ABSTRACT

AIM

To determine (1) if the General Movement Optimality Score (GMOS) at term age enhances prediction of motor impairment at 12 and 24 months of age in high-risk infants, when compared to a global General Movement Assessment (GMA), and (2) compare predictive validity for two high-risk populations: infants born preterm and infants born at term with hypoxic ischaemic encephalopathy who have received therapeutic hypothermia.

METHODS

Fifty-nine extremely preterm or term age infants with hypoxic ischaemic encephalopathy underwent term age GMA. A GMA score of normal or abnormal, and a comparative numerical General Movement Optimality Score (GMOS, total values 5-42) were assigned. Neurology and motor assessment were carried out at age 12 and 24 months using standardised assessments; Alberta Infant Motor Scale, Bayley Scales of Infant and Toddler Development or Ages and Stages Questionnaire. Outcomes were recorded as normal, motor delayed or cerebral palsy. Motor outcome prediction at 12 and 24 months of age was calculated using the GMA and, using ROC analysis, GMOS cut-off scores were determined.

RESULTS

At both 12 and 24 months global GMA sensitivity for preterms was 80% and 100% for term HIE infants. Specificity values for preterm infants at 12 and 24 months were 68.8% and 60% versus 28.8% and 21.4% for term HIE. Median GMOS scores were lower in the term HIE group than the preterm group in the normal and poor repertoire categories. Optimality cut off scores enhanced specificity, but values remained low.

INTERPRETATION

At term age, specificity for identification of infants with later normal motor outcome is low. The GMOS may assist identification of infants with the highest probability of motor impairment, enabling targeted intervention during critical periods for neuroplasticity.

Keywords; General Movements, optimality, preterm infant, hypoxic ischemic encephalopathy, motor outcome, predictive value

INTRODUCTION

There is inconclusive evidence to ascertain the benefits of early motor intervention in high-risk infants.[1] Not all infants classed as "high risk" will go on to develop motor disorders, with motor outcomes varying from typical development to different levels of motor delay and cerebral palsy.[2]

The most sensitive period for motor development is likely to be in the first year of life; however, the average age of diagnosis of CP is one to two years.[2] Early, accurate identification at term age of those infants with a high probability of motor impairment could enable efficient, effective targeted intervention during the critical periods of neuroplasticity. It could also enhance subject selection for motor intervention studies to either support or discount the evidence. Furthermore, accurately identifying those infants who will have typical motor development will avoid unnecessary treatment and allow more efficient use of available resources.

The General Movement Assessment (GMA) evaluates spontaneous infant movements. Writhing movements are present from term until 6-9 weeks of age when they gradually disappear and are replaced by fidgety movements which are present until 20 weeks of age.[3] The GMA demonstrates high predictive validity in identifying infants at high risk of neuromotor deficit however prediction appears superior when comparing GM assessment in preterm infants to term infants with HIE. [4,5] It has superior validity during fidgety movement age when compared with writhing age, especially when abnormal general movement complexity is combined with absent fidgety movements.[6] A semi-quantitative optimality score, which examines in detail different aspects of general movements, can be applied to the GMA at both writhing and fidgety age. [7,8] The majority of research using the GMA has been with preterm or mixed populations, with limited studies exploring the predictive value of GMA in infants with HIE at term equivalent age (TEA), and very limited studies on those treated with therapeutic hypothermia (TH). However, there is evidence that hypokinesis and transient abnormalities in the quality of GMs at writhing age in infants with HIE are common in the first few weeks after birth [9,10].

Furthermore, there is a lack of studies to determine if the semi-quantitative General Movement Optimality Score can, compared to a global, categorical GMA classification, enhance prediction of motor impairment at TEA.

The aim of this study is to

1. Determine if application of the General Movement Optimality Score (GMOS) to a global General Movement Assessment (GMA), at TEA, undertaken at the point of discharge, in term infants who have received TH for HIE can enhance prediction of motor impairment at 12 and 24 months.
2. Compare predictive validity for motor outcome when used to assess preterm infants at TEA compared with term born infants with hypoxic ischaemic encephalopathy who have received TH.

METHOD

Participants

A retrospective cohort study was undertaken of high-risk infants selected from a cohort admitted to a Level 3 Neonatal Intensive Care Unit (NICU) in the United Kingdom, between 2011 and 2017. Infants were retrospectively, consecutively selected from those enrolled into a clinical follow-up programme. As part of the programme, all had a Prechtl General Movement Assessment (GMA) at term age.[3] Inclusion criteria were born less than 28 weeks' gestation or born at term with moderate to severe hypoxic ischaemic encephalopathy which required treatment with TH. Infants were excluded if they had a GMA not adhering to the General Movement (GM) standardisation requirements[3] or no neuromotor outcomes recorded at 12 or 24 months. To avoid review bias, each infant was given a unique data collection number and the first author was blinded to the infants prenatal, postnatal, and neonatal history, and any longitudinal developmental outcomes.

Fifty-nine infants were recruited to the study, 21 preterm and 38 term born infants with HIE. Characteristics of the cohort are presented in Table 1. GMA was undertaken just prior to hospital discharge for most infants. Average age for term GMA was later in the HIE group as these infants would have undergone 72 hours of TH and, post treatment, would have stayed on the neonatal unit until ready for discharge.

Table 1: Infant characteristics

	Preterm infants (n=21)	**Infants with HIE** (n=38)
Mean (SD) Gestational age (wks)	25.72 (1.22)	39.8 (1.7)
Mean (SD) Birthweight (g)	918.9 (354.9)	3449.4 (752.5)
Males, n (%)	8 (38.1)	20 (52.6)
Mean (SD) Age of term GMA, (wks)	40.2 (1.9)	41.8 (1.9)

Informed written open consent for infant movement video assessment and its use for research had been gained from parents. Ethical approval was obtained from the NHS Health Research Authority (IRAS 227136) the higher education institute (ERGO 26151) and site-specific approval was granted by the hospital involved.

General Movement Assessment and optimality scoring

At term age, Prechtl's GMA was carried out according to standardised procedure, prior to the infant being discharged from the neonatal unit.[3] General movement (GM) sequences were analysed, and an abnormal or normal movement category was assigned. Normal GMs are complex, variable and fluent, involving the whole body. Abnormal movements are classified as poor repertoire (monotonous and lack variety and complexity), cramped synchronised (rigid, lack fluency) or chaotic (abrupt and of large amplitude)[3].

The same assessment film was then numerically scored by the first author according to criteria set for the General Movement Optimality Score (GMOS).[7] This involved a detailed analysis of aspects of the General Movements including amplitude, speed, spatial range, rotatory components, and fluency. Score ranges are 5-42 with a higher score indicating the most optimal movement performance.

All videos were blindly scored by two therapists who are advanced trained and certified by the GM Trust, both have clinical experience in the use of the GMA. Inter-rater reliability was established with an inter-observer agreement of 89% with Cohen's Kappa calculated at 0.83 (95% C.I 0.79-0.87). Interrater agreement for the GMOS was calculated in 10 infants

from video recordings. There was 100% agreement in 7/10 infants with the remaining three having scores with a difference of one mark out of 42. Where a difference occurred, the higher value was used. The results for these 10 infants were used in analysis.

Outcome assessments

After all GM assessments had been evaluated outcome data at 12 and 24 months were retrieved from the clinical database. Ages were corrected for prematurity for all outcome measures.

At 12 months of age, the Alberta Infant Motor Scale (AIMS)[11] was administered as part of routine, high-risk infant clinical follow up by a senior physiotherapist with expertise in early years development and experience in using the assessment. The AIMS is a norm-referenced standardised scale, with strong psychometric properties, evaluating gross motor function of infants through observation of spontaneous motor activity in four positional planes. The accumulated score for each positional plane is plotted on an age-based percentile rank. The AIMS is a good predictor of atypical development in the later months of infancy.[11] Motor impairment was recorded at 12 months of age if the AIMS score was below the 5th centile or if there was the presence of CP. Diagnosis of cerebral palsy (CP) was made by a Consultant Paediatric Neurologist from clinical assessment, using the criteria of the Surveillance of Cerebral Palsy in Europe (SCPE) and a Gross Motor Function Classification System (GMFCS E&R) score was assigned.

At 24 months of age the Bayley Scales of Infant & Toddler Development III (BSITD III)[12] was carried out as part of routine clinical follow up. The BSITD III is a standardised norm-referenced test, which has been validated in the United Kingdom. It was administered according to guidelines set out in the manual by an administrator who had attended a BSITD III course. The motor composite score combines gross and fine motor scores and a cut off threshold of less than 85 was classified as impaired motor development.[12]

For those infants who did not complete a BSITD III assessment the Ages and Stages Questionnaire-3 (ASQ)[13] was completed by parents. The ASQ is a parent reported developmental screening assessment where gross motor assessment is classified as normal, borderline and delayed. The cut off threshold used for the assessment was a finding of delay in the gross motor section. Reasons for not completing the BSITD-III assessment

were non-attendance, or lack of ability to complete the assessment due to behavior or severe motor difficulties e.g., cerebral palsy.

Statistical analysis

Data were analysed using Statistical Package for the Social Sciences version 26 (SPSS; SPSS, Inc., Chicago, IL, USA). Predictive values of abnormal global GMA for determining motor impairment were calculated: sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratios. Additionally, Receiver Operator Curve (ROC) analysis was undertaken to determine optimal cut off scores for motor impairment using the GMOS. Group differences for the GMOS scores were analysed using non-parametric testing with a significance level set at $p<0.05$.

RESULTS

Global GMA results

In the preterm group 11 infants (57.1%) had normal GMs, 8 (38.1%) had PR and 1 (4.8%) had CS movements. Six HIE infants had normal movements (15.8%) and 6 had CS movements (15.8%). The majority of these infants had PR movements n= 26 (68.4%). No infants were classified as having chaotic movements. In the HIE cohort almost twice as many (84.2%) had an abnormal GMA compared with the preterm cohort (42.9%).

<u>Motor outcomes at 12 months</u>

At 12 months, 2 infants did not attend for an assessment, both were from the HIE group. In the preterm group 76.2% had a normal outcome compared with 55.2% of the term group All those with a normal GMA had a normal outcome and all those with CS movements had an abnormal outcome. Of the preterm infants with abnormal motor outcome, 5 had motor delay (23.8%), 1 with CS movements and four with PR movements. None had CP. Five out of the 8 infants with PR had a normal motor outcome at 12 months. In the HIE group, 9 (23.7%) were diagnosed with CP by 12 months of age, all had an abnormal GMA, 6 with CS movements, and 3 with PR. GMFCS classification levels were 5 infants at level 5, one

at level 4, two at level 2, and one at level 1. Six infants had motor delay not related to CP (16.7%). Fifteen infants had PR and normal outcome (41.7%).

Motor outcomes at 24 months

In the preterm group, by 24 months, 20 infants (95.2%) had a normal outcome. Only 1 infant presented with motor delay, they had PR movements.

Twenty-eight term HIE infants (73.7%) had a normal motor outcome, all those had a normal GMA. One infant had motor delay and the rest were part of the 9 infants with CP. Twenty - two infants (57.9%) had PR and normal outcome. All infants with CS GMs had CP. Predictive values for motor outcomes are reported in Table 2.

Table 2: Predictive values for the General Movement Assessment and motor outcomes at 12 and 24 months

Predictive value	**Preterm Infants**		**Term HIE Infants**	
	12 months	**24 months**	**12 months**	**24 months**
Sensitivity (95% C.I.)	80.0% (28.4-99.5%)	100% (2.5-100%)	100% (78.2-100.00%)	100% (69.2-100%)
Specificity (95% C.I.)	68.75% (41.3-88.9%)	60.00% (36.1-80.9%)	28.75% (11.3-52.2%)	21.43% (8.3-41.0%)
PPV	44.44%	11.11%	50.00%	31.25%
(95% C.I.)	(25.5 -65.2%)	(6.8-17.6%)	(43.3-56.7%)	(27.3-35.6%)
NPV	91.67%	100%	100.00%	100.00%
(95% C.I.)	(64.9-98.1%)			
PLR	2.56	2.50	1.40 (1.1-1.8)	1.27 (1.1-1.5)
(95% C.I.)	(1.1-6.0)	1.5-4.3)		
NLR	0.29	0.00	0.00	0.00

(95% C.I.) (0.1-1.7)

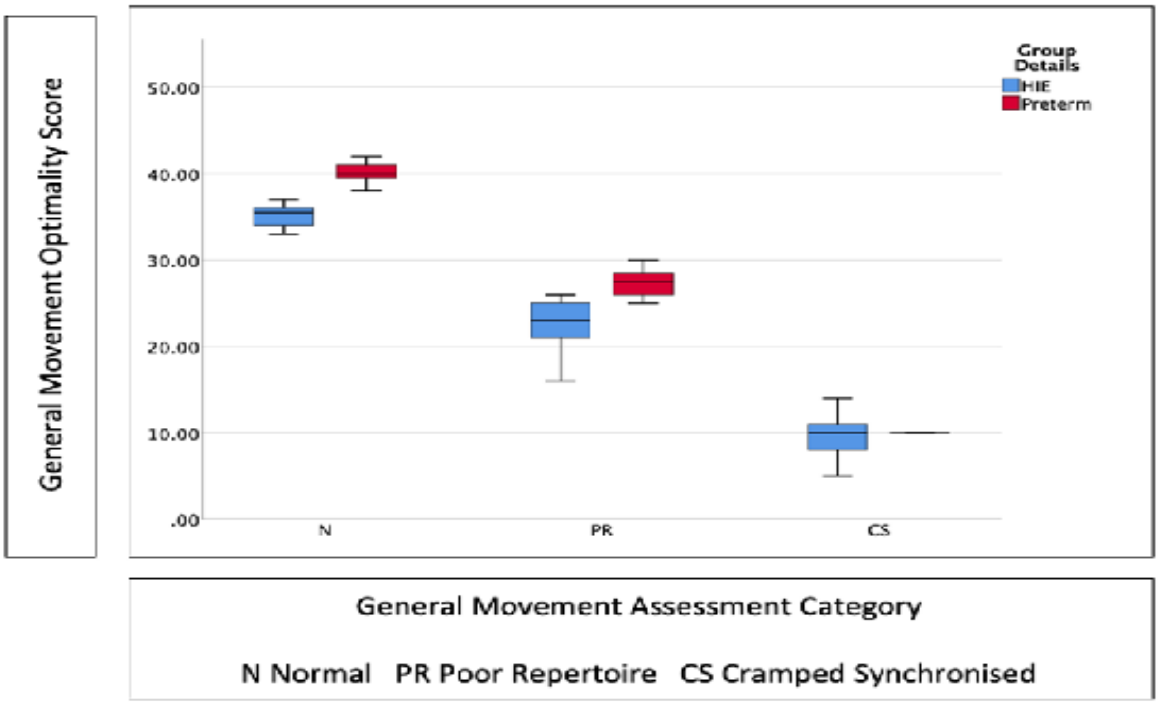
PPV Positive Predictive Value NPV Negative Predictive Value

PLR Positive Likelihood Ratio NLR Negative Likelihood Ratio C.I. Confidence interval

GMOS results

GMOS scores ranged from a minimum of 5 to a maximum of 42. When comparing scores for the preterm and HIE groups, the HIE infants had lower median scores than the preterm infants in both the normal (median 34 vs 40; Independent -Samples Median Test p=0.002) and poor repertoire categories (median 23 vs 27.5; Independent-Samples Median Test p=0.0001). Ranges for PR GMOS scores were also more widely spread for HIE infants (16-26 vs 25-30) (Figure 1)

Figure 1: GMOS scores for GMA categories in preterm and term infants with HIE



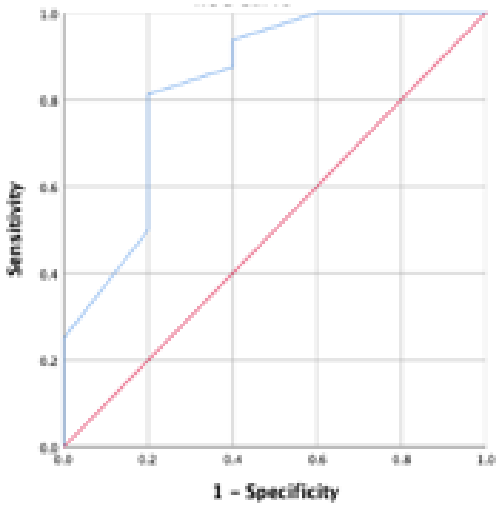
At 12 months of age, in the preterm group median GMOS scores for infants with motor delay and normal outcome were 26 and 39.5 respectively. In the term HIE group median

GMOS scores for infants with motor delay and normal outcome were 16 and 36 respectively, with a median score of 11 for those infants with CP.

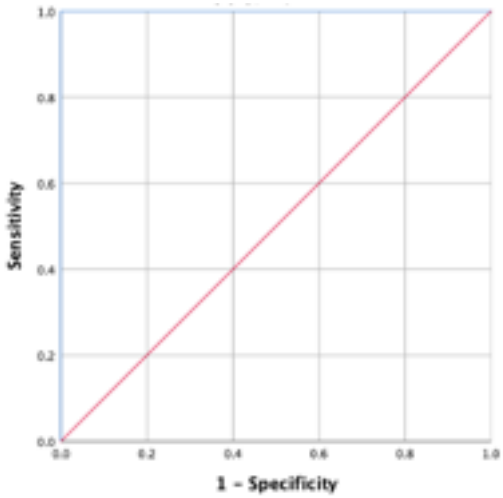
At 24 months of age, in the preterm group median GMOS score for infants with a normal outcome was 38. The single infant with motor delay at 24 months had a GMOS of 30. In the term HIE group median GMOS scores for infants with a normal outcome was 25. The one infant with motor delay had a GMOS of 16. At 12 and 24 months, Receiver Operated Curves (ROC) were produced for each group (Figure 2).

Figure 2: ROC Curves for preterm and term HIE groups at 12 and 24 months of age

Preterm Group

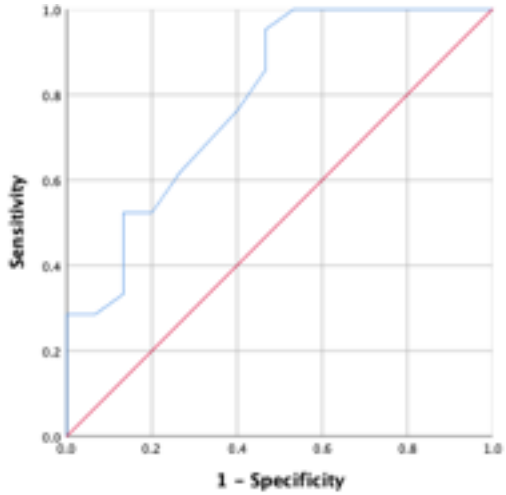


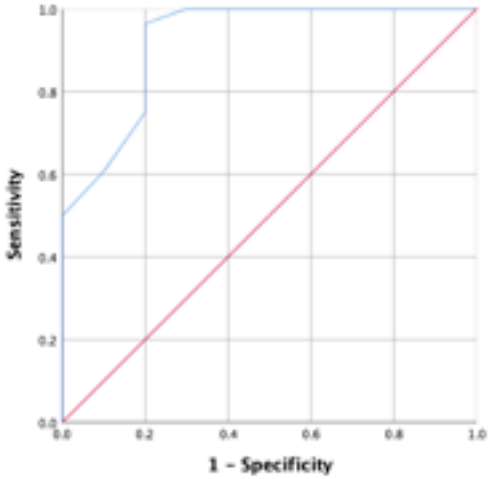
12 months (AUC 0.84)



24 months (AUC 1.00)

Term HIE Group





12 months (AUC 0.79) 24 months (AUC 0.921)

AUC – Area under the curve

The Area Under the Curve values at 12 and 24 months of age show that the GMOS is good for determining motor outcomes at 12 months of age and excellent at 24 months of age. Sensitivity and specificity values for using different GMOS scores as cut-offs for outcomes at 12 and 24 months in comparison with the global GMA were analysed and optimal cut-off scores, where sensitivity and specificity were both maximised are shown for both groups at the two different age points (Table 3).

Table 3: Comparison of GMA sensitivity and specificity values with GMOS optimal cut off scores for sensitivity and specificity as determined by ROC analysis for preterm and term HIE infants at 12 and 24 months of age

	GMA		GMOS		GMOS
PRETERM	***Sensitivity***	***Specificity***	***Cut Off***	***Sensitivity***	***Specificity***
12 months	80%	68.75%	25.5	100%	60%
			26.5	94%	60%
			27.5	87.5%	60%
			28.5 *	81.3%	80%

24 months	100%	60%	21 * 25 26.5	100% 94.7% 84.2%	100% 100% 100%
TERM HIE					
12 months	100%	28.75%	16 * 19 20.5 20.5	100% 95.2% 85.7%	46.7% 53.3% 53.3%
24 months	100%	21.43%	16 * 19 20.5	100% 96.4% 89.3%	70% 80% 80%

*suggested optimal cut off score

DISCUSSION

The GMA at term age showed superior predictive ability for preterm infants when compared with term infants with HIE. The predictive validity of the global GMA during writhing movement age showed good sensitivity for predicting motor outcome at 12 and 24 months for both groups, but low specificity, particularly in the term HIE group. These predictive values are similar to other studies examining both preterm and term infants at term age, where low specificity was also recorded (40-46.2%).[5] Term infants in our study were much more likely to have an abnormal GMA than preterm infants and a large proportion of term infants with HIE had poor repertoire GM's.

The presence of a GMA category of either normal or cramped synchronised movements was highly predictive of a normal or abnormal outcome in both groups. Cramped synchronised movements have been shown to be highly predictive of motor impairment including CP.[14] Many infants with poor repertoire GM's, particularly in the term HIE group, had a normal outcome at 12 months with percentages increasing at 24 months. These movements are frequently seen in high-risk infants [15,16] and other studies report their low predictive value.[17,18] It has been suggested that specificity is comparatively low at writhing age due to the common occurrence of transient movement abnormalities (in particular poor repertoire movements) in high-risk infants up until the third month.[17,19] There is an association, when poor repertoire GM's persist beyond term age, of a lower IQ in infants when compared with those with normal GM's.[20]

The majority of research using the GMA has been with preterm or mixed populations, with limited studies specifically involving term HIE infants who have undergone TH. There is some evidence that transient or prolonged abnormalities in the quality of GMs in infants with HIE before the era of TH are common.[9,,21,22] It has been suggested that the acute systemic illnesses associated with HIE may induce temporary abnormal GMs.[21,22]. However, these studies were undertaken prior to the advent of treatment using TH for HIE. Soleimani et al [23] studied a small sample of infants with HIE but only at fidgety age and prior to the era of TH. Sensitivity and specificity of the General Movements Assessment for neurodevelopmental outcomes at age 12-18-months were 80%-83% and 67%-100%, respectively. Ferrari et al [24] again studied infants with HIE prior to TH at both writhing and fidgety age and found that the GMA carried out at 1 month of age had comparable predictive ability of predicting motor outcome as neuroimaging with MRI. Since TH has been a standardised treatment for infants with HIE a limited number of studies have been published using GMs as an assessment tool. Dekkers et al [25] studied infants with HIE who had received TH at fidgety age only and found that term infants with abnormal GMs later developed CP or developmental difficulties. It is unclear whether GMs in infants who have undergone TH are like those who have not undergone TH. When taking into consideration treatment with TH and recovery times, the optimal timing for a GMA at writhing age for infants with HIE is uncertain. The average age for assessment for our term HIE cohort was approximately two weeks, undertaken just before discharge from the neonatal unit. Assessment at this timepoint is common in clinical practice in the UK, as it enables quality filming and avoids the inconvenience and challenges of parents returning for assessment so soon after discharge home. A recent study examining GMs in an HIE cohort who have received TH demonstrated that assessment at this timepoint is also common clinical practice in America.[10]

Although the high sensitivity of the GMA ensures that infants with motor impairment can be identified at term age and therefore early intervention packages implemented, our study demonstrates the high proportion of false positive results of the GMA at term age.

The distributions of the GMOS varied across both the global GMA categories as well as the preterm and term HIE groups. GMOS score medians for term infants were lower in the

normal and poor repertoire groups than for the preterm groups suggesting quality of GMs is poorer in the term HIE group. Higher GMOS scores were associated with normal GM's, with a gradual decrease in scores as movement repertoire deteriorated. This mirrors the findings from the study by Einspieler et al examining the relationship between a global and a detailed assessment of GM's.[7] In our study the application of optimality scores to the GMA showed that cut off scores can be derived to enhance specificity, particularly in preterm infants, however, specificity values remain low for term infants with HIE.

Limitations

This was a retrospective study of limited sample size in a clinical setting. Therefore, our findings should be interpreted with caution as we are unable to extrapolate the data to the general population. In a clinical setting it is commonplace for just one GMA to be carried out and this was the case in our sample too. Despite this study looking at very early prediction of motor impairment in order to implement intervention within the first few months of life, it has been shown that a trajectory of movements, including at fidgety movement age can enhance the predictive ability of the GMA[3]and this has to be kept in mind in the interpretation of our findings. It was not possible to blind the assessor who carried out the outcome measures at 12 and 24 months as they were involved in clinical care of the infant. In our study, the mean age for GMA for infants with HIE was 2 weeks post term. It could be suggested that a GMA carried out later in the writhing period may be more beneficial in determining those infants with transient abnormalities[10,23].

The improvement in outcome between 12 and 24 months of age might be attributed to the implementation of early motor intervention, for all those infants who scored below the 5th centile on the AIMS. Furthermore, the two outcome assessments have some differences in what they record. The 12 months outcomes using the AIMS looks only at gross motor outcome. The 24 months outcomes using the BSITD III looks at the motor scale which includes fine and gross motor in the composite score. Combining the gross and fine motor scaled scores to create a composite score when using the BSITD III could skew the outcome results and may not truly reflect the gross motor ability of a few cases. There were some infants who scored below the expected values for gross motor ability, who, however, had high scores for fine motor ability. The composite scores for these infants therefore met the cut off for normal motor development despite the gross motor domain scoring below the expected range for the age

CONCLUSION

This study suggests that GMA at term age is less predictive in term HIE infants than preterm infants. The mean age for GMA for infants with HIE was 2 weeks post term. It could be suggested that a GMA carried out later in the writhing period may be more beneficial in determining those infants with transient abnormalities.

However, GMOS cut off scores can improve the specificity of abnormal GM's at term age. This could enable selection of infants with the highest probability of motor impairment for studies into the effects of early motor intervention. Furthermore, it could highlight those infants who would benefit from targeted, motor intervention during the most sensitive times for neuroplasticity. This would allow prioritisation of service delivery, particularly in resource poor areas, and have an effect of lessening the burden on paediatric rehabilitation caseloads.

Suggestions for future research

A longitudinal study to examine the trajectory of GMs and the GMOS in infants who have undergone TH is needed to determine if there is a period in the first few weeks of life when transient abnormal movements are likely to resolve.

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