Title

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Journal

Congenital Heart Disease, 7(6)

ISSN

1747-079X

Authors

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Publication Date

2012-11-01

DOI

10.1111/j.1747-0803.2012.00678.x

Peer reviewed

Published in final edited form as:
Congenit Heart Dis. 2012 November ; 7(6): 544–550. doi:10.1111/j.1747-0803.2012.00678.x.

Short Term Neurodevelopmental Outcomes in Neonates with Congenital Heart Disease: the Era of Newer Surgical Strategies

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Abstract

Objective—To determine neurodevelopmental outcomes up to 30 months of age in a cohort of neonates requiring surgical intervention without circulatory arrest for congenital heart disease and to correlate these outcomes with characteristics detected prior to hospital discharge.

Design and Setting—An observational cohort of surviving neonates who underwent surgical intervention without circulatory arrest for congenital heart disease between 2002–2003 was studied at a single tertiary care institution.

Patients—Thirty-five patients were followed from 4–6 months of age until 24–30 months of age.

Outcome Measures—Neuromotor abnormalities, use of special services, and degree of developmental delay at set intervals between 4 to 30 months of age were retrospectively obtained from clinical reports. The relationship between these outcomes and clinical characteristics prior to hospital discharge was analyzed.

Results—Those with neuromotor abnormalities prior to discharge were likely to have persistent abnormalities in muscle strength, tone, and symmetry until 4–6 months of age, OR 6 (1.3–29). By 24–30 months of age, motor abnormalities or developmental delay occurred in 10 of 20 infants (50%), but were no longer significantly associated with pre-discharge findings.

Conclusions—Infants undergoing surgical intervention for congenital heart disease are at risk for neurodevelopmental abnormalities, which may not become apparent until months after hospital discharge. Early impairment may also resolve over time. Close developmental follow-up in this high-risk cohort of patients is warranted.

Keywords

congenital heart disease; outcomes; neonate; surgery

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Author Contributions

Valerie Y. Chock: Study design, Data collection and analysis, Drafting of the manuscript, Final approval of the manuscript's content.
Irene J. Chang: Data collection, Manuscript revision, Final approval of the manuscript's content.
V. Mohan Reddy: Approval of research design, Manuscript revision, Final approval of the manuscript's content.

Conflict of Interest: None

Introduction

Neonates with congenital heart disease (CHD) are at risk for neurological deficits and developmental delay. Multiple factors may contribute to neurodevelopmental injury including issues during the prenatal, early neonatal, peri-operative, and post-operative time periods (1). Specifically, infants requiring deep hypothermic circulatory arrest (DHCA) to allow for a bloodless operative field during their surgical repair have been reported to have higher rates of neurodevelopmental impairment (2, 3). Newer surgical strategies including regional low flow perfusion have been increasingly utilized to eliminate the need for DHCA. However, limited studies have followed neonates not receiving DHCA during surgery to determine both short and longer-term neurodevelopmental outcomes.

Our institution is one of the few that uses antegrade cerebral perfusion instead of DHCA during surgical repair. By removing a significant surgical risk factor, our population of infants with surgically-repaired congenital heart disease is uniquely suited to investigate other contributions to neurologic injury. We reported earlier on a cohort of these infants, of which 16% had neurologic abnormalities prior to hospital discharge (4). Short-term neurodevelopmental follow-up data of this cohort are now reported. We hypothesized that this cohort of infants requiring surgical intervention for congenital heart disease would remain at increased risk for neurodevelopmental impairment at intervals up to 30 months of age and that impairment would be associated with abnormalities detected prior to hospital discharge.

Methods

A retrospective chart review for neurodevelopmental follow-up data beginning at 4–6 months of age was performed on a cohort of patients with a neonatal diagnosis of CHD who were admitted to the neonatal or cardiac intensive care units for the period 3/1/02 to 2/28/03. Data from the initial hospital admission was previously collected (4). The Institutional Review Board approved this medical record review.

All patients with CHD were eligible for follow-up assessment at an on-site developmental and behavioral clinic or at 2 outlying satellite clinics. Developmental follow-up data from other non-affiliated provider visits were not available. Developmental screening results were obtained from standardized clinic reports describing neuromotor abnormalities, use of special services, and the presence and degree of developmental delay as assessed by a developmental pediatrician using a Denver Developmental Screening Type II test or the Capute Scales: Cognitive Adaptive Test and Clinical Linguistic and Auditory Milestone Scale (CAT/CLAMS). Assessments by specialists including neurologists, occupational or physical therapists, clinical psychologists, or speech and language therapists were also included. Evaluations occurred at set periods of age between 4–6 months, 9–12 months, 13–15 months, 18–22 months, and 24–30 months. Of note, speech and language assessment was not formally performed until the 13–15 month visit. Neuromotor abnormalities were further classified into abnormalities of muscle strength, tone, or symmetry. Developmental delay was defined as a ≥2 month delay in gross motor, fine motor, language, or social skills at subject's adjusted age. Cerebral palsy was defined as a nonprogressive central nervous system disorder characterized by abnormal muscle tone in at least 1 extremity and abnormal control of movement or posture. Special services were subclassified into physical therapy, occupational therapy, speech and language therapy, or other assistance.

Statistical Analyses

Logistic regression analyses adjusted for birth weight (SAS v. 9.1) assessed the relationship between outcomes of neuromotor abnormalities, developmental delay, and use of special

services at each of the follow-up periods with clinical patient characteristics prior to hospital discharge. Statistical significance was established for $p<0.05$.

Results

Characteristics at hospital discharge

Thirty-five surviving patients with CHD were seen for an initial developmental assessment at a local clinic visit between 4–6 months of age. Demographics and pre-discharge characteristics of the follow-up cohort are listed in Table 1. Gestational age ranged from 33–42 weeks and 6 (20%) of the cohort were preterm (<37 weeks gestation). All cardiac diagnoses requiring surgical repair were included in the cohort and consisted of 21 (60%) with cyanotic heart disease and 12 (34%) with left-sided, obstructive lesions. In addition 9 (26%) required single ventricle repair. Of the 35 subjects, 17 (49%) had neurologic abnormalities documented prior to hospital discharge. Neurologic abnormalites were defined as the occurrence of seizures, motor tone abnormalities, or asymmetry. In addition, 5 (14%) had abnormal pre-operative brain imaging, and 10 (28%) had abnormal post-operative brain imaging defined as hemorrhage, white matter injury, or ventriculomegaly prior to hospital discharge.

Short-term Neurodevelopmental Follow-up

Consistent follow-up was achieved at 4–6 months, 9–12 months, and 13–15 months of age for all 35 subjects. By 24–30 months of age, the follow-up rate had declined to 57% (20 subjects). One patient died during the course of follow-up. A formal diagnosis of cerebral palsy was made in one patient at the 24–30 month visit (5%). Figure 1 illustrates the rate of neuromotor abnormalities, any type of developmental delay, and use of special services at set time intervals. Motor abnormalities were most common at the 4–6 month follow-up visit (58%), but the rate of motor abnormalities declined by the 24–30 month visit (35%). Indication of developmental delay ranged from 31–58% during the entire follow-up period, but reflected an earlier predominance of gross motor delay (50% at 4–6 months of age) transitioning to a later predominance of speech and language delay (50% at 24–30 months). Figure 2 demonstrates this more detailed delineation of abnormalities at set time intervals. At the 13–15 month visit, all subjects with developmental delay at least demonstrated gross motor delay and subjects receiving special services at least had physical therapy involved in their care. However, by the 24–30 month visit, all subjects with developmental delay at least demonstrated speech and language delay.

Figure 3 demonstrates how *specific* patients with neuromotor abnormalities changed over time. From discharge to the first 4–6 month visit, 4 patients normalized their neuromotor exam. However, 7 subjects exhibited new neuromotor findings that were not present at hospital discharge. By 15 months, only 35% (6/17) of the original infants with neuromotor findings at hospital discharge still exhibited neuromotor abnormalities. Furthermore, of the 20 subjects with neuromotor findings at the 4–6 month visit, only 6 of them (30%) had abnormal neuromotor findings by 15 months. Ninety-three percent (13/14) of those infants whose exams normalized by 15 months had received physical therapy services. Minimal change in neuromotor findings occurred after 15 months.

Relationship of delay with pre-discharge characteristics

Lower birth weight was associated with neuromotor abnormalities ($p=0.06$), developmental delay ($p=0.04$), and increased use of special services ($p=0.03$) by 18 months of age. Higher gestational age, independent of birth weight, was associated with a decreased need for special services by 12 months of age (OR 0.5, $p=0.03$). However no other patient characteristics were significantly associated with use of special services. Aside from

prematurity and low birth weight, motor and developmental abnormalities detected until 30 months of age were also not significantly associated with a majority of the patient characteristics listed in Table 1, including presence of congenital anomalies, male sex, 5-minute Apgar score, or prior abnormal neuroimaging.

Those with neuromotor abnormalities prior to hospital discharge were likely to have persistent abnormalities in muscle strength, tone, and symmetry until 4–6 months of age with OR 6 (1.3–29), p=0.02. By 24–30 months of age, the number of subjects with documented motor abnormalities decreased from 21 (60%) to 7 (35%), with a trend towards association with pre-discharge neuromotor findings (Table 2).

Prenatal diagnosis of the cardiac lesion also was associated at the 24–30 month visit with both the occurrence of neuromotor abnormalities (p=0.03) and developmental delay (p=0.05), but not at earlier time points. Prenatal diagnosis itself was associated more with left-sided obstructive cardiac lesions rather than cyanotic heart defects, OR 6 (1.2–29), p=0.03. However, type of cardiac defect was not significantly associated with abnormal outcomes.

Discussion

This small cohort of patients receiving regional cerebral perfusion during their surgically repaired congenital heart disease demonstrated a 35 to 60% rate of persistent neuromotor abnormalities, developmental delay, or need for special services by 30 months of age. Initial neuromotor abnormalities prior to hospital discharge were associated with persistent neuromotor impairment at 4–6 months of age. Receiving a prenatal diagnosis of congenital heart disease was associated with neuromotor abnormalities and developmental delay at 24–30 months of age. However, these adverse outcomes were not significantly associated with abnormal pre-discharge neuroimaging.

Comparison with other follow-up cohorts

Very few clinical studies have looked at similar cohorts repaired with regional cerebral perfusion (without DHCA). Visconti, et al. compared outcomes at one year of age in a non-randomized study between 9 infants who received regional cerebral perfusion and 20 infants repaired with DHCA (5). These authors found no difference in mental or psychomotor developmental indices. A similar lack of difference at one-year follow-up was found in a larger randomized study of 77 single-ventricle patients (6). While our study did not have a DHCA group for comparison, the incidence of neuromotor abnormalities and developmental delay documented at 24–30 months of age is consistent with this literature.

Larger studies have compared outcomes between subjects receiving DHCA and low-flow cardiopulmonary bypass. These studies found that prolonged duration of DHCA was a risk factor for the development of post-operative seizures (7), as well as later neurodevelopmental delay as assessed by testing at 12–18 months of age and impaired gross and fine motor skills and speech apraxia at 4 years of age (2, 8, 9). In contrast, other investigators have found that selective use of limited periods of DHCA was not associated with worse neurodevelopmental outcomes at 4 years of age (10). Also, DHCA explained only 0.3% or 1% of the variation in neurodevelopmental scores by 8 years of age (11, 12). Therefore, the cohort of infants repaired without DHCA in our study further demonstrates the contribution of *other* factors in addition to peri-operative compromise of cerebral blood flow, which may lead to later neurodevelopmental impairment.

Patient characteristics of interest

Multiple factors contributing to neurodevelopmental compromise may be of greater importance than the limitation of cerebral blood flow that occurs with DHCA. Such factors in the peri-operative period could include the hemodynamic instability and inflammation associated with cardiopulmonary bypass. Prenatal abnormalities in cerebral blood flow as well as post-operative vulnerability to cerebral ischemia may also contribute to injury beyond that which can be controlled during the peri-operative period. Other patient-specific factors including genetic syndromes, genetic polymorphisms, low socioeconomic status, and low birth weight were more predictive than the use or duration of DHCA to neurodevelopmental outcomes at 1 year of age (12).

Our study did confirm that low birth weight was associated with developmental delay at 18 months of age. Other investigators have reported low birth weight and prematurity as predictors of poor neurologic outcome after cardiopulmonary bypass (13–15). Infants with congenital heart disease are more likely to be small for gestational age with low birth weight, perhaps due to poor fetal growth from abnormal fetal circulation patterns (16). However, despite the risk factor of low birth weight, the timing of surgical repair may not be significantly influenced by weight and age (17). A growing number of preterm, low birth weight infants now undergo successful cardiac repair with better outcomes.

Our study, similar to previous reports (8), also demonstrated that neuromotor abnormalities by clinical examination prior to initial hospital discharge were more closely associated with adverse outcomes than abnormal neuroimaging findings. The more subjective nature of neurologic examinations compared to neuroimaging defects should not deter clinicians from performing thorough neurologic evaluations prior to discharge. Dent, et al. studied infants with hypoplastic left heart syndrome and found that 14% had post-operative neuromotor abnormalities and 73% developed new or worsened ischemic lesions by MRI despite their similar use of low flow cerebral perfusion during surgical repair (18). While a relatively high incidence of neuroimaging abnormalities in post-operative infants has been reported (18, 19), our study and others have not determined a direct association between abnormal neuroimaging and subsequent neurodevelopmental deficits (8, 20, 21). In fact, some investigators have shown a common resolution of MRI lesions 4 to 6 months after surgery (21). Therefore, early radiologic findings remain of unclear long-term significance and underscore the need for clinical correlations.

A prenatal diagnosis of congenital heart disease was also associated with adverse outcomes by 24–30 months in our study. However, those infants with a prenatal diagnosis were also more likely to have had left-sided, obstructive heart defects and be at higher risk for poor in-utero and pre-operative cerebral perfusion. Those not prenatally diagnosed may have had less complicated heart lesions, allowing for optimal early care in spite of a lack of forewarning. Literature reports decreased acidosis and a decreased need for mechanical ventilation or emergent surgery in infants prenatally diagnosed with CHD (22, 23), but no change in mortality rates or neurodevelopmental outcomes at one year of age (24). Given ongoing advances in obstetrical imaging, prenatal diagnosis of congenital heart disease will likely increase, requiring further research into long-term outcomes.

Limitations

In this retrospective analysis of neurodevelopmental outcomes in a cohort of infants with congenital heart disease, attrition limited our sample size and power to detect significant associations. Small sample size also limited our ability to make any determinations about specific cardiac lesions and outcomes, although infants with single ventricle physiology would likely have worse outcomes (25). We also were unable to adjust for the impact of

maternal education and socioeconomic status on outcomes. In addition, longer-term and more comprehensive developmental testing both in infancy and at school age and into adolescence may have yielded further evidence for neurodevelopmental impairment as suggested by longitudinal studies in larger cohorts of subjects receiving DHCA (11, 26). Furthermore, other investigators have found that neurodevelopmental testing at one year of age did not identify >50% of children with congenital heart disease having poor outcomes at eight years of age (27). Finally, while our study cohort was fairly heterogeneous in regards to specific cardiac defect and birth weight, results from this single center study may be a reflection of unique medical and surgical care provided at this institution and less applicable to other settings.

Conclusion

Infants undergoing surgical intervention without DHCA for congenital heart disease remain at increased risk for neurodevelopmental abnormalities. Neurodevelopmental deficits may not become apparent until months after hospital discharge, although earlier impairment may also resolve over time. These findings underscore the need for continued close developmental follow-up in this high-risk population.

Acknowledgments

This work was supported by the Stanford NIH/NCRR CTSA grant number KL2RR025743.

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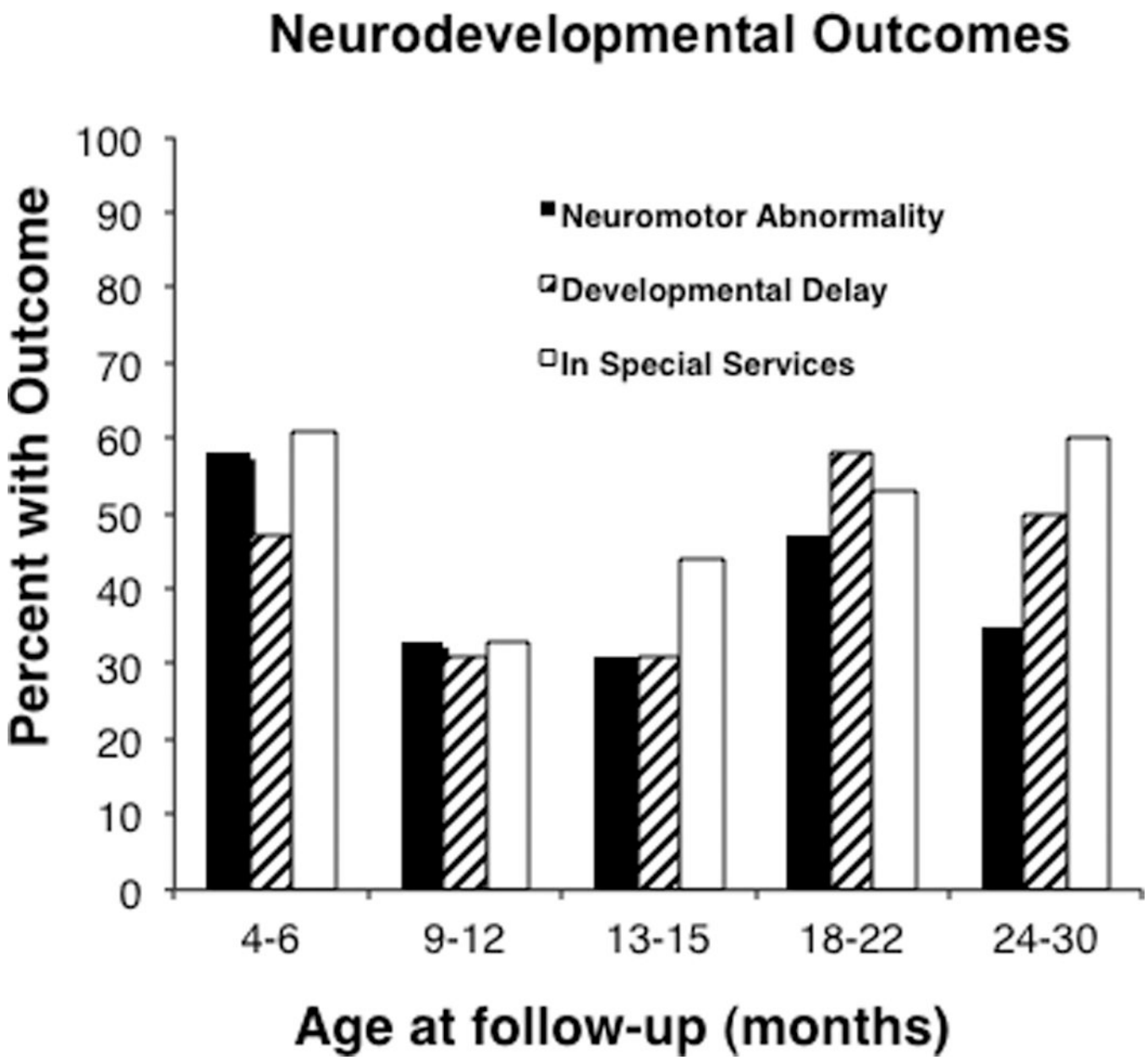

Figure 1. Neurodevelopmental Follow-up

The rate of neuromotor abnormalities slightly decreased between 4–6 months and 24–30 months of age. However, the rate of developmental delay and use of special services increased during this same time period.

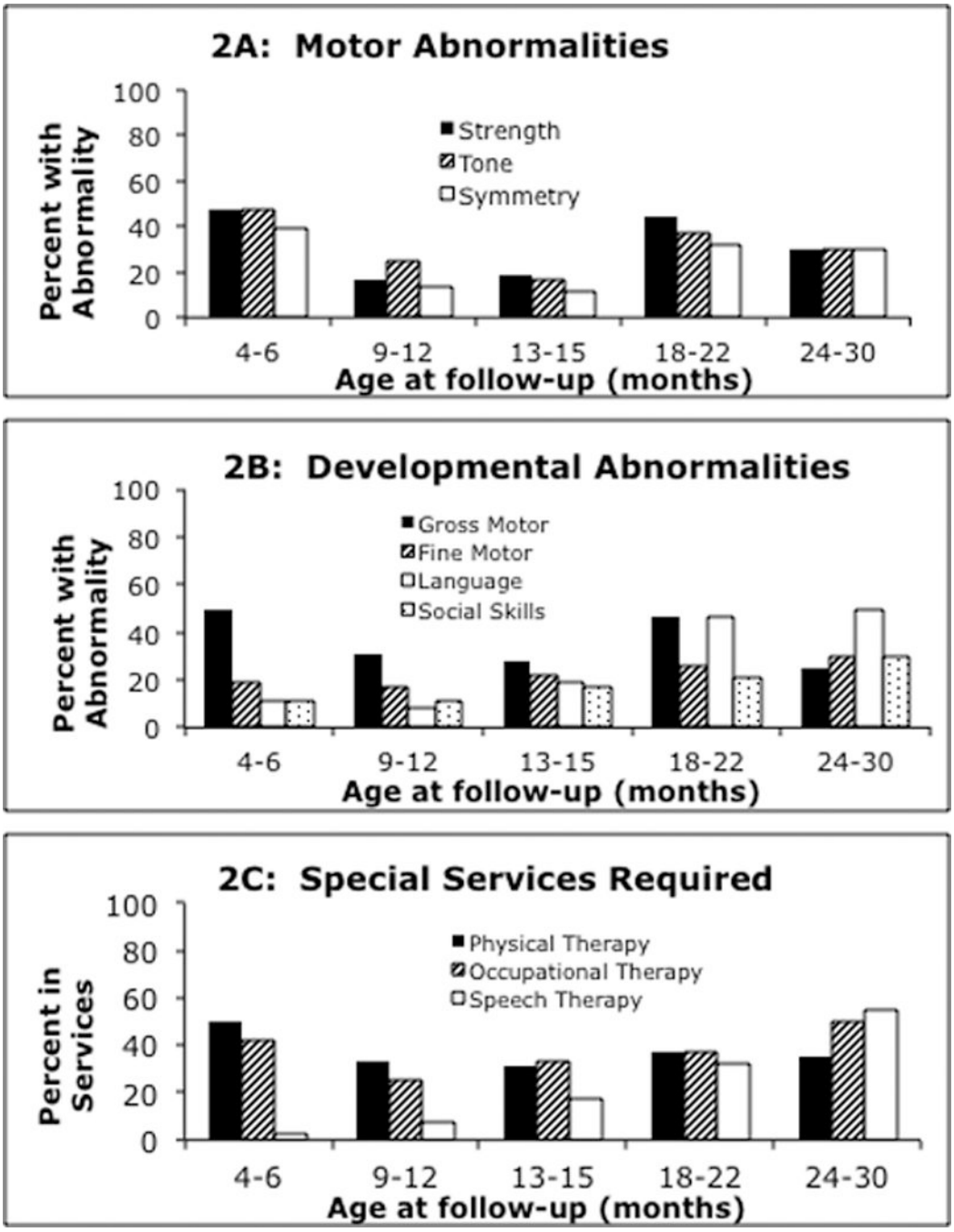

Figure 2. Detailed Follow-up Characteristics over Time

(A) Motor abnormalities were fairly consistently divided between abnormalities in muscle strength, tone, and symmetry.

(B) Developmental delays were predominantly gross motor delays at 4–6 months of age, but speech and language delays at 24–30 months of age.

(C) Physical and occupational therapy were substantially utilized by subjects throughout the follow-up period, and speech therapy utilization increased by 24–30 months of age.

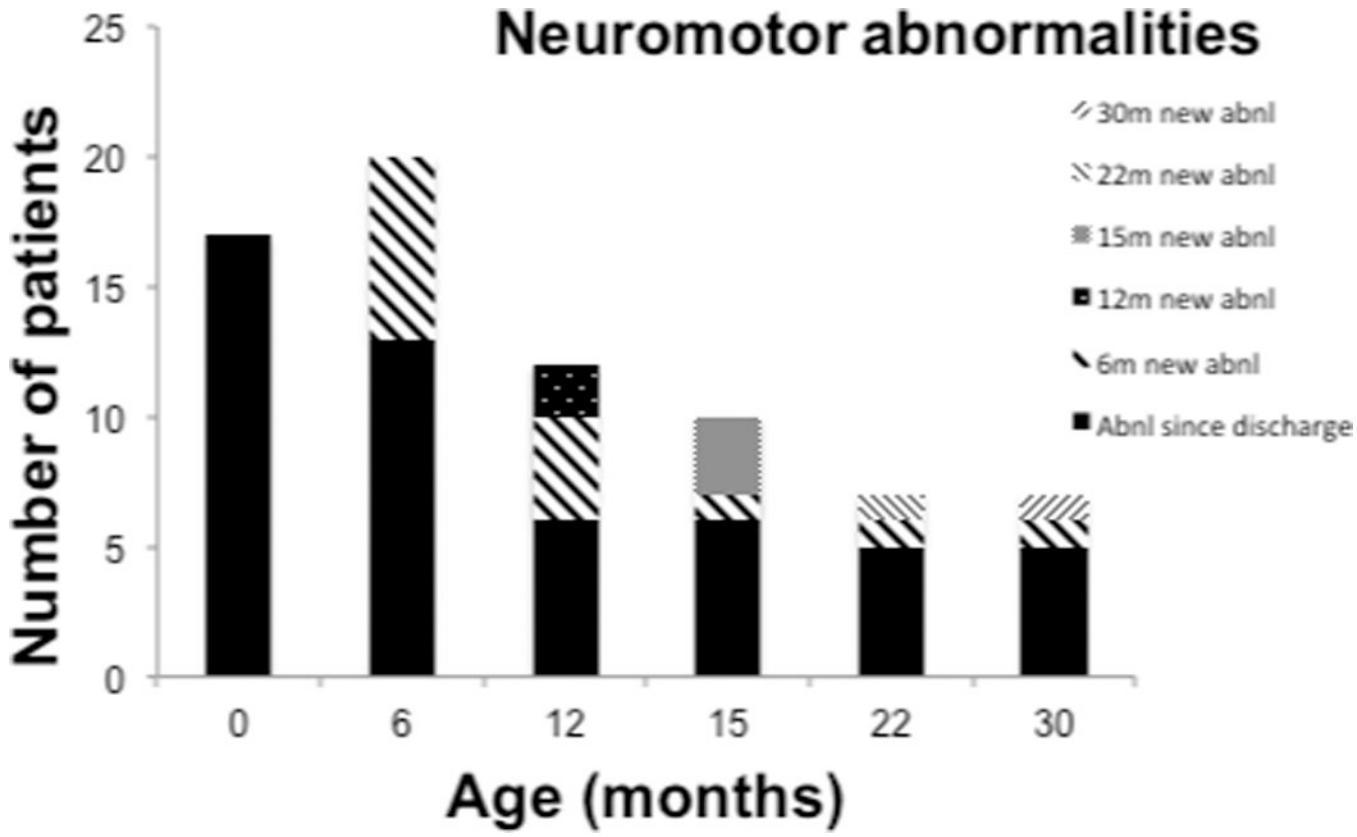

Figure 3. Neuromotor Abnormalities

Neuromotor abnormalities of individual subjects identified prior to hospital discharge showed improvement by 12 months of age. However, new and persistent neuromotor abnormalities were also identified in some subjects after hospital discharge.

Table 1

Pre-discharge demographics and patient characteristics

Characteristic (N=35)	N (%) or Mean ± SD
Birth weight (grams)	3125 ± 681
Low birth weight (<2500 g)	5 (14)
Gestational age (weeks)	39 ± 2
Preterm (<37 weeks)	6 (17)
Male	20 (56)
Prenatal diagnosis	12 (34)
Maternal race Caucasian Hispanic Asian/Pacific Islander African American	18 (51) 10 (29) 5 (14) 2 (6)
Presence of congenital anomalies	9 (26)
Average 1-min APGAR	7 ± 1
Average 5-min APGAR	8 ± 1
Cyanotic heart disease	21 (60)
Single-ventricle repair	9 (26)
Abnormal neuroimaging*	12 (34)
Pre-discharge neurologic abnormalities**	17 (49)

*Abnormal neuroimaging: hemorrhage, white matter injury, ventriculomegaly

**Neurologic abnormalities: seizures, hyper or hypotonia, choreoathetosis

Table 2

Pre-Discharge Characteristics Associated with Abnormalities

Characteristic	Follow-up Period (months)	Odds Ratio	95% Confidence Interval	p-value
ASSOCIATION WITH NEUROMOTOR ABNORMALITIES				
Pre-discharge neurologic abnormalities **	4–6 24–30	6 8.3	1.3–29 0.9–76	0.02 0.06
Prenatal Diagnosis	4–6 24–30	0.9 15	0.2–4.1 1.3–174	0.9 0.03
Abnormal neuroimaging *	4–6 24–30	4.4 3.4	0.8–26 0.5–25	0.1 0.2
Congenital anomalies	4–6 24–30	1 1.8	0.2–4.6 0.2–17	0.9 0.6
ASSOCIATION WITH DEVELOPMENTAL DELAY				
Pre-discharge neurologic abnormalities **	4–6 24–30	3.4 5.8	0.8–14 0.7–51	0.09 0.1
Prenatal Diagnosis	4–6 24–30	0.6 13	0.1–2.5 1–158	0.5 0.05
Abnormal neuroimaging *	4–6 24–30	3.3 1.1	0.7–16 0.2–7	0.1 0.9
Congenital anomalies	4–6 24–30	1.3 17	0.3–6.3 0.7–420	0.7 0.08

* Abnormal neuroimaging: hemorrhage, white matter injury, ventriculomegaly

** Neurologic abnormalities: seizures, hyper or hypotonia, choreoathetosis