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Episodes of hypocarbia and early-onset sepsis are risk factors for cystic periventricular leukomalacia in the preterm infant

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ABSTRACT

Background: Septic episodes in preterm infants recently have been reported to be associated with periventricular leukomalacia (PVL). The role of hypocarbia as an independent risk factor for PVL in clinical studies raises many questions without conclusive answers.
Aims: To evaluate risk factors for cystic PVL focussing on the influence of hypocarbia.
Study design: Retrospective single centre case-control study.
Subjects: Preterm infants 24 to 35 weeks of gestational age and matched (1:2 for gender, birth year, gestational age and birth weight) controls.
Outcome measures: Multivariate analysis of perinatal factors being associated with cystic PVL diagnosed by serial ultrasound examinations.
Results: Univariate analysis of risk factors revealed lower 5 and 10 min Apgar scores, and higher rates of neonatal seizures, early-onset sepsis, neonatal steroids, respiratory distress syndrome with surfactant replacement therapy, and episodes of hypocarbia significantly being associated with PVL. Multivariate analysis using a logistic regression model revealed early-onset sepsis and hypocarbia being significantly associated with PVL ($p = .022$ and .024, respectively). Lowest $PaCO_2$ values did not differ as did not the duration of hypocarbia, but the onset of hypocarbia was significantly later in PVL cases compared to controls (mean 26 vs. 15 h, $p = .033$). Neurodevelopmental follow-up at a median time of 46 months was poor showing 88% of the cases having an adverse neurological outcome.
Conclusion: We found early-onset sepsis and episodes of hypocarbia within the first days of life being independently associated with PVL.

1. Introduction

Cystic periventricular leukomalacia (PVL) is one of the most severe and frequent cause of cerebral palsy in children surviving preterm birth. The pathogenesis of PVL yet is not completely understood. The majority of the theories consider the necrotic foci to be hypoxic–ischemic lesions, resulting from impaired perfusion at the vascular border zones between ventriculopedal and ventriculofugal arteries, as the latter are poorly developed in preterm infants. Besides periventricular vascular anatomic factors and pressure-passive cerebral circulation the intrinsic vulnerability of cerebral white matter (a particular vulnerability of rapidly differentiating oligodendroglial cells) of preterm infants plays an important role [1]. An alternative view focuses on the role of intrauterine infection and the fetal inflammatory response syndrome [2]. When microorganisms or their antigens gain access to the foetus, they can stimulate the production of cytokines and a systemic response termed foetal inflammatory response syndrome, which has been implicated as a cause of foetal or neonatal injury that leads to damage of the brain and others organs [3,4]. The risk of cerebral palsy is influenced by the extent and site of cyst formation. Extensive occipito-parietal cysts have the worst prognosis, the best being isolated frontal cysts [5].

Early detection of cysts is often associated with chorioamnionitis and premature rupture of the membranes, multiple pregnancy (death of co-twin, placental vascular anastomoses) or antenatal haemorrhage. Other factors that have been reported to be associated with cystic PVL, and some of them are discussed controversially, include asphyxia, perinatal acidosis, respiratory distress, septicaemia and bacterial infections, hyperbilirubinaemia, persistent ductus arteriosus, mode of delivery, preeclampsia, pneumothorax, necrotising enterocolitis, arterial hypotension, and hypocarbia [6,7]. The role of hypocarbia as an independent risk factor for PVL in clinical studies raises many questions without conclusive answers [8].

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The aim of the study was to evaluate risk factors for PVL focussing on the influence of hypocarbia by means of a retrospective case-control study.

2. Patients and methods

This study was a retrospective analysis of all infants with PVL documented by ultrasound scans (US) admitted to the Division of Neonatology of the Department of Pediatrics of the Medical University of Graz, Austria, compared to matched controls between 1999 and 2008. The medical charts, the US and the data from our Ambulatory of Neurodevelopmental Follow-up were reviewed. The study was approved by the local ethic committee (21-051 ex 09/10).

For the *analysis of risk factors* prenatal characteristics including maternal age, number of pregnancy, multiple pregnancy, history of abortion, maternal haemorrhage, preeclampsia/eclampsia, preterm premature rupture of the membranes (PPROM), clinical chorioamnionitis (CCA), abnormal prepartal cardiotocography, breech presentation, caesarean section, perinatal characteristics including maternal steroids, maternal antibiotics, Apgar scores at 1, 5 and 10 min, umbilical artery pH, capillary pH within 30 min after birth, birth weight, small for gestational age (SGA), gender, and postnatal characteristics including asphyxia, early-onset sepsis (EOS), arterial hypotension, hyperbilirubinaemia, intra-/periventricular haemorrhage, persistent ductus arteriosus, respiratory distress syndrome, respiratory support (mechanical ventilation including continuous positive airway pressure ventilation-CPAP), hypocarbia, seizures, and apnoeas infants with diagnosis of PVL were compared with two controls matched for gestational age (±1 week), birth weight (±200 g), sex, and year of birth. If there was no adequate control we recruited controls from the year before or after.

2.1. Definitions of risk factors

Small for gestational age (SGA) was defined as birth weight below 10th percentile. Foetal distress was defined as abnormal cardiotocography and/or meconium stained amniotic fluid. Preeclampsia was diagnosed when a pregnant woman developed high blood pressure (two separate readings taken at least 6 h apart of 140/90 or more) and proteinuria. PPROM was defined as onset before labour. CCA was defined as maternal fever higher than 38 °C together with at least one of the following symptoms: maternal or foetal tachycardia, uterine tenderness, foul-smelling amniotic fluid or maternal leukocytosis/C-reactive protein (CRP) values above 50 mg/L [9]. Maternal steroids included two doses of betamethasone given parenteral to induce lung maturation. Maternal antibiotics included maternal treatment with antibiotics during labour. Asphyxia was characterized by foetal distress, an Apgar score of 5 or less after 5 min, and an umbilical artery pH less than 7.10. Apnoeas were defined as either desaturation below 80% or bradycardia below 80 bpm or both with the need of stimulation or an increase of inspired fraction of oxygen. Arterial hypotension was defined as a mean arterial blood pressure, measured with Dinamap, below 95% limits [10] and requiring treatment. Hyperbilirubinaemia was defined as increased bilirubin values with the need for phototherapy. Neonatal seizures were defined as paroxysmal alterations in neurological function, either subtle, tonic, clonic, or myoclonic, with autonomic nervous system changes and different from the symmetrical tremor of jitteriness that was confirmed in most cases by cerebral function monitoring or EEG. Neonatal steroids were given in case of oxygen dependency>40% or failure to extubate the baby between days 7 and 10 of life. Until 2006 dexamethasone was used and since 2007 treatment was started with hydrocortisone and switched in case of unresponsiveness to betamethasone; duration was always restricted to a seven-day treatment course. Intraventricular haemorrhage (IVH) grades I to III was diagnosed by ultrasound scans (US) and classified according to Papile [11]. Periventricular haemorrhage (IVH grade IV) was not present in the study group. Persisting ductus arteriosus Botalli was always confirmed by echocardiography with need for treatment with ibuprofen. Routinely infants with diagnosis of respiratory distress syndrome (RDS) and treatment with surfactant receive indomethacine prophylaxis for three days. RDS was defined as dyspnoea presenting within 4 to 6 h of delivery, additional oxygen requirement to prevent cyanosis, and reticulogranular chest X-ray appearance. Hypocarbia was defined as an arterial carbon dioxide partial pressure (pCO_2) less than 35 mmHg (<4.67 kPa) for at least 1 h within the first five days of life. Transcutaneous pCO_2 measurement in case of prematurity is not performed at our ward, thus, values derive from repeated arterial blood gas measurements. The shortest time interval in our records between two repeated blood gas measurements was 2 h. In case of normalization of pCO_2 by the second measurement the estimated duration thus was calculated as 1 h. Additionally minimal values, time of onset in hours post partum, duration in hours, repeated episodes, and the total duration of hypocarbic episodes in hours were noted. Usually preterm infants with need for mechanical ventilation have arterial canulas for regular monitoring of blood gases at our ward, and values are documented on separate sheets within the medical records including details on respiratory support (mechanical ventilation and continuous positive airway pressure—CPAP). The diagnosis EOS was divided in blood culture and clinical proven sepsis. Blood cultures were drawn from every patient with suspected infection before starting antibiotic treatment. However, cases with positive microbial growth likely to derive from contamination were not classified as true infections. For clinical EOS at least three out of five clinical signs of sepsis with positive maternal risk factors and/or positive laboratory sepsis screen had to be present within the first 72 h of life [12] with antibiotic treatment for ≥7 days. In all cases diagnosed as having early-onset sepsis CRP values were above 8 mg/L. Clinical signs of sepsis included: a) respiratory symptoms (apnoea, tachypnoea, retractions, cyanosis, respiratory distress); b) cardiocirculatory symptoms (tachy- or bradycardia, arterial hypotonia); c) neurological symptoms (lethargy, irritability, seizures); d) hypo- or hyperthermia (core temperature >38.5 °C or <36.0 °C); e) poor skin colour or prolonged capillary refilling time >2 s [13,14]. Maternal risk factors included PPROM, intra-amniotic infection and fever during labour [15]. For a positive laboratory sepsis screen at least two out of four measured parameters had to be out of normal ranges: CRP >8 mg/L, white blood cell count >34,000/μL or <9000/μL, absolute neutrophil count>14,400/μL or <7000/μL (<2000/μL in the first 24 h of life), immature to total neutrophil ratio >.2 [16,17].

Cranial US scans were routinely obtained in all preterm infants on days 1, 3, 5, and thereafter once a week in case of pathological findings. Real-time US scans were performed with a commercially available unit (Advanced Technology Laboratories Inc., Bothell, WA, USA) using a 7.5 or 8.2 MHz transducer, and multiple images were obtained in the coronal and sagittal planes through the anterior fontanel. The US scans were reviewed for the day of diagnosis of periventricular echodensities (PVE) and cystic PVL, the site of the cysts and the maximum diameter of the largest cysts. PVE were defined as confluent areas of increased echogenicity comparable with the echogenicity of the choroid plexus. Confirmation of the findings in both the coronal and sagittal planes was required before a definitive diagnosis was made. The site of the cysts was described in terms of its being anterior (A)—anterior to the frontal horn of the lateral ventricle, parietal (P)—lateral to the body of the lateral ventricle, or occipital (O)—adjacent and lateral to the occipital horn of the lateral ventricle. The maximum diameters of the largest cysts were measured in both the coronal and sagittal planes and the maximum value was noted [18].

For *neurodevelopmental outcome* infants were examined at the corrected for prematurity age of 4, 8, 12, 18 and 24 months, thereafter once a year. Assessment of outcome was made using the developmental