İzmir Dr. Behçet Uz Çocuk Hast. Dergisi 2015; 5(1):22-27
doi:10.5222/buchd.2015.022

Klinik Araştırma

Relationship between ultrasonographic findings of periventricular hemorrhagic infarction and short-term survival in preterm infants

Preterm bebeklerde periventriküler hemorajik enfarkt ultrasonografik bulgularının kısa dönem sağkalımla ilişkisi

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ABSTRACT

Objective: Periventricular hemorrhagic infarction (PVHI) is a serious complication of germinal matrix-intraventricular hemorrhage in preterm infants and it is a major contributing factor to patient survival. Our main purpose in this study was to investigate whether cranial ultrasonographic findings of PVHI could help predict short-term survival and to evaluate the relationship between PVHI and perinatal risk factors.
Methods: Preterm infants (<2500 g) with PVHI were retrospectively determined by an electronic search for a 3-year period. A total of 35 preterm infants with PVHI were found but only 28 patients enrolled due to exclusion criteria of the study. Finally, 28 preterm infants with PVHI and 35 control subjects were included in the study. Cranial ultrasonographic images and clinical data of the patients were evaluated. Variables were simply compared by using chi-square and Fisher's exact tests and multiple logistic regression analysis was used to evaluate independent risk factors.
Results: Preterm infants with extensive, bilateral and left-sided unilateral PVHI had higher mortality rates. PVHI was found to be more frequent in patients who required cardiopulmonary resuscitation in the delivery room and those with hypotension and sepsis. detected within the first days.
Conclusion: This study revealed that cranial ultrasonographic findings may help predict mortality in preterm infants with PVHI.

Key words: Ultrasonography, grade IV intraventricular hemorrhage, premature infants, survival, risk factors

ÖZET

Amaç: Periventriküler hemorajik enfarkt preterm infantlarda germinal matriks-intraventriküler kanamanın ciddi bir komplikasyonudur ve hasta sağkalımına başlıca etki eden bir faktördür. Bu çalışmada amacımız periventriküler hemorajik enfarkt kranial ultrasonografi bulgularının kısa dönem sağkalımı öngürmeye yardım edip edemeyeceğini araştırmak ve periventriküler hemorajik enfarkt ile perinatal risk faktörlerinin ilişkisini değerlendirmekti.
Yöntemler: Elektronik aramayla 3 yıllık periodda periventriküler hemorajik enfarktı olan preterm infantlar (<2500 g) retrospektif olarak belirlendi. Periventriküler hemorajik enfarktı olan toplam 35 hasta bulundu ama çalışmanın dışlama kriterleri nedeni ile yalnızca 28 hasta çalışmaya alındı. Sonuç olarak, 28 preterm infant ve 35 kontrol olgusu çalışmaya dâhil edildi. Hastaların kraniyal ultrasonografik görüntülerini ve klinik bilgilerini yine değerlendirdik. Değişkenler ki-kare ve Fisher's exact test ile basitçe karşılaştırıldı ve bağımsız risk faktörlerini değerlendirmek için multipl lojistik regresyon analizi kullanıldı.
Bulgular: Geniş, çift taraflı ve solda tek taraflı periventriküler hemorajik enfarktı olan preterm infantlarda mortalite daha fazlaydı. Periventriküler hemorajik enfarkt, doğum odasında kardiyopulmoner canlandırma gerektiren, yaşamın ilk günlerinde hipotansiyonu ve sepsisi bulunan hastalarda daha sık bulundu.
Sonuç: Bu çalışma periventriküler hemorajik enfarktı olan preterm infantlarda kranial ultrasonografik bulguların mortaliteyi öngörmeye yardım edebileceğini göstermektedir.

Anahtar kelimeler: Ultrasonografi, grade 4 intraventriküler kanama, prematüre infantlar, sağkalım, risk faktörleri

Alındığı tarih: 15.01.2015
Kabul tarihi: 12.02.2015

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INTRODUCTION

Periventricular hemorrhagic infarction (PVHI) is a complication of the germinal matrix hemorrhage and has a major impact on mortality and morbidity of preterm infants [1]. Although it has been considered to be the most severe form of germinal matrix-intraventricular hemorrhage (GM-IVH), it is actually not a case of bleeding from the ventricle into the adjacent white matter. Recent studies have shown that it is a hemorrhagic venous infarction that is due to obstruction or impaired drainage of terminal veins secondary to intraventricular hemorrhage (IVH) [2].

Periventricular hemorrhagic infarction usually develops in preterm infants within the first weeks of their lives , especially in the first day. Early diagnosis may help to take suitable measures to prevent injury and consequently neurological sequelae. Although several risk factors related to germinal matrix-intraventricular hemorrhage have been reported, only a few studies have investigated perinatal risk factors that are related to PVHI [1-5]. Identification of potential risk factors may aid to predict the patients who are most likely prone to PVHI. Imaging studies are mostly related to long-term neurovelopmental outcome and have shown that there is a strong association between cranial ultrasonographic features and survival [1-5]. Description of ultrasonographic findings is important because they may help to predict mortality and morbidity [6]. Together with other clinical parameters, they can support the neonatologists while counseling the parents. The purpose of this study was to investigate whether ultrasonographic findings can help to predict short-term outcome and to evaluate the relationship between PVHI and some perinatal risk factors.

MATERIAL and METHODS

Patients

This retrospective study was approved by the institutional review board, and written informed consent was waived. We performed an electronic search from our picture archiving and communication system (PACS) for a 3-year period (January 2010-December 2012). We evaluated preterm infants (<2500 g) who had a diagnosis of PVHI. In all cases, we reviewed the first and the follow-up images to confirm the diagnosis.

A total of 35 preterm infants with PVHI and 35 sex-and age-matched control patients were reviewed. The exclusion criteria were known (definite diagnosis) or suspected (with clinical diagnosis) congenital and chromosomal anomalies (3 patients), metabolic disorders (2 patients), central nervous system infections (1 patient), and unknown or missed perinatal clinical data (1 patient).

Ultrasonography

Ultrasonographic scanning was performed at the bedside and within 7 days after birth. As a routine practice in our neonatal intensive care unit, a minimum of two cranial US were performed during the first week of life and examinations were repeated weekly or more frequently as clinically indicated within the first month. Cranial US studies were performed by a radiologist using a portable US machine (Mindray M5, Shenzhen, China) with a transducer frequency of 6.5 MHz to 8.5 MHz. Standardized images, including anterior, posterior, and mastoid fontanel views were obtained.

Initial and follow-up cranial ultrasonography images were retrospectively re-evaluated by a radiologist who is experienced in pediatric neuroradiology and was blinded to the infants' clinical data and outcome. The ultrasonographic criteria that were defined by Bassan et al [1] were used. PVHI was defined as hyperechogenic areas in the periventricular white matter that are associated with intraventricular hemorrhage. Patients with bilateral and symmetric echogenities that were compatible with periventricular leukomalacia alone were excluded from the study.

Localization (unilateral/bilateral) and extent (one lobe/more than one lobe) of the PVHI, existence of midline shift (defined as displacement of the septum

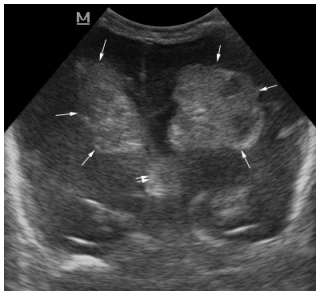

Figure 1. Bilateral massive PVHI. Anterior fontanel, coronal view shows bilateral asymmetric PVHI (arrows) and left-to-right midline shift. The double arrows indicate hemorrhage in the third ventricle.

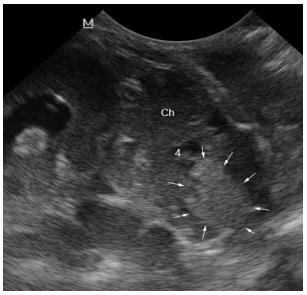

Figure 2. Cerebellar hemorrhage. Mastoid fontanel view shows cerebellar hemorrhage (arrows). Ch: cerebellar hemisphere, 4: Fourth ventricle.

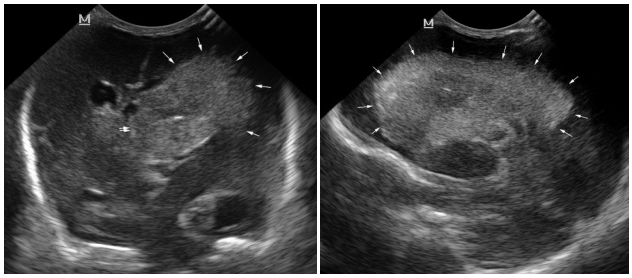

Figure 3a,b. Unilateral massive PVHI. Anterior fontanel, coronal view (a) and sagittal view (b) demonstrate unilateral massive PVHI (arrows) and left-to-right midline shift due to mass effect. The double arrows indicate hemorrhage in the third ventricle.

pellucidum for more than 3 milimeters) and cerebellar hemorrhage were recorded. We evaluated the localization and extension of PVHI with the method that was described by Bassan et al [1], (Fig. 1-3).

Collection of clinical data

The following perinatal clinical data were retrospectively collected by an experienced neonatologist who was blinded to the cranial US findings of the patients. Demographic characteristics (gender, gestational age at birth, birth weight, multiple birth and mode of delivery) were recorded. Antenatal corticosteroid treatment for the prevention of respiratory distress syndrome (two doses with an interval of 24 hours given at least 48 hours before birth), maternal diabetes mellitus (infants of mothers with gestational and pregestational diabetes mellitus), preeclampsia, premature rupture of the membranes (PROM) were noted. Cardiopulmonary resuscitation in the delivery room, early onset neonatal infectious disease defined by sepsis (with positive blood culture) and hypotension (within first days, and requiring inotropic treatment) were recorded. Short-term follow-up (during 6 months) of the patients were also evaluated.

Statistical Analysis

Data analyses were performed by using statistical software (SPSS 15.0 for windows; SPSS inc., Chicago, IL, USA). The clinical parameters of infants with and without PVHI were compared using Fisher's exact test for categorical variables and Mann-Whitney U for continuous variables. Ultrasonographic features were simply compared between fatal and nonfatal PVHI by Pearson chi-square and Fisher's exact test. An intergroup difference with a $p<0.05$ was considered significant. The clinical parameters at which univariate analyses were significant were entered into logistic regression analysis to identify independent risk factors for PVHI.

RESULTS

Patients

Between January 2010, and December 2012, we identified 28 preterm infants with PVHI that met our inclusion criteria. The study population included 28 infants (mean gestational age at birth, 26.57 weeks; range 23-32 weeks) and the control group consisted of 35 preterm infants (mean gestational age at birth, 27.54 weeks; range 24-32 weeks). In the study group 15 patients were male (53,6%) and 13 were female (46,4%). In the control group 18 preterm infants were male (45,5%) and 17 were female (43,3%).

Perinatal risk factors for PVHI

Perinatal risk factors associated with PVHI are outlined in Table 1. Univariate analysis showed that gender, gestational age, birth weight and mode of delivery were not associated with the presence of PVHI. All of the multiple births were twins in our

study. Hemorrhage was more common in twins, but it was not statistically significant (p=.06). Antenatal corticosteroid treatment, maternal diabetes mellitus, preeclampsia and PROM were not found to be significantly related to PVHI in our study. Among all the risk factors, cardiopulmonary resuscitation in the delivery room was found to be the most important factor (p<.001). Hypotension and sepsis were significantly associated with PVHI (p=.001 and .014, respectively).

Table 1. Maternal and neonatal variables.

Variable	PVHI (n=28)	Control group (n=35)	p
Gender			
Male	15	18	1.00
Female	13	17	
Gestational age (weeks±SD)	26.6±2.7	27.5±2.6	.12
Birth weight (g; mean±SD)	916.7±261.6	1094±418.2	.10
Multiple birth	9	4	.06
Mode of delivery			
Vaginal	12	14	.51
Caesarean section	16	21	
Antenatal corticosteroid treatment	7	15	.19
Maternal diabetes mellitus	2	3	1.00
Preeclampsia	4	3	.69
PROM	6	6	.75
Cardiopulmonary resuscitation	19	4	<0.001
Sepsis	5	0	.01
Hypotension	8	0	<0.001

PVHI:Periventricular hemorrhagic infarction, PROM:Premature rupture of the membranes, SD:Standard deviation, g:gram

Variables that showed significant differences in the univariate analyses such as cardiopulmonary resuscitation in the delivery room, sepsis and hypotension were used in a multiple logistic regression analysis to determine correlation between positive risk factors and PVHI (Table 2). Cardiopulmonary resuscitation and hypotension were found to be independent risk factors.

Table 2. Results of multiple logistic regression analysis.

Variable	Regression Coefficient (B)	SD	Odds ratio	95% CI	p
Cardiopulmonary resuscitation	2.712	.697	15.055	3.844-58.973 1.057-118.453	<0.001
Hypotension	2.415	1.204	11.191		.045
Constant	-1.482	.419	.227		<0.001

CI: Confidence for interval, SD: Standard deviation.

Ultrasonographic features and relation to mortality

The first cranial US was performed within 1-3 days after birth. The second and third ultrasonographies were performed at an average of 3.5 and 5 days after the first ultrasonography. All of the cases with PVHI were diagnosed within the first 7 days of life.

Ultrasonographic findings were summarized in Table 3. Frontal lobe was the most commonly involved localization, followed by parietal, occipital and temporal lobes. Unilateral lesions were more often on the left side. Mortality rates were significantly higher in the left-sided unilateral, and bilateral lesions (p=.003). PVHI was extensive in most of the bilateral cases. Mortality rates were higher in patients with extensive PVHI (p=.02). Midline shift was not found to be associated with higher mortality rates (p=.396). We had only one patient with cerebellar hemorrhage who died during the follow-up period.

Table 3. Ultrasonographic findings and short-term outcome of PVHI.

Findings	No. of patients n=28	Mortality (n=15)	Survivors (n=13)
Unilateral PVHI, n (%)	20	7 (35)	13 (65)
Left hemisphere	13	6 (46.2)	7 (53.8)
Right hemisphere	7	1 (14.3)	6 (95.7)
One lobe	11	2 (18.2)	9 (81.8)
More than one lobe	9	5 (63.6)	4 (44.4)
Bilateral PVHI, n (%)	8	8 (100)	0 (0)
One lobe	1	1 (100)	0 (0)
More than one lobe	7	7 (0)	0 (100)
Midline shift, n (%)	7	5 (71.4)	2 (28.6)
Unilateral PVHI	5	3 (60)	2 (40)
Bilateral PVHI	2	2 (100)	0 (0)
Cerebellar hemorrhage, n (%)	1	1 (100)	0 (0)

PVHI: Periventricular hemorrhagic infarction.

DISCUSSION

This study demonstrated that some cranial ultrasonographic findings may help to predict mortality in

preterm infants with PVHI. Preterm infants with extensive, bilateral and left-sided unilateral PVHI seem to have higher mortality rates. Periventricular hemorrhagic infarction was more frequent in patients with cardiopulmonary resuscitation in the delivery room and those with hypotension within the first days.

Periventricular hemorrhagic infarction remains as an important complication of prematurity which is associated with short-and long-term adverse outcomes [7]. Diagnosis of PVHI relies mainly on findings by bedside ultrasonography. Prediction of the mortality is clinically relevant and it helps clinicians in the management of the patients. Recent studies have shown that describing ultrasonographic findings is important. Bassan et al [1] developed a cranial ultrasonography-based severity scoring system. They divided brain into anterior frontal, posterior frontal, parietal, temporal and occipital regions on a sagittal view and categorized extension as localized and extensive according to the affected territories. They also considered midline shift while calculating the score. Higher PVHI severity scores were shown to be associated with higher mortality rates and worse long-term outcomes [1]. Another study re-emphasized the importance of ultrasonographic findings and suggested that preterm infants with unilateral PVHI have better neurodevelopmental outcome than infants with bilateral PVHI [7]. We classified patients according to Bassan et al [1] and found higher mortality rates in patients with extensive, bilateral, and left-sided unilateral PVHIs.

Midline shift was considered as a sign of higher probability of death [1,6]. But in the present study, mortality was not found to be statistically significant in patients with midline shift. This may be due to the number of patients. The cause of the midline shift accompanying PVHI is still unclear but it is thought to be due to mass effect exerted by a large parenchymal hemorrhagic lesion [8]. Gibson et al [6] demonstrated that early occurrence of midline shift was associated with worse outcome.

Some investigators suggested that localization and extension of the PVHI were not related to mortality and functional outcome [9]. Roze et al [9] stated that 'PVHI should no longer be considered a devastating lesion and be associated with the withdrawal of care'in their study. Although we agree with this assertion, previous studies [1,6] and our findings have shown that PVHI and its severity demonstrated by ultrasonographic findings may affect short, and long-term outcomes. The relationship between PVHI and mortality needs to be verified by multicenter prospective studies with larger sample size.

Mortality in preterm infants with PVHI has been found to range between 38 and 60 percent [10,11]. Fifty percent of the preterm infants in our study died due mostly to respiratory and/or circulatory failure that was unresponsive to treatment. Because of high mortality rates in these patients, early diagnosis is very important so as to take some measures.

We investigated some clinical parameters which may predict PVHI. Of all clinical data, only cardiopulmonary resuscitation in the delivery room and hypotension within the first days were found to be statistically significant. Minimum risk was reported for severe IVH in preterm infants who were never intubated in delivery room or during the first 3 days of life [12]. Preterm infants that need mechanical ventilation were found to have an increased risk for GM-IVH in many studies [13,14]. Cardiopulmonary resuscitation may reflect the severity of the illness but it is also associated with fluctuations in blood pressure in preterm infants which is thought to be the main cause of GM-IVH [13]. PVHI is a major complication of IVH and it is also expected to be higher in patients with cardiopulmonary resuscitation.

Hypotension can lead to a decrease in cerebral blood flow which may traumatize the germinal matrix capillaries by reperfusion [14]. It has been reported as a significant factor for predicting GM-IVH [14]. We have found that patients with hypotension in the first days were more vulnerable to PVHI.

Sepsis is identified as a potential risk factor for the development of IVH in preterm infants [14,15]. It has been suggested that GM-IVH may be due to disrup-

tion of the fetal blood-brain barrier by cytokines [2,13]. PVHI is also expected to be more prevalent in patients with sepsis, as we have found in our study.

There are several limitations in our study. First, the number of patients was limited in this study. Second, this was a retrospective, single center study. Although we tried to include all preterm infants with PVHI, we still might miss some of them. Third, we only reviewed the determined risk factors, while the other risk factors for IVH such as pulmonary hemorrhage, trombophilia etc. were not investigated. Finally, the potential of our ultrasonographic findings to predict mortality should be evaluated in further prospective studies with larger sample size before taking radical decisions about treatment of the patients.

In conclusion, this study revealed that some cranial ultrasonographic findings may help to predict mortality in preterm infants with PVHI. Preterm infants with extensive, bilateral and left-sided unilateral PVHIs seem to have higher mortality rates. Periventricular hemorrhagic infarction is more frequent in patients with cardiopulmonary resuscitation in the delivery room and those with hypotension occurring within the first days of life. Further studies with larger sample size are needed to obtain better estimates of predictive value of ultrasonographic features.

Conflict of Interest: The authors have no conflicts of interest to disclose.

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