venous system.[8, 16] Fetal CH usually located in the neck area and is characterized by single or multiple cysts surrounding the neck.[17] The differential diagnoses of CH cases include nuchal edema, meningocele, encephalocele, cervical teratoma, hemangioma and placental cyst.[16, 18]

Factors that worsen the prognosis in CHs include aneuploidy, presence of malformation, short gestational week, and septation.[3] In CH patients, even if the karyotype is normal, it causes poor prognosis in 86% of patients.[15, 19]

In studies performed with CH cases, additional anomalies such as single umbilical artery, Dandy Walker syndrome, renal cyst, cranium defect, midline defects, and micromelia accompany CH. However, VSD, hydrops, cardiomegaly, echogenic bowel omphalocele, lower leg, choroid plexus cysts, ventriculomegaly, abnormalities such as holoprosencephaly, and neural tube defects may be accompanied by a CH.[20] The respiratory, skeletal and urinary system anomalies are largely accompanied by CH.[3] In our study, no additional congenital anomalies were seen in patients with CH. Studies have shown that if isolated CH has no accompanying USG anomaly and a normal karyotype is detected, the probability of poor prognosis is reduced.[19]

In the studies performed, intrauterine karyotype analysis is recommended in the presence of subcutaneous edema in USG such as nuchal edema, CH, or non-immune hydrops.[4, 12] Because of the CH patients at risk for bad obstetric history invasive prenatal diagnostic tests for use in these patients is recommended. There are studies advocating that karyotype analysis should be performed with methods such as amniocentesis and CVS in cases where CH is detected.[17] In our study, we performed invasive diagnostic tests such as amniocentesis in 52 patients, CVS in 26 patients, cordocentesis in four patients and fetal tissue sampling in two patients.

In studies showing an increase in aneuploidy with an increase in NT thickness, aneuploidy risk was found to be 48% inthose with NT thickness between 3 and 5 mm and 60% in the fetuses with NT thickness >5 mm.[12, 21] In another study conducted in this regard, it was determined that every 1-mm increase in NT thickness increased the abnormal karyotype ratio by 44% and the major congenital anomaly rate by 26%.[15] In our study, the aneuploidy risk was 36.1% in patients with NT thickness between 3 and 5 mm, and the aneuploidy risk was 56% in patients with NT thickness >5 mm. Statistically comparing these two groups, we found that NT thickness >5 mm increased the risk for karyotype anomaly, but it was not statistically significant (p =0.232). It was evaluated that Trisomy 21 (64.7%) was the most common karyotype anomaly in CH patients with NT thickness 3–5 mm, whereas Turner syndrome (47.6%) was the most common karyotype anomaly in patients with NT thickness >5 mm.

CH cases are most often associated with Turner's Syndrome characteristically.[21] In some studies, the incidence of Trisomy was evaluated to be higher than the incidence of Turner syndrome.[7, 22] In a study conducted in this regard and belonging to patients with a CH diagnosis, 55% of the 40 patients had karyotype anomalies; 40% of these patients had Turner syndrome and 14% had Trisomy 21.[23] In our study, 38 patients had abnormal karyotypes; 18 (47.3%) were detected to have Trisomy 21, 14 (36.8%) had Turner syndrome, five (13.1%) had Trisomy 18, and one had Trisomy 22.

In CH patients, fetal outcomes and parameters affecting fetal karyotype are the most curious topics. In studies conducted on this subject, CH septation, NT thickness, and presence of accompanying anomalies are the most discussed parameters.[24-27]

The fact that CHs are with or without septation depends on the degree of obstruction in the lymphatic system. Septal CH cases are caused by complete obstruction, whereas septate CH cases are caused by obstruction of lymphatic drainage and transient accumulation of lymphatic fluid.[24]

In a study conducted, 125 patients with CH were evaluated and found that 98% of patients with nonseptate CH were regressed and only 44% of patients with septate CH were regressed.[25] In CH cases with septation and additional anomalies, spontaneous regressions were observed to be relatively low in previous studies.[26, 27] In another study that supported poor perinatal outcomes of CH with septation, the rate of karyotype anomaly in these patients was over 40%, and it was emphasized that in patients without karyotype anomaly, 36% were determined with an accompanying structural anomaly.[14] The rate of normal karyotype was 52% in CH patients with septation and 61% in CH patients without septation. In other previous studies, the rate of aneuploidy in CH patients with septation was found to be higher than in CH patients without septation.[8, 11, 15, 19, 28] In our study, similar to previous studies, the aneuploidy rate of CH cases with septation was found as 79%, whereas the rate of aneuploidy in CH cases without septation was evaluated as 9.7%. In statistical comparisons of CH groups with and without septation, we found that the CH septation was statistically significant in terms of karyotype anomaly. Trisomy 21 was the most common karyotype anomaly detected in the CH group with septation, whereas Turner syndrome (50%) was the most frequently detected karyotype anomaly in the CH group without septation.

CH cases without septation, unlike CH cases with septation, are significantly associated with normal karyotype and normal fetal echocardiography. There are studies reporting that there may be a decline of up to 44% in CH cases without septation.[10] Another important point to note here is that cases with increased NT thickness in early gestational weeks are interpreted as having CH.[1] When patients with CH are compared with patients with isolated NT thickness, the risk of aneuploidy in CH patients was five times higher, the risk of cardiac anomaly was 12 times higher and the risk of perinatal death was six times higher.[8] In another study on this subject comparing the pregnancy outcomes of patients with isolated increased NT and patients diagnosed with CH, the pregnancy outcomes of CH patients were determined to be poorer.[23] Another previous study reported that there was a potential error rate of approximately 70% in cases with CH diagnosis in the prenatal period. Therefore, it is necessary to be very careful and attentive when diagnosing CH.[1]

In pregnancies in which CH is diagnosed, 89% of the families decide on the termination of their pregnancy.Therefore, true spontaneous abortion and live-birth rates are unknown in these patients. However, spontaneous abortion and intrauterine mortality rates are found to be 17% and 39% in two different studies.[11, 15] In another study, they reported a live-birth rate of 24% in patients with CH.[1]

As a result, with the introduction of a fetal CH diagnosis, it is important to note that karyotype anomalies are detected at high rates in these patients and karyotype analysis of this disease should be recommended. In particular, the presence of additional anomalies in septated CH cases suggests a high likelihood of karyotype abnormalities. The fact that NT thickness >5 mm does not increase the likelihood of karyotype anomalies is due to the less number of patients in this study. Further studies are required with more patients. We think that taking this situation into consideration during diagnosis will be effective when deciding on the consultation to be given to the family and termination of the pregnancy.

Disclosures

Ethics Committee Approval: Permission was obtained from the ethics committee for the study.

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