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Prenatal karyotype results of fetuses with nuchal edema, cystic hygroma, and non-immune hydrops

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Summary

Purpose: Subcutaneous edema detected sonographically in the forms of nuchal edema, cystic hygroma (CH), or non-immune hydrops (NIH) may be a sign of chromosomal abnormalities. The aim of this study was to investigate the chromosome abnormality incidence in fetuses with nuchal edema, CH, or NIH. *Materials and Methods:* The authors performed cytogenetic analysis of 218 singleton fetuses with ultrasound diagnosis of subcutaneous edema in the forms of nuchal edema in the first and second trimesters. *Results:* Chromosomal abnormality rates were 30.4, 10.4, 36.8, 34.1, and 60% in the nuchal translucency (NT), nuchal fold thickness (NF), CH, NIH, and CH with NIH groups, respectively. In 71 cases with detected chromosomal abnormalities, 37%, 44%, 15%, and 4% of the pathologic karyotypes were identified as monosomy X, trisomy 21, trisomy 18, and trisomy 13, respectively. *Conclusions:* This study confirms that subcutaneous edema detected sonographically, in the forms of nuchal edema, CH, or NIH, is a significant indicator of abnormal karyotype and deserves further investigation.

Key words: Nuchal edema; Cystic hygroma; Non-immune hydrops; Chromosome abnormalities.

Introduction

Ultrasonography has been approved as a useful diagnostic modality for identifying fetuses with chromosomal abnormalities [1]. Subcutaneous edema detected sonographically in the forms of nuchal edema, cystic hygroma (CH), or non-immune hydrops (NIH) may be a sign of intrauterine infection, fetal anemia, fetal heart disorders, and complicated twin pregnancies [2-4]. Whether or not these pathologies exist, there is a need for further investigation because of an increased risk of chromosomal abnormalities.

There are numerous studies of the incidence of chromosomal abnormalities in the presence of major fetal anomalies or various ultrasonographic soft markers in the literature. Over the limit value of nuchal translucency (NT), pathological chromosomal sets have been reported in more than 20% of cases [5-9]. According to previous studies, the chromosome abnormality rate varies from 3.4% to 39% when nuchal fold thickness is present [10, 11]. The risk of chromosomal abnormalities is reported to be even greater in cases with CH and ranges from 23% to 60% [12-15]. NIH is also frequently accompanied by aneuploidy and mostly results in the loss of the fetus [13].

The aim of this study was to describe the association between abnormal sonographic markers, such as nuchal edema in the first and second trimesters, as well as cystic hygroma, non-immune hydrops, and CH with non-immune hydrops, with chromosomal abnormalities, and to calculate the predictive value of these markers for chromosomal abnormalities in a retrospective study of 218 subjects.

Materials and Methods

There are differences in the descriptions of nuchal edema in the first and second trimesters. In the first trimester, the term NT is used to define nuchal edema, which is the thickness of the translucency between the internal border of the skin and the soft tissue overlying the cervical spine in longitudinal section [16, 17]. The proposed limit of NT is three mm in general practice [5, 6]. In the second trimester, "nuchal fold thickness" (NF) measurement is used to describe nuchal edema, which is the distance from the external border of the occipital bone to the external border of the nuchal skin measured at the level of the cerebellum and posterior cerebral fossa on the axial plane. Although some authors suggest < five mm, generally the normal value for NF is accepted as < six mm [18, 19].

Fetal CH is characterized by edema and single or multiple fluid-filled collections located at sites of lymphatic-venous connection, usually in the posterior neck and back of a fetus [20]. NIH is defined as excessive fluid accumulation in two or more extravascular compartments such as the pleural and pericardial spaces, peritoneal cavity, skin, and placenta, without any identifiable circulating antibody to red blood cell antigens [21, 22].

The present authors have performed a retrospective single-center study of 218 singleton fetuses with ultrasound diagnosis of subcutaneous edema, in the form of nuchal edema, CH, or NIH, seen in the Perinatology Unit of Tepecik Training and Research Hospital during the period 2009 through 2013. The study was ap-

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Table 1. — *Clinical characteristics of the study groups.*

	Nuchal edema in the first trimester (NT group)	Nuchal edema in the second trimester (NF group)	CH group	NIH group	CH associated with NIH (CH and NIH group)	Total
Cases*	56 (25.7)	48 (22)	38 (17.4)	41 (18.8)	35 (16.1)	218 (100)
Maternal age (y)**	28.3 ± 6.6	28.6 ± 6.4	27.6 ± 6.3	29.6 ± 5.3	26.6 ± 6.4	28.2 ± 6.2
Gestational age at diagnosis (w)**	12.3 ± 0.8	19.6 ± 2.8	14.2 ± 2.8	19 ± 4.4	15.5 ± 3.1	16 ± 4.1
Female to male ratio	29/27 (1.07)	27/21 (1.28)	21/17 (1.23)	21/20 (1.05)	27/8 (3.37)	125/93 (1.34)
Nuchal fold thickness (mm)**	4.2 ± 1.5	6.8 ± 0.9	N/A	N/A	N/A	N/A
Chrosomal abnormalities*	17(30.4)	5 (10.4)	14 (36.8)	14 (34.1)	21(60)	71 (32.6)

Values are expressed as *: n (%); **: mean ± standard deviation.
CH = cystic hygroma; NIH = non-immune hydrops; N/A: not available; y = year; w = week; mm = millimeter
Maternal age (y) $p = 0.132$; female to male ratio $p = 0.134$; chromosomal abnormalities $p \leq 0.001$

Table 2. — *Distribution of the chromosome abnormalities among all fetuses.*

Chromosome abnormality type	Nuchal edema in the first trimester (NT group) n = 56	Nuchal edema in the second trimester (NF group) n = 48	CH group n = 38	NIH group n = 41	CH associated with NIH (CH and NIH group) n = 35	Total n = 218	*p* value
45, X	1 (1.8)	-	9 (23.7)	3 (7.3)	13 (37.1)	26 (11.9)	
Trisomy 21	12 (21.4)	5 (10.4)	3 (7.9)	9 (22)	2 (5.7)	31 (14.2)	
Trisomy 18	3 (5.4)	-	2 (5.3)	2 (4.9)	4 (11.4)	11 (5)	0.134
Trisomy 13	1 (1.8)	-	-	-	2 (5.7)	3 (1.4)	
Total	17 (30.4)	5 (10.4)	14 (36.8)	14 (34.1)	21 (60)	71 (32.6)	
p values	0.008	-	0.030	0.092	0.005	-	

All values are expressed as n (%); CH = cystic hygroma; NIH = non-immune hydrops.

proved by the Independent Bioethics Committee for Scientific Research of Tepecik Training and Research Hospital. All ultrasonographic examinations were performed by experienced radiologists using a two-dimensional gray scale ultrasonographic system and a 3-7-MHz convex probe.

Nuchal edema was evaluated by NT and NF thickness measurements, which were performed as described previously. Inclusion criteria were: all fetuses with NT ≥ three mm at $11–13^{+6}$ weeks of gestation or whose fetal crown-rump length was between 45 and 84 mm and fetuses with NF thickness ≥ five mm at 15–24 weeks gestation. All fetuses diagnosed as CH and NIH as described above between ten and 25 weeks gestation were also included in the study. Exclusion criteria were presence of multiple gestations and the presence of identifiable circulating antibody to red blood cell antigens and detection of any intrauterine fetal infection.

Cytogenetic studies were successfully performed in all 218 patients using invasive techniques such as chorionic villus sampling (CVS), amniocentesis (AS), or cordocentesis. Information on maternal demographics, ultrasound findings, and cytogenetic results were obtained from the maternal charts of the present perinatology unit, radiology medical records, and the pathology database.

Fetuses were classified into five groups according to the ultrasound findings. Cases with nuchal edema in the first and second trimester were investigated separately as NT and NF groups. Cases of cystic hygroma and non-immune hydrops were designated CH and NIH groups, respectively. Cases of NIH associated with CH were evaluated separately as the "CH with NIH" group.

Collected data was assessed by Shapiro–Wilk's test, Kruskal–Wallis test, Pearson's χ^2 test, and One–Sample Kolmogorov–Smirnov test. A p value < 0.05 was considered to indicate statistical significance. All statistical tests were performed using the SPSS software, version 20.0.

Results

A total of 218 fetuses met the inclusion criteria. Mean maternal age of the study group was 28.2 years (range, 16–46). Mean gestational age at the time of initial diagnosis was 16 weeks (range, 10–25). Gestational ages of the NT, NF, CH, NIH, and CH with NIH groups were 12.3, 19.6, 14.2, 19, and 15.5 weeks, respectively. Gender was male in 93 (42.7%) and female in 125 (57.3%); with a female-to-male ratio of 1.34, which was statistically insignificant ($p = 0.134$). Table 1 summarizes the clinical characteristics of each study group.

Karyotype analysis was performed by AS in 127 (58.3%) patients, by cordocentesis in 23 (10.6%) patients, and by CVS in 68 (31.2%) patients. Of the 218 fetuses, there were 71 (32.6%) with abnormal karyotypes. The chromosomal abnormality rates in the NT, NF, CH, NIH, and CH with NIH groups were 17 of 56 fetuses (30.4%), five of 48 fetuses (10.4%), 14 of 38 fetuses (36.8%), 14 of 41 fetuses (34.1%), and 21 of 35 fetuses (60%), respectively. The chromosomal abnormality rate was statistically significantly higher in the CH with NIH group ($p \leq 0.001$). Table 2 summarizes the distribution of chromosomal abnormalities in each group and among all fetuses.

The limit value of nuchal fold thickness for indication of karyotyping was accepted as ≥ five mm in the current study. In the NF group, six of the 48 fetuses' NF thicknesses were ≥ five mm and < six mm, and all had normal karyotypes.

In 71 cases with detected chromosomal abnormalities, 37%, 44%, 15%, and 4% of the pathologic karyotypes were identified as monosomy X, trisomy 21, trisomy 18, and trisomy 13, respectively. Trisomy 21 was the most common pathological chromosome anomaly detected in the NT (21.4 %) and NIH (22%) groups, with almost equal proportions. In the NF group, trisomy 21 was the only detected abnormal karyotype, with an incidence of 10.4%. Monosomy X was found to account for the highest proportion among the detected chromosomal abnormalities in the CH (23.7%) and CH with NIH (37.1%) groups. The incidences of trisomy 21 in NT group (p = 0.008), monosomy X in CH group (p = 0.03), and monosomy X in CH and NIH group (p = 0.03) were statistically significant.

Discussion

Genetic sonogram has been proven to be a useful tool for identifying fetuses with chromosomal abnormalities. The presence of various soft markers and major anomalies increases the patient's risk for an anomaly and necessitates further investigation. Noia *et al.*, in their study evaluated the natural history of cystic hygroma in the fetal and neonatal periods, suggested that ultrasonography on its own cannot diagnose a chromosomal anomaly; therefore, suspected lesions require confirmation by invasive investigations such as villus biopsy, AS, or cordocentesis [23].

During prenatal genetic counseling, the present authors' aim to identify as many fetuses with abnormal karyotypes as possible while trying to avoid increasing the risk of abortion through unnecessary invasive interventions. An accurate prediction of the chromosomal abnormality rate is essential to satisfy parents and to protect the counselor. This study presents the genetic results for fetuses with subcutaneous edema in the forms of nuchal edema, CH, or NIH detected sonographically in the present clinic.

The results of the present study reveal that nuchal edema increases the risk of trisomy 21, trisomy 18, trisomy 13, and X-monosomy in the first trimester. In accordance with the literature, trisomy 21 was the most common of all chromosomal abnormalities in this group (NT group), with an incidence of 21.4%, and trisomy 18 was second most common, with an incidence of 5.4% [9]. Although NT alone has a good detection rate for trisomies, its sensitivity is better when combined with pregnancy-associated plasma protein-A and free β-human chorionic gonadotropin [24]. Trisomy 10, triploidy, 47XXY, 47XYY, 47 XXX, 46,XX/47, and XX+12 are the other very rare chromosomal abnormalities detected in previous studies; none of these was identified in the present study groups [6, 25, 26].

Unlike in many previous publications, trisomy 21 was the only abnormal karyotype identified in the 10.4% of fetuses with second trimester nuchal edema (NF group) in the present study. Trisomy 18 and other chromosomal abnormalities were also detected in the literature, but trisomy 21 was the dominant abnormality [10, 11, 27].

Chromosomal anomalies were detected in 60% of cases in the CH with NIH group in the present study. Considering that the chromosomal abnormality rate was 36.8% in the CH group, the authors conclude that association with NIH results in a twofold increase in the rate of abnormal karyotype. Supporting the present findings, Beke *et al.* discovered chromosomal abnormalities in 20% of CH cases, while the chromosomal abnormality rate was 53.8% in cases of CH with NIH [7]. In a similar study by Nadel *et al.*, chromosomal abnormalities were identified in 46.5% of CH cases, while CH and NIH occurring together was associated with pathological karyotypes in 83.78% [13].

In the present investigation, in the CH with NIH group, monosomy X accounted for 37.1% of karyotypes and was followed by trisomy 18 (11.4%), trisomy 21 (5.7%), and trisomy 13 (5.7%). The present results and the previous reports are contradictory in terms of the distribution in types of chromosomal abnormalities in fetuses with CH with NIH. Many researchers agree that monosomy X is the most common type and trisomy 21 is the second most common in this group; however, Beke *et al.* reported higher rates of trisomy 18 (38.46%) than monosomy X (15.38%) in their study [7].

In the CH group, the chromosomal abnormality rate of 36.8% was in agreement with the literature [14]. Monosomy X was the most common karyotype abnormality in the present study, with an incidence of 23.7%. The types of chromosomal abnormalities detected in this study were also concordant with previous reports [8, 14, 28]. However, some authors reported an incidence of trisomy 21 of 21.4–37.3%, with the highest proportion in this group [12, 15].

Hematologic, cardiovascular and metabolic diseases, infections, tumors, and many other conditions may give rise to NIH, including trisomy 21, trisomy 18, and monosomy X [7, 13]. In agreement with the literature, monosomy X and trisomy 21 were the most common types of aneuploidy in our investigation. Fritsch *et al.*, in their study of 116 NIH patients, reported that in 22.4% of them, the etiology was chromosomal abnormalities [29]. Schwanitz *et al.* evaluated cases of NIH and found a pathological karyotype in 27.6%; the present data at 34.1% are consistent with these findings [30].

In this study, the authors were not able to rule out submicroscopic genomic alterations, single gene diseases, and other genetic syndromes; they consider this a limitation. Further studies are needed using other techniques, such as cytogenetic microarray analysis, which might indicate a different incidence of genetic abnormalities associated with fetal subcutaneous edema.

Conclusion

The present study confirms that subcutaneous edema detected sonographically, in the forms of nuchal edema, CH, or NIH, is a significant indicator of an abnormal karyotype

and deserves further investigation. CH in association with NIH results in a twofold increase in the abnormal karyotype rate. By analyzing the distribution of chromosomal abnormalities, the authors established that nuchal edema and NIH mainly increase the risk of trisomy 21. CH with or without NIH is mainly associated with monosomy X.

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