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Neurodevelopmental and Cognitive Outcomes in Children with Intestinal Failure

Patrick Chesley, M.D.¹, Sabrina E. Sanchez, M.D., M.P.H.¹, Lilah Melzer, B.A.¹, Assaf Oron, Ph.D.², Simon Horslen, M.B., Ch.B.³, F. Curt Bennett, M.D.³, and Patrick J. Javid, M.D.¹

¹Department of Surgery, Seattle Children's Hospital, University of Washington School of Medicine, Seattle, WA

²Core for Biomedical Statistics, Seattle Children's Hospital, University of Washington School of Medicine, Seattle, WA

³Department of Pediatrics, Seattle Children's Hospital, University of Washington School of Medicine, Seattle, WA

Abstract

Objectives—Recent advances in medical and surgical management have led to improved long-term survival in children with intestinal failure. Yet, limited data exist on their neurodevelopmental and cognitive outcomes. The aim of this study was to measure neurodevelopmental outcomes in children with intestinal failure.

Methods—Children enrolled in a regional intestinal failure program underwent prospective neurodevelopmental and psychometric evaluation using a validated scoring tool. Cognitive impairment was defined as a mental developmental index < 70. Neurodevelopmental impairment was defined as: (1) cerebral palsy; (2) visual or hearing impairment or (3) cognitive impairment. Univariate analyses were performed using the Wilcoxon rank sum test. Data are presented as median (range).

Please address correspondence to: Patrick J. Javid, MD, Seattle Children's Hospital, 4800 Sand Point Way NE, OA.9.220, Seattle, WA 98105, Phone: (206) 987-6129, Fax: (206) 987-3925, Patrick.javid@seattlechildrens.org.

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Contributors' Statement Page

Dr. Chesley performed data acquisition and interpretation, drafted the initial manuscript and contributed to revisions, has approved the final version of the manuscript and agrees to be accountable for all aspects of the work related to accuracy and integrity.

Dr. Sanchez contributed to the study design and conception, revised the manuscript critically for important intellectual content, has approved the final version of the manuscript, and agrees to be accountable for all aspects of the work related to accuracy and integrity.

Ms. Melzer performed data acquisition, revised the manuscript critically for important intellectual content, has approved the final version of the manuscript, and agrees to be accountable for all aspects of the work related to accuracy and integrity.

Dr. Oron performed data analysis and interpretation, revised the manuscript critically for important intellectual content, has approved the final version of the manuscript, and agrees to be accountable for all aspects of the work related to accuracy and integrity.

Dr. Horslen contributed to the study design and conception, assisted with data interpretation, revised the manuscript critically for important intellectual content, has approved the final version of the manuscript, and agrees to be accountable for all aspects of the work related to accuracy and integrity.

Dr. Bennett contributed to the study design and conception, assisted with data interpretation, revised the manuscript critically for important intellectual content, has approved the final version of the manuscript, and agrees to be accountable for all aspects of the work related to accuracy and integrity.

Dr. Javid led the conception and design of the study, performed data acquisition, analysis and interpretation, revised the manuscript critically for important intellectual content, has approved the final version of the manuscript, and agrees to be accountable for all aspects of the work related to accuracy and integrity.

Results—Fifteen children with a remnant bowel length of 18 (5 – 85) cm were studied at age 17 (12 – 67) months. Thirteen patients remained dependent on parenteral nutrition. Twelve (80%) subjects scored within the normal range on cognitive testing. Each child with cognitive impairment was noted to have additional risk factors independent of intestinal failure including cardiac arrest and extreme prematurity. On univariate analysis, cognitive impairment was associated with longer inpatient hospital stays, increased number of surgical procedures, and prematurity ($p<0.02$). In total, four (27%) children demonstrated findings consistent with neurodevelopmental impairment.

Conclusions—A majority of children with intestinal failure demonstrated normal neurodevelopmental and cognitive outcomes on psychometric testing. These data suggest that children with intestinal failure without significant co-morbidity may be at low risk for long-term neurodevelopmental impairment.

Keywords

intestinal failure; short bowel syndrome; cognition; neurodevelopment

Introduction

Over the past decade, the medical and surgical management of pediatric intestinal failure has evolved with the implementation of multi-disciplinary intestinal rehabilitation programs. Advances in intestinal failure care – including nutritional therapies to prevent and reverse intestinal failure-associated liver disease, techniques for surgical bowel lengthening and tapering, and preventative strategies against catheter-related sepsis – have contributed to improved survival in this population (1–4). Recent reports demonstrate that long-term survival in pediatric intestinal failure is now common with survival rates from tertiary pediatric centers ranging from 73–90% (6–9). Yet, the quality of long-term survival in pediatric intestinal failure has not been fully studied.

Similar to other young patients with complex medical and surgical pathology, children with intestinal failure may be at risk for poor neurodevelopmental and cognitive outcomes. Multiple procedures under general anesthesia, long hospital stays, frequent blood stream infections, and distinct alterations in nutritional delivery and provision all put children with intestinal failure at risk for neurocognitive morbidity (10–15). Despite this fact, there are limited data in the literature on neurodevelopmental outcomes in this population. Only two studies to date have evaluated neurodevelopment in children with intestinal failure. The first study, published over 15 years ago, focused on the identification of cognitive deficits in a small cohort of 8 school-aged children with short bowel syndrome (16). The second study measured long-term cognition in 8 short bowel patients in China who had been successfully weaned from parenteral nutrition (PN) for an average of 7 years (17). While neither study identified significant developmental delay, there was a suggestion of deficits in visual-spatial and psychomotor skills. Importantly, both studies were performed prior to the current era of multi-disciplinary intestinal rehabilitation and improved long-term patient survival; in this way, it is possible that long-term survivors in the previous era were healthier at baseline thereby leading to biased results on neurodevelopmental testing.

The primary aim of this study was to objectively measure the neurodevelopment outcomes and cognitive capacity of a contemporary cohort of children with intestinal failure treated at a regional, multi-disciplinary intestinal rehabilitation center and to compare these data with standardized normative values for healthy children. A secondary aim was to explore associations between neurodevelopmental outcomes and risk factors specific to the intestinal failure population.

Patients and Methods

After approval from the Seattle Children's Institutional Review Board (IRB #13422), patients in the Intestinal Care Program at Seattle Children's Hospital ages one to five years were approached for enrollment. Subjects were excluded for any of the following: (1) a known or suspected chromosomal anomaly; (2) abdominal surgery within 30 days of study participation; (3) documented active infection as defined by fever $> 38.5^{\circ}\text{C}$, positive blood culture within 14 days, or positive urine culture within 5 days of study participation; or (4) inpatient status at time of study. Apart from chromosomal abnormalities, exclusion criteria were considered temporary and did not preclude subjects from future enrollment into the study once specific criteria were no longer applicable.

Enrolled patients underwent a complete neurodevelopmental evaluation during a single visit to the High Risk Infant Follow-Up Clinic at the University of Washington Center for Human Development and Disability. This clinic was established in 1975 and performs neurodevelopmental evaluations in 500–600 children annually. The evaluation included age-appropriate psychometric testing and a complete physical and neurologic examination including hearing and visual assessment by a developmental pediatrician. Psychometric testing was performed by a child psychologist using the Bayley Scales of Infant Development-II (BSD-II) for children up to 3 years of age and the Differential Ability Scales or Weschler Preschool and Primary Scale of Intelligence for older children (18). Hearing examination was performed using visual reinforcement audiometry or play audiometry depending on subject age. Assessments of vision were performed using historical information and formal examination to rule out strabismus.

Medical records of subjects, including outside hospital charts when appropriate, were reviewed to collect data pertaining to surgical and medical risk factors. Length of stay data were tabulated from all hospital admissions as documented in our electronic medical record and outside hospital paper charts. Bowel length was measured using a sterile suture along the anti-mesenteric border of the small bowel when measured at our institution and recorded from dictated operative notes when measured at an outside facility. All subjects underwent formal nutritional evaluation at each Intestinal Care outpatient clinic visit by a registered dietician who specializes in pediatric intestinal failure nutrition. Central line associated blood stream infections were defined using the Centers for Disease Control and Prevention National Healthcare Survey Network criteria (19).

Cognitive impairment was defined as a score greater than two standard deviations below the normative mean (less than or equal to 70) on the mental developmental index (MDI) as recorded in the BSD-II (or equivalent). We defined cerebral palsy as a non-progressive

neurological disorder characterized by abnormal limb tone and decreased range or control of movement and posture. Neurodevelopmental morbidity was defined as one or more of the following: (1) cerebral palsy on neurologic exam; (2) visual or hearing impairment on physical exam; (3) cognitive impairment as defined previously; or (4) a score greater than two standard deviations below the mean (less than or equal to 70) on the psychomotor developmental index (PDI) on the BSD-II.

Associations of risk factors with neurocognitive impairment were determined using the Wilcoxon rank-sum nonparametric test with significance defined as $p < 0.05$. The statistical modelling and analyses were performed using R 3.1.0 software. Data are presented as median (range).

Results

Fifteen children, including 12 males, were studied at age 17 (12–67) months. Etiologies of intestinal failure included gastroschisis ($n=6$), jejunoileal atresia (3), midgut volvulus (2), necrotizing enterocolitis (2), meconium peritonitis (1), and long segment Hirschsprung's disease with aganglionosis beginning at 130 cm from the ligament of Treitz (1). The median gestational age in this cohort was 35 weeks 3 days (26 week 6 days – 41 weeks 4 days) (Table I). All patients had undergone extensive bowel resection as young infants, and remnant small bowel length was 18 (5 – 85) cm. Both subjects with midgut volvulus were diagnosed within the first 10 days of life. At the time of evaluation, only two subjects (13%) had attained enteral autonomy for 3 and 11 months, respectively. Of the remaining patients, 4 subjects were completely dependent on PN for their nutritional intake (Table I). In total, subjects had been exposed to PN for 522 (367–2036) days and were receiving 75 (0–88) kcal/kg from PN at the time of neurodevelopmental testing. Seven patients (47%) had been treated with intravenous fish-oil based lipid emulsion for 21 (11–54) months (Omegaven®, Fresenius Kabi, Lake Zurich, IL) for PN-associated cholestatic liver disease. Bowel lengthening using the serial transverse enteroplasty (STEP) technique had been performed in 3 patients, and 12 subjects had undergone gastrostomy placement. One child was diagnosed with congenital heart disease at birth (transposition of the great vessels).

Known risk factors for neurodevelopmental impairment were recorded for each subject. Prior to evaluation, subjects had been hospitalized for 118 (36 – 362) days, undergone 11 (1 – 21) operations under general anesthesia, and experienced 6 (0 – 14) central line-associated blood stream infections. Three children had received intravenous vasopressor agents during their acute surgical course as young infants. Two subjects had a documented history of cardiac arrest requiring cardiopulmonary resuscitation. Prior head imaging had been performed in 7 patients, and abnormalities were identified in 3 subjects (focal cystic encephalomalacia on MRI in the child born at 26 weeks, and evidence of hypoxic injury in the two subjects who experienced cardiac arrest).

Thirteen children underwent psychometric evaluation using the BSD-II and one child each with the Differential Ability Scales and Weschler Preschool and Primary Scale of Intelligence. Detailed testing results are presented in Table 2. The median MDI and PDI values for the overall cohort were 82 and 77, respectively. Cognitive impairment, as defined

by an MDI (or equivalent) less than 70, was identified in 3 (20%) subjects. Of the remaining 12 patients, one child scored above the normative mean, and six children scored between one and two standard deviations below the mean (Figure 1). Of the subjects with scores indicative of cognitive impairment, one child was born at 26 weeks gestation and two children had survived cardiopulmonary arrest. On univariate analysis, total hospital days and number of surgical procedures performed under general anesthesia were significantly associated with cognitive impairment in our study cohort ($p=0.02$). In addition, full-term children born at a gestational age of 37 weeks or greater had a significantly higher MDI score when compared to preterm subjects (96 vs 77, $p=0.004$, Figure 2). There were no associations between neurodevelopmental risk factors and PDI values.

In total, 4 (27%) study subjects were found to be neurodevelopmentally impaired. This group includes the three children with cognitive impairment on psychometric testing. One additional child with normal cognition was found to have profound hearing impairment (greater than or equal to 90 dB) on examination. No child exhibited gross vision abnormalities. Cerebral palsy was noted in 2 subjects, both of whom were also diagnosed with cognitive impairment based on MDI scores.

Discussion

Infants and children who suffer from intestinal failure are now surviving into school age and beyond due in large part to the recent success of intestinal rehabilitation at multidisciplinary referral centers (6-9, 20). These patients were previously at high risk for complications of intestinal failure that limited their life expectancy including PN-associated liver disease, sepsis, and coagulopathy. Within the past decade, however, significant advances have been made in the medical, surgical, and nutritional aspects of intestinal rehabilitation. For example, alterations in the lipid allotment and composition in PN can prevent and reverse liver disease (1,2). Ethanol lock therapy has been shown to reduce the incidence of central line-associated blood stream infection in these patients (4, 5). Innovative techniques in autologous intestinal reconstruction now allow for safe bowel lengthening and tapering (3). While these children remain at risk for significant morbidity, pediatric intestinal failure is evolving into a chronic lifelong disease process, and the quality of the group's survival has become a relevant area of investigation.

Yet, there are limited data as to the neurodevelopmental outcomes of these children. It is well established that this cohort is exposed to a multitude of iatrogenic and pathophysiologic factors known to increase the risk of neurodevelopmental impairment. These patients routinely require multiple exposures to general anesthesia, lengthy inpatient hospitalization, and significant alterations in nutritional provisions. In this way, the aggressive medical and surgical therapies that allow for long-term survival in this population may also contribute to chronic neurodevelopmental morbidity. The potential for cognitive deficits is especially relevant in this population as the first cohort of long-term survivors have now reached school age. These data would be valuable as they would provide important prognostic information to families early in the process of intestinal rehabilitation. In addition, this information may allow for timely identification of patients at risk for neurodevelopmental impairment who may be ideal candidates for early cognitive intervention.

In this study, a small group of children with chronic intestinal failure underwent prospective psychometric testing and neurodevelopmental examination by expert providers who were not involved in subjects' intestinal failure care. The study participants represented a group of young children with significant intestinal dysfunction and short bowel syndrome. For example, the study population's small bowel remnant length of 18 cm is less than 10% of the estimated length of a full-term newborn's small intestine. The etiologies for intestinal failure encompassed a wide variety of intestinal pathology, and all subjects had undergone extensive surgical resection. Nearly all participants still required PN for sustenance, and four subjects could not tolerate any enteral nutrition at the time of the study. In addition, the distribution of diagnoses in our intestinal failure cohort was similar to previously published data from our center with the exception of fewer children with necrotizing enterocolitis enrolled in this study (21). Thus the study cohort, while small in number, was a reasonable representation of the current generation of long-term pediatric intestinal failure survivors.

The data in this study demonstrate that a substantial majority of children with intestinal failure scored within the normal range on psychometric testing and did not exhibit deficits in neurodevelopment. Of the three subjects with cognitive impairment, each child had additional risk factors for poor cognition independent from intestinal failure including extreme prematurity and cardiopulmonary arrest. Similar to previous data in preterm infants, prematurity was associated with lower cognitive testing scores in the intestinal failure population (22, 23). Children with intestinal failure born after 37 weeks gestation were solidly within the normal range for mental function on psychometric testing. Taken together, these data suggest that children with intestinal failure without significant co-morbidity may be at low risk for neurodevelopmental morbidity. This finding will help to define the natural history of intestinal failure in the current era of increased survival.

However, while the neurodevelopmental outcomes in this study were promising, the distribution of cognitive testing scores was far from optimal and trended lower than expected from general population data. In our data, six of the 15 subjects generated MDI scores between one and two standard deviations below the normative mean of 100, and only one subject in this study attained an MDI score above the mean (Figure 1). This distribution of MDI test scores suggests that although many of the study participants with intestinal failure will not harbor distinct cognitive disability, they may still be at risk for mild developmental delay and learning challenges as they mature. This patient population would likely benefit from aggressive early intervention services, occupational and physical therapy, and formal neurodevelopmental evaluation as part of their routine intestinal care and rehabilitation.

Several limitations to the study must be acknowledged. The study population is small which is of particular relevance to a disease with wide heterogeneity such as intestinal failure. The patients were studied at various ages, and different neurodevelopmental measurement instruments were required for the older subjects. This, in turn, may limit comparison among patients in our small cohort. It is also possible that our data reflect a selection bias as enrollment in this study was voluntary; in total, three families refused participation, and three additional families expressed interest but subsequently moved out of our geographic region. It is possible that subjects and families who were motivated to participate in this study had different cognitive capacity and home learning environments compared to subjects

who were not enrolled. Finally, and important to the evaluation of neurodevelopment, the range of prematurity in study participants may not reflect the general population of pediatric intestinal failure patients. While 10 subjects were born at less than 37 weeks gestation, only one subject experienced extreme prematurity. These data, then, may be less reflective of the population of children with intestinal failure secondary to necrotizing enterocolitis.

Future investigation should also focus on the long-term effects of omega-3 fatty acid supplementation. It is hypothesized that polyunsaturated fatty acids are important for brain development in the young infant (24, 25). The fatty acid composition of omega-3 fatty acid emulsions differs considerably from more standard intravenous fat emulsions as well as the normal lipid provision in a healthy infant's oral diet. In this study, nearly half of the children had been administered intravenous omega-3 fatty acid supplementation at some point in their intestinal rehabilitation including two of the three children with cognitive impairment.

As the care of infants and children with intestinal failure evolves, research investigating the quality of this cohort's long-term survival is increasingly valuable. The data presented here may be useful in counseling families of young infants with intestinal failure beginning in the neonatal intensive care unit and continuing throughout the process of intestinal rehabilitation. These data demonstrating reasonable neurodevelopmental outcomes may contribute to the discussion of prognosis when early decisions as to long-term survival and urgent surgical care are required. Ultimately, the favorable outcomes demonstrated in this study serve to further justify the aggressive medical and surgical treatments required to promote long-term survival in pediatric intestinal failure patients.

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What is Known about this Subject

- Long-term survival in pediatric intestinal failure has improved dramatically in the past decade with children surviving into school age and beyond
- Yet there are no data as to the neurodevelopmental and cognitive outcomes in this contemporary cohort of children.

What is New

- In this study, a majority of children with intestinal failure had normal cognition and neurodevelopment.
- Those children with neurodevelopmental impairment suffered from additional risk factors separate from intestinal failure known to increase cognitive morbidity.
- The findings suggest that survivors of intestinal failure without significant co-morbidity may be at low risk for neurodevelopmental impairment.

Figure 1.

Detailed MDI testing results are presented. Figure 1a presents the data for each subject. The distribution of MDI data stratified by standard deviation is presented in Figure 1b. Only 3 (20%) subjects demonstrated cognitive impairment based on MDI scores (MDI < 70). Six subjects (40%) tested between one (solid line) and two standard deviations (dotted line) below the mean (MDI range 71–84).

Figure 2. MDI scores, graphed by gestational age, were significantly higher in subjects born at 37 weeks gestation (vertical line) or greater.

Table I

Demographic data of the intestinal failure study cohort

Subject	Diagnosis	Gestational Age (weeks)	Remnant Bowel Length (cm)	PN (kcal/kg) at Time of Study	Age at Time of Study (months)
1	NEC	26 6/7	37	68	19
2	Gastroschisis	32 3/7	18	57	26
3	Gastroschisis	36	15	68	38
4	Hirschsprung's	40	85	*	16
5	Meconium cyst	35 2/7	32	35	13
6	Atresia	37	10	81	32
7	NEC	34	11	82	12
8	Gastroschisis	31	25	80	12
9	Gastroschisis	37 3/7	52	*	55
10	Gastroschisis	34 6/7	34	61	16
11	Gastroschisis	36 4/7	10	75	67
12	Atresia	37	54	29	15
13	Volvulus	34	10	77	17
14	Atresia	35	18	88	35
15	Volvulus	41 4/7	5	79	16

* Subjects who had weaned from PN at time of study

NEC = necrotizing enterocolitis; PN = parenteral nutrition

Table 2

Detailed Psychometric Testing and Physical Examination Results

Subject	MDI (or equivalent)	PDI	Physical Exam Finding?
1	64	<50	Y (CP)
2	<50	<50	N
3	<50	<50	Y (CP)
4	94	86	N
5	82	77	N
6	104	91	N
7	80	83	Y (Hearing)
8	90	103	N
9	89 [*]	*	N
10	75	81	N
11	76 [*]	*	N
12	96	70	N
13	82	74	N
14	77	70	N
15	96	78	N

^{*} WPPSI and DAS were used to evaluate Subjects 9 and 11, respectively. Therefore, PDI data were not available for these subjects.

MDI = mental developmental index; PDI = psychomotor developmental index; CP = cerebral palsy