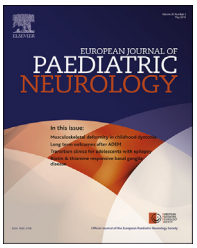
EUROPEAN JOURNAL OF PAEDIATRIC NEUROLOGY XXX (2016) 1–6

Official Journal of the European Paediatric Neurology Society



Original article

Early psychomotor development of low-risk preterm infants: Influence of gestational age and gender

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ARTICLE INFO

Article history:
Received 14 October 2015
Received in revised form
3 March 2016
Accepted 10 April 2016

Keywords:
Gender differences
Hammersmith infant neurological examination
Preterm
Late preterm

ABSTRACT

Background: The influence of gestational age and gender in the neurodevelopment of infants during the first year of age is not yet fully elucidated.
Aims: The purpose of this study was to identify the early occurrence of neurodevelopmental differences, between very preterm, late preterm and term born infants and the possible influence of the gender on the neurodevelopment in early infancy.
Methods: A total of 188 low-risk infants, 69 very preterms, 71 late-preterms, and 48 term infants were assessed at 3, 6, 9, 12 months corrected age using the Hammersmith Infant Neurological Examination (HINE). At two years of age infants performed the Mental Developmental Index (MDI) of the Bayley Scales of Infant Development.
Results: The main results indicate that both very preterms and late-preterms showed significant lower global scores than term born infants at each evaluation ($p < 0.001$) at HINE and namely, at 3 months for the subsections "cranial nerve" and "posture" and at every age for "tone"; no gender differences has been evidenced in neurological performances. At the MDI, very preterms showed significant lower scores ($p < 0.01$) than both late-preterm and term born infants; gender differences were observed for preterms only (very and late), with best performances for females.
Conclusions: Our results point out the presence of gestational age and gender-dependent differences in the development of infants assessed during the first 2 years of life.

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http://dx.doi.org/10.1016/j.ejpn.2016.04.011
1090-3798/

1. Introduction

In the last two decades preterm birth has become more frequent[1] due to several risk factors including maternal ones (alcohol, drugs, diabetes, nephropathy etc.), pregnancy complications, intra-uterine grow retardation, multiple births etc. Preterm infants usually showed good developmental outcomes, similar to term born infants, but a proportion of them may develop important and long-lasting neurological sequelae.[2] The neurological outcome of preterm infants has been extensively investigated especially in those born at a gestational age (GA) of 32 weeks or less.[3–10] Most studies reported that 10–20% of preterm infants develop severe neurological disabilities while another 20–30% have minor neurological impairments. However, identification of differences and variations in development of preterm infants should be interpreted cautiously, as infants could be reported as having problems when their developmental course is simply different from that of term born infants.[11] Another issue that should be clarified is the role of gender in early infancy; multiple differences between males and females both in normal physiology and pathophysiology of diseases have been reported by some recent studies.[12–17] Histomorphometric studies confirmed a sexual dimorphism in human cerebral cortex, as males show higher average neuronal density, but with smaller neuronal units than females.[13,14] Furthermore, a greater biological vulnerability of male infants has been claimed on the basis of possible genetic disorders involving the X chromosome, influence of female hormones reducing the effects of brain damage, incidence of infections and metabolic disorders.[18] More recently[19] genetic factors such as polymorphisms of the interleukin 6 gene (IL6), has been reported to have a specific role in the development of CP. Although this increasing interest for the influence of gender on the early brain development, very little is known about possible differences on the neurodevelopment outcome in low-risk preterm infants.

The aim of the present study was to identify the possible influence of gestational age on the neurodevelopment of very preterm, late preterm and term infants at low neurological risk. We also wished to evidence whether the gender has a specific influence on the early neurodevelopment.

2. Materials and methods

The infants described in this study are part of a large cohort admitted to the Neonatal Unit of the University of Catania between January 2007 and December 2008 and consecutively enrolled in a follow-up prospective research program for infants born less than 37 weeks. For the purpose of this study, infants were selected from the whole population according to the following inclusion criteria: i) normal cranial US or transient flares (lasting less than 2 weeks) or germinal layer haemorrhages grade 1 (IVH I) according to Volpe,[20] ii) weight appropriate for gestational age (GA) (weight between 10th and 90th percentile), iii) absence of congenital malformations or genetic disorders, iv) absence of neurosensory deficits. A control cohort of low risk term infant were enrolled at birth at the postnatal ward of the same Institute and followed up to 2 years. This latter group included infants with a GA of 37–42 weeks and birth-weight equal to or greater than 2550 g, with no history of major prenatal, perinatal or postnatal medical complications. The preterm cohort was subdivided in 2 subgroups according to GA: very preterm (GA $\leq$ 32 weeks) and late preterm (GA between 33 and 36 weeks). Parental permission was obtained in all cases. The Ethical Committee of our Institution approved the study.

2.1. *Cranial ultrasound*

In preterm infants cranial ultrasound (US) examinations were performed within the first week of life and then at least weekly up to discharge, and always around term age. In term infants cranial ultrasound (US) examination was performed before discharge at birth.

2.2. *Neurodevelopmental assessment*

The Hammersmith Infant Neurological Examination (HINE) was performed at 3, 6, 9 and 12 months corrected age (CA)[21,22] for preterm infants and chronological age for term born ones. This is a simple and scorable method for assessing infants between 2 and 24 months of age, including items for cranial nerve, posture, movements, tone and reflexes. An optimality score is obtained by calculating the distribution of the frequency of the scores in the normal population, defining as optimal all the scores found in at least 90% of the cohort. The overall score ranges from a minimum of 0 to a maximum of 78. At 9 and 12 months, a score $\geq$73 is regarded as optimal, <73 as sub-optimal[21]; while at 3 and 6 months a score between 67 and 70 is considered within the normal range.[22]

A further neurodevelopmental assessment was performed at 2 years of CA; it included a structured neurological examination according to Touwen[23] and a developmental assessment, the Mental Developmental Index (MDI) of the Bayley Scales of Infant Development, Second Edition (BSID II),[24] which is widely used for cognitive function in high-risk infants.[25] All neurological and developmental examinations were performed by one of the authors (DMMR), who was blind of the birth characteristics of the infants.

2.3. *Statistical analysis*

The anthropometric variables (weight and gestational age) and MDI results at BSID II were reported as mean ± SD (standard deviation). HINE scores were reported as median and range at different ages, for each group of infants (very preterm, late preterm, term born infants). Comparisons across gestational age groups (very preterm, late preterm, term born infants) were done by a non-parametric test (Kruskall-Wallis test); comparisons between gender groups and between US scans (normal Vs IVH or transient flairs) were analysed by the Wilcoxon rank-sum test (Mann-Whitney U test).

To assess the independence between gender and gestational age on HINE scores, a multivariate analysis was conducted by linear regression.

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Statistical analysis was performed using the "Stata Statistical Software: Release 10" (StataCorp LP, College Station, Tx). The level of significance was set at $p < 0.01$.

3. Results

A total of 203 infants were eligible for the study. Fifteen of them did not attend one or more of the assessments and were therefore excluded. One hundred and eighty-eight infants represented the final population, 69 very preterm, 71 late preterm and 48 term infants.

The main characteristics of the three groups of infants were reported in Table 1. Males represented more than 50% of infants in all the groups.

3.1. *Cranial ultrasound*

A normal US scan was observed in about 35% of preterm infants, transient flares in 59% and IVH in 6%. A normal US scan was observed in 100% of term cohort. No gender differences were observed in US scans.

3.2. *Neurological examination*

Term born infants reported better scores at each evaluation than both very preterm and late preterm infants, as showed in Table 2. A significant statistical difference has been reported for global scores ($p < 0.001$) and tone ($p < 0.001$) at each age assessment (3, 6, 9, 12 months) and at 3 months for the subsections "cranial nerve" and "posture". On the other hand in the subsections "reflexes" and "movements", no significant difference has been evidenced between these three groups.

No significant differences were observed between late preterm and very preterm infants in the neurological evaluation at 3, 6, 9 and 12 months of life. No statistical significant difference according to the gender has been evidenced. No statistical significant difference according to US scans has been evidenced in both very and late preterm.

3.3. *Neurodevelopmental assessment at two years*

All the infants assessed showed a normal neurological and neurodevelopmental outcome. The MDI at BSID II was >85 in all the three group of infants. The mean scores were significantly lower ($p < 0.01$) in very preterm (92.9 ± 8.2) than both late-preterm (96.7 ± 9.3) and term born infants (97.1 ± 6.5); the last two groups showed similar MDI scores ($p > 0.05$). Gender differences were reported for very preterm ($p < 0.001$) and late-preterm ($p < 0.01$) with better scores for females, whereas in term born infants no gender differences were observed ($p > 0.05$).

3.4. *Multivariate analysis*

Gestational age was independently associated to HINE global scores at 3, 6, 9 and 12 months; no gender association with HINE scores was found. These results are showed in Table 3.

4. Discussion

During the first year of life, the HINE has been reported to have a good predictive power for motor outcome both in very preterm and late preterm infants as well as in term born infants with hypoxic-ischemic encephalopathy.[3,9,26–30] The scores obtained in our sample of infants are consistent with those previously reported in other studies with infants at similar GA,[3,9,21,22,28] but for the first time we compared the neurological development of these three groups of infants, specifically looking at the influence of gestational age, excluding infants with moderate and severe brain lesions and neurosensory deficit.

The scores observed in term born infants are similar to those already reported by Haataja et al.[21,22] Therefore, we had the possibility to compare the neurological development of very preterm and late preterm infants with those of term born infants since 3 months, longitudinally, up to 12 months CA. Our data showed that both very preterms and late preterms, scored significantly lower than term born infants in most of the subsections evaluated (3/5). The subscores of tone at all ages, and posture at 3 months were significantly lower in preterm infants. These results are in keeping with previous studies, reporting tone and posture patterns as discriminating between preterm and term born infants from neonatal age to two years.[3–6,31,32]

It is of interest, however, that although very preterm reported a trend of HINE scores generally lower than late preterm infants, these differences were not statistically significant. This can be explained by a similar modality of development of the immature brain in both population even in those infants with no major brain damage[33]; this might

Table 1 – Clinical characteristics of the total population.

	≤32 weeks n = 69		33–36 weeks n = 71		37–41 weeks n = 48	
	Male	Female	Male	Female	Male	Female
Sex (M/F)	38	31	39	32	28	20
Gestational age	29.3 ± 2.3	29.6 ± 2.0	35.0 ± 1.1	35.0 ± 0.8	38.4 ± 1.4	38.0 ± 1.1
Birth weight	1322 ± 334	1279 ± 317	2510 ± 552	2361 ± 532	3220 ± 435	2804 ± 502
US						
Normal	12	12	12	13	28	20
Transient flares	23	16	26	18	0	0
IVH	3	3	1	1	0	0

US: ultrasound scan; IVH: Intraventricular Haemorrhage.

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Table 2 – Median and range of global and subsection scores in very preterm, late-preterm and term born infants.

	Cranial N	Posture	Movements	Tone	Reflexes	Global score
	Median -range	Median -range	Median -range	Median -range	Median -range	Median -range
3 Months						
Very preterm	14 (12–15)	14 (6–16)	6 (2–6)	19 (16–23)	9 (4–13)	62 (51–67)
Late-preterm	14 (12–15)	14 (9–16)	6 (4–6)	19 (14–22)	9 (6–14)	62 (57–69)
Term	15 (13–15)#	15 (12–18)*	6 (5–6)	21 (17–22)*	10 (5–14)	65.5 (62–69)*
6 Months						
Very preterm	15 (12–15)	15 (9–18)	6 (2–6)	20 (16–23)	10 (5–15)	66 (52–71)
Late-preterm	15 (13–15)	15 (10–18)	6 (4–6)	20 (16–24)	11 (7–15)	66 (60–72)
Term	15 (13–15)	16 (12–18)	6 (5–6)	22 (18–24)*	11.5 (7–14)	69 (64–74)*
9 Months						
Very preterm	15 (14–15)	16 (11–18)	6 (2–6)	21 (18–24)	12 (6–15)	70 (57–76)
Late-preterm	15 (13–15)	16 (14–18)	6 (5–6)	22 (17–24)	13 (8–15)	71 (63–75)
Term	15 (13–15)	17 (15–18)	6 (5–6)	23 (19–24)*	13 (9–15)	72.5 (65–78)*
12 Months						
Very preterm	15 (14–15)	17 (12–18)	6 (2–6)	22 (19–24)	13 (7–15)	72 (60–77)
Late-preterm	15 (13–15)	17 (15–18)	6 (5–6)	22 (18–24)	13 (8–15)	73 (64–77)
Term	15 (13–15)	17 (15–18)	6 (5–6)	23 (19–24)*	13 (11–15)	74 (65–78)*

*P < 0.001; #P < 0.01.

suggest that low-risk preterm infants follow a specific neurological development during the first year of age, irrespective to GA. Besides, while it is not surprising that very preterm infants show a more immature neurological and neurodevelopmental outcome compared to term infants, it is of interest that late preterm infants showed significant differences compared to term infants for neurological findings only. This could be explained looking at the timing of cortical grey and white matter development for which the last 6 weeks of gestation are essential.[10,34] This can explain why late preterm infants are at higher risk of neurological deficit than term born infants up to 12 months[10] even when no major brain lesions are detected, but scoring slightly better than very preterms. On the other hand at two years results of the Bayley scales and Towen neurological assessments where similar in late preterm and term born infants as previously reported,[35] this confirming that differences between these two groups of infants are transient and disappear at 2 years when no neurological specific risks are present.

Table 3 – Univariate analysis of associations between the independent variables and HINE global scores.

	Crude OR (95% CI)	P
Hine assessment at 3 months CA		
Gender		
Male	−0.449 (−1.351–0.452)	0.327
Gestational age		
Term born (baseline)	–	–
Late-preterm	−4.238 (−5.377–−3.098)	**0.0001**
Very-preterm	−4.135 (−5.293–−2.977)	**0.0001**
Hine assessment at 6 months CA		
Gender		
Male	−1.0366 (−1.922–0.160)	0.021
Gestational age		
Term born (baseline)	–	–
Late-preterm	−1.872 (−2.979–−0.765)	**0.001**
Very-preterm	−3.233 (−4.357–−2.108)	**0.0001**
Hine assessment at 9 months CA		
Gender		
Male	−0.115 (−0.936–0.706)	0.782
Gestational age		
Term born (baseline)	–	–
Late-preterm	−1.603 (−2.641–−0.565)	**0.003**
Very-preterm	−2.801 (−3.855–−1.747)	**0.0001**
Hine assessment at 12 months CA		
Gender		
Male	−0.356 (−1.113–0.401)	0.355
Gestational age		
Term born (baseline)	–	–
Late-preterm	−1.927 (−2.883–−0.970)	**0.0001**
Very-preterm	−2.509 (−3.480–−1.537)	**0.0001**

Significant results ($p < 0.01$) are indicated in bold type.
OR: odds ratio; CI: confidence interval.

Several studies have reported that female preterms show higher survival rate and better neurological outcome,[1,10,15,36] but many studies included in their cohort infants with brain lesions and sensory impairments. For this reason we choose to include in the present research only those infants at low risk, reducing possible clinical bias. Our data evidenced that infants without major brain lesions or sensorial problems show no significant differences in the early neurological development due to gender irrespective of GA. On the contrary, the neurodevelopmental assessment showed significantly differences between the two gender in preterm (both and very) but not in term infants with males presenting lower scores compared to female infants. These results are in agreement with previous studies that evidenced a greater biological vulnerability of male preterm infants that can cause a higher risk for neurodevelopmental delay.[15,16] In fact, gender differences in presence of injuries in the immature brain are reported in literature[37–39] and indicate that male gender remains an independent risk factor for adverse neurodevelopmental outcomes due to a different resistance to hypoxia and a higher incidence of preterm birth.[39] It is of note that these differences are still present excluding infants at high neurological risk, implying that gender per se has a specific influence on the early neurodevelopment in preterm

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infants. This can be explained looking at both grey and white matter volumes in low risk preterm infants that are described as significantly reduced specifically in preterm males.[36,39]

Although we identified a specific influence of GA and gender on the early development of preterm infants, the relatively short follow-up period (24 months) doesn't allow any speculation on later development, and assessment at older ages could probably result in a more accurate measure of final neurodevelopmental outcome.

4.1. *Conclusion*

In conclusion, our study confirm and extend the data of the literature on the neurological vulnerability of preterm infants according to GA and gender in comparison to term born infants.

Our longitudinal data evidence the modality of development of preterm infants and can be considered as reference data for the development of low risk preterm infants. These results can be useful for clinicians involved in the preterm follow up in order to discriminate whether the early neurological development of a preterm infant is different from the term born one but similar to other low risk preterms or is showing specific pathological signs that should be further investigated or that need possible early treatment.[11] With these information it is also possible to reassure parents who are questioning the future of their child who is not following the usual development of full term infants.[5]

Conflicts of interest

None.

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