Original Article

Journal of Child Neurology
1-6

DOI: 10.1177/0883073820930487
journals.sagepub.com/home/jcn
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Disability Prediction by Early Hammersmith Neonatal Neurological Examination: A Diagnostic Study

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Abstract

Background and Objectives: Hammersmith Neonatal Neurologic Examination (HNNE) is used to identify term and preterm infants at risk of neurodevelopmental disability. The test is recommended at corrected term age in preterm; and around 2 weeks postnatal age in term neonates. As the current trend is to discharge based on physiological stability, it may not be feasible to perform HNNE at recommended age. The authors investigated whether predictive ability of the test for neurodevelopmental disability remained unchanged if performed early (before discharge). **Methods:** The authors enrolled preterm and at-risk term neonates. HNNE PE was performed before discharge in all infants. The test was repeated in preterm infants at 40 weeks postmenstrual age and in term neonates at 2 weeks of age (HNNE RA). Neurodevelopmental disability was assessed at 1 year of age. **Results:** HNNE PE was done in 125 neonates (103 preterm, 22 term neonates). HNNE RA was done in 58% infants. Neurodevelopmental disability was assessed in 84 (67%) of infants. Neurodevelopmental disability was noted in 14/84 (16.6%) babies. The receiver operating characteristic curve of raw scores showed that area under the curve for HNNE PE (0.71) and HNNE RA (0.66) were similar. The sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio for both the tests were similar for a cutoff optimality score of 32.5. HNNE PE could be performed up to 4 weeks earlier than HNNE RA with the same predictive ability for neurodevelopmental disability. **Conclusions:** HNNE PE was as reliable as HNNE RA in predicting neurodevelopmental disability at 1 year of age. Completion of the test is assured and provides several weeks lead time for early intervention.

Keywords

at-risk neonates, Hammersmith Neonatal Neurological Examination, neurodevelopmental disability

Received January 25, 2020. Received revised March 27, 2020. Accepted for publication May 4, 2020.

Intensive care has markedly improved survival of sick neonates. However, at-risk neonates may have neurological sequelae.[1] Early identification and intervention are necessary to improve outcomes. Neurological examination and neuroimaging may be used to prognosticate. Neuroimaging requires resources, and specialists who are trained in interpretation. Comprehensive, yet succinct neurological examination tools like Hammersmith Neonatal Neurological Examination (HNNE) may help identify most neonates who are at risk of neurodevelopmental disability.[2] An optimality score for HNNE has also been described which can be used for research purposes.[3] The PIPARI Study Group and others found that HNNE performed around 2 weeks of age in term neonates; and at estimated term age in preterm neonates has the best in terms of accuracy in predicting neurodevelopmental disability.[4,5] However, in resource limited settings, preterm as well as high risk term neonates are most often discharged before they reach this recommended age. Neurological examination performed before discharge has several less tangible benefits. It allows the neonatologist more time to perform the examination, and better chances of finding the baby in the right neurobehavioral state. Moreover, no infant will be missed, if examined before discharge from hospital. The test can be repeated as well, in case of doubtful or incomplete assessments. Intervention programs can be started earlier if at risk infants are identified. These are clear benefits when compared to neurological examination performed during follow-up visits in a busy outpatient setting. The authors hypothesized that HNNE can be performed

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before discharge with reasonable ability to predict neurodevelopmental disability.

Aim and Objectives

To compare the diagnostic accuracy of Hammersmith Neonatal Neurological Examination (HNNE) performed early (HNNE PE) (before discharge from hospital) with HNNE at recommended age (HNNE RA), in babies discharged from the neonatal intensive care unit, in predicting neurodevelopmental disability at 1 year of age.

Methodology

This diagnostic study was conducted in a 26 bedded level III B unit (accredited by National Neonatology Forum of India) of a private sector hospital, in India. Discharge decisions in the authors' setting cannot be based on any particular postmenstrual age, or postnatal age. Infants are discharged once oral feeds and maternal confidence in care are well established, there are no acute concerns, risks of apnea are safely ruled out, and weight gain is recorded after a period of rooming in with mother. Neonates were enrolled from September 2017 to April 2018. Enrolled infants were followed up till May 2019. Inclusion criteria included the following: (1) All preterm neonates admitted within 1 week of life during the study period and (2) term neonates admitted within 1 week of life with any one of the following risk factors: (a) neonatal encephalopathy, (b) neonates requiring cardiorespiratory support (invasive or noninvasive ventilation, inotropes), (c) proven/possible sepsis: blood culture positive or C-reactive protein positive (>10 mg/L), (d) serum bilirubin >20mg/dl), (e) symptomatic hypoglycemia or needing high glucose infusion rates (>12mg/kg/min). Those who had proven intrauterine infection, major congenital malformations requiring surgery, proven inborn errors of metabolism, proven genetic/syndromic condition before enrolment were excluded.

Study Protocol

All the eligible neonates were enrolled in the study after informed consent from parents. Perinatal risk factors were recorded from pregnancy to discharge, in real time, on a case form as a part of an ongoing multisite follow-up study.[6] HNNE (PE and RA) were performed by pediatricians after they underwent a short training process. Doctors were "privileged" to conduct the test after they attended a theory session with audiovisual aids followed by an observation of 2 procedures. The first two tests conducted were supervised by a previously privileged staff. Interobserver reliability was assessed by performing HNNE on consecutive days by 2 observers on initial 20 enrolled neonates.

HNNE PE was performed after the baby was roomed in with the mother, after intensive care was completed. As babies spend 2-3 days in the room, HNNE PE could be repeated on the next day, if the baby was not in the right state or some items could not be evaluated.

Appointments for HNNE RA were scheduled for term neonates at 2 weeks of age and at estimated term age (40 weeks postmenstrual age) for preterm. Parents were educated regarding the importance of test; appointment date and time was noted in discharge summary and follow-up booklet; an automated reminder was sent to the registered phone number.

Scoring of HNNE

The observations were recorded on the standard proforma and scored as raw scores (1 to 5) which were later converted to optimality scores. Calculating the optimality score for HNNE PE was done with guidance from published studies.[3] Raw scores between the 10th and 90th percentile was given a score of 1; below the 10th and above the 90th percentile was given a score of 0.

Follow-Up Protocol

Hearing evaluations by brain stem evoked response audiometry were done before 6 months of corrected age. Retinopathy of prematurity screening was done according to standard guidelines.[7] Vision assessment (refraction and squint examinations) was done before 12 months of corrected age. Formal assessment at 12 months corrected age was done by the Development Assessment Scale for Indian Infants (an Indian adaptation of the Bayley Scale of Infant Development).[8] Neurodevelopmental disability was defined as any 1 or more of the following: (a)development delay—mental and/or motor development quotient <70 assessed by the Development Assessment Scale for Indian Infants at 12 months of age, corrected for prematurity; (b) cerebral palsy—motor delay with neurological signs; (c) presence of seizures; (d) requirement of hearing aid; (e) blindness in one or both eyes.

The unit has a developmental pediatrician and 3 trained developmental therapists who performed the tests. They educate families regarding importance of follow-up and remind appointments by phone.

Sample Size Calculation and Statistical Analysis

The expected sensitivity and specificity of HNNE PE to predict neurodevelopmental disability at one year were 0.70 and 0.70, respectively. The prevalence of neurodevelopmental disability in a previously performed study in the authors' unit (unpublished data) was 15% (0.15). The desired precision was taken as 0.25. Based on the above values, the sample size was calculated as 87. Expecting an attrition of 30% for follow-up, total number of patients planned was 125.

Statistical Analysis

Statistical analysis was performed using SPSS version 20. Receiver operator characteristic curve was drawn between the HNNE score and neurodevelopmental disability to determine

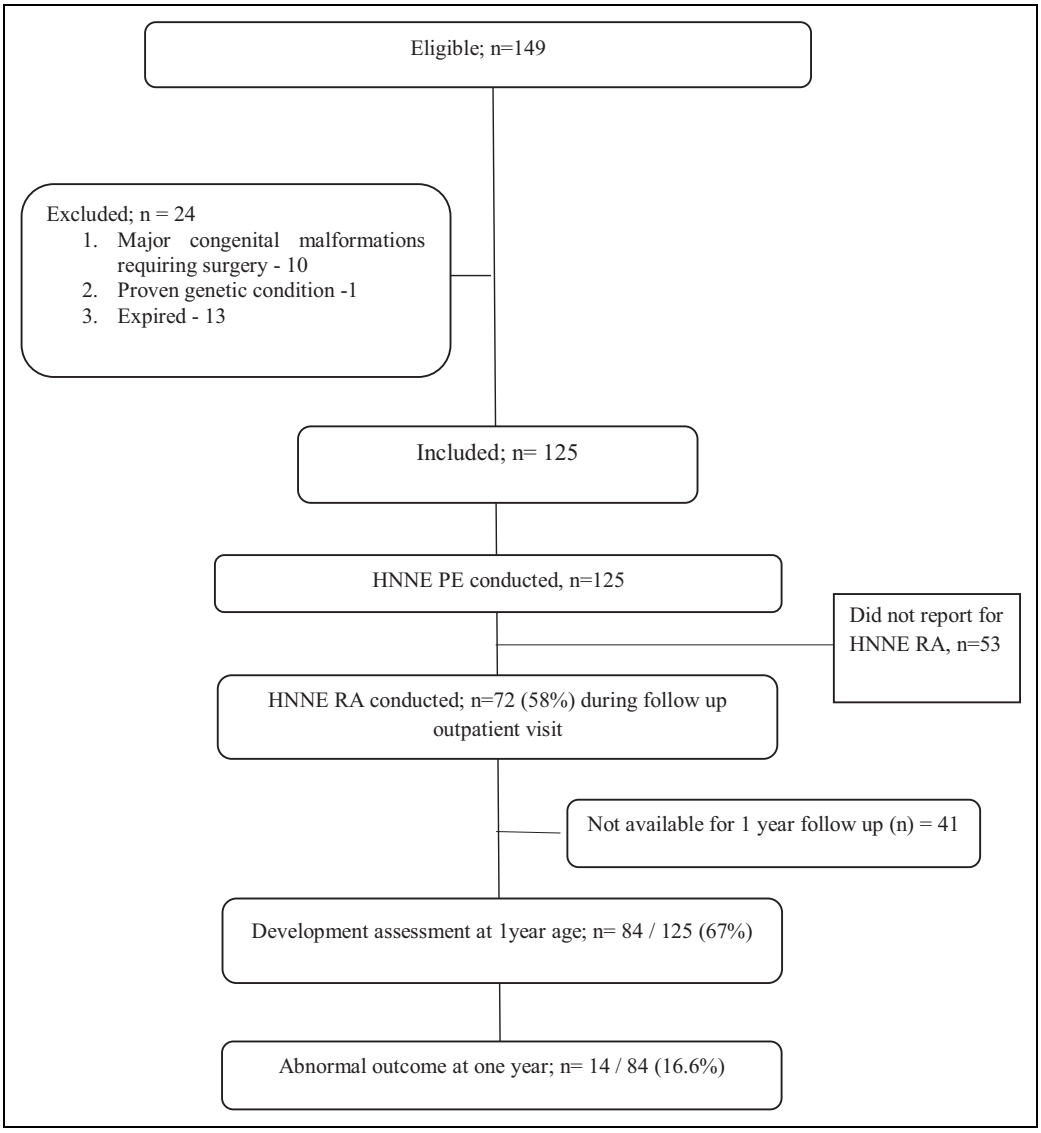

Figure 1. Study flow diagram.

the area under the curve; sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio were calculated for HNNE PE and HNNE RA to predict neurodevelopmental disability.

Consent

Consent was obtained from parents and the institution for use of baby's information for research.

Ethics

Institute ethics committee clearance was obtained.

Results

Of all the eligible babies, 125 were enrolled. HNNE PE was performed in 103 preterm neonates and 22 term at-risk neonates admitted to the neonatal intensive care unit during the study period. The authors could repeat HNNE at recommended age only in 72 (58%) babies; others did not report on scheduled date (Figure 1). Most of the infants included were preterm and late preterm (Table 1). Cerebral palsy was the most common neurodevelopmental disability noted in the authors' cohort (Table 2). Some infants had more than one abnormality at 1 year of age. Mean gestational age at which HNNE PE was performed in preterm neonates was 36.1 weeks (Table 3). In this study HNNE could be performed almost 4 weeks earlier than recommended age (40 weeks). In term neonates, HNNE PE was done at a mean postnatal age of 8.6 ($\pm$3.6) days (range 3-17 days). On evaluation of distribution of raw scores -HNNE PE and HNNE RA showed similar patterns (supplementary online material, Tables S1 and S2).

Optimality scores for HNNE PE and HNNE RA were calculated as elaborated in methodology. Receiver operating characteristic curves were drawn to determine best cutoffs that

Table 1. Baseline Characteristics of the Study Population.

Baseline characteristics	n	%
Gestation age		
≤28 weeks	7	5.6%
29-32 weeks	31	24.8%
33-36 weeks	65	52%
Term	22	17.6%
Sex		
Male	69	55.2%
Female	56	44.8%
Mode of delivery		
Vaginal	29	23.2%
Caesarean section	96	76.8%

Table 2. Description of Babies with NDD at 1 Year of Age.

NDD at 1 year	n
Any NDD	14
More than one disability	4
Disability count	18
• Cerebral palsy	9
• Development delay	4
• Seizures	3
• Cortical visual impairment	1
• Bilateral hearing impairment	1

Abbreviation: NDD, Neurodevelopmental disability

Table 3. Gestational Age at Which the HNNE PE Was Performed in Preterm Neonates.

Post menstrual age	n (%)
34 weeks	8 (7.8%)
35 weeks	27 (26.2%)
36 weeks	31 (30.1%)
37 weeks	25 (24.3%)
38 weeks	11 (10.7%)
40 weeks	1 (1%)

Abbreviation: Hammersmith Neonatal Neurological Examination performed early.

predicted neurodevelopmental disability (Figures 2 and 3). In a tradeoff between the sensitivity and specificity, a cutoff of 32.5 for the cumulative optimality score was obtained. Area under the curve of 0.713 (95% CI 0.57–0.85, SE 0.07, $P = .01$) was obtained for HNNE PE, and 0.664 (95% CI 0.462–0.866, SE 0.103, $P = .109$) for HNNE RA.

HNNE PE $\leq$ 32.5 was significantly associated with neurodevelopmental disability (OR 3.6; $P = .01$ (95% CI 1.3–9.7)) (Table 4). The diagnostic abilities of both the tests, HNNE PE and HNNE RA to predict neurodevelopmental disability were comparable (Table 5).

Interobserver analysis showed high reliability for most of the items in HNNE (supplementary online material, Table S3).

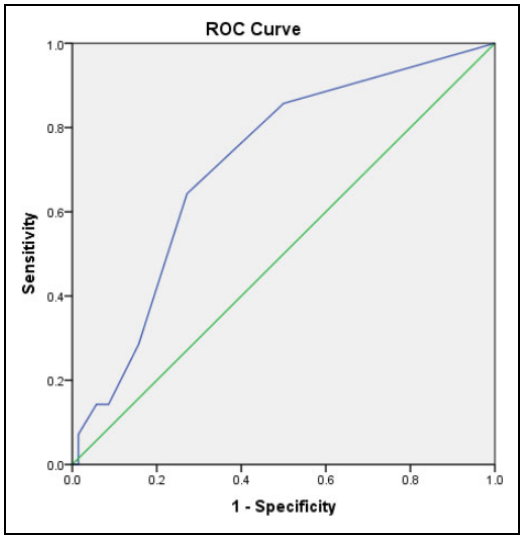

Figure 2. Receiver operating characteristic curve for HNNE PE score and neurodevelopmental disability.

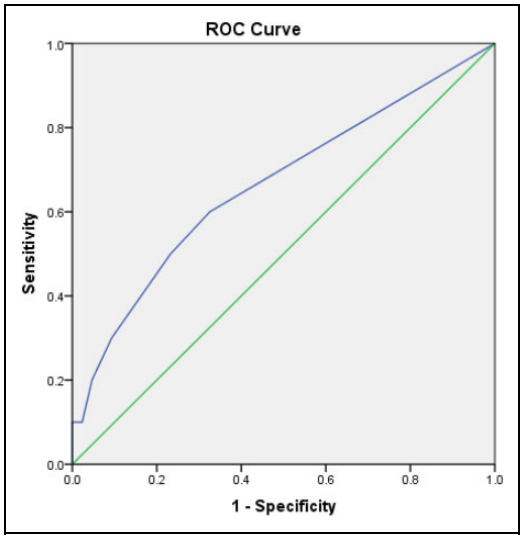

Figure 3. Receiver operating characteristic curve for HNNE RA score and neurodevelopmental disability.

Table 4. Association of HNNE PE Results With Outcome.

	NDD	No NDD
HNNE PE ≤ 32.5	9 (64.3%)	19 (27.1%)
HNNE PE > 32.5	5 (35.7%)	51 (72.8%)

Abbreviations: Hammersmith Neonatal Neurological Examination performed early; NDD, neurodevelopmental disability.

Subgroup testing at each gestation at which HNNE was performed in preterm would be useful, but this study was not powered for this analysis.

Out of the 125 neonates, 41 neonates were not available for one-year follow-up; 31 were preterm neonates and 10 were term neonates. The mean birth gestation age of the preterm

Table 5. Comparison of HNNE PE and HNNE RA for Composite Optimality Score $\leq$ 32.5.

Timing of HNNE	Sensitivity	Specificity	PPV	NPV	PLR	NLR	AUC
HNNE PE	64%	73%	32%	91%	1.2	0.9	0.71
HNNE RA	50%	77%	33%	87%	1.1	0.7	0.66

Abbreviations: AUC, area under the curve; HNNE PE, Hammersmith Neonatal Neurological Examination performed early; HNNE RA, Hammersmith Neonatal Neurological Examination at recommended age; NLR, negative likelihood ratio; NPV, negative predictive value; PLR, positive likelihood ratio; PPV, positive predictive value.

neonates who did not return for follow-up was 34.2 ($\pm$2.0) weeks. It is possible that the neonates who were lost to follow-up were mostly neonates at lower risk of disability.

Discussion

The authors undertook this study to compare the accuracy of HNNE PE (performed before discharge from hospital) with HNNE RA in predicting neurodevelopmental disability at 1 year of age in at-risk neonates. The diagnostic abilities of both the tests, HNNE PE and HNNE RA to predict neurodevelopmental disability, were comparable.

It is imperative that a neurological assessment tool needs to satisfy a few criteria to be used eloquently and meaningfully in clinical practice.[9] The tool should include items which are age specific as changes occur very rapidly during the pre- and early postnatal period. The diagnostic procedure must be noninvasive and relatively quick to perform and should be repeatable to document the evolution of neurological abnormalities. Other critical requirements are prognostic capability and good interobserver agreement.

Many neurological examination schemes were developed, some of which were based on tone and primitive reflexes, which in fact reflects lower neurological function. Such schemes of neurological examination, obviously were not accurate in predicting the higher cerebral function.[10] Assessment of spontaneously generated movements in preterm and term infants, the Prechtl examination, is one of the most detailed and comprehensive one available.[11] Evidence suggests that abnormal general movements are predictive of later cerebral palsy though milder abnormalities like poor repertoire are less predictive of adverse outcome.[12] A recent study has demonstrated that the quality of the general movements is related to white matter abnormalities in the post neonatal period.[13] The obvious disadvantages of Prechtl examination are that it requires long time to perform, is complex, it encompasses a large number of items and each of these have to be observed in its optimal state. The conduct of the test requires specialized training.

The HNNE is a simple, objective recording system, based on simple diagrams, recorded on a proforma that includes definitions and intelligible drawings. These are easy to "check off" and are suitable for staff with no particular expertise or experience in neonatal neurology. The test is easy to learn. In the ideal behavioral state, the examination does not take more than 15 minutes to perform making it suitable for repeated examinations. Hence, this can be used as part of the routine clinical assessment of new-born infant. Evolution of normal or abnormal behavior in preterm neonates can also be documented. The authors of the tool designed a compound optimality score—a simple summation of the scores of individual items. A total score less than 30.5 was reported as abnormal.[3] Abnormal HNNE scores were demonstrated in 76.5% of the neonates and it predicted adverse outcome with a specificity of 89%, but a sensitivity of only 19%.[14] Higher HNNE total scores were associated with higher cognitive scores on the Bayley Scale of Infant Development–III. There was a three times higher odds of having a cognitive delay in those infants who had a HNNE total score in the suboptimal range.[4] The examination has been validated at recommended age in full term and preterm infants.[15]

In the developing world, in order to optimize resource utilization, most babies are discharged from hospital before they reach the ideal age for HNNE testing (estimated term age in preterm and 2 weeks age for term babies).[16] Even in the western hemisphere, trends towards discharging neonates based on physiologic stability rather than post menstrual age are emerging.[17]

For these reasons, the authors selected HNNE as a neurological examination tool; and studied diagnostic accuracy of the test performed before discharge. HNNE PE could be performed much earlier than HNNE RA; a lead time of 4 weeks in preterm and 1 week in term neonates was achieved. This early assessment was possible without loss of diagnostic accuracy. The authors could repeat HNNE RA only in 72 (58%) babies; others did not report for the test. This, the authors feel, is expected and supports the distinct advantage of performing HNNE before discharge. Compliance is assured, besides the added benefit of early identification of at-risk babies. One can easily envisage that HNNE PE is more likely to be done than HNNE RA in all settings.

On comparison of predictive abilities of HNNE PE and HNNE RA, area under the curve of the receiver operating characteristic curves drawn were similar.

In the study conducted by Amess et al, the sensitivity and specificity of HNNE in healthy term neonates in predicting abnormal neurological outcome at 12 months of age was 19% and 89% respectively. The positive predictive value was 86% and negative predictive value was 24% in the same study. In low-risk preterm neonates, the neurological examination done at term age predicted abnormal neurological outcome at 12 months of age with a sensitivity of 50% and specificity of 89%. The corresponding positive and negative predictive values were 43% and 95%.[14] The authors conducted this study on low-risk preterm neonates and HNNE was performed at estimated term age. Exhaustive head to head comparisons with other studies are not possible as this is a first of its kind analysis; literature on the topic is exiguous.

The authors also found a high degree of inter observer reliability in almost all the items except Moro reflex, Startle response, Visual orientation and Irritability. Other studies have also shown very high interrater reliability (96%) in performing HNNE.[2]

Strengths and Limitations

Risk factors were recorded on a standard proforma. Follow-up plans were based on written protocols that have been strictly adhered to for several years in the unit. Formal development assessments were made by dedicated developmental therapists who were not biased by clinical details. HNNE could be performed by Pediatricians with good interobserver reliability, even after short training.

The authors accept that there were infants who were lost to follow-up in spite of the best efforts made. The authors are aware of the limitation of a short follow-up, 1-year assessment in predicting long term outcomes.

Conclusion

Neurological Examination done before discharge from hospital (performed 4 weeks earlier than recommended, HNNE PE) had similar diagnostic accuracy compared to a later exam at recommended age (HNNE RA) in outpatient follow-up; in prediction of neurodevelopmental disability among neonates discharged from the neonatal intensive care unit. Neurologic exam before discharge allows complete evaluation, ensures compliance and gives us valuable advantage of several weeks lead time in offering early intervention. The findings are relevant to all settings where early discharge from hospital is necessitous.

Author Contributions

SKRGV was the principal investigator, drafted the protocol, collected data, analyzed the results, and drafted the manuscript. FP helped draft the protocol, analyze and interpret the results, and draft the manuscript. JP and AN critically reviewed the manuscript. NJ conceptualized the study, supervised the data collection and analysis, and approved the final manuscript. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

Declaration of Conflicting Interests

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

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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Supplemental Material

Supplemental material for this article is available online.

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