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Using cluster analysis to provide new insights into development of very low birthweight (VLBW) premature infants



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ABSTRACT

Background: Very low birthweight (VLBW) premature infant follow-up studies report on single developmental outcome variables but do not assess profiles of development. *Aims:* To identify developmental profiles of VLBW premature infants based on cognitive and language development and their association with demographic, perinatal, and behavior variables. *Study design:* Retrospective chart review.

Subjects: 117 children < 1250 g BW seen at 18 months post-term on the Bayley Scales—III and Child Behavior Checklist 1 $\frac{1}{2}$ -5 (CBCL 1 $\frac{1}{2}$ -5), a behavior problem questionnaire. Demographic and perinatal variables were obtained from medical records.

Outcome measures: Bayley Cognitive, Expressive Language, and Receptive Language scores were used to cluster the subjects into developmental profiles. Demographic, perinatal, and CBCL variables were analyzed as they related to clusters.

Results: Children were clustered into 4 groups based on their Bayley Cognitive, Expressive Language, and Receptive Language scores: Consistently High, Consistently Average, Average with Delayed Expressive Language, and Consistently Low. Socioeconomic status, bronchopulmonary dysplasia, Grades III–IV intraventricular hemorrhage, and summary Behavior Problems and Attention Deficit/Hyperactivity (ADHD) Problems scores were significantly related to clusters.

Conclusion: Cluster analysis defined distinct outcome groups in VLBW premature children and provides an informative means of identifying factors related to developmental outcome. This approach may be useful in predicting later outcome and determining which groups of children will require early intervention.

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1. Introduction

The survival rates of very low birthweight (VLBW) infants have shown major improvements over the last decades. However, morbidity in surviving infants also has increased [1], particularly as it relates to more subtle developmental deficits in cognition, language, and behavior problems [2–4]. VLBW premature children are significantly more likely than full terms to have cognitive deficits [5], and these frequently occur independent of neuromotor and neurosensory disabilities [6,7]. Language impairments, both in expressive and receptive language, also are far more common in children born prematurely [8,9], and it has been suggested that these are associated with a higher rate of languagebased learning disabilities at school-age [10,11].

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Further, prematurely born children have been shown to have more behavioral and psychiatric problems, with increased rates of internalizing behaviors (anxiety, depressive symptoms, withdrawn behaviors) and externalizing behaviors (aggression, oppositional behaviors and attention problems) [4,12–14]. Behavior problems and, particularly, attention-deficit disorders can negatively affect learning abilities [15] and, therefore, may be associated with lower cognitive and language function.

Much work has been done examining the predictive relationship between demographic variables and/or perinatal conditions to the outcomes of cognition, language, and behavior, with a view to improving such outcomes in the future [16–18]. Of the demographic variables, the effects of social class have been most widely studied, with general findings that higher socioeconomic status (SES) is significantly related to better outcomes [19]. With regards to perinatal variables, it is well known that lower birthweight and gestational age are significantly associated with higher rates of cognitive and language impairments, as well as greater prevalence of behavior problems [5]. Studies also have demonstrated that neonatal illness, such as bronchopulmonary dysplasia (BPD) [20,21], intraventricular hemorrhage (IVH) [22,23], and necrotizing enterocolitis [24] are significantly related to neurodevelopmental deficits.

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To date, neurodevelopmental follow-up studies have exclusively examined discrete aspects of development, such as cognition and language [9,25,26]. There are no known studies that have looked at profiles of development in VLBW infants and the association of demographic, perinatal, and behavioral factors to these profiles. The purpose of this study is to determine whether a new approach of examining developmental profiles is informative in understanding development of prematurely born children. The specific aims are two-fold: first to determine if there are distinct profiles of VLBW children, based on their cognitive and language outcomes; and second, whether such profiles are associated with demographic, perinatal, and behavior problem variables.

2. Participants and methods

2.1. Subjects

Subjects were 117 children born between 2006 and 2012 with a BW of <1250 g, who attended the Neurodevelopmental Follow-up Clinic at a major metropolitan hospital. All were in-born, had normal motor function and were from English speaking homes.

During the period between July 2006 and January 2012, 442 infants with birth weights < 1250 g were discharged from the hospital neonatal intensive care unit (NICU), including 216 inborn and 226 outborn. Outborn children were not included in follow-up, as most were in the NICU for only a few days for procedures, and relatively little perinatal information was obtainable for them. Of the inborn children, 32 (15%) did not return to follow-up. Of those followed, 22 (12%) from non-English speaking families were excluded, since the Bayley Language Scales are performed in English. An additional 45 (28%) children with non-normal neuromotor development, i.e., abnormalities in muscle tone and delays sufficiently significant to qualify for physical/ occupational therapy through Early Intervention, also were excluded, as the Bayley Cognitive results rely on sensorimotor abilities. This prevalence of neuromotor deficit is comparable to that reported in other studies [25,27].

Perinatal variables obtained from the medical records included: plurality, in vitro fertilization, type of delivery (vaginal/cesarean-section), antenatal corticosteroids, and Apgar score < 7 at 5 min. Neonatal variables included bronchopulmonary dysplasia (BPD), Grades III–IV intraventricular hemorrhage (IVH), and neonatal seizures. BPD was based on the requirement of supplemental oxygen at 36 weeks post conceptual age [28]. Presence and severity of IVH were determined using the Volpe classification system [29] on head ultrasounds. Seizures were defined by clinical observation and electroencephalographic confirmation. Social class was determined by parental occupation and education [30].

2.2. Procedure

At 18 months post-conceptual age, children were evaluated with the Cognitive Scale and the Language Scale of the Bayley Scales of Infant and Toddler Development–III as part of clinical care [31]. The Language Scale yields separate scores for Expressive Language and Receptive Language. All scores have a mean of 100 \pm 15. Parents completed the Child Behavior Checklist 1 ½–5 (CBCL 1 ½–5) [32], a parent questionnaire that rates children on 5 psychiatrically oriented scales (Affective Problems, Anxiety Problems, Pervasive Developmental Problems, Attention Deficit/Hyperactivity (ADHD) Problems, and Oppositional Defiant Problems), and provides summary scores for Internalizing Behaviors (Emotionally Reactive, Anxious/Depressed, Somatic Complaints and Withdrawn Behavior Syndromes); Externalizing Behaviors (Attention Problems and Aggressive Behavior Syndromes); and Total Behavior Problems (scores from all previous behavior syndromes plus Sleep Problems and Other Problems). All CBCL scores are normalized using a T-scale (mean of 50 + 10), with scores between 65 and 69 considered Borderline and those > 70, considered Clinical. Since ADHD is the most common behavioral problem of prematurity, [33,34] only parental rating for ADHD Problems, as well as the three behavior problem summary scores, was considered in the data analysis.

2.3. Statistical analysis

Descriptive statistics were conducted for demographic and perinatal variables, Bayley scores, and CBCL 1 1/2-5 scores. A hierarchical cluster analysis of cases was performed to determine whether there were distinct groups of children within the sample, based on Bayley Cognitive, Expressive Language, and Receptive Language scores, transformed into Z scores (with a mean of 0 and a SD of 1). In order to group participants who scored similarly on the three developmental areas, Ward's method was used to combine the clusters using a squared Euclidean distance measure [35]. Analyses of variance and chi-square analyses were then used to determine whether and which demographic, perinatal, and behavioral variables were associated with cluster categories. Given the large number of perinatal variables, only the five variables most highly associated with cluster outcome (Apgar score at 5 min, BPD, Grades III-IV IVH, seizures, and antenatal corticosteroids) were entered in the analyses. Post-hoc analysis was conducted using Scheffe's tests. All values are expressed as mean \pm standard deviation (SD) unless stated otherwise.

This retrospective study was approved by the Institutional Review Board of the institution.

3. Results

3.1. General characteristics of the overall sample

The 117 infants had a BW 858 \pm 174 g (77% were <1000 g) and gestational age (GA) of 27 \pm 2 weeks (see Table 1). Seventy-three (62%) were female, and 69 (59%) Caucasian. Twenty-eight percent were from upper to upper middle; 41%, from middle to lower middle; and 31%, from lower income families. Table 2 shows the incidence of perinatal variables for the group.

3.2. Developmental and behavioral characteristics of the overall sample

Children in the study performed within the Average range on the Cognitive and Receptive Language measures of the Bayley examination (90.8 \pm 14.4 and 90.3 \pm 16.9, respectively) and in the Low Average range on the Expressive Language measure (84.5 \pm 18.7). Scores on the CBCL were within the normal range on ADHD Problems (55.1 \pm 6.8) and on the summary Internalizing (45.0 \pm 11.4), Externalizing (47.2 \pm 10.4), and Total Behavior Problem scores (50.1 \pm 10.9). Individually, 15% of children received Borderline to Clinical relevant scores on ADHD Problems; 6%, on Internalizing Problems; and 7%, on Externalizing and Total Behavior Problems, respectively.

Table 1

Demographic variables of all children (N = 117).

Variable	М	SD	Ν	%
Birthweight in grams	858	174	117	-
Gestational age (wks)	26.9	2.1	117	-
Corrected age in months	18.9	1.8	117	
Gender				
Male	-	-	44	38%
Female	-	-	73	62%
Race				
Caucasian	-	-	69	59%
Asian	-	-	10	9%
Hispanic	-	-	13	11%
African-American	-	-	24	21%
Socioeconomic status				
Upper-upper middle			33	28%
Middle-lower middle			48	41%
Lower			36	31%

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