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MOTOR DEVELOPMENT OUTCOMES OF CHILDREN WHO HAVE UNDERGONE THERAPEUTIC HYPOTHERMIA: WITH PARENTS' VIEWS*

TERAPÖTİK HİPOTERMİ TEDAVİSİ ALAN ÇOCUKLARIN MOTOR GELİŞİM SONUÇLARI: EBEVEYN GÖRÜŞLERİ İLE BİRLİKTE

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ABSTRACT

Objective: Neurodevelopmental follow-up of infants with hypoxic ischemic encephalopathy (HIE) and supporting their development have great importance for the later years of their life. The aim of this study was to evaluate motor development outcomes of children with HIE who have undergone therapeutic hypothermia (TH) in Turkiye with an objective assessment and the point of view of the parents, and to compare these two assessment methods.

Materials and Methods: Twenty two cases (11 girls, 11 boys) with HIE who have undergone TH were included. Sixteen (72.7%) of the cases were classified as Sarnat Stage-2, and six (27.3%) of the cases were classified as Sarnat Stage-3. Motor development of the cases were evaluated by the Bayley Scales of Infant and Toddler Development-Third Edition (Bayley-III). Parents'views on their children's development were examined with The Ages and Stages Questionnaire-2 (ASQ-2).

Results: 68.2% (n=15) of the cases had normal motor development, 18.2% (n=4) had mild-moderate motor delay and 13.6% (n=3) had severe motor delay according to the Bayley-III motor scale results. When looking at the sub-areas of motor development, 68.2% (n=15) of the cases had normal gross motor development and 86.4% (n=19) of the cases had normal fine motor development. Additionally, 68.2% (n=15) of the cases demonstrated normal gross motor & fine motor development according to ASQ-2 results.

ÖZET

Amaç: Hipoksik iskemik ensefalopatili (HİE) bebeklerin nörogelişimsel takibi ve gelişimlerinin desteklenmesi yaşamlarının sonraki yılları için büyük önem taşımaktadır. Bu çalışmanın amacı, terapötik hipotermi (TH) tedavisi alan HİE'li çocukların motor gelişim sonuçlarını objektif bir değerlendirme yöntemi ve ebeveynlerin bakış açısıyla değerlendirmek ve bu iki değerlendirme yöntemini karşılaştırmaktır.

Gereç ve Yöntem: TH tedavisi alan 22 HİE'li (11 kız, 11 erkek) olgu dahil edildi. Olguların 16'sı (%72,7) Sarnat Evre-2, 6'sı (%27,3) ise Sarnat Evre-3 olarak sınıflandırıldı. Olguların motor gelişimleri Bayley Bebek ve Küçük Çocuklar için Gelişim Ölçeği (Bayley-III) ile değerlendirildi. Ebeveynlerin çocuklarının gelişimi ile ilgili görüşleri Erken Gelişim Evreleri Anketi-2 (ASQ-2) ile incelendi.

Bulgular: Bayley-III motor skalasına göre olguların %68,2'sinde (n=15) normal motor gelişim saptanırken; %18,2'sinde (n=4) hafif-orta motor gelişim geriliği ve %13.6'sında (n=3) şiddetli motor gelişim geriliği saptandı. Motor gelişimin alt alanlarına bakıldığında olguların %68,2'sinin (n=15) normal kaba motor gelişimi, %86,4'ünün (n=19) normal ince motor gelişimi olduğu görüldü. Öte yandan ASQ-2 sonuçlarına göre olguların %68,2'si (n=15) normal kaba motor ve ince motor gelişim gösterdiği görüldü.

Sonuç: Objektif değerlendirme sonuçları ile ebeveyn görüşleri kaba motor gelişim açısından paralellik gösterse de ince motor gelişim açısından farklılık göstermektedir. Ancak ASQ-2, bir uzmana erişimin sınırlı veya zor olduğu durumlarda HİE'li çocukla-

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Conclusion: Although there are some parallels in the results of the objective assessments and parental views regarding gross motor development, they differ in terms of fine motor development. However, ASQ-2 can be helpful for follow-up of children with HIE in situations where access to a clinician is limited or difficult and also it can provide an opinion to parents about their children's development.

Keywords: hypoxic ischemic encephalopathy, therapeutic hypothermia, motor development

rın takibinde yardımcı olabilir ve ayrıca ebeveynlerine çocuklarının gelişimi hakkında fikir verebilir.

Anahtar Kelimeler: Hipoksik iskemik ensefalopati, terapötik hipotermi, motor gelişim

INTRODUCTION

Despite today's advances in neonatal care and technology, hypoxic ischemic encephalopathy (HIE) is one of the most significant health problems causing morbidity and mortality (1, 2). According to the data published by the Hypoxic Ischemic Encephalopathy Study Group of the Turkish Neonatology Society, HIE occurs at the rate of 2.6 per 1000 live births and 1.2% among patients hospitalized in intensive care units in Turkiye (3, 4).

While some of the newborns with HIE die in the postpartum period, 25% of survivors are at risk of neurodevelopmental problems such as epilepsy, cognitive problems, cerebral palsy, visual-hearing disorders and sensory perception problems (5, 6). The prognosis varies depending on the severity and duration of the hypoxia, the gestational age of the newborn, the location of the damage and the accompanying complications (7). Post-discharge neurodevelopmental follow-up of newborns with HIE and supporting their early motor and cognitive development have great importance for the later years of their life.

Today, Therapeutic hypothermia (TH) is accepted as an evidence-based neuroprotective treatment for newborns with moderate-severe HIE in terms of improving survival and reducing long-term disability (8-10).

In the meta-analysis, it was stated that TH significantly reduced the mortality rates and severe developmental delay rates (11). Alongside this, newborns with HIE received similar scores in cognitive, language and motor areas with their healthy term-born peers according to Bayley-III (12, 13). Moreover, in studies that used ASQ-2, it was stated that TH treatment positively affected the motor development and was effective in increasing the survival rate and decreasing the rate of neurological sequelae in newborns with HIE (14, 15).

Hypoxic ischemic encephalopathy is one of the significant causes of developmental problems in Turkiye as well as in the world. There are limited number of studies evaluating the developmental outcomes of newborns undergoing TH (16, 17). To the best of our knowledge, there is no study presenting the post-discharge motor development outcomes of children with HIE who have undergone TH, together with an objective assessment and parental views. The aim of the present study was to evaluate motor development outcomes of children with HIE who have undergone TH in Turkiye with an objective assessment and the point of view of the parents.

MATERIALS AND METHODS

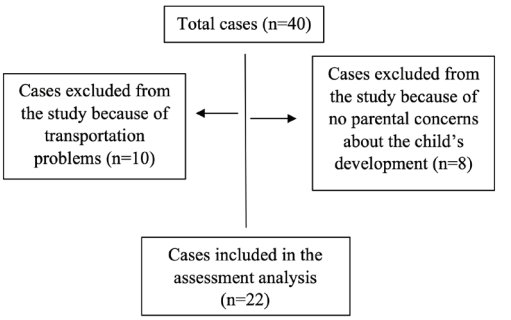
Study design and participants

This study was carried out between 04.09.2019 and 19.01.2020 at Istanbul University Istanbul Faculty of Medicine Pediatric Neurology Outpatient Clinic in accordance with the Declaration of Helsinki. Ethical approval was obtained from the Clinical Research Ethics Committee of Istanbul Univesity, Istanbul Faculty of Medicine (Dated 15.08.2019, Numbered 993).

Inclusion criteria for the study were children born term, diagnosed with HIE and classified as Sarnat & Sarnat Stage-II or Stage-III, have undergone whole-body therapeutic hypothermia, aged between 6 months-42 months, without any vision or hearing impairment. The exclusion criteria were having genetic syndrome and/or metabolic disease.

The sample size of the study was determined by the study of Mackin et al. by power analysis using the GPower v 3.1 program (18). It was calculated as 16 individuals with 95% power (α=0.05, effect size=0.88).

We accessed cases of 40 children who met the inclusion by scanning hospital files. The parents were informed about the purpose of the study, and they were invited to the study by phone call. A total of 22 children (11 girls, 11 boys) who agreed to participate in the study were included in the study (Chart I).



The study was initiated by obtaining informed consent form the parents of the children. Clinical & Demographic characteristics of the children in the study were recorded. MRI and EEG findings were recorded according to the reports of the imaging performed in the first week following birth. Each child was evaluated respectively within a period of approximately 60 minutes.

Assessments

Bayley scales of infant and toddler development, third edition (Bayley-III)

Bayley Scales of Infant and Toddler Development is an assessment tool that is accepted as the gold standard and is frequently used in research. It is an individually applied scale that evaluates the developmental functions of 1- to 42-month-old children. It examines the development of infants and toddlers in five areas-cognitive, language, motor, social-emotional and adaptive skills. The test starts from the item corresponding to the child's corrected age and is scored as 1 (achieved) or 0 (failed). According to the child's score, the raw score, scale score, composite score, percentile and confidence interval are recorded from the relevant tables and interpreted as normal development, mild-moderate delay or severe delay according to the developmental age equivalents of the child (19).

In our study, only the motor scale was used. In this scale, there are two subscales: gross motor and fine motor. According to the scale score of gross motor and fine motor subscales, a score >7 points was interpreted as normal development, 4-6 points as mild-moderate delay, and <4 points as severe delay. According to the motor scale composite score, a score of >85 was categorized as normal development, 70-84 as mild-moderate delay and <70 points were interpreted as severe delay. These cut-off values were determined by the study of Chalak et al. (20).

Bayley-III was performed in one season for each child and carried out by the certificated researcher G.U.

Ages and stages questionnaires (ASQ-2)

This is a parent-completed development screener consisting of 19 age-specific questionnaires. It evaluates the development of infants and toddlers aged between 4-60 months. Each questionnaire consists of a total of 5 domains and 30 items: communication (6 items), gross motor skills (6 items), fine motor skills (6 items), problem-solving capacity (6 items), personal & social development (6 items). Answers are recorded and scored as follows: 'yes' as 10 points, 'sometimes' as 5 points and 'not yet' as 0 points. A score for each domain is calculated. Children who are two standard deviations above the mean in any domain are interpreted as "normal development" and children two standard deviations below the mean in any domain are interpreted as "developmental delay" (14). The questionnaires were administered by the researcher G.U., in line with the parents' responses.

The reliability and validity study of the questionnaire in Turkish was conducted by Kapçı et al. (21). The main advantages of using ASQ are its low cost and that it does not require trained personnel for application. Also, using this parent-report screening tool promoted parents to involving their child's developmental follow-up (22).

Statistical data analysis

Statistical analysis was performed using the IBM Statistical Package for Social Sciences (SPSS) version 15.0. The conformity of the variables to the normal distribution was analyzed with the Shapiro-Wilk test. The data were expressed as mean±standard deviation (SD) for quantitative variables and as percentage (%) for categorical variables. The intra-group variation that showed normal distribution was analyzed with the paired samples t-test, and those that did not show normal distribution were analyzed with the Wilcoxon signed-rank test. The Pearson Correlation Test was used for correlation analysis. The total type-1 error level was accepted as 5% and a p-value lower than 0.05 was set for statistical significance.

RESULTS

The study group consisted of 22 children (11 girls, 11 boy). The mean age at the assessment was 17.50±8.31 months. The clinical and demographic characteristics of the children are given in Table 1.

According to the Bayley-III motor scale composite score, 15 cases demonstrated normal motor development, four cases had mild-moderate motor developmental delay and three cases had severe motor developmental delay. Three cases with severe motor developmental delay were diagnosed with spastic quadriparesis cerebral palsy and epilepsy after discharge (Table 2).

According to the Bayley-III gross motor subscale scores, 15 cases demonstrated normal development, four cases had mild-moderate developmental delay and three cases had severe developmental delay. Alongside this, 19 cases demonstrated normal development and three cases had severe developmental delay in the fine motor subscale (Table 3).

Parental views about children's development are shown in Table 4 according to ASQ-2.

There was a strong positive statistically significant correlation between the Bayley-III gross motor subscale and the ASQ-2 gross motor domain ($p<0.001$, $r=0.772$), and a moderately positive statistically significant correlation

Table 1: Clinical and demographic characteristics

Gender (n) (%)		
Girls	11	50.0
Boys	11	50.0
Age (month) (mean) (SD)	17.50 (median=17.60)	8.31
Birth type (n) (%)		
NSD	12	54.5
CD	10	45.5
Birth weight (gram) (mean) (SD)	3004.18	481.49
Gestational age (week) (mean) (SD)	38.50	1.73
Apgar scores (mean) (SD)		
1st minute	3.00 (median=4.00)	1.84
5th minute	5.36 (median=6.00)	1.96
10th minute	7.00 (median=7.00)	1.90
Cordon blood gases (mean) (SD)		
pH	6.99	0.25
PCO_2	61.32 (median=48.00)	43.30
HCO^{-3}	12.99 (median=11.75)	4.57
Base excess	-16.08 (median=-16.50)	6.14
Lactate	13.50 (median=13.20)	6.53
NICU stay (day) (mean) (SD)	17.68 (median=15.50)	9.92
Resuscitation (n) (%)	8	36.4
PPV (n) (%)	15	68.2
Convulsion and using antiepileptics in NICU (n) (%)	13	59.1
Sarnat & Sarnat stages (n) (%)		
Stage-2 (Moderate)	16	72.7
Stage-3 (Severe)	6	27.3
MRI findings (n) (%)		
Normal	12	54.5
Pathological	10	45.5
EEG findings (n) (%)		
Normal	16	72.7
Pathological	6	27.3
Kinship between parents (n) (%)		
Yes	4	18.2
No	18	81.8

n=number of cases, SD: standard deviation, NSD: normal spontaneous delivery, CD: cesarean delivery, NICU: neonatal intensive care unit, PPV: positive pressure ventilation, MRI: magnetic resonance imaging, EEG: electroencephalography

Table 2: Developmental Outcomes According to Bayley-III Composite Scores of Motor Scale

	n (%)
Normal development	15 (68.2)
Mild-moderate delay	4 (18.2)
Severe delay	3 (13.6)

n=number of cases

between the Bayley-III fine motor subscale and the ASQ-2 fine motor domain (p<0.001, r=0.681).

According to the Bayley-III results, the rate of mild-moderate developmental delay in cases born by CS was found to be statistically significantly higher than in cases born by NSD (p=0.012). The rate of severe motor development delay in cases with Sarnat Stage 3 was found to be statistically significantly higher than others (p=0.017).

Table 3: Developmental outcomes according to Bayley-III scale scores of gross motor and fine motor subscales

	Gross motor subscale n (%)	Fine motor subscale n (%)
Normal development	15 (68.2)	19 (86.4)
Mild-moderate delay	4 (18.2)	0
Severe delay	3 (13.6)	3 (13.6)

n=number of cases

Table 4: Developmental outcomes according to ASQ-2 scores

	Communication n (%)	Gross motor n (%)	Fine motor n (%)	Problem-solving n (%)	Personal and social n (%)
Normal development	13 (59.1)	15 (68.2)	15 (68.2)	12 (54.5)	9 (40.9)
Developmental delay	9 (40.9)	7 (31.8)	7 (31.8)	10 (45.5)	13 (59.1)

n=number of cases

In cases with severe motor developmental delay, the rate of those with pathological MRI findings was found to be statistically significantly higher than in cases with normal motor development (p=0.028).

The ASQ-2 fine motor score was found to be statistically significantly lower in cases with pathological MRI findings compared to others (p=0.007).

DISCUSSION

In this study, the motor development outcomes of children with HIE who had undergone TH was evaluated with an objective assessment and the point of view of the parents. A high degree of agreement was found concerning gross motor development of the children.

HIE is a major cause of mortality and long-term disabilities in children (23, 24). In spite of technological improvements in neonatal care, HIE and its long-term developmental consequences continue to effect children in all countries.

In studies showing the effectiveness of TH with the Bayley scale, Battin et al. investigated the neurodevelopmental outcomes of newborns with and without TH and they reported that normal motor development was observed in 75% of the cases and developmental delay in 25% of the cases in the TH group (25). In the study of Kali et al. in which they investigated the neurodevelopmental outcomes of 1-year-old children with TH, normal development or mild developmental delay was found in 82% of the cases, while moderate-severe delay was found in 18% (12). When national data as well as international data were examined, Çelik stated that motor developmental delay was found in 42.5% of the cases in a study conducted in Turkiye (17). In our study, 68.2% of the cases showed normal development according to the Bayley-III motor scale composite score, while developmental delay was found in 31.8% of the cases. Although TH gives positive results in the treatment of newborns with HIE, a significant number of children have motor developmental delay in different rates. We think that the effects of the clinical characteristics of the children and the socioeconomic and cultural diversity of the parents on neurodevelopment cause different developmental delay rates to be obtained as a result of the studies.

Cognitive delay is an important developmental problem in children who have undergone TH. In the studies conducted, the rate of mild-moderate cognitive delay at 18-24 months varies between 5-27%, while the rate of severe cognitive delay varies between 15-23% (13, 24, 25). In our study, children were evaluated in communication, problem-solving capacity, and personal & social development with the ASQ-2 questionnaire as measures of cognitive development. 40.9% of the cases had developmental delay in communication, 45.5% of the cases had developmental delay in problem-solving capacity and 59.1% of the cases had developmental delay in the personal & social development. Although no objective assessment was made for cognitive development in our study, these ASQ-2 findings highlight the need for early follow up of cognitive development as well as motor development in children who have undergone TH. We would like to emphasize the importance of special education programs that support communication, problem-solving and personal & social development from the early period in early intervention programs. Supporting the children in a holistic manner by a multidisciplinary team has great importance for the later years of their lives.

With the strong correlation between Bayley-III and ASQ-2, objective evaluation and parental views show parallels

in terms of gross motor development. However, the correlation between these two assessment scales was not strong for the fine motor area. There is disagreement about the child's fine motor development. The ASQ-2 is a parent-rated assessment tool. On the other hand, The Bayley-III is an objective scale applied impartially by trained experts. Bayley-III has various and special materials that are encountered in daily life activities but may not be found in every family environment. This difference in favor of objective assessment in fine motor development led us to think that it may not be possible for children to experience different fine motor skills in their daily living activities in the home environment, due to the lack of appropriate materials and environmental diversity in every family. The children were capable of doing different fine motor skills, but because of the diversity of the materials, the families may not have observed this before, so they may have negatively answered the ASQ-2 questions. Enrichment of the child's environment will positively affect the fine motor skills of the child as well as other developmental skills.

In a study by Gardiner et al, the development of children with HIE who have undergone TH was evaluated with Bayley-III. As a result of the study, it was stated that all cases with mild HIE showed normal development, while 60% of cases with moderate-severe HIE showed normal development (26). In our study, severe developmental delay was not found in any of the children with Sarnat Stage 2, while the rate of severe developmental delay was found to be higher in children with Sarnat Stage 3. In line with the literature, it has been stated that developmental outcomes are directly related to the severity of hypoxia, and that TH gives more favorable results in mild-moderate HIE.

In addition, in our study, according to the Bayley-III scores, the incidence of developmental delay in children born by CS was found to be higher than the incidence of developmental delay in children born by NSD. CS is thought to be a risk factor for motor development prognosis for the children with HIE who have undergone TH, but we do not have gynecological data on why CS is needed.

Chalak et al. examined the relationship between Bayley-III results and MRI results in newborns who have undergone TH and reported that developmental delay was observed in 26% of the cases with normal MRI results, while developmental delay was observed in 70% of the cases with pathological MRI results (20). In a study investigating the effect of the presence of pathological findings in MRI on the prognosis in newborns with HIE by Lakatos et al., it was stated that the findings in MRI provided a strong prediction for the developmental outcomes of asphyxiated newborns treated with TH, and that MRI findings would be beneficial in terms of prognosis (27). In line with the literature, 91.6% of the cases with normal MRI results had normal motor development and the frequency of severe developmental delay was found to be higher in cases with pathological MRI in our study. MRI findings contain important information for the developmental prognosis of newborns with HIE who have undergone TH. In the follow-up of newborns with HIE, developmental assessments' results should be considered in addition to imaging findings.

In the long-term prognosis review, the neurodevelopmental results of newborns with moderate HIE who have undergone TH were examined between 18 months and 10 years, and it was stated that developmental delay is more pronounced in school age and later in life (6). Thus, we would like to emphasize the necessity of regular treatment and follow-up of children with developmental delay, as well as the importance of neurodevelopmental follow-up of children with normal development. We think that performing neurodevelopmental assessments of all children with HIE at school age and making necessary interventions are also important for their academic success.

Studies showing the development of children with HIE after TH with Bayley-III are limited in Turkiye. However, to the best of our knowledge, no study has been found that presents objective assessments and parental views together on the development of children with HIE who have undergone TH. The necessity of long-term follow-up of children with HIE increases the importance of clinician-family cooperation. The parallels in the evaluation results between the objective assessment and parental views confirms that the use of ASQ-2 in the motor development follow-up of children with HIE may be an option in regions where access to hospitals or specialists is limited or disadvantageous. The fact that the study was conducted in a single center and the number of cases was limited reduces the generalizability of the results. In future studies, objective assessment of children's cognitive, language and social-emotional development will contribute to the literature.

Ethics Committee Approval: This study was approved by the ethics committee of Istanbul University, Istanbul Faculty of Medicine (Date: 15.08.2019, No: 993).

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