Neurodevelopmental profile in children with benign external hydrocephalus syndrome. A pilot cohort study.

Running Title: Neurodevelopmental profile in benign external hydrocephalus syndrome**.**

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Abstract

Purpose. The management of children with benign external hydrocephalus (BEH) remains controversial. Most BEH children do well in the long-term, but a substantial number have temporary or permanent psychomotor delays. The study aims to assess the prevalence and pattern of neurodevelopmental delay in a cohort of children with BEH. **Methods.** We conducted a cohort study of 42 BEH children (30 boys and 12 girls, aged 6 to 38 months). A pediatric neurosurgeon performed a first clinical evaluation to confirm/reject the diagnosis according to the clinical features and neuroimaging studies. Two trained evaluators assessed the child's psychomotor development using the third edition of the Bayley Scales of Infant and Toddler Development (Bayley-III). Developmental delay was defined as a scaled score < 7 according to the simple scales and/or a composite score < 85. **Results.** Eighteen children (43%) presented statistically lower scores in the gross motor and composite motor of the Bayley-III scales compared to their healthy peers. **Conclusion.** In BEH, it is important to establish a diagnostic algorithm that helps to discriminate BEH patients that have self-limiting delays from those at risk of a persistent delay that should be referred for additional studies and/or interventions that might improve the natural evolution of a disease with high impact on the children and adult's quality of life.

Key Words: Bayley III scales, child development, psychomotor assessment, macrocephaly.

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Consent to participate: written informed consent was obtained from parents/guardians prior to the child's enrolment in the study.

Consent for publication: the authors affirm that human research participants provided informed consent for publication of their data

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Abbreviations

Bayley III: Third Edition of Bayley Scales of Infant and Toddler Development; **BEH:** Benign external hydrocephalus, **CSF:** Cerebrospinal fluid; **HC:** Head circumference; **ICP:** Intracranial Pressure: **Max:** Maximum; **Min:** Minimum; **SD:** Standard Deviation.

The term ‘external hydrocephalus’ was first mentioned by Dandy and Blackfan in 1914 in his classical paper reviewing the clinical presentation and experimental models on hydrocephalus. [11] Dandy later used the same term in 1946 to describe in a 27-months-old boy with what would later come to be known as subdural hygroma. [10] The so-called ‘benign enlargement of the subarachnoid spaces’ is a syndrome originally described in 1981 by the pediatric neurologist Laura Ment et al. [20] Many other terms have been used in the literature to define the same phenomenon (e.g., idiopathic macrocephaly, extraventricular obstructive hydrocephalus, benign external hydrocephalus, benign extra-axial fluid collections), but for the reasons raised in the discussion, we prefer to use the term ‘benign external hydrocephalus’ (BEH) proposed by many. [16, 19, 21, 31, 33, 37–39]

BEH is an entity usually diagnosed in infants within the first year of life presenting with macrocephaly or a rapid increase of the head circumference (HC), and in whom neuroradiological exams show enlarged subarachnoid spaces – especially overlying the frontotemporal lobes – and normal or moderately enlarged ventricles. [20, 22] BEH is more frequent in boys than in girls, and is frequently associated with complications of prematurity [18, 20], and ~~is associated~~ with a positive family history of macrocephaly. [15, 21] In a population-based study in Norway, it was found that the incidence of BEH was 0.4 per 1000 live births in non-premature children. [36] The clinical relevance of BEH and its management is still a matter of considerable debate among health practitioners, neurologists, and pediatric neurosurgeons. As is implicit in the name, BEH is generally considered a ‘benign’ self-limiting condition related to familiar macrocephaly that does not require any specific treatment. [2, 13, 31, 34] However, there is conflicting evidence regarding the long-term resolution of the neuroradiological findings, the evolution of HC over time, and whether or not these children have a completely normal development compared with their healthy peers. Many authors have raised concerns regarding the term ‘benign’ applied to this syndrome because although most children with BEH do well in the long-term, a substantial number of them may have temporary or permanent psychomotor delays. [2, 3, 17, 38] Infants with BEH have an increased risk of subdural hematomas, hypotonia [3, 24, 35], fine and gross motor skill delay, attention deficit, and hyperactivity [26].

There are two issues that confound BEH: the lack of consensus and the multiple terms used in the literature to describe this entity, and the fact that many genetic and/or acquired conditions can present with identical neuroradiological findings. It is well known that mucopolysaccharidoses, achondroplasia, Sotos syndrome, and glutaric aciduria type I frequently have enlargement of the subarachnoid spaces. [25] Acquired disorders associated with BEH are complicated prematurity (premature graduating from the neonatal ICU requiring ventilatory support), traumatic brain injury, and intraventricular hemorrhage, among others. [20] In this secondary form of BEH, development delays are frequently found, but in these children, BEH – and the associated delays – is an epiphenomenon of underlying structural brain damage. In clinical practice, most BEH patients have no known factors except for uncomplicated prematurity. In this group, BEH is still a neglected condition with contradictory evidence and only a few studies focusing on the psychomotor deficits detected at diagnosis and at the long-term follow-up.

We hypothesized that BEH is an underlying condition for neurodevelopment delay in children since it reflects an alteration in the cerebrospinal fluid (CSF) dynamics and, in some children, an increase in the intracranial pressure (ICP) that might lead to permanent but potentially avoidable developmental delays. The current study aims to assess

the prevalence and pattern of neurodevelopmental delay in a cohort of children with BEH by using the Bayley-III scales. [1, 6, 8]

METHODS

Setting and Participants

We conducted a prospective study to assess the psychomotor development in 51 consecutive young children diagnosed with BEH at the Vall d'Hebron University Hospital (VHUH), Barcelona, Spain, from May 2017 to February 2020. The criteria used to diagnose BEH were: from birth to 42 months of age (the age limit for the Bayley-III scales) [1]; HC above the 97.5th percentile according to Spanish population nomogram, or a rapidly increasing HC during the first year of life (at least crossing two percentiles); and enlarged subarachnoid spaces, associated with normal ventricular size (Evans' Index < 0.30) or mild ventriculomegaly (Evans' Index ≥ 0.30 and ≤0.35) [8, 21] **(Fig.1)**. We excluded patients with known diseases, genetic syndromes, prematurity who graduated from the neonatal ICU with pulmonary disorders that required either mechanical ventilation or extracorporeal membrane oxygenation, previous history of meningitis, traumatic brain injury of any severity, intracranial hemorrhage, or other known causes of hydrocephalus. Most patients with suspected BEH are referred to our unit by a pediatrician or pediatric neurologist. The general workup includes a first clinical evaluation conducted by a pediatric neurosurgeon who confirms/rejects the diagnosis according to the clinical features and neuroimaging studies (see Supplementary Information). In all cases, the HC of the parents was measured, and they were classified as macrocephalic if they exceed the 97.5th percentile of the reference studies for the Spanish population. [27] The child's psychomotor development was evaluated by two trained evaluators (FM, LG) using the third edition of the Bayley Scales of Infant and Toddler Development (Bayley-III) [1] (see Supplementary Information). An initial psychomotor evaluation was performed as soon as possible after the diagnosis. When any delay in language, cognitive, or motor skills milestones were detected, children were referred to a children's rehabilitation unit to enter programs for early psychomotor stimulation (Centre for Child Development and Early Intervention; CDIAP), and clinical and psychomotor follow-up was scheduled every six months. Neurodevelopment delay was considered when the children presented any delay in at least one of the five areas of the simple scales and/or in one of the three composite scales of the Bayley-III scales. Developmental delay was defined as a scaled score < 7 according to the simple scale. [7] A composite score < 85 was used for the composite scales as the best cut-off recommended by Johnson et al. for detecting neurodevelopmental delay. [14] We decided to take into consideration both the composite and simple scales in order to have a detailed profile of the child's development.

Statistical analysis

Descriptive statistics were obtained for each variable. The mean and the standard deviation were used to describe continuous variables that followed a normal distribution and the median, maximum, and minimum values for continuous variables that were not normally distributed. Percentages and sample sizes were used to summarize categorical variables. To compare between-group differences (in categorical variables), $\chi 2$ statistics or the Fisher exact test were used as appropriate. Between-group differences were determined by an independent 2-sample t-test or the Mann–Whitney U test, depending on the statistical distribution. Multiple logistic regression model (MLR) was

used to explore the relationships between predictors and the outcome variable from the effects of covariates [10] (see Supplementary Information).

Statistical analyses were carried out with R distribution v4.0.1 [29] and the integrated development environment R Studio v1.2.5042 (RStudio, Inc., Boston, MA, USA; http://www.rstudio.com). The following R packages were used in the analysis: XLConnect, gmodels, and caret.

RESULTS

Participants

Fifty-one patients with the diagnosis of BEH were initially included in the study. Nine patients were excluded for the following reasons: three were older than 42 months, one was Arab and not Spanish speaking, two presented a genetic syndrome that could affect the evaluation's results, two were born premature and presented severe complications during their stay in the neonatal ICU and one had an EI>0.35. Our final cohort had 42 patients, 30 boys and 12 girls, with a median age of 14.5 months (min: 6, max: 38). The demographic and clinical data of the children and their families are summarized in **Table 1**. Three children had a subdural hematoma detected after the BEH diagnosis, but none of these patients were excluded because the concomitant diagnosis was incidental, and they were evaluated several weeks after surgical treatment. Macrocephaly was present in most of the patients (n = 32, 76%), while the remaining 10 patients (24%) presented rapid HC growth. Eleven patients (26%) presented one or two associated clinical symptoms (**Table 1**), and six presented hypotonia (14%). Eleven children (26%) had a positive family history of macrocephaly, hydrocephalus, or subdural hematoma. Most of our children (n = 31) were Spanish, and those of another ethnicity (n = 11) were born in Spain. Twenty children (48%) had an Evans' Index ≥ 0.30.

Psychomotor development assessment

Twenty-one children (50%) were born at term, and 21 (50%) were premature (**Table 1**). At baseline, the presence of delay in at least one simple and/or composite scale was detected in 18 (43%) of the total cohort. The Bayley-III results were separated between patients born at term and premature. Neurodevelopmental delay was detected in 14 of the 21 premature children (66.6%) and in 4 of the 21 infants born at term (19%). These differences were statistically significant ($\chi 2 = 7.8$, df = 1, p = 0.0050). On the simple scales, 26 (62%) children of the total cohort had normal development, nine (21%) presented a delay in only one scale, and seven (17%) presented a delay in more than one scale. According to the composite scales, 29 (69%) children presented no delay, ten (24%) presented a delay just in one area, and three (7%) children had more than one delay. In **Table 2**, the baseline scores are presented for the total cohort, full-term, and preterm groups. The differences in the evaluated scores for children born at term and premature were statistically non-significant except for the fine, gross motor and composite motor scales (**Table 2**), and therefore the whole cohort scores were compared using one-sample two-sided t-test with the normative data used to develop the Bayley-III scales. The comparison between BEH children and healthy population scores are summarized in **Table 3**. Statistically significant differences were found for the gross motor subscale ($p< 0.0001$), and the composite motor score ($p = 0.005$) (**Table 3**).

Multiple logistic regression analysis

Prematurity – defined as a gestational age ≤ 37 weeks – was the only statistically significant -independent predictor of children with BEH presenting a delay in any single or composite score (coefficient= 2.14, SE= 0.72, Z= 2.96, p= 0.0031). The OR for prematurity was 8.50 (95% CI: 2.22–39.3). In summary, premature children with BEH had 8.5-times greater odds of presenting any neurodevelopment delay than full-term children.

DISCUSSION

The main finding of our study was that nearly half the infants and children with BEH (not related to complicated prematurity, perinatal brain damage, or genetic syndromes) showed a neurodevelopmental delay in at least one of the Bayley-III's scales. The results of our MLR model show that prematurity was the only clinical and demographic variable related to any detected neurodevelopment delay (OR: 8.5; 95% CI: 2.22–39.3). Although the delay was most frequent in premature children, the neurodevelopment profile was not significantly different from children delivered at term, except in the fine, gross motor and composite motor scores (**Table 2**). When considering the whole cohort, BEH children presented statistically lower scores in the gross motor, and composite motor scales compared to their healthy peers (**Table 3**).

The term 'benign' has strongly biased the topic of BEH and its clinical importance in infants. There is a long-running controversy on BEH and polarized opinions. Several authors have defined BEH as a benign condition that does not require intervention because it resolves spontaneously with age. [2, 13] In one of the pivotal papers on BEH, Alvarez et al. stated that '*Recent claims of successful surgical treatment of this condition using a subdural peritoneal shunt are disturbing…Given the many complications of shunts, and the apparently benign and self-limited nature of the condition, one must question whether surgical intervention is warranted for idiopathic external hydrocephalus'*. [2] Although most children with BEH do well in the long-term, a substantial number of them show temporary or permanent psychomotor delays. [2, 3, 17, 38] Prassopoulos et al. reported that BEH in infants is associated with minor neurological disturbances, such as mild gross motor delay or symmetrical hypotonia, but that the developmental prognosis was good. [28] In a prospective study of nine infants, Nickel and Gallenstein found seven children showing a delayed gross motor development at baseline that normalized to age-appropriate motor development at follow-up. [23] However, in three children, speech and language delays were detected at follow-up. [23] Shen et al. showed that in children from 6 to 24 months old, BEH was associated with a higher risk of developing autism spectrum disorders. [30] Zahl et al. reported reduced quality of life in a long-term follow-up of a cohort of BEH children. [37] Some of these children presented developmental delay, social and cognitive problems, and more learning difficulties at school relative to their healthy peers. [37] Muenchberger et al., in a prospective neuropsychological study of 15 children, found that the general intellectual ability of most participants was within the normal range, but in some of them specific cognitive difficulties and gross motor delay were found. [22]

Here, we show that children with BEH can present significant delays. Our data are in apparent contradiction with the result of a retrospective study reported by Halevy et al. [13] These authors included 20 children (14 delivered at term

and six premature) and used the Mullen Scales of Early Learning test to assess their development. Halevy et al. did not find any significant difference between the mean scores of their BEH cohort and the standardized scores of the matched general population. [13] However, an important difference with our study is that, in their cohort, Halevy et al. enrolled children with a head circumference above the 50th percentile [13], while in our cohort, only children who were above the 97.5th percentile or a rapidly increasing HC during the first year of life (at least crossing two percentiles) were included.

An interesting finding is that 20 of the 42 children (48%) of our cohort had a ventricular dilatation defined by an Evans index above or equal to 0.30 (**Table 1**). However, ventricular dilatation was not an independent predictor of delay. Most papers referring to BEH state that neuroimaging in these children shows a 'normal to slightly increased ventricular size' [2, 13], but only a few studies have quantified the ventricular size by using reliable, objective indexes. Our data suggest that both communicating and external hydrocephalus coexists in nearly half of these children, indicating that abnormalities in CSF dynamics are more relevant than suggested in previous studies. We hypothesize that the different neuroradiological phenotypes of BEH are part of the same disease spectrum. We believe that BEH is probably a continuum that has early dilatation of the subarachnoid spaces in early stages preceding ventricular enlargement that occurs later when the fontanelles and sutures close, converting the infant's cranium to a closed and rigid container. As suggested by others, the increase in the size of the frontal subarachnoid spaces is the result of the gravitational force exerted by the developing brain contained inside a non-rigid cranium partially opened to the atmosphere. [2, 13] Our hypothesis is in line with the presumed pathophysiology of BEH that suggests that a partial or complete block in the arachnoid granulations—in some infants age-dependent— and, therefore, in the CSF absorption is the main disturbance together with a non-closed container in BEH. [2, 4] However, to verify or refute this hypothesis, new prospective studies are needed in which the children have long-term periodic clinical and neuroradiological follow-up. An additional pathophysiological theory postulated by others is that –in some cases an elevated venous pressure may be the cause of an elevation in CSF pressure, which enlarges the skull relative to the brain size while the fontanelles and sutures are open, thus creating widened subarachnoid spaces. [5]

To improve our knowledge of the natural evolution and potential outcomes of children with BEH, there is a need to introduce standardized evaluation for screening children's development and for subsequent monitoring of the child's developmental progress. Early screening requires valid developmental diagnostic assessment tools with good psychometric properties. The Bayley Scales and its different revisions are one of the most robust and widely used tools for developmental surveillance and clinical research. [6, 9, 32]

Our goal was to provide information on the neurodevelopmental and neuropsychological features of BEH children, thereby increasing awareness among health practitioners and improving the detection of children with potential neurodevelopmental delay and screening of candidates for additional studies, such as for ICP monitoring. We believe early detection of BEH is crucial so that interventions can be made as soon as possible, including counseling families regarding the most appropriate strategies to avoid permanent development delays and therefore allow these children to fulfill their developmental potential. As remarked by Fischer et al. '…children below the age of 3 years have more frequent contacts with health facilities, an important opportunity for identification and management of disabilities' and 'children at such a young age are more responsive to interventions'. [12]

Conclusions

Nearly half the infants and children with BEH (non-related to complicated prematurity, perinatal brain damage or genetic syndromes), showed a neurodevelopmental delay in at least one of Bayley-III's scales. Prematurity was a strong predictor of delay in children with BEH. The term 'benign' incorporated in the definition is misleading, and we propose that 'idiopathic external hydrocephalus' is a much better term. Children with BEH should be referred for close follow-up when detected and followed at least until the school-age, in order to exclude the presence of any neurodevelopmental delay. Standardized scales, such as the Bayley-III scales or similar, should be routinely incorporated into the clinical workup for these children to detect early delay and monitor their evolution. It is important to establish a diagnostic algorithm that helps clinicians to discriminate patients that have associated self-limiting delays, but that will develop normally from those at risk of a persistent developmental delay that should be referred for additional studies and/or interventions that might improve the natural evolution of a neglected disease with high impact on the children and adult's quality of life.

FIGURES

Figure 1. Example of a 33-month-old girl referred to us for evaluation of rapid growth of the head circumference (HC). The girl's gestational age was 35 weeks, born in a eutocic delivery (weight = 2020 g, height = 45 cm, and HC = 33 cm), with an Apgar score of 6 9 9. Magnetic Resonance images showing the characteristic findings of benign enlargement of subarachnoid spaces in the frontal lobes: (a) craniocortical width (8.4 mm), (b) sinocortical width (12.4 mm), and (c) interhemispheric fissure (12 mm). The Evans' Index in this patient is 0.29 (A/B).

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Table 1: Demographic and clinical data in benign external hydrocephalus patients (n= 42)

Sex: boys/girls	30 (71%) / 12 (29%)
Age in months	16.04 ± 7.9 (6 - 38)
Gestational age	
• Very preterm (28 to 31 wk)	6 (14%)
• Moderate preterm (32 to 33 wk)	3 (7%)
• Late preterm (34 to 37 wk)	12 (29%)
• Full term birth (38 to 42 wk)	21 (50%)
Birth Weight	
• Extremely Low (<1000g)	1 (2%)
• Very Low (<1500g)	2 (5%)
• Low (1501-2500g)	11 (26%)
• More than 2500g	28 (67%)
Macrocephaly (HC > 97.5th)	32 (76%)
Associated problems	
• Postural plagiocephaly	6 (14%)
• Subdural hematoma	3 (7%)
• Torticollis	2 (5%)
• Spinal arachnoid cyst	2 (5%)
• Chiari malformation type 1	1 (2%)
Ventricular size	
• Evans' Index	0.29 ± 0.03 (0.23 - 0.34)
• Evans' Index < 0.30	22 (52%)
• Evans' Index ≥ 0.30	20 (48%)
Clinical symptoms	
• Hypotonia	6 (14%)
• Irritability	6 (14%)
• Headache	2 (5%)
• Vomiting	2 (5%)
• Frequent night awakening	1 (2%)
• Seizures	1 (2%)
Positive family history	
• Macrocephaly	6 (14%)
• Hydrocephalus	4 (9%)

• Subdural hematoma	1 (2%)
Ethnicity*	
• Spanish	31 (74%)
• North African	5 (12%)
• Latin American	4 (10%)
• South Asian	1 (2%)
• Romanian	1 (2%)
Parents' education (y)	
• Maternal	14.2 ± 2.3 (10 - 18)
• Paternal	13.0 ± 2.9 (6 - 21)

Results are expressed as n (%). **WK:** Weeks; **HC:** Head Circumference. **Y:** Years. * Despite belonging to different ethnicities, all the children included and the parents spoke and understood Spanish correctly. Continuous variables (Age, Evans index and parent's education years were summarized with the mean ± SD, the min and max values)

Table 2. Baseline evaluation in children with benign external hydrocephalus (BEH)

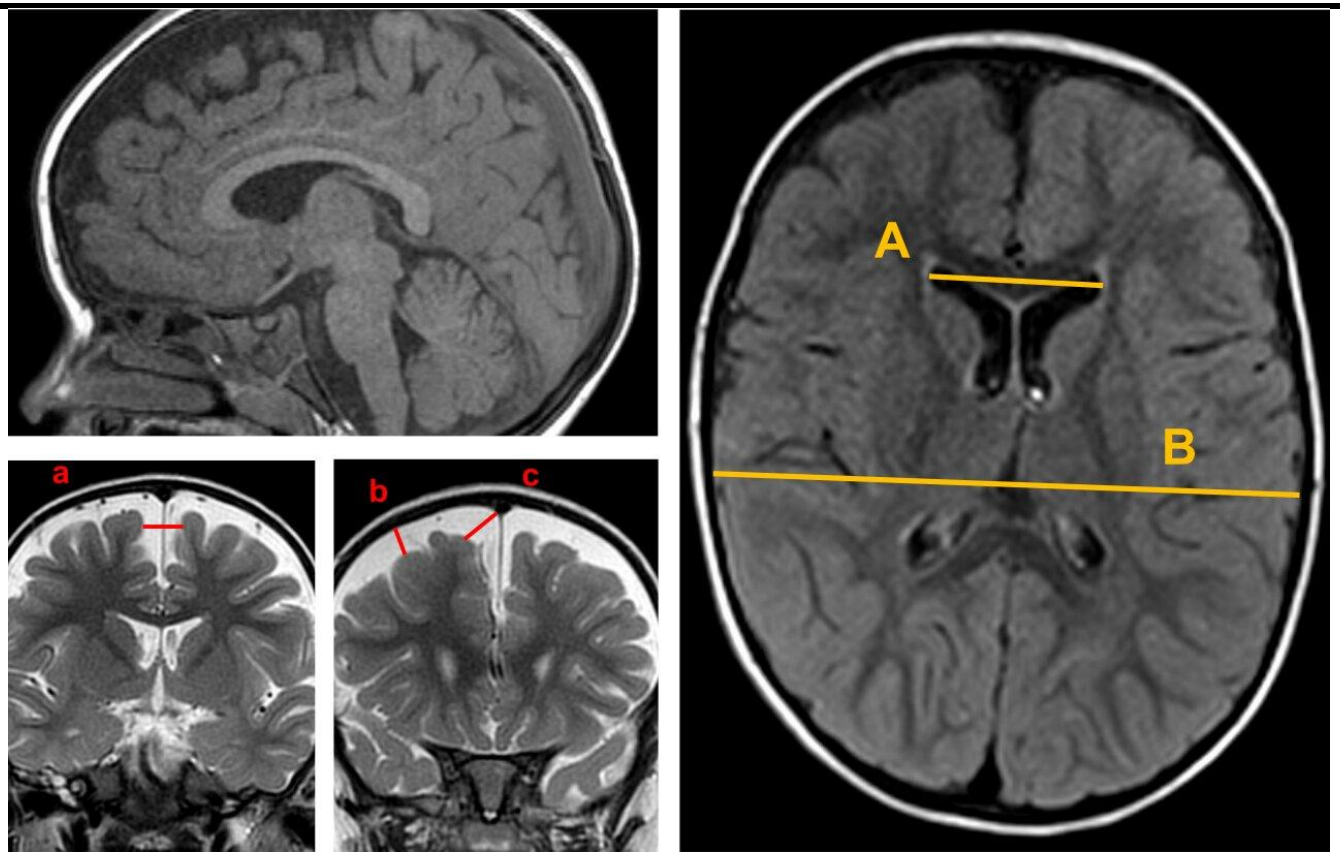
	Total cohort (N=42)		Full-term (N=21)		Preterm (N=21)		Full term/preterm comparison	
	Mean ±SD	Delay	Mean ± SD	Delay	Mean ±SD	Delay	t	*p* value
Cognitive (composite)	101 ± 11.1 [80-120]	4.8 %	102 ± 10.6 [85-120]	0 %	99.6 ± 11.4 [80-115]	9.5%	0.9	.3
Cognitive	10.2 ± 2.1 [6-14]	4.8 %	10.7 ± 1.9 [8-14]	0 %	9.8 ± 2.2 [6-13]	9.5 %	1.5	.1
Language (composite)	97.7 ± 12.4 [77-135]	14.2 %	97.7 ± 10.6 [77-124]	4.7 %	97.5 ± 14 [77-135]	23.8 %	0	1
Receptive	9.9 ± 2.5 [5-17]	9.5 %	10 ± 2.1 [6-16]	4.7 %	9.9 ± 2.8 [5-17]	14.2 %	0.1	.9
Expressive	9.3 ± 2.2 [4-15]	9.5 %	9.3 ± 1.9 [6-12]	9.5 %	9.2 ± 2.5 [4-15]	9.5 %	- 0.06	.9
Motor (composite)	93.1 ± 15.2 [58-121]	28.5 %	97.9 ± 12.9 [77-121]	14.2 %	88.5 ± 15.7 [58-118]	42.8 %	2.1	**.04**
Fine	10.2 ± 2.7 [5-16]	9.5 %	11.3 ± 2.3 [8-16]	0 %	9.1 ± 2.6 [5-14]	19 %	2.7	**.008**
Gross	7.4 ± 2.7 [1-13]	33.3 %	8.2 ± 2 [5-13]	19 %	6.5 ± 3.1 [1-12]	47.6 %	2	**.04**

The reference values of the healthy population at the Bayley-III test are for the scaled score a mean of 10 ± 3 and a score range between 1– 19; for the composite score a mean of 100 ± 15 and a score range between 40–160.The all BEH population and full term and preterm group scaled and composite score are described. An unpaired t-test was used to verify the null hypothesis of no difference between the full and preterm population. In p values, results in bold indicates a statistically significant finding with $p<.05$. SD: Standard Deviation; min: minimum; max: maximum.

Table 3. Comparison between BEH and healthy population baseline assessment score.

Domain	BEH population (n=42)	Healthy population		
	Mean ±SD	**Mean ± SD**	**t**	***p* value**
Cognitive (composite)	101.1 ± 11.1	100.0 ± 15.0	0.55	.58
Cognitive	10.2 ± 2.1	10.0 ± 3.0	0.78	.43
Language (composite)	97.7 ± 12.4	100.0 ± 15.0	-1.18	.24
Receptive	9.9 ± 2.5	10.0 ± 3.0	-0.1	.9
Expressive	9.3 ± 2.2	10.0 ± 3.0	-1.88	.06
Motor (composite)	93.1 ± 15.2	100.0 ± 15.0	-2.91	**.005**
Fine	10.2 ± 2.7	10.0 ± 3.0	0.56	.57
Gross	7.4 ± 2.7	10.0 ± 3.0	-6.01	**<.0001**

A one sample two-sided t test was used to compare the results of the Bayley-III scales with the healthy normative population. In p values, results in bold indicates a statistically significant difference. SD: Standard deviation.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