ORIGINAL ARTICLE

Neurodevelopmental Outcomes of Infants with Benign Enlargement of the Subarachnoid Space

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Abstract

Objective

Benign enlargement of the subarachnoid space (BESS) is the most common cause of macrocephaly in infants. This study aimed to evaluate the neurodevelopmental outcomes in infants with BESS.

Materials & Methods

In this follow-up study, all records of infants diagnosed with BESS in 2012-2016 were assessed. A clinical follow-up examination was carried out at 6, 12, 18, and 24 months of age to assess the macrocephaly outcomes. Denver Developmental Screening Test-II (DDST-II) was used for evaluating the psychomotor development of infants at 24 months of age. All data were entered in SPSS Version 13, and descriptive statistics were measured.

Results

Out of 32 infants included in this study, 28 (87.5%) were boys. Five cases of prematurity history (15.6%), and 23 cases of macrocephaly in the family (71.9%) were recorded. The mean age of BESS diagnosis was 6.8 months (SD=3.2). subdural hematoma was reported in one infant (3.1%). Also, 28 infants showed macrocephaly at 18 months of age (83.3%). Seven patients had developmental delay, according to DDST-II (22%). The mean head circumference at birth and six months of age was significantly greater in infants with developmental delay compared to those with normal development. There was a significant difference between the mean head circumference at birth (P=0.05) and the mean head circumference at six months of age (P=0.02).

Conclusion

Developmental delay is frequent in BESS infants, especially those

with macrocephaly at birth and six months of age, and requires medical attention.

Keywords: Benign enlargement of the subarachnoid space; Development; External hydrocephalus; Infant; Macrocephaly

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Introduction

Benign enlargement of the subarachnoid space (BESS), also called benign external hydrocephalus, is the most common cause of macrocephaly in infants (1). BESS, as a subgroup of hydrocephaly, is defined as macrocephaly, combined with increased cerebrospinal fluid (CSF) in the subarachnoid space. Mild ventriculomegaly may also be seen on neuroimaging (3). Cerebro-Venous hypertension is a frequent cause of BESS. The arachnoid villi immaturity results in the impairment of CSF absorption, causing Cerebro-Venous hypertension (3). In infants with opened fontanels and sutures, accumulation of CSF would result in widening of subarachnoid spaces fostered by the growing skull (2) This clinical condition occurs in 0.4 per 1000 live births (4). there are few studies on the developmental outcomes of BESS in infants (5، 8). The aim of this study is evaluation of developmental outcome in infants with BESS.

Materials & Methods

In this follow-up study, after obtaining approval from the Ethics Committee of Isfahan University of Medical Sciences (ethical approval code: IR.MUI.REC.1396.3.583), all infants (<1 year) with macrocephaly or other symptoms, who were referred to the pediatric neurology clinic of Isfahan University of Medical Sciences and diagnosed with BESS during 2012-2016, were enrolled. On the other hand, patients with known neurological diseases and complications (i.e., brain hemorrhage and need for shunts) were excluded from the study. Variables, such as age of BESS diagnosis (months), gender, head circumference (HC) at birth and admission, neurological signs and symptoms, prematurity history, and family history of macrocephaly, were recorded in this study. Macrocephaly was defined as HC more than two standard deviations (SDs) above the mean for age and sex. A clinical follow-up examination was carried out at the age of 6, 12, 18, and 24 months to assess HC. All patients were examined at 24 months of age in terms of the developmental status, using Denver Developmental Screening Test (DDST-II). DDST-II was used for the evaluation of psychomotor development at the age of 24 months. This test was used for the assessment of child development from birth until six years of age. The DDST was developed by Frankenburg in 1967 and validated in many studies (10). DDST-II evaluates four general areas: (1) personal-social (25 items); (2) fine motor-adaptive (29 items); (3) language (39 items); and (4) gross motor (32 items) (5, 11). In the present study, the results of the test were interpreted as either normal development (the child performs the task successfully, or the parents report that the child can do it) or abnormal development (there is at least one failure in one of the items, or the child doesn't perform the skill, or the parents report that the child cannot do it). Previous studies have used DDST-II for the developmental

evaluation of children with BESS (5, 12-14).

The mean and SD were measured to describe the quantitative data, and percentages were calculated to describe the qualitative data. Chi-square test and Fisher's exact test were used to determine differences between variables. Student's t-test was used for mean comparisons of quantitative data. P-value less than 0.05 was considered statistically significant. SPSS Version 13 (SPSS Inc., Chicago, Illinois, USA) was used for data analysis.

Results

During the study, 37 infants were referred to the clinic and diagnosed with BESS. Two infants were excluded from the study, one of whom underwent shunting, and the other one was diagnosed with Sotos syndrome during the follow-up. Also, three infants were lost to follow-up during the study; one child expired due to respiratory failure, and the parents of two infants were uncooperative. Finally, 32 infants were enrolled in the study and analyzed. The mean age of BESS diagnosis was 6.8±3.2 months. Twenty-eight infants with BESS were male (87.5%), and five infants had a history of prematurity (15.6%). Also, 72% of cases had a family history of macrocephaly. Table 1 presents the characteristics of infants with BESS.

One of the infants (a 13-month-old boy) developed a bulging fontanel, the sunset eye sign, and irritability. Brain imaging and laboratory examinations were unrevealing, and no definite etiological factor was determined as the cause of pseudotumor cerebri. We could not perform cerebrospinal fluid (CSF) manometry because of parental reluctance. The patient's clinical signs and symptoms improved with four weeks of acetazolamide treatment. A subdural hematoma was reported in one infant (3.1%). Also, a four-month-year-old boy with macrocephaly showed head lag and subdural hematoma at 13 months of age. He was treated observationally and showed normal development at the age of two.

Table 2 presents the infants' mean HC at birth and at 6, 12, and 18 months of age, based on gender. Twenty-eight infants (83.3%) had macrocephaly at the age of 18 months. Seven infants (22%) showed developmental delay, based on the DDST-II results. Five patients showed delay in two or more areas of DDST-II (Table 2).

Table 3 shows the relationship between the developmental outcomes of BESS patients. In both genders, the mean HC at birth and six months of age was significantly higher in infants with developmental delay as compared to those with normal development. There was a significant difference in the mean HC at birth (P=0.05) and at six months of age (P=0.02).

Table 1. The characteristics of infants with BESS

Variables		Number	Percentage (%)
Age at BESS diagnosis (mean±SD)		6.7±3.2	
Gender			
	Male	28	87.5
	Female	4	12.5
Prematurity history		5	15.6
Family history of macrocephaly		23	71.9
Cause of referral			
	Macrocephaly	30	93.8
	Head lag	1	3.1
	Head trauma	1	3.1
Medical history			
	Seizure	1	3.1

Table 2. The outcome findings of infants with BESS

Variables		Number	Percentage (%)
Complications			
	subdural hematoma	1	3.1
Growth and developmental delay		7	22
	Gross motor delay	5	15.6
	Fine motor delay	4	12.5
	Personal-social delay	5	15.6
	Language delay	5	15.6
Affected areas of DDST-II			
	One area	2	6.2
	Two areas	1	3.1
	Three areas	1	3.1
	Four areas	3	9.4
Macrocephaly at 6 months		23	71.8
Macrocephaly at 12 months		29	90.6
Macrocephaly at 18 months		28	83.3
Macrocephaly at 24 months		28	83.3

HC at birth (mean±SD) (boys)		35.6±2.2	
HC at 6 months (mean±SD) (boys)		46.1±1.7	
HC at 12 months (mean±SD) (boys)		49.1±1.4	
HC at 18 months (mean±SD) (boys)		50.5±1.6	
HC at birth (mean±SD) (girls)		35.7±0.5	
HC at 6 months (mean±SD) (girls)		46.1±2.5	
HC at 12 months (mean±SD) (girls)		49.6±1.6	
HC at 18 months (mean±SD) (girls)		51.3±1.1	

HC: Head circumference.

Table 3. Comparison of infants with BESS and developmental outcomes

Variables	Delay (%)	Normal (%)	P-value
Age at BESS diagnosis (mean±SD)	7.2±3.7	6.5±3.1	0.6
HC at birth (mean±SD)	37.1±3	35.2±1.2	0.05
HC at 6 months (mean±SD)	45.8±1.1	47.8±3.3	0.02
HC at 12 months (mean±SD)	50.2±2	48.9±1.2	0.09
HC at 18 months (mean±SD)	51.2±2	51.7±2	0.1
HC at BESS diagnosis (mean±SD)	47.5±3	46.3±2	0.3
Prematurity history	1 (14.3)	4 (16)	0.7
Family history of macrocephaly	5 (71.4)	18 (72)	0.6
Male gender	6 (85.7)	22 (88)	0.6

HC: Head circumference.

Discussion

Macrocephaly is the main characteristic of BESS in a healthy child and is also the main cause of presentation to pediatric neurology clinics (1, 4, 15). In the present study, most of the patients were referred to the clinic due to macrocephaly. The increase in HC occurs around the age of six months (5, 16) and is generally steady before the age of 18 months (15, 17). Statistics show that 11-87% of BESS cases remain with macrocephaly (12, 18). The present study showed that the mean HC of BESS infants, regardless of gender, was above the 97th percentile at 6 and 12 months of age, and 83% of cases had HC above the 97th percentile at 18 months.

One infant in our study showed a subdural hematoma as a BESS complication. Overall, subdural hematoma (brain hemorrhage) is the most serious complication of BESS in infants (19-22); it may occur spontaneously or after a minor trauma (22,

23). Our study showed that 7 (22%) patients had developmental delay, according to the DDST-II results at the age of two. Five infants showed developmental delays in more than two areas of DDST-II. Previous studies have reported developmental delays, especially in gross motor function (5, 7, 9, 11, 12). Yew et al. reported that 20 out of 99 infants with BESS (20%) had gross motor delays, four infants had verbal delays, and four infants showed fine motor delays (7). Moreover, Alper et al. reported that two out of 16 infants with BESS had fine motor delay, according to DDST-II at 20 months of age (12).

Furthermore, Amouian et al. reported 11 (26.8%) cases of development delay, including eight cases of motor delay (9). Also, a study by Nickel described nine BESS infants, seven of whom had gross motor delays at diagnosis (11). Moreover, Alvarez et al. reported 36 cases of BESS, 17 of whom showed gross motor delays (5). Muenchberger et al. also showed that two infants had motor delays at 12 months of age, and four out of 15 infants had developmental delays at 20 months (motor delay in one infant, fine motor delay in one infant, and language delay in two infants) (8). However, according to most previous studies, developmental delays are transient and improve until the age of 3-4 years (5, 7, 11).

In the current study, we compared HC (at birth, at 6, 12, and 18 months of age, and at BESS diagnosis), prematurity, family history of macrocephaly, and male gender in two groups of infants with delayed and normal development. Our findings showed that the mean HC at birth and at six months of age was significantly larger in the developmental delay group compared to the normal development group. So far, only one study has evaluated this finding. Yew et al. evaluated the relationship between gross motor delay and head size. They reported developmental delay in 28% of infants with macrocephaly versus 18% of cases without macrocephaly; they did not observe any relationship between the head size and developmental delay (7). It should be noted that in our study, we compared HC at birth, at 6, 12, and 18 months of age, and at BESS diagnosis, whereas Yew et al. only measured HC at diagnosis (eight months of age).

Several hypotheses have been proposed to explain the cause of developmental delay in children with BESS. Theoretically, the high pressure excreted on the brain tissue due to increased CSF in the subarachnoid space during infancy may create inappropriate conditions during the critical period of development. Also, the excess CSF pressure may cause cortical hypoperfusion and lead to persistent and irreversible developmental problems (19). Another hypothesis is that the early onset of macrocephaly in infants makes it harder to develop head control, resulting in motor delay. Finally, coexistence of megalencephaly (even its benign form) and macrocephaly (15) or the associated conditions has been proposed (19, 24). Nevertheless, our findings can be alarming for the management and follow-up of BESS infants with macrocephaly at birth or the first months of life to identify the associated conditions or other causes of macrocephaly; however, further research with a large sample size is needed to test this hypothesis.

In Conclusion

According to the results of this study and previous research, in contrast to the traditional view, BESS is not always a benign condition. Developmental delay is frequent in BESS infants, especially those with macrocephaly at birth or six months of age, and requires attention.

Acknowledgment

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Author's Contribution

Jafar Nasiri and Yahya Madihi designed and supervised all the processes. Azadeh Sadat Mirzadeh and Mahdi Mohammadzadeh collected the data and prepared the primary manuscript . All the authors contributed to the revision of the manuscript and approved the final version.

Conflict of Interest

The authors declare that there is no conflict of interest.

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