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**LETTER TO THE EDITOR**

# Familial nuchal cystic hygroma without fetal effects: Genetic counselling and further evidence for an autosomal recessive subtype

Nuchal cystic hygroma (NCH) is a congenital malformation in which distended fluid-filled spaces develop typically in the region of the fetal neck at incidences of 1/6000 at birth and 1/750 among spontaneous abortions (Chen *et al*. 1996). Prenatal diagnosis by ultrasound is based on the demonstration of a bilateral, mostly symmetric, cystic structure located in the occipitocervical region with the lesion either septated by internal trabeculae (septated) or not (nonseptated). Septated NCH may result from complete obstruction in the cervical lymphatic sacs preventing communication with the jugular venous system and causing large multilocular cysts. In contrast, it is believed that nonseptated NCH result from a temporary accumulation of lymphatic fluid due to incomplete obstruction of lymphatic drainage (Brumfield *et al*. 1996). Increased pressure in the lymphatic system may sometimes overcome the incomplete obstructions, thus explaining the spontaneous resolution of these lesions (Bernstein *et al*. 1991).

Differential diagnosis is made with nuchal translucency (NT), which is defined as measurement of the size of the translucent space behind the neck of the fetus using ultrasound at between 10 and 14 weeks of pregnancy, reflecting the amount of fluid that has accumulated under the skin of the fetus. Increased NT is associated with an increased risk of chromosomal abnormality and is a marker for major cardiac defects, noncardiac structural defects, and rare genetic syndromes.

When cystic hygroma appears septated, the prognosis is considered even worse than the nonseptated form. Fetuses with NCH are at high risk for adverse outcome and detailed prenatal diagnosis, including invasive procedures, should be offered because the condition has been reported to be associated with normal chromosomes in 20–40% of cases, and is frequently associated with chromosomal aberrations such as X monosomy and trisomy 21, 18, and 13. It is also known to be associated with cardiac anomalies and no immune hydrops fetalis. Compared with simple increased NT, cystic hygroma has five-fold, 12-fold, and six-fold increased risks of aneuploidy, cardiac malformation, and perinatal death, respectively (Malone *et al*. 2005). Moreover, to determine fetal outcome in NCH cases with normal karyotypes, detailed sonography should be concentrated beside the exclusion of fetal heart defects and existence of hydrops fetalis, on the skeletal, urogenital and craniofacial anomalies, as these might cause severe morbidity (Tanriverdi *et al*. 2005). Interestingly, *in utero* resolution of NCH with advancing gestational age has been described both in chromosomally normal (Bronshtein *et al*. 1989) and abnormal (Rodis *et al*. 1988) fetuses with resolution of the cystic hygroma in the 10% of the aneuploid cases and 17.6% of the euploid cases (Ganapathy *et al*. 2004). NCH has often a very poor fetal outcome (Tanriverdi *et al*. 2001); however, it can resolve spontaneously and isolated NCH with a normal karyotype and no other suspicious sonographic findings has a moderately good prognosis and most pregnancies with normal evaluation at the completion of the second trimester result in a healthy infant with a normal pediatric outcome (Malone *et al*. 2005). Knowledge of the natural history of this condition has implications in counseling, invasive testing and follow-up of fetuses diagnosed with this condition.

Familial cases have been described suggesting a genetic basis of the condition with possible Mendelian inheritance. Dallapiccola *et al*. (1984) described two sib fetuses with NCH and normal chromosomes and suggested the existence of an autosomal recessive type of cystic hygroma. Tricoire *et al*. (1993) reported eight cases of familial cystic hygroma concerning three families with parental consanguinity. Watson *et al*. (1990) described a patient who had three consecutive fetuses with cystic hygroma and hydrops, two of which had documentation of normal karyotype. Rotmensch *et al*. (2004) described 18 families in which 18 pairs of siblings were affected by transient nonseptated cystic hygromata.

We have observed two families in which there was a recurrence of septated NCH in two consecutive pregnancies. In all four fetuses the karyotypes were normal and no other known causes were detected (such as associated anomalies or infection). The first couple decided to voluntary terminate the pregnancies in the second trimester. Fetal autopsy showed no congenital anomalies other than those detected by ultrasound. In the second family prenatal diagnosis of septated NCH was made in two consecutive pregnancies and after evidence of no abnormalities (karyotype, ultrasound and infections) the couple decided to continue the pregnancies with the birth of two healthy babies; NCH decreased in the late second trimester and disappeared progressively.

Even if an autosomal recessive pattern of inheritance has been postulated, cystic hygroma may also occur in association with a variety of syndromes, like Noonan syndrome, some of which have other patterns of inheritance. Prenatal diagnosis is often made in the first or early in the second trimester, and it is frequently very difficult for prenatal genetic counseling to give a fetal prognosis in the absence of anomalies or to give a recurrence risk for future pregnancies after a voluntary terminated pregnancy in the second trimester without evidence of known etiologies.

Malone *et al*. (2005) have proposed a step-by-step prenatal counseling based on a standardized diagnostic algorithm when a diagnosis of septated cystic hygroma in the first trimester is made. Initial counseling should occur immediately after sonographic diagnosis, and an overall risk of fetal aneuploidy of one in two should be quoted. After confirmation of a normal fetal karyotype, a second counseling session should be provided. At that time, prospective parents should be given a residual risk of one in two of a major structural fetal abnormality or spontaneous fetal death. After completion of detailed fetal anatomic sonography and echocardiography by 16–20 weeks of gestation, patients with normal findings can then be quoted a 95% chance of a normal pediatric outcome.

Our case of recurrence without neonatal anomalies and the other two cases without evidence of a recognizable cause confirm the suggested existence (Rotmensch *et al*. 2004) of an inconsequential genetic syndrome without fetal effects related presumably to lymphatic development with an autosomal recessive inheritance pattern. The existence of this possible genetic subtype may be included in prenatal genetic counseling of NCH fetus without known etiology.

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