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Review / Derleme

Intraventricular hemorrhage in preterm babies

Prematürede intraventriküler kanama

Eren Özek, Sinem Gülcan Kersin

Division of Neonatology, Department of Pediatrics, Marmara University Faculty of Medicine, Pendik Training and Research Hospital, İstanbul, Turkey

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Abstract

Germinal matrix-intraventricular hemorrhage (GM-IVH) is a major complication of prematurity and inversely associated with gestational age and birth weight. The hemorrhage originates from the germinal matrix with an immature capillary bed where vascularization is intense and active cell proliferation is high. It occurs in around 20% of very low-birth-weight preterm neonates. Germinal matrix-intraventricular hemorrhage is less common in females, the black race, and with antenatal steroid use, but is more common in the presence of mechanical ventilation, respiratory distress, pulmonary bleeding, pneumothorax, chorioamnionitis, asphyxia, and sepsis. Ultrasonography is the diagnostic tool of choice for intraventricular hemorrhage and its complications. Approximately 25–50% of the germinal matrix-intraventricular hemorrhage cases are asymptomatic and diagnosed during routine screening. These cases are usually patients with low-grade hemorrhage. Neurologic findings are prominent in severe intraventricular hemorrhage cases. The major complications of the germinal matrix-intraventricular hemorrhage in preterm babies are periventricular hemorrhagic infarction, posthemorrhagic ventricular dilatation, periventricular leukomalacia, and cerebellar hemorrhage. It is an important cause of mortality and morbidity. The management of hemodynamics and ventilation of patients, appropriate follow-up, and early diagnosis and treatment can minimize morbidity. Prognosis in intraventricular hemorrhage is related to the severity of bleeding, parenchymal damage, and the presence of seizures and shunt surgery. The main determinant of prognosis is periventricular hemorrhagic infarction and its severity. Moderate-severe intraventricular hemorrhage can cause posthemorrhagic hydrocephalus, cerebral palsy, and mental retardation. Even mild germinal matrix-intraventricular hemorrhage can result in developmental disorders. Long-term problems such as neurodevelopmental disorders and cerebral palsy are as important as short-term problems. Improving the quality of life of these babies should be aimed through appropriate treatment and follow-up. In this review, intraventricular hemorrhage and complications are discussed.

Keywords: Intraventricular hemorrhage, posthemorrhagic ventricular dilatation; preterm

Öz

Germinal matriks-intraventriküler kanama, prematüreliğin majör bir komplikasyonu olup gestasyonel yaş ve doğum ağırlığıyla ters orantılıdır. İntraventiküler kanama, nöroglial öncül hücrelerin damarlanmasının yoğun olduğu ve aktif hücre proliferasyonunun fazla olduğu germinal matrikste gerçekleşmektedir. Çok düşük doğum ağırlıklı bebeklerde yaklaşık %20 sıklıkla görülmektedir. Germinal matriks-intraventriküler kanama, kız cinsiyette, siyah ırkta ve antenatal steroid kullanımında daha az; mekanik ventilasyon, respiratuar distres, pulmoner kanama, pnömotoraks, koryoamniyonit, asfiksi, sepsis varlığında daha sık görülmektedir. Ultrasonografi, tanıda ilk seçilecek yöntemdir. Germinal matriks-intraventiküler kanamaların yaklaşık %25–50'si asemptomatiktir. Rutin taramalar sırasında tanı alan bu olgularda, genellikle düşük evre kanamalar saptanmaktadır. Ağır kanamalarda nörolojik semptomlar ön plandadır. Pretermde intraventriküler hemoraji, periventriküler hemorajik infarkt, posthemorajik ventriküler dilatasyon, periventriküler lökomalazi, serebellar hemoraji gibi komplikasyonlarla birlikte olabilmektedir. Önemli bir hastalık ve ölüm nedenidir. Doğru hemodinami ve ventilasyon yönetimi, uygun izlem, erken tanı ve zamanında müdahale ile hastalıklar en aza indirilebilir. İntraventriküler kanamada seyir, kanamanın ciddiyeti, parankim hasarı, nöbet ve şant varlığı ile ilişkilidir. Seyirin ana belirleyicisi de periventriküler hemorajik infarkt ve bu infarktın ciddiyetidir. Orta-ağır şiddetteki intraventriküler kanama posthemorajik hidrosefali, serebral palsi, zeka geriliğine neden olabilmektedir. Hafif intraventriküler kanama dahi, gelişimsel bozukluklarla sonuçlanabilmektedir. Kısa dönemde karşılaşılan sorunlar kadar uzun dönemde nörogelişimsel bozukluk, serebral palsi gibi sorunların takibinin yapılması; gerekli tedavi ve özel eğitim ile bu bebeklerin yaşam kalitesinin artırılması amaçlanmalıdır. Bu derlemede germinal matriks-intraventriküler kanama ve komplikasyonları tartışılmaktadır.

Anahtar sözcükler: İntraventriküler kanama, posthemorajik ventriküler dilatasyon, prematüre

Corresponding Author/Sorumlu Yazar: Sinem Gülcan Kersin E-mail/E-posta: sinemgulcan@hotmail.com
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Introduction

As a result of technological advancements in the science of neonatology, survival rates of very-low- birth weight preterms are increasing. Despite survival rates increasing to approximately 70%, intraventricular hemorrhage (IVH) takes an important place in mortality and morbidity (1). The frequency of IVH is 10–20% in preterms born before the 30th gestational week, and rates of serious IVH increase up to 35–45% in babies born with a birth weight below 750 grams (2, 3). Posthemorrhagic ventricular dilatation develops in approximately half of these babies and a permanent ventriculoperitoneal (VP) shunt is needed in 20–40% (3).

Current information related to intraventricular hemorrhage is included in this review.

Pathogenesis

The germinal matrix is a region rich in large, irregular, rapidly growing, immature capillary vessels with high blood supply harbouring neuroglial cells. This structure localized adjacent to the fetal ventricular system disappears at the 36th gestational week (4). The risk of IVH is inversely proportional to gestational age and is an important problem for small premature babies. Approximately half of IVHs occur in the first 6 hours of life, and hemorrhage rarely occurs after the postnatal 5th day (2). The etiopathogenesis of hemorrhage is multifactorial. It starts in the region of germinal matrix, is transfered to the lateral ventricles, and leads to IVH.

The germinal matrix is at the end of the arterial region and is directly connected to the vein of Galen. The terminal vein, which is the main vein of the system, anatomically turns around the germinal matrix structure in a U-shaped manner, and conditions in this region such as ischemia, reperfusion, and venous congestion may cause injury in the germinal matrix (2, 5). Changes in cerebral blood flow have an important role in the pathogenesis of IVH. Critical changes in cerebral blood flow are not expected because of cerebral autoregulation. However, it is known that this compensatory mechanism is not fully developed, and therefore, sudden changes in blood pressure have a direct effect on the brain in preterm babies. Low gestational age, low birth weight, and hypotension disrupt cerebral autoregulation (6). Hypercarbia, hypoxia, and hypoglycemia, which are frequently observed in preterm babies, cause cerebral vasodilatation and this increases the risk of IVH (5, 7).

The role of inflammation and chorioamnionitis in the pathogenesis of IVH has still not been explained. Cytokine release occurs as a result of triggering by inflammation. The coagulation system is disrupted by endothelial damage, and cerebral autoregulation is disrupted by hemodynamic changes (8).

Despite the anatomic and hemodynamic predisposition in preterm babies, it is known that IVH never develops in some high-risk preterms. On the other hand, serious IVH may occur unexpectedly in some preterms who have a relatively more stable clinical picture. Tioseco et al. (9) reported that grade III-IV IVH was more frequent in the male sex. It was reported that IVH in one twin increased the risk in the other twin, and it was proposed that this might be related to a genetic predisposition, which could cause hemorrhage. In the pathogenesis, the importance of genes related to coagulation and inflammation has also been emphasized. It was found that a polymorphism in the Factor V Leiden gene was associated with IVH, which occurred with an atypical timing. Studies found that the MTHFR 677C>T polymorphism and low Apgar score at the 5th postnatal minute increased the risk of IVH and the IL-6-177CC genotype was associated with grade III-IV IVH (10–12).

Risk factors

The most important risk factor for germinal matrix-IVH is very low gestational age. Babies born with a gestational age below 32 weeks constitute the population with high risk. It is observed less frequently in the female sex, black race, and with antenatal steroid use, but it is observed more frequently in the presence of mechanical ventilation, respiratory distress, pulmonary hemorrhage, pneumothorax, chorioamnionitis, asphyxia, sepsis, and patent ductus arteriosus (2, 7). A close relationship was shown between fluctuations in cerebral blood flow and an increase in arterial blood pressure and the occurrence of IVH. The main causes of the increase in cerebral blood flow include disruption of cerebral autoregulation, rapid volume replacements, hypercarbia, low hematocrit level and hypolgycemia (7). Dalton et al. (13) reported that hypernatremia was also an independent risk factor for IVH in preterms with very low birth weight.

Diagnosis

Ultrasonography is the first diagnostic method to be preferred; its main advantages are that it is portable and inexpensive, and does not involve ionizing radiation, and its disadvantages are that it cannot clearly display cerebellum hemorrhage and small injuries in the white and gray matter. The IVH grading system, which was established by Papile in 1978 according to computed tomography (CT) findings (Table 1), was adapted to ultrasonographic findings by Volpe in 2008 (Table 2) (4, 5, 14). In this grading system, the grades were qualified as follows: grade I

Table 1. Intraventricular hemorrhage grading using cranial computed tomography (4)

Grade I	Germinal matrix hemorrhage
Grade II	Hemorrhage fills less than 50% of the lateral ventricle
Grade III	Hemorrhage fills and enlarges the lateral ventricle
Grade IV	Intraparenchymal hemorrhage

Table 2. Intraventricular hemorrhage grading using cranial ultrasonography (2)

Grade I	Germinal matrix hemorrhage (no or minimal hemorrhage in the ventricle)
Grade II	IVH filling 10–50% of the ventricle at the parasagittal section
Grade III	IVH filling more than 50% of the ventricle and causing ventricular enlargement
Grade IV	Periventricular echodensity

IVH: Intraventricular hemorrhage.

- hemorrhage in the region of germinal matrix, very little hemorrhage or no hemorrhage in the ventricle; grade II - hemorrhage filling 10–50% of the ventricle; grade III - hemorrhage filling more than 50% of the ventricle; grade IV - periventricular echodensity. This hemorrhage, which was named grade IV previously, is currently classified as periventricular hemorrhagic infarction (PVHI). Grade I and II are defined as mild grades and grade III and PVHI are defined as advanced grades.

Screening with cranial ultrasonography is recommended in all preterm babies born before the 32nd gestational week and in all high-risk babies born after the 32nd gestational week who are clinically unstable and have neurologic findings (15). Screening protocols change from center to center. In our unit, screening is performed in high-risk babies on the 1st, 3rd, 7th, and 15–30th days, and before discharge. According to risks, the numbers of screening in the first week may be reduced in some conditions. Some protocols repeat screening at the 7th and 14th days and the postmenstrual 35–40th week.

However, ultrasonography is insufficient in demonstrating minor injuries in the cerebellum and gray and white matter. Especially in very-low-birth-weight babies, follow-up with only ultrasonography may cause injuries to be missed even if hemorrhage grades are low. Magnetic resonance imaging (MRI) is the gold standard for showing white matter injury (16). It is difficult to perform MRI in all cases because most babies are not stable for transportation in the early period, the imaging time is long, anesthesia is needed, and it is an expensive investigation method. It has been reported that conventional MR imaging, which evaluates the dimensions and localization of hemorrhage and related white matter injury after reaching the postconceptional 40th week, is associated with complications, mortality, and short- and long-term neurodevelopmental outcomes (16, 17).

Clinical findings

Approximately 25–50% of germinal matrix-IVHs are asymptomatic (18). Generally, low-grade hemorrhages are found in these subjects who are diagnosed during routine screenings. In babies with serious IVH and PVHI, change in the level of consciousness, cardiopulmonary symptoms, a sudden reduction in hematocrit, acidosis, and hypoglycemia/hyperglycemia may be observed. Sometimes, hyperbilirubinemia that cannot be explained otherwise and persists, may be the first sign of IVH in the early period of hemorrhage. Tense fontanelle, hypotonia, lethargia, narrow popliteal angle and seizure may be found on physical examination. It should be kept in mind that inappropriate ADH release may be observed in these babies (15, 18).

Prevention

The best way to prevent IVH is to prevent preterm deliveries. The first steps to be taken include providing intrauterine transport of the baby to a center where a neonatal intensive care unit is available, preventing inflammation in the fetal period and establishing optimal delivery conditions in case of premature labor because it is currently impossible to prevent preterm deliveries.

Studies have been conducted with many pharmacologic agents predicting that these agents could prevent IVH. However, the only pharmacologic agent that has been found to be efficient so far is antenatal steroids. Studies have found that antenatal steroids decrease the frequency of IVH in all grades (15). Although some studies found that prophylactic use of indomethacin reduced the frequency of IVH, its routine use is not recommended because its effect on mortality and long-term outcomes could not be proven (19).

To prevent IVH in the postnatal period, hemodynamics should be managed accurately, conditions that could lead to sudden changes in cerebral blood flow should be avoided, an appropriate ventilation strategy should be established and used, and bleeding disorders should be corrected (5). Although studies showed that delayed cord clamping and the milking method reduced the frequency of IVH, a positive effect on the frequency of serious IVH could not be found (20, 21). Studies on mesenchymal stem

cell and erythropoietin therapies directed at reducing neuronal injury in preterm babies with intraventricular hemorrhage are being conducted (22–24).

Treatment

There is no specific treatment for IVH. Adjustment of hemodynamics, providing optimal oxygenation and ventilation, fluid and nutritional support, controlling convulsions, and applications directed to complications, constitute the treatment (4, 11, 18).

Complications

Intraventricular hemorrhage may result in complications such as PVHI, posthemorrhagic ventricular dilatation (PHVD), periventricular leukomalacia, and cerebellar hemorrhage (5).

Periventricular hemorrhagic infarction is generally unilateral and develops on the second or third day in the region of hemorrhage. It is observed with a rate of 4% in babies born with a birth weight below 1500 g and with a rate of 15–30% in babies with very low birth weight (5, 25). In unilateral cases, spastic hemiparesia is observed, and spastic diplegia and tetraplegia are observed in bilateral cases. As a result of PVHI, injury occurs in the corticothalamic pathways, neuronal and glial migration is affected, and development of gray matter is influenced negatively. Mortality increases as the dimension of injury increases. Cerebral palsy is observed in 60% of cases, cognitive problems are observed in 50%, visual field defects are observed in 25%, and epilepsy is observed in 20%; about 30–40% of these babies are lost (3, 25).

Posthemorrhagic ventricular dilatation is one of the most important complications of IVH. It occurs in 1–3 weeks following severe hemorrhage. It is transient and spontaneously recovers in some babies, but transient or permanent surgical intervention is needed in most cases. Posthemorrhagic hydrocephalus develops in one-third of very-low-birth-weight preterm babies with IVH (3). In approximately half of all babies with severe IVH, progressive hydrocephalus develops; surgical intervention is performed in about 15% of these cases (3). Fibrin formed as a result of hemorrhage in the acute period causes obstruction, and transforming growth factor (TGF-β) released from platelets leads to hydrocephalus by stimulating inflammation and fibrosis pathways in the chronic period (5, 26). Demonstration of TGF-β in cerebrospinal fluid (CSF) in different studies was associated with the development of PHVD and the need for shunt (26).

Posthemorrhagic ventricular dilatation comprises increased intracranial pressure, a reduction in cerebral blood flow and cerebral oxygenation, mechanical damage by way of direct action on periventricular axons and cytokine, and free oxygen radicals damage the central nervous system (2, 15). Posthemorrhagic ventricular dilatation is an important cause of morbidity and mortality in preterm babies; it is possible to minimize this injury with early diagnosis by serial ultrasonographic screenings and timely intervention.

Diagnosis and treatment of posthemorrhagic ventricular dilatation

Posthemorrhagic ventricular dilatation is observed in approximately half of all preterm babies with serious IVH; progressive PHVD develops in about 25–30% of these babies (17, 27). The diagnosis is made using ultrasonography. The measurement performed from the middle line up to the lateral margin at the mid-coronal level gives the dimension of the lateral ventricle (28). According to the Papile grading system, follow-up with ultrasonography is recommended at least once a week for four weeks and at the time of discharge in grade I-II IVH, and two times a week until the time of discharge in grade III-IV IVH (29, 30).

Serial head circumference measurement is essential in preterms with IVH. An increase of 1 mm daily is expected in the head circumference in babies in the postnatal 26–32th weeks and an increase of 0.7 mm is expected in the postnatal 32–40th weeks; this is an indicator of healthy growth (31). A persistent increase of 2 mm/day in head circumference should be considered abnormal. However, an increase of 4 mm in 2 days is a warning and helpful in deciding in terms of treatment because it may be difficult to detect this small difference of 2 mm. An increase of 14 mm in one week is considered abnormal (30).

It is important to differentiate PHVD from ventricular dilatation caused by white matter loss. The normal CSF pressure is 3 mm Hg and the upper limit is 6 mm Hg (30). In cases of increased cerebrospinal fluid pressure, slow or rapid enlargement in the ventricles and an increase in head circumference are observed. In ventricular dilatation caused by atrophy, CSF pressure is not increased, ventricular dimensions are stable, ventricular margins are irregular, and the increase in head circumference is normal or slow (5, 32).

Findings such as bulging fontanelle due to increased intracranial pressure, separation in sutures, vomiting, apnea, changes in consciousness level, hypotonia, hypertonia, and irritability may be found in babies with PHVD. To minimize the need for VP shunt in PHVD, transient interventions are performed to reduce the negative effects that could be caused by increased intracranial pressure until a

shunt is placed. It is still not clear which intervention type should be performed and when this intervention should be performed. A lateral ventricle width measurement performed at the mid-coronal level from the medial margin up to the lateral margin 4 mm above the 97th percentile specified for that specific week, is considered an indication for intervention (19). The prospective randomized ELVIS study was performed to investigate the effects of early intervention because this timing was thought to be late and did not change poor prognosis (33). In this study, which included 126 preterms with PHVD born before the 34th gestational week, the partial results of which were published in 2019, applications of intervention were compared between low-threshold (97th percentile) and high-threshold (97th percentile +4 mm) groups; it was reported that brain injury occurred with a higher rate and larger ventricles were found in the high threshold group. The study group, which reported that early intervention had positive effects in PHVD is expected to publish neurodevelopmental outcomes at the age of two years (34).

Sometimes, it may be observed that the ventricles do not enlarge laterally; they may enlarge roundly or in the shape of a balloon or towards the occipital region. In these cases, Davies curves, which involve horn width, thalamo-occipital distance and 3rd ventricle width measurements, should be used (35). In this curve, the 95th percentile is 3 mm for anterior horn width, 25 mm for thalamo-occipital distance, and 2 mm for the third ventricle; the finding that all bilateral measurements are 1 mm above the 95th percentile supports the decision of intervention (32, 35).

Posthemorrhagic ventricular dilatation develops in about 30–50% of the preterms with serious IVH and dilatation spontaneously regresses without the need for intervention in some babies. A VP shunt is needed in 25% of the cases (3). Many interventional methods have been tried for the treatment of PHVD. It has been observed that none of the methods among repeated lumbar punctures, drugs decreasing the production of CSF (acetazolamide/furosemide), intraventricular fibrinolytic treatment, external ventricular drainage, ventriculosubgaleal shunt, ventricular reservoir, choroid plexus coagulation and endoscopic third ventriculostomy, is the ideal treatment to minimize neurologic injury and the need for VP shunt (33).

Currently, VP shunt is still the main surgical intervention in PHVD (35). However, the fact that the baby is small and unstable and the ventricle is filled with blood, renders shunt operation impossible in the early period. Intraventricular pressure is attempted to be controlled using ventricular reservoir or ventriculosubgaleal shunt methods, which are used frequently today; VP shunt surgery is planned if PHVD requiring intervention persists when the baby becomes 2–2.5 kg. However, there is no consensus on the ideal body weight to place a shunt (36). Studies have reported that rates of infection and shunt dysfunction are higher in shunt procedures performed before the first 35 days of life (37). To minimize shunt dysfunction caused by obstruction, CSF protein level should be 1.5 g/L and below, the CSF erythrocyte count should be below 100/m^3, and infection should be absent. It should be kept in mind that VP shunt is not a definitive treatment. In these babies, the possibility of shunt dysfunction is high, and it should be known that each shunt revision effects the prognosis (3).

Prognosis

In IVH, the prognosis is associated with the severity of hemorrhage, parenchymal injury, and presence of seizure and shunt (5, 17). The main determinant of prognosis is PVHI and the severity of this infarction. In the past, it was thought that the morbidity of low-grade IVH was low, and low-grade IVH did not lead to neurodevelopmental disorders. However, publications have reported that these hemorrhages could also result in severe morbidity (38). Owing to diffusion tensor imaging, which is a technological innovation that provides more detailed imaging compared with conventional MRI and renders even the smallest diffusion limitations in white matter visible, uncomplicated cases can be examined (39). In patients with grade I-II IVH, neurodevelopmental delay, hearing loss, and cerebral palsy have been found at the adjusted age of 2 years. Cerebral palsy is observed with a rate of 6.8% in grade I IVH and with a rate of 8.1% in grade II IVH; these rates increase to 8.1% and 12.2% in the presence of ventricular dilatation and cystic or echodense periventricular leukomalacia (40). However, no difference was found between groups in some other studies (41).

In grade III-IV IVH, the frequency of cerebral palsy is above 50% and special education is needed in 75% (15). In another study, severe neurodevelopmental disorder was found in 55% of subjects with advanced grade IVH, and it was reported this rate increased to 86% in the presence of PVHI and shunt (3).

Sixty percent of babies with PHVD become stable spontaneously or with treatment, but progressive hydrocephalus may be observed months later in 5%; therefore, follow-up up to one year is recommended (5). Development of PHVD following IVH increases the risk of neurodevelopmental delay by 3–4-fold. The rate of cerebral palsy is 40% in cases of PHVD not accompanied by echodense lesion or cyst, whereas it increases up to 90% in the presence of parenchymal infarction (5, 15).

Conclusion

Intraventricular hemorrhage constitutes an important problem for babies with very low birth weight and currently and this problem has yet to be solved. Although it is observed with a lower rate in the female sex, black race, and with antenatal steroid use, there is a higher rate in the presence of mechanical ventilation, respiratory distress, pulmonary hemorrhage, pneumothorax, chorioamnionitis, asphyxia, and sepsis; a reduction of its frequency does not seem possible unless the number of preterm deliveries decreases. Morbidity can be minimized with accurate management of hemodynamics and ventilation, appropriate follow-up, early diagnosis, and timely intervention. Long-term problems such as neurodevelopmental disorder and cerebral palsy should be followed up as well as short-term problems, and it should be aimed to increase the quality of life in these babies with the necessary treatment and special education.

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