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Correlation of Brain Ultrasonography Scans to the Neuromotor Outcome of Very-Low-Birth-Weight Infants During the First Year of Life

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Abstract

To evaluate the consistency of the Hammersmith Infant Neurological Examination scores of very-low-birth-weight infants at 6 and 12 months of age and its correlation to cranial ultrasonography findings, we designed a prospective study between January 2005 and January 2008, in the tertiary Neonatal Unit of Aristotle University of Thessaloniki, Greece. All infants enrolled had a cranial ultrasonography performed at term. Preterm infants born at <32 weeks gestation with a birth weight <1500 g were eligible for the study. One hundred seventy-four infants were finally enrolled; out of those, 46 (26%) had an optimal score at 6 and 76 (44%) at 12 months of age. Mean global scores were 61 and 69 at 6 and 12 months, respectively. The Hammersmith Infant Neurological Examination score significantly increased between 6 and 12 months, equally in all ultrasonography groups. The presence of cystic periventricular leukomalacia was associated to lower scores and neurologic impairment.

Keywords

neurodevelopment, neonates, prematurity, ultrasonography

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The advantages of perinatal care have improved the survival rate of very preterm neonates during the last decade.[1,2] However, those infants are at high risk for neurodevelopmental impairment as a consequence of brain lesions acquired in the perinatal period.[3]

Cranial ultrasonography is an easily performed, costless examination that can provide the clinicians with important information about intracranial lesions, associated to the neurodevelopmental outcome of the infant.[4,5]

The Hammersmith Infant Neonatal Examination is a scorable test for examining infants between 2 and 24 months of age, initially developed by Dubowitz and Dubowitz in 1981. The test was updated and standardized in low-risk full-term neonates,[6] providing optimality scores at the age of 12 and 18 months. Further studies[7] expanded the examination in younger ages (from 3 months onwards). Hammersmith Infant Neurological Examination consists of 3 sections (neurologic examination, developmental milestones, and behavior); in particular, the neurologic examination includes the assessment of cranial nerve function, posture, movements, tone, and reflexes/reaction. Among others, the examination has been used to evaluate the neurologic outcome of premature neonates at term corrected gestational age,[8] the outcome of late preterms at term equivalent age,[9] and the small for gestational age neonates at 18 months of corrected gestational age.[10]

The cranial ultrasonography has been correlated to the Hammersmith Infant Neurological Examination scores in order to predict the neuromotor outcome of the neonates in previous studies.[11,12] However, the lack of the Hammersmith Infant Neurological Examination consistency regarding the different cranial ultrasonography findings is remarkable, as there has been no assessment of the progress of the scores between different time frames for different cranial ultrasonography groups.

The aim of the present study was threefold: firstly to assess the neuromotor outcome (evaluated by Hammersmith Infant Neurological Examination score) of an unselected cohort of very-low-birth-weight infants at 6 and 12 months of corrected gestational age, secondly to estimate the progress of the scores during those 6 months, and finally to determine the correlation

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of the term cranial ultrasonography findings to the Hammersmith Infant Neurological Examination score and its progress, at both 6 and 12 months of age.

Methods

Population

The study cohort included preterm infants born at <32 weeks gestation with birth weight <1500 g receiving care in the level 3 neonatal intensive care unit of the Aristotle University of Thessaloniki, Papageorgiou General Hospital, Greece, between January 2005 and January 2008. The infants were enrolled in ultrasonography examination series and a neurodevelopmental follow-up program according to local protocols.

Infants that had cranial ultrasonography performed at term or near term (36-40 weeks corrected gestational age) and attended both 6- and 12-month follow-up appointment were eligible for the study and were used for further analyses.

Infants with genetic or syndromic disease or gross chromosomal abnormalities were excluded from the study, as well as infants that missed either term cranial ultrasonography or one of the follow-up appointments.

Gestational age, birth weight, Apgar scores, mode of delivery, antenatal steroid exposure, preeclampsia, prolonged rupture of membranes, respiratory distress syndrome, patent ductus arteriosus, necrotizing enterocolitis, bronchopulmonary dysplasia, days of hospitalization, and the performance of physiotherapy sessions were the independent variables prospectively recorded.

Case Summary

Cranial Ultrasonography Series. All infants of the study population underwent cranial ultrasonographic scan between 36 and 40 weeks corrected gestational age. The apparatus used was a mechanical sector scanner (Toshiba Ultrasound System, NEMIO SSA-550A) with a 5- or 6-MHz probe. All images were stored on videotapes. Those tapes were reviewed by at least 2 experienced observers and the diagnosis was agreed by consensus.

For the purposes of the study, the cranial ultrasonography findings were classified in the following categories according to current literature[13] (Figure 1).

1. Normal: no detectable lesions on either side of the brain.
2. Periventricular echodensities: increased parenchymal echodensities that did not progress into cysts.
3. Pseudocyst: benign coarctation of the lateral ventricle.
4. Ventricular dilation.
5. Cystic periventricular leukomalacia: cystic lesion within the periventricular white matter, not preceded by hemorrhagic parenchymal infarction.

Hammersmith Infant Neurological Examination. The Hammersmith Infant Neurological Examination was performed at 6 and 12 months corrected age. All infants were examined by a trained neonatologist and a neonatal physiotherapist at both 6 and 12 months of age. The examination was used to assess neuromotor status and was given a global optimality score ($\geq$70 at 6 months[7] and $\geq$73 at 12 months[6]) based on the frequency distribution of the scores of a low-risk full-term population. Each part of the examination (cranial nerve function, posture, movements, tone, reflexes/reactions) was scored separately and then added together, giving the global optimality score. The optimality scores that have been previously defined for each section at the age of 12 months are as follows: cranial nerves function $\geq$ 15, posture $\geq$ 16, movement $\geq$ 6, tone $\geq$ 22, and reflexes/reactions $\geq$ 13.

Statistical Analyses

The data were analyzed using IBM SPSS Statistics, version 20.0, and STATISTICA 8.0. All tests were performed at a significance level (alpha) of 5% using a 2-sided Mann-Whitney test. The general linear model for repeated measures and Tukey's post hoc procedure were used to assess the variability of the Hammersmith Infant Neurological Examination scores over the time frame and the relationship between cranial ultrasonography groups and Hammersmith Infant Neurological Examination scores at 6 and 12 months corrected age. The power of the analyses was estimated using PASS 11.0 (Kaysville, Utah).

Results

Demographics

Of the 298 infants that were born at <32 weeks and <1500 g during the study period, 219 infants met the inclusion criteria. However, 45 of them lost either the first or the second follow-up appointment, and therefore 174 infants were finally enrolled for analyses (Figure 2).

Perinatal and neonatal characteristics of the patients are fully presented in Table 1. Males were 53%, with mean gestational age $29^{+1} \pm 2$ weeks and birth weight 1112 ± 233 g. Preeclampsia or chorioamnionitis were recorded in 24% and 5% of the pregnancies, respectively. Cesarian section was the mode of delivery in 88% of the cases. Antenatal corticosteroids were administered to 84% of the fetuses. Forty-six (26%) neonates were small for gestational age. The majority of the neonates developed respiratory distress syndrome (87%). Patent ductus arteriosus was recorded in 11% of the neonates, whereas 11% of the study group developed necrotizing enterocolitis and 30% bronchopulmonary dysplasia. The mean duration of hospitalization was 60 ± 28 days. One hundred seventeen (67%) infants were enrolled in physiotherapy starting during the hospitalization.

Cranial Ultrasonography Series

Cranial ultrasonography was performed on each infant of the study at 36 to 40 weeks. The majority (128) of the neonates had a normal examination (74%). Periventricular echodensities were noted in 25 neonates (14%), pseudocyst in 3 (2%), ventricular dilation in 12 infants (7%), and cystic periventricular leukomalacia in 6 neonates (3%).

Hammersmith Infant Neurological Examination

The Hammersmith Infant Neurological Examination along with a standardized neurologic examination was performed on 174 neonates at the corrected age of 6 and 12 months. Table 2 demonstrates the mean Hammersmith Infant Neurological

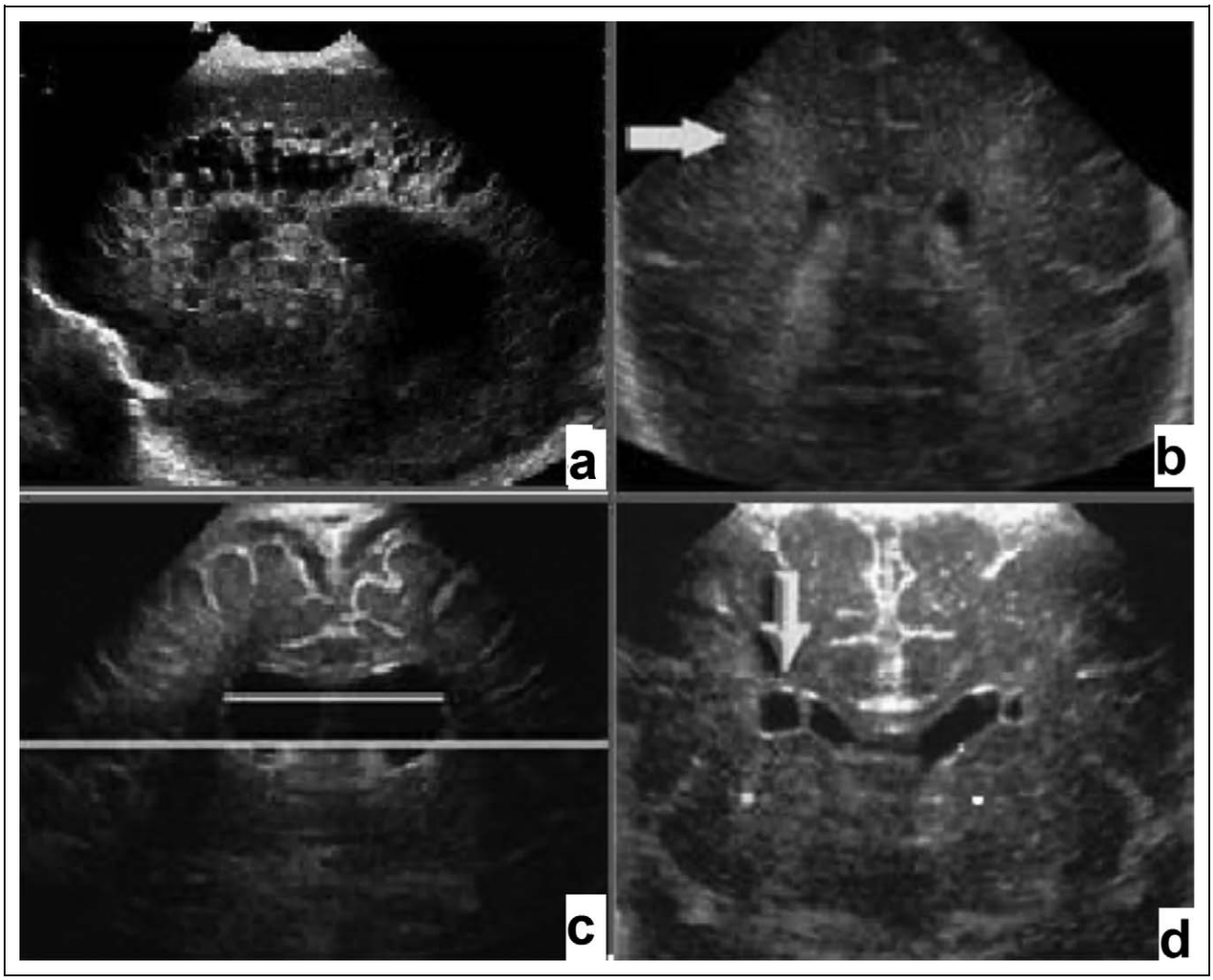

Figure 1. Cranial ultrasonographic scan images demonstrating (A) cystic periventricular leukomalacia, (B) periventricular echodensities, (C) ventricular dilation, and (D) pseudocyst.

Examination scores within the different groups according to the cranial ultrasonography findings and, in total, at both times. The optimality scores are also noted at the end. The percentage of the infants that scored optimally at the 6- and 12-month follow-up appointments is presented in Table 3.

Six-Month Examination

At the age of 6 months, the mean global score of the study group was 61 $\pm$ 9 (37-78), which was within the normal range (61-74), still suboptimal (<70). The lowest mean score (9) was recorded in the reflexes/reactions section and was outside the normal range. Only 46 neonates (26%) had an optimal global score at the age of 6 months.

Twelve-Month Examination

At age 12 months, the study group had a mean score of 69 $\pm$ 8 (31-78), which was within the normal range (63-78) but suboptimal (<73). Suboptimal mean score (14) was documented in the posture section as well, where only 38 neonates (41%) scored optimally. Regarding the global score, only 76 neonates (44%) had an optimal score at that age.

Correlation of Hammersmith Infant Neurology Examination and Cranial Ultrasonography Series

Six-Month Examination. The mean global score at 6 months of age was suboptimal, regardless the cranial ultrasonography findings (Table 2). Neonates however with normal cranial ultrasonography or periventricular echodensities scored within the normal range (62 and 65 respectively) but marginally low, compared to low-risk full-term neonates. Neonates, however, with pseudocyst, ventricular dilation, or cystic periventricular leukomalacia scored outside the normal range (58, 57, and 42, respectively), with the lowest score being of the cystic periventricular leukomalacia group. The development of cystic

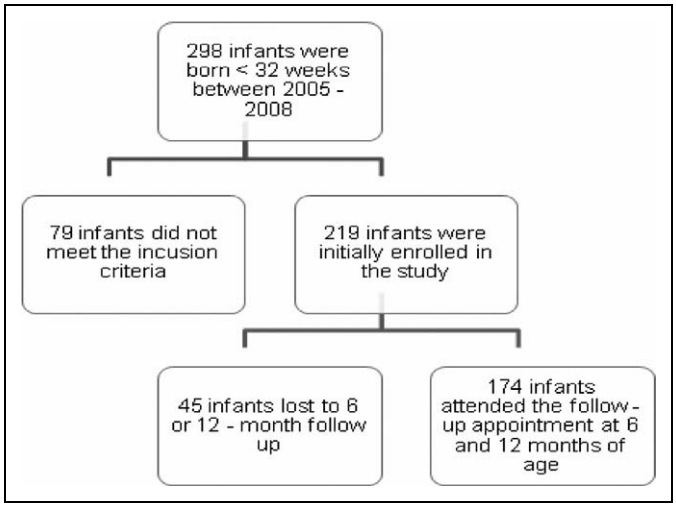

Figure 2. Flow of patients from enrollment to follow-up at 6 and 12 months of corrected gestational age.

periventricular leukomalacia was strongly associated ($P < .001$) to lower Hammersmith Infant Neurological Examination global scores compared to all other groups.

Twelve-Month Examination. At the age of 12 months, all groups apart from cystic periventricular leukomalacia had mean global scores within the normal range, however suboptimal (<73). Furthermore, neonates with cystic periventricular leukomalacia had suboptimal scores in all remaining categories of the Hammersmith Infant Neurological Examination. The cystic periventricular leukomalacia development was strongly associated ($P < .001$) to lower global score (45) in comparison to the normal (70), periventricular echodensities (72), ventricular dilatation (71), and pseudocyst (66) groups.

The overall global score in each different cranial ultrasonography group increased significantly over the time frame (from 6 to 12 months) ($P < .001$), thus performed in an equal way in between the groups ($P > .05$).

Neurologic Outcome. The majority of the infants (157%-90%) had a normal neurologic outcome. However, hemiplegia was noted in 5 neonates (3%), and diplegia or behavior disorders in 4 (2.3%), whereas 2 neonates developed quadriplegia and another 2 visual disorders (1.2%). The cranial ultrasonographic findings and the global score at 6 and 12 months of corrected age for the neonates that developed neurologic sequel is presented in Table 4. Higher global scores at 6 and 12 months was strongly associated to normal outcome ($P < .001$, 95% confidence interval 8.1-16.8, and $P < .001$, 95% confidence interval 11.9-19, respectively).

Discussion

The Hammersmith Infant Neurological Examination has been shown to be a reliable predictor of the motor outcome in 2 years when performed in very preterm infants at the age between 9 and 18 months.[12] Nevertheless, the study of Romeo and coworkers[14] expanded the predicted value of the examination to the outcome at 2 years, as it was performed in preterm neonates at the age of 3, 6, 9, and 12 months of corrected gestational age. Additionally to the previous investigators, in this study we performed the Hammersmith Infant Neurological Examination at both 6 and 12 months of corrected gestational age in a cohort of premature neonates, assessing the consistency of the scores over the time frame between the 2 follow-up appointments.

Table 1. Perinatal characteristics and complications during the neonatal period.

Perinatal/neonatal characteristics	Mean ± standard deviation
Gestational age (wk)	$29^{+1} \pm 2$
Birth weight (g)	1112 ± 233
Gender male, n (%)	93 (53)
Apgar score 1st minute	6.7 ± 1.4
Apgar score 5th minute	8.2 ± .8
Conception—in vitro fertilization, n (%)	80 (47)
Antenatal steroids exposure, n (%)	147 (84)
Prolonged rupture of membranes >24 h, n (%)	47 (27)
Chorioamnionitis, n (%)	9 (5)
Preeclampsia, n (%)	33 (24)
Singleton pregnancy, n (%)	106 (61)
Mode of delivery—caesarian section, n (%)	154 (88)
Intrauterine growth restriction, n (%)	32 (18)
Small for gestational age neonates, n (%)	46 (26)
Respiratory distress syndrome, n (%)	151 (87)
Patent ductus arteriosus, n (%)	20 (11)
Necrotizing enterocolitis, n (%)	20 (11)
Bronchopulmonary dysplasia, n (%)	53 (30)
Days of hospitalization	60 ± 28
Physiotherapy performed, n (%)	117 (67)

The first outcome of the present study is that it highlights the width of the Hammersmith Infant Neurological Examination score (37-78 and 31-78) of the premature infants at 6 and 12 months respectively. In comparison to low-risk full-term neonates, the majority of the preterms (74% at 6 months and 56% at 12 months) had suboptimal scores. Those findings, in correlation to previous studies of Romeo and coworkers[14] and Amess and coworkers,[11] probably demonstrate the level of immaturity of the nervous system rather than a pathologic pathway. Cranial nerves functional scores were normal in all cranial ultrasonographic scan categories in the 6-month follow-up and in all but the cystic periventricular leukomalacia category at 12 months; however, 10% of the infants developed neuromotor impairment (Table 4). The fact that our study population consists of the premature neonates that survived 36 weeks of corrected gestational age and thus have better outcome could probably explain the poor prognostic value of the cranial nerve function score. Posture and reflexes/reaction were the particular sections of the Hammersmith Infant Neurological Examination score that premature infants predominantly scored lower. Haataja and coworkers[7] have noted that even full-term neonates, when assessed at the age of 6 months,

Table 2. Mean Hammersmith Infant Neurological Examination score in study group according to cranial ultrasonography findings and in total as well as optimality scores[6,7] at the age of 6 and 12 months of corrected gestational age.

	Cranial nerves function		Posture		Movement		Tone		Reflexes/reactions		Global	
	6 mo	12 mo	6 mo	12 mo	6 mo	12 mo	6 mo	12 mo	6 mo	12 mo	6 mo	12 mo
Normal	15	15	11	14	5	6	21	24	9	13	62	70
Periventricular echodensities	15	15	12	14	6	6	22	26	11	14	65	72
Pseudocyst	15	15	11	12	4	6	16	22	10	14	58	66
Ventricular dilation	15	15	10	16	6	6	19	24	8	14	57	71
Cystic periventricular leukomalacia	14	10	5	7	4	3	15	16	6	7	42	45
Total	15	15	11	14	5	6	21	24	9	13	61	69
Optimality scores[a]		≥15		≥16		≥6		≥22		≥13	≥70	≥73
Normal range scores[a]		12-15		6-18		3-6		17-24		11-15	61-74	63-78

[a]As defined by the scores of low-risk full-term infants.

Table 3. Percentages (%) of optimal scores in different groups at the 6- and 12- month follow-up.

	Cranial nerves function		Posture		Movement		Tone		Reflexes/ reactions		Global	
	6 mo	12 mo	6 mo	12 mo	6 mo	12 mo	6 mo	12 mo	6 mo	12 mo	6 mo	12 mo
Normal	100	100	21	38	75	87	56	80	30	73	26	43
Periventricular echodensities	96	100	32	47	84	94	68	94	36	77	40	56
Pseudocyst	100	100	50	50	50	100	33	50	0	100	33	0
Ventricular dilation	91	86	18	71	82	100	64	86	18	86	17	58
Cystic periventricular leukomalacia	75	33	0	0	25	0	0	0	0	0	0	0
Total	98	97	22	41	76	87	56	80	29	73	26	44

Table 4. Hammersmith Infant Neurological Examination score and cranial ultrasonography characteristics of neonates with impaired neurologic outcome.

	Cranial ultrasonography	Global score at 6 mo	Global score at 12 mo
Hemiplegia			
Infant 1	Cystic periventricular leukomalacia	40	31
Infant 2	Normal	64	39
Infant 3	Cystic periventricular leukomalacia	37	52
Infant 4	Pseudocyst	50	67
Infant 5	Normal	63,5	73
Diplegia			
Infant 6	Cystic periventricular leukomalacia	38	45
Infant 7	Normal	40	52
Infant 8	Normal	51,5	55
Infant 9	Cystic periventricular leukomalacia	50	57
Quadriplegia			
Infant 10	Cystic periventricular leukomalacia	42	37
Infant 11	Cystic periventricular leukomalacia	42	49
Autism/behavior disorders			
Infant 12	Normal	58,5	52
Infant 13	Periventricular echodensities	56	60
Infant 14	Periventricular echodensities	71	72
Infant 15	Normal	62	77
Visual disorders			
Infant 16	Periventricular echodensities	46	55
Infant 17	Ventricular dilation	37	70

present high variability in the posture, tone, and reflexes/reaction section because of the immaturity of the axial tone and saving reactions. Besides, premature neonates that are born before 34 weeks of corrected gestational age have their normal neuron loss and axon retraction procedure interrupted.[15] Basal ganglia, optic radiation, caudate nucleus, and cerebellum, which are

particularly critical areas for neuromotor control, are exposed to increased vulnerability during the neonatal period.[16] Furthermore, the studies of Mercuri and coworkers[17] and Ricci and coworkers[8] demonstrated that premature infants, when assessed at term, had a wider range of neurologic scores compared to full-term infants. Finally, Romeo and coworkers[9] in a recent study reported that late preterms (born at 35 and 36 weeks of gestational age) had lower scores regarding the tone and head control at term examination, compared to full terms.

The consistency of the Hammersmith Infant Neurological Examination scores of our cohort is another aspect of the present study. All prematures that were finally enrolled had 2 consequent examinations at 6 and 12 months. The examination scores, as evaluated by the general linear model, were significantly increased within that time period, most probably reflecting the ongoing maturation procedure of the nervous system. Yet, physiotherapy was performed on the majority of the infants (67%) and could probably contribute to the increase of the Hammersmith Infant Neurological Examination score and neuromotor outcome, although the current literature indicates that early interventions have greater effect in cognitive development rather than in motor development.[18,19]

The present study, moreover, has evaluated the correlation of the cranial ultrasonography findings at term examination to the Hammersmith Infant Neurological Examination score at both follow-up times. Infants with cystic periventricular leukomalacia had the lowest score. Furthermore, all infants with cystic periventricular leukomalacia had abnormal scores at both the 6- and 12- month follow-up and none survived without neurologic impairment. In former studies, high-risk cranial ultrasonography findings (ie, porencephalic cyst, parenchymal infarction, cystic periventricular leukomalacia, atrophy) have been associated to suboptimal scores at 12 months for preterm neonates.[11,12] Parenchymal lesions (especially bilaterally) have been also associated to poorer outcome in neuromotor ability compared to nonparenchymal lesions.[20] Special precaution however is needed in the evaluation of neonates with intermediate findings (ie, ventricular dilatation, hydrocephalus without atrophy) as those findings can be associated to both normal and abnormal neurodevelopment.[4,21,22] In the present study, neonates with cystic periventricular leucomalacia were more likely to score outside the normal range of the Hammersmith Infant Neurological Examination at both 6 and 12 months. The same group had also significantly lower scores compared to neonates of all other cranial ultrasonography groups (normal, pseudocyst, periventricular echodensities, ventricular dilatation). The correlation of the low Hammersmith Infant Neurological Examination scores to the outcome at 2 years of age had been previously reported by Frisone and coworkers.[12] In the present study, the lower scores at 6 and mainly at 12 months of corrected gestational age were strongly associated to impaired neurologic outcome. Infants with lowest scores had the poorest neurologic outcome, such as quadriplegia or hemiplegia.

The results of our study, however, should be evaluated with caution. Cranial ultrasonography, when performed alone, has limited value in predicting later neuromotor findings. In the present study, 6 of 128 neonates with normal cranial ultrasonography developed neurologic impairment whereas 35 of 46 had abnormal ultrasonography but normal outcome whatsoever. The normal findings of the examination have been associated to confident prediction of reduced risk for neuromotor impairment; however, when abnormalities are detected, the confidence limits are wide.[4,23] Images showing cystic periventricular leukomalacia had pooled positive predictive value of cerebral palsy of 74%, as demonstrated in the meta-analyses of Nongela et al.[4] Furthermore, the pooled positive predicted value of imaging of ventricular dilation or hydrocephalus was lower (22% and 27%, respectively).[24,25] Brain magnetic resonance imaging (MRI) is another useful tool for the prediction of neurologic outcome. Images revealing severe white matter abnormalities have positive predicted value of neurodevelopmental impairment of 35% while the positive predicted value of ventricular enlargement (with ventricular diameter >8 mm) can be as high as 88%.[26] The combination of magnetic resonance imaging in addition to cranial ultrasonography should be considered, as both studies together improve the prediction value of reduced neurologic outcome.

Strength

Our data analyses were 2-sided and performed at a level (alpha) of .05. The power of the analyses to detect differences between the cystic periventricular leukomalacia group and all the other ultrasonography groups was estimated at 95%.

Limitations

The present study is limited regarding the considerable number of neonates that failed to attend either the 6- or the 12-month follow-up appointment. Moreover, the number of cases with pseudocyst and ventricular dilation were low and a larger sample would be required to determine their prognostic value.

Conclusion

In conclusion, our results support the previously demonstrated findings that preterms have mostly suboptimal Hammersmith Infant Neurological Examination scores compared to low-risk full-term infants. Cystic periventricular leukomalacia is a major ultrasonography finding that is strongly associated with low score at both 6 and 12 months of age and poor neurologic outcome.

Acknowledgments

The present study was performed in the level 3 neonatal intensive care unit of Aristotle University of Thessaloniki, Papageorgiou General Hospital, Greece.

Author Contributions

PK, DR, and MK wrote the first draft of the manuscript and performed the data analyses. PP cared for the patients. CT and NN provided their support and mentorship.

Ethical Approval

The study was approved by the Ethical Committees of Papageorgiou General Hospital and Aristotle University of Thessaloniki (# 473).

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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