Caso Clínico
Clinical Case

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Corioamnionite e lesão pulmonar no recém-nascido de extremo baixo peso

Chorioamnionitis and lung damage in the extremely low birth weight infant

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Resumo

Alguns estudos experimentais sugerem que a exposição a infecção intra-uterina associa-se, não só, a maturação pulmonar e menor risco de doença das membranas hialinas, mas também a atraso na formação alveolar e maior risco de displasia broncopulmonar. **Objectivo:** Avaliar a associação entre corioamnionite histológica e lesão pulmonar no recém-nascido pré-termo de extremo baixo peso. **Métodos**: Estudo retrospectivo em 63 recém-nascidos com peso ao nascimento inferior a 1000 g, apropriados à idade gestacional, nascidos em três centros hospitalares do Norte de Portugal, entre

Abstract

Some experimental work suggests that exposure to intrauterine infection is associated, not only, with lung maturation and a reduced risk of respiratory distress syndrome, but also, with delayed alveolarization and increased risk of bronchopulmonary dysplasia. **Aim:** To evaluate the association between histological chorioamnionitis and lung disease in extremely low birth weight preterm infants. **Methods:** A retrospective chart review of 63 less than 1000 g birthweight, appropriated for gestational age neonates, delivered at three tertiary medical centers in the north of Portugal, between

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2001 e 2002. A associação entre corioamnionite histológica e lesão pulmonar (doença das membranas hialinas e displasia broncopulmonar) foi avaliada através do cálculo de *odds ratio*. **Resultados:** Em 32 recém-nascidos as mães apresentaram corioamnionite histológica e em 31 a condição não estava presente. A associação entre corioamnionite histológica e doença das membranas hialinas foi OR 0,23 (IC 95% 0,01 – 2,51). A associação entre corioamnionite histológica e displasia broncopulmonar foi OR 1,61 (IC 95% 0,38 – 6,97). A associação entre corioamnionite histológica e displasia broncopulmonar ajustada para a idade gestacional, gestação múltipla e parto por cesariana não foi estatisticamente significativa: OR 2,66 (IC 95% 0,36 – 19,60) para corioamnionite sem funisite ou vasculite e OR 1,68 (IC 95% 0,25 – 11,18) para corioamnionite com funisite e/ou vasculite. **Conclusão:** Este estudo não nos permitiu confirmar a existência de menor risco de doença das membranas hialinas ou de maior risco de displasia broncopulmonar no recém-nascido pré-termo de extremo baixo peso com corioamnionite histológica.

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Palavras-chave: Corioamnionite, displasia broncopulmonar, doença das membranas hialinas.

2001 and 2002. The association between histological chorioamnionitis and lung damage (respiratory distress syndrome and bronchopulmonary dysplasia) was evaluated through the calculation of crude and adjusted odds ratio. **Results:** There were 32 newborns from mothers with histological chorioamnionitis and 31 without the condition. The association between histological chorioamnionitis and respiratory distress syndrome was OR 0.23 (95% CI 0.01 – 2.51). The association between chorioamnionitis and bronchopulmonary dysplasia was OR 1.61 (95% CI 0.38 – 6.97). The association between histological chorioamnionitis and bronchopulmonary dysplasia when adjusted for gestational age, multiple birth and C-section revealed no statistical significance: OR 2.66 (95% CI 0.36 – 19.60) for chorioamnionitis without funisitis or vasculitis and OR 1.68 (95% CI 0.25 – 11.18) for funisitis and/or vasculitis. **Conclusion:** In this study we could not confirm a decreased risk of respiratory distress syndrome nor an increased risk of bronchopulmonary dysplasia in extremely low birth weight preterm neonates with histological chorioamnionitis

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Key-words: Chorioamnionitis, bronchopulmonary dysplasia, respiratory distress syndrome.

Introduction

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

Clinical observations and experimental data suggest that inflammation plays a role in the pathogenesis of respiratory distress syndrome and bronchopulmonary dysplasia[2]. Indeed, some experimental work suggests that exposure to intrauterine infection is associated not only with lung maturation and a reduced risk of respiratory distress syndrome[3] but also with delayed alveolarization[4] and increased risk of bronchopulmonary dysplasia. However, available epidemiologi-

cal data do not unanimously support this "early-protection[5-7], late-damage[8,9]" scenario. Kent and Dahlstrom[10] concluded that the risk of developing bronchopulmonary dysplasia is not increased following exposure to chorioamnionitis or funisitis in the context of current antenatal steroid and surfactant use. The most significant predictor for developing bronchopulmonary dysplasia is gestational age at the time of delivery.

In this paper we try to evaluate the role of chorioamnionitis in acute and chronic lung disease of the extremely low birth weight neonate.

Material and methods

We conducted a retrospective study on appropriated for gestational age, less than 1000g birthweight neonates, 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.

Gestational age was assessed by menstrual age (women with regular menstrual cycles), ultrasound examination (when a discrepancy of two or more weeks existed between the age derived by menstrual dating and the age derived sonographically, or in the absence of a menstrual date)[11] or the New Ballard Score (in the absence of obstetrical indexes)[12].

Exclusion criteria included: small for gestational age (birth weight < 10th centile of Alexander's fetal growth charts)[13] , because intrauterine growth restriction can be protective against respiratory distress syndrome; outborns; neonates affected by a TORCH infection, a chromosomal or a major congenital anomaly, and any inborn error of metabolism detected during the neonatal period; absence of histological study of the placenta.

In the three medical centers, placenta is routinely submitted for histopathology analysis in all cases of preterm delivery. Histological chorioamnionitis was classified according to the method proposed by Blanc[14] after being analysed by one masked pathologist: stage I – intervilositis; stage II – chorionitis; stage III – chorioamnionitis; funisitis – polymorphonuclear leukocytes in the Wharton's jelly or umbilical vessel walls; vasculitis – polymorphonuclear leukocytes in chorionic or umbilical blood vessel walls.

Antenatal steroid 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[15].

Maternal treatment decisions and indicated deliveries 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[16] (acute respiratory illness characterized by dyspnoea, with a predominantly diaphragmatic breathing pattern, that require oxygen to prevent cyanosis and with a characteristic reticulogranular chest x-ray appearance as a result of widespread atelectasis). Bronchopulmonary dysplasia was defined in neonates dependent on supplemental oxygen at 36 weeks corrected gestational age and a total oxygen therapy for at least 28 days[17]. 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.

Results

Sixty three extremely low birth weight infants [M 34 / F 29; BW 850 (590 – 996) g; GA 26 (23 – 29) wk] were included in the study.

Table I compares the obstetrical and neonatal characteristics of the study population according to the presence or absence of histo-

Table I – Obstetrical and neonatal characteristics of the study population according to presence of histological chorioamnionitis

Characteristics	Histological chorioamnionitis		p value
	Absent (n = 31)	Present (n = 32)	
Maternal age (y) median (min-max)	29 (17-40)	30.5 (14-40)	0.09
Cesarean n (%)	27 (87.1)	14 (43.8)	0.001
Multiple birth n (%)	16 (51.6)	11 (34.4)	0.26
Antenatal steroids (full cycle) n (%)	21 (67.7)	23 (71.9)	0.93
Clinical chorioamnionitis n (%)	0 (0)	4 (12.5)	0.06
Gestational age at birth (wk) median (min-max)	27 (23-29)	26 (23-29)	0.003
Birthweight (g) median (min-max)	880 (590-996)	825 (630-975)	0.07
Sepsis n (%)	17 (54.8)	25 (78.1)	0.09
Patent ductus arteriosus n (%)	7 (22.6)	8 (25.0)	0.94
Neonatal death n (%)	10 (32.3)	9 (28.1)	0.93
NICU stay (days) * median (min-max)	70 (38-117)	74 (58-116)	0.16

NICU – neonatal intensive care unit; * deaths excluded

logical chorioamnionitis. Neonates in whom histological chorioamnionitis was present had inferior rates of cesarian section and multiple birth, presented inferior gestational age, higher morbidity, and had longer hospitalisation period. Table II shows the association between chorioamnionitis and acute (respiratory distress syndrome) and chronic (bronchopulmonary dysplasia) lung damage.

Sixteen 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 III).

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

Logistic regression revealed that there is no statistical significance for the association between chorioamnionitis and bronchopulmonar dysplasia when adjusted for gestational age, multiple birth and C-section (Table IV).

Discussion

In this retrospective study, including 63 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[18], chorioamnionitis was more common in infants who presented without respiratory distress syndrome.

Table II – Association between histological chorioamnionitis and acute and chronic lung damage

Characteristics	Histological chorioamnionitis		Odds ratio intervals	95% confidence	p
	absent (n = 31)	present (n = 32)			
Respiratory distress syndrome n (%)	30 (96.7)	28 (87.5)	0.23	0.01-2.51	0.35
Surfactant n (%)	27 (87.1)	24 (75)	0.44	0.10-1.95	0.37
Mechanical ventilation – ETT (days) median (min -max)	7 (1-71)	14 (1-90)	–	–	0.72
Oxygen n (%)	29 (93.5)	31 (96.9)	2.14	0.14-64.27	0.61
Oxygen ≥ 28 days * n (%)	15/ 23 (65.2)	20/ 24 (83.3)	2.92	0.60-15-07	0.27
Oxygen at 36 wk and ≥ 28 days * n (%)	7/ 22 (31.8)	9/ 23 (39.1)	1.61	0.38-6.97	0.67
Oxygen at discharge * n (%)	3/ 21 (14.3)	3/ 23 (13)	0.90	0.12-6.72	1.00

ETT – endrotracheal tube; * excluded those that died before the considered period

Table III – Epidemiological and clinical characteristics at 36 weeks postconceptional age according to presence or absence of brochopulmonary dysplasia

Characteristics	Bronchopulmonary dysplasia		p value
	Present (n =16)	Absent (n = 29) *	
Gestational age at birth (wk) median (min-max)	26 (24-29)	27 (23-29)	0.35
Birth weight (g) median (min-max)	855 (635-975)	900 (720-996)	0.53
Cesarian section n (%)	12 (75)	20 (69)	0.74
Multiple birth n (%)	3 (18.8)	16 (55.2)	0.04
Antenatal steroids (full cycle) n (%)	11 (68.8)	20 (69.0)	1.00
Sepsis n (%)	12 (75)	21 (72.4)	1.00
Patent ductus arteriosus n (%)	4 (25)	4 (13.8)	0.43
Mechanical ventilation – ETT (days) median (min-max)	35.5 (1-90)	6 (1-40)	0.001
NICU stay (days) median (min-max)	85.5 (59-117)	71 (38-112)	0.01

ETT – endrotracheal tube; **NICU** – neonatal intensive care unit; * excluded those that died before the considered period

Table IV – Crude and adjusted association between histological chorioamnionitis and bronchopulmonary dysplasia

Placental histology	Crude OR 95% CI	Adjusted OR 95%CI *
No inflammation 1	1	
Chorioamnionitis without funisitis or vasculitis	1.39 (0.33-5.90)	2.66 (0.36-19.60)
Funisitis and/or vasculitis	2.00 (0.40-10.11)	1.68 (0.25-11.18)

CI – confidence interval; **OR** – odds ratio; * – adjusted for gestational age, multiple birth and C-section

Chorioamnionitis was also significantly associated with the presence of interleukin (IL) 1β in tracheal fluid on day one of intubation. Previous studies have demonstrated that IL 1β stimulates the release of corticotrophin[19,20]. This hormone would be expected to enhance the production of cortisol resulting in accelerated lung maturation[21] and a decreased incidence of respiratory distress syndrome. Both antenatal inflammation and glucocorticoid exposure appear to improve postnatal lung function[3]. These prominent similarities

between the pulmonary effects of antenatal inflammation and glucocorticoids suggest that they might be biologically related.
Also, surfactant production appears to be stimulated by inflammatory challenge more than by glucocorticoid, while concurrent exposure to both stimuli do not result in a further increase[22].
In this study we could not confirm a statistically significant decrease of respiratory distress syndrome or surfactant use in neonates with histological chorioamnionitis.
In the Watterberg et al study, infants whose mothers had received prenatal steroids were excluded. In our sample, a full cycle of antenatal steroids had been administered in about 65% of the cases. This may explain the different results of our study.

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 to emerge[23], 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. 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[24]. 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[17].
There is increasing evidence that pro-inflammatory cytokines may be a common pathway in lung inflammation, which can result in bronchopulmonary displasia[25]. Intrauterine inflammation, as evidenced by increased amniotic fluid interleukin (IL) 6, tumour necrosis factor (TNF) alpha, IL 1, and IL 8[26] and increased umbilical cord blood IL 6[27] 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[18] suggesting the importance of intrauterine inflammation, perhaps initiated by uteroplacental infection[28].
Postnatal infection or colonisation of the airways may also cause the inflammatory response, which could contribute to the development of bronchopulmonary dysplasia[18].
The spectrum of disease in patients with intra-amniotic inflammation is wide[27].
Data on fetal inflammation and bronchopulmonary dysplasia are sparse and some[8,9] had not been able to confirm a late lung damage suggested by others[5-7,18].
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 present when the inflammation

is maximum in the amnion, less severe in the chorion and minimal in the intervillous space[29]. Using these definitions, subacute, but not acute, chorioamnionitis is associated with an increased risk for bronchopulmonary dysplasia[29]. One interpretation of this finding is that long-standing exposure to antenatal inflammation might be associated with a risk increase for bronchopulmonary dysplasia, while exposure of short duration is not[30].

In this study we were not able to distinguish between acute or subacute chorioamnionitis. In our study, logistic regression revealed no statistical significance for the association between chorioamnionitis and bronchopulmonar dysplasia when adjusted for gestational age, multiple birth and C-section.

These results suggest that chorioamnionitis may play a role in the development of pulmonary lesion, but is not an independent risk factor. In fact, bronchopulmonary dysplasia is a multifactorial dependent lesion in which gestational age seems to be of great importance.

The change in clinical practice to use antenatal steroids more widely, altered antibiotic prescription or increased use of surfactant, may thus have altered the previously recognised association between histological chorioamnionitis and chronic lung disease.

Funisitis/vasculitis and bronchopulmonary dysplasia

Among the few available reports only some[27,31,32], but not all[8] support a positive relationship between fetal vasculitis and bronchopulmonary dysplasia.

In the study of Matsuda T *et al* [31], 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 histological finding of chorioamnitis without vasculitis or funisitis. Also, logistic regression analysis revealed no statistical significance for the association when adjusted for gestational age, multiple birth and C-section, suggesting that this histological findings may play a role in the mechanism of pulmonary lesion, but does not act as an independent risk factor.

Our results are according to those of Kent A *et al* [10], the risk of developing bronchopulmonary dysplasia is not increased following exposure to chorioamnionitis or funisitis in the context of current antenatal steroid and surfactant use. The most significant predictor for developing bronchopulmonary dysplasia is gestational age at the time of delivery.

Conclusions

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.

The results of this study may be a function of a small sample and 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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