Original Article
Received on 06.05.2016, **Accepted on** 30.05.2016

Indian Journal of Trauma and Emergency Pediatrics
Volume 8 Number 3, September - December 2016
DOI: http://dx.doi.org/10.21088/ijtep.2348.9987.8316.5

Neonatal Risk Factors for Cerebral Palsy in Very Preterm Babies

Sunil Mhaske*, Bipin Rathod, Liza Bulsara****

Abstract

Objective: To identify neonatal risk factors for cerebral palsy among very preterm babies and in particular the associations independent of the coexistence of antenatal and intrapartum factors. *Design:* Case-control study. *Subjects:* Singleton babies born between January 2015 to December 2015 at less than 32 weeks' gestation who survived to discharge from hospital: 59 with cerebral palsy and 234 randomly selected controls without cerebral palsy. *Main outcome Measures:* Adverse neonatal factors expressed as odds ratios and 95% confidence intervals. *Results:* Factors associated with an increased risk of cerebral palsy after adjustment for gestational age and the presence of previously identified antenatal and intrapartum risk factors were patent ductus arteriosus (odds ratio 2.3; 95% confidence interval 1.2 to 4.5), hypotension (2.3; 1.3 to 4.7), blood transfusion (4.8; 2.5 to 9.3), prolonged ventilation (4.8; 2.5 to 9.0), pneumothorax (3.5; 1.6 to 7.6), sepsis (3.6; 1.8 to 7.4), hyponatraemia (7.9; 2.1 to 29.6) and total parenteral nutrition (5.5; 2.8 to 10.5). Seizures were associated with an increased risk of cerebral palsy (10.0; 4.1 to 24.7), as were parenchymal damage (32; 12.4 to 84.4) and appreciable ventricular dilatation (5.4; 3.0 to 9.8) detected by cerebral ultrasound. *Conclusion:* A reduction in the rate of cerebral palsy in very preterm babies requires an integrated approach to management throughout the antenatal, intrapartum, and neonatal periods.

Keywords: Cerebral Palsy; Very Preterm Babies; Risk Factors; Management.

Introduction

Preterm birth is associated with a clear increase in risk of cerebral palsy [1-5]. During the early 1980s there was an increase in the survival of very preterm babies which was accompanied by a sharp increase in the rate of cerebral palsy in this group. The aetiology of the cerebral damage has been the focus of considerable attention, and emphasis has recently shifted from intrapartum and neonatal factors to antenatal and prenatal events [6-9]. Several hypotheses have been proposed to explain the origins of cerebral palsy in very preterm babies. Firstly, it may be the result of an ischaemic insult in utero leading to both preterm birth and damage to the white matter.[1]This damage may be manifest later as cerebral palsy. Secondly, it may be that immature babies who are particularly vulnerable to cerebral haemorrhage and ischaemia sustain injury as a result of intrapartum and neonatal complications [10]. A third possibility is that cerebral palsy represents the endpoint of a continuum of adverse events which occur throughout the period when the brain is especially vulnerable to ischaemia. These events may occur before, during, and after birth.

A better understanding of the aetiology of preterm cerebral palsy is necessary for preventive strategies and treatments to be developed. In efforts to understand aetiological factors, however, an attempt must be made to disentangle neonatal factors that are causes of cerebral palsy from those that are consequences of earlier disturbances. In a recent case-control study of antenatal and intrapartum risk factors for cerebral palsy in very preterm babies we found associations between chorioamnionitis, prolonged rupture of membranes, and maternal infection and an increased risk of cerebral palsy [8]. We also found associations between pre-eclampsia and delivery without labour and a decreased risk of cerebral palsy. Although adverse antenatal events seem to be important to our understanding of the

Author Affiliation: *Professor & Head, **Resident, Department of Paediatrics, PDVVPF's Medical College, Ahmednagar, Maharashtra.

Reprint Request: Sunil Mhaske, Professor & Head, Department of Paediatrics, PDVVPF's Medical College, Vilad Ghat, Ahmednagar, Maharashtra 414111.
E-mail: liza.bulsara@gmail.com

origins of cerebral palsy, it is likely that these events contribute only to some of the cases of preterm cerebral palsy and that others have their origins in adverse neonatal events or as a result of a continuum of adverse effects throughout antenatal and early neonatal life. To investigate this further we carried out a case-control study on our original study population of singletons born before 32 weeks of gestation that was designed to identify neonatal risk factors for cerebral palsy in very preterm babies and, in particular, the associations independent of the coexistence of previously identified antenatal and intrapartum factors.

Methods

Selection of Subjects

All the selected babies were singletons of less than 32 completed weeks of gestation who survived to hospital discharge, born to mothers in our hospital from January 2015 to December 2015. Multiple births were excluded from this study as current evidence suggests that the risk factors for cerebral palsy in this group may differ from those in singleton births [11]. Gestational age for all groups was estimated by using a combination of menstrual dates and an ultrasound scan performed before 20 weeks' gestation. The scan date was preferred if the menstrual date was uncertain or there was a discrepancy of more than 14 days between the menstrual date and the scan estimate.

Cases

Fifty nine children with cerebral palsy were identified of early childhood impairments [12]. The definition of cerebral palsy used by the register is that of a permanent impairment of voluntary movement or posture presumed to be due to permanent damage to the immature brain.

Controls

A total of 474 babies who survived to discharge and did not develop cerebral palsy were identified from two sources to ensure maximum ascertainment. We predicted that a study population of 59 cases of cerebral palsy with four controls for each case would be large enough to detect for each neonatal factor an odds ratio of 2.5 with 80% power and an α level of 0.05. We wished, therefore, to select approximately half of the potential controls, and 235 controls were thus randomly selected. Controls were selected from the entire geographical population of very preterm babies (<32 completed weeks' gestation) but were not matched with the cases for gestational age. An unmatched case-control study design allowed us to investigate the relation between gestational age and cerebral palsy among very preterm babies.

Data Sources

The neonatal notes of babies included in the study were reviewed by a researcher unaware of the children's outcomes. A detailed dataset was completed, encompassing 52 variables including characteristics at birth; cardiovascular, respiratory, systemic, and metabolic complications; neurological sequelae; and cerebral ultrasound findings. Patent ductus arteriosus (clinical diagnosis supported by cardiac ultrasonography, requiring indomethacin or surgical ligation), hypotension (mean blood pressure <30 mm Hg on at least two occasions), blood transfusion for either anaemia or hypotension, prolonged mechanical ventilation (duration of at least seven days), pneumothorax (diagnosis confirmed by chest *x* ray, requiring insertion of chest drain), and sepsis (clinical diagnosis confirmed with microbiology, requiring antimicrobial therapy) were of special interest. Details of diagnosis, onset, duration, and management were recorded. Birth trauma referred to severe bruising or *X*- ray evidence of a fracture.

Ultrasound data were included if at least two scans were available, the first recorded during the first week of life and the second as near as possible to six weeks after birth. This approach was likely to identify lesions developing in both the early and late neonatal periods. In fact most babies had daily scans for the first week and weekly scans thereafter, with additional scans if clinically indicated. Ultrasound scanners (Advanced Technical Laboratories) used were the ATL 300C until 1988 and the UM4 thereafter with 7.5 MHZ transducer heads. The findings were described by using a classification modified from a data sheet used in a neonatal trial (OSIRIS) [13]. The right and left cerebral hemispheres were described separately in terms of germinal layer or intraventricular haemorrhage, ventricular dilatation, parenchyma echodensity, and parenchyma cysts. Moderate ventricular dilatation was assigned where the ventricular index was above the 97th centile and hydrocephalus was assigned when the dilatation was more than 4 mm above the 97th centile, using a centile chart from an unpublished study by M Levene *et al*. Parenchyma cyst was an umbrella term used for any parenchymal echolucency suggesting a cavity. For the purposes of this study parenchymal echodensities and echolucencies were grouped together and termed parenchyma damage.

Antenatal and intrapartum data had been recorded from the obstetric notes of the mothers; these data were available from our earlier study [8]. Factors included in the logistic regression model as potentially important confounders were antepartum haemorrhage, maternal infection, chorioamnionitis, prolonged rupture of membranes, pre-eclampsia, and the mode of delivery.

Statistical Methods

The odds ratio associated with a given factor estimates the risk of cerebral palsy given the factor relative to the risk of cerebral palsy without the factor. The 95% confidence intervals for crude odds ratios were calculated with the programme CIA [14]. The odds ratios with adjustment for potential confounders were calculated by logistic regression, using the statistical package for the social sciences.

As the study populations were unmatched for gestational age, in the first instance an odds ratio was calculated for each neonatal factor with adjustment for gestational age. Biologically plausible interactions of neonatal factors were investigated by entering variables into a logistic regression model in a forward conditional fashion. Only variables with a strong association with cerebral palsy remained significant ($P<0.05$) independent of the other variables. We included these factors in further regression models, looking for relations between neonatal factors and cerebral palsy independent of the presence of adverse antenatal factors and the delivery mode. There were no more than six variables in a logistic regression model at any one time. Trends in the rates of survival and cerebral palsy among survivors by gestational age were tested by χ^2 tests for trend.

Results

Of 638 singleton babies born alive at less than 32 completed weeks' gestation to mothers in our Hospital 105 died before discharge. The survival rate increased with increasing gestational age ($P<0.0001$; Figure 1) and the incidence of cerebral palsy among survivors decreased with increasing gestational age ($P<0.0001$; Figure 2).

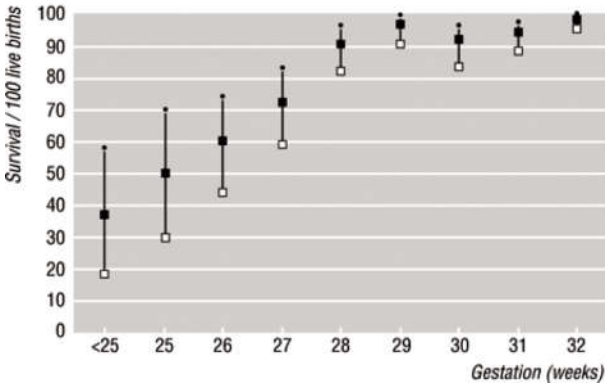

Fig. 1: Survival of very preterm infants in relation to gestational age. Bars are 95% confidence intervals

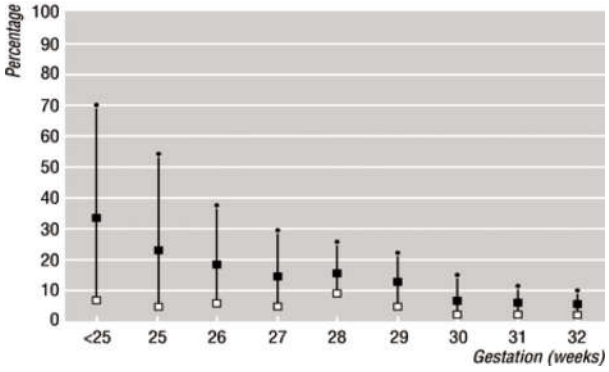

Fig. 2: Percentage of surviving very preterm infants with cerebral palsy. Bars are 95% confidence intervals

Neonatal notes were available for all 59 children with cerebral palsy and 234 controls, a total of 293 babies. Mean gestational age at birth for children with cerebral palsy was 1.3 (95% confidence interval 0.7 to 1.9) weeks less than for the controls (mean 28.6 (SD 2.3; range 24-32) weeks *v* 29.9 (1.9; 23-32) weeks; $P<0.0001$). As this difference in gestational age confounds any comparison between cases and controls, odds ratio estimates were adjusted for gestational age. Further adjustment for birth weight did not affect the results; hence odds ratios are reported without this adjustment.

Cardiovascular and respiratory complications were common among these babies: 232 (79%) had at least one complication. Patent ductus arteriosus, hypotension, transfusion, prolonged ventilation, and pneumothorax were associated with cerebral palsy after gestational age was adjusted for (Table 2). On forward conditional logistic regression of the cardiovascular and respiratory factors described, transfusion and pneumothorax were independently associated with cerebral palsy (odds ratios 2.2 (1.1 to 4.7) and 4.8 (2.2 to 10.8) respectively).

Sepsis, total parenteral nutrition, and hyponatraemia were associated with an increased risk of cerebral palsy (Table 3). The numbers with hyponatraemia were small, however, and this association could be a chance finding. The association

with sepsis was independent of other systemic, cardiovascular, or respiratory complications (odds ratio 3.3 (1.6 to 6.8)). The sequence of antenatal infection and neonatal sepsis was strongly associated with cerebral palsy, but this occurred in only a few subjects (Table 4).

Neonatal seizures occurred in 28 (9.6%) babies and were associated with a highly significant increased risk of cerebral palsy (Table 5). Cerebral ultrasound scans were available for a total of 239 (82%) babies, with a similar proportion for cases and controls. Isolated intraventricular haemorrhage was not associated with an increased risk of cerebral palsy, but there was a strong association between cerebral palsy and parenchymal lesions and ventricular dilatation. Retinopathy of prematurity (all grades) occurred more frequently among cases than controls, but the difference was not significant at the 5% level.

Neonatal Factors Controlled for Antenatal and Intrapartum Events

Patent ductus arteriosus, hypotension, transfusion, prolonged ventilation, pneumothorax, sepsis, hyponatraemia, and total parenteral nutrition were associated with an increased risk of cerebral palsy after adjustment by logistic regression for gestational age, antenatal complications, and the mode of delivery (Table 6). The only antenatal factors of importance in the logistic regression model were chorioamnionitis, any maternal infection, and mode of delivery.

Table 1: Characteristics at birth in very preterm babies with and without cerebral palsy

Characteristics	No (%) cases (n=59)	No (%) controls (n=234)	Odds ratio* (95% CI)
Male sex	37 (63)	133 (57)	1.3 (0.7 to 2.3)
	Small for gestational age‡:		
Birth weight	4 (7)	30 (13)	0.5 (0.2 to 1.5)
Head circumference	3 (5)	31 (13)	0.3 (0.1 to 1.1)
Apgar score at 5 minutes ≤3	5 (8)	4 (2)	5.3 (1.4 to 21)
Cord blood available	24 (41)	128 (55)	0.6 (0.3 to 1.1)
pH umbilical artery ≤7.10‡	6/24 (25)	16/123 (13)	2.3 (0.8 to 6.8)
Birth trauma	13 (22)	35 (15)	1.1 (0.5 to 1.6)

Table 2: Cardiovascular and respiratory factors in very preterm babies with and without cerebral

Factors	No (%) cases (n=59)	No (%) controls (n=234)	Odds ratio* (95% CI)
Patent ductus arteriosus	28 (48)	56 (24)	2.0 (1.1 to 3.7)
Cardiac disease	3 (5)	4 (2)	3.1 (0.6 to 15.3)
Hypotension	21 (36)	33 (14)	2.2 (1.1 to 4.5)
Transfusion	45 (76)	96 (41)	3.2 (1.6 to 6.7)
Thrombocytopenia	2 (3)	11 (5)	0.5 (0.1 to 2.4)
Prolonged ventilation	36 (61)	65 (28)	2.7 (1.3 to 5.7)
Hyaline membrane disease	48 (81)	151 (65)	1.5 (0.7 to 3.1)
Pneumonia	7 (12)	21 (9)	1.0 (0.4 to 2.7)
Recurrent apnoeas	28 (48)	84 (36)	1.0 (0.5 to 1.9)
Pneumothorax	19 (32)	21 (9)	3.4 (1.6 to 7.2)
Bronchopulmonary dysplasia	7 (12)	8 (3)	1.6 (0.5 to 5.1)

Table 3: Systemic and metabolic neonatal factors in very preterm babies with and without cerebral palsy

Factors	No (%) cases (n=59)	No (%) controls (n=234)	Odds ratio* (95% CI)
Renal disease	5 (9)	15 (6)	1.5 (0.5 to 4.4)
Metabolic acidosis	19 (32)	42 (18)	1.7 (0.9 to 3.3)
Sepsis	27 (46)	41 (18)	2.8 (1.5 to 5.5)
Necrotising enterocolitis	8 (14)	16 (7)	1.6 (0.6 to 4.1)
Total parenteral nutrition	29 (49)	42 (18)	3.0 (1.5 to 6.0)
Hyponatraemia	9 (15)	4 (2)	6.8 (1.9 to 24.2)
Hypocalcaemia	6 (10)	14 (6)	1.0 (0.3 to 3.0)
Hypoglycaemia	7 (12)	26 (11)	0.9 (0.3 to 2.2)
Hypothermia	0 (0)	14 (6)	
Umbilical artery catheter	37 (63)	95 (41)	1.6 (0.9 to 3.1)

Table 4: Antenatal infection and neonatal sepsis in very preterm babies with and without cerebral palsy

Factors	No (%) cases (n=59)	No (%) controls (n=234)	Odds ratio* (95% CI)
Chorioamnionitis and neonatal sepsis	5 (8)	2 (1)	7.1 (1.2 to 40.6)
Any maternal infection and neonatal sepsis	11 (19)	9 (4)	4.2 (1.6 to 11.2)

Table 5: Neurological neonatal factors in very preterm babies with and without cerebral palsy

Factors	No (%) cases (n=59)	No (%) controls (n=234)	Odds ratio* (95% CI)
Seizures	20 (34)	8 (3)	10.0 (4.1 to 24.7)
Cerebral ultrasound scan performed	50 (85)	189 (81)	1.3 (0.6 to 2.9)
Intraventricular haemorrhage	13 (26)	48 (25)	1.0 (0.5 to 2.1)
Parenchymal damage‡	30/50 (60)	7/190 (4)	32 (12.4 to 84.4)
Ventricular dilatation‡	28/50 (56)	19/190 (10)	5.4 (3.0 to 9.8)
Retinopathy	7 (12)	5 (2)	3.1 (0.9 to 11.2)

Table 6: Neonatal factors adjusted for gestational age, antenatal factors, and intrapartum factors in very preterm babies with and without cerebral palsy

Factors	No (%) cases (n=59)	No (%) controls (n=234)	Odds ratio* (95% CI)
Patent ductus arteriosus	28 (48)	56 (24)	2.3 (1.2 to 4.5)
Hypotension	21 (36)	33 (14)	2.3 (1.3 to 4.7)
Transfusion	45 (76)	96 (41)	4.8 (2.5 to 9.3)
Prolonged ventilation	36 (61)	65 (28)	4.8 (2.5 to 9.0)
Pneumothorax	19 (32)	21 (9)	3.5 (1.6 to 7.6)
Sepsis	27 (46)	41 (18)	3.6 (1.8 to 7.4)
Hyponatraemia	9 (15)	4 (2)	7.9 (2.1 to 29.6)
Total parenteral nutrition	29 (49)	42 (18)	5.5 (2.8 to 10.5)

Neonatal Complications

Several cardiovascular, respiratory, and systemic factors investigated in this study of very preterm babies were associated with an increased risk of cerebral palsy. In earlier studies, hypotension, transfusion, and patent ductus arteriosus have been associated with periventricular leukomalacia [16-19] an ultrasound finding which predicts later handicap (especially cerebral palsy) more accurately than any other antecedent [21-29]. Pneumothorax and prolonged ventilation have been associated with both periventricular leukomalacia [17,19,30] and cerebral palsy [31,32]. The findings in this study are consistent with these observations, supporting the hypothesis that cardiovascular and respiratory disturbances have a role in the aetiology of cerebral ischaemia in very preterm babies.

A second hypothesis concerns infection, and several studies have shown associations between neonatal sepsis and both periventricular leukomalacia [17,18,19] and cerebral palsy [32]. Our results support this hypothesis as neonatal sepsis and cerebral palsy were strongly associated even after other potentially confounding neonatal complications were adjusted for.

These findings suggest a role for several neonatal complications in the aetiology of cerebral palsy in preterm babies. The difficulty in interpreting these findings, however, lies in determining which neonatal factors are causes of cerebral palsy and which are consequences of earlier disturbances in the antenatal and intrapartum periods and already part of the outcome. Some neonatal factors, such as transfusion, may be markers of severity of neonatal illness or may be the consequence of a disabling cerebral haemorrhage. Our previous study of antenatal and intrapartum risk factors for cerebral palsy in very preterm babies found a strong association between maternal infection and, in particular, chorioamnionitis and an increased risk of cerebral palsy. Maternal infection occurred, however, in only 37% of cases and 17% of controls and is likely to explain only a proportion of cases of preterm cerebral palsy. It is possible, therefore, that the origins of cerebral palsy lie in the neonatal period for a large proportion of very preterm babies. In addition, because of the design of a case-control study it is not possible to predict the timing of cerebral damage in relation to the insult and it is possible that the ischaemia associated with chorioamnionitis is not manifest until the neonatal period and may occur only if the baby suffers an additional further insult in the neonatal period. Our finding that the sequence of maternal infection followed by neonatal sepsis was strongly associated with cerebral palsy lends some strength to the theory of a continuum of insults in the pathogenesis of preterm cerebral palsy. However, this sequence of events affected only a small proportion of the study population.

Cerebral Lesions

As in previous studies of periventricular leukomalacia and cerebral palsy, we found strong associations between neonatal seizures, ultrasonically diagnosed parenchymal damage and ventricular dilatation, and preterm cerebral palsy. It

is possible, of course, that cerebral ultrasound lesions arise incidentally as a result of severe physiological disturbances which in themselves cause cerebral palsy. This is unlikely, though, because ultrasound findings are so much more predictive of cerebral palsy than are cardiorespiratory complications. The statistical power of this study was limited for assessment of the complex interaction of these neurological factors and antenatal, intrapartum and neonatal events, and the results of multivariate analyses could be misleading. These interrelationships could be evaluated, however, with combined data from multiple sources.

Conclusion

We suspect that cerebral palsy has multiple risk factors, both causes and modifiers, but that a proportion of cases of cerebral palsy among very preterm singletons have their origins in the neonatal period. It would seem, therefore, that a major reduction in cerebral palsy among very preterm babies will arise only from an integrated approach throughout the antenatal, intrapartum, and neonatal periods to the management of any baby at risk. The possibility that new neonatal interventions may lead to a reduction or an increase in the frequency of cerebral palsy among very preterm babies can be tested by well designed randomised controlled trials.

References

1. Pharoah P, Cooke T, Cooke R.W., Rosenbloom L. Birthweight specific trends in cerebral palsy. 1990; 65:602–6.
2. Stanley FJ, Watson L.The cerebral palsies in Western Australia: trends, 1968 to 1981. 1988; 158:89–93.
3. Escobar GJ, Littenberg B, Petitti DB. Outcome among surviving very low birthweight infants: a meta-analysis. 1991; 66:204–11.
4. Murphy DJ,Hope PL, Johnson AM. Ultrasound findings and clinical antecedents of cerebral palsy in very preterm infants. 1996; 74: F105–9.
5. Nelson KB, Ellenberg JH. Antecedents of cerebral palsy: univariate analysis of risks1985; 139:1031–8.\
6. Nelson KB, Grether JK. Can magnesium sulfate reduce the risk of cerebral palsy in very low birthweight infants? 1995; 95:263.
7. O'Shea M, Savitz DA, Hage ML, Feinstein KA. Prenatal events and the risk of Subependymal / intraventricular haemorrhage in very low birthweight neonates. 1992; 6:352–62.
8. Murphy DJ, Sellers S, MacKenzie IZ, Yudkin PL, Johnson AM. Case-control study of antenatal and intrapartum risk factors for cerebral palsy in very preterm singleton babies. 1995; 346:1449–54.
9. Grether JK, Nelson KB, Stanley Emery III E, Cummins SK. Prenatal and perinatal factors and cerebral palsy in very low birth weight infants. 1996; 128:407–14.
10. Leviton A, Paneth N. White matter damage in preterm newborns: an epidemiologic perspective 1990; 24:1–22.
11. Petterson B, Nelson KB, Watson L, Stanley F. Twins, triplets and cerebral palsy in births in Western Australia in the 1980s. 1993; 307:1239–43.
12. Johnson A, King R. A regional register of early childhood impairments: a discussion paper. 1989; 11:352–63.
13. OSIRIS Collaborative Group. Early versus delayed neonatal administration of a synthetic surfactant: the judgement of OSIRIS. 1992; 340:1363–9.
14. Gardner M, Altman D. Statistics with confidence: confidence intervals and statistical guidelines. London: BMJ Publications, 1989.
15. Norusis MJ. SPSS advanced statistics guide. Chicago: McGraw Hill, 1985.
16. Calvert SA, Hoskins EM, Fong KW, Forsyth SC. Etiological factors associated with the development of periventricular leukomalacia. 1987; 76:254–9.
17. Sinha SK, D'Souza SW, Rivlin E, Chiswick ML. Ischaemic brain lesions diagnosed at birth in preterm infants: clinical events and developmental outcome. 1990; 65:1017–20.
18. Watkins AMC, West CR, Cooke RWI. Blood pressure and cerebral haemorrhage and ischaemia in very low birthweight infants. 1989; 19:103–10.
19. De Vries LS, Regev R, Dubowitz MS, Whitelaw A, Aber VR. Perinatal risk factors for the development of extensive cystic leukomalacia. 1988; 142:732–5.
20. Graham M, Trounce JQ, Levene MI, Rutter N. Prediction of cerebral palsy in very low birthweight infants: prospective ultrasound study. 1987; 1:593–6.
21. Graziani LJ, Pasto M, Stanley C, Didcock F, Desai H, Desai S, et al. Neonatal neurosonographic correlates of cerebral palsy in preterm infants. 1986; 78:88–95.
22. Low JA, Galbraith RS, Sauerbrei EE, Muir DW, Killen HL, Pater N, et al. Motor and cognitive development of infants with intraventricular hemorrhage, ventriculomegaly, or periventricular parenchymal lesions. 1986; 155:750–6.
23. DeVries LS, Dubowitz V, Lary S, Whitelae A, Dubowitz LMS, Kaiser A, et al. Predictive value of cranial ultrasound in the newborn: a reappraisal. 1985; 2:137–40.
24. Cooke RWI. Early and late cranial ultrasonographic appearances and outcome in very low birthweight

infants. 1987; 62:931–7.

25. Bozynski MEA, Nelson MN, Genaze D, Rosati-Skeritch C, Matalon TAS, Bazan U, et al. Cranial ultrasonography and the prediction of cerebral palsy in infants weighing d"1200 grams at birth. 1988; 30:342–8.
26. Pidcock FS, Graziani LJ, Stanley C, Mitchell DG,Merton D. Neurosonographic features of periventricular echodensities associated with cerebral palsy in preterm infants. 1990; 116:417–22.
27. Weisglas-Kuperus N, Baerts W, Fetter WPF, Sauer PJJ. Neonatal cerebral ultrasound, neonatal neurology and perinatal conditions as predictors of neurodevelopmental outcome in very low birthweight infants. 1992; 31:131–48.
28. Van de Bor M, den Ouden L, Guit GL. Value of cranial ultrasound and magneti resonance imaging in predicting neurodevelopmental outcome in preterm infants. 1992; 90:196–9.\
29. Pinto-Martin JA, Riolo S, Cnaan A, Holzman C, Susser MW, Paneth N. Cranial ultrasound prediction of disabling and non-disabling cerebral palsy at age two in a low birthweight population. 1995; 95: 249–54.
30. Weindling AM, Wilkinson AR, Cook J, Calvert SA, Fok T, Rochefort MJ. Perinatal events which precede periventricular haemorrhage and leukomalacia in the newborn. 1985; 92:1218–23.
31. Marlow N, Hunt LP, Chiswick M. Clinical factors associated with adverse outcome for babies weighing 2000 g or less at birth. 1988; 63:1131–6.
32. Powell TG, Pharoah PO, Cooke RW, Rosenbloom L.. Cerebral palsy in low-birthweight infants. II. Spastic diplegia: associations with fetal immaturity. 1988; 30:19–25.