

Investigating Associations Between Neonatal Post-Hemorrhagic Hydrocephalus Management Protocols and Subsequent Developmental Outcomes

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Abstract

Objective: Investigate associations between proactive vs. historical neonatal post-hemorrhagic hydrocephalus (PHH) surgical management and subsequent neurodevelopmental impairment (NDI).

Study Design: Single-center retrospective, matched cohort of VLBW infants with PHH. Cases underwent earlier ventricular reservoir placement, serial imaging-guided cerebrospinal fluid withdrawal, reservoir weaning. Controls received historical management with later reservoir placement, symptom-driven cerebrospinal fluid withdrawal, earlier shunt conversion.

Capute Cognitive Adaptive Test (CAT), Clinical Linguistic and Auditory Milestone Scale (CLAMS), Modified Peabody Developmental Motor Scale (PDMS-M) and Ages and Stages Questionnaires®, (ASQ) neurodevelopmental assessments during first two years compared between groups using Sign, McNemar-Bowker, Wilcoxon signed-rank and matched t-tests.

Result: 48 subjects (24/group) included. NDI was common (67% Cases, 75% Controls). Composite NDI, individual NDI composite outcome components (CAT/CLAMS/PDMS-M), nor ASQ scores differed between groups.

Conclusion: Proactive management was not associated with worse NDI, supporting its potential safety. Higher-powered studies with longer follow-up intervals are needed to assess potential developmental benefits.

Introduction

Post-hemorrhagic hydrocephalus (PHH) is a frequent complication of extremely preterm birth that gives rise to devastating neurodevelopmental sequelae including cerebral palsy, motor and cognitive impairment, hearing and visual deficits, and developmental delay(1, 2). Infants born at very low birth weight (VLBW, i.e., birth weight < 1,500 grams) are at high risk for germinal matrix intraventricular hemorrhage (IVH), with approximately 22% of these infants developing PHH(3). Despite extensive research and advancements in neonatal care, a definitive, evidence-based method for preventing IVH and its progression to PHH remains elusive(4). As a result, optimizing management of IVH and PHH through cerebrospinal fluid (CSF) diversion remains a critical focus(1). Neurosurgical management for CSF diversion can be broadly categorized into either temporizing or permanent procedures. Temporizing procedures include ventricular reservoirs and ventriculo-subgaleal shunts while permanent methods include ventriculoperitoneal shunts (VPS) and endoscopic third ventriculostomy(5, 6). Current strategies focus on further enhancing available treatments with specific considerations including surgical approach, timing of CSF diversion, ventricular caliber thresholds, and advanced neuroimaging findings indicative of brain injury(7, 8).

Although the connection between PHH and subsequent neurodevelopmental impairment (NDI) is well characterized, the most effective surgical management strategy to minimize NDI and maximize neurodevelopmental outcomes remains unknown. Significant variability in surgical techniques and assessment tools in this complex population have contributed to inconsistent findings across the literature, with some methodologies focusing on surgical parameters and others examining NDI with mixed results(9, 10). Some protocols suggest early intervention improves outcomes, while others caution against aggressive approaches due to associated risks and lack of benefit(6). Given the lack of consensus, studies like the present investigation offer valuable insight into alternative management strategies for this vulnerable and understudied population.

The present retrospective matched cohort study seeks to elucidate associations between

neonatal PHH management protocols and subsequent neurodevelopmental outcomes in the first two and a half years of life. This analysis compares neurodevelopmental outcomes in extremely preterm, VLBW infants managed with either (1) a novel, proactive PHH surgical management protocol consisting of earlier ventricular reservoir implantation followed by proactive, imaging-guided serial CSF withdrawal intended to reduce ventricular distention during a period of rapid brain growth or (2) a historical, more conservative PHH strategy in which CSF withdrawal after reservoir placement was performed reactively in response to clinical signs of progressive hydrocephalus or elevated intracranial pressure (ICP), with earlier conversion to VPS when ongoing CSF diversion was required. While numerous surgical refinements have emerged in recent years, the methods described in this study integrate advantageous aspects of previously described concepts to establish an earlier, more proactive PHH management strategy. We hypothesize that earlier reservoir placement followed by preemptive imaging-guided CSF drainage will be associated with differential neurodevelopmental outcomes compared with the historical strategy of symptom-driven CSF withdrawal.

Methods

Study Population

This single center retrospective matched cohort study included VLBW infants treated for PHH via neurosurgical intervention in the Medical University of South Carolina (MUSC) neonatal intensive care unit (NICU) between 2005 and 2022. Eligible infants were required to have documented longitudinal neurodevelopmental follow-up evaluations conducted between 3 and 30 months of age in the MUSC Newborn Developmental Clinic, a multidisciplinary clinic providing standardized developmental surveillance for high-risk NICU graduates.

Inclusion criteria included preterm birth (gestational age < 37 weeks), VLBW status, and a diagnosis of severe IVH, defined as grade III or IV IVH(11). Exclusion criteria included hydrocephalus attributable to etiologies other than PHH, death prior to neurodevelopmental follow-up, absence of documented developmental follow-up, and patients for which a historical match could not be made.

Data Collection

Retrospective chart review was conducted using the electronic medical record and approved by the MUSC Institutional Review Board with waiver of informed consent. Demographic characteristics collected included birth weight (BW), gestational age (GA), sex, race (White/Caucasian, Black/African American, or other/unknown), ethnicity (Hispanic or non-Hispanic), and indication for delivery (pre-eclampsia, preterm labor, placental abruption, fetal distress, maternal indication, or other). NICU course details and medical complications collected included hemodynamically significant patent ductus arteriosus, hypotension, bronchopulmonary dysplasia, supplemental oxygen at home, tracheostomy, gastrostomy, spontaneous intestinal perforation, necrotizing enterocolitis, sepsis, meningitis, periventricular leukomalacia, failed hearing screen, retinopathy of prematurity (stage 1, 2, or 3), and VPS placement.

Clinical neurodevelopmental outcome measures consisted of the following standardized developmental assessments: the Capute Cognitive Adaptive Test (CAT), Clinical Linguistic and Auditory Milestone Scale (CLAMS), and the Modified Peabody Developmental Motor Scale (PDMS-M)(12, 13). Parental-reported outcomes were assessed using the Ages and Stages Questionnaires®, Third Edition (ASQ®-3), and the Ages and Stages Questionnaires®: Social-Emotional, Second Edition (ASQ®:SE-2)(14, 15). Neurosurgical variables included IVH grade and type of CSF diversion, including ventricular reservoir placement and subsequent VPS placement.

Study data were collected and managed using REDCap electronic data capture tools hosted at the Medical University of South Carolina(16, 17).

Exposure

The primary exposure of interest was the PHH surgical protocol utilized during the neonatal period. Infants were classified into one of two exposure groups based on the PHH management strategy in place at the time of their clinical care.

‘Cases’ were defined as infants managed using the novel, proactive PHH protocol. This protocol was informed by longitudinal clinical observations of progressive ventricular enlargement immediately preceding the need for temporizing CSF diversion. Progressive ventricular enlargement was determined via cranial ultrasonography obtained twice weekly. For each infant, the first ultrasound demonstrating enlargement of the biventricular diameter, measured on a coronal image at the level of the foramen of Monro, was designated as that infant’s baseline for subsequent ventricular progression. The 30% threshold was calculated from this first enlarged ventricular measurement, as opposed to any prior negative studies. In otherwise clinically stable infants, a progressive increase in biventricular diameter of more than 30% above this individualized baseline prompted ventricular reservoir placement. Infants who developed clinical signs or symptoms of elevated ICP or PHH underwent prompt reservoir insertion prior to achieving the 30% imaging threshold. Following reservoir placement, infants in the Case cohort

underwent proactive serial CSF withdrawal. Drainage was guided by serial cranial ultrasonography with the goal of decreasing ventricular size and limiting sustained ventricular distention during a period of rapid cerebral growth, thereby reducing mechanical constraint on the developing brain mantle. At approximately 38 weeks' postmenstrual age, all Case infants underwent a reservoir-weaning period. Infants who remained dependent on CSF diversion and could not tolerate weaning subsequently underwent VPS placement; thus, VPS placement in the Case cohort represented failure of the reservoir-weaning strategy.

'Controls' were defined as infants managed using the historical PHH protocol, characterized by later ventricular reservoir placement. After reservoir placement, CSF withdrawal in the Control cohort was performed reactively in response to clinical symptoms of progressive PHH or elevated ICP rather than proactively on the basis of serial imaging. Controls were also converted to VPS earlier when ongoing CSF diversion was considered necessary.

Subjects were matched 1 Case:1 Control based on the following parameters: BW $\pm$ 200 grams, GA $\pm$ 1 week, sex, and IVH severity.

Outcomes

The primary outcome was NDI, defined as a composite outcome of a developmental quotient (DQ) $<$ 70 on one or more standardized developmental assessments: CAT, CLAMS, or PDMS-M, at either of two developmental assessments (12, 13). DQ was calculated by dividing a child's developmental age (i.e., 'age equivalent') by their chronological age and multiplying by 100 to allow for developmental comparisons of children of different ages. To account for prematurity, DQs were corrected for gestational age until the patient reached 2 years of age; for this correction, age equivalent was divided by corrected age before multiplying by 100. If a subject's development was assessed multiple times between 3 and 30 months of age, data was collected from the patient's initial follow-up visit in MUSC Newborn Developmental Clinic and follow-up visit closest to 24-months of age.

Several secondary outcomes were evaluated including individual components of the NDI composite outcome (i.e., CAT, CLAMS, PDMS-M). Additionally, caregiver-assessment of neurodevelopment was assessed and determined using the ASQ®-3, a validated screening tool that evaluates five domains of child development: communication, gross motor, fine motor, problem solving, and personal-social (14). The ASQ®:SE-2 was also administered to assess social-emotional functioning. Cumulative scores per domain are compared to established age-specific normative cutoffs and designated *Pass*, *Borderline*, or *Fail*. *Pass* scores were defined as scores within 1 standard deviation (SD) of the age-specific normative mean, *Borderline* scores as those between 1 and 2 SD below the mean, and *Fail* scores as those $\geq$ 2 SD below the mean(14). The ASQ®-SE-2 was scored separately, and scores are classified as *Pass* or *Fail* by comparison of child's total score to an established age-specific cutoff threshold(15).

Statistical Analysis

Descriptive statistics were reported as frequencies (percentages) for categorical data and means ($\pm$ SD) for normally distributed continuous data and median (interquartile ranges, IQR) for nonparametric continuous data. Comparisons of demographic and baseline characteristics, neurodevelopmental testing variables (including chronologic age, corrected age, age equivalencies, DQs, failed assessment counts, and ASQ®-3 and ASQ®:SE-2 questionnaire data), as well as NICU course details were made between Cases and Controls using Sign test or McNemar's test/McNemar-Bowker test for nominal data, Wilcoxon signed-rank tests for ordinal data, and Wilcoxon signed-rank tests or matched t-tests for continuous data as appropriate. Alluvial/Sankey diagram was used to depict changes in developmental testing results from initial to follow-up assessments across the CAT, CLAMS, and PDMS-M assessments. An a priori p value of < 0.05 was selected to determine statistical significance. All analyses were performed using IBM® SPSS® Statistics v. 28.0.1.0 (142) (Armonk, NY). Findings are reported in accordance with the STROBE recommendations(18).

Results

Study Population

In total, 48 patients were included in this analysis, 24 Cases with 24 matched, historical Controls. Baseline birth and demographic characteristics were similar between groups with a median BW of 792 grams [IQR 698–1090], a median GA of 26 weeks' [IQR 24–27 weeks'], and a primarily male (67%) cohort delivered in the setting of preterm labor most commonly (Table 1).

Table 1
Demographic and Baseline Characteristics

Characteristics	Total (n = 48)	Cases (n = 24)	Controls (n = 24)
Growth category at birth[¢]			
SGA	2 (5%)	1 (4%)	1 (5%)
AGA	31 (72%)	17 (71%)	14 (74%)
LGA	10 (23%)	6 (25%)	4 (21%)
Race^f			
White/Caucasian	19 (40%)	10 (42%)	9 (39%)
Black/African American	27 (58%)	13 (54%)	14 (61%)
Other/Unknown	1 (2%)	1 (4%)	0
Ethnicity^f			
Hispanic	2 (4%)	2 (8%)	0
Non-Hispanic	45 (96%)	22 (92%)	23 (100%)
Reason for delivery			
Pre-eclampsia	5 (10%)	2 (8%)	3 (13%)
Preterm labor	32 (67%)	16 (67%)	16 (67%)
Abruption	7 (15%)	5 (21%)	2 (8%)
Fetal distress	3 (6%)	1 (4%)	2 (8%)
Maternal indication	1 (2%)	0	1 (4%)
Other	5 (10%)	2 (8%)	3 (13%)
Categorical variables presented as count (percentage). [¢] Growth category at birth available for n = 43 (24 Cases, 19 Controls); SGA, small for gestational age, defined as birthweight < 10th %; AGA, average for gestational age, defined as birthweight between 10th % and 90th %; LGA, large for gestational age, defined as birthweight > 90th %. ^f Race and Ethnicity available for n = 47 (24 Cases, 23 Controls). There were no significant differences detected between groups (all p > 0.05).			

Details of NICU courses and potential complications are presented in the Supplemental Table. Neither specific course details nor complication rates differed between Cases and Controls.

Primary Outcome

We did not detect a difference between Cases and Controls when examining rates of the primary outcome, composite NDI, diagnosed at either initial or follow-up developmental assessment. Unfortunately, composite NDI was common, impacting 67% of Cases and 75% of Controls overall (Table 2).

Table 2
Outcomes: Neurodevelopmental Testing Results

Outcomes and Neurodevelopmental Tests	Cases (n = 24)	Controls (n = 24)
Primary Outcome:		
Overall Neurodevelopmental Impairment (Composite, at either visit) [‡]	16 (67%)	18 (75%)
Secondary Outcomes:		
Initial Newborn Developmental Clinic		
Neurodevelopmental Impairment (Composite)[‡]	14 (58%)	(n = 23) 13 (57%)
Chronologic age at time of testing (months)	7.7 [7.1–9.1]	7.0 [6.0-9.5]
Corrected age at time of testing (months) ^f	4.1 [3.3–5.4]	3.2 [2.8–5.2]
Cognitive Adaptive Test age equivalent (months)	3.3 [2.6–4.1]	(n = 23) 2.6 [1.7–4.3]
Cognitive Adaptive Test adjusted DQ or DQ ^f	85.4 [69.3–95.6]	(n = 23) 71.4 [46.9–96.9]
Failed Cognitive Adaptive Test (i.e., adjusted DQ or DQ < 70)	6 (25%)	(n = 23) 11 (48%)
Clinical Linguistic and Auditory Milestone Scale age equivalent (months)	3.75 [3.0-5.1]	(n = 23) 3.5 [3.0-5.5]
Clinical Linguistic and Auditory Milestone Scale adjusted DQ or DQ ^f	91.7 [74.4-103.4]	(n = 23) 107.1 [79.9-122.8]
Categorical variables presented as count (percentage). Continuous variables presented as median [IQR]. [‡] Neurodevelopmental impairment is a composite outcome defined as a developmental quotient (DQ) < 70 on one or more of the following standardized developmental assessments: Capute Cognitive Adaptive Test, Clinical Linguistic and Auditory Milestone Scale, or Modified Peabody Developmental Motor Scale. ^f 1 Case seen at 28.9 months; 1 Control seen at 24.9 months. No significant differences identified between groups for any outcome variable. Folio, M.R. and R.R. Fewell, <i>Peabody Developmental Motor Scales, Second Edition (PDMS-2)</i> . 2000, Austin, TX: PRO-ED. Capute, A.J. and P.J. Accardo, <i>The Capute Scales: Cognitive Adaptive Test/Clinical Linguistic and Auditory Milestone Scale (CAT/CLAMS)</i> . 2005, Baltimore, MD: Brookes Publishing.		

Outcomes and Neurodevelopmental Tests	Cases (n = 24)	Controls (n = 24)
Primary Outcome:		
Failed Clinical Linguistic and Auditory Milestone Scale (i.e., adjusted DQ or DQ < 70)	5 (21%)	(n = 23) 5 (22%)
Modified Peabody Developmental Motor Scale age equivalent (months)	3.0 [2.0-3.6]	(n = 23) 2.0 [1.8–4.5]
Modified Peabody Developmental Motor Scale adjusted DQ or DQ^f	70.2 [53.8–89.7]	(n = 23) 71.4 [46.6–98.2]
Failed Modified Peabody Developmental Motor Scale (i.e., adjusted DQ or DQ < 70)	12 (50%)	(n = 23) 11 (48%)
Follow-up Newborn Developmental Clinic Evaluation		
	Cases (n = 16)	Controls (n = 21)
Neurodevelopmental Impairment (Composite)[‡]	12 (75%)	14 (67%)
Chronologic age at time of testing (months)	24.8 [18-27.1]	28.6 [24.0-30.8]
Corrected age at time of testing (when applicable, months)	(n = 7) 14.8 [13.1–15.1]	(n = 5) 16.1 [11.3–16.8]
Cognitive Adaptive Test age equivalent (months)	(n = 14) 14.6 [8.0-19.7]	(n = 19) 18.5 [10.4–22.7]
Cognitive Adaptive Test adjusted DQ or DQ^f	(n = 14) 63.9 [40.9–86.9]	(n = 19) 68.9 [47.9–95.0]
Failed Cognitive Adaptive Test (i.e., adjusted DQ or DQ < 70)	9 (64%)	10 (53%)
Categorical variables presented as count (percentage). Continuous variables presented as median [IQR]. [‡] Neurodevelopmental impairment is a composite outcome defined as a developmental quotient (DQ) < 70 on one or more of the following standardized developmental assessments: Capute Cognitive Adaptive Test, Clinical Linguistic and Auditory Milestone Scale, or Modified Peabody Developmental Motor Scale. ^f 1 Case seen at 28.9 months; 1 Control seen at 24.9 months. No significant differences identified between groups for any outcome variable. Folio, M.R. and R.R. Fewell, <i>Peabody Developmental Motor Scales, Second Edition (PDMS-2)</i> . 2000, Austin, TX: PRO-ED. Capute, A.J. and P.J. Accardo, <i>The Capute Scales: Cognitive Adaptive Test/Clinical Linguistic and Auditory Milestone Scale (CAT/CLAMS)</i> . 2005, Baltimore, MD: Brookes Publishing.		

Outcomes and Neurodevelopmental Tests	Cases (n = 24)	Controls (n = 24)
Primary Outcome:		
Clinical Linguistic and Auditory Milestone Scale age equivalent (months)	12.8 [7.3–18.0]	(n = 20) 19 [10.8–23.3]
Clinical Linguistic and Auditory Milestone Scale adjusted DQ or DQ ^f	65.2 [42.3–80.6]	(n = 20) 71.7 [36.0–93.2]
Failed Clinical Linguistic and Auditory Milestone Scale (i.e., adjusted DQ or DQ < 70)	10 (63%)	(n = 20) 8 (40%)
Modified Peabody Developmental Motor Scale age equivalent (months)	16.3 [6.7–21.0]	(n = 18) 15.0 [11.0–18.0]
Modified Peabody Developmental Motor Scale adjusted DQ or DQ ^f	73.0 [50.1–87.7]	(n = 17) 65.5 [46.2–77.3]
Failed Modified Peabody Developmental Motor Scale (i.e., adjusted DQ or DQ < 70)	8 (50%)	11 (65%)
Categorical variables presented as count (percentage). Continuous variables presented as median [IQR]. [‡] Neurodevelopmental impairment is a composite outcome defined as a developmental quotient (DQ) < 70 on one or more of the following standardized developmental assessments: Capute Cognitive Adaptive Test, Clinical Linguistic and Auditory Milestone Scale, or Modified Peabody Developmental Motor Scale. ^f 1 Case seen at 28.9 months; 1 Control seen at 24.9 months. No significant differences identified between groups for any outcome variable. Folio, M.R. and R.R. Fewell, <i>Peabody Developmental Motor Scales, Second Edition (PDMS-2)</i> . 2000, Austin, TX: PRO-ED. Capute, A.J. and P.J. Accardo, <i>The Capute Scales: Cognitive Adaptive Test/Clinical Linguistic and Auditory Milestone Scale (CAT/CLAMS)</i> . 2005, Baltimore, MD: Brookes Publishing.		

The initial visit in the MUSC Newborn Developmental Clinic for the 48 included patients, 24 Cases and 24 Controls, occurred at median chronological age of 7.6 months of age (IQR 6.3–9.2). Forty-six patients, 23 Cases and 23 Controls, were seen for this initial visit prior to 24 months of age and thus were corrected for prematurity and found to have a median corrected age of 3.7 months of age (IQR 2.9–5.5) at this visit. Two patients, 1 Case and 1 Control, were seen at 28.9 months and 24.9 months for this initial visit, respectively, and thus no correction to their age was performed. There were no significant differences between Cases and Controls in chronologic age or corrected age at this initial visit (Table 2). Rates of composite NDI at the time of initial visit (Cases: 14 (58%), Controls: 13 (57%)) did not differ significantly between groups.

Data from a follow-up visit in MUSC Newborn Developmental Clinic within the first 30 months of life was available for 37 (77%) patients, 16 (67%) Cases and 21 (88%) Controls, and occurred at a median chronologic age of 25.6 months (IQR 20.8–30.7). Twelve patients, 7 Cases and 5 Controls, were seen

prior to 24 months of age and thus were corrected for prematurity and found to have a median corrected age of 14.8 months (IQR 11.5–16.3) at this visit. Neither chronologic age nor corrected age differed significantly between Cases and Controls for this follow-up visit (Table 2). Rates of composite NDI diagnosed at this follow-up visit (Cases: 12 (75%), Controls: 14 (67%)) did not differ significantly between groups.

Secondary Outcomes

Individual Components of Neurodevelopment Assessment

When examining individual components of the composite NDI, we did not detect differences in age equivalents, DQs/adjusted DQs, or rates of failed individual tests for the CAT, CLAMS, or PDMS-M between Cases and Controls at either the initial or the follow-up visit (Table 2).

When examining the distribution of subjects who failed one assessment (i.e., CAT/CLAMS/PDMS-M) vs. two assessments vs. all three neurodevelopmental physician-led assessments, no differences were detected between Cases and Controls (Fig. 1).

Figure 2 is an Alluvial/Sankey diagram depicting the change in developmental testing from the initial visit to the follow-up visit across the CAT, CLAMS, and PDMS-M for Cases and Controls. Notably, more Cases progressed from a $DQ < 70$ (i.e., Fail) to $DQ \geq 70$ (i.e., Pass) than Controls between visits, although these transition patterns were not analyzed as evidence of treatment effect.

Parental Assessment of Neurodevelopment

Parental assessment of neurodevelopment using the ASQ®-3 and ASQ®:SE-2 questionnaires were evaluated both at the initial and follow-up neurodevelopmental assessments as well (Figs. 3 and 4). There were no differences between Cases and Controls in any of the domains assessed at either visit.

Discussion

PHH remains a common and serious complication of prematurity and a major contributor to neurodevelopmental morbidity among infants with severe IVH(19). Despite advances in neonatal and neurosurgical care, uncertainty persists regarding the optimal timing and intensity of CSF diversion to support long-term developmental outcomes. In this retrospective matched cohort study, we evaluated whether a novel, proactive PHH management protocol was associated with differences in neurodevelopmental outcomes in the first 30 months of life compared with a more conservative historical strategy. To assess this comprehensively, we included (1) physician assessments of neurodevelopment including CAT, CLAMS, and PDMS-M testing results and (2) parental assessments of neurodevelopment including ASQ®-3 and ASQ®:SE-2 results. We hypothesized that earlier reservoir placement followed by proactive, imaging-guided CSF withdrawal aimed at controlling ventricular size would be associated with differential neurodevelopmental outcomes compared with the historical

strategy of symptom-driven CSF withdrawal. While statistically significant differences in NDI rates were not observed, our findings suggest NDI remains high in this population, underscoring the severity of the problem; furthermore, earlier intervention for PHH was not associated with significantly worse neurodevelopmental outcomes.

Severe cognitive and motor disabilities are common amongst preterm infants with PHH but few interventions are known to improve outcomes(20). Survival of extremely preterm infants, including those down to 22 weeks of gestation, continues to improve, however rates of major neurosensory disability remained unchanged(21). Consequently, a growing number of infants may develop PHH, underscoring the need for interventions that improve long-term outcomes in this condition for which no established method of primary prevention exists(1, 22). Early CSF diversion may reduce secondary injury related to impaired cerebral perfusion, inflammation, and mechanical distortion, mechanisms that have been previously implicated in adverse neurodevelopment following severe IVH(23, 24). Drainage, irrigation, and fibrinolytic therapy (DRIFT), aimed to decompress distended ventricles early and reduce distortion, free iron, and cytokines and subsequent secondary injury, was evaluated in an international, randomized trial in the early 2000's, but the trial was stopped early due to higher mortality and rebleeding rates in the DRIFT arm(25). Interestingly, however, death or severe disability at 2 years of age was reduced in DRIFT with sustained cognitive improvement at 10 years of age in adjusted analysis, suggesting interventions aimed at reducing subsequent injury in PHH may be beneficial long term though require ongoing study(26, 27). In a subsequent study of two different treatment thresholds for reservoir insertion for PHH called the ELVIS trial (Early vs. Late Ventricular Intervention Study (ELVIS) trial, ISRCTN43171322) and a nested sub-study, early intervention at a lower threshold of ventriculomegaly in preterm infants with PHH was associated with lower odds of death or severe neurodevelopmental disability at 24 months' corrected age, while intervention at a higher threshold was associated with significantly higher global brain abnormality scores, larger fronto-occipital horn ratios, and larger ventricular volumes (28–30). These findings again support the potential positive impacts of early intervention for neonates with PHH.

From a neurosurgical perspective, the clinically relevant distinction between the described management strategies extends beyond the selection of a ventricular reservoir versus a VPS and encompasses the timing of reservoir placement and the philosophy of CSF management after implantation. In the historical Control cohort, reservoir taps were performed reactively after the emergence of clinical signs of progressive hydrocephalus or elevated ICP. In contrast, patients in the proactive PHH protocol cohort (Cases) underwent serial imaging to guide CSF withdrawal after reservoir placement, even when infants were clinically asymptomatic, with the goal of decreasing ventricular size and limiting sustained ventricular distention during a critical period of rapid brain growth. This approach is grounded in the physiologic rationale that reducing ventricular distention and associated pressure during rapid cerebral growth would minimize mechanical constraint on the developing brain mantle, allowing continued expansion and maturation. All infants of the Cases group subsequently underwent a reservoir-weaning period, with VPS placement reserved for those who remained dependent on CSF diversion after unsuccessful weaning. Thus, permanent shunt placement represented persistent CSF-diversion dependence rather than the intended endpoint of the temporizing strategy. The present study was not

designed to directly quantify longitudinal changes in ventricular size or brain mantle thickness during active drainage; therefore, this proposed mechanistic benefit remains to be tested with serial quantitative imaging. Importantly, earlier reservoir placement and proactive, imaging-guided CSF withdrawal were not associated with worse early neurodevelopmental outcomes or a higher rate of subsequent VPS placement. These findings should not be interpreted as demonstrating developmental superiority of proactive intervention, but they support its apparent neurodevelopmental safety and provide rationale for prospective evaluation.

Regarding the specific neurodevelopmental outcomes assessed, we found infants in the proactive Cases cohort demonstrated similar rates of NDI compared with matched, historical 'Controls' as determined by results of the CAT, CLAMS, and PDMS-M testing at 3–30 months of age. While we did not detect differences between our groups, longer term follow up of our cohorts could unveil neurodevelopmental differences that become apparent only later in childhood. Early infancy assessments may lack sensitivity to subtle differences in neurodevelopment, particularly in domains such as cognitive reasoning and communication that evolve rapidly beyond the first two years of life. One retrospective cohort study found that infants assessed at 21–24 months corrected age had higher rates of developmental delay and Bayley composite scores 3–4 points lower than those assessed at 18–20 months, suggesting that earlier testing may underestimate impairment(31).

In the present study, developmental outcomes were assessed early in childhood, initially at a median corrected age of 3.7 months and again at a median corrected age of 14.8 months for children younger than 24 months or a median chronological age of 25.6 months for those older than 24 months. It is possible these intervals precede the emergence of more complex developmental skills. Accordingly, we suspect the relatively early timing of assessments in this cohort contributed to the lack of statistically significant differences between groups, and potential benefits of proactive PHH management may become more apparent as developmental demands increase over time. Of note, we found a greater number of Cases than Controls transitioned from failing to passing classifications at the follow-up neurodevelopmental assessment, particularly on the PDMS-M. The greater proportion of Cases transitioning to a passing classification on the PDMS-M may provide preliminary evidence of improved developmental trajectories or greater neurologic recovery relative to Controls, as motor function may be more readily assessed than cognitive reasoning and communication during a brief clinical visit. Parental assessments, however, may be more sensitive than physician assessment to emerging functional and communicative abilities that become more apparent as children age, suggesting that differences related to PHH management strategy may, again, not be fully detectable during these early assessments but emerge later in childhood. The observed trends between the initial and follow-up evaluations underscore the importance of continued developmental surveillance in this population.

Importantly, the present study's incorporation of both clinician- and caregiver-reported outcomes provides a comprehensive characterization of neurodevelopment within this understudied population. The observed discordance between physician-assessed and caregiver-reported communication

outcomes further highlights the value of multimodal developmental assessment in detecting early differences that may not be fully captured by either approach alone.

Of note, this study employed the Capute Scales (CAT and CLAMS) and the PDMS-M to evaluate neurodevelopment before 30 months of age, while the Bayley Scales of Infant and Toddler Development (BSID) are considered the gold standard for neurodevelopmental assessment. Despite this, CAT/CLAMS has demonstrated strong correlation with BSID, with reported sensitivity of 81% and specificity of 85% for overall NDI, and higher accuracy for detection of severe NDI (sensitivity 100%, specificity 96%)(32).

Limitations include reliance on office-based evaluations, which may constrain accurate assessment of communication and task completion due to limited time and variable infant engagement during physician-administered testing. The higher rate of communication delays identified on caregiver-completed ASQ®-3 at the second follow-up visit may reflect increased sensitivity of parent-reported measures at later ages, as well as the advantage of caregivers' broader observation of children across naturalistic settings compared with brief clinical encounters. Our cohorts include infants cared for over a long period of time during which changes in NICU and post-discharge practices may bias our findings. However, no significant differences in major comorbidities or NICU complications make this less likely. Retrospective designs confer inherent limitations that apply to the present study, including susceptibility to selection bias, incomplete documentation, and limited control over exposures. Additionally, our study included a relatively small sample size limiting statistical power and generalizability. Although matching was performed on key clinical variables, residual confounding related to evolving neonatal practices over time cannot be excluded. Detailed longitudinal neuroimaging correlates of ventricular reduction and brain mantle expansion during active CSF drainage were not evaluated; therefore, the proposed mechanistic effect of proactive drainage on ventricular distention and brain mantle development remains untested in the present study and represents an important area for future investigation. Strengths of this study include its comprehensive assessment, matched cohort design, multimodal neurodevelopmental follow-up using standardized assessment tools, and management within a single tertiary care center, which minimized variability in clinical and surgical decision-making. Prior studies examining the timing and intensity of PHH intervention have reported mixed results, likely reflecting variability in surgical thresholds, outcome measures, and follow-up duration. The present study contributes to this literature by directly comparing two institution-specific management strategies within a matched cohort and by integrating both clinician- and caregiver-reported neurodevelopmental outcomes.

Conclusion

The novel, proactive PHH surgical protocol, defined by earlier trajectory-based reservoir placement followed by proactive, image-guided CSF withdrawal and a subsequent reservoir-weaning trial, was associated with similar neurodevelopmental outcomes in early childhood compared with a historical symptom-driven CSF drainage strategy in all assessed domains. Although no significant differences were detected in primary clinician-assessed or secondary caregiver-assessed outcomes, observed

trends warrant further study of potential benefits of proactive CSF management. Notably, the absence of worse developmental outcomes provides reassurance regarding the neurodevelopmental safety of earlier, protocolized surgical management of PHH. Future studies incorporating serial quantitative imaging may help determine whether proactive ventricular decompression alters ventricular trajectory or brain mantle development and whether such changes are associated with later neurodevelopmental outcomes. Additional investigation is warranted to characterize longer-term developmental outcomes as this cohort continues to mature and undergo additional comprehensive neurodevelopmental testing.

Declarations

Competing Interests

The authors declare no competing interests.

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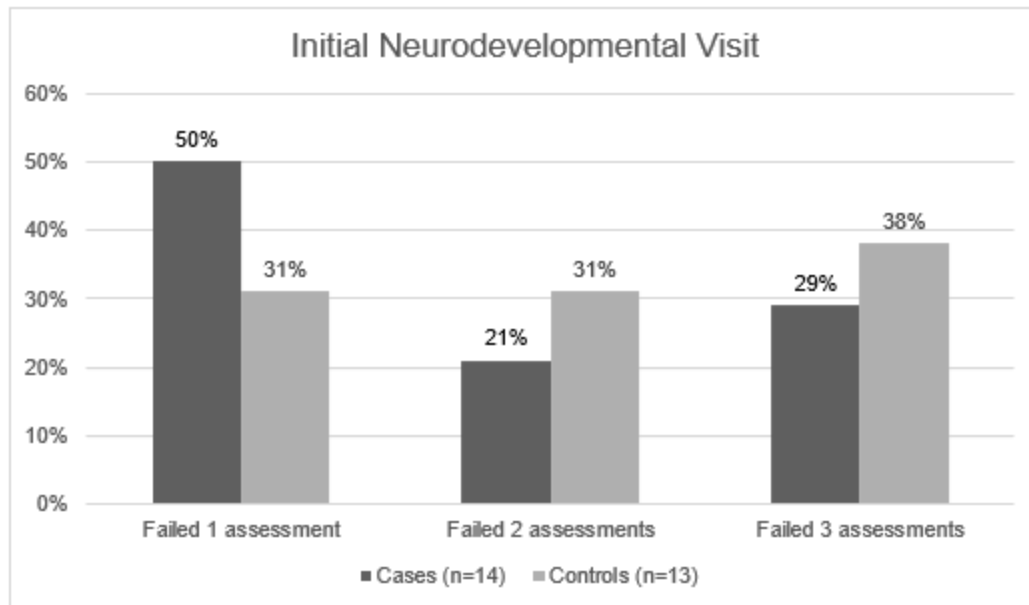
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Figures

Panel A.



Panel B.

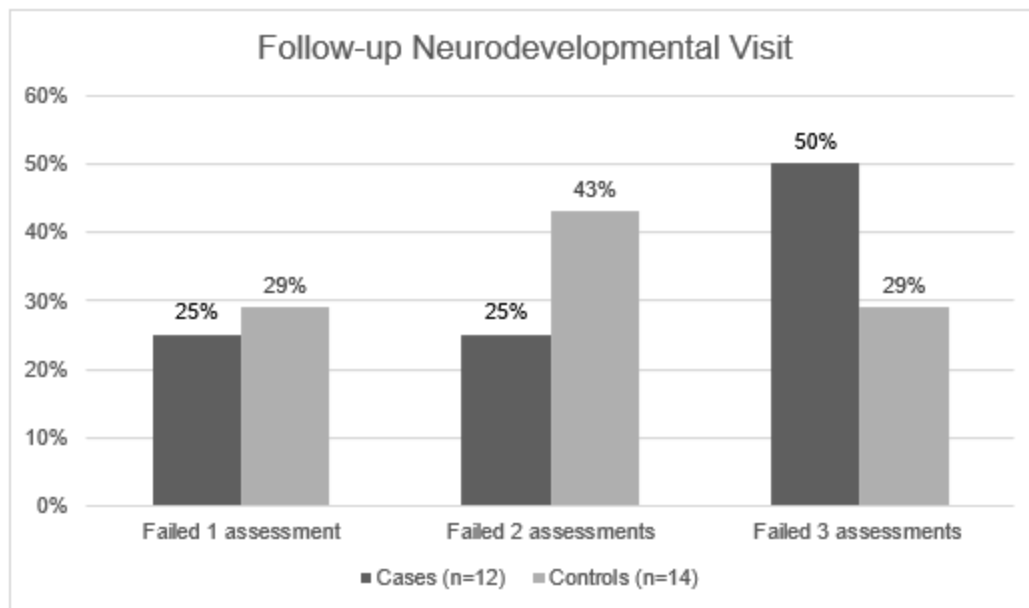


Figure 1

Distribution of Cases vs. Controls who Failed One vs. Two vs. Three Neurodevelopmental Assessments including the Capute Cognitive Adaptive Test (CAT), Clinical Linguistic and Auditory Milestone Scale (CLAMS), and the Modified Peabody Developmental Motor Scale (PDMS-M). Panel A. Initial Neurodevelopmental Assessment. Panel B. Follow-up Neurodevelopmental Assessment. There were no significant differences noted in the distribution of failures between Cases and Controls at either assessment (all $p>0.05$). Folio, M.R. and R.R. Fewell, *Peabody Developmental Motor Scales, Second Edition (PDMS-2)*. 2000, Austin, TX: PRO-ED. Capute, A.J. and P.J. Accardo, *The Capute Scales: Cognitive*

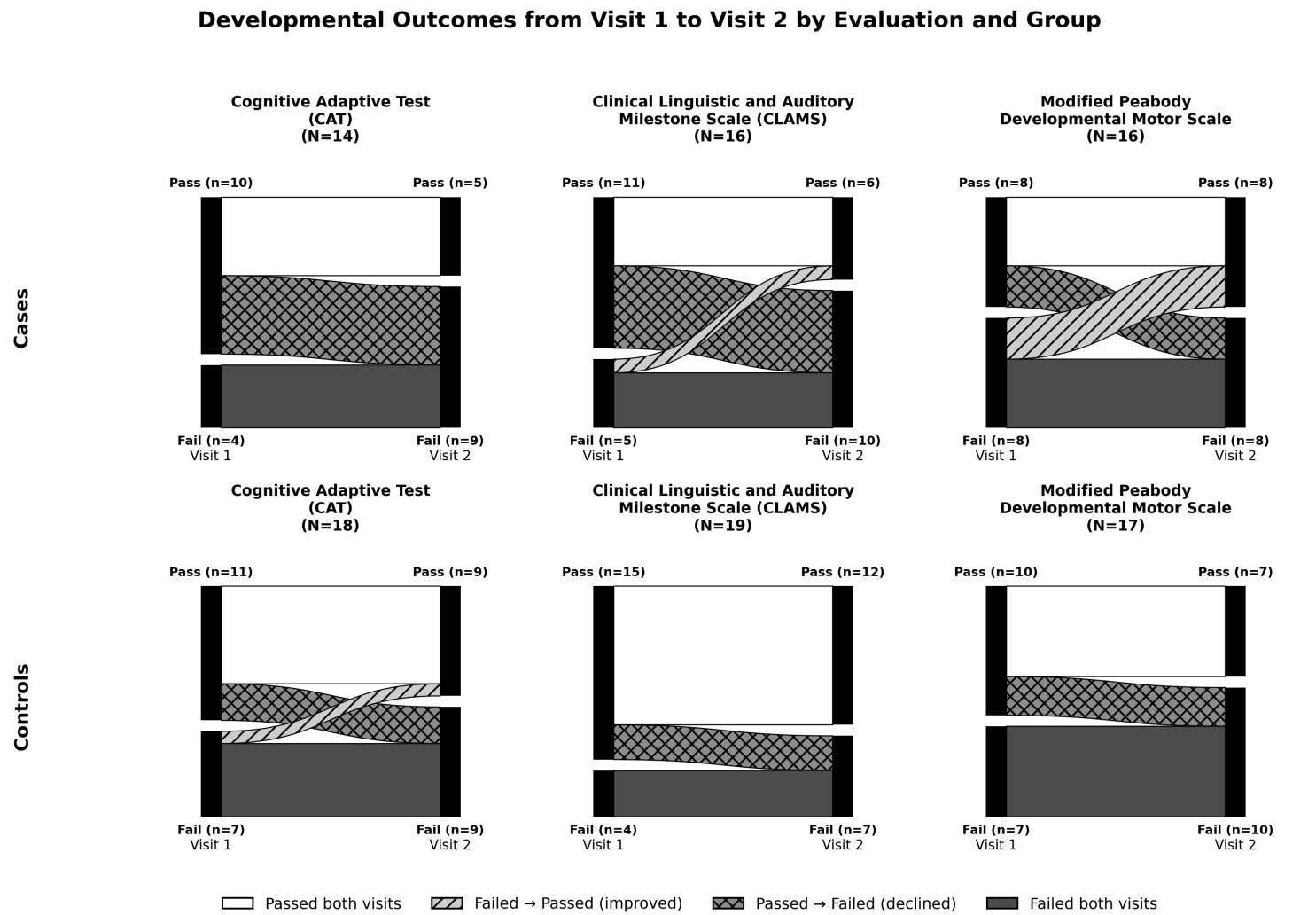


Figure 2

Alluvial/Sankey diagram depicting the change in developmental testing from the initial visit to the follow-up visit across the Capute Cognitive Adaptive Test (CAT), Clinical Linguistic and Auditory Milestone Scale (CLAMS), and the Modified Peabody Developmental Motor Scale (PDMS-M) for Cases and Controls. Folio, M.R. and R.R. Fewell, *Peabody Developmental Motor Scales, Second Edition (PDMS-2)*. 2000, Austin, TX: PRO-ED. Capute, A.J. and P.J. Accardo, *The Capute Scales: Cognitive Adaptive Test/Clinical Linguistic and Auditory Milestone Scale (CAT/CLAMS)*. 2005, Baltimore, MD: Brookes Publishing.

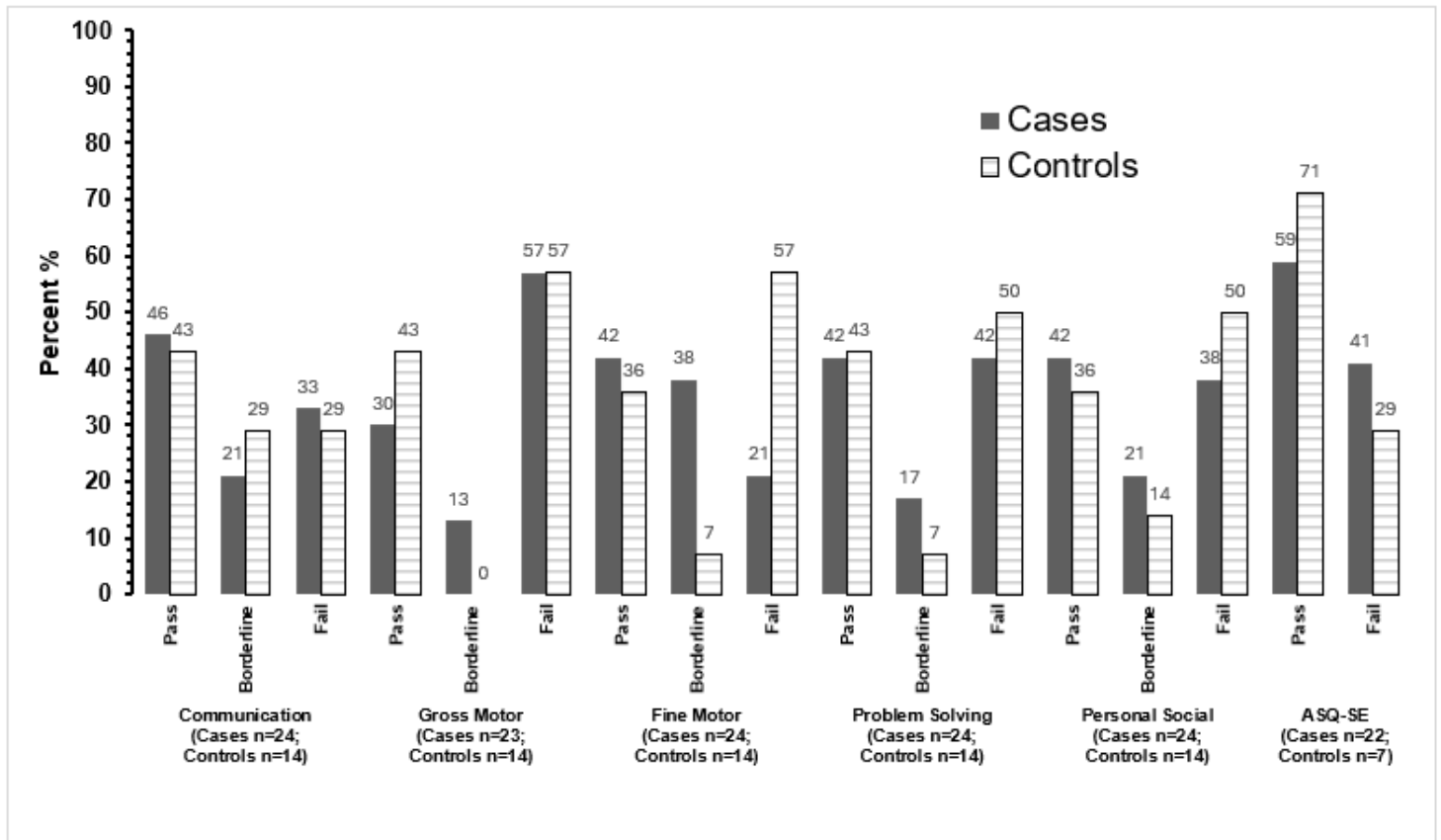


Figure 3

Findings from parental assessments of neurodevelopment using the Ages and Stages Questionnaires®, Third Edition (ASQ®-3), and the Ages and Stages Questionnaires®: Social-Emotional, Second Edition (ASQ®:SE-2) at the initial Newborn Developmental Clinic evaluation. The initial visit in Newborn Developmental Clinic occurred at median chronological age 7.6 (IQR 6.3-9.2) and corrected age of 3.7 months of age (IQR 2.9-5.5). No significant differences between groups were detected for any domains. Squires, J., D. Bricker, and E. Twombly, *Ages & Stages Questionnaires®, Third Edition (ASQ®-3): A Parent-Completed Child Monitoring System*. 2009, Baltimore, MD: Paul H. Brookes Publishing Co. Squires, J., D. Bricker, and E. Twombly, *Ages & Stages Questionnaires®: Social-Emotional, Second Edition (ASQ®:SE-2)*. 2015, Baltimore, MD: Paul H. Brookes Publishing Co.

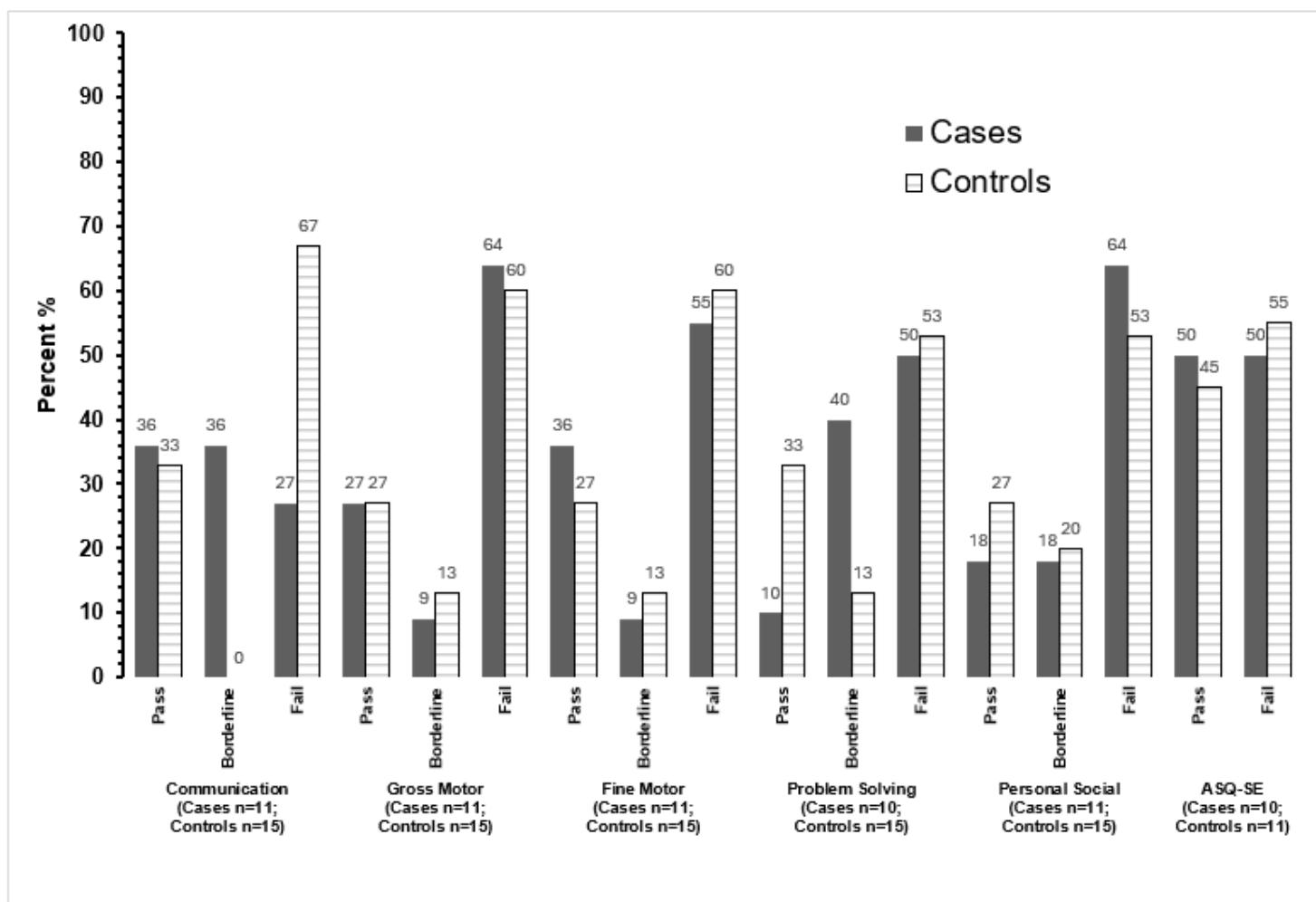


Figure 4

Findings from parental assessments of neurodevelopment using the Ages and Stages Questionnaires®, Third Edition (ASQ®-3), and the Ages and Stages Questionnaires®: Social-Emotional, Second Edition (ASQ®:SE-2) at the follow-up Newborn Developmental Clinic evaluation. A follow-up visit in MUSC Newborn Developmental Clinic data was available for 37 patients, 16 Cases and 21 Controls, at a median chronologic age of 25.6 months (IQR 20.8-30.7). Twelve patients, 7 Cases and 5 Controls, were seen prior to 24 months of age and thus were at a median CA of 14.8 months of age (IQR 11.5-16.3) at this visit. No significant differences between groups were detected for any domains. Squires, J., D. Bricker, and E. Twombly, *Ages & Stages Questionnaires®, Third Edition (ASQ®-3): A Parent-Completed Child Monitoring System*. 2009, Baltimore, MD: Paul H. Brookes Publishing Co. Squires, J., D. Bricker, and E. Twombly, *Ages & Stages Questionnaires®: Social-Emotional, Second Edition (ASQ®:SE-2)*. 2015, Baltimore, MD: Paul H. Brookes Publishing Co.

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