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Early prediction of cerebral palsy after neonatal intensive care using motor development trajectories in infancy

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ABSTRACT

Neonatal intensive care unit (NICU) patients are at high risk for developmental disabilities such as cerebral palsy (CP). Early identification of CP is essential to effective rehabilitation, but diagnosis is often delayed, especially in preterm infants. We hypothesized that through the longitudinal evaluation of motor trajectories in the NICU follow-up clinic, we could distinguish infants who develop CP by 3 years of age.

Study design and subjects: This was a retrospective study of 606 patients in the NICU Follow-up Clinic at Vanderbilt University with birth weight <1500 g or a diagnosis of hypoxic ischemic encephalopathy.

Outcomes measures: Assessments included neurologic exams, the Developmental Assessment of Young Children (DAYC), the Bayley Scales of Infant Development (BSID) and the Gross Motor Function Classification Scale.

Results: A decrease in DAYC scores between 6 and 12 months was present in preterm and term infants later diagnosed with CP, but not in children without CP (−23 vs. +1.5, $p < 0.001$). DAYC score decreases in infancy were highly predictive of later CP ($p < 0.001$). BSID scores quantified severe motor delays but did not add to prediction of CP diagnosis.

Conclusion: Standardized assessments of motor milestones quantitatively predict the risk of CP in former NICU patients by 12 months, allowing for timely diagnosis, counseling and therapy in high-risk infants.

1. Introduction

Infants discharged from the neonatal intensive care unit (NICU) are at increased risk for poor neurodevelopmental outcomes [1–4]. Of all infants born before 27 weeks gestational age (GA), 14% develop cerebral palsy (CP) compared to 0.2% of the general population [2]. Almost 2/3 of 11,000 children diagnosed every year with CP in the United States are former preterm infants or term infants with severe birth-related complications [5–7]. Excellent predictive models exist to help identify which NICU patients will be at highest risk for CP [8–12]. However, for an individual infant, it is essential to establish a diagnosis of CP as early as possible in order to optimize the effectiveness of rehabilitative interventions. Infancy and early childhood are periods of maximal neural plasticity during which therapeutic interventions have the greatest potential for long-term effectiveness [13–17]. Additionally, early identification can help prevent or moderate the complex communication, social and emotional associations that can have functional consequences into adulthood [18–22].

CP is challenging to diagnose in young children due to the complexity of signs, symptoms and developmental progression involved [23]. An initial diagnosis of CP can be especially difficult to make in premature infants whose neurological patterns of maturation and unique pathology complicate their presentation [24,25]. In addition, the developmental surveillance of NICU patients is highly variable, ranging from none to greater than 90% in research studies supporting systematic NICU follow-up [26]. Thus, many NICU patients identified as high risk for CP will face delayed diagnosis due to a lack of specialized providers and assessments.

Given the implications and challenges of early diagnosis of CP, developing simple tools for early identification and screening in high-risk infants is a priority. Research has focused mainly on highly specialized tools, from imaging to complex neurological assessments, while few studies examine the value of more basic developmental milestone trajectories. Therefore, the goals of this study were to characterize the evolution of motor milestones in the first three years in high-risk infants discharged from the NICU. We hypothesized that the trajectory of motor test scores on an interactive developmental assessment would predict CP in the first year of life, before the

Abbreviations: BSID, Bayley Scales of Infant Development; CP, Cerebral palsy; DAYC, Developmental Assessment of Young Children; DFC, Developmental follow-up clinic; NICU, Neonatal intensive care unit; IVH, Intraventricular hemorrhage; PCP, Primary care provider; PVL, Periventricular leukomalacia; GMFCS, Gross Motor Function Classification System.

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administration of gold standard neurodevelopmental tests and neurologic exams at 24 to 36 months.

2. Methods

We conducted a retrospective database review of prospectively acquired data on patients seen in the NICU Developmental Follow-Up Clinic (DFC) at the Monroe Carell Junior Children's Hospital (MCJCH) at Vanderbilt from 2005 to 2008. Inclusion criteria were infants with birth weights <1500 g and those with a diagnosis of hypoxic ischemic encephalopathy (HIE) at time of discharge from the MCJCH NICU. Patients were seen at 6, 12, 24 and 36 months chronological age, with interim visits if concerns existed. At the 6- and 12-month visits to the DFC, children were tested using the Developmental Assessment of Young Children (DAYC) [27], a standardized assessment with normative data in the motor development domain. The DAYC is an interactive questionnaire with milestones reported as achieved by parents. These milestones are challenged when a threshold is met by observation and interaction with the patients using common toys (rattle, small blanket, etc.). Most of the observations are made throughout the routine course of the visit as parent and child interact. Some elements of gross motor function such as rolling from side to supine or head up while prone are observed and challenged during the regular physical exam, while others are formally tested. For example, a 6-month milestone would be "Does your child transfer a toy from one hand to the other?" If the parent replied yes, and no more advanced skills were reported, the examiner would then state "Let's see if she would do this for me too" and hand the child a toy prepared for this purpose. If the child could not perform this milestone, the examiner would then test the preceding milestone. The DAYC was administered by clinic providers who were all trained using standardized observation followed by monitored DAYC administration before independence to maximize inter- and intra-observer reliability. At the 24- and 36-month visits, trained examiners administered the Bayley Scales of Infant Development (BSID) exam [28]. Due to a change in testing formats, the BSID II was used prior to 2007 and the BSID III was used after that year [29]. Therefore, we extracted only composite motor scores from the database instead of scores for fine and gross motor scales.

All patients identified in the DFC database with CP had later concurrence of the diagnosis by pediatric neurologists, movement disorder specialists and rehabilitation providers. CP was defined as a group of permanent disorders of the development of movement and posture, causing activity limitations that are attributed to non-progressive disturbances that occur in the developing fetal or infant brain [23]. CP was classified according to both the algorithm used in the Extremely Low Gestational Age Newborns (ELGAN) study group [25] and according to the Gross Motor Function Classification System (GMFCS) [30] on the basis of the neurological exam at the last visit [31]. Spasticity and dystonia are not part of this classification. The rationale for omitting distinctions of elevated tone is the frequency with which spasticity and dystonia co-occur and the variability of their presentations in infancy [25]. Cranial imaging data were extracted from the medical record and the most severe radiographic findings were reported. Data from these clinic visits were gathered prospectively and maintained in a repository database approved by the Institutional Review Board (IRB) at Vanderbilt University. Vanderbilt IRB approval was subsequently obtained for review and extraction of these data.

3. Statistical analysis

Baseline descriptive statistics by birth status were compared using the Wilcoxon rank sum test for continuous outcomes and Pearson's chi-squared test for categorical outcomes. We summarized DAYC and BSID motor scores at each time point using the median and interquartile range (IQR). Using quartiles allowed us to incorporate all motor scores in the analysis, including subjects that were documented too low to be accurately tested. We confirmed from the medical record that "not testable" scores were lower than any measurable score and gave them the lowest possible score on the test. We compared median motor scores at each clinic visit and change in scores from one visit to the next using the Wilcoxon rank sum test. Time from birth to CP diagnosis by birth status was estimated using the log-rank test. Logistic regression analysis was used to determine the probability of CP based on changes in DAYC scores. In the detailed analysis, infants were separated into 2 groups: the first group was composed of preterm infants below 34 weeks GA at birth, the second included late preterm (LPT) (34–36 weeks GA) and term infants (born at 37 weeks GA or above).

4. Results

During the study period, 850 infants with birth weights <1500 g were discharged alive from the MCJCH NICU. Of these, 572 were seen on multiple occasions in the MCJCH DFC for a follow-up rate of 68% at 3 years of age. During this period, 61 infants with a diagnosis of HIE were discharged alive, and 34 were seen in the DFC for a follow-up rate of 56% at 3 years of age. A definitive diagnosis of CP was made in 46 of the 606 patients seen in the DFC (32 were preterm and 14 late preterm (LPT) or term) for a rate of diagnosis of 7.6%. All children received their documented diagnosis of CP for the first time in the DFC. As expected, preterm and LPT/term infants with CP differed significantly with respect to GA (median of 28 weeks, IQR = 26–29 vs. median of 38 weeks, IQR = 37–40) and birth weight (930 g, IQR = 729–1404 vs. 3358 g, IQR = 2741–3642). The differences between the preterm children with CP and those without were less pronounced, with a median GA of 28 weeks (IQR = 26–30) in children without CP vs. a median of 29 weeks (IQR = 26–37) in children with CP ($p = 0.02$). All children diagnosed with CP were referred to rehabilitative specialists and specialized motor disorders clinics at the time of diagnosis. Additionally, the diagnosis was communicated immediately to the state's early intervention program coordinators.

4.1. Characteristics of children with CP

All children with CP had cranial imaging performed prior to discharge from the NICU (Table 1). As expected, findings on cranial imaging were significantly different between the preterm and LPT/term groups ($p < 0.001$). The majority (69%) of the preterm group had intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL) or both, whereas LPT/term infants had findings consistent with ischemic encephalopathy (64%) as ascertained by pediatric radiologists. Twenty percent of preterm infants with CP had no abnormal findings on cranial imaging.

The two groups were significantly different in the overall distribution of CP types ($p = 0.04$), with 79% of the LPT/term group having quadriparesis and 7% with diparesis. In the preterm group, diparesis and quadriparesis were equally represented (44% for both). Hemiparesis was the least common type of CP in this population, with no differences between preterm and LPT/term groups (12% vs. 14%). Infants in the LPT/term group had the least functional types of CP with 93% receiving a GMFCS score of 2 or above vs. 69% in the preterm group. More preterm infants had a GMFCS score of 1 (31% vs. 7% in the LPT/term group), but this difference did not reach statistical significance ($p = 0.07$).

4.2. Evolution of standardized scores for motor development in the DFC

Median DAYC motor scores for corrected age were significantly lower for children with CP at the 6- and 12-month visits than those in children with no CP (Table 2). In children who later developed CP, DAYC scores decreased by a median of 23 points (IQR = 36–11) between the 6-month and the 12-month visits. However, in children