REVIEW ARTICLE

Prenatal Ultrasound Evaluation and Outcome of Pregnancy with Fetal Cystic Hygromas and Lymphangiomas

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Received 17 January 2017; accepted 21 February 2017
Available online 17 April 2017

KEYWORDS

cystic hygroma, hydrops fetalis, lymphangioma, nuchal translucency

Abstract Cystic hygroma is a type of lymphangioma, which is a vascular anomaly associated with lymphatic malformations and formed by fluid accumulation mainly located at the cervicofacial and axillary regions. Cystic hygroma is mostly located in the neck (75%), followed by axilla (20%), retroperitoneum and intra-abdominal organs (2%), limbs and bones (2%), and mediastinum (1%). It is often associated with chromosome aneuploidies, hydrops fetalis, and even intrauterine fetal demise. The prognostic factors of the fetal cystic hygroma or lymphangioma are chromosome abnormalities, hydrops fetalis, septations, or thickness of the cystic hygroma and are associated with other major malformations. Prenatal managements including ultrasound serial follow-up, magnetic resonance imaging, or even intrauterine injection of sclerosing agents are suggested. For fetus with the risk of airway obstruction at delivery, ex utero intrapartum treatment is also indicated. Detailed prenatal counseling is necessary for better neonatal outcome.

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Introduction

There are different nomenclatures of cystic hygroma. Cystic hygroma is a type of lymphangioma, which is also called nuchal edema or increased nuchal translucency (NT) during the first trimester. It is a vascular anomaly associated with lymphatic malformations and formed by fluid accumulation mainly located at the cervicofacial and axillary regions [1]. It is mainly located in the neck (75%), followed by axilla (20%), retroperitoneum and intra-abdominal organs (2%), limbs and bones (2%), and mediastinum (1%) [2,3]. The thickness is usually ≥ 3 mm. The incidence of nuchal cystic hygroma is about 1/6000 at birth and about 1/750 in spontaneous abortion [4].

It is not only associated with lymphatic malformation but also with chromosome aneuploidies, hydrops fetalis, and even intrauterine fetal demise (IUFD). The prognosis is often considered poor. However, cystic hygroma could be transient in ultrasound findings. It might regress during pregnancy because of recanalization or the formation of collaterals [5].

Here, we will review the diagnosis, factors that affect the prognosis, and the possible management of fetal cystic hygroma for better perinatal outcome.

Prenatal ultrasound findings

Ultrasound findings of cystic hygroma include thin-walled and serpiginous or multiseptated intradermal fluid collections which are often found at cervical regions [6]. Ville et al [7] defined nuchal cystic hygroma as an area of sonolucency in the soft tissue of the occipital region, consisted of two symmetrical cavities completed separated by a midline septum, with or without the internal trabeculae (multiloculated cysts). NT is the presence of unilocular collection of nuchal fluid ≥ 3 mm³. The thickness of the cystic hygroma is measured at its widest part from the intact skull or skin at the transverse view. Prenatal ultrasound of cystic hygroma may show increased nuchal thickness (≥ 3 mm), with or without septation at the neck region or thin-walled, sonolucent, and multilocular structure at other regions (Figures 1 and 2). Color Doppler may show no obvious internal flow which can be distinguished from hemangioma (Figure 3). Besides, the color Doppler ultrasound is also effective for the detection of intraleSIONal hemorrhage. It may show pulsations from the septums toward the cysts [8]. Furthermore, differential diagnosis should also include encephalocle or cervical teratoma. Head and spine morphologies should be further evaluated for suspected neural tubal defects. Polyhydramnios is also an indicator of neural tube defect but seldom seen in cystic hygroma.

Cystic hygroma in the anterior triangle of the neck is often associated with airway compression, which needs more aggressive intrapartum management. Further image evaluation using MRI is also recommended prior to birth for definite tumor size and infiltration pattern.

Common associated ultrasound findings are hydrops fetalis, cardiac malformations, and skeletal abnormalities. Cardiac malformations are the main anomalies detected in fetuses with normal karyotype (62.2–72.7%) [9]. Other major malformations, such as hydrocephalus, arthrogryposis, agenesis of corpus callosum, pes equinovarus, diaphragmatic hernia, amniotic band syndrome, mesomelia, and bilateral hydronephrosis, were also reported in patients with septated cystic hygroma and normal karyotype [10].
Outcome

Cystic hygroma is well known with poor outcome because the fetuses usually have chromosomal abnormalities and hydrops fetalis or IUFD often occurs during pregnancy. The unfavorable outcome is 77.8%. However, there are also patients with cystic hygroma with resolution or survive at birth without other malformations (16.7–22.2%) [9,11]. There are several factors that can affect and predict the outcome of cystic hygroma (Table 1).

About 50% of fetal cystic hygromas are found with chromosomal abnormalities [9,11–13]. The most common chromosome abnormalities associated with cystic hygroma are Trisomy 21 and Turner syndrome. Other abnormalities, such as Trisomy 18, Trisomy 13, and Triploidy, were also reported. Beside aneuploidies, recent studies showed that some copy number variants (CNVs) were also associated with cystic hygroma or increased NT, and it can be detected by using microarray [14,15]. A meta-analysis showed that the most common pathologic CNVs are 22q11.2 microdeletion syndrome and then 22q11.2 duplication. Others are 10q26.12q26.3 deletion, 12q21q22 deletion, 1p36 deletion, and Sotos syndrome. Genomic microarray provides a 5.0% incremental yield of detecting CNVs in fetuses with increased NT and normal karyotype [14]. Noonan syndrome is also frequently noted in fetuses with cystic hygroma. Other genetic disorders, such as Roberts syndrome, Cornelia de Lange syndrome, and multiple pterygium syndrome, are rare; however, they were also reported in the first-trimester cystic hygroma, and 4p deletion and unbalanced chromosome 10 were reported at second-trimester cystic hygroma [9,16] (Table 2).

Although cystic hygroma might be resolved during pregnancy, whether it would be resolved or not is not related to the fetal karyotype. However, when it progresses to hydrops fetalis, the prognosis is not favorable. Several studies showed that the thickness was also associated with the prognosis. Tanriverdi et al [12] showed that fetuses with normal karyotype and nuchal size > 6.5 mm had worse prognosis. Graesslin et al [11] also showed that fetuses with cystic hygroma < 6 mm had good prognosis but not including those with hydrops fetalis. Scholl et al [17] showed that the increased thickness of NT is associated with the increase of the odds of abnormal karyotype, major congenital anomaly, perinatal loss, and other poor outcomes.

Rosati and Guariglia [5] reported that 63.2% of nonseptated cystic hygromas and 28.6% of septated cystic hygromas regressed spontaneously in utero. Compared with nonseptated cystic hygromas, septated cystic hygromas have more risk of aneuploidy and worse prognosis, such as hydrops fetalis [5,16,18]. Turner syndrome was found in septated hygromas only (30/39), and Trisomy 21 was the most commonly found abnormal karyotype in nonseptated hygromas (5/16). Hydrops fetalis was more common in septated cystic hygromas than in nonseptated cystic hygromas (60% vs. 19%). Besides, the survival rates were higher in nonseptated cystic hygromas (27%) than in septated cystic hygromas (2%).

Nuchal lymphangiomas are likely to be associated with chromosomal abnormalities. However, when the mass is located at axilla, the relationship between lymphangioma and aneuploidies is slightly lower than nuchal lymphangioma [8]. It is uncertain that non-nuchal lymphangiomas have same risk of chromosome abnormalities because of the paucity of available data. Lymphangiomas at the anterior neck have the possibility of airway compression, which needs airway protection and neonatal resuscitative service intrapartum. For those fetuses with lymphangioma at the trunk region, dystocia and hemorrhage secondary to trauma should be alerted and cesarean section delivery is indicated [19]. Mondal et al [20] reported a case of congenital fetal lymphangioma causing shoulder dystocia and uterine rupture without prenatal diagnosis. IUFD was also noted at laparotomy.

Management

For the management of fetal cystic hygroma or lymphangioma, the first common step is cytogenetic study for suspected aneuploidy, and array comparative genomic hybridization is also recommended for other genetic disorders. Detailed and serial ultrasound examination for follow-up of the growth of the tumor is necessary. These results are important for prenatal counseling. For patients with normal karyotype and favorable prognosis, further consultation with a pediatric surgeon was also needed for postnatal management. Because huge cystic hygroma may cause dystocia, neonatal airway compression, or feeding

| Table 1 | Poor prognostic factors of cystic hygromas and lymphangiomas. |
|-----------------------------|-------------------------------------------------------------|
| Chromosome abnormalities    |                                                             |
| Hydrops fetalis             |                                                             |
| Thickness of cystic hygroma | ≥ 6mm                                                        |
| Septated cystic hygomas     |                                                             |
| Nuchal cystic hygroma       |                                                             |
| Associated with other major malformations |                          |

| Table 2 | Aneuploidies and genetic disorders associated with cystic hygromas and lymphangiomas. |
|---------|----------------------------------------------------------------------------------------|
| Aneuploidies | Trisomy 21  |
|           | Turner syndrome  |
|           | Trisomy 18  |
|           | Trisomy 13  |
|           | Triploidy  |
| Copy number variants | 22q11.2 deletion  |
|                    | 22q11.2 duplication  |
|                    | 10q26.12q26.3 deletion  |
|                    | 1p36 deletion  |
|                    | 4p deletion  |
| Others            | Roberts syndrome  |
|                    | Cornelia de Lange syndrome  |
|                    | Sotos syndrome  |
|                    | Multiple pterygium  |
problems. MRI can be used to assess the size and infiltration of cystic hygroma.

Several studies have suggested that patients with fetal cystic hygroma and hydrops fetalis without chromosome abnormalities or other structural abnormalities are candidates for intrauterine sclerotherapy [21–23]. Mikovic et al [23] reported two patients with fetal neck lymphangiomas with intrauterine injection of OK-432 at 28 weeks of gestational age. Aspiration of fluid in cystic hygroma and injection of same volume of OK-432 were performed. Increased echogenicity of the cysts was noted after injection. After the regular follow-up, both the patients were born without the obvious neck mass and good outcome. Direct OK-432 injection of the lymphangioma is widely used in patients with lymphangioma postnatally. However, the case numbers are sparse in intrauterine injection, and more case studies are warranted.

After thorough assessment of fetal anatomy, for those with the risk of airway obstruction at delivery, ex utero intrapartum treatment is the gold standard strategy. It can protect the fetuses from neonatal hypoxia and brain injury. It should be performed under the supervision of a multi-disciplinary team of obstetricians, anesthesiologists, pediatric surgeons, neonatologists, otolaryngologists, and a group of operating room nurses and personnel. Therefore, prenatal counseling is crucial.

Postnatal management includes surgical excision, direct injection of sclerosing agents, and oral sirolimus. Surgical excision is one of the treatments, especially for localized lesions. Increased echogenicity of the cysts was noted after injection. After the regular follow-up, both the patients were born without the obvious neck mass and good outcome. Direct OK-432 injection of the lymphangioma is widely used in patients with lymphangioma postnatally. However, the case numbers are sparse in intrauterine injection, and more case studies are warranted.

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Postnatal management includes surgical excision, direct injection of sclerosing agents, and oral sirolimus. Surgical excision is one of the treatments, especially for localized lymphangioma, but local recurrence has been reported after surgery [24]. Injection of sclerosing agents, such as Bleomycin or OK-432, directly into the mass has been applied for decreasing the mass size or for total resolution. Oral sirolimus was used after birth with decreasing size of axillary lymphangioma, but the outcome should be followed [25].

Although cystic hygromas or lymphangiomas are common fetal anomalies during pregnancy and often associated with poor outcome, in some cases, appropriate counseling and prenatal evaluation can result in better outcome for the fetuses.

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