Early Human Development 90 (2014) 21–25

Contents lists available at ScienceDirect

Early Human Development

journal homepage: www.elsevier.com/locate/earlhumdev

Placental pathology and neurological morbidity in preterm infants during the first two weeks after birth☆,☆☆

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ARTICLE INFO

Article history:
Received 10 June 2013
Received in revised form 13 November 2013
Accepted 15 November 2013

Keywords:
Placental pathology
General movements
Preterm infants

ABSTRACT

Background: The placenta plays a crucial role during pregnancy and dysfunction causes long-term neurological problems. Identifying placenta-related risks for neurological problems shortly after birth may provide clues for early interventions aiming to improve neurological outcome.
Objective: To determine the association between placental pathology and neurological morbidity in preterm infants during the first two weeks after birth.
Study design: Placentas of 52 singleton, preterm infants (GA: 25–31 weeks, BW: 560–2250 grammes) were examined for histopathology. The infants' neurological condition shortly after birth was determined by assessing the quality of their general movements (GMs): normal, abnormal, or hypokinetic, on days 5, 8, and 15. A motor optimality score (MOS) was also assigned.
Results: Examination of the placentas revealed maternal vascular underperfusion (n = 29), ascending intrauterine infection (AIUI) (n = 19), villitis of unknown aetiology (n = 6), chronic deciduitis (n = 11), foetal thrombotic vasculopathy (FTV) (n = 9), and elevated nucleated red blood cells (NRBCs) as a marker for foetal hypoxia (n = 7). None of the placental lesions were significantly associated with the quality of GMs or MOS.
Conclusions: This study indicated that placental lesions were not associated with infants' neurological condition as measured by the quality of their general movements during the first two weeks after birth.

1. Introduction

Preterm birth is one of the main causes of long-term neurodevelopmental problems in preterm infants [1]. Placental pathology may act as a causative factor of preterm birth, with major implications for the child if placental function is impaired. A previous study suggested that several placental lesions are associated with early neonatal morbidity in preterm infants [2]. We also know that several placental lesions are associated with long-term neurological morbidity [3,4]. These lesions include ascending intrauterine infection, chronic villitis of unknown aetiology, meconium associated vascular necrosis, and foetal thrombotic vasculopathy. The appearance of elevated nucleated red blood cells, which is a marker for foetal hypoxia rather than a placental lesion, is also associated with long-term neurological morbidity [3,4]. What we do not know, however, is whether these same placental lesions are associated with neurological morbidity in preterm infants shortly after birth. Placental dysfunction possibly has its greatest impact shortly after birth. A detailed understanding of the relation between placental lesions and an infant's neurological condition shortly after birth is necessary to identify placenta-related risks for neurological problems and could provide clues for early interventions aiming to improve neurological outcome.

The most reliable method to evaluate the neurological condition of preterm infants shortly after birth is Prechtl's method of assessing the quality of their general movements (GMs) [5,6]. In addition to the qualitative assessment of GMs, a semi-quantitative analysis of several qualitative aspects of GMs is expressed by a motor optimality score (MOS) [7]. The assessment of GMs is a sensitive and non-invasive method with high interobserver agreement (Kappa-value = 0.88) [6]. GMs are predictive of neurological outcome [6].

Abbreviations: AIUI, ascending intrauterine infection; BW, birth weight; FTV, foetal thrombotic vasculopathy; GA, gestational age; GMs, general movements; NRBC, nucleated red blood cells; MVU, maternal vascular underperfusion; MOS, motor optimality score; PPROM, preterm pre-labour rupture of the membranes; SNAPPE, score of neonatal acute physiology perinatal extension; VUE, villitis placenta of unknown aetiology.

☆ All the authors declare that they have nothing to disclose. The study has been approved by the Institutional Review Board, and informed consent was obtained from the parents.

☆☆ Financial support: This study was part of the research programme of the Postgraduate School for Behavioral and Cognitive Neurosciences (BCN), University of Groningen. A.M. Roescher, M.M. Hitzert and E.A. Verhagen were financially supported by a Junior Scientific Master Class grant of the University of Groningen.

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0378-3782/$ – see front matter
http://dx.doi.org/10.1016/j.earlhumdev.2013.11.004

Our objective was to determine whether placental pathology was associated with neurological morbidity in preterm infants during the first two weeks after birth as expressed by GM quality. We hypothesized that in the presence of placental pathology the quality of GMs of preterm infants is poorer and their MOS lower.

2. Methods

2.1. Patient population

Our cohort consisted of 57 preterm, singleton infants. All infants had been admitted to the Neonatal Intensive Care Unit of the Beatrix Children's Hospital in Groningen, the Netherlands. The inclusion criteria were singleton infants with a gestational age (GA) of less than 32 weeks. Exclusion criteria were major chromosomal and congenital abnormalities. We also excluded infants whose placentas were not available for pathological examination ($n = 4$) or if the video recordings to assess GMs on days 5, 8, and 15, were lacking ($n = 1$). Our final study group consisted of 52 preterm singleton infants.

We recorded several clinical characteristics of the infants, including illness severity, based on the Score of Neonatal Acute Physiology Perinatal Extension (SNAPPE) [2].

2.2. Placental pathology

The placentas were examined by a perinatal pathologist (AT) in accordance with the guidelines published by the Royal College of Obstetricians and Gynaecologists and the Royal College of Pathologists in Britain, and the College of American Pathologists [8,9]. With the exception of GA, the pathologist was blinded as to clinical outcome. We included all the placental lesions for which an association with neurological impairment was suggested [3,4]. The lesions were: placental pathology consistent with maternal vascular underperfusion (MVU) [10], ascending intrauterine infection (AIUI) [11], chronic villitis of unknown origin (VUE) [12], chronic deciduitis [13], perivillous fibrinoid [14], foetal thrombotic vasculopathy (FTV) [15], meconium associated vascular necrosis [16], chorioamniotic haemosiderosis [17], elevated nucleated red blood cells (NRBCs) [18], chorangiosis [19], and umbilical cord abnormalities [20]. Definitions and scoring criteria are presented in Table 1.

2.3. Video recording of general movements

We video recorded each infant's general movements on days 5, 8, and 15. Each recording lasted 50 min. The infant lays supine in the incubator wearing only a nappy. We placed the video camera high above the infant at the foot of the incubator so as to obtain an unobstructed view of the infant's entire body and face. The infant could move its limbs and trunk freely. GMs during crying, hiccupping, or while the infant was sucking on a dummy were excluded from the analysis [5,21].

2.4. Analysis of general movements

AMR, MMH, and AFB assessed the quality of GMs according to Prechtl's method [5]. This method assesses the GMs on the basis of visual Gestalt perception. Normal GMs involve the infant's entire body, can last a few seconds to several minutes, and are characterized by a complex and variable sequence of arms, legs, neck, and trunk. GMs are scored as abnormal if they lack complexity, variability, and fluency. There are three types of abnormal GMs that apply to the preterm period: poor repertoire, chaotic, and cramped-synchronized GMs [22,23]. If GMs are absent or very short (<3 s), the infant was assessed as being hypokinetic [7].

A more detailed analysis of GMs is obtained by the motor optimality score (MOS) based on Prechtl's optimality concept. For this purpose, we used a score sheet developed by Ferrari et al. [22] and modified by De Vries et al. [7]. The highest, most optimal score is 18 and the lowest score is 8 [7]. A hypokinetic infant is assigned an 8. The assessors were blinded as to placental lesions.

2.5. Statistical analysis

MOS was taken as our primary outcome measure for calculating sample size. In a previous study the standard deviation of MOS was 3 [7]. With MOS ranging from 8 to 18, we considered a difference of 4.5 as relevant. We expected to find five large categories of placental lesions: MVU, AIUI, chronic deciduitis, FTV, and elevated NRBCs. On average 1 in 4 placentas are affected [2]. We set the level of significance at $\alpha = 0.01$, applying the Bonferroni correction with regard to the five categories of placental lesions. With a power of 0.8 and a ratio of 1 to 4 with regard to the presence of placental lesions, we calculated that we needed to include at least 34 infants for the purpose of our study.

We used SPSS 20.0 software for Windows (SPSS Inc., Chicago, Illinois, USA) for the statistical analyses.

To analyse the course of infants' GM quality and MOS during the study period, we used the chi-square test for trend and Spearman's rho. We used the Wilcoxon signed rank test to analyse the course of the MOS for a specific placental lesion. For these tests $P < .05$ was considered statistically significant.

Table 1
Diagnostic terminology and definition of the placental lesions.

Diagnostic terminology	Definition and scoring criteria
Maternal vascular underperfusion (MVU)	Decidual vasculopathy, eg. incomplete or absent spiral artery remodelling, acute atherosis, fibrinoid necrosis or thrombosis; parenchymal pathology such as placental hypoplasia, increased syncytial knotting, villous agglutination, increased perivillous fibrin, distal villous hypoplasia, infarction, retroplacental hematoma [10].
Ascending intrauterine infection (AIUI)	Acute inflammation of the extraplacental membranes and chorionic plate. Acute chorioamnionitis and chorionitis represent the maternal response; chorionic or umbilical vasculitis represents the foetal response [11].
Villitis of unknown aetiology (VUE)	Chronic lymphohistiocytic inflammation of the stem- and chorionic villi, with or without obliterative vasculopathy of stem villus vessels [12].
Chronic deciduitis	Chronic lymphohistiocytic or plasmacytic inflammation of the decidua [13].
Maternal floor infarction (MFI)/massive perivillous fibrinoid deposition (MPVFD)	Excessive perivillous fibrin deposition, either basally at a thickness of ≥3 mm on at least one slide (MFI) or transmural encasing ≥50% of villi on at least one slide (MPVFD) [14].
Foetal thrombotic vasculopathy (FTV)	Foetal vascular thrombosis, intimal fibrin cushions, fibromuscular sclerosis, hemorrhagic endovasculitis and groups of at least 5 avascular fibrotic villi without inflammation or mineralization and/or adherent thrombi in stem vessels [15].
Meconium associated vascular necrosis	Meconium associated necrosis of smooth muscle cells in the wall of chorionic plate vessels [16].
Chorioamniotic haemosiderosis	Presence of hemosiderophages in the amnion and chorion [17].
Elevated nucleated red blood cells (NRBCs)	Only rare NRBCs are normal after the first trimester. More than an occasionally NRBC was considered as abnormal [18].
Chorangiosis	Diffuse increase in the number of villous capillaries [19].
Umbilical cord abnormalities	Obstruction or disruption of the umbilical cord blood flow (e.g. umbilical cord prolapse, entanglement, knots, disrupted velamentous vessels, hyper/hypo-coiling) [20].