Living with Severe Bronchopulmonary Dysplasia—Parental Views of Their Child's Quality of Life

Jennifer M. Brady, MD[1,2,3], Huayan Zhang, MD[3], Haresh Kirpalani, BM[3], and Sara B. DeMauro, MD, MSCE[3]

Objective To assess parents' views of their children's health-related quality of life (HRQoL) and the association between neonatal morbidities and HRQoL in children with severe bronchopulmonary dysplasia (BPD) who survived to 18-36 months of corrected age.

Study Design Study population included infants born <32 weeks of gestational age with severe BPD. At 18-36 months of corrected age, parents of children with severe BPD completed age appropriate validated Pediatric Quality of Life Inventory assessing parental views of their child's physical (PHY-QoL) and psychosocial HRQoL (PS-QoL). Ten neonatal morbidities provided a composite morbidity score between 0 and 10. Linear regression evaluated associations between PHY-QoL and PS-QoL with composite morbidity score, adjusting for gestational age, sex, corrected age at assessment.

Results Seventy children (67% male, gestational age 26.1 ± 2.0 weeks, and birth weight 797 ± 318g) were enrolled at 27.1 ± 5.8 months of corrected age. Mean PHY-QoL and PS-QoL were 78.0 ± 21.9 and 75.3 ± 17.9, respectively, both significantly lower than reported means for term and preterm cohorts, with the exception of emotional QoL. Adjusted postnatal composite morbidity score was cumulatively associated with poorer PHY-QoL ($P = .002$) and poorer PS-QoL ($P = .015$). Presence of each additional neonatal morbidity was associated with a 4.4-point decrease in PHY-QoL and 2.8-point decrease in PS-QoL.

Conclusions In this cohort, parental perceived HRQoL for their child with severe BPD was lower than expected for term and preterm populations. Neonatal morbidities had an additive association with poorer parental assessment of PHY-QoL and PS-QoL. These findings may aid in care of children with severe BPD and their families, both in the intensive care nursery and postdischarge. *(J Pediatr 2019;207:117-22).*

See editorial, p 14

Bronchopulmonary dysplasia (BPD) is the most common severe complication of prematurity.[1] Survivors with BPD have increased risk for lasting impairments of general medical and respiratory health that often persist past childhood and into adulthood.[2] Yet, whether and by how much this impacts health-related quality of life (HRQoL) is largely unknown. HRQoL, as described by Healthy People 2020,[3] is "a multidimensional concept that includes domains related to physical, mental, emotional, and social functioning. It goes beyond direct measures of population health, life expectancy, and cause of death, and focuses on the impact health status has on quality of life."[3]

The few studies that have assessed HRQoL in adolescent and adult survivors with BPD in comparison with preterm and full-term controls show conflicting results.[4-7] When compared with full-term born adults, Beaudoin et al found no difference in HRQoL,[4] whereas Gough et al found significantly lower HRQoL in adults with BPD.[5] When comparing HRQoL in adults of former preterm infants with and without BPD, neither Beaudoin et al nor Gough et al reported significant differences.[4,5] Studies by Bozzetto et al and Gray et al found similar HRQoL in adolescents with BPD and their term and preterm equivalents, respectively.[6,7] No studies have explored parent-perceived HRQoL of their children with severe BPD during early childhood. It is also unknown if the number of morbidities experienced by the child during the neonatal period affects HRQoL during early childhood. Better understanding of the HRQoL of these children in early life could lead to improved identification and targeted intervention of children at high risk for poor quality of life, as well as improve counseling and preparation of parents at hospital discharge.

This study aimed to assess parental views of their children's HRQoL and the relationship between neonatal morbidities and HRQoL in early childhood in children with severe BPD.

BPD	Bronchopulmonary dysplasia
HRQoL	Health-related quality of life
NICU	Neonatal intensive care unit
PedsQL	Pediatric Quality of Life Inventory
PHY-QoL	Physical HRQoL
PS-QoL	Psychosocial HRQoL

From the [1]Perinatal Institute, Cincinnati Children's Hospital Medical Center; [2]Department of Pediatrics, University of Cincinnati, College of Medicine, Cincinnati, OH; and [3]Division of Neonatology, Children's Hospital of Philadelphia, Philadelphia, PA

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Methods

Study participants were born between April 2011 and July 2013 and enrolled in the study between May 2014 and May 2015. Children were previously cared for in 1 of 3 tertiary/quaternary hospital neonatal intensive care units (NICUs) in the Philadelphia region, were born at <32 weeks of gestational age, and were 18-36 months of corrected age during the study enrollment period. All participants met criteria for a diagnosis of severe BPD, as modified from the National Institutes of Health consensus definition[8]: receipt of ≥30% fraction of inspired oxygen (FiO_2) or >2 L flow via nasal cannula at 36 weeks of postmenstrual age. Eligible children were identified via an existing database of infants that documented level of respiratory support at 36 weeks of postmenstrual age. Data necessary for diagnosis of severe BPD were confirmed in hospital electronic medical records. Children with known major congenital malformations (ie, myelomeningocele, omphalocele) or genetic conditions known to independently affect development were excluded. A convenience sample was based on projected eligible participants during the study enrollment period, with goal enrollment for the study of 70 participants. Verbal informed consent was obtained from parents or primary guardians of all study participants. The study was approved by the Institutional Review Boards at the Children's Hospital of Philadelphia and the University of Pennsylvania.

All participants were initially contacted via telephone to obtain consent. Following consent, a current mailing address was obtained from the caregiver and study assessments were mailed to the caregiver for completion. If the child had an upcoming neonatal follow-up clinic visit at time of consent, parents were offered the option of completing the study forms during the follow-up appointment. Further data were obtained from the electronic medical record.

The first study assessment evaluated parents' views of their children's HRQoL. Parents completed the Pediatric Quality of Life Inventory (PedsQL), a widely used and previously validated Likert item questionnaire.[9,10] Parents were asked to complete the age-appropriate PedsQL questionnaire based on the current corrected age of their child. The PedsQL Infant Scales was used for children 13-24 months of age, and the PedsQL 4.0 Generic Core Scales for Toddlers (age 2-4 years) was used for children 24-36 months of corrected age. Questionnaires consisted of 45 and 21 Likert questions, respectively. Possible scores ranged from 0 to 100 and assessed 2 developmental domains: physical HRQoL (PHY-QoL) and psychosocial HRQoL (PS-QoL). PS-QoL was further broken down into emotional QoL, social QoL, cognitive QoL (for the Infant Scales) and school function QoL (for the Toddler Scales).

Electronic medical charts were then reviewed to assess the presence or absence of 10 neonatal morbidities for each participant. These morbidities were selected a priori for well-established associations with adverse neurodevelopmental outcomes as well as likely postdischarge impact on daily functioning for the child and family. The following morbidities were selected to represent a full range of possible adverse sequelae of prematurity: grade III or IV intraventricular hemorrhage; ventriculo-peritoneal shunt; retinopathy of prematurity requiring laser therapy or intravitreal anti-vascular endothelial growth factor therapy; surgical necrotizing enterocolitis; culture positive sepsis (defined as positive blood culture associated with clinical decision by the medical team to treat with antibiotics for at least 7 days); patent ductus arteriosus requiring surgical ligation; pulmonary hypertension (defined as clinical evidence of pulmonary hypertension requiring treatment with nitric oxide, sildenafil, and/or remodulin); tracheostomy; gastrostomy tube; and need for any respiratory support at time of discharge. Tracheostomy and need for any respiratory support at time of discharge were both included as morbidities because these were considered to be pragmatic measures of severity of respiratory disease, which can vary widely among infants with severe BPD. The presence of each morbidity was counted to determine a composite morbidity score for each enrolled participant, with potential scores between 0 and 10 for each participant.

Post hoc analyses were conducted to evaluate the association between level of respiratory support at discharge and PHY-QoL and PS-QoL. Participants were categorized into 3 groups: (1) room air, (2) nasal cannula, or (3) tracheostomy at discharge.

Statistical Analyses

Standard descriptive statistics were used to describe the study population and parents' views of their children's HRQoL. Linear regression was used to evaluate the associations between PSY-QoL and PS-QoL and the composite postnatal morbidity score, adjusted for gestational age, corrected age at time of evaluation, and sex. One-way ANOVA was used to compare PHY-QoL and PS-QoL across the 3 groups categorized by level of respiratory support at time of NICU discharge. One-sample *t* tests were used to compare HRQoL data from this cohort to means previously reported for term and preterm toddler cohorts. Stata v 13.0 (StataCorp, College Station, Texas) software was used for all analyses, and *P* values of <.05 were considered significant.

Results

We attempted to contact parents of 106 children with severe BPD, of whom 70 were enrolled and completed all study assessments (66% of those approached). Of the 36 children who did not enroll, 8 declined participation, 12 were unable to be contacted, and 16 initially agreed to enrollment but did not complete study forms. Baseline characteristics and neonatal morbidities of the study participants are provided in **Table I**. Birth weight, gestational age, and sex did not differ between those that did and did not enroll in the study. Although all children met entry criteria of severe BPD, the cohort included a broad range of disease severity. At time of discharge from the hospital, 43% no longer required supplemental oxygen, 57%

Table I. Characteristics of the study population

General characteristics (n = 70)	
Male sex	47 (67%)*
Birth weight (g)	797 ± 318†
Gestational age (wk)	26.1 ± 2.0
PMA at discharge (wk)	50.4 ± 10.8
Corrected age at time of study enrollment (mo)	27.1 ± 5.8
Neonatal morbidities	
ROP requiring laser treatment or intravitreal anti-VEGF therapy	22 (31%)
Culture positive sepsis	25 (36%)
Surgical NEC	11 (16%)
Grade III or IV IVH	15 (21%)
Ventriculo-peritoneal shunt	4 (6%)
Pulmonary hypertension	25 (36%)
PDA requiring ligation	21 (30%)
Gastrostomy tube at discharge	31 (44%)
Respiratory support requirement at time of discharge	40 (57%)
Tracheostomy at discharge	8 (11%)

IVH, intraventricular hemorrhage; *NEC*, necrotizing enterocolitis; *PDA*, patent ductus arteriosus; *PMA*, postmenstrual age; *ROP*, retinopathy of prematurity; *VEGF*, vascular endothelial growth factor.
*n (%).
†Mean ± SD.

required some degree of supplemental oxygen at time of discharge, and 11% required a tracheostomy.

Twenty-three parents completed the PedsQL Infant Scales (33% of the cohort) and the remaining 47 parents (67%) completed the PedsQL 4.0 Generic Core Scales for Toddlers. There was not a significant difference in HRQoL scores between those that completed the Infant Scales and those that completed the Generic Core Scales for Toddlers PedsQL 4.0. Therefore, all analyses combined data from these 2 assessments.

Both physical HRQoL (PSY-QoL) and psychosocial HRQoL (PS-QoL) were measured from the parental perspective for their child. For this cohort of children with severe BPD, mean PSY-QoL was 78.0 ± 21.9 and mean PS-QoL was 75.3 ± 17.9. PS-QoL was further broken down into subscales, which included emotional QoL with a mean of 82.1 ± 15.4, social QoL with a mean of 78.8 ± 23.7, cognitive QoL with a mean of 55.2 ± 25.5, and school function QoL with a mean of 65.7 ± 25.8.

In comparison with previously reported HRQoL in healthy term toddlers,[9,11] mean PHY-QoL and PS-QoL were significantly lower in this cohort of children with severe BPD (**Table II**). Subscales of PS-QoL were significantly lower with the exception of Emotional QoL.

In comparison with previously reported HRQoL in preterm toddlers,[11] PHY-QoL was also significantly lower in this cohort with severe BPD (**Table II**). Previously reported data for preterm toddlers was only available for PS-QoL subscales, not the composite PS-QoL score. Although the social QoL subscale was statistically lower in the cohort with severe BPD, the Emotional QoL subscale was not statistically different.

The neonatal morbidity composite score ranged from 0 to 9 for individual study participants (possible score of 0-10) with a mean neonatal morbidity composite score of 3 ± 2 (**Figure 1**). Adjusted linear regression models demonstrated a significant association between both composite morbidity score and PHY-QoL ($P = .002$) and PS-QoL ($P = .015$). The presence of each additional neonatal morbidity was associated with a mean 4.4-point decrease in PSY-QoL (95% CI −1.7, −7.2) and a mean 2.8-point decrease in PS-QoL (95% CI −0.6, −5.1), respectively (**Figure 2**). There was not a statistically significant difference in PHY-QoL (1-way ANOVA $P = .21$) or PS-QoL ($P = .5$) in groups based on level of respiratory support at time of NICU discharge.

Discussion

As increasing numbers of extremely preterm infants survive into childhood and adulthood, consideration of the impact of prematurity and associated morbidities on HRQoL is essential. A few small studies have evaluated HRQoL and identified lower self-esteem, poor functional outcomes, and lower objective quality of life in very preterm-born adults, compared with term-born controls.[12,13] Because BPD is the most common morbidity of prematurity, with medical effects lasting throughout childhood, we sought to determine the impact of severe BPD on HRQoL during early childhood in a

Table II. Parental reported HRQoL in study cohort of children with severe BPD in relation to previously reported HRQoL in term and preterm toddler counterparts

	Study cohort (severe BPD) (n = 70)	Healthy term (n = 455*) (n = 141†)	Preterm/ VLBW (n = 672*)	Severe BPD study cohort vs healthy term *P* value	Severe BPD study cohort vs preterm/ VLBW *P* value
PHY-QoL	78 ± 22	95 ± 9*	89 ± 16*	**<.001**	**<.001**
		89 ± 8†		**<.001**	
PS-QoL	75 ± 18	83 ± 11†	Unavailable	**<.001**	n/a
Emotional QoL subscale	82 ± 15	82 ± 14*	82 ± 15*	.95	.95
		79 ± 13†		.05	
Social QoL subscale	79 ± 24	94 ± 15*	90 ± 14*	**<.001**	**<.001**
		91 ± 11†		**<.001**	
Cognitive QoL subscale (PedsQL Infant Scales)	55 ± 25	85 ± 16†	Unavailable	**<.001**	n/a
School Function QoL subscale (PedsQL 4.0 Generic Core Scales for Toddlers)	66 ± 26	Unavailable	Unavailable	n/a	n/a

VLBW, very low birth weight.
Bold text indicates a statistically significant correlation with a *P* value less than 0.05.
*Data from Palta M, Sadek-Badawi M. PedsQL relates to function and behavior in very low and normal birth weight 2- and 3-year-olds from a regional cohort. Qual Life Res 2008;17:691-700.
†Data from Varni JW, Limbers CA, Neighbors K, et al. The PedsQL Infant Scales: feasibility, internal consistency reliability, and validity in healthy and ill infants. Qual Life Res 2011;20:45-55.

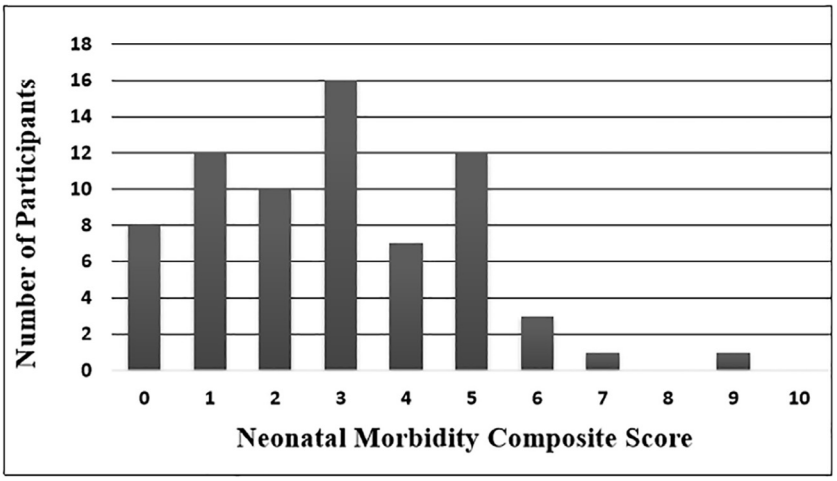

Figure 1. Distribution of neonatal morbidity composite scores.

contemporary cohort. In this study of 18- to 36-month of corrected age children with severe BPD, parents perceived that their children's HRQoL was significantly lower than the general healthy population.[9,11] Neonatal morbidities were common in this cohort of children with severe BPD, and the presence of each additional postnatal morbidity was associated with a significant decrease in both PSY-QoL and PS-QoL.

Prior studies that compared HRQoL in former preterm infants with BPD to HRQoL in preterms without BPD did not report significant differences.[4,5,7] Gray et al reported no difference in parent-perceived HRQoL between school-age children with BPD and preterm-born peers without BPD.[7] Two studies have reported no difference in HRQoL of adults with a history of BPD as compared with preterm-born peers.[4,5] In contrast, studies comparing HRQoL in survivors of BPD with full-term counterparts have conflicting results.[4-6] Gough et al reported a significantly lower HRQoL reported by BPD survivors in adulthood than term equivalents,[5] whereas Beaudon et al and Bozzetto et al reported no difference in self-reported HRQoL in BPD survivors and term equivalents during adulthood and adolescence, respectively.[5,6] These studies highlight the difficulty of comparisons of HRQoL across the lifespan in different study cohorts, with much unknown about how HRQoL changes over the lifetime among survivors of prematurity, both with and without BPD.

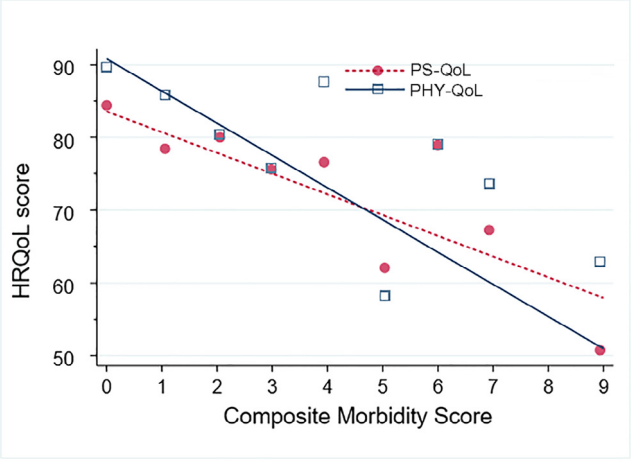

Figure 2. Mean PS-QoL and PHY-QoL scores in relation to postnatal composite morbidity score. Best fit line adjusted for gestational age, corrected age, and sex. PS-QoL (*circles, dotted line*) and PHY-QoL (*squares, solid line*) in relation to neonatal composite morbidity score, demonstrating the best fit lines adjusted for gestational age, corrected age at time of enrollment, and sex.

In comparison with previously reported HRQoL in healthy term[9,11] and preterm[11] infants, we found our cohort of young children with BPD to have both far lower mean PHY-QoL and PS-QoL, with the exception of emotional QoL, a subscale of PS-QoL. Emotional QoL did not statistically differ between our cohort with severe BPD and that previously reported in both healthy term and preterm toddler populations.

Our finding of emotional QoL scores in our cohort with severe BPD that are similar to those reported in preterm and term populations is consistent with prior studies that also did not identify differences in emotional QoL between term and preterm populations. Questions for this measure assess how much of a problem in the past month the child has had with items such as feeling afraid or scared, feeling sad or blue, and feeling angry. Previous validity studies have reported significant differences in Emotional QoL between cohorts of healthy and chronically ill children at 13-24 months of age.[9] Nevertheless, it is plausible that Emotional QoL may be a domain that is particularly difficult to measure accurately by parent-proxy in a toddler cohort. Alternately, our findings may suggest that emotional QoL is an area of resiliency for children with severe BPD during early childhood—despite overall lower physical and psychosocial QoL, parents perceive these children to have emotional QoL similar to healthy peers.

The relationship between morbidities at time of NICU discharge and childhood HRQoL in children with severe BPD has not been studied. Huhtala et al evaluated prematurity-related morbidities such as cerebral palsy, significant cognitive delay, and visual impairment, as diagnosed in childhood, with HRQoL at 8 years of age in very low birth weight infants.[14] The study found that children with 1 or more prematurity-related morbidities had significantly lower HRQoL than both very low birth weight infants without any prematurity-related morbidities and term counterparts.[14] Our study used morbidities at the time of NICU discharge to capture earlier markers of increased risk of HRQoL. Earlier identification of risk may allow for targeted interventions to improve HRQoL. Landsem et al suggested that it is possible to improve HRQoL of high-risk populations with specific interventions.[15] This randomized study evaluated the impact of a modified version of the Mother-Infant Transaction Program in preterm infants. The intervention included sessions with parents during the last week before discharge and 4 home visits during the first 12 weeks after discharge compared with no intervention. At 9 years of age, children in the early intervention group had higher self-reported physical well-being, and parents perceived that children in the early intervention group had higher emotional well-being than the preterm group who did not receive any interventions.[14]

Findings from our study suggest that children with severe BPD who are at risk for low HRQoL during the toddler years can be identified at the time of NICU discharge. Discharge is a critical time for transition of care of high-risk infants: we have previously reported that approximately one-quarter of infants with severe BPD never attend a single neonatal follow-up clinic appointment, despite referral at time of NICU discharge.[16] The results of the current study can be used by clinicians to help identify infants with severe BPD at highest risk for poor HRQoL in early childhood based on postnatal morbidities at time of NICU discharge. This information may be used to frame the anticipatory guidance that is provided to families before hospital discharge and support the recommendation for multidisciplinary neonatal follow-up after discharge. Families of children at highest risk may benefit from increased psychosocial supports or even targeted allocation of early intervention resources in the early years after discharge. Further, our findings support the critical importance of institutional support for multidisciplinary follow-up, including both medical and psychosocial follow-up, with medical providers, social workers, and psychologists for high-risk infants and their families. This multidisciplinary approach to postdischarge care together with increased family and clinician awareness may ultimately improve the outcomes of children at risk for poor HRQoL.

We recognize some limitations of our study. All participants were enrolled from tertiary and quaternary care centers in the Philadelphia region, which may limit generalizability to other geographic areas. Hospitals included in this study care for both local and regionally referred infants from broad socioeconomic and demographic backgrounds. We did not have a study control group, so we were unable to directly compare HRQoL in our cohort of children with severe BPD with either preterm or full-term peers. Furthermore, although the simple additive postnatal morbidity composite score was created to capture disease severity at time of NICU discharge, this score has not yet been validated in previous studies. However, similar cumulative counts of postnatal morbidities have been used in prior studies and are predictive of later developmental outcomes.[17]

There were also several important strengths of this study. The study cohort was comprised of not only children who followed up in neonatal follow-up clinic, but also telephone assessment of children who did not attend follow-up clinic, improving generalizability of our findings. Furthermore, this study evaluated both parents' views of their children's HRQoL and the impact of severity of illness at NICU discharge on HRQoL in young children with severe BPD.

In conclusion, we found that parent-perceived physical and psychosocial HRQoL of children with severe BPD at 18-36 months of corrected age was far lower than previously reported norms for term and preterm children,[9,11] with the exception of emotional HRQoL. Emotional HRQoL may identify an under-recognized area of resilience in this population. Furthermore, an increased number of postnatal morbidities was associated with poorer parent-perceived HRQoL. These findings may inform counseling of parents and allocation of resources to children with severe BPD and their families both at time of NICU discharge and over the first few years of life. Further research is needed to investigate changes in both parental perceptions of their children's HRQoL and children's own perceptions of their HRQoL over time, as well as strategies to mitigate the adverse effects of prematurity and neonatal morbidities on HRQoL over time in our vulnerable patients. ■

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Reprint requests: Jennifer M. Brady, MD, Cincinnati Children's Hospital Medical Center, 3333 Burnet Ave MLC 7009, Cincinnati, OH 45259. E-mail: jennifer.brady@cchmc.org

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50 Years Ago in *The Journal of Pediatrics*

Gluconeogenesis and Insulin in the Ketotic Variety of Childhood Hypoglycemia and in Control Children

Senior B, Loridan L. J Pediatr 1969;74;4:529-39

Ketotic hypoglycemia is a well-established and common cause of hypoglycemia in the pediatric population. It is now considered a benign diagnosis of exclusion in the toddler and young child. When it was investigated in the mid-1960s, little was known about the biochemical etiology or the predisposing factors in the development of ketotic hypoglycemia.

Senior and Loridan present a prospective study comparing 3 groups: children with ketotic hypoglycemia, children with no history of hypoglycemia, and healthy adults. They evaluated various biochemical markers implicated in metabolic homeostasis before and after a 2-day low carbohydrate, low calorie, and high-fat diet punctuated by prolonged fasting of 15-20 hours.

In addition to the eloquent explanation of the mechanisms of glucose and metabolic homeostasis, Senior and Loridan offered a thorough and thoughtful study design to evaluate biochemical markers. This process is particularly commended, given the historical context. They proposed, evaluated, and drew conclusions on concepts that are salient and critical to understanding hypoglycemia in childhood 50 years later.

The most notable finding was that ketotic hypoglycemia was induced in both case and control patients. They were able to suggest a causal relationship between ketotic hypoglycemia and fasting in the setting of low carbohydrate intake. They demonstrated that both case and control children are at risk for ketotic hypoglycemia at equal rates and equal severity in the setting of a prolonged fast. They also demonstrated that these children do not have impaired gluconeogenesis via glycerol disposal measures and have appropriately low insulin confirmed via serum insulin and beta-hydroxybuterate levels. This finding is further supportive of the now well-established assertion that carbohydrate stores and prolonged fasting play a critical role in the development of ketotic hypoglycemia. They also hypothesized that the dearth of ketotic hypoglycemia in adults may be due a relative increase in both cerebral surface area and fuel use in children, thereby resulting in increased metabolic demands. They importantly hypothesized and demonstrated that ketotic hypoglycemia is not due to a persistent pathologic condition.

This study by Senior and Loridan has fundamentally shaped the understanding of this very common condition in childhood for pediatricians and pediatric endocrinologists alike. Their conclusions remain relevant and foundational today in medical education, patient education, and the management of ketotic hypoglycemia.

Ananta Addala, DO, MPH
David M. Maahs, MD, PhD
Department of Pediatrics
Division of Pediatric Endocrinology and Diabetes
Stanford University School of Medicine
Stanford, California