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.

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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
neurobehavioral assessment have been proposed by eminent authors such as Milani Comparetti, Bradzelon 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 pre-natal 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 respective 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 Esato 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 29–316/7 wks; group 3 encompassed 66/280 moderate preterm (MPT) children with GA of 32–336/7 wks; group 4 included 92/280 Late Preterm (LPT) children, with GA between 34–366/7 wks, group 5 included 27 Early Term (ET) children with GA of 37–386/7 wks; and finally, group 6 including 42 Full Term (FT) children with GA beyond 396/7 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 categorical variables as numbers and percentages. Examined variables did not present normal distribution as verified by Kolmogorov Smirnoff 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. Categorical 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
neonatal neurology of our Unit between January 2011 and November 2014, were retrospectively recruited in the study. Among the 320 children, 40 were excluded for several reasons: severe neonatal encephalopathy (NE) with cUS showing severe echogenicity changes associated to increased risk of cerebral palsy \[13\] (n = 13), chromosomal disorders or other genetic or acquired disorders associated to neurodevelopmental impairment (Down syndrome n = 5; Noonan syndrome n = 1; Edward syndrome n = 1; congenital hypothyroidism n = 3; neurofibromatosis type 1 n = 1; withdrawn or short follow-up duration n = 15). Finally, 280 patients, 149 M (53.2%) and 131 F (46.8%), 224/280 preterms (80%) and 56/280 full terms (20%) were enrolled in the study. All patients showed moderate echogenicity changes at cUS (periventricular grades 1–2, intraventricular grades I–II; local basal ganglia/thalamus-BGT) \[14\]. Mean and median values of BW, Apgar scores at 1 and 5 min and time of achievement of each developmental milestone of the sample are summarized in Table 1.

4.3. Comparisons of developmental milestones among the six groups

Group 1 EPT children, showed significantly delayed gross motor abilities if compared to all the other groups. Language, visual and social milestones showed none or less significant differences only if group 1 was compared to groups 2 and 3. Significant differences still emerged on gross motor, visual and social, but not in language milestones between group 2 and group 3. In contrast, group 2 showed a global delayed neurodevelopmental profile in comparison with all the other groups. Conversely, a significant discrepancy still remained on early gross motor development (head control, sitting and standing) between group 3 versus groups 4–6; whereas, only visual and social skills were significantly delayed in children of group 4, LPT, if were compared to children of groups 5 and 6, namely ET and FT. Moreover, no significant differences for any of the developmental milestones arose between group 5 and group 6. Related \(p\)-values of all couples comparisons are shown in Table 2.

4.4. Neurodevelopmental disorders among the six groups

Given the young age of our patients, none received diagnosis of ADHD according to DSM-5 criteria, however, dysfunctional behavioral patterns were clinically assessed and semilogically defined. For this reason pattern of low attention \((p = 0.053)\) was found with predominance in group 1, EPT children \((90\% ; p = 0.001)\). Pattern of hyperactivity/impulsivity was diagnosed in 12.1% of children among which 40% in group 1 \((p = 0.009)\). Differently, ASD satisfying DSM-5 criteria, was diagnosed in 6/280, 2.1% of children, among which 2/6 (33.3%) in group 2, 1/6 (16.6%) in group 5 and 3/6 (50%) in group 6. No significant differences emerged in the ASDs rate among the six groups \((p = 0.670)\).

To note, children with diagnosis of ASDs were mostly born at mean GA 36.3 SD ± 4.2 \(\text{median 38; range 31–40}\). Major neurological signs (hypertonus and hyperexcitability) were more frequent in group 1, but their rate did not reach statistical significance probably due to the lower number of subjects within this group. Other disorders related with preterm behavioral phenotype such as emotional instability, aggression and sleep-wake disturbances were also assessed, however, for simplicity and clarity’s sake, we chose to commit these findings to further works.

4.5. Outcomes of the GMDS among the six groups

Locomotor subscale was pathologic in 79.7% of PT children among which 90% belonged to group 1 \((p = 0.005)\). Language subscale was pathologic in 78.2% of PT among which 90% in group 1. Eye and Hand Coordination subscale was pathologic in 80% among which the majority was placed in group 1. Performance subscale was pathologic in 79.6%

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**Table 1**

<table>
<thead>
<tr>
<th>Group 1 ( (N = 10) )</th>
<th>Group 2 ( (N = 43) )</th>
<th>Group 3 ( (N = 66) )</th>
<th>Group 4 ( (N = 92) )</th>
<th>Group 5 ( (N = 27) )</th>
<th>Group 6 ( (N = 42) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>B.W.</td>
<td>1.22 ± 0.26</td>
<td>1.42 ± 0.26</td>
<td>1.78 ± 0.35</td>
<td>2.21 ± 0.47</td>
<td>2.83 ± 0.38</td>
</tr>
<tr>
<td>Apgar 1</td>
<td>5.90 ± 1.72</td>
<td>6.72 ± 1.56</td>
<td>7.07 ± 1.43</td>
<td>7.80 ± 1.23</td>
<td>8.00 ± 1.77</td>
</tr>
<tr>
<td>Apgar 5</td>
<td>7.70 ± 0.94</td>
<td>8.20 ± 0.98</td>
<td>8.52 ± 0.96</td>
<td>8.88 ± 0.89</td>
<td>9.14 ± 1.16</td>
</tr>
<tr>
<td>Head control</td>
<td>6.00 ± 1.82</td>
<td>4.37 ± 0.90</td>
<td>4.06 ± 0.72</td>
<td>3.72 ± 0.81</td>
<td>3.29 ± 0.60</td>
</tr>
<tr>
<td>Fixation</td>
<td>10.70 ± 3.62</td>
<td>8.27 ± 1.27</td>
<td>7.95 ± 0.88</td>
<td>7.52 ± 1.38</td>
<td>7.11 ± 1.08</td>
</tr>
<tr>
<td>Standing</td>
<td>14.60 ± 3.59</td>
<td>11.13 ± 1.31</td>
<td>10.81 ± 1.25</td>
<td>10.65 ± 1.39</td>
<td>10.07 ± 1.10</td>
</tr>
<tr>
<td>Walking</td>
<td>18.10 ± 3.17</td>
<td>14.72 ± 1.73</td>
<td>13.93 ± 1.87</td>
<td>13.76 ± 1.88</td>
<td>13.40 ± 1.30</td>
</tr>
<tr>
<td>Babbling</td>
<td>9.80 ± 2.74</td>
<td>8.90 ± 2.10</td>
<td>8.60 ± 2.29</td>
<td>8.03 ± 1.73</td>
<td>8.33 ± 2.18</td>
</tr>
<tr>
<td>Single words</td>
<td>16.10 ± 3.07</td>
<td>14.13 ± 2.70</td>
<td>13.39 ± 1.94</td>
<td>12.81 ± 1.98</td>
<td>13.48 ± 2.77</td>
</tr>
<tr>
<td>Smiling</td>
<td>5.10 ± 0.73</td>
<td>4.65 ± 1.32</td>
<td>4.16 ± 1.27</td>
<td>4.01 ± 0.93</td>
<td>3.55 ± 0.93</td>
</tr>
<tr>
<td>Fixation</td>
<td>4.20 ± 0.78</td>
<td>4.30 ± 1.33</td>
<td>3.71 ± 0.94</td>
<td>3.54 ± 0.73</td>
<td>3.33 ± 0.78</td>
</tr>
<tr>
<td>Following</td>
<td>4.50 ± 0.84</td>
<td>4.46 ± 1.35</td>
<td>3.98 ± 0.93</td>
<td>3.70 ± 1.076</td>
<td>3.51 ± 0.97</td>
</tr>
<tr>
<td>Pointing</td>
<td>16.44 ± 3.39</td>
<td>13.38 ± 2.31</td>
<td>12.58 ± 1.89</td>
<td>13.04 ± 2.93</td>
<td>12.26 ± 2.45</td>
</tr>
</tbody>
</table>
among which 80% was in group 1 \((p = 0.002)\). Personal-Social subscale showed pathologic scores in 67.2%, however, two peaks of prevalent pathologic results emerged at the two extremitities of GA: one in group 1 \((40\% , p = 0.011)\) and one in group 6 \((38.1\%)\).

### 4.6. Univariate and multivariate regression analyses

The interdependence among GA and other perinatal variables with the age of achievement of developmental milestones and rate of neurodevelopmental disorders were explored. Achievement of head control, sitting, standing and walking was significantly dependent on BW, GA, Apgar scores at 1 and 5 min, WMA and IVH I-II, conversely, the earlier milestones of language development such as babbling and single word fixation were not dependent on the same variables. The occurrence of neonatal seizures negatively influenced both gross motor and language development. On long-term assessment, significant interdependence emerged among all the above mentioned variables and Locomotor, Language, Eye and Hand Coordination and Performance GMDs subscales. No interdependence between Personal and Social subquotients’ scores and all the examined pre-perinatal variables, emerged in our patients. Conversely, later age of achievement of early gross motor, language and social-communicative milestones were significantly associated to abnormal results in Locomotor, Language, Eye and Hand Coordination and Performance subscale of GMDs. Finally, delayed achievement of all early gross motor and communicative- verbal milestones was associated to higher rate of low attention and delayed achievement of all early gross motor and communicative milestones. The occurrence of neonatal seizures negatively influenced both gross motor and language development. On long-term assessment, significant interdependence emerged among all the above mentioned variables and Locomotor, Language, Eye and Hand Coordination and Performance GMDs subscales. No interdependence between Personal and Social subquotients’ scores and all the examined pre-perinatal variables, emerged in our patients. Conversely, later age of achievement of early gross motor, language and social-communicative milestones were significantly associated to abnormal results in Locomotor, Language, Eye and Hand Coordination and Performance subscale of GMDs. Finally, delayed achievement of all early gross motor and communicative-verbal milestones was associated to higher rate of low attention and hyperactivity symptoms on long-term observation. Statistical results of the regression models analyses are summarized in Tables 3–6.

### 5. Discussion

A classic neurological, milestones-based, evaluation throughout the first 18 months of life allowed us to identify different temporal neurodevelopmental profiles in groups of PT and FT children that were compared according to ranges of GA. Long-term evaluation performed by GMDs showed stability of the global developmental delay of the first 18 months only for the EPT group, whereas, the older peers did not show failures evidenced in early clinical assessment. We evaluated the children considering the chronological age with the aim to identify the exact, prematurity-dependent, neuromotor and neuro-behavioral gap and the time point when the adaptive developmental trajectory of the PT groups would have taken similar direction of the FT ones, if it would. In fact, maturation after premature birth proceeds according to atypical speed and trajectory not always in accordance with the presumed neurobiological maturation level of CNS [15]. One of the major concepts of neural bases of neurodevelopment is that critical periods represent epochs of highest brain plasticity on which experience and environmental influences produce permanent changes in neuronal circuits, after that, the same experience is no longer able to elicit the same modifications [3]. Bearing in mind that critical periods onset are conditioned by the more enriched environmental stimuli rather than age, time of achievement of each milestone in PT children potentially represent a measure of their brain’s ability of assimilation and adaptation to experience and sensory forces. We hypothesized that a classic model of neurological examination of the first 18 months could be an easy and accessible tool to trace psychomotor trajectories of GA-related groups, detect their adaptive developmental pathways and help to forecast long-term outcome. In our study, as it could be expected, the EPT group showed globally delayed developmental milestones respect to the older groups, remaining stable over time. In detail, developmental gap on gross motor skills was progressively disappearing across the groups up to MPT and LPT that showed minor differences compared to the FT ones, and to LTP, ET and FT, that showed similar motor development profiles. Only later appearance of visual fixation and following was stable across the PT groups, even in the older, compared to the FT ones. At least, gross motor skills appeared to be uniformly gained starting from the MPT children up to the older ones, whereas, visual and social skills were constantly delayed even across the older. However, this gap was not evidenced at the long-term evaluation even by the GMDs subscales testing visual and visuo-motor coordination skills such as Eye and Hand Coordination and Performance, except for the EPT children. Two reasons could explain this finding: a recovery of visual skills in PT children at long-term testing, or, a more likely insufficient sensibility of GMDs to detect quite selective neuropsychological visual defects. The atypical maturation of visual pathways in PT children have been reported and related to their

### Table 3

Regression coefficients of univariate regression models for dependence of each developmental milestone from prenatal and perinatal variables \((p < 0.050\) was indicated as *; \(p < 0.001\) as **).
long term neurodevelopmental failures [15]. Evidence is accumulating that the ability to visually explore the environment contribute to form the bases for social interaction and self-regulation, skills which are fundamental to cognitive development [15]. Vicari et al. reported on combined deficits in visuospatial processing, spatial working memory, and attentional skills in PT children at pre-school age [16]. Moreover, school-aged PT children were reported to show lower scores in visual and visuo-spatial tasks if compared to the FT ones [17]. Attention deficit that represents one of the cornerstone of ADHD is likely to take origin during the early development in infancy, hence, as opposed to the more frequent use to assess attentional children’s abilities during the school-age, there would be a serious need to assess children between birth and 6 years of age in order to understand this developmental process and, most importantly, to target effective intervention [18].

The delayed visual skills disclosed by an accurate early neurologic examination in PT children may be subsequently investigated by standardized tasks and trained early in infancy [19]. Beside early visual attention, also motor skills take part to the development of higher cognitive functions, since dorsal-stream informations feeds into systems used during visual–spatial manipulation and visual control of action [19]. Two neurofunctional systems are known to subservice visual perception. The ventral ‘perceptual’ stream, projecting from early visual areas to inferior temporal cortex, contributes to detailed visual representations of objects and events, attach significance to them and establish their causal relations. By contrast, the dorsal ‘action’ stream, projecting from early visual areas to the posterior parietal cortex, plays a critical role in the real-time control of action, transforming information about the location and disposition of goal objects into the coordinate frames of the effectors being used to perform the action [20]. Impaired motor development early in life may affect children’s ability to explore their environment and gain experiences, which may in turn result in later cognitive delay, intellectual disability, or behavioral problems [21]. Johnson and Marlowe reported on a unique neuropsychological profile of PT children in which the core dysfunctions were characterized by inattention/hyperactivity, social, and emotional difficulties [22]. A recent meta-analysis confirmed pronounced attention and internalizing problems in VPT and VLBW children [23]. Significant correlations between motor ability and adaptive functions in children with ADHD, especially in their adaptive domains of home living, socialization, and self-direction were evidenced [24]. Although none of our children fulfilled DSM-5 criteria for ADHD, the rate of atypical neurobehavioral patterns such as low attention and hyperactivity was significantly higher in EPT children, that obviously showed major gross motor and visual skills delay at classic neurologic assessment. In contrast, LPT children, that did not present higher rate of such neurodevelopmental patterns, showed the absence of significant gross motor delay, despite slower achievement of visual skills. A prominent role of motor skills rather than visual ones might be hypothesized in our series on long-term occurrence of pathologic neurodevelopmental patterns, suggesting that their early identification and treating could provide more effective management of these children. Although other classification systems are currently employed to diagnose neurodevelopmental disorders in young children, we chose to categorially define only those neuropsychiatric disorders satisfying DSM-5 criteria [9]. Indeed, despite of some limited awareness of early developmental and educational differences, DSM-5 has been shown to provide a better connection of early infant psychiatric disorders to the rest of child and adolescent psychiatry [25]. This was in accordance with our aim of a trajectory forecast and a future longer neurological and neurobehavioral follow-up of our children. Differently than attention and behavioral skills, ASDs were apparently more frequent in the FT respect to the PT group in our study, and, Personal-Social subscale of the GMDS was the sole not significantly affected by extreme prematurity. While the association between ADHD and preterm birth was well documented, the prevalence of ASDs is being more recently explored with more debated results [26–29]. The high rate of positive EPT children at ASDs screening studies could be overestimated by the frequent co-occurrence of cognitive and language impairments associated to severe prematurity whose long-term neuropsychiatric implications would require larger longitudinal studies [30]. However, although a genetic complex background is well-known to underlie ASDs obviously independent from GA [31], nonetheless, the impact of epigenetic or environmental factors, possibly GA-related, may be at play in premature birth and later atypical development [30]. How and to what extent did the pre-perinatal variable influence milestones achievement in our PT children? Gross motor, visual and social but not language delay were dependent from BW, that, resulted to be the sole variable significantly different across all the groups. Until the 90s perinatal and later developmental outcomes of PT children were related to the children’s BW that appeared to be the sole not significant across the different groups. Furthermore, although other genetic or environmental factors, possibly GA-related, may be at play in premature birth and later atypical development [30]. How and to what extent did the pre-perinatal variable influence milestones achievement in our PT children? Gross motor, visual and social but not language delay were dependent from BW, that, resulted to be the sole variable significantly different across all the groups. Until the 90s perinatal and later developmental outcomes of PT children were related to the children’s BW that appeared to be the sole not significantly affected by extreme prematurity. While the association between ADHD and preterm birth was well documented, the prevalence of ASDs is being more recently explored with more debated results [26–29]. The high rate of positive EPT children at ASDs screening studies could be overestimated by the frequent co-occurrence of cognitive and language impairments associated to severe prematurity whose long-term neuropsychiatric implications would require larger longitudinal studies [30]. However, although a genetic complex background is well-known to underlie ASDs obviously independent from GA [31], nonetheless, the impact of epigenetic or environmental factors, possibly GA-related, may be at play in premature birth and later atypical development [30]. How and to what extent did the pre-perinatal variable influence milestones achievement in our PT children? Gross motor, visual and social but not language delay were dependent from BW, that, resulted to be the sole variable significantly different across all the groups. Until the 90s perinatal and later developmental outcomes of PT children were related to the children’s BW that appeared to be the sole significantly different across all the groups.

Table 4
Regression coefficients of multivariate regression models for dependence of each developmental milestone from prenatal and perinatal variables (p < 0.050 was indicated as *; p < 0.001 as **).

<table>
<thead>
<tr>
<th>Head control</th>
<th>Sitting</th>
<th>Standing</th>
<th>Walking</th>
<th>Babbling</th>
<th>Single words</th>
<th>Smiling</th>
<th>Fixation</th>
<th>Following</th>
<th>Pointing</th>
</tr>
</thead>
<tbody>
<tr>
<td>G.A.</td>
<td>−0.140**</td>
<td>−0.075</td>
<td>−0.055</td>
<td>−0.008</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>−0.067**</td>
<td>−0.055</td>
</tr>
<tr>
<td>B.W.</td>
<td>0.127</td>
<td>−0.131</td>
<td>−0.132</td>
<td>−0.324</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>−0.097</td>
<td>−0.073</td>
</tr>
<tr>
<td>Appar 1</td>
<td>−0.091*</td>
<td>−0.121*</td>
<td>−0.168*</td>
<td>−0.142</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>0.100</td>
<td>/</td>
</tr>
<tr>
<td>Appar 5</td>
<td>/</td>
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<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>Neonatal seizures</td>
<td>0.587</td>
<td>1.357</td>
<td>0.856</td>
<td>0.956</td>
<td>4.914**</td>
<td>3.345*</td>
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<tr>
<td>L.V.H.</td>
<td>0.721*</td>
<td>1.318**</td>
<td>1.001*</td>
<td>1.228*</td>
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<tr>
<td>W.M.A.</td>
<td>−0.060*</td>
<td>0.157</td>
<td>0.310</td>
<td>0.522</td>
<td>0.657*</td>
<td>0.502*</td>
<td>0.055</td>
<td>0.193</td>
<td>0.598</td>
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<td>B.G.T.</td>
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<td>/</td>
<td>/</td>
<td>3.771**</td>
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Table 5
Odds Ratio (OR) and relative 95% Confidence Interval (CI) of univariate logistic regression models for dependence of each GMDS subscale score from prenatal and perinatal variables (p < 0.050 was indicated as *; p < 0.001 as **).
risk of major disabilities, PT infants born weighing between 501 and 1500 g were shown to have the higher mortality and morbidity [17]. In addition, minor neurodevelopmental dysfunctions were more likely to occur in smaller, more premature infants in previous reports [32]. The effects associated with low BW may be distinct from those of prematurity alone. A regression analysis found that ADHD symptoms were associated with babies small for gestational age rather than preterm [33] with early fetal growth restriction being possibly the precursor of the delays and abnormalities of brain development [34]. GA was later preferred as a more reliable measure of physical and neurological states of newborns [35] because it seemed to play a major determinant of brain maturation with consequent either vulnerability or resilience related to preterm delivery [35,36]. Indeed, multiple perinatal factors were related to short and long term outcome of PT children most of them related to both GA and BW [17]. The relationship that we evidenced between Apgar scores and both early and long term gross and fine motor development was debated in previous works. Mercure et al. showed that 28% of newborns presenting with NE with Apgar scores < 3 had normal brain MRI scans or minor WMA, whereas, 95% of the infants with Apgar scores > 7 and abnormal clinical assessment at 48 h after birth, had abnormal scans [37]. Few previous population-based Scandinavian studies have found an association between Apgar score at 5 min and childhood outcome [38]. Among 988 children evaluated at 5 years with diagnosis of cerebral palsy (CP), 11% had Apgar score < 3 versus and the 0.1% with Apgar score > 10 (odds ratio (OR) 53) showing a high risk for CP in children with lower Apgar score at 5 min [39]. Patterns of brain damage were significantly related to the time of achievement of early milestones in our study. In a previous work we showed the relationship between WMA and GA, now we evidenced the wide effect on global development played by white matter pattern of maturation [40]. WMA could express widespread dysmaturative brain abnormalities that may be related both to genetic and acquired environmental factors [40]. Antenatal events such as infections, exposure to drugs or toxic agents, utero-placental dysfunctions or thrombophilic factors may expose fetal brain to long-standing intrauterine insults potentially inducing WMA and subsequent later neurodevelopmental impairment [41]. Moreover, the impact of early life health on neonatal brain has been stressed by Chau et al. that showed that systemic illnesses and critical care therapies in PT children are linked to abnormal brain microstructure and metabolism, in its turn, robustly associated to abnormal psychomotor outcome at 18 months of corrected age [42]. From a clinical point of view, the predominance of some variables at multivariate analysis included the neonatal WMA on early language and social skills might be interpreted as a major influence of connection pathways on more complex neurodevelopmental skills compared to the postural and motor ones. The other pattern of brain damage, IVH grades I–II, was significantly associated to delayed gross motor abilities at short and long-term outcome in our study, although it was not an isolated finding but occurred in association with WMA in 83.3% of patients. Not many large studies investigated the effect of low-grade IVH on neurocognitive development in contrast with the much more assessed profiles associated to severe IVH grades III–IV. Bolisetty et al. showed among a wide population of 1472 EPT children, that, patients with IVH I–II, both independently and associated to other pathological pattern at cUS, displayed an increased risk of neurosensory impairment, CP, developmental delay and deafness if compared to those without IVH [43]. In contrast, a very recent paper by Ann et al. failed to demonstrate the role of IVH grades I–II as an independent risk factor associated with lower outcomes in intelligence, academic achievement or problem behavior at age 3, 8 and 18 years [44]. Finally, as we observed in our patients, reduced visual function was present in VLBW children and were shown to be predictive of poor motor skills. The role of low BW, IVH, intrauterine growth retardation and low Apgar scores at 1 min on reduced visual function was previously reported and supported accurate follow-up and early intervention programs [45]. In conclusion, the classic neurologic examination applied during the follow-up visits was able to early identify neurodevelopmental pitfalls across our preterm children with a persistent involvement of visual and visuo-motor skills. The well-known self-standing developmental profile at long term observation of the EPT children appeared to rely on early slower motor and visual maturation. Since the gross motor skills resulted to be the milestones mostly related to later neurodevelopmental dysfunctions, encouraging early appropriate intervention could provide more addressed children maturation and developing trajectory. Moreover, many acquired perinatal factors were shown to have a strong impact on milestones achievement and, consequently, with the trajectory pathways. Furthermore, the neurological framework of early psychomotor development of preterm infants according to this model could be related to a previous neonatal neurobehavioral evaluation in future works.

### Table 6

<table>
<thead>
<tr>
<th></th>
<th>Locomotor</th>
<th>Personal/social</th>
<th>Language</th>
<th>Eye-hand coordination</th>
<th>Performance</th>
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<td>0.957</td>
<td>(0.822–1.114)</td>
<td>/</td>
<td>0.997 (0.913–1.089)</td>
<td>1.093 (0.985–1.213)</td>
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<td>B.W.</td>
<td>1.750</td>
<td>(0.882–1.472)</td>
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<td>/</td>
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<tr>
<td>Apgar 1</td>
<td>1.151</td>
<td>(0.971–1.364)</td>
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<tr>
<td>Apgar 5</td>
<td>/</td>
<td>/</td>
<td>1.147 (0.898–1.465)</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>Neonatal seizures</td>
<td>/</td>
<td>/</td>
<td>0.181 (0.015–2.164)</td>
<td>/</td>
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<tr>
<td>IVH</td>
<td>0.315</td>
<td>(0.095–1.045)</td>
<td>/</td>
<td>0.427 (0.236–0.762)*</td>
<td>0.797 (0.399–1.592)</td>
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<tr>
<td>W.M.A.</td>
<td>0.563</td>
<td>(0.314–1.010)</td>
<td>/</td>
<td>/</td>
<td>/</td>
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<tr>
<td>B.G.T.</td>
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### References


