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Association of chorangiomas to hypoxia-related placental changes in singleton and multiple pregnancy placentas

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ABSTRACT

Introduction: Chorangiomas (CAs) are the most frequent non-trophoblastic tumor-like-lesions of the placenta, and since they occur with an unusual frequency in pregnancies at high altitude, they are considered as a part of a spectrum of hypoxia-related vascular lesions of the placenta. The aim of our study is to describe the morphological features of the CAs and to show associations between CAs and other hypoxia related morphological changes in placentas of singleton and multiple pregnancies.
Materials and methods: Placentas from singleton (121 vs 242) and multiple (49 vs 98) pregnancies, with and without CAs, respectively, were selected from a cohort of 15,742 placentas and enrolled into a case control study.
Results: Singleton placentas with CAs showed increased incidence of hypoxia-related placental changes including accelerated maturation of chorionic villi (OR = 2.40, $p < 0.001$), infarction (OR = 2.89, $p < 0.001$), decidual arteriopathy (OR = 3.24, $p < 0.001$), fetal thrombosis (OR = 4.05, $p < 0.001$) and hypercoiled umbilical cords (OR = 5.55, $p < 0.001$). The incidence of CAs in multiple placentas was higher in our studied cohort and a significant associated change was shown with fetal thrombosis (OR = 4.58, $p = 0.017$). There were no significant morphological changes between CAs in singleton compared to multiple pregnancies.
Discussion: In singleton placentas, CA is associated with several placental changes related to hypoxia, whereas in multiple pregnancies this relationship is not present. We speculate that CAs in multiple pregnancies might reflect an adaptive mechanism for relative hypoxia per se in these pregnancies.
Conclusion: Our study provides evidence that CAs are associated with an increased rate of hypoxia related changes in singleton placentas.

1. Introduction

Chorangiomas (CAs), first described by John Clarke in 1789, are placental hemangiomas, composed of capillary-vascular channels with variable amount of intervening perivascular stroma, containing fibroblasts, macrophages and scanty fibrous tissue [1,2]. CAs are frequently located in poorly perfused areas of the placenta (subchorionic and marginal areas) and they can be observed from the second trimester [2]. They are usually single but occasionally can be multiple with an incidence ranging approximately between 0.5 and 1% of all examined placentas [1]. Most CAs are incidental findings measuring less than 0.5 cm. Lesions up to 4 cm in diameter are normally asymptomatic, but large CAs (>4 cm), with an incidence of 1/3500 to 1/20 000 births, are often associated with arteriovenous shunting within the placenta and may be etiologically linked to a number of pregnancy complications, including fetal anemia, thrombocytopenia, non-immune fetal hydrops, polyhydramnios, antepartum hemorrhage with premature placental detachment, preterm labor, intrauterine fetal growth restriction (IUGR) and increased perinatal mortality [3]. The overall mortality rate associated with large CAs is about 30% [4], whereas the clinical

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significance of microscopic CAs remains unknown. It has been reported that the presence of CA is related to an increased maternal age and multiple gestations, and associated with preeclampsia, gestational diabetes, HELLP (hemolytic anemia, elevated liver enzymes and low platelet count) syndrome and placental hypoxia status [2,4]. The aim of our study is to describe the morphological characteristics of the CAs and to evaluate associations between CAs and other hypoxia related morphological changes in placentas of singleton and multiple pregnancies.

2. Materials and methods

15,742 placentas, including 2112 (13.4%) from multiple pregnancies (2095 twin placentas and 17 triplet placentas), were examined at the Section of Perinatal Pathology, Karolinska University Hospital, Stockholm, Huddinge. All placentas were collected at sea level. Regional consensus indications for pathological referral of the placenta included maternal indications (prematurity > 32 weeks, preeclampsia including HELLP syndrome, repeated hemorrhage, abruption) and fetal/neonatal indications (asphyxia (Apgar < 7 at 5 min) and/or umbilical artery pH < 7.0, non-immune hydrops, IUGR, fetal or perinatal death, macroscopically abnormal placenta or umbilical cord and suspicion of chorioamnionitis). Twin placentas were referred in cases of complicated pregnancy (i.e. prematurity, twin to twin transfusion syndrome and IUGR), whereas chorionicity alone was clearly not an indication for referral.

During the period of 1996–2001 placentas from Karolinska Hospital, Solna and Danderyd Hospital were examined at the respective Pathology Department. During 2002–2012 all placentas from the major Stockholm area were directly referred to the Section of Perinatal Pathology. Placentas were examined according to a standardized, detailed protocol including macro- and micromorphologic analysis. At least 1 section from the umbilical cord and the membranes and 2 sections from macroscopically normal placenta were subjected to histopathologic examination. Furthermore, all of the macroscopically detected focal changes in the placentas were sampled.

Gestational age was retrieved from medical records and evaluated according to ultrasound examinations performed in the beginning of the second trimester.

CAs were diagnosed in 170 cases (121 singletons and 49 multiple pregnancies) and coded as hemangiomas according to the Systematized Nomenclature of Medicine (SNOMED). Histological slides of 169 CA cases were re-reviewed by two perinatal pathologists, whereas in one case slides were destroyed and data were taken from original report. From a cohort of 3000 selected placentas that have been morphological examined during the period of 2012–2013, 242 singleton and 98 multiple placentas without CAs (two reference placentas for every case) were selected in our study as controls. The controls matched with cases by gestational age group (group 1: 20–23 gestational weeks; group 2: 24–28 gestational weeks; group 3: 29–32 gestational weeks; group 4: 33–37 gestational weeks and group 5: 38–43 gestational weeks) and by the outcome of the pregnancy (liveborn/stillborn infants). Placentas with CAs were analyzed in two groups, placentas from singleton and multiple pregnancies, compared to the matched control group. Placental weight adequacy to gestational age was assessed according to the table by Pinar H et al. [5]. The histological variables that have been evaluated in all placentas were villous maturation, presence of decidual arteriopathy, infarction, intervillous thrombosis, abruption, fetal thrombi, chorioamnionitis and villitis also length, insertion site, coiling index and number of vessels of the umbilical cord. Decidual arteriopathy was defined as fibrinoid necrosis of the artery wall with or without the presence of acute atherosis. The diagnosis of abruption was based on the presence of a retroplacental hematoma. Fetal thrombosis was defined by the presence of thrombosis in chorionic plate and/or stem villous vessels. Normal values for umbilical cords coiling index were considered between 0.07 and 0.3; coiling index was not calculated for umbilical cord shorter than 20 cm or for formalin-fixed placentas. Umbilical cords insertion up to 1 cm from the edge of placenta was defined as the marginal/velamentous insertion group. CAs were measured and localization, morphological form (nodular or lobular) and presence of multiple or single lesions were assessed.

2.1. Statistical analysis

Statistical analysis performed using the R software (version 3.0.3). Pearson's Chi-squared Fisher's exact, Wilcoxon rank-sum and/or Kruskal–Wallis test used where appropriate, and logistic regression analysis applied to estimate odds ratio (OD) values with Wald's confidence intervals (CI). A p value of <0.05 was considered significant for all analyses.

A local Ethics Committee approved the study.

3. Results

The incidence of CAs within our cohort (N = 15,742) was significant higher in the group of multiple pregnancies compared to the singleton group (2.32% vs 0.89%, respectively, p < 0.0001). The gestational age of placentas (N = 170) with CAs was ranged from 20 to 43 weeks (35.76 ± 4.01 weeks). The frequency distribution between gestational age groups was: group 1: [N = 1 (0.59%)], group 2: [N = 10 (5.88%)], group 3: [N = 21 (12.35%)], group 4: [N = 71(41.76%)] and group 5: [N = 67 (39.41%)]. The gestational age of singleton placentas (N = 121) with CAs ranged between 20 and 43 weeks (35.57 ± 4.32 weeks), whereas in multiple placentas (N = 49) ranged between 27 and 41 weeks (36.24 ± 3.07 weeks). There were no significant differences in distribution between gestational age groups in singleton and twin/triplet placenta groups (p = 0.76). The largest tumor was measured 13.5 cm and the smallest 0.05 cm in diameter. The median diameter with the interquartile range (IQR) of CAs showed no significant difference between singleton and multiple placenta groups (p = 0.879). The majority of the tumors were macroscopically discovered (N = 95, 55.88%), subchorially located (N = 122, 71.76%), showing nodular structure (N = 144, 84.70%) and presented as single lesions (N = 140, 82.35%). There were no significant differences in morphological characteristics of CAs between singleton and twin/triplet placenta groups (Table 1).

Table 1
Morphological characteristics of chorangiomas in singleton and multiple placentas.

Chorangiomas	Singleton placentas	Multiple placentas	P
Median diameter mm (IQR)	11 (6–18)	12 (5–20)	0.879
Localization (n, %)			0.73
Subchorial	87 (71.90)	35 (71.43)	
Basal	7 (5.79)	4 (8.16)	
Central	17 (14.05)	8 (16.33)	
Transplacental	10 (8.26)	2 (4.08)	
Discovered (n, %)			1
Macroscopically	68 (56.20)	27 (55.10)	
Microscopically	53 (43.80)	22 (44.90)	
Structure (n, %)			0.64
nodular	101 (83.47)	43 (87.75)	
lobular	20 (16.53)	6 (12.25)	
Lesion (n, %)			0.41
single	102 (84.30)	38 (77.55)	
multiple	19 (15.70)	11 (22.45)	