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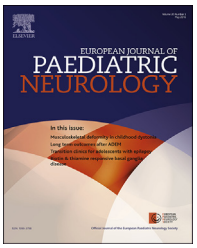

Original article

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

Domenico M. Romeo [a,*], *Claudia Brogna* [a,d], *Francesca Sini* [a], *Mario G. Romeo* [b], *Francesco Cota* [c], *Daniela Ricci* [a]

[a] *Pediatric Neurology Unit, Catholic University Rome, Italy*
[b] *Neonatal Intensive Care Unit, Department of Paediatrics, University of Catania, Italy*
[c] *Neonatal Intensive Care Unit, Catholic University Rome, Italy*
[d] *Unit of Child and Adolescent NeuroPsychiatry, Laboratory of Molecular Psychiatry and Neurogenetics, University "Campus Bio-Medico", Rome, Italy*

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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.

* *Corresponding author*. Pediatric Neurology Unit, Catholic University, Largo Gemelli, 8, 00168, Rome, Italy. Tel.: +39 0630156307; fax: +39 0630154363.
E-mail address: domenicomarco.romeo@policlinicogemelli.it (D.M. Romeo).

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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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