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# The Long-Term Outcome and Rehabilitative Approach of Intraventricular Hemorrhage at Preterm Birth

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Technological advances in neonatology led to the improvement of the survival rate in preterm babies with very low birth weights. However, intraventricular hemorrhage (IVH) has been one of the major complications of prematurity. IVH is relevant to neurodevelopmental disorders, such as cerebral palsy, language and cognitive impairments, and neurosensory and psychiatric problems, especially when combined with brain parenchymal injuries. Additionally, severe IVH requiring shunt insertion is associated with a higher risk of adverse neurodevelopmental outcomes. Multidisciplinary and longitudinal rehabilitation should be provided for these children based on the patients' life cycles. During the infantile period, it is essential to detect high-risk infants based on neuromotor examinations and provide early intervention as soon as possible. As babies grow up, close monitoring of language and cognitive development is needed. Moreover, providing continuous rehabilitation with task-specific and intensive repetitive training could improve functional outcomes in children with mild-to-moderate disabilities. After school age, maintaining the level of physical activity and managing complications are also needed.

**Key Words :** Cerebral intraventricular hemorrhage · Premature birth · Neurodevelopmental disorders · Rehabilitation.

## INTRODUCTION

Technological advances in neonatology have improved the survival rate of preterm infants with low birth weights. Intraventricular hemorrhage (IVH) is a major complication of premature birth. Approximately 12000 infants are born annually with IVH only in the United States[7]. The frequency of IVH is 10–20% in preterm infants born before 30 weeks of gestation, and the rate of severe IVH increases to 35–45% in these infants with less than 750 g of birth weight[1,11]. Germinal matrix hemorrhage-IVH is the most common variety of neonatal intracranial hemorrhage[48]. The germinal matrix is a highly vascular structure that is vulnerable to hemorrhage, as the thickness of the germinal matrix decreases after 24 gestational weeks and almost disappears by 36–37 gestational weeks[10]. Disturbance in cerebral blood flow and fragility of germinal matrix vasculature primarily contributes to the development of germinal matrix hemorrhage-IVH[9]. IVH causes complications such as post-hemorrhagic ventricular dilatation (PHVD) and brain parenchymal lesions, whose incidence is proportional to the severity of IVH[76]. Even though there was no apparent parenchymal lesion, ventricular blood clots and associated inflammatory reaction caused by blood breakdown products in the ventricles may result in brain injury[42]. More-

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over, some cases of PHVD require a permanent ventriculoperitoneal shunt[1]. These structural brain lesions as well as the presence of a shunt are related to unfavorable neurodevelopmental outcomes[71,91,100]. When these long-term sequelae remain, multimodal approaches including family and social support should be integrated[22]. Especially, the need for rehabilitation throughout the patients' life is becoming more important[26]. In this review, we discuss the long-term effects of IVH in premature babies and rehabilitative approaches throughout their life.

## LONG-TERM OUTCOME OF IVH AT PRETERM BIRTH BASED ON THE CLINICAL DISEASE ENTITY

The survival rate of preterm infants has improved over the past three decades[5,31,93]. Ironically, the advances in neonatal intensive care improving the survival of extremely preterm infants have, by extension, led to a relative increase in the number of infants with IVH development[89]. Many survivors diagnosed with IVH may live with a long-term neurodevelopmental disability, and the severity of the disability is proportional to the IVH grade[32,78]. Moreover, severe IVH that requires shunt insertion poses a great risk for adverse neurodevelopmental outcomes when compared to IVH without a shunt[1]. And prolonged and frequent treatments for shunt-related complications including revision could be one of the factors associated with increased disability and reduced quality of life[51,60]. Meanwhile, approximately 20–30% of extreme preterm survivors (gestational age <28 weeks) with IVH were diagnosed with cerebral palsy (CP), 30–35% with minor motor dysfunction which was not enough to be diagnosed with CP, 20% with a major neurosensory disability, and 15% with impaired academic skills[44,88]. A quarter of preterm survivors (gestational age <36 weeks) without neuromotor symptoms develop psychiatric disorders, such as major depressive disorder and obsessive-compulsive disorder[88]. In this section, we describe the long-term outcomes of preterm babies diagnosed with IVH according to disease entities.

### Cerebral palsy

CP is a group of permanent, but changing, disorders that affect the ability to move and maintain posture and balance caused by non-progressive interference, lesions, or abnormality of the immature brain[12,85]. There are many risk factors associated with the prevalence of CP, such as low birth weight and premature birth[96]. In South Korea, the overall prevalence of CP was 6.2–6.6% in extremely low birth weight infants, and it had an inverse relationship with gestational age[54]. IVH at preterm birth is one of the major causes of CP[92]. Overall, approximately 10–20% of preterm babies with IVH develop CP[6,88]. The incidence of CP is related directly to the grade of IVH, and almost 60–100% of grade 4 IVH results in CP[72]. IVH may induce brain parenchymal lesions such as periventricular leukomalacia (PVL) or PHVD, or both. The association between IVH without parenchymal injury and CP incidence is still controversial[71]. In contrast, IVH with parenchymal injury is closely related to the prevalence and incidence of CP. PVL is a predominant form of brain injury and an independent risk factor for CP[28]. In 50% of children with CP, CP is associated with PVL[29]. Meanwhile, PHVD is also one of the main complication of IVH. When ventricular dilation is more severe and clinical symptoms develop (full fontanelle, splaying sutures, irritability, apneas, sunsetting), the term post-hemorrhagic hydrocephalus is used[57]. 60% of infants with PHVD become stable without surgical treatment or need transient treatment such as external ventricular drainage. About 25% of PHVD require permanent surgical intervention[1]. Overall, CP is diagnosed in about 40% of infants with PHVD, and the risk factors for this poor developmental outcome are high-grade IVH and increased head circumference[32].

CP usually involves a variety of neuromuscular problems that depend on the variable location and severity of brain lesions[34,50]. These problems include not only muscle weakness but also spasticity, dystonia, poor balance, and loss of selective motor control. All of these are correlated in a complex manner, which disturbs children's gross motor function and performance of daily activities. Non-ambulatory children with CP reach their maximum gross motor function earlier than ambulatory children do. $Age_{90}$, the average age at which children achieve 90% of their expected limit in gross motor ability, significantly differs according to the Gross Motor Function Classification System (GMFCS) level. The GMFCS is a five-level scale that rates a child's gross motor function with an emphasis on movement initiation, sitting control, and walking. Level I represents the highest gross motor function, whereas level V represents the lowest. The average of $Age_{90}$ for

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GMFCS I and II is between 4 and 5 years of age, less than 4 years for GMFCS III to IV, and 2.7 years for GMFCS V. Moreover, the children with GMFCS III-V reach their peak of gross motor function before adolescence (7 years 11 months, 6 years 11 months, and 6 years 11 months, respectively) which decline as they grow up[41,84].

Meanwhile, children with CP could have progressive musculoskeletal complications caused by various factors, mainly due to failure of longitudinal growth of skeletal muscle[36]. Clinically, deficiency in muscle relaxation as well as reduced activity could induce contracture of the joints, especially at the ankle[50]. The imbalance between the growth of long bones and muscle-tendon units itself could induce relative muscle shortening and limited range of motion[106]. Moreover, bone and joint changes are usually progressive, especially for the spine and lower extremities, such as scoliosis, hip subluxation, and subluxation of the talonavicular joint[66], which could result in functional regression and chronic pain[37]. As a result, children with CP have a considerably higher burden of medical, neurological, and mental/behavioral disorders than the non-CP population[45]. Regular monitoring and management of musculoskeletal pain are also needed across the entire range of motor impairment[79].

## Cognitive abnormality and language development without neuromotor symptoms

Children with a history of IVH at preterm birth have a higher risk of cognitive impairment than children born full-term. It has been reported that 35% of children with a history of IVH at preterm birth without brain parenchymal injury and up to 76% with injury, such as grade III-IV IVH, PVL, or ventriculomegaly, need special education whereas only 10% of children born full-term need it[58]. IVH was reported to be an independent risk factor for cognitive development, with the severity of impairments being proportional to IVH grade[88]. The total IQ was significantly lower in children with post-hemorrhagic ventricular dilatation, especially in those who had undergone surgical intervention such as ventriculoperitoneal shunt and external ventricular drainage, than in children with a history of preterm birth but no ventricular dilatation[46]. In contrast, the presence of cognitive dysfunction was not associated with low-grade IVH[55,88,98]. However, when the follow-up period is extended up to adolescence, low-grade IVH is also a risk factor for cognitive dysfunction[7,73].

Language disability is also common in children with a history of extremely preterm birth (32 weeks) and very low birth weight (<1500 g)[80], and functional communication skills in preterm toddlers with IVH could be impaired[52].

The pathophysiological mechanism of these symptoms has not yet been established in children with IVH in the absence of brain parenchymal lesions. The preterm brain itself showed reduced white matter connectivity[94]. However, a previous study analyzing brain images demonstrated that very premature infants with low-grade IVH may present with regional abnormalities, such as a decrease in the total volume of cortical gray matter associated with the visual association, functional anisotropy, and microstructural immaturity of major white matter tracts[8]. Further studies are needed to clarify the mechanism.

## Other complications

Several other complications are associated with IVH. All grades of IVH correlate with a higher incidence of optic atrophy[70]. Mild IVH (grade I or II) is associated with deleterious effects on cortical vision development and function based on visually evoked potential in infants with 5–7 months of corrective age[98]. Infants with severe IVH (grade III or IV) showed a higher incidence of visual-motor coordination dysfunction[98]. Moreover, in children who had no evident white matter damage, a history of IVH at preterm birth was associated with double the risk of microcephaly and impaired visual fixation. Children with IVH and white matter damage show a higher risk of visual field impairment[71].

Hearing impairment is also one of the severe consequences of prematurity, and its prevalence is inversely proportional to gestational age[103]. However, there was no evidence of increased risk of hearing impairment in preterm infants with any degree of IVH compared to preterm infants without IVH. However, in children with PVL, the risk of hearing impairment increases[35,40].

Epilepsy is one of the most common complications in extremely preterm infants. Seizure disorders were present in about 4–5% of preterm infants, and the incidence of epilepsy was inversely proportional to gestational age at birth[99,102]. IVH with white matter injury at preterm birth and a history of neonatal convulsions were strongly associated with an increased risk of epilepsy. However, there have been no reports of epilepsy incidence in children with IVH without white

matter injury[43]. Further studies are needed to accurately analyze the correlation between IVH and epilepsy.

Considering psychiatric disorders, children with IVH were three times more likely to develop autism spectrum disease, especially post-hemorrhagic ventricular dilatation in a low birth weight population[67]. Moreover, IVH without brain parenchymal injury increased the risk of adolescent major depressive disorder and obsessive-compulsive disorder, whereas IVH with brain injury increased the risk of tic disorder, obsessive-compulsive disorder, and attention deficit hyperactivity disorder-inattentive type only[101]. In contrast, prematurity and low birth weight were significantly correlated with all types of attention deficit hyperactivity disorders at the school age[25].

## REHABILITATIVE APPROACH : FROM EARLY DETECTION TO LONG-TERM CARE BASED ON LIFE CYCLE

For patients diagnosed with brain injury, including IVH, several variables could affect long-term outcomes. We should consider the severity of brain lesions, current level of function, degree of spasticity, and anticipatory growth of bone and muscle and accordingly provide multidisciplinary and lifelong rehabilitation plans. In this section, we review the rehabilitative approach according to age.

### Early detection and intervention

For children with brain injuries, including IVH, a comprehensive and individualized rehabilitation plan based on the patient's life cycle is needed. Around birth, it is essential to detect high-risk babies and provide early interventions. Brain magnetic resonance imaging (MRI) is the most suitable modality for early evaluation of the site and severity of brain lesions[15]. Meanwhile, observing general movements (GMs) in preterm and term-born infants during their first few months also has similar sensitivity and specificity to detect neurological abnormalities as MRI[63]. GMs are characterized as spontaneous gross movements of the entire body with no distinctive pattern or sequence in movement of each body part. Prechtl et al.[77] developed a highly predictive tool for later neurological impairments by observing these GMs, particularly for spastic CP[30] as well as the dyskinetic type. Moreover, the prediction was significantly enhanced when the GM assessment was combined with MRI findings[90]. Some studies claimed that the quality of GMs can also predict cognitive and behavioral development other than motor abnormalities[16,19,39]. Other neurological examinations, such as the Hammersmith Infant Neurological Examination, could also play an important role in the diagnosis and prognosis of infants at risk of poor neurodevelopmental outcomes[38,83]. Even after the early infant period, it is necessary to closely observe the delay of development in motor, language, cognitive, and socio-emotional functions.

After neurological impairments are detected, early intervention is important in terms of neural plasticity. In South Korea, rehabilitative support after discharge was provided to approximately 35–38% of very low birth weight infants[54]. For infants who exhibit difficulty following commands for motor training, providing an enriched environment is important for maximizing neurological outcomes. A key feature of an enriched environment is the provision of environmental complexity with the enrichment of objects that provide a range of opportunities for visual, somatosensory, and olfactory stimulation. Providing enriched environments could promote structural and chemical brain plasticity in animal studies[68,97]. Although the term "enriched environment" has been widely used, there is no agreed definition for an enriched environment for human infants. One previous study proposed the definition of "enriched environment" for infants, which aims to enrich the multiple aspects of the infant's environment to promote learning : e.g., interventions aiming to enhance parent-infant interaction and stimulate self-generated motor activity by adapting the physical and play environment[65]. Recently, early intervention incorporating self-initiated movement was reported to have a positive effect on motor development as well as intellectual development in high-risk infants with brain injury[56,64].

### Rehabilitative approach in toddlers and preschoolers

Language and cognitive development progress rapidly in toddlers and preschoolers[20]. Moreover, children who have not been diagnosed with CP often show language and cognitive abnormalities at this age[2]. Therefore, attention should be paid to language and cognitive development, especially in children without neuromotor symptoms.

Continuous rehabilitation should be provided to children with neuromotor impairment. Task-oriented and intensive repetitive motor training has been shown to improve motor function, especially in children with mild-to-moderate dis-

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abilities[49,87]. Even for children with severe disability, rehabilitation could have a potentially positive impact on pediatric CP survival rate through the complication management[47]. In accordance with the principles of motor learning, various rehabilitation treatment methods, including conventional physical therapy, occupational therapy, hydrotherapy, and electrical stimulation therapy, have been developed to improve motor function and activities of daily living. Recently, advanced technologies have been applied to achieve more effective motor learning. For example, robot-assisted training has been introduced, and its effectiveness has been reported in many studies[33,104]. Moreover, the application of virtual reality technologies improved not only motor function[24] but also cognitive function[53] by boosting motivation and participation[59].

Spasticity is one of the most common neuromotor symptoms that can lead to long-term complications. There are many modalities to reduce spasticity : from non-surgical management, such as conventional stretching, serial casting, and anti-spastic medication, to surgical management, such as insertion of an intrathecal baclofen pump, selective dorsal rhizotomy, and orthopedic surgery[95]. One of the most effective non-surgical treatments for spasticity is intramuscular botulinum toxin injection. Botulinum toxin injection not only promotes selective motor control by reducing spasticity[13] but also avoids the development of bony deformities secondary to abnormal muscle pull and contracted tendons. Botulinum toxin injection could delay or decrease the need for orthopedic or neurosurgical operations[74]. Even after these complications are managed by surgical interventions, postoperative intensive rehabilitation would be very helpful not only for recovering prefunctional levels but also for improving functional outcomes[4,61].

### Rehabilitative approach for adolescents and adults

After school age, long-term negative health consequences of inactivity could increase the risk of musculoskeletal complications such as scoliosis[86], osteoporosis, fracture, and arthritis[69], as well as systemic metabolic diseases such as sarcopenia, obesity[75], and cardiovascular disease[62]. Considering the influence of adolescent lifestyle on adult health status, the importance of interventions for adolescents cannot be overemphasized[17]. Nevertheless, across all ages and levels of motor function, young people with neuromotor impairments participated in 13–53% less habitual physical activity than able-bodied persons[21]. Therefore, it is important to encourage physical activity through a multidisciplinary and integrated approach involving medical rehabilitation as well as social and family support[18,82].

Complication management is also needed. Patients with neuromotor disorders are very vulnerable to musculoskeletal chronic pain, which could adversely influence life satisfaction[27]. Therefore, alleviating chronic pain is critical, and treatment for chronic pain includes pharmacological interventions such as conventional pain-modulating medication as well as new medications such as nerve growth factor and calcitonin gene-related peptide[14]. However, the most important factor for alleviating pain is the maintenance of a light level of physical activity, which is an efficient pain coping strategy, and perseverance in participation[81].

## NECESSITY OF A REGISTRY SYSTEM FOR HIGH-RISK BABIES DIAGNOSED WITH IVH

In South Korea, there have been some retrospective cross-sectional studies on the incidence, prevalence, and various characteristics of preterm children with IVH[3,105]. Only a few studies have analyzed the outcomes of high-risk infants. However, they retrospectively analyzed the payment data of the Korean National Health Insurance, which was not collected for academic study[23]. The Korean Neonatal Network[54], which is a web-based registry of very low birth weight infants formed through voluntary participation of hospitals nationwide from 2013 to 2016, has reported useful data to help improve the outcomes of premature infants and their health. However, we do not have a prospective registry system for children with IVH or CP which is a major neuromotor complication in preterm children with IVH. A few Western countries only have their own CP registry systems : The Cerebral Palsy Research Registry in the USA, the Surveillance of Cerebral Palsy in Europe, and the Australian Cerebral Palsy Register. These registry systems have provided informative data to build clinical practice guidelines and public healthcare policies to improve the health status of children with CP. However, there is no registry system for children with IVH. If we have our own registry system encompassing IVH and CP, it could be a cornerstone not only for the care of Korean children but also for East Asian children with IVH and/or CP.

## CONCLUSION

IVH is a major complication of prematurity and can induce poor long-term developmental outcomes, including gross motor dysfunction, language and cognitive impairments, and psychiatric problems, especially in children with brain parenchymal injuries. Lifelong management is needed, which ranges from early detection and intervention to long-term care.

## AUTHORS' DECLARATION

### Conflicts of interest

No potential conflict of interest relevant to this article was reported.

### Informed consent

This type of study does not require informed consent.

### Author contributions

Conceptualization : JH, DR; Data curation : JH; Formal analysis : JH, DR; Methodology : JH, DR; Project administration : JH; Visualization : JH; Writing - original draft : JH; Writing - review & editing : DR

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None

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