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Placental changes in a group of full-term newborns with hypoxic-ischemic encephalopathy

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ABSTRACT

Objectives. The aim of this study was to present and describe specific macroscopic and microscopic placental findings in patients with hypoxic-ischemic encephalopathy (HIE).
Materials and methods. We conducted an observational prospective study which included 84 patients diagnosed with HIE and had available placental histopathological examination. HIE diagnosis was performed according to Sarnat Score. Both macroscopical and microscopical placental lesions were identified. Patients were divided into 2 groups according to the presence of placental lesions.
Outcomes. Placental lesions were associated with HIE. Patients with both HIE and placental lesions had lower pH value ($p < 0.001$) and lower Apgar scores ($p = 0.001$).
Conclusion. Antenatal placental lesions are present in full-term infants with encephalopathy and seem to define exactly one of the causes of this syndrome.

Keywords: Hypoxic Ischemic Encephalopathy, microscopic placental lesions, macroscopic placental pathology

INTRODUCTION

Hypoxic-ischemic encephalopathy (HIE) is one of the most serious neonatal disorders due to its multifactorial etiology as well as the associated severe neurological sequelae that profoundly influence the development and quality of life of patients and their families. In order to prevent irreversible brain lesions rapid diagnosis and adequate therapeutic approach is mandatory [1].

Maternal medical history, pregnancy complications and physical examination at birth, which integrates both the intrauterine and extrauterine developments should also be evaluated during neurological check-up of the newborn. Fetal brain development can be influenced by genetical and environmental factors [2].

Maternal-placental disease is important to be defined in order to establish the etiology of encephalopathy and the occurrence of brain damage. As such, placental examination should be performed routinely in high-risk pregnancies [3].

OBJECTIVES

The aim of the study was to associate placental pathology with the presence of HIE in full-term neonates. The identification of placental changes is very important in predicting the evolution of the disease and neurological sequelae.

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PATIENTS, MATERIAL AND METHOD

Between 2017 and 2019 we conducted an observational, prospective, non-interventional study in "Filantropia" Clinical Hospital, Bucharest, Romania. The study has the approvement of the Ethics Council of "Filantropia" Clinical Hospital and respected the privacy rules of the patients enrolled. An informed consent agreement was signed by parents/legal guardians before the enrollment of the mother and the newborn. Also the study was conducted with respect of the Declaration of Helsinky on Human Rights.

The study included 84 full-term infants diagnosed with neonatal encephalopathy. They were classified as mild, moderate, or severe by Sarnat Score. The inclusion criteria were new-born with HIE, presence of placental histopathological examination and acceptance to participate in the study. The newborns with congenital anomalies, inborn errors of metabolism and congenital infections were excluded.

After birth, the placentas were examined by a pathologist. Both macroscopic and microscopic lesions were evaluated. These included placental weight, membranes and umbilical cord examination. Microscopic examination was performed with Zeiss Axioscope 5. Six categories of microscopical changes were defined according to Amsterdam Criteria (corioamnionitis, maternal vascular malperfusion, fetal vascular malperfusion, chronic villitis of unknown etiology, delayed maturation of villous and abrupto placentae) [4].

All data were collected from maternal and infant medical records. Statistical analysis was performed with IBM SPSS version 25 (version for Windows) and Excel. P-value <0.05 was considered significant.

RESULTS

The study included 84 patients diagnosed with HIE according to the Sarnat Score, as follows: Sarnat 1 (42.9%), Sarnat 2 (38.1%) and Sarnat 3 (19%).

Patients were divided into 2 groups according to the presence of placental changes. 53 patients with placental pathology (63%) and 31 without changes (37%). Descriptive data about patients are summarized in table 1.

15 patients (41.7%) with Sarnat 1 did not associate placental lesions. 14 patients (43.8%) with Sarnat 2 group did not have any placental abnormalities compared to only 3 patients (12.5%) in the Sarnat 3 group. As such, a statistically significant association between Sarnat scores and placental changes was describe (p = .04), Figure 1.

The characteristics of the membranes and umbilical cord are presented in table 2.

DISCUSSIONS

The etiology of neonatal encephalopathy and the sequelae associated with hypoxic-ischemic injury that occur after full-term birth are heterogeneous and poorly understood. At least three different mechanisms can be distinguished: teratogenic diseases (infections, toxins, food deficiencies or inborn errors of metabolism) that affect the brains' primary development; distant antenatal hypoxic-ischemic lesion leading to brain development abnormalities; and acute hypoxic-ischemic injury that occurs during labor and delivery [5].

Placental pathology has the potential to explain neonatal encephalophaty due to its ability to identify and quantify the distinct pathological processes that occur during pregnancy. Although many studies have investigated maternal risk factors and prenatal events as predictors of neurological outcome in full-term infants, few have addressed the association between placental findings and neurological outcome [6].

Redline et al demonstrated the association of placental injury in cases of cerebral palsy and neurological impairment in full-term infants, although the study was in a small group of 40 patients [7]. As in our study, only placentas from newborns diagnosed with cerebral palsy were analyzed.

TABLE 1. Patients characteristics (g = grams, NS = non-significant)

	Placental pathology (n=53)	Normal placenta (n=31)	p-Value
Gestational age (weeks)	38,04 +/- 1,48	37.48 +/- SD 1.38	NS
Birth weight (g)	3089.25 +/- 597.57g	2931.29 +/- 607.86g	NS
Cesarean section (%)	49.3%	15.4%	.05
Median ventilation duration (days)	3.23 +/- 3.05	1.45 +/- 2.03	.00
Length of hospital stay (days)	19.72 +/- 12.03	13.06 +/- 10.00	.00
Male gender (%)	35.8%	21.5%	NS
APGAR 5 min	4.57 +/- 1.5	5.52 +/- 1.42	.00
Umbilical cord pH	7.03 +/- .09	7.08 +/- .07	.01
Umbilical cord pCO2 (mmHg)	63.2+/-.07	60.5 +/- .05	.00
Umbilical cord base deficit (mmol/L)	-13.4 +/- .01	-10.4 +/- .03	.01

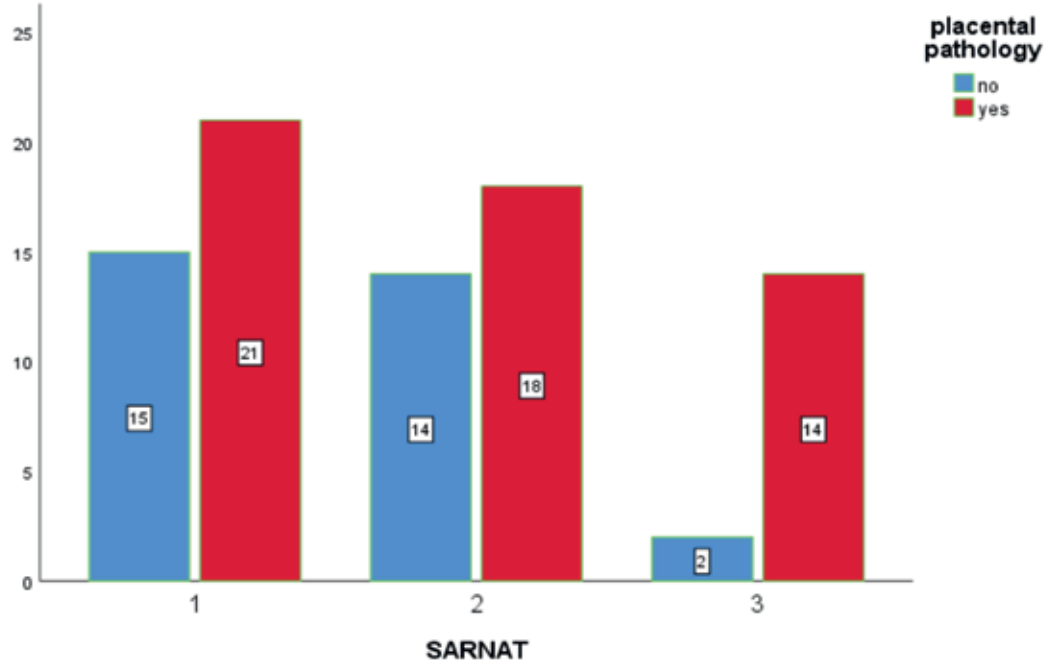

FIGURE 1. Distribution of Sarnat Scores according to the presence of placental changes

TABLE 2. Placental weight, membranes appearance, umbilical cord appearance (g= grams, NS=non-significant)

	Placental pathology (n=53)	Normal placenta (n=31)	p-value
Placental weight (g)	453.42 +/- 89.54	425.32 +/- 90.53	.01
Circumvallate membranes (%)	10 (18.8%)	11 (35.4%)	NS
Unique umbilical artery (%)	25 (47.2%)	11 (35.4%)	NS
Insertion anomalies of the umbilical cord (%)	18 (34.0%)	8 (29.2%)	NS

Our study confirms that severe metabolic acidosis is present in newborns with low Apgar scores at birth, being a statistically significant association between the presence of placental lesions and low pH (p = .01). As Pelman et al. presented, low Apgar scores and metabolic acidosis are not the only independent predictors of neonatal encephalopathy, but they help to identify children who are prone to a poor neurodevelopmental outcome [8].

McIntyre et al showed in a previous study that a large proportion of newborns with normal Apgar score at 5 minutes developed cerebral palsy. As such, there is a great interest to associate the Apgar score with placental changes [9]. In our study, there was a significant association between an Apgar score less than 6 at 5 minutes and presence of placental lesions on histopathological examination (p = .00). Wong et al also stressed upon the need for placental examination in all infants with an Apgar score of less than 6 to 5 minutes and metabolic acidosis, identifying the causes of cerebral palsy in newborns [10].

It should also be noted that in our study a statistically significant association was found between the presence of placental changes in newborns with encephalopathy and the length of hospital stay (p = .00). This implies high hospitalization costs and the predisposition for nosocomial infections of vulnerable patients.

According to the data obtained in our study, placental changes were present mainly in newborns with encephalopathy, especially in Sarnat 2 and 3 classes (p = .04). We did not find an association between placental changes in Sarnat 1 patients (p = .09). This findings explain the subsequent evolution of newborns in which severe neurological sequelae such as cerebral palsy are associated with Sarnat scores 2 and 3.

The uniqueness of our study comes from the inclusion criteria of patients who were strictly diagnosed with neonatal encephalopathy according to the Sarnat classification, as opposed to studies in the literature that also included neonates admitted to intensive care.

The main limitation of this study was that the pathologist was not blinded and was aware of all intrapartum events, the presence / absence of cesarean section, Apgar score, umbilical cord blood pH, Sar-

nat score and neurological changes. Another limitation of our study was the relatively small sample size. Due to the small group size some differences between the two groups did not have statistically significant.

CONCLUSION

In conclusion, placental pathology is present in full-term infants with encephalopathy and seems to define exactly one of the etiology of this syndrome.

Also, according to the data analyzed, full-term patients diagnosed with encephalopathy and placental lesions showed a lower Apgar score in the first five minutes of life, lower pH values in the umbilical cord and a higher Sarnat Score than the newborns with neonatal encephalopathy without placental lesions.

Conflict of interest: none declared
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