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Research Article

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Neurodevelopmental Outcome at Preschool Age 38-months and Full-Scale Intelligence Quotient Evaluation at Age 7.2-years: In Children Treated for Persistent Pulmonary Hypertension of Newborn

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Abstract

Background: *There is lack of literature on long-term neurodevelopmental outcome in children who have survived persistent pulmonary hypertension of newborn (PPHN).*

Objective: *To evaluate neurodevelopmental outcomes at preschool age 38 months and subsequently, assess full scale intelligence quotient (FSIQ) at 86 months in children post therapy for severe PPHN.*

Methods: *Study of 81 children successfully treated with high frequency oscillatory ventilation, exogenous surfactant, inhaled nitric oxide (n=37) and intragastric sildenafil (n=44) for severe PPHN. Developmental assessment was performed at age 38 months with Bayley Scales of Infant and Toddler Development–Third EditionUK (Bayley-III). Intellectual ability was evaluated at age 86 months with Wechsler Intelligence Scale for Children-Fourth EditionUK (WISC-IV FSIQ). Composite scores are presented as mean with standard deviation (SD) in parenthesis.*

Results: *Bayley-III scores in sixty-six (81%) children at age 38 months, for developmental domains were between 106 and 114 (normal: ≥85). Ten percent had mild neurological impairment (70-84) and 9% showed moderate to severe delay (55 -69). Neurologically normal children (81%) at age 86 months scored either average (90-109) or high-average (110-119) with WISC-IV. FSIQ was 112.09 (13.20). Mild severity of neurological disability occurred in 10% with FSIQ: 64.19 (8.79). Moderate severity of impairment was observed in 9% with FSIQ: 46.44 (8.52).*

Conclusions: *Qualitatively, eighty-one percent of neurologically normal children at age 7.2 years showed average to high-average intelligence. Incidence of normal neurological development and intelligence quotient was 81% in children treated for severe PPHN.*

Keywords: Children, Intelligence Quotient, Neurodevelopment, Persistent Pulmonary Hypertension of Newborn

Abbreviations

Bayley-III: Bayley Scales of Infant and Toddler Development–Third Edition[UK]; FSIQ: Full Scale Intelligence Quotient; PPHN: Persistent Pulmonary Hypertension of Newborn; WISC-IV: Wechsler Intelligence Scale for Children-Fourth Edition[UK].

Introduction

Bayley Scales of Infant and Toddler Development–Third EditionUK (Bayley-III) is a recognised psychometric tool for evaluating neurodevelopmental outcomes. Bayley-III standardization involved a heterogenous population. Ninety percent with normal neurology and 10% having or at risk of developmental impairments, such as, prematurity, cerebral palsy, and trisomy 21 were incorporated. Inclusion of children with neurological deficiencies in a normal population inevitably raises concerns of over estimation of abilities [1,2]. However, clinically this acts positively when assessing children who have successfully been treated for severe persistent pulmonary hypertension of

newborn (PPHN) in the neonatal period. As it enables examination of children with high and low functioning levels and abilities, without the unintentional effect of under or over estimation of neurodevelopmental outcomes.

Habituation, novelty preferences and reaction times of infants and toddlers are useful predictors of childhood intelligence [3]. Normal development compromises of gaining knowledge and incorporating complex skills. These incremental abilities undergo qualitative progression through interaction between internal genetic and hereditary influences, and external environmental and socioeconomic factors, leading to variability in neurodevelopmental outcomes [4,5]. The developing child continuously improves vocabulary, comprehends complex concepts, and understands changing experiences. Full scale intelligence quotient and general ability index evaluation at 7.2 years would predict intelligence quotient, which is a stable character of mental intelligence if environmental circumstances remain consistently constant [6]. Hence, Wechsler Intelligence Scale for Children-Fourth EditionUK (WISC-IV FSIQ) evaluation at 7.2 years should predict current intelligence, also to a certain extent future intellectual capability.
Purpose of this study was to evaluate neurodevelopmental outcomes at age 38 months with Bayley-III, and subsequently, at age 86 months, intelligence quotient assessment with WISC-IV FSIQ. Children in studied cohort had severe PPHN, which was successfully treated with high frequency oscillatory ventilation, exogenous surfactant and adjuvant pulmonary vasodilators inhaled nitric oxide or intragastric sildenafil [7].

Methods

Study Cohort

Prospective linear study evaluating neurodevelopmental outcomes at age 38 months with Bayley-III, and subsequently, intelligence quotient with WISQ-IV FSIQ at age 86 months of 81 children post therapy for severe PPHN [7]. Study was conducted at two 'University Teaching Hospitals'. Consent was obtained for data collection and follow-up. Research and ethics committee (No.02-5250022: 04/2006), approved study protocol, which confirmed with provisions of Declaration of Helsinki 1995 (Revised Edinburgh 2000).

Study cohort comprised of 81 children who were treated for severe PPHN with high frequency oscillatory ventilation, exogenous surfactant, and adjuvant pulmonary vasodilators inhaled nitric oxide (n=37) or intragastric sildenafil (n=44) [7].

Evaluation

All 81 children were assessed by psychologists who were trained and competent in utilisation of Bayley-III and WISQ-IV FSIQ. Vision was assessed by optometrists. Three children with cochlear implants continued to be reviewed by specialists. Neurological evaluation was performed utilising gross motor function classification system [8]. Motor impairment was categorised as follows: (1). Asymmetrical gait. (2). Toe walking with heels of ground. (3). Decreased or increased tone of deep tendon reflexes. (4). Ankle clonus greater than five beats. (5). Limited movements of hip abductors and extensors. Children were categorised as having normal neurology without intellectual disability, minor neurological impairment, and moderate to severe neurological deficit. Respiratory specialists, general paediatricians, and paediatric surgeon completed the evaluation board at age 38 months and subsequently, 86 months.

Bayley-III

At age 38 months, standardised polytomous 'Bayley Scales of Infant and Toddler Development–Third EditionUK' was utilised to evaluate neurodevelopmental outcomes. Developmental domains assessed were:
1. Cognitive Index (Cognitive-language and Cognitive-language-motor)
2. Language Index (receptive and expressive communication)
3. Motor Index (fine-motor and gross-motor skills).
Bayley-III enabled comparison between child's performance and same-age peers through normed scores (Index; M=100, SD=15). Standardised mean score is 100 (15), with scores ≥ 85 representing normal neurodevelopment; < 85 indicating mild neurological impairment and <70 demonstrating moderate to severe neurological disability.

WISQ-IV FSIQ

Wechsler Intelligence Scale for Children-Fourth EditionUK was used to measure intellectual ability at age 86 months. Ten core subtests were evaluated, which are: (1). Similarities, (2). Vocabulary, (3). Comprehension, (4). Block Design, (5). Picture Concepts, (6). Matrix Reasoning, (7). Digit Span, (8). Letter-Number Sequencing, (9). Coding and (10). Symbol Search. Raw scores were converted to scale scores (M=10, SD=3) and summed up into four indices (M=100, SD=15) representing distinct intellectual abilities. Four factor indices are:
1. Verbal Comprehension Index assessed verbal comprehension, verbal concept formation and verbal reasoning. Child's crystallised intelligence from earlier learning experiences were extracted.
2. Perceptual Reasoning Index evaluated block design, picture concepts and matrix reasoning that measured nonverbal and logic reasoning, visual-spatial and visual-motor skills.
3. Working Memory Index estimated digit span and letter-number sequencing, which evaluated working memory, attention, and executive functions.
4. Processing Speed Index assessed coding and symbol search that measured speed of information processing, attention, and differentiation of visual stimuli.
Full Scale Intelligence Quotient (FSIQ) represents sum of scale scores of all four indices. General ability index, which estimated general intellectual capacity was derived from 'Verbal Comprehension Index' and 'Perceptual Reasoning Index'. FSIQ and four indices, as well as subtests, have excellent reliability and validity [9,10].

Statistics

It was determined that numbers required at follow-up (age 38 months and subsequently, 86 months) were minimum (n=62) and maximum (n=66) [7]. Descriptive data is presented as number with

percentage in parenthesis or mean scores with standard deviation (SD) in parenthesis. Composite scores for Bayley-III and WISQ-IV are presented as true mean value (μ) with 95% Confidence Intervals (CI). Confidence intervals were calculated using standard error of estimation. Pearson's (r) correlation coefficient was calculated between WISC-IV subtests and indices. Strength of linear association between two variables were estimated as moderate correlation (0.4−0.59), strong correlation (0.6−0.79) and very strong correlation (0.8–1). Univariate linear regression analysis for impact between WISQ-IV FISQ and maternal and neonatal anthropometric data described in Table 1 was performed. Parametric (t tests) and nonparametric (Mann–Whitney U) analyses were conducted to compare groups on WISC-IV FSIQ. P value <0.05 was considered significant. Statistical analysis was performed using Statistical Package for Social Sciences software (SPSS 21 for Windows, SPSS Inc., Chicago, Ill., USA).

Results

Demographics

Studied cohort of neonates were predominantly male (69%). Birth weight (50th and 75th percentile), head circumference (25th and 50th percentile) and length (50th percentile) were appropriate for mean gestational age 37 (2.6) weeks (Table 1). Mean maternal age was 28 (3) years (Table 1). Parental ethnicity was Indians (60%), Arabs (19%), British-Indians (15%), and Caucasians (6%). Parents were bilingual (100%), and affluent (61%) with a high educational level (82%). Majority were non-smokers (91%). Positive linear association between FSIQ and maternal educational levels was significant (p=0.001, slope=2.11, r = 0.56). Socioeconomic affluence (p=0.001, slope=2.01, r=0.66), parental educational levels (p=0.001, slope=2.00, r=0.68) were strongly correlated with FSIQ. Gender (p=0.74, slope=0.56, r=0.33), gestational age (p=0.77, slope=0.45, r=0.39), birth weight (p=0.66, slope=0.54, r=0.31) and ethnicity (p=0.56, slope=0.41, r=0.32) were not significantly associated with FSIQ.

Attributes	**Number (%)**
Multiparity	68 (84)
Nonsmokers	74 (91)
University Education	66 (82)
General Certificate of Secondary Education or Secondary School Leaving Certificate	10 (12)
Neonatal Gender: Male	56 (69)
Anthropometric Data	**Mean (SD)**
Maternal age in years	28 (3)
Neonates gestational age in weeks	37 (2.6)
Birth weight in grams	3211 (456)
Birth weight: z scores	0.12 (0.81)
Head Circumference in centimetres	32.5 (1.5)
Length in centimetres	49 (2)

Note: SD: standard deviation and percentage in parenthesis.

Table 1: Maternal and Neonatal Features of 81 Children Evaluated.

Bayley III

At 38 months mean weight was 16 (1.6) Kg and mean height was 102 (4.7) cm. Anthropometric measurements of weight (50th percentile), height (75th percentile) and head circumference (75th percentile) were all age appropriate. Bayley-III scores were normal, ≥85 in 66 (81%) of children (Table 2). There was a strong correlation between neonates studied in this cohort, who were neurologically normal (81%) and normative data for the four-developmental domains: **Personal and Social:** ***p*** =0.88, 95% CI: 0.79–0.93, **Language**: ***p***=0.93, 95% CI: 0.89 - 0.96, **Fine motor:** ***p***=0.89, 95% CI: 0.82-0.94, and Gross motor: p=0.86, 95% CI: 0.77-0.92 (Table 2). In 15 (19%), mean difference in developmental quotient of children neurologically impaired was significant. Eight (10%) had mild impairment (70-84) and seven (9%) showed moderate delay (55-69) (Table 2).

Neurologically Normal Children (81%)				
Test	**CS: μ (SD)**	**95% CI**	**γ**	**κ**
Cognitive Index	109.8 (13.3)	106–110	0.09	0.91
Language Index	111.35 (14.6)	108–114	0.12	1.12
Motor Index	113.60 (14.4)	110–119	0.16	1.18
Cognitive – Language	107.68 (12.6)	104–109	0.17	0.98
Cognitive-language-motor	109.60 (12.8)	103–110	0.15	1.16

Neurologically Impaired Children (19%)				
Test	**CS: μ (SD)**	**95% CI**	**γ**	**κ**
Cognitive Index	61.82 (7.8)	46–64	0.09	0.83
Language Index	64.06 (9.7)	44–68	0.13	0.91
Motor Index	62.71 (8.2)	42–68	0.19	0.98
Cognitive–Language	64.59 (7.5)	44–70	0.16	0.88
Cognitive-language-motor	62.02 (7.1)	48–66	0.18	0.99

Note: Composite scores (CS) are true mean (μ) with standard deviation (SD) in parenthesis and 95% confidence interval. Skewness (γ) and Kurtosis (κ) are shown.

Table 2: Bayley III at age 38 months.

WISC-IV FSIQ

At 86 months mean weight was 23.6 (1.1) Kg (50th percentile) and mean height was 118.7 (5.3) cm (75th percentile). All neurologically normal children assessed were bilingual and fluent in English language. They had not developed sensory impairment, mental health disorders or disabilities. Descriptive statistics for neurologically normal children, 66 (81%), illustrates univariate and multivariate normality for skewness (0.16 to 0.83) and kurtosis (1.05 to 1.82) well under the criterion of 3.0 (Table 3). Mean composite scores for the four indices were close to stipulated 100, (99 to 117) and SD 15, (13.28). Qualitatively, neurologically normal children 66 (81%) scored either average (90-109) or high-average (110-119) (Table 3 and Figure 1).

Descriptive data for children with developmental impairment 15 (19%) are summarized in table 4. Mean composite scores for all four indices and FSIQ were significantly lower than the normal group. Mean composite scores for FSIQ for mild intelligence disability was 64.91 (8.79) and moderate severity was 46.44 (8.52) (Figure 1).

Measurements	**CS: μ (SD)**	**95% CI**	**γ**	**κ**
Verbal Comprehensive Index	**117.70 (13.89)**	**114–121**	**0.30**	**1.43**
Similarities	13.74 (2.34)	12.6–14.3	0.29	1.38
Vocabulary	12.96 (2.41)	12.4–13.5	0.23	1.38
Comprehension	12.18 (3.04)	11.5–12.9	0.30	1.29
Perceptual Reasoning Index	**110.09 (13.07)**	**107–113**	**0.83**	**1.37**
Block Design	11.83 (2.66)	10.8–12.2	0.17	1.06
Picture Concept	11.67 (2.43)	11.0–12.6	0.16	1.08
Matrix Reasoning	10.75 (3.29)	8.8–12.7	0.25	1.06
Working Memory Index	**101.12 (12.36)**	**98–104**	**0.27**	**1.11**
Digital Span	10.92 (2.92)	9.8–11.6	0.24	1.06
Letter-Number Sequencing	9.57 (2.52)	8.9–10.2	0.26	1.05
Processing Speed Index	**99.44 (13.47)**	**96–103**	**0.65**	**1.69**
Coding	8.08 (2.68)	7.4–9.7	0.24	1.78
Symbol Search	10.82 (2.58)	9.4–11.6	0.31	1.82
General Ability Index	**117.57 (13.68)**	**114–121**	**0.22**	**1.64**
Full Scale Intelligence Quotient	**112.09 (13.20)**	**109–115**	**0.21**	**1.72**

Note: Composite scores are true mean (μ) with standard deviation (SD) in parenthesis, and 95% Confidence Interval (CI). Skewness (γ) and Kurtosis (κ) are shown.

Table 3: Wechsler Intelligence Scale for Children–Fourth Edition at age 7.2 years in Neurologically Normal Children (81%).

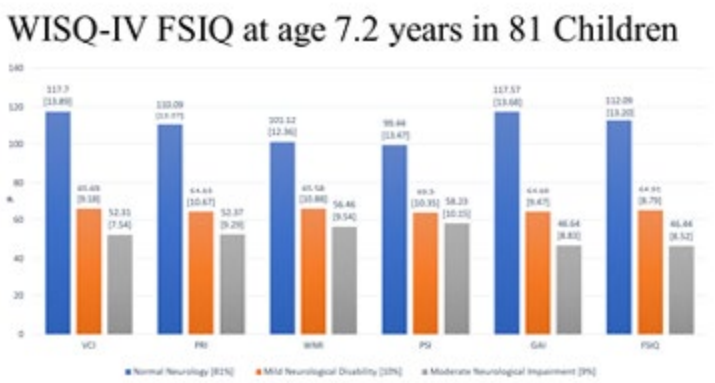

Figure 1: Descriptive data representing mean composite scores (μ) with standard deviation (SD) in parenthesis of all 81 children. X-axis represents core indices; VCI: Verbal Comprehension Index; PRI: Perceptual Reasoning Index; WMI: Working Memory Index; PSI: Processing Speed Index; GAI: General Ability Index; FSIQ: Full Scale Intelligence Quotient. Y–axis shows mean composite scores (μ).

Population

Of the 81 children evaluated, 66 (81%) were neurologically normal with normal intelligence quotient at age 7.2 years. Mild neurological impairment with intellectual disability occurred in 8 (10%) and moderate neurological impairment with intellectual disability was seen in 7(9%). In this specific cohort, incidence of neurodevelopmental delay was 19%.

There was a strong correlation between the two pulmonary vasodilator categorises inhaled nitric oxide and intragastric sildenafil for the four indices, general ability index, and FSIQ (Table 5). Verbal comprehension index (r=0.81); Perceptual reasoning index (r=0.86); Working memory index (r=0.83); Processing speed index (r=0.82); General ability index (r=0.88); and FSIQ (r=0.84) (Table 5).

Comparatively, significant statistical difference was observed in neurological impaired children treated with sildenafil 3 (4%) versus 12 (15%) with inhaled nitric oxide (***p***=0.001). Similarly, in the cohort with normal neurodevelopment and intelligence, children treated with sildenafil performed better: sildenafil 41 (50%) versus 25 (31%) inhaled nitric oxide (p=0.032; 95% CI: 0.010-0.052) (Table 5). Incidence of normal neurodevelopment and intelligence quotient was 81% in children treated for severe PPHN.

Measurements	CS: μ (SD)	95% CI	γ	κ
Verbal Comprehensive Index	**59.45 (8.41)**	**54-61**	**0.09**	**1.23**
Similarities	4.16 (2.84)	3.8–4.9	0.38	1.25
Vocabulary	3.09 (1.12)	2.8–3.7	0.36	1.13
Comprehension	4.33 (1.96)	3.8–4.9	0.45	1.03
Perceptual Reasoning Index	**58.64 (9.07)**	**54–60**	**0.53**	**1.37**
Block Design	4.23 (1.69)	3.9–4.7	0.27	1.06
Picture Concept	3.08 (2.21)	2.9–3.3	0.54	1.04
Matrix Reasoning	3.25 (1.94)	2.8–3.6	0.25	1.08
Working Memory Index	**61.32 (10.32)**	**46-62**	**0.09**	**1.11**
Digital Span	4.84 (1.75)	3.6–5.1	0.34	1.06
Letter-Number Sequencing	4.13 (1.72)	3.8–4.7	0.11	1.05
Processing Speed Index	**66.37 (9.66)**	**54-68**	**0.57**	**1.14**
Coding	4.28 (1.68)	3.8–4.6	0.54	1.11
Symbol Search	4.16 (2.58)	3.6–4.3	0.53	1.09
General Ability Index	**55.35 (9.08)**	**50–59**	**0.56**	**1.05**
Full Scale Intelligence Quotient	**56.29 (8.81)**	**49–58**	**0.54**	**1.08**

Note: Composite scores are true mean (μ) with standard deviation (SD) in parenthesis, and 95% Confidence Interval (CI). Skewness (γ) and Kurtosis (κ) are shown.

Table 4: Wechsler Intelligence Scale for Children–Fourth Edition at age 7.2 years in Neurologically Impaired Children (19%).

Measurements	CS: μ (SD) iNO (n = 25)	CS: μ (SD) iGS (n = 41)	*P* value (95% CI)
Bayley III: Neurologically Normal Children (81%)			
Cognitive Index	108 (11.6)	111 (11.4)	0.75 (0.68-0.98)
Language Index	111 (12.8)	112 (12.6)	0.69 (0.54-0.82)
Motor Index	112 (14.2)	114 (13.8)	0.68 (0.58-0.88)
Cognitive–Language	106 (13.6)	109 (13.2)	0.57 (0.49-0.66)
Cognitive-language-motor	108 (12.9)	110 (12.8)	0.66 (0.57-0.79)
WISC-IV FSIQ: Neurologically Normal Children (81%)			
Verbal Comprehensive Index	116.38 (13.60)	118.51 (14.07)	0.63 (0.43-0.75)
Perceptual Reasoning Index	110.01 (13.08)	111.11 (13.04)	0.79 (0.60-0.90)
Working Memory Index	101.31 (12.43)	100.22 (12.32)	0.53 (0.34-0.64)
Processing Speed Index	99.96 (13.46)	99.12 (13.47)	0.90 (0.81-0.94)
General Ability Index	117.17 (13.53)	117.81 (13.78)	0.82 (0.77-0.90)
Full Scale Intelligence Quotient	111.91 (13.14)	112.18 (13.22)	0.78 (0.66-0.88)

Note: Composite scores (CS) are true mean (μ) with standard deviation (SD) in parenthesis, and probability value with 95% confidence interval in parenthesis. iNO: inhaled nitric oxide and iGS: intragastric sildenafil.

Table 5: Comparative Evaluation of Children treated with Pulmonary Vasodilators Inhaled Nitric Oxide (iNO) and Intragastric Sildenafil (iGS) for Persistent Pulmonary Hypertension of Newborn.

Discussion

Study was powered to detect difference in neurodevelopmental outcome between the two pulmonary vasodilators inhaled nitric oxide and intragastric sildenafil [7]. Comparative analysis showed normal neurodevelopment and intelligence quotient predominantly occurred in sildenafil treated neonates (50%) (Table 5). Sildenafil effect in neonatal period was global leading to preserved intellectual, cognitive, and neurological outcome, in later childhood, 7.2 years.

WISC-IV FSIQ showed normal intelligence quotient in 66 (81%) children with verbal comprehension index scores being high 117.70 (13.89), strongly correlating with general ability index (r=0.84) and FSIQ (r=0.81). Processing speed index scored the lowest 99.44 (13.47) with lowest mean subtest scores on 'coding: 8.08 (2.68)'. Working memory index composite scores were 101.12 (12.36) with low 'letter-number sequencing' subtest scores 9.57 (2.52). Greater variability and lower overall performance on subtests that measure processing speed index and working memory index were noted. Overall, children with PPHN that had been successfully treated by pulmonary vasodilators and high frequency oscillatory ventilation achieved scores equivalent to published normal population data [9,10]. Our study, for inhaled nitric oxide category mirrors normative data published for early inhaled nitric oxide recipients [11,12].

General intelligence comprises of crystallized and fluid intelligence. Crystallized intelligences are learnt abilities from experiences, involving verbal comprehension and long-term memory. Fluid intelligence concerns logical reasoning and abstract problem solving. Information processing and memory shape intelligence are influenced by interplay with genetic, hereditary, environmental, and socioeconomic factors [3-5]. In this cohort, socioeconomic affluence, and good parental educational levels had significant impact, which significantly contributed to high cognitive trajectories at 38 months. This was reflected subsequently, at age 7.2 years with elevated general ability index: 117.57 (13.68) and average to high-average FSIQ: 112.09 (13.20).

Eighty-one percent of children studied were medically and neurologically normal with complete resolution of disease processes without sequelae. Relatively high socioeconomic status and good parental education contributed positively towards language skills, cognitive index scores and normal neurodevelopment at 38 months (Bayley-IIIUK scores ≥85), with narrow 95% confidence interval between studied children and normative data for all four-developmental domains. This positive neurological outcome continued at age 86 months with WISQ-IV FSIQ scores being average or high-average. This was comparable between those treated by nitric oxide or sildenafil with no significant statistically difference between duration of either therapy [7].

Occurrence of impaired neurodevelopment 15 (19%) was predominantly observed in children treated with nitric oxide 12 (15%). This incidence was comparable with that reported in the literature 12.8% to 21.5% [11,12]. In children treated with sildenafil, incidence of neurological abnormalities was 4%. Impaired intellectual and cognitive function in children could be due to impairment of glutamate-nitric oxide-cyclic guanosine monophosphate pathway. Increasing extracellular cyclic guanosine monophosphate by sildenafil maybe a new therapeutic approach to improve cognitive and neurological function in neonates and children.

Limiting factor of this study was homogeneity of population, wherein, bilingual parents were well-educated (82%), affluent (61%) and had low smoking rates (91%). This may not reflect study populations of neonates with severe PPHN in other centres or countries. Socioeconomic factors may have effectively impacted language skills [13,14]. This meant word comprehension and productive vocabulary, enabled better engagement and interaction, leading to higher scores during assessment. Studied children encountered constructive environmental experiences, which positively affected cognitive trajectories leading to better intellectual capabilities [13,14].

Majority of children were bilingual with no severe sensory impairment, intellectual disabilities, or mental health disorders, which was reflected in Bayley-III assessment at 38 months. Bayley-III in this cohort depicted the child's current functioning level providing a useful basis for early intervention plans in remaining 15 (19%). Early diagnosis and intervention in neurological impaired children should be individualized with targeted treatment plans. Children who had recovered without sequelae were near term and healthy, enabling exploration of their environment fully, ably assisted by well-educated parents who were socioeconomically well-off. They progressed to have average to high-average intelligence quotient at age 7.2 years with WISQ-IV FSIQ.

Conclusion

Current study evaluated neurodevelopmental outcomes of 81 children with severe persistent pulmonary hypertension of newborn, successfully treated by high frequency oscillatory ventilation, inhaled nitric oxide, and intragastric sildenafil. Sixty-six (81%) at age 7.2 years were neurologically normal with full scale intelligence quotient between average and high-average. Majority (50%) of children treated with pulmonary vasodilator sildenafil showed normal neurological development and intelligence quotient. In this specific cohort, incidence of neurodevelopmental delay was 19%; 15% in children previously treated with inhaled nitric oxide and 4% in sildenafil treated progenies. Occurrence of normal neurodevelopment and intelligence quotient was 81% in children treated for severe PPHN.

Contributors Statements and Declarations

Both authors approved final manuscript as submitted.

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Conceptualised and designed study. Acquired data, analysed, and interpreted data. Approved final manuscript as submitted. Agree to be accountable for all aspects of the work.

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Conceptualised and designed study. Analysed and interpreted data. Drafted initial and final manuscript and approved final manuscript as submitted.

Author Contribution Statement

Both authors conceptualised and designed study. Material preparation and data collection was performed by Dr. Rajiv Parapurath. Both authors analysed and interpreted data that had been collated. First and final draft of article was written by Dr. Madan Samuel. Final manuscript was approved by both authors. Authors have no conflict of interest relevant to this article to disclose.

Competing Interests

Conflict of Interest

Authors have no conflict of interest relevant to this article to disclose.

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