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PLACENTAL LESIONS IN THE STAGING OF HYPOXIC-ISCHEMIC ENCEPHALOPATHY

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The placenta is the connecting organ between the mother and the fetus, bringing nutrients and oxygen for its normal development. When an imbalance occurs at the placental level, the fetus suffers. Neonatal encephalopathy is the most important cause of neonatal mortality and can be generated by placental factors. This article aims to bring to the forefront what we know so far about the role of the placenta in the occurrence of hypoxic-ischemic encephalopathy. We performed a prospective population-based study over four years (2016–2020), including 84 neonates diagnosed with hypoxic-ischemic encephalopathy, classified as mild, moderate, or severe according to the Sarnat classification, for whom placental examination data were accessible. We employed the Amsterdam Criteria to classify placental lesions. The findings indicated a strong statistical correlation between maternal and fetal vascular malperfusion lesions and moderate to severe hypoxic-ischemic encephalopathy.

Keywords: placenta, Amsterdam Criteria, hypoxic-ischemic encephalopathy, Sarnat Scale.

INTRODUCTION:

Hypoxic-ischemic encephalopathy (HIE) in neonates represents a significant clinical concern, associated with elevated morbidity and mortality rates[1]. Neonates diagnosed with HIE grades II and III exhibit a heightened risk for the development of cerebral palsy (CP), cognitive disabilities, epilepsy, hearing impairment, and cortical visual impairment[2,3]. Hypoxic-ischemic encephalopathy (HIE) is associated with various perinatal factors, such as disturbances in uterine and fetal blood flow or hypoxia; however, in many instances, the specific cause and timing of the event are not identified[4].

A well-functioning placenta and umbilical cord are crucial for normal pregnancy development, delivery, and fetal well-being. Microscopic placental processes may serve as perinatal risk factors for certain adverse neonatal outcomes in term asphyxiated neonates undergoing hypothermia treatment. Numerous studies examining placental and umbilical cord abnormalities have primarily concentrated on stillbirths[5].

Recent studies, including one by Harteman *et al.*, have examined the correlation between placental pathology and the occurrence of brain lesions in term infants experiencing neonatal encephalopathy following a presumed hypoxic-ischemic injury[6]. Nonetheless, limited research exists examining placental and umbilical cord abnormalities in relation to hypoxic-ischemic encephalopathy (HIE) when compared to healthy infants or matched cohorts in the intensive care unit.

This study evaluated the association between microscopic placental lesions and neonates with hypoxic-ischemic encephalopathy, in comparison to a cohort of neonates without encephalopathy. Providing such information in early pregnancy may enhance risk assessment and facilitate individualized monitoring throughout pregnancy and delivery. This information may assist clinicians in identifying the cause of hypoxia and its timing, which could enhance the prognosis. The objective is to decrease the occurrence of severe neurological sequelae via surveillance and targeted therapy at an optimal time for progression. Additionally, the goal is to characterize placental lesions in neonates who are not experiencing hypoxic-ischemic encephalopathy but still require intensive care.

MATERIALS AND METHODS

Subject information

A four-year observational, prospective, non-interventional study was conducted at Bucharest's "Filantropia" Clinical Hospital from 2016 to 2020. The study was carried out with the necessary approval from the Ethics Council of "Filantropia" Clinical Hospital and in accordance with the privacy protocols established for the participating patients. Before the mother and newborn were included in the study, the parents or legal guardians signed an informed consent agreement. The study was conducted in accordance with the principles established in the Declaration of Helsinki on Human Rights.

Maternal information, encompassing social, medical, and familial background, was collected alongside data regarding the newborn. The data included fetal heartbeat during labor, gestational age, delivery method, newborn weight, and sex. Furthermore, data from the clinical assessment of the neonates, including alterations linked to prenatal hypoxia and Apgar score, were also supplied. Furthermore, laboratory results were recorded, encompassing hemograms, metabolic parameters, pH, and acid-base balance metrics, all of which were gathered dynamically. The database was updated with data from placental histopathology examinations, encompassing both microscopic and macroscopic images.

Study groups and criteria

The study cohort comprised 84 neonates who had perinatal asphyxia, with a gestational age exceeding 36 weeks and a diagnosis of hypoxia at delivery (classified as mild, moderate, or severe). The control group comprised 69 babies with a gestational age above 36 weeks who necessitated neonatal intensive care for at least 3 days due to any pathology, except hypoxia.

We did not include newborns with metabolic disorders, congenital abnormalities, congenital viral infections (TORCH), genetic syndromes, or stillbirths.

Examination procedures

The inquiry encompassed a comprehensive analysis of the placenta, umbilical cord, and membranes. A seasoned pathologist performed the placental analysis. Microscopic inspection of fresh placenta slices was conducted prior to their embedding in paraffin and staining with hematoxylin and eosin. Five samples, each measuring 1.5–2 cm in thickness, were collected for microscopic analysis: one from the membranes, one from the umbilical cord, and three from the placental parenchyma. In instances when the placenta investigation could not be performed immediately post-delivery, the samples were refrigerated at 4˚C for a maximum duration of 24 hours. The inspection utilized a Zeiss Axioscope 5 microscope, and images were acquired with a Zeiss Axiocam 208 (Zeiss AG).

The classification encompassed the six basic pre-established categories of injuries as per the Amsterdam Criteria: maternal vascular malperfusion, fetal vascular malperfusion, chronic villitis of unclear etiology, delayed villous maturation, chorioamnionitis, and abruption (Table 1). Placentas exhibiting unique lesions across the six categories were omitted from the analysis.

Table 1

Histopathological characteristics of placental lesions

Criteria	**Characteristics**
Chorioamnionitis	The presence of inflammatory cells in the chorionic layers of the membranes and placenta with/without the presence of necrosis.
Maternal vascular malperfusion	Includes: placental hypoplasia (weight below the 10th percentile for gestational age), decidual vasculopathy, distal villous hypoplasia, presence of syncytial nodes, perivillous fibrin deposits, villous necrosis, fibrin islands in the trophoblast, presence of giant cells at the site of trophoblast implantation, and placental infarction.
Fetal vascular malperfusion	The disorder include thromboses in the chorion and placental vessels, with or without vessel obstruction, as well as avascular villi. Thrombosis can be categorized as high-grade (fewer than 5 villi per image) or global (affecting significant regions of either occlusive or non-occlusive thromboses).
Chronic villitis of unclear etiology	The condition is characterized by the presence of inflammatory cells and vascular damage, resulting from either arterial obstruction or the presence of avascular villi.It may be of low or high quality.
Delayed villous maturation	The condition is characterized by the presence of villi that exhibit a diminished quantity of vasculosyncytial membranes relative to gestational age, along with centrally located capillaries. It may be localized (less than 30% of parenchyma) or widespread (30% or more of parenchyma).
Abruption	A retroplacental hematoma exists.

Statistical analysis

Statistical analysis of the recorded data was conducted using SPSS 25.0 for Windows (IBM Corp.). The Chi-squared test or an unpaired t-test was utilized for independent sample analyses, while Mann-Whitney tests were applied to non-parametric variables. Fisher's test was utilized for each variable with a count of ≤ 5. A P value of less than 0.05 was deemed indicative of a statistically significant difference.

RESULTS

The cohort was categorized into:

- 84 neonates with hypoxia ischemic encephalopathy (mild, moderate, and severe);
- 48 neonates devoid of encephalopathy.

In the study, all babies received placental pathology investigation, revealing placental abnormalities in 77% (n = 65) of patients with hypoxic ischemic encephalopathy, compared to 47% (n = 23) in the control group. A chi-square test indicated a statistically significant correlation between placental anomalies and the diagnosis of hypoxic-ischemic encephalopathy (p = 0.00).

We examined the occurrence of placental alterations across each Sarnat group (1- mild, 2- moderate, 3- severe) in relation to the control group and utilized the chi-squared test for each variable. The presence of chorioamnionitis (p = 0.00) and delayed villous maturation (p = 0.00) lesions was correlated with mild prenatal HIE (Sarnat 1). The Chi test results for the Sarnat 1 group were as follows (Table 2):

Table 2

Placental microscopic lesions (MVM = maternal vascular malperfusion, FVM = fetal vascular malperfusion, VUE = chronic villitis of unknown etiology, NS = non-significant) in mild HIE

Placental lesions	**Sarnat 1 (n = 23)**	**Control (n = 69)**	**Chi Pearson**	**p-value**
MVM	1	0	3.17	0.07
FVM	0	1	.32	0.57
VUE	1	9	1.23	0.26
Delayed villous maturation	10	5	17.90	0.00
Chorioamnionitis	8	4	13.74	0.00
Abruptio	1	3	.00	0.96

Moderate HIE (Sarnat 2) cases exhibited both maternal (p = 0.00) and fetal vascular malperfusion (p = 0.00) lesions, together with chronic villitis of unknown cause type lesions (p = 0.04).

Table 3

Placental microscopic lesions (MVM = maternal vascular malperfusion, FVM = fetal vascular malperfusion, VUE = chronic villitis of unknown etiology, NS = non-significant) in moderate HIE

Placental lesions	**Sarnat 2 (n = 16)**	**Control (n = 69)**	**Chi Pearson**	**p-value**
MVM	3	0	7.70	0.00
FVM	9	1	20.70	0.00
VUE	0	9	4.04	0.04
Delayed villous maturation	4	5	1.21	0.27
Chorioamnionitis	5	4	3.52	0.06
Abruptio	4	3	3.00	0.08

The examination of placental alterations concerning severe HIE shown substantial correlations between maternal (p = 0.00) or fetal (p = 0.00) vascular malperfusion lesions and severe HIE (Sarnat 3).

Table 4

Placental microscopic lesions (MVM = maternal vascular malperfusion, FVM = fetal vascular malperfusion, VUE = chronic villitis of unknown etiology, NS = non-significant) in severe HIE

Placental lesions	**Sarnat 3 (n = 23)**	**Control (n = 69)**	**Chi Pearson**	**p-value**
MVM	7	0	27.24	0.00
FVM	7	1	22.52	0.00
VUE	2	9	.09	0.75
Delayed villous maturation	1	5	.10	0.75
Chorioamnionitis	1	4	.01	0.91
Abruptio	1	3	.02	0.87

Several lesions were omitted during the placental histological investigation as they could not be identified according to the Amsterdam criteria, and the examination (0.7%) did not indicate any chirangiosis. Furthermore, in cases of numerous simultaneous lesions (3 cases, 2.2%), they were categorized based on the severity of the most severe lesions (exceeding 30%).

DISCUSSION

In our investigation, microscopic placental alterations were observed in 77% of individuals with encephalopathy, in contrast to merely 47% in the control group. Similar to our work, Bingham *et al*. similarly emphasized the occurrence of placental alterations in 90% of individuals with hypoxic-ischemic encephalopathy. Numerous research in the literature examine placental alterations linked to hypoxic-ischemic encephalopathy and cerebral abnormalities. Placental alterations linked to HIE are diverse and encompass: vascular modifications of the MVM and MVF types, chorioamnionitis, inflammation, and abruptio placentae.

This study utilized a pre-specified classification of placental lesions for a systematic and reproducible methodology, categorizing the lesions into six groups based on the Amsterdam classification. Alternative research have proposed different classifications; for instance, Chang *et al*.[11] categorized placental lesions as vascular, inflammatory, or miscellaneous. Redline and O'Riordan[8] analyzed 10 placental lesions of differing severity and breadth. McDonald *et al*.[9] documented 16 abnormal placental lesions.

In our research, similar to the investigation conducted by Wintermark *et al*., alterations in maternal and fetal vascular malperfusion were correlated with the occurrence of hypoxic ischemic encephalopathy ($p = 0.03$)[12]. Fetal vascular malperfusion includes fetal thrombotic vasculopathy and indicates the involvement of major fetal arteries, leading to significant vasculopathy. We identified a statistically significant correlation between mild and severe encephalopathy and the occurrence of vascular alterations ($p = 0.00$). This underscores a persistent thrombotic process in the fetal and placental arteries, which are intricately interconnected. Encephalopathy is linked to the existence of thrombi in any location within the fetoplacental circulation. Our findings align with those of Redline, who identified a statistically significant correlation between prenatal vascular malperfusion and hypoxic-ischemic encephalopathy. Nielsen *et al.* demonstrated in their study a correlation between the occurrence of placental infarction and a fourfold increase in the prevalence of cerebral palsy. The occurrence of placental infarction was statistically significant in newborns with moderate and severe hypoxic-ischemic encephalopathy ($p = 0.00$), as seen in our study. This occurrence is attributed to placental vascular lesions that induce prolonged fetal hypoxia, rendering the fetus incapable of adapting to traumatic events during labor or delivery, owing to the abnormal placental environment.

Prior research has established a strong correlation between maternal infections, chorioamnionitis, and cerebral abnormalities in preterm newborns. Fetal-responsive chorioamnionitis, characterized by inflammation in the umbilical cord, correlates with the severity of newborn encephalopathy and the incidence of cerebral palsy in term infants[8]. A retrospective investigation revealed no correlation between chorioamnionitis and the occurrence of brain lesions detected by imaging in newborns diagnosed with encephalopathy. Our investigation identified a statistically significant correlation between chorioamnionitis and hypoxic-ischemic encephalopathy in term newborns ($p = 0.00$).

In accordance with the research conducted by Mir *et al*., our data indicates that persistent inflammation of the chorionic villi correlates with mild forms of encephalopathy ($p = 0.00$). This histopathological lesion diminishes the placental exchange surface, resulting in disruptions to the oxygen and nutrition transfer between the mother and the fetus. Greer *et al*. established that persistent inflammation of high-grade chorionic villi correlates with fetal acidemia ($pH < 7$ in the umbilical artery), serving as a risk factor for neonatal encephalopathy.

Abruptio placentae has been recognized in the literature as a risk factor for cerebral palsy[18]. While placental abruption is mostly a clinical diagnostic, our investigation reveals that histological indicators of abrutio placentae may serve as significant markers and correlate with the occurrence of encephalopathy. In the study by Bingham *et al*., abruptio placentae, while more prevalent in cases of encephalopathy, was not

statistically significant (p = 0.62), reflecting both clinical and placental observations within the examined groups[7].

The updated ISOUG guidelines[19] underscore the significance of ultrasonographic assessment of the placenta and umbilical cord, particularly during the third trimester of gestation. Neonatologists emphasize the importance of transfontanellar ultrasonographic evaluations in both term and preterm neonates to determine therapeutic management and prognosis[20]. A crucial factor in determining the prognosis for neonates with HIE is the early neurological assessment based on general movements examination[21].

The primary drawback of this study is the relatively small sample size of hypoxic-ischemic encephalopathy cases and a control group restricted to neonates in neonatal intensive care. However, the latter underscores the significance of the control group in ascertaining correlations between placental alterations and HIE. The second drawback of our study is the absence of follow-up regarding the neurological development of the enrolled newborns, as follow-up examinations are not conducted in our clinic. A further drawback is the absence of evidence for hypoxic-ischemic lesions through comprehensive imaging studies (MRI), as our clinic lacks the necessary equipment.

This study's merits encompass the clearly delineated criteria for encephalopathy (Sarnat classification) and a systematic classification of placental abnormality. A notable strength of the study is its prospective, population-based design, executed in a tertiary maternity hospital with a significant incidence of complex births. This study's findings indicate that the six types of placental lesions can be utilized to prospectively assess correlations between placental pathology and hypoxic-ischemic encephalopathy with established control groups.

CONCLUSIONS

The primary drawback of this study is the relatively small sample size of hypoxic-ischemic encephalopathy patients and a control group restricted to neonates receiving care in neonatal critical care units. Nonetheless, the latter underscores the significance of the control group in establishing correlations between placental alterations and HIE. The second drawback of our study is the absence of follow-up on the neurological development of the enrolled babies, as follow-up tests are not conducted in our clinic. A further limitation is the absence of evidence of hypoxic-ischemic lesions through comprehensive imaging studies (MRI), as our clinic lacks the necessary equipment.

Conflicts of Interests

The authors declare that they have no conflict of interests.

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