

Accepted Manuscript

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PII: S1090-3798(17)30145-9

DOI: [10.1016/j.ejpn.2018.02.013](https://doi.org/10.1016/j.ejpn.2018.02.013)

Reference: YEJPN 2395

To appear in: *European Journal of Paediatric Neurology*

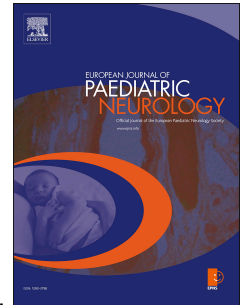
Received Date: 2 March 2017

Revised Date: 8 February 2018

Accepted Date: 27 February 2018

Please cite this article as: Chatzioanidis I, Kyriakidou M, Exadaktylou S, Antoniou E, Zafeiriou D, Nikolaides N, Neurological outcome at 6 and 12 months corrected age in hospitalised late preterm infants -a prospective study, *European Journal of Paediatric Neurology* (2018), doi: 10.1016/j.ejpn.2018.02.013.

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Neurological outcome at 6 and 12 months corrected age in hospitalised late preterm infants -a prospective study

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1. Introduction

Late preterm infants (LPI) are defined as those born at 34-0/7 to 36-6/7 weeks gestational age (GA).^{1,2} They are born near term and are usually considered by parents, caregivers, and health care professionals as developmentally mature and at low risk of morbidity.³

Nevertheless, compared with full-term infants, LPI are immature^{3,4} and at increased risk for neonatal morbidity and mortality.^{4,5} LP newborns comprise the fastest growing subset of neonates, accounting for ~74% of all preterm births, ~8% to 9% of total births in the United States⁶ and 20% to 25% of NICU admissions.⁷

LPI have smaller brains and larger cerebrospinal fluid spaces in comparison with term born infants, but low rates of injury overall. Therefore, the expected trajectory of brain growth that would normally occur during the last 6 weeks of gestation, a critical period of growth and development,⁸ may be disrupted by LP birth.⁹

Numerous reports indicate that LPI are at increased risk for health and developmental sequelae,^{10,11} at three fold increased risk for developing cerebral palsy,^{12,13} with mounting evidence for more subtle neurodevelopmental issues such as cognitive deficits,¹⁴⁻¹⁷ learning difficulties¹⁸⁻²⁰ and behaviour problems at school age;²¹ however, some studies have reported no differences compared with term-born controls.^{22,23}

The common practice is not to follow LPI in neurodevelopmental centers. In order to allow reliable, yet early detection of neurodevelopmental sequelae, assessment at 2 years of age is recommended.²⁴ Reports of neurodevelopmental outcomes during the first 2 years of life are relatively scarce and have produced conflicting results. Some have reported an excess of neuromotor, sensory and cognitive impairments in LPI,^{13,14,25-28} while others have found no significant differences after adjustment for confounders or correction for prematurity.^{25,27,29}

The Hammersmith Infant Neurological Examination is a simple and scorable method for examining infants between 2 and 24 months of age.³⁰ This assessment and the obtained optimality scores were standardized in a low-risk population³¹ and in healthy term infants between 12 and 32 weeks of age.³² The examination has also been validated in a population of term infants who had suffered perinatal asphyxia³³ and has been standardized in very preterm infants between 6 and 15 months corrected age.³⁴ HINE was also applied to a large population of LPI selected on the basis of a normal neurodevelopmental outcome at 24 months. Therefore, the range and frequency distribution of HINE neurological scores in low risk LPI throughout the first year of life have been established. The optimality scores have been developed on the basis of the frequency distribution of the findings for each item.³⁵

Given the paucity of the research to date for neurodevelopmental outcomes in LPI during the first 2 years of life, the conflicting results that these reports produce, and the fact that several authors have asserted the need for large prospective population-based studies,^{4,36} we followed prospectively hospitalized LPI in order to describe the neurological/neuromotor outcome at 6 and 12 months corrected age and the change in neurological scores over this time. Additionally, we attended to identify factors associated with the neurological outcome.

2. Material and Methods

Participants were all LPI with a gestational age 34-0/7 to 36-6/7 weeks being born from December 2013 to December 2014. The study sample group included 157 LP infants that were admitted at our level III neonatal intensive care unit. LPI with genetic or syndromic disease (including major chromosomal abnormalities), as well as LPI hospitalised for less than 48 hours in the NICU and discharged from the maternity unit, were excluded from the study.

The following variables were recorded prospectively: gestational age, birth weight, head circumference, gender, multiparity, birth set (singleton, twin or multiple births), conception method, chorioamnionitis, eclampsia, antenatal steroids exposure, gestational diabetes, intrauterine growth retardation (IUGR), mode of delivery, Apgar scores, small for gestational age (SGA), respiratory distress syndrome, transient tachypnea, pneumothorax, respiratory variables (use of ventilation, duration of oxygen therapy and need for surfactant administration), patent ductus arteriosus, sepsis, intraventricular haemorrhage, periventricular leukomalacia, and days of hospitalization. All 157 infants had early (<72hrs of life) brain ultrasound scans and all also had one at discharge. Cranial scans were assessed by a neonatologist and were classified as 'normal' or 'abnormal' if flares, ventricular dilatation, porencephalic cysts, or atrophy were present, alone or in combination.

Infants were scheduled to be followed up at 6 and 12 months of corrected age. At this appointment, Hammersmith Infant Neurological Examination was performed after a standardized physical examination. All infants were assessed both by a trained neonatologist and a paediatric physiotherapist. The optimality score is based on the frequency distribution of the scores in a low-risk LPI population at 6, 9, and 12 months corrected age.³⁵ The test includes 26 items assessing cranial nerve function, posture, movements, tone, and reflexes. The options for each item are subdivided into four columns and the examiner marks each item by circling the relevant response. A score of 3 is given to the findings of column 1, a score of 2 for column 2, a score of 1 for column

3 and a score of 0 for column 4. The examination gives a sub-score for each subsection and an overall optimality score, ranging from a minimum of 0 to a maximum of 78. In the follow-up visit, parents reported about motor milestones of development such as head control, sitting, rolling, crawling, standing, and walking as they described in section 2 from the Hammersmith Infant Neurological Examination.

2.1 Statistical Methods

The relation between categorical variables was investigated using χ^2 or Fisher exact tests. To determine the relation between continuous variables, the Mann-Whitney or the t test was used depending on the distribution. To prove correlations between test results and basic characteristics of study infants, the Spearman rank correlation coefficient was used. Linear regression was used to examine the relation between perinatal/neonatal characteristics of LPI and global scores at 6 and 12 months corrected age.

A difference in statistical significance was considered if P value was <0.05 . The data was analysed using the SPSS 11.5 statistical software. The study was approved by hospital's ethical committee.

3. Results

3.1 Characteristics of Population

During that period 157 LPI were admitted in our NICU. Of those, 23 were excluded: 6 were found to have genetic disorders, 1 died, and 16 were hospitalised in the NICU for less than 48 hours and transferred to the maternity unit. A total of 134 infants included in the follow-up examination. At 6-month follow-up, 118 (88.05%) LPI were examined at a corrected age of mean (\pm SD) 6.04 (\pm 1.02) months, whereas at 12 months follow up, 106 (79.1%) infants were examined at a corrected mean (\pm SD) age of 12.41 (\pm 1.54). In total, 106 infants (79.1%) received both the assessments at 6 and 12 months' corrected age.

The mean (\pm SD) gestational age was 34.86 (\pm 0.75) weeks while the mean (\pm SD) birth weight was 2281.86 (\pm 469.22) g. Perinatal, neonatal characteristics and complications during hospital stay of infants that completed the study and those lost to follow up were comparable and are listed on Table 1. Reasons for loss to follow-up were families moving to other countries, parental refusal to cooperate and multiparity.

3.2 Hammersmith Infant Neurological Examination Testing

3.2.1. Function of cranial nerves

LPI had the same median score of 15 (ranged from 13 to 15) both at 6 and 12 months corrected age, without statistically significant differences ($p=0.322$) and with minimal changes of distribution of scores over time for single item of this subsection. A score of 14-15 was regarded as optimal and a score below 14 as suboptimal both at 6 months and 12 months (maximum score possible, 15) (Table 2).

3.2.2 Posture

There were statistically significant differences in the sub-scores of posture subsection between 6 months (median of 8, ranged from 6 to 18), and 12 months corrected age (median of 14, ranged from 6 to 18) ($p<0.001$). In posture subsection, head in sitting position, trunk posture in sitting position, hands, arms at rest showed the most marked differences over time ($p<0.001$), and also feet and leg posture ($p=0.006$ and $p=0.019$ respectively). At 6 months the scores between 14 and 18 were regarded as optimal and below 14 as suboptimal. At 12 months a score between 16 and 18 was regarded as optimal and below 16 as suboptimal (maximum score possible, 18) (Table 2).

3.2.3 Movements

LPI had the same median score of 6 (ranged from 4 to 6), both at 6 and 12 months corrected age, without statistically significant differences, ($p=0.159$) (maximum score possible, 6). A score of 5-6 was regarded as optimal and below 5 at 6 months and below 6 at 12 months as suboptimal (Table 2).

3.2.4 Tone

There were statistically significant differences in the sub-scores of tone subsection between 6 (median 22, ranged from 14 to 24) and 12 months corrected age (median 24, ranged from 18 to 24) ($p=0.008$). The tone subsection, passive shoulder elevation ($p=0.05$), popliteal angle ($p=0.009$), pull to sitting ($p=0.001$) and ventral suspension ($p=0.0144$) were the items that showed the most marked differences over time. At 6 months a score between 19 and 24 was regarded as optimal and below 19 as suboptimal. At 12 months a score between 20 and 24 was regarded as optimal and below 20 as suboptimal (maximum score possible, 24) (Table 2).

3.2.5 Reflexes and reactions

There were statistically significant differences in the sub-scores of subsection. Reflexes and reactions between 6 (median of 7, ranged from 4 to 15), and 12 months corrected age (median of 13, ranged from 10 to 15) ($p<0.001$). The subsections of reflexes, arm protection ($p=0.01$), vertical suspension ($p=0.006$), lateral tilting ($p=0.001$) and forward parachute ($p=0.002$) items had the most significant differences over time. At 6 months a score between 8 and 15 was regarded as optimal and below 8 as suboptimal while at 12 months a score between 11 and 15 as optimal and below 11 as suboptimal (Table 2).

3.2.6 Global Score

There were statistically significant differences in the global score between 6 (median of 59 ranged from 47 to 76), and 12 months corrected age (median of 70, ranged from 58 to 78) ($p < 0.001$) (Table 2).

Based on frequency distribution, at 6 months a global score between 64 and 78 was regarded as optimal while below 64 as suboptimal.³⁵ Optimal scores achieved in 25.4% (30/118) of LPI. At 12 months a global score between 70-78 was regarded as optimal and below 70 as suboptimal (35). Optimal scores achieved in 63.2% (67/106) of LPI (Table 2, 3). Table 3 illustrates the frequency distribution of global scores at 6 and 12 months corrected age.

3.2.7 Global Scores and Subscores according to Gestational Age

No significant differences were found between infants born at 34 and those born at 35 weeks both for sub-scores and global scores at 6 and 12 months corrected age. On the other hand, significant differences were found between infants born at 34 and those born at 36 weeks both for posture sub-score and global scores at 12 months corrected age. In advance, significant differences were found between infants born at 35 and those born at 36 weeks both for posture and reflexes sub-scores and global scores at 12 months corrected age (Table 4).

3.2.8 Factors associated with Global Scores at 6 and 12 months Corrected Age

The regression analysis indicated that significant independent factors and factors at $p < 0.15$ that potentially influenced the global score at 6 months corrected age included: SGA ($p < 0.001$), chorioamnionitis ($p = 0.001$), IUGR ($p = 0.086$), and eclampsia ($p = 0.092$). Those statistically significant factors were selected for a further evaluation of interactions between factors. Multiple

regression analysis revealed that SGA ($p= 0.003$) was the only factor that significantly influenced the Hammersmith Infant Neurological Examination score.

At 12 months corrected age, a similar analysis was used. Significant independent factors and factors at $p < 0.15$ that potentially influenced the global score at 12 months of corrected age included SGA ($p= 0.016$), and use of antenatal steroids ($p= 0.091$). All significant variables were entered into the multiple linear regression models as a first step. SGA ($p= 0.025$) was also the only factor that significantly influenced the global score at 12 months of corrected age.

3.2.9 Need for physiotherapy

At 6 months follow up, 42/106 (39,6%) infants were referred to early intervention physiotherapy services, while at 12 months follow up, 19 more infants needed to be referred to early intervention services (Total 61/106, 57.54%)

3.2.10 Neuromotor Outcomes

Head control was exhibited at a mean (\pm SD) 4.31 (± 0.59) months. Stable sitting was apparent at a mean (\pm SD) 8.31 (± 0.59) months, while rolling at a mean (\pm SD) 5.22 (± 1.27) months. Crawling was achieved at a mean (\pm SD) 9.65 (± 1.79) months, and standing at a mean (\pm SD) 9.81 (± 2.92) months. At 12 months follow up 58.5% (62/106) achieved independent walking at a mean (\pm SD) 12.10 (± 1.50) months.

4. Discussion

The main purpose of the current study was to describe the neurological/neuromotor outcome in an LPI population, followed longitudinally at 6, and 12 months corrected age, the change in neurological scores over this time, and the factors that possibly influenced global scores in both time intervals. In the current study, the Hammmersmith Infant Neurological examination was applied at the corrected age of 6 and 12 months. Although the study population was born only a few weeks before term age, when the optimality score for term infants at 12 months was applied,³¹ only 34.9% (37/106) showed optimal scores. Seemingly, in the study by Romeo et al, only 55% of LPI demonstrated optimal scores.³⁵ All LPI of the current study were at risk for developing neuromotor disorders, since they all were hospitalized in a level III NICU. Romeo and coworkers could show that the 10th percentile and the median global HINE score of their near-term cohort were lower than in the term population.³⁵ They also suggested that, when examining infants born at 35 and 36 weeks, the criteria of optimality developed for infants born full-term should not be applied, even if they are assessed at the corrected age.

We could demonstrate that 74.6 % of LPI in our study had suboptimal scores (below 64 and the 10th percentile developed for LPI) ranged from 47 to 76 at 6 months corrected age and 36.8% had suboptimal scores (below 70 and 10th percentile developed for LPI) ranged from 63 to 78 at 12 months corrected age.³⁵

The neurological scores in our study population statistically changed over time from 6 to 12 months corrected age showing a progressive increase in global scores with different rates of increase in the different sub-sections. Posture, tone, and reflexes showed marked differences over time, thus indicating a gradual change towards normality at 12 months corrected age.

When we analyzed the HINE scores in the study population according to their gestational age at birth, we couldn't find any significant differences between infants born at 34 and 35 weeks, at 6 and 12 months corrected age. We found significant differences between infants born at 34 and 36

weeks for the subscore of posture and the global score at 12 months corrected age.³⁵ It is of interest however, that contrary to Romeo et al, we found significant differences between infants born at 35 and 36 weeks for subscores of posture, reflexes, and global score at 12 months corrected age. These results may be attributed to the fact that all LPI were born with similar clustering between 34 and 36 weeks GA: 31, 1%, 36, 7%, and 32%, at 34, 35, and 36 weeks GA, respectively.

Furthermore, born SGA was the only factor that significantly influenced the global score at 6 and 12 months corrected age. The exact mechanisms underlying the association of the above factor to outcome remain unknown. It has been noted that SGA infants as a group when compared to AGA infants using the HINE, scored within optimal range; however lower than AGA infants in the median global score.³⁷

In the current study, suboptimal HINE scores in LPI population during the first year of life could be also attributed to brain immaturity and its vulnerability to injury. The last half of gestation (including the late prematurity period) is described as a “critical period” for brain development and characterized by rapid and/or dramatic changes in 1 or more molecular, neurochemical, and/or structural parameters.³⁸ At 34 weeks’ gestation, the brain weighs 65% of term brain weight and gyral and sulcal formation is incomplete.³⁹

Romeo et al could not exclude a further increase of HINE scores in LPI after 12 months of corrected age, allowing them to reach the scoring levels of low-risk term infants. On the other hand, it is very well known that LPI have disorders of sensory integration, cognitive and emotional regulation difficulties that affected their functioning at school age, and an increased incidence of attention, behavioral problems when compared with term-born children.^{19,40} It could be hypothesized that HINE suboptimal scores are related to suboptimal long-term neurodevelopmental outcomes, with cognition being at the highest risk and persisting the longest at an older age. Therefore, an assessment at 6 and 12 months might allow for earlier identification of a problem and permit prompt intervention potentially reducing the subsequent need for special education.

Currently, LPI do not routinely followed after NICU or maternity ward discharge and are not referred to early intervention services, a program that might minimize subsequent disability.^{8,41} The population of the current study was followed up until 12 months corrected age and referred to an early intervention physiotherapy program according to NDT/Bobath method once a week. The percentage of infants needed early intervention physiotherapy program was gradually increased over time showing a higher need with increasing age.

However, these results should be interpreted with caution. The current study did not involve a population-based cohort, which may have limited the replication of findings to other populations. It did reflect care provided at a regional neonatal intensive care unit. Cranial ultrasonography was the neuroimaging study of choice but it demonstrates poor sensitivity in the detection of diffuse white matter abnormalities.^{42,43} In addition, there is a lack of a neurodevelopmental outcome at 18-24 months in order to confirm the presence of suboptimal neurological assessment and to relate the scores obtained within 12 months to the presence of cerebral palsy or mild disability or normal outcome.

5. Conclusions

We believe that LPI discordant to a typical development after 1 year of age need to be closely monitored. While the risks of an atypical development may be lower for LPI than for extremely preterm infants (with a relatively low and stable incidence), they account in total for 74% of all preterm births.⁷ Therefore, a small deviation in neurodevelopmental outcome could put a larger strain on the educational and medical systems. Physicians, early intervention programs, policies makers, parents, therapists, and teachers need to be aware of the long-term neurodevelopmental risks associated with LPI. In conclusion, a reorganization of services with better allocation of resources to late preterm infants could detect an early developmental delay and ameliorate later developmental problems through early intervention services.

Acknowledgements

We would like to thank Tzoulakis Christos, MD for collecting data for this study.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors

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7. Appendices

Table 1: Basic Perinatal, neonatal characteristics and complications during neonatal period of study infants

	<i>Assessed (n=106)</i>	<i>Not-assessed (n=14)</i>	<i>P-value</i>
Gestational age (weeks) ^a	35 (34-36)	35 (34-36)	ns
Birthweight (g) ^b	2289.9 (461.2)	2484.3 (519.8)	ns
Head Circumference (cm) ^b	32.2 (1.72)	32.4 (1.75)	ns
Gender (male), n(%) ^c	58 (54.7)	8 (57.1)	ns
Multiparity (n) ^a	40 (37.7)	10 (71.4)	0.021
Multiple gestation, n (%) ^c	17 (16)	2 (14)	ns
Conception-IVF, n (%) ^c	25 (23.6)	4 (28.6)	ns
Mode of delivery (caesarean section), (n%) ^c	95 (89.6)	12 (85.7)	ns
Chorioamnionitis ,n (%) ^c	5 (4.7)	1 (7.7)	ns
Eclampsia, n(%) ^c	3 (2.8)	0	ns
Gestational diabetes, n(%) ^c	9 (8.5)	0	ns
APGAR scores 5min ^a	9 (5-10)	8 (7-10)	ns
Prenatal steroids, n(%) ^c	70 (67.3)	8 (57.1)	ns
Small for gestational age, n(%) ^c	40 (37.7)	3 (23.1)	ns
Intrauterine Growth Retardation, n (%) ^c	22 (20.8)	3 (23.1)	ns
Respiratory distress syndrome, n(%) ^c	18 (17)	3 (21.4)	ns
Surfactant administration n(%) ^c	12 (11.3)	2 (14.3)	ns
Transient Tachypnea, n(%) ^c	33 (31.1)	3 (21.4)	ns
Pneumothorax, n(%) ^c	7 (6.6)	2 (14.3)	ns
Patent ductus arteriosus, n(%) ^c	16 (15.1)	1 (7.14)	ns
Nosocomial sepsis, n(%) ^c	12 (11.3)	2 (15.4)	ns
Ventilation days (n) ^a	0.15 (0-8)	0.2 (0-4)	ns
O ₂ days (n) ^a	0.5 (0-24)	0.5 (0-4)	ns
Flares/mild ventricular dilatation, n(%)	7 (6.6)	1 (7.1)	ns
Intraventricular Hemorrhage I-IV	0	0	
Periventricular Leucomalacia	0	0	
Hospital stay (days) ^a	9 (2-34)	8 (2-40)	ns

a. Mann –Whitney U test was used; data presented as median (range)

b. The t-test was used for probability value; data presented as mean (\pm SD)

c. Fisher exact or χ^2 exact t-test accordingly; data presented as n (%)

*Flares, mild ventricular dilatation

Table 2: Median, range and 10th percentile of global and subsection scores

	6months		12months		12months
	Median	Optimal	Median	Optimal	Optimal score**
	(Range)	score*	(Range)	score *	
Cranial nerve	15 (13-15)	15 (12-15)	15 (13-15)	15(13-15)	15 (12-15)
Posture	8 (6-18)*	16 (7-18)	14 (6-18)	17 (8-18)	18 (6-18)
Movements	6 (4-6)	6 (3-6)	6 (4-6)	6 (3-6)	6 (3-6)
Tone	22 (14-24)*	21 (16-24)	24 (18-24)	23 (17-24)	24 (17-24)
Reflexes	7 (4-15)*	11 (5-15)	13 (10-15)	13 (8-15)	15 (11-15)
Global	59 (47-76)*	68 (60-74)	70 (58-78)	73 (63-78)	76 (63-78)
score					

*p<0.01 between 6mo and 12mo

*The optimal scores from Romeo et al [35], are reported in this column

**The optimal scores from Haataja et al [31], are reported in this column

Table 3: The Frequency Distribution of the Global Scores at 6 and 12 months

Score 6mo(n=118)	Frequency n(%)	Score 12mo(n=106)	Frequency n(%)
47	2 (1.7)	47	0
48	2 (1.7)	48	0
50	6 (5.1)	50	0
51	4 (3.4)	51	0
52	4 (3.4)	52	0
53	8 (6.8)	53	0
54	6 (5.1)	54	0
55	6 (5.1)	55	0
56	4 (3.4)	56	0
57	6 (5.1)	57	0
58	10 (8.5)	58	2 (1.9)
59	6 (5.1)	59	1 (0.9)
60	4 (3.4)	60	0
61	4 (3.4)	61	1 (0.9)
62	8 (6.8)	62	1 (0.9)
63	8 (6.8)	63	0
64	4 (3.4)	64	4 (3.8)
65	2 (1.7)	65	0
66	4 (3.4)	66	8 (7.5)
67	2 (1.7)	67	5 (4.7)
68	6 (5.1)	68	13 (12.2)
69	2 (1.7)	69	4 (3.8)
70	2 (1.7)	70	15 (14.2)
71	0	71	2 (1.9)
72	2 (1.7)	72	13 (12.3)
73	2 (1.7)	73	2 (1.9)
74	2 (1.7)	74	13 (12.3)
75	0	75	3 (2.8)
76	2 (1.7)	76	14 (13.2)
77	0	77	1 (0.9)
78	0	78	4 (3.8)

Table 4: Median and range of global and subsection scores according to gestational age

GA		34 (33)	35(39)	36 (34)	34 vs 35	34 vs 36	35 vs 36
(n)		Median (Range)	Median (Range)	Median (Range)			
6mo	Global score	58 (47-76)	60 (50-74)	58 (50-68)	<i>ns</i>	<i>ns</i>	<i>ns</i>
	Cranial nerves	15 (13-15)	15 (13-15)	15	ns	Ns	ns
	Posture	8 (6-18)	8,5 (6-16)	6 (6-16)	ns	ns	ns
	Movements	6	6 (4-6)	6	ns	ns	ns
	Tone	22 (14-24)	22 (18-24)	22 (18-24)	ns	ns	ns
	Reflexes	6,5 (4-13)	9 (5-15)	6 (4,5-13)	ns	ns	ns
12mo	Global score	70 (58-78)	70 (61,5-76)	75 (58-78)	<i>ns</i>	0.013	0.011
	Cranial nerves	15 (13-15)	15 (13-15)	15	ns	Ns	ns
	Posture	14 (6-18)	14 (6-16)	16 (6-18)	ns	0.022	0.004
	Movements	6	6 (4-6)	6	ns	Ns	ns
	Tone	24 (3-24)	24 (18-24)	23 (20-24)	ns	ns	ns
	Reflexes	12 (10-15)	11,5 (10,5-15)	15 (11-15)	ns	ns	0.031

Highlights

- Late Preterm Infants had suboptimal scores in Hammersmith Infant Neurological Examination
- The neurological scores statistically increased over time from 6 to 12 months
- Being born Small for Gestational Age was the only factor adversely related to outcome