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Predictive role of early milestones-related psychomotor profiles and long-term neurodevelopmental pitfalls in preterm infants

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ABSTRACT

Background: Developmental milestones are useful signposts developed to assess the pace and the trajectory of maturation occurring during specific time-windows called *critical periods*. The predictive role of their clinical assessment in premature infants is challenging, however, it actually represents an easy and reliable tool at follow-up.
Aim and study design: Relying on a milestone-based neurological examination, we aimed to detect the interdependence between time of achievement of each milestone with long-term neuropsychological and neurodevelopmental outcomes. The influence of pre-perinatal events was also considered.
Patients & methods: Two-hundred-eighty patients (53.2% M) were serially assessed by classic neurological examination during the first 18 months and subsequently evaluated by Griffiths Developmental Mental Scale. Children were sorted by ranges of gestational age and compared according to their different profiles.
Results: The Extremely PreTerms appeared to have a globally delayed development with subsequent attentional and behavioral troubles. Differently, the older peers, from Moderately to Full Term ones, although did not show significant differences in achievement of gross motor skills, had a stable delay of visual and social skills across the age ranges. This gap was not evidenced at the long-term evaluation, except for the Extremely PreTerm children. Pre-perinatal factors played a significant role on short and long term neurodevelopmental outcome.
Conclusions: Early assessed classic neurological examination might address neurodevelopmental trajectories in PreTerm children in which visual and social skills appear to be the mostly affected. It remains the easiest and most reliable tool of evaluation throughout the follow-up programs.

1. Introduction

Brain development is the result of the combined work played by genetic, epigenetic and environmental factors [1]. Developmental milestones are useful signposts developed to assess the pace and the trajectory of maturation occurring during specific time-windows called critical periods [2]. A critical period is a time during early postnatal life when the development and maturation of functional properties of the brain, its "plasticity," is not merely dependent by age but rather by experience and enriched environment [3]. The duration of gestation is one of the many factors that influence fetal and post-natal maturational pace and its trajectory, in fact, preterm delivery <37 weeks of gestational age (GA), interrupts a unique condition of protected, multisensory stimulation that allows neural system to develop and mature, causing a deviation of the planned trajectory of fetal maturation and placing newborns into an unexpected unforeseen developmental pathway [3]. Several studies explored neurodevelopmental features of preterm (PT) children, usually focusing on specific ranges of GA. Major attention has been paid to extremely preterm (EPT) children that usually present with perinatal neurological morbidities but also a wide constellation of long-term neurodevelopmental disorders, behavioral troubles and academic failure [4]. In contrast, there is a more recent interest about moderately and late preterm children (MPT and LPT) that, in the past, were considered at low risk both as neonates and postdischarge [4,5]. Very early developmental profile might address subsequent mode of maturation of behavioral and adaptive skills [6] and help to identify atypical trajectories, possibly taking advantages from early intervention. Short and long-term neurological outcomes in preterm children have been explored using different methods. Validated models of neonatal

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neurobehavioral assessment have been proposed by eminent authors such as Milani Comparetti, Bradzelton and Prechtl for the evaluation of the at-risk newborns in the neonatal intensive care units and at the follow-up services, all mainly aimed to estimate selected early functional indicators such as autonomic stability, motor repertoire and behavioral modulation [7]. However, despite they offer a significant comprehensive assessment of very young children, most of them, such as analysis of general movements or application of standardized developmental scales, are not readily applicable in all neonatal or pediatric units and require a significant time for administration. The milestones-based approach could be an easy and reliable tool, with specific time-related goals, widely applicable throughout the follow-up visits. The old question "what should I expect and when" from a preterm baby might be a confounding factor that need to be faced to forecast a trajectory.

The aim of this study was to identify the milestones-based scheme of developmental profiles in specific groups of PT children sorted by ranges of GA, examined by a classic scheme of neurological examination proposed by Dubowitz and Dubowitz [8]. Then we explored the interdependence between time of achievement of each of the examined skills with long-term outcome assessed by Griffiths Developmental Mental Scale (GMDS) [9], and, the long-term rate of neurodevelopmental disturbances (low attention, hyperactivity, Autism Spectrum Disorders-ASDs) diagnosed by DSM-5 criteria [10]. We also investigated the influence of prenatal and perinatal events on time of achievement of each of gross motor, communicative-verbal and visual skills. To the best of our knowledge, this kind of clinical, time-related, milestones-based approach by specific groups of GA has never been used before to perform a systematic analysis of early adaptive developmental trajectories and their correspective long term outcomes, so far.

2. Patients & methods

The children sample had been previously included into a neuropsychiatric follow-up program of the at risk newborn starting at 3 months of age, with further assessments at 6, 9, 12, 18, 24, 30 and 36 months. Clinical and demographic data included: age, sex, GA, birth weight (BW), Apgar score at 1 and 5 min, perinatal adversities (premature rupture of membranes-PROM, hypoglycemia, seizures and sepsis). Neuroimaging data were gained by cranial ultrasound scans (cUS) performed by an Esaote AUS with a 7.5 MHz sector probe transducer to all newborns, by the same experienced neonatologist. Serial cUSs were performed at days 1–3, day 7 and at term corrected age (CA). Funduscopy and acoustic otoemission test and/or auditory evoked potentials were performed in all children. Time of achievement of developmental stages was investigated by the Hammersmith Infant Neurological Examination scheme [8], assessed by Dubowitz and Dubowitz [8] to evaluate neurological exam, motor function and state of behavior in infants from 2 to 24 months [8]. The scale was administered by two child neurologists among the authors (GD and MB), highly experienced on neonatal and infant neurological assessment, and, attribution of each time of milestone achievement was accurately discussed. The main psychomotor milestones were included for our analysis. Among gross motor skills head control, sitting, standing and walking were considered. Appearance of autonomous walking was also reported by the children's parents. Time of appearance of babbling, single words (for single words we meant at least 5–10 words with a semantic role), smiling and pointing were obtained from the parents' interviews and/or patients observation. Visual skills were explored by the model proposed by Egan [11]. Early visual fixation and the ability to follow the examiner's face or a moving object were assessed. The examiner placed the infants in a supine, held upright position, to some 20–25 cm from his face and talked gently until the baby fixed his eyes. The examiner moved his head slowly to each side to induce following and full abduction of the infant's eyes. Visual fixation and following were also assessed by a red ball suspended on a string at some 20–25 cm from the baby's face, then, moving the ball slowly first to one side then the other to induce full abduction [7,8,11]. Long-term assessment of neurodevelopmental disorders such as low attention, hyperactivity/impulsivity and ASDs was performed. Based on GA, children were divided into 6 groups. Group 1 included 10/280 extremely preterm (EPT) children with GA below 28 wks; group 2 included 43/280 very preterm (VPT) children with GA between 29–$31^{6/7}$ wks; group 3 encompassed 66/280 moderate preterm (MPT) children with GA of 32–$33^{6/7}$ wks; group 4 included 92/280 Late Preterm (LPT) children, with GA between 34–$36^{6/7}$ wks, group 5 included 27 Early Term (ET) children with GA of 37–$38^{6/7}$ wks; and finally, group 6 including 42 Full Term (FT) children with GA beyond $39^{6/7}$ wks [4]. Long-term evaluation was performed in all children at the mean age of 33.7 using Griffiths Mental Development Scale-Revised (GMDS 2–8; section III frame (25–36 months), as it is usually scheduled in our follow-up program [9]. GMDS was administered by a highly trained psychologist, and, for the purposes of this study we defined a "normal" DQ as ≥80 [9]. Demographic and perinatal features of the patients are summarized in Table 1. Approval from the Local Ethical Committee was obtained for this study.

3. Statistical analyses

The numerical data were expressed as mean, median and range (minimum and maximum) and the categorial variables as numbers and percentages. Examined variables did not present normal distribution as verified by *Kolmogorov Smirnov test*; consequently the non-parametric approach has been used. The role of GA were evaluated by comparing the mean time of achievement of the single developmental milestones by a given group and each of the subsequent groups (e.g. group 1 versus groups 2, 3, 4, 5 and 6; group 2 versus groups 3, 4, 5 and 6; group 3 versus groups 4, 5, and 6; group 4 versus groups 5 and 6; group 5 versus group 6). The *Mann Whitney test* was estimated to perform, for each numerical parameter (BW, Apgar 1 and Apgar 5, age of achievement of head control, sitting, standing, walking, babbling, single words, smiling, visual fixation and following, pointing) statistical pairwise comparisons. In this analysis, the *Bonferroni correction procedure* was applied in order to control the multiple type I error rate when multiple hypotheses have to be tested. According to this procedure, the α level (0.050) must be divided into the total number of pairwise comparisons (15) with 6 groups, thus, the resulting corrected α value was 0.003. The non-parametric *Spearman correlation test* was applied to assess the existence of any significant interdependence between GA with Apgar at 1 and 5 min, PROM, hypoglycaemia, seizures, sepsis, cUS findings. Categorial variables (each GMDS subquotients and hypertonus) were assessed by *Chi Square test* or, alternatively, the exact *Fisher test*, if necessary (i.e. in cases in which a frequency in the contingency table was <5). *Linear regression models* were estimated to assess the possible dependence of age of achievement of head control, sitting, standing, walking, babbling, single words, smiling, visual fixation and following, pointing from some potential explicative variables such as GA, BW, Apgar 1 and 5, PROM, hypoglycaemia, sepsis, neonatal seizures, cUS findings. *Logistic regression models* were estimated to verify the possible dependence of each dichotomous variable such as outcomes of GMDS subscales on some potential explicative variables such as age of achievement of head control, sitting, standing, walking, babbling, single words, smiling, visual fixation and following, pointing. Statistical analyses were performed using SPSS 11.0 for Window package. $p < 0.050$ was considered to be statistically significant [12].

4. Results

4.1. Demographic and clinical features

Three-hundred twenty children, 54% M, aged between 24 and 36 months, mean 30.5, followed-up at the outpatients service of