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Original Article

An epidemiological study investigating the relationship between chorangioma and infantile hemangioma

Alessia Selmin[a], Francesca Foltran[b], Silvia Chiarelli[c], Rosaria Ciullo[d], Dario Gregori[b,*]

[a] Department for Women and Neonatal Care, Abano Terme General Hospital, Abano, PD, Italy
[b] Unit of Biostatistics, Epidemiology and Public Health, Department of Cardiac, Thoracic and Vascular Sciences, University of Padova, Italy
[c] Department of Medicine, University of Padova, Italy
[d] Department for Mother and Pediatric Care, Obstetrics and Gynecology Clinic, A.O. 2, Padova, Italy

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ABSTRACT

Objectives: This study aimed to verify whether the infantile hemangioma (IH) incidence in children whose placentas showed a chorangioma is higher than in the general population, thus addressing the hypothesized relationship between chorangioma and IH.
Methods: All chorangioma diagnoses by the 1st Service of Pathology, University of Padova in 2004–2010, based on the analysis of placentas sent by the Department of Gynecological Sciences and Human Reproduction (University of Padova), were identified. Demographic, anamnestic and clinical data were collected from the mothers and newborns; mothers and pediatricians were interviewed by telephone within 1 year after birth to verify if any IH appeared. The incidence rates of IH and other adverse events (IUGR, preterm delivery, cesarean section, stillbirth) were compared with national and regional data, when available, or with estimates from the scientific literature.
Results: Thirty-eight chorangioma diagnoses were found. Of 33 infants born with a placenta affected by chorangioma, 18 infants had IH. The IH incidence recorded in our series (55%) was significantly higher than that recorded in national and regional surveys and in the scientific literature. Similar findings have been observed for the incidence of stillbirth, preterm birth and low birth weight incidence.
Conclusions: The IH incidence observed in our series appears to be significantly higher than that recorded among the general population, suggesting that an association between placental chorangioma and IH could exist which should be further verified in prospective studies.

Introduction

Chorangioma, originally described by Clarke in 1798 [14], is the most common tumor of the placenta, with a reported prevalence of approximately 0.5–1.0% [30]. As the name indicates, it is an hamartoma of the primitive chorionic mesenchyme that arises from angioblastic tissue [24] and is defined as an expansible nodular lesion composed entirely of capillary vascular channels, intervening stromal cells, and surrounding trophoblasts [17,50]. Most placental hemangiomas are small and within the placental substance and, hence, are unlikely to be observed and diagnosed unless the placenta is systematically sliced after delivery [20]. The clinical importance of this tumor lies not only in the association with obstetric, fetal and neonatal complications (such as pre-eclampsia, preterm delivery, abruption placenta, hydramnios, intra-uterine growth retardation, non-immune hydrops, cardiomegaly, congenital malformations, congestive heart failure, and even fetal demise) [2,7,8,13,18,19,21,34–36,42,46,49,58,59,65–69], but also in a possible role of chorangioma in the genesis of infantile hemangiomas (IH) [15,24,34,38,43,45,60].

IH is the most common vascular tumor of infancy, and although the natural history and progression of these lesions are well described, their origin remains unknown. In the last twenty years, many theories have been developed; a fundamental step was made in 2000 in discovering that IH expresses GLUT-1, a glucose transporter protein similar to that expressed by endothelial cells of the placenta capillaries and understanding that the placenta and IH share various other markers, such as Lewis Y antigen and merosin [47,48]. These findings support the "Placental Theory," which hypothesizes a relationship between IH and placental

* Corresponding author at: Unit of Biostatistics, Epidemiology and Public Health, Department of Cardiac, Thoracic and Vascular Sciences, University of Padova, via Loredan, 18, 35121 Padova, Italy. Tel.: +39 049 8275384; fax: +39 02 700445089.
E-mail address: dario.gregori@unipd.it (D. Gregori).

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capillary endothelial cells [3]. This idea is further encouraged by the high level of similarity in gene expression between IH and placenta (such as 17-β hydroxysteroid dehydrogenase type 2 and tissue factor pathway inhibitor 2) [4,38] and by the increased incidence of IH in infants whose mothers underwent chorionic villus sampling, a procedure that is believed to cause embolization of trophoblasts as a result of placenta disruption [12,31,60]. Additional support lies in the "Metastatic Niche Theory," which raises the possibility that the chorangioma, or the placenta itself, secretes substances preparing the sites where IH occur [38].

However, despite the biological plausibility of the relationship between placental chorangioma and IH, few studies (primarily single case reports and brief case series) have reported original data suggesting an association [13,15,24,34,39,43].

The aims of the present study were to describe feto-neonatal outcomes, including Intrauterine Growth Restriction (IUGR), preterm delivery, cesarean section, stillbirth, low birth weight, Apgar index <7, and IH in a case series of infants born from a placenta affected by chorangioma and, to verify whether the incidence of the considered outcomes, with particular regard to IH, is higher than in the general population, supporting theories hypothesizing the existence of a relationship between chorangioma and IH.

Methods

Data collection

In our institution, placental examination is always performed whenever a pathological process occurred during pregnancy, labor or delivery, including polyhydramnios, oligohydramnios, multiple gestation, IUGR, preeclampsia, placenta previa, abruption placenta, preterm delivery, preterm premature rupture of membranes, abnormal triple test, non-reassuring fetal heart rate during labor, postpartum hemorrhage, meconium stained amniotic fluid, macrosomia, fetal malformation, and perinatal mortality.

All chorangiomas diagnosed by the 1st Service of Pathology, University of Padova in the last 5 years (2004–2010) through analysis of placentas performed by the UOC of Gynecology and Obstetrics Department of Gynecological Sciences and Human Reproduction (University of Padova) have been identified.

The demographic, anamnestic and clinical data and information about pregnancy were collected for the mothers. Additionally, mothers and pediatricians were interviewed by telephone within 1 year after birth to verify whether, during the first 12 months of life, any IH appeared. Data regarding IH number, location, size and type were also recorded.

Statistical analysis

Mothers' demographic, anamnestic and clinical data and information about pregnancy have been described. Continuous variables were always expressed as median and inter-quartile differences, and categorical variables as percentages and absolute numbers.

Moreover, the probability (95% confidence interval) of main outcomes of interest was calculated, including IH occurrence, IUGR, preterm delivery (<37 weeks), cesarean section, stillbirth, Apgar score lower than 7 at the 5th minute and birth weight lower than 2500 g. Calculations were performed separately for children born from placenta with a chorangioma and for those born from a twin pregnancy where only one placenta presented the tumor.

To verify whether the probability of each outcome in our series was higher than those recorded in the general population, our results have been compared with national and regional data when available, or, alternatively, with estimates taken from the scientific literature.

Cumulative incidences during the period 2004–2010 for IH, preterm delivery, cesarean section, stillbirth, Apgar score lower than 7 and birth weight lower than 2500 g were calculated in Italy (60.3 million inhabitants, approximately 550.000 births/year) and the Veneto Region (North-east of Italy, 4.7 million inhabitants, approximately 44,000 births/years) from occurrence data published yearly by the National Health Ministry, which are based on the CEDAP (certificate of attendance at birth) data collection. CEDAP constitutes a national birth registry created by the Decree of the Minister of Health on 16 July 2001 that reports information on the socio-demographic characteristics, obstetric history, pregnancy, prenatal care and delivery for the parents, as well as information for the newborn, including adverse fetal and neonatal outcomes [56]. Because CEDAP data collection performed in 2004 was incomplete, we assumed that the same number of deliveries and outcomes occurred in 2004 as occurred in 2005 when calculating cumulative incidence. Moreover, national and regional data referring to 2008–2010 have not yet been published; therefore, we assumed the same annual distribution of delivery and outcome observed in 2007 for this period [25].

Furthermore, to take into account the underestimation of IH incidence that almost certainly affects CEDAP data (registration is made at birth without any follow up), the IH probability calculated in our case series was compared with estimates reported in the scientific literature. In particular, starting from data reported by Kilcline and colleagues [33] which systematically reviewed in 2008 all published papers about IH incidence, a pooled estimate of IH occurrence was performed and taken as a reference (Table 1).

Moreover, IUGR probability, not recorded in CEDAP data, has been compared with literature data, considering the findings of Kramer [37] and Mandruzzato [41] as references.

Finally, the association between the main features of chorangioma (number, maximum diameter and site) and IH occurrence was evaluated using the Chi-Square Fisher test. The statistical significance level was established as $p < 0.05$.

The R System (release 2.7.0) statistical analysis software was used for analysis [61].

Results

Between 2004 and 2010, 38 cases of placental chorangioma occurred in 37 pregnancies.

Mothers' demographic, anamnestic and clinical data and information about pregnancy are presented in Table 2.

Among the identified pregnancies, 7 were twins (one diamniotic triplets, 5 dichorionic diamniotic and one monochorionic) with a total of 43 placentas (5 without chorangioma). A total of 39 infants were born with a placenta affected by chorangioma, and 6 infants were born with a healthy placenta.

Among the births with a healthy placenta, not one experienced fatal outcomes. In contrast, only 33 live births occurred in the 39 pregnancies with placentas affected by chorangioma. The 6 fatal outcomes were 3 fetal intrauterine deaths, 2 died after birth and one miscarriage. Among the 3 intrauterine deaths, one fetus had hypoplastic cerebellar vermis, ventriculomegaly, hydrocephalus and Dandy–Walker syndrome. Another fetus had the umbilical cord tightened around the neck, retro-placentar hematoma and kidney malformations, and the last infant had heart and kidney defects and overlapping of the brain-parietal bone. Among the infants who died after birth, one died after the first 2 days of life due to severe prematurity (26 weeks gestation), and one infant died after one month of life despite surgery for diaphragmatic hernia. As for the spontaneous abortion (22 weeks gestation), the fetus had severe