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Histological Chorioamnionitis and Lung Damage in Preterm Newborns

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Introduction: Clinical and experimental data suggest that exposure to intrauterine infection is associated not only to lung maturation and reduced risk of respiratory distress syndrome, but also with delayed alveolarization and increased risk of broncopulmonary dysplasia.
e aimed to evaluate the association between histological chorioamnionitis and lung disease in preterm newborns.
Methods: A retrospective study of 452 neonates less than 34 weeks gestational age, delivered at three tertiary medical centers in the north of Portugal, between 2001 and 2002. The association between histological chorioamnionitis and lung damage (respiratory distress syndrome and bronchopulmonary dysplasia) was evaluated through the calculation of odds ratio.
Results: one hundred and twenty five newborns from mothers with histological chorioamnionitis and 327 without the condition. The association between histological chorioamnionitis and respiratory distress syndrome was OR 1.5 (95% CI 0.94 - 2.31). The association between chorioamnionitis and bronchopulmonary dysplasia was OR 2.6 (95% CI 1.16 - 6.03).
The association between histological chorioamnionitis and bronchopulmonary dysplasia when adjusted for gestational age and small for gestational age revealed no statistical significance: OR 1.2 (95% CI 0.51 - 2.95) for any placental finding and OR 1.4 (95% CI 0.46 - 4.09) for funisitis and/ or vasculitis.
Conclusion: In this study we could not confirm a decrease of respiratory distress syndrome in neonates with histological chorioamnionitis nor an association to increased risk for bronchopulmonary dysplasia, as described in some studies.
Key-words: chorioamnionitis; bronchopulmonary dysplasia; respiratory distress syndrome.
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INTRODUCTION

Intrauterine infection contributes to preterm delivery and initiates a complex immune process, the fetal inflammatory response syndrome (1,2).

Clinical observations and experimental data suggest that inflammation is related to the pathogenesis of respiratory distress syndrome and bronchopulmonary dysplasia (3). Indeed, some experimental work suggests that exposure to intrauterine infection is associated not only to lung maturation and a reduced risk of respiratory distress syndrome (4) but also to delayed alveolarization (5) and increased risk of bronchopulmonary dysplasia. However, available epidemiological data do not unanimously support this “early-protection (6-8) , late-damage (9,10) “ scenario.

In this paper we try to evaluate the role of chorioamnionitis in acute and chronic lung disease of the preterm newborn.

METHODS

We conducted a retrospective study of neonates less than 34 weeks gestational age, and respective mothers, delivered at three tertiary medical centers (Hospital de São João, Centro Hospitalar de Vila Nova de Gaia and Maternidade Júlio Dinis) in the north of Portugal, from January 2001 to December 2002.

All maternal, obstetrical and neonatal records were reviewed. Outborns and neonates affected by a TORCH infection, a chromosomal or a major congenital anomaly, and any inborn error of metabolism detected during the neonatal period, were excluded, as well as those whose histological study of the placenta were not available.

Gestational age was assessed by menstrual age, ultrasound examination or the New Ballard Score (11). Small for gestational age were defined as those at birth weight < 10th centile for gestational age, according to Lubchenco‘s fetal growth charts (12).

In the three medical centers, placenta is routinely

submitted for histopathological analysis in all cases of preterm delivery. Histological chorioamnionitis was classified according to the method proposed by Blanc (13).

Antenatal steriod therapy was done with intra-muscular dexamethasone (total dose of 24 mg, divided into two doses given every 12 hours) to promote fetal lung maturation, whenever possible (14) (Betamethasone was not used in the three centers in 2001 and 2002).

Maternal treatment decisions and indicated deliveries or cesarean sections were used at the discretion of the attending obstetrician. At birth all neonates were managed by certified neonatologists and promptly transported to neonatal intensive care units.

Respiratory distress syndrome (hyaline membrane disease) was defined according to Rudolf et al criteria (15). Bronchopulmonary dysplasia was defined as dependency on supplemental oxygen at 36 weeks corrected gestational age and a total oxygen therapy for at least 28 days (16). Proven neonatal sepsis was defined as any systemic bacterial infection documented by a positive blood culture. Hemodynamically significant patent ductus arteriosus was diagnosed on the basis of the echocardiographic findings.

Continuous variables were compared using nonparametric tests (Kruskal-Wallis). Categoric variables were compared through chi square.

The association between histological chorioamnionitis (for any histological finding and for funisitis and/ or vasculitis) and bronchopulmonary dysplasia was evaluated through the calculation of crude and adjusted odds ratio. Logistic regression was used to adjust the association for gestational age and small for gestational age.

RESULTS

From 511 neonates with gestational age under 34 weeks, 452 (M 235 / F 217); birth weigth 1440 (515 - 2620) g; gestacional age 31 (23 - 33) weeks fulfilled the inclusion criteria and were included in the study.

Table 1 compares the obstetrical and neonatal characteristics of the study population according to the presence or absence of histological chorioamnionitis. Neonates in whom histological chorioamnionitis was present

Table 1- **Obstetrical and neonatal characteristics of the study population according to presence of histological chorioamnionitis.**

	histological chorioamnionitis		
characteristics	**absent (n=327)**	**present (n=125)**	**p value**
maternal age (years)			
median (min-max)	29 (16-45)	29 (14-44)	0,463
cesarean			
n (%)	259 (78.7)	70 (56)	<0,001
multiple birth			
n (%)	136 (41.6)	35 (28)	0,01
antenatal steroids (full cycle)			
n (%)	214 (65.4)	79 (63.2)	0,87
gestational age at birth (weeks)			
median (min-max)	31 (23-33)	30 (23-33)	0,0002
birthweigth (g)			
median (min-max)	1450 (540-2620)	1400 (515-2515)	0,344
small for gestational age			
n (%)	49 (15)	5 (4)	0,002
sepsis			
n (%)	73 (22.3)	45 (36)	0,004
patent ductus arteriosus			
n (%)	18 (5.5)	16 (12.8)	0,015
death			
n (%)	24 (7.3)	16 (12.8)	0,1
NICU stay (days)[II]			
median (min-max)	29 (1-190)	33 (4-126)	0,06

NICU - neonatal intensive care unit. [II]deaths exclued

had lower gestational age, higher morbidity, and had a longer hospitalisation period. Table 2 shows the association between chorioamnionitis and acute (respiratory distress syndrome) and chronic (bronchopulmonary dysplasia) lung damage.

Six neonates died in the first 72 hours (3 with chorioamnionitis). Thirty two newborns died before day 28 of life (13 with histological chorioamnionitis) and 37 died before 36 weeks postconceptional age (14 with hitological chorioamnionitis).

Thirty neonates developed bronchopulmonary dysplasia. Neonates that developed bronchopulmonary dysplasia were more immature and presented higher morbidity when compared to those that did not develop the condition (table 3).

Three patients with bronchopulmonary dysplasia died after 36 wk postconceptional age, because of sepsis (2) and respiratory failure (1).

The statistical significance of the association between funisitis and/ or vasculitis and bronchopulmonary dysplasia was similar to that of any placental finding (table 4).

Logistic regression revealed that there is no statistical significance for the association between chorioamnionitis and bronchopulmonar dysplasia when adjusted for gestational age and small for gestational age (table 4).

Risk factors for bronchopulmonary dysplasia in a multivariable logistic regression model are presented in table 5.

DISCUSSION

In this retrospective study, including 452 preterm neonates, we tried to evaluate the role of histological chorioamnionitis in respiratory distress syndrome and bronchopulmonary dysplasia. We tried also to evaluate the association between funisitis with or without vasculitis (considered a marker of the fetal inflammatory response syndrome) and bronchopulmonary dysplasia.

Chorioamnionitis and Respiratory Distress Syndrome

In the Watterberg et al study (17), chorioamnionitis was more common in infants who presented without respiratory distress syndrome and was also significantly associated with the presence of interleukin (IL) (1) in tracheal fluid on day one of intubation. In that study, infants whose mothers had received antenatal steroids were excluded. In our sample, a full cycle of antenatal steroids had been administered in about 65% of the cases.

Previous studies have demonstrated that IL 1(stimulates the release of corticotrophin (18,19), which is expected to enhance the production of cortisol resulting in accelerated lung maturation (20) and decrease the incidence of respiratory distress syndrome.

Also, surfactant production appears to be stimulated by inflammatory challenge more than by glucocorticoid,

Table 2 - **Association between histological chorioamnionitis and acute and chronic lung damage.**

	histological chorioamnionitis			
characteristics	**absent (n=327)**	**present (n=125)**	**odds ratio**	**95% confidence intervals**
respiratory distress syndrome				
n (%)	176 (53.8)	79 (63.2)	1,5	0.94-2.31
surfactant				
n (%)	130 (39.8)	57 (45.6)	1.3	0.82-1.97
mechanical ventilation (ETT)				
n (%)	178 (54.4)	84 (67.2)	1.7	1.08-2.72
mechanical ventilation (days)				
median (min-max)	4 (1-72)	6 (1-186)	2.6	1.17-6.02
oxygen				
n (%)	177 (58.4)	73 (67)	1.4	0.89-2.36
oxygen ≥28 days¶				
median (min-max)	36 (11.7)	30 (26.8)	2.8	1.54-4.96
oxygen at 36 wk and ≥28 days¶				
n (%)	16 (5.2)	14 (12.7)	2.6	1.16-6.03
oxygen at discharge¶				
n (%)	6 (2)	5 (4.6)	2.4	0.61-9.13

ETT - endrotracheal tube. ¶exclued those that died before the considered period.

Table 3 - **Epidemiological and clinical characteristics at 36 weeks postconceptional age according to presence or absence of bronchopulmonary dysplasia.**

	bronchopulmonary dysplasia		
characteristics	**present (n=30)**	**absent (n=387)**	**p value**
gestacional age at birth (weeks)			
median (min-max)	27 (24-31)	31 (23-33)	<0.0001
birth weight			
median (min-max)	888 (590-2620)	1500 (565-2515)	<0.0001
small for gestational age			
n (%)	5 (16.7)	42 (11.1)	0.37
cesarian section			
n (%)	23 (76.7)	280 (72.9)	0.81
multiple birth			
n (%)	6 (20)	153 (39.5)	0.05
antenatal steroids			
n (%)	30 (100) full cycle 20 (66.7)	348 (90) full cycle 247 (63.8)	0.91
sepsis			
n (%)	19 (63.3)	80 (20.7)	<0.0001
patent ductus arteriosus			
n (%)	6 (20)	19 (4.9)	0.006
mechanical ventilation			
n (%)	30 (100)	197 (50.9)	<0.0001
mechanical ventilation (days)			
median (min-max)	37 (1-86)	3 (1-72)	0.00001
NICU stay (days)			
median (min-max)	92 (44-186)	28 (1-190)	<0.00001

NICU - neonatal intensive care unit.

while concurrent exposure to both stimuli do not result in a further increase (21).

In this study we could not confirm a decrease of respiratory distress syndrome or surfactant use in neonates with histological chorioamnionitis. In fact these neonates developed more respiratory distress syndrome (63.2% vs 53.8%) and surfactant use (45.6% vs 39.8%) than those without the condition.

Chorioamnionitis and Bronchopulmonary Dysplasia

Traditionally, bronchopulmonary dysplasia has been viewed as the major adverse outcome of respiratory distress syndrome, ventilation-associated barotrauma and oxygen toxicity. More recently a new bronchopulmonary dysplasia appears (22), frequently in very immature babies without typical respiratory distress syndrome.

Just as the clinical presentation of bronchopulmonary dysplasia has varied over the past years, so too, have its criteria of classification. The more recent definition (oxygen dependency at 36 weeks postconceptional age) appears to be a better predictor of abnormal pulmonary signs and symptoms at two years, than the previously suggested definition (oxygen dependency at 28 days of life), as reflected by positive predictive values of 83% and 38%, respectively (23). Current consensus favours an even wider definition of bronchopulmonary dysplasia as oxygen dependency at 36 weeks postconceptional age plus a total oxygen exposure for at least 28 days (16).

There is increasing evidence that pro-inflammatory cytokines may be a common pathway in lung inflammation, which can result in bronchopulmonary dysplasia (24). Intrauterine inflammation, as evidenced by increased amniotic fluid interleukin (IL) (6), tumour necrosis factor (TNF) alpha, IL 1, and IL 8 (25) and increased umbilical cord blood IL 6 (26), can predict the development of chronic lung disease.

Inflammatory cytokines, specially IL 1, are increased in the tracheal lavage fluid after chorioamnionitis, in the first day after birth in those who develop bronchopulmonary dysplasia (17) suggesting the importance of intrauterine inflammation, perhaps initiated by uteroplacental infection (27).

Postnatal infection or colonisation of the airways may also cause the inflammatory response, which could con-

Table 4 - **Crude and adjusted association between histological chorioamnionitis (any placental finding and funisitis and/ or vasculitis) and bronchopulmonary dysplasia.**

placental histology	crude OR 95% CI	adjusted OR 95% CI**	adjusted OR 95% CI††
chorioamnionitis (any placental finding) (n=125)	2.6 (1.16-6.03)	0.6 (0.53-2.95)	1.2 (0.51-2.95)
funisitis and/or vasculitis (n=44)	2.25 (0.97-6.56)	2.3 (0.78-7.05)	1.4 (0.46-4.09)

*CI - confidence interval; OR - odds ratio. ** adjusted for gestational age; †† adjusted for gestational age and small for gestational age.*

tribute to the development of bronchopulmonary dysplasia (17).

The spectrum of disease in patients with intra-amniotic inflammation is wide (26).

Data on fetal inflammation and bronchopulmonary dysplasia are sparse and some (9,10) have not been able to confirm a late lung damage suggested by others (6-8,17).

Alteration of developmental processes takes time. Currently, only very limited information is available regarding the duration of exposure to infection / inflammation and risk for bronchopulmonary dysplasia.

Some pathologists distinguish between acute and sub-acute (or chronic) chorioamnionitis. In acute chorioamnionitis, well-preserved polymorphonuclear leukocytes are distributed continuously from the intervillous space to the amnion, while subacute chorioamnionitis can be defined as being present when the inflammation is maximum in the amnion, less severe in the chorion and minimal in the intervillous space (28).

Using these definitions, subacute, but not acute, chorioamnionitis is associated with an increased risk for bronchopulmonary dysplasia (28). One interpretation of this finding is that long-standing exposure to antenatal inflammation might be associated with an increased risk for bronchopulmonary dysplasia, while exposure of short duration is not (29).

In this study we were not able to distinguish between acute or subacute chorioamnionitis. Logistic regression revealed no statistical significance for the association between chorioamnionitis and bronchopulmonar dysplasia when adjusted for gestational age (OR 0.6, IC: 0.53 - 2.95).

These results suggest that chorioamnionitis may play a role in the development of pulmonary lesion, but is not an independent risk factor.

In this study, as in other studies, neonates that developed bronchopulmonary dysplasia also presented higher incidences of neonatal morbidity, including sepsis and patent ductus arteriosus, as well as longer mechanical ventilation and hospitalisation periods. These morbidities also play a role in the pathogenesis of bronchopulmonary dysplasia. In fact, bronchopulmonary dysplasia is a multifactorial dependent lesion in which gestational age seems to be of great importance.

Funisitis / Vasculitis and Bronchopulmonary Dysplasia

Among the few available reports only some (26,30), but not all (9) support a positive relationship between fetal vasculitis and bronchopulmonary dysplasia.

In the study of Matsuda T et al (30), significant correlations were found between necrotizing funisitis and bronchopulmonary dysplasia (oxygen requirement at 28 days of age), need for dexamethasone therapy for chronic lung disease, duration of oxygen supplementation and length of hospital stay.

In our study, the association between bronchopulmonary dysplasia and funisitis and/ or vasculitis was similar to that found for any histological finding of chorioamnionitis (OR 2.5, IC: 0.97 - 6.56). Also, logistic regression analysis revealed no statistical significance for the association when adjusted for gestational age (OR 2.3, IC: 0.78 - 7.05), or both, gestational age and small for gestational age (OR 1.4, IC: 0.46 - 4.09), suggesting that these histological findings may play a role in the mechanism of pulmonary lesion, but do not act as an independent risk factor. In this particular case of funisitis and /or vasculitis, the analysis of 44 cases may not be enough for a conclusion. Perhaps larger samples may conduct us to a different result.

We propose that the lung is a potential target organ during the course of the fetal inflammatory response syndrome.

We could not confirm a decrease of respiratory distress syndrome in neonates with histological chorioamnionitis nor an association to increased risk for bronchopulmonary dysplasia. Bronchopulmonary dysplasia is a multifactorial dependent lesion in which gestational age and ventilation length seem to be of great importance.

Table 5 - **Risk factors for bronchopulmonary dysplasia in a multivariate logistic regression model.**

risk factors	adjusted odds ratio	95% confidence interval
gestational age (weeks)	0.7	0.58-0.89
histological chorioamnionitis	1.3	0.54-3.31
sepsis	0.7	0.25-1.88
patent ductus arteriosus	0.8	0.26-2.24
mechanical ventilation > than 7 days	13.5	4.16-43.94

Further studies are required to determine the precise contribution of damaged pulmonary tissue of the fetus to acute respiratory failure of preterm neonates and the subsequent development of bronchopulmonary dysplasia.

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