Early Human Development 90 (2014) 851–856

Contents lists available at ScienceDirect

Early Human Development

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

Neurological examination combined with brain MRI or cranial US improves prediction of neurological outcome in preterm infants

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ARTICLE INFO

Article history:
Received 22 April 2014
Received in revised form 17 September 2014
Accepted 18 September 2014
Available online xxxx

Keywords:
Cerebral palsy
The Dubowitz neurologic examination
The Hammersmith Infant Neurological Examination
Long-term development
Predictive value

ABSTRACT

Background: The predictive value of the combination of neurological examination and brain magnetic resonance imaging (MRI) or cranial ultrasound (cUS) in preterm infants is not known.
Aims: To study the prognostic value of the combination of neurological examination and brain MRI at term equivalent age (TEA) or serial neonatal cUS in very preterm infants for neurosensory outcome at 2 years of corrected age.
Study design: A prospective follow-up study.
Subjects: A total of 216 very preterm infants (birth weight 1132 g [SD 331 g]) born in Turku University Hospital, from 2001 to 2006, were included.
Outcome measures: The Dubowitz neurologic examination and brain MRI were done at TEA, and serial cUS examinations were performed until TEA. The Hammersmith Infant Neurological Examination (HINE) and neurosensory impairments (NSI) were assessed at 2 years of corrected age.
Results: Of all infants, 163 (76%) had one or more deviant neurological items at TEA, and 32 (15%) had the HINE total score below the 10th percentile at 2 years of corrected age. A total of 17 (8%) infants had NSI. Neurological examination at TEA improved the negative and positive predictive values of brain MRI for NSI from 99% to 100%, and from 28% to 35%, respectively, and the negative and positive predictive values of cUS from 97% to 100%, and from 61% to 79%, respectively.
Conclusions: The combination of the Dubowitz neurologic examination and the brain MRI at TEA or serial neonatal cUS provides a valuable clinical tool for predicting long-term neurosensory outcome in preterm infants.
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1. Introduction

The prognostic value of neonatal brain magnetic resonance imaging (MRI) findings on the long-term developmental outcome of preterm infants has been debated. The current practice in neonatal care includes most commonly only cranial ultrasound (cUS) imaging. MRI has potentially better prognostic value compared to cUS providing more information especially on the white matter and cerebellum. We have previously reported the positive (PPV) and negative (NPV) predictive values of brain pathologies on MRI at term equivalent age (TEA) on neurodevelopmental impairments in a cohort of 217 very low birth weight (VLBW)/very low gestational age (VLGA) infants [1]. Normal MRI findings had NPV of 99.2% on cerebral palsy (CP), but the PPV of major brain pathologies remained low being 6.1% and 44.0% for one or several major pathologies, respectively. We emphasized that MRI findings should always be interpreted in parallel to the clinical information.

The Dubowitz neurologic examination [2,3] is widely used both clinically and in research. The assessment method and the most frequent findings in low-risk full term infants have been described in detail previously [3]. The intra and inter-observer reliabilities of the examination are also known [4]. The Dubowitz neurologic examination can also be used as a quantitative measure. However, the total optimality score (the sum of the optimality scores of individual test items) considered as normal for full-term infants [3] cannot be applied to VLBW preterm infants because the variation in neurological findings at TEA in low-risk preterm infants is much wider compared to term infants [5]. The norms for low-risk preterm infants at TEA have been published in a European multicentre study [6].

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http://dx.doi.org/10.1016/j.earlhumdev.2014.09.007
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The Hammersmith Infant Neurologic Examination (HINE) [7] is based on the same principles as the Dubowitz neurologic examination. The test has been standardized for full-term infants between 12 and 18 months of age [7] and has been shown to be a reliable prognostic assessment tool also for VLBW infants who have a high risk for developmental impairments [8,9].

Our aim was to study the combined prognostic value of neurological examination and brain MRI at TEA or serial neonatal cUS in very preterm infants using results of neurological examination and prevalence of neurosensory impairment (NSI) at 2 years of corrected age as endpoints. We hypothesized that adding the information of neurological examination to the information from brain MRI or cUS yields better PPV and NPV compared to either of these alone.

2. Material and methods

2.1. Participants

This study is part of the multidisciplinary PIPARI Study (the development and functioning of Very Low Birth Weight infants from infancy to school age), a prospective study of VLBW or VLGA infants born to Finnish- or Swedish-speaking families between 2001 and 2006, in the Turku University Hospital, Finland. The inclusion criterion was a birth weight ≤1500 g in preterm infants born <37 gestational weeks, from 2001 to the end of 2003. From the beginning of 2004, the inclusion criteria were broadened to include all infants born below the gestational age of 32 weeks, regardless of birth weight. The flow chart of the participants is shown in Fig. 1. All parents gave informed consent for the follow-up study. The PIPARI Study protocol was approved by the Ethics Review Committee of the Hospital District of the South-West Finland in December 2000.

2.2. Magnetic resonance imaging of the brain

The brain MRI was performed at TEA with an open 0.23-T Outlook GP (Philips Medical, INC, Vantaa Finland) (infants born between 2001 and 2003, n = 119) that was upgraded to the 1.5-T Philips Intera (Philips Medical Systems, Best Netherlands) (infants born between 2004 and 2006, n = 97). One neuroradiologist (R.P.) analyzed all the images and was blinded both to the clinical information and to the result of the cUS examinations of the infant. The MRI findings were categorized into three groups: normal findings consisted of normal brain anatomy (cortex, basal ganglia and thalami, posterior limb of internal capsule, white matter, germinal matrix, corpus callosum and posterior fossa structures), width of extracerebral space <5 mm, ventricular/brain (V/B) ratio <0.35 and no ventriculitis; minor pathologies consisted of consequences of intraventricular hemorrhage grades 1 and 2, caudothalamic cysts, width of the extracerebral space of 5 mm and V/B ratio of 0.35; major pathologies consisted of consequences of intraventricular hemorrhage grades 3 and 4, injury in cortex, basal ganglia, thalamus or internal capsule, with injury of corpus callosum, cerebellar injury, white matter injury, increased width of extracerebral space >5 mm, V/B ratio >0.35, ventriculitis or other major brain pathology (infarcts). [1] The infants were categorized into three groups (normal, minor brain pathologies, and major brain pathologies) based on the MRI findings at TEA [10] to evaluate the relation between brain pathology and neurosensory outcome.

2.3. Cranial ultrasound

cUS examinations were performed at 3 to 5 days, at 7 to 10 days, at 1 month of age, monthly thereafter until discharge from the hospital and at TEA. The cUS examinations were performed with a 7-MHz vector transducer (Sonos 5500 Hewlett-Packard, Andover, Mass). Intraventricular hemorrhages were classified from grades 1 to 4 [11]. The cUS examination at TEA was performed with a 7.5-MHz vector transducer (Aloka SSD 2000, Aloka Co., Ltd., Tokyo, Japan) from January 2001 to August 2002 and an 8-MHz vector transducer (General Electric Logic 9 [General Electric, Waukesha, WI]) from September 2002 to March 2007. The cUS examination at TEA was performed by a pediatric radiologist blinded both to the clinical information and to the result of the MRI examination of the infant. The infants were categorized into three groups (normal,

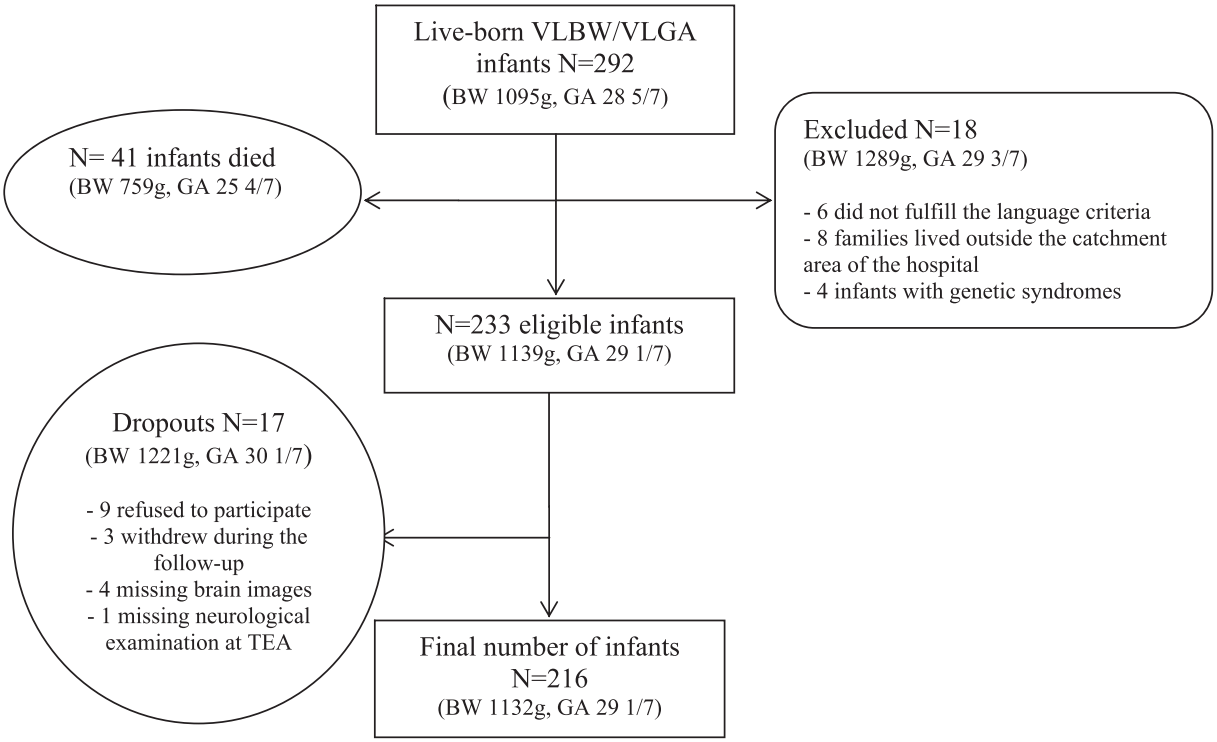

Fig. 1. The flow chart of the participants, mean birth weights (BW) and gestational ages (GA) in weeks.

minor brain pathologies, and major brain pathologies) according to the most serious findings on cUS examinations. [12] The division into these groups was done as previously described [13].

2.4. Neurosensory outcome

Neurological examination at TEA was performed by an experienced physician and physiotherapists, using a standardized proforma of the Dubowitz neurologic examination [4]. It includes 34 qualitative and quantitative items for preterm and term infants with measurement subscales of tone and posture (10 items), tone patterns (5 items), reflexes (6 items), spontaneous movements (3 items), abnormal signs (3 items), and behavior (7 items). The assessment proforma consists of 5 alternative findings for each of the items, and the examiner is supposed to circle the one that corresponds most closely to the infant's performance. The deviant items are defined according to the gestational age specific norms [6]. The two subgroups with the lowest gestational ages (infants born <25 weeks and between 25 0/7 and 27 6/7 weeks) were assessed according to same criteria as well as the two subgroups with the highest gestational ages (infants born between 33 0/7 and 34 6/7 weeks and ≥35 weeks). The cut-off value for a deviant result in the neurological examination was set at ≥1 because even a single deviation from the TEA norm reference [6] in the neurological examination indicated an increased risk for later impairment. Neurological development was reassessed at 2 years of corrected age by an experienced physician and physiotherapists, using the HINE [7]. It consists of 37 items that are further divided into three sections: cranial nerve function, posture, movements, tone and reflexes (first section of 26 items), description of motor development (second section of 8 items), and description of behavioral state of the infant during examination (third section of 3 items). All the item scores in the first section can be summed up yielding a maximum score of 78. The optimal total scores for full-term infants are ≥73 and ≥74 at 12 and 18 months of age, respectively [7]. A cut-off score of >70 was used for this preterm population. We defined the cut-off as the 90th percentile of the healthy preterm infants (i.e. brain MRI normal or with minor pathologies and no NSI), as there are no norms for preterm infants at 2 years of corrected age.

The diagnosis of CP including the grading of severity by Gross Motor Function Classification System (GMFCS) [14] was ascertained by one child neurologist (L.H.) at 2 years of corrected age after a systematic clinical follow-up. Severe hearing impairment was categorized as a hearing impairment with a cut-off of 40 dB or hearing loss requiring amplification in at least one ear, and severe visual impairment was determined as a visual acuity <0.3, or blindness [1,10]. NSI included at least one of the following findings: CP, severe hearing impairment or severe visual impairment.

2.5. Statistical analysis

Univariate associations between either brain MRI or cUS and continuous response variables were studied using a linear model. This linear model was also used to study the association between the Dubowitz neurologic examination at TEA and the HINE at 2 years of corrected age. The associations were further studied using either MRI or cUS and the Dubowitz neurologic examination as predictor variables of the HINE. The associations between the Dubowitz neurologic examination at TEA and NSI at 2 years of corrected age were studied using logistic regression analysis. The association was further studied controlling for either brain MRI or cUS. All statistical models were fitted using the scores of the Dubowitz neurologic examination and the HINE as continuous variables, but descriptive statistics are also shown for dichotomized values of the two variables. Univariate associations between the subscales of the Dubowitz neurologic examination and response variables were studied using Pearson correlation for the HINE and point biserial correlation for NSI. Statistical analyses were done using SAS for Windows version 9.3. p-Values below 0.05 were considered as statistically significant.

The NPV was defined as the percentage of children with no deviant findings in the Dubowitz neurologic examination and no or minor brain pathologies either in the brain MRI or cUS resulting in a developmental outcome without NSI at 2 years of corrected age. The PPV was defined as the percentage of children with one or more deviant findings in the Dubowitz neurologic examination and major brain pathologies either in the brain MRI or cUS resulting in an abnormal developmental outcome with NSI.

3. Results

The neonatal characteristics of the 216 preterm infants are shown in Table 1. All the infants were examined by brain MRI and serial cUS. The findings are shown in Table 2. All the infants were examined at TEA and 208 (96.3%) were examined at 2 years of corrected age. Of all the infants, 14 (6.5%) had CP and 4 (1.9%) had severe hearing impairment. There were no children with severe visual impairment.

3.1. The Dubowitz neurologic examination at term equivalent age

The gestational age subgroups are shown in Table 1. The mean postmenstrual age of the infants at the time of examination was 40 weeks (SD 2.5 days, [38 5/7, 42 1/7]). The mean number of deviant items in the Dubowitz neurologic examination was 2.0 (SD 2.1, [0.0, 13.0]). The number of deviant items was 1.8 (SD 1.8, [0.0, 9.0]) in the infants with normal MRI findings, 1.8 (SD 2.0, [0.0, 10.0]) in the infants with minor MRI pathologies, and 2.5 (SD 2.6, [0.0, 13.0]) in the infants with major MRI pathologies. The number of deviant items was 1.6 (SD 1.7, [0.0, 9.0]) in the infants with normal cUS findings, 2.4 (SD 2.4, [0.0, 13.0]) in the infants with minor cUS pathologies, and 2.3 (SD 2.0, [0.0, 6.0]) in the infants with major cUS pathologies.

Fifty-three (24.5%) of the infants had no deviant items. Of these infants, brain MRI was normal in 32 (60.4%), 9 (17.0%) had minor pathologies, and 12 (22.6%) major pathologies. cUS was normal in 35 (66.0%) of these infants, 14 (26.4%) had minor pathologies, and 4 (7.6%) had major pathologies, respectively.

There wasn't any single test item which alone correlated significantly with the HINE total scores or NSI at 2 years of corrected age. The subscales that correlated with the HINE total scores were tone patterns ($r = -0.25$, $p < 0.001$), posture and tone ($r = -0.18$, $p = 0.01$) and behavior ($r = -0.13$, $p = 0.07$). The same subscales correlated with NSI: tone patterns ($r = -0.18$, $p = 0.01$), posture and tone ($r = -0.13$, $p = 0.06$) and behavior ($r = -0.19$, $p = 0.01$).

Table 1
Neonatal characteristics of the VLBW or VLGA infants (n = 216).

Characteristics	Data
Birth weight, mean (SD) [minimum, maximum], g	1132 (331) [400, 2120]
Gestational age at birth, mean (SD) [minimum, maximum], week	29 1/7 (2 5/7) [23 0/7, 35 6/7]
Males, females, n (%)	121 (56.0), 95 (44.0)
Cesarean section, n (%)	133 (61.6)
Small for gestational age, n (%)	81 (37.5)
Bronchopulmonary dysplasia, n (%)	28 (13.0)
Sepsis, n (%)	35 (16.4)
Necrotizing enterocolitis, surgical, n (%)	10 (4.7)
Retinopathy of prematurity, laser treated, n (%)	8 (3.8)
Gestational age subgroups, n (%)	
<25 weeks	15 (6.9)
25 0/7–27 6/7 weeks	55 (25.5)
28 0/7–29 6/7 weeks	61 (28.2)
30 0/7–31 6/7 weeks	56 (25.9)
32 0/7–34 6/7 weeks	26 (12.0)
≥35 weeks	3 (1.4)

Table 2
Brain MRI and cUS findings, n (%).

	MRI	cUS
Normal findings	120 (55.6)	113 (52.3)
Minor pathologies	38 (17.6)	85 (39.4)
Major pathologies	58 (26.9)	18 (8.3)

3.2. The Hammersmith Infant Neurological Examination at 2 years of corrected age

Mean age at examination time was 2 years of corrected age (SD 9 days, [−71 days, +60 days]). The mean total score of the examinations was 72.9 (SD 5.6, [38.0, 78.0]).

The Dubowitz neurologic examination was significantly related to the variation in the HINE total scores ($R^2 = 0.04$, $b = -0.6$, $p = 0.003$). The NPV of no deviant items in the Dubowitz neurologic examination for HINE total score >70 was 88.5%, and the PPV of one or more deviant items for total score ≤70 was 16.7%.

Brain MRI explained 11.9% of the variation in the HINE total scores ($p < 0.0001$). Major brain pathologies on MRI reduced the HINE total scores compared to normal findings ($b = -0.7$ for minor pathologies and $b = -4.5$ for major pathologies, respectively). cUS explained 13.2% of the variation in the HINE total scores ($p < 0.0001$). Major brain pathologies on cUS reduced the HINE total scores compared to normal findings ($b = -1.4$ for minor pathologies and $b = -7.9$ for major pathologies, respectively).

One hundred and seventy-six (84.6%) of the children had HINE scores >70. Of these infants, brain MRI was normal in 108 (61.4%), 31 (17.6%) had minor pathologies, and 37 (21.0%) had major pathologies. cUS was normal in 97 (55.1%) of these infants, 71 (40.3%) had minor pathologies, and 8 (4.6%) had major pathologies, respectively.

The NPV of normal findings or minor pathologies on brain MRI for the HINE scores >70 was 90.3%, and the PPV of major pathologies for total score ≤70 was 31.5%. The NPV of normal findings or minor pathologies on cUS for the HINE scores >70 was 87.1%, and the PPV of major pathologies for total score ≤70 was 46.7%. Neurological examination and brain MRI at TEA together explained 14.9% of the variation in the neurological examination at 2 years of corrected age. Neurological examination and cUS together explained 17.2% of the variation in the neurological examination at 2 years of corrected age. Thus neurological examination at TEA improved the predictive value of MRI (R^2 change = 0.03, $p = 0.01$) and cUS (R^2 change = 0.04, $p = 0.002$). The PPV improved to 35.7% (MRI) and to 63.6% (cUS), and the NPV of 90.3% (MRI) and 87.1% (cUS) remained the same (Table 3).

3.3. Neurosensory impairment

A total of 17 (7.9%) infants had NSI at 2 years of corrected age. Brain MRI was normal in 1 (5.9%) of these infants, none had minor pathologies, and 16 (94.1%) had major pathologies. cUS was abnormal in all of these infants, 6 (35.3%) had minor pathologies, and 11 (64.7%) had major pathologies. All the children with NSI had abnormal result in the Dubowitz neurologic examination at TEA: five infants (29.4%) had 1 deviant item, two infants (11.8%) had 2 deviant items, three infants (17.7%) had 3 deviant items, two infants (11.8%) had 4 deviant items, one infant (5.9%) had 5 deviant items, three infants (17.7%) had 6 deviant items, and one infant (5.9%) had 13 deviant items. A higher number of deviant items increased the risk for NSI (OR = 1.4, CI 95% 1.1–1.6, $p = 0.002$), and the association remained when controlling for either brain MRI (OR = 1.3, CI 95% 1.0–1.7, $p = 0.03$) or cUS findings (OR = 1.4, CI 95% 1.1–1.9, $p = 0.005$). The NPV of no deviant items in the Dubowitz neurologic examination for development without NSI was 100%, and the PPV of one or more deviant items for NSI was 10.4%. Neurological examination improved the NPV and PPV of brain MRI from 99.4% to 100.0%, and from 27.6% to 34.8%, respectively (Table 3). Neurological examination improved the NPV and PPV of cUS from 97.0% to 100%, and from 61.1% to 78.6%, respectively (Table 3).

All infants with CP had at least one deviant item in the Dubowitz neurologic examination (Table 4). A higher number of deviant items increased the risk for CP (OR = 1.4, CI 95% 1.2–1.8, $p = 0.0006$). There were 4.1 (SD 3.1, [1.0, 13.0]) and 1.9 (SD 1.9, [0.0, 10.0]) deviant items in infants with and without CP, respectively. The mean total score in the HINE was 54.3 (SD 10.34, [38.0, 74.0]) and 73.9 (SD 2.6, [67.0, 78.0]) in infants with and without CP, respectively (Table 4).

4. Discussion

This prospective follow-up study of a regional cohort of very preterm infants showed that a systematical use of the Dubowitz neurologic examination at TEA is a valuable tool to predict neurological development in preterm infants. This neurological examination combined with either the brain MRI or cUS improves the predictive value of the brain MRI or cUS alone considering neurosensory outcome at 2 years of corrected age.

Table 3
The predictive values of the Dubowitz neurologic examination and brain MRI at term equivalent age and serial neonatal cUS for total score ≤70 of the Hammersmith Infant Neurologic Examination (HINE) and neurosensory impairment (NSI) at 2 years of corrected age.

	HINE ≤70 (n = 32, 15.4%)	NSI (n = 17, 7.9%)
The Dubowitz neurologic examination		
No deviant items, n = 53 (24.5%)	NPV = 88.5%	NPV = 100%
One or more deviant items, n = 163 (75.5%)	PPV = 16.7%	PPV = 10.4%
Brain MRI findings		
Normal findings or minor pathologies, n = 158 (73.2%)	NPV = 90.3%	NPV = 99.4%
Major pathologies, n = 58 (26.9%)	PPV = 31.5%	PPV = 27.6%
cUS findings		
Normal findings or minor pathologies, n = 198 (91.7%)	NPV = 87.1%	NPV = 97.0%
Major pathologies, n = 18 (8.3%)	PPV = 46.7%	PPV = 61.1%
The Dubowitz neurologic examination and brain MRI findings		
No deviant items and normal findings or minor pathologies, n = 41 (19.0%)	NPV = 90.0%	NPV = 100%
One or more deviant items or major pathologies, n = 129 (59.7%)	PPV = 10.3%	PPV = 0.78%
One or more deviant items and major pathologies, n = 46 (21.3%)	PPV = 35.7%	PPV = 34.8%
The Dubowitz neurologic examination and cUS findings		
No deviant items and normal findings or minor pathologies, n = 49 (22.7%)	NPV = 87.5%	NPV = 100%
One or more deviant items or major pathologies, n = 153 (70.8%)	PPV = 12.8%	PPV = 3.9%
One or more deviant items and major pathologies, n = 14 (6.5%)	PPV = 63.6%	PPV = 78.6%

Table 4
The characteristics of the infants with CP (n = 14).

Characteristics	Data
CP type, n (%)	
Spastic diplegia	7 (50.0)
Spastic hemiplegia	4 (28.6)
Spastic triplegia	2 (14.3)
Dystonic	1 (7.1)
Gross Motor Function Classification System (GMFCS), n (%)[a]	
I	2 (15.4)
II	6 (46.2)
III	3 (23.1)
IV	2 (15.4)
V	0 (0.0)
Gestational age at birth, mean (SD) [minimum, maximum], week	27 5/7 (22 4/7) [23 3/7, 35 1/7]
Number of deviant items in the Dubowitz neurologic examination at term equivalent age, n (%)	
0	0 (0)
1	3 (21.4)
2	1 (7.1)
3	3 (21.4)
4	2 (14.3)
5	1 (7.1)
6	3 (21.4)
7–12	0 (0)
13	1 (7.1)
Items that were more frequently outside the normative range in the Dubowitz neurologic examination at term equivalent age, n (%)	
Posture: opisthotonus or arms flexed and legs extended	6 (42.9), p = 0.002
Eye appearance: does not open eyes, persistent nystagmus, strabismus, roving eye movements or downward deviation	2 (14.3), p = 0.01
Visual orientation: does not follow or focus on stimuli, stills, focuses, follows briefly to the side but loses stimuli	5 (35.7), p = 0.004
Flexor tone (compare arm and leg traction): arm flexion > leg flexion: difference >1 column	4 (28.6), p = 0.01
Head control (sitting): neck extension > neck flexion: difference >1 column	2 (14.3), p = 0.04
Brain MRI findings, n (%)	
Normal findings	1 (7.1)
Minor pathologies	0 (0.0)
Major pathologies	13 (92.9)
cUS findings, n (%)	
Normal findings	0 (0.0)
Minor pathologies	5 (35.7)
Major pathologies	9 (64.3)
Total score of the Hammersmith Infant Neurologic Examination at 2 years of corrected age, mean (SD) [minimum, maximum]	54.3 (10.3) [38.0,74.0]

[a] Data missing for 1 (7.1%) child.

Our results support the validity of preterm norms of the Dubowitz neurologic examination [6]. None of the deviant items alone predicted abnormal outcome, but any single deviation increased the risk for later neurosensory impairment. Importantly, specific subscales (tone patterns, posture and tone, and behavior) correlated to developmental outcome. Our findings are in agreement with a previous study showing that the Dubowitz neurologic examination at TEA was related to concurrent cerebral abnormalities in MRI [15]. With regard to predicting CP, our results differed from a previous study including infants with major ultrasound pathologies showing often 7 or more deviant items in infants later developing CP [6]. In our study, only one infant with CP had 7 or more deviant items. This difference may be due to the differences in the populations as we included all preterm infants regardless of brain pathology. The items that were most commonly deviant in children with CP were posture, eye appearance, visual orientation, flexor tone, and head control. In addition, the children with CP had good functional level as the majority of children were independently mobile and only two of them needed assistive device. It is noteworthy also from this perspective that all children with even mild CP had at least one deviant item in the Dubowitz neurologic examination at TEA. On the other hand, there were seven infants with 7 or more deviant items without CP. Some of these infants might have performed suboptimally due to disturbances related to the examination situation, and some had neurological abnormalities other than CP.

It has been previously shown that Amiel-Tison Neurological Assessment at TEA predicts psychomotor and behavioral development at 2 years of corrected age [16]. A meta-analysis of neurological examination methods at TEA pointed out that neurological examination could reach as good sensitivity and specificity as brain MRI to predict CP [17]. The meta-analysis did not show sensitivity and specificity for the combined information of these methods. The sensitivity of prediction of combined brain MRI and neurobehavioral assessment has been evaluated using the general movement analysis and the neurobehavioral assessment of preterm infants [18]. A combination of the two methods increased sensitivity and specificity for CP. The HINE and general movement analysis at 3 months of age were shown more effective than either of the assessments alone or serial cUS in predicting neurologic outcome at 2 years of age [19].

The present study is the first showing the combined predictive value of the Dubowitz neurologic examination and either brain MRI or cUS in preterm infants. All these examinations were excellent in predicting normal neurological outcome at 2 years of corrected age. Normal findings in the Dubowitz neurologic examination provide valuable information for clinicians and families by predicting with a very high likelihood a good neurosensory development irrespective of the available imaging facilities. Obtaining a high PPV is challenging as many neurological deviations normalize during the development in early infancy due to the unique plasticity of the neonatal brain. Compared to either brain MRI or cUS alone, a combination of neurological examination and brain imaging improved the prediction for abnormal outcome. However, it should be emphasized that even though the Dubowitz neurologic examination together with either the brain MRI or cUS aid clinicians in identifying those infants who are later at a high risk of developmental problems, good functional outcome can be achieved despite several deviant items or major lesions. The significant proportion of normal development in the infants with either major MRI or cUS pathologies also supports the use of functional measures like the Dubowitz neurologic examination. The neurological examination is valuable also in follow-up as it can easily be repeated in order to see which of the abnormal findings normalize, worsen or remain stable.

MRI has a value for predicting also cognitive outcome as we showed in our previous study [1]. The PPV of one or several major pathologies in MRI was 39% and 75%, respectively, for neurodevelopmental impairments including also the cognitive development at 5 years of age. New imaging methods or combinations of neurological examinations and imaging techniques may be able to improve the PPV for abnormal outcome. For example, diffusion-weighted MRI has been shown to be associated with a poorer developmental performance in later childhood and may be of prognostic value for neurodevelopmental outcome in preterm infants with no abnormalities on conventional brain MRI [20]. Brain volumes also associate with later development [21].

The strengths of this study included a high coverage of the examinations at TEA and at 2 years of corrected age with very little variation in the age at the examinations. As there are no norms for preterm children for the HINE at 2 years of corrected age, the cut-off scores were defined according to this cohort. These data could be used in future as a reference when examining preterm infants.

A possible technical limitation of this study was the upgrading of the MRI equipment during the study period. Comparability was supported by our findings about the incidence of brain lesions, which did not increase after the MRI equipment upgrading in our study population.

In conclusion, this study showed that the combination of the neurological examination and either brain MRI or cUS provides an effective tool to estimate long-term neurosensory development in preterm

infants. The families need individualized information which is as accurate as possible about the neurodevelopmental prognosis of their child. It is important not to forget the great potential for compensation provided by the maturing brain in optimal growth environment.

Conflict of interest

The authors report no conflict of interest.

Financial support

This work was supported by grants from the Foundation for Paediatric Research, Arvo and Lea Ylppö Foundation and The Foundation of Märtha Donner.

Abbreviations

CP	cerebral palsy
cUS	cranial ultrasound
HINE	Hammersmith Infant Neurologic Examination
MRI	magnetic resonance imaging
NSI	neurosensory impairment
PPV	positive predictive value
NPV	negative predictive value
TEA	term equivalent age
VLBW	very low birth weight
VLGA	very low gestational age
V/B	ventricular/brain

Acknowledgments

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