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Original Article

The Neurological Outcome of Isolated PVL and Severe IVH in Preterm Infants: Is It Fair to Compare?

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ABSTRACT

OBJECTIVE: We compared the neurological outcome of isolated periventricular leukomalacia and severe intraventricular hemorrhage in a cohort of very low birth weight infants born and managed at single tertiary-care center in Saudi Arabia. **METHODS:** We undertook a descriptive retrospective chart review of the neurological status of very low birth weight infants who were born and managed over a 5-year period at King Abdulaziz Medical City, Riyadh. The neurological outcome of neonates with isolated periventricular leukomalacia and severe intraventricular hemorrhage (grades III and IV) was studied and compared in relation to developmental delay and cerebral palsy. **RESULTS:** A total of 20 patients with isolated periventricular leukomalacia and 26 with severe intraventricular hemorrhage (grades III and IV) were identified for this study. Of 20 patients with isolated periventricular leukomalacia, 9 (45%) had good developmental outcome and 11 (55%) had bad developmental outcome. Of 26 patients of severe intraventricular hemorrhage, 14 (54%) had good developmental outcome and 12 (46%) had bad developmental outcome ($P = 0.55$). Significant motor neurological deficit affecting function is distributed as follows: 11/20 (55%) in the isolated periventricular leukomalacia group and 7/26 (27%) in the severe intraventricular hemorrhage group ($P = 0.05$). Cerebral palsy was diplegic in 7/11 (64%) and quadriplegic in 4/11 (36%) in the isolated periventricular leukomalacia group, and hemiplegic 3/7 (43%), diplegic in 1/7 (14%), and quadriplegic in 3/7 (43%) in the severe intraventricular hemorrhage group ($P = 0.03$). Distribution of the neurological outcome according to periventricular leukomalacia grade was as follows: for periventricular leukomalacia grade I (n = 8), 6/8 (75%) had good neurological outcome and 2/8 (25%) had bad neurological outcome. In periventricular leukomalacia grade II (n = 4), good neurological outcome was seen in three patients (75%) and bad neurological outcome was seen in one patient (25%). All patients (n = 8) with periventricular leukomalacia grade III had bad outcome ($P < 0.01$). **CONCLUSION:** About half of patients with isolated periventricular leukomalacia and severe intraventricular hemorrhage had a poor developmental outcome. However, the severity of cerebral palsy was greater in the isolated periventricular leukomalacia patients and correlates highly with periventricular leukomalacia grade. Symmetrical diplegic cerebral palsy is the most common motor deficit associated with isolated periventricular leukomalacia, whereas asymmetrical hemiplegic cerebral palsy is seen exclusively with severe intraventricular hemorrhage.

Keywords: isolated PVL, severe IVH, outcome, cerebral palsy

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Introduction

Over the past three decades, there have been striking improvements in the survival rates of very low birth weight infants. Serious long-term neurological complications, however, including motor deficiency in the form of cerebral palsy[1] (CP) and developmental delay in the form of cognitive and learning disabilities,[2] remain an ongoing problem. The leading causes of such chronic neurological complications in preterm newborn infants are periventricular leukomalacia (PVL) and severe intraventricular hemorrhage (sIVH).[3,4] Both sIVH and PVL share some risk factors, predominantly prematurity, because this tends to occur more frequently in extremely premature infants and becomes

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less common as gestation age increases.[5] Fluctuation of blood pressure and impaired cerebrovascular autoregulation can predispose the immature brain to bleeding in IVH[6] and ischemic injury in PVL.[7] Also, infection and inflammation may contribute to periventricular white matter damage in PVL through the excess of cytokines that activate the astrocytes in the periventricular white matter, resulting in insult to the immature oligodendorcytes.[8] Similarly, infection and inflammation increase the risk of IVH in premature infants.[9] The presentation of sIVH is usually acute and obvious during the neonatal period in the form of apnea, seizures, and encephalopathy. However, the presentation of PVL in neonates is usually silent in the neonatal period; neuroimaging investigations are necessary for its diagnosis. The usual presentation is developmental delay and motor deficit observed beyond the neonatal period—more frequently in the second half of the first year of life or even later. Early diagnosis of PVL is vital for parental counseling and initiating appropriate early interventions. PVL can be reliably diagnosed by sequential bedside cranial ultrasonography, and by brain magnetic resonance imaging (MRI).[10] However, there are limitations to the timing of neuroimaging use in classification of PVL with evidence of disappearance of cystic changes when neuroimaging is done early or late in the perinatal period.[11] Previous studies discussed the outcome of PVL[12-14] or IVH[15-17] in isolation. The two types of brain injury have some similarities. Bilateral periventricular white matter damage can be isolated as in PVL or associated with IVH.[18] Diplegic and quadriplegic CP are seen in babies affected with either pathology,[19-24] although there is a greater prominence of hemiplegic CP in grade IV IVH because of hemorrhagic infarction in the side affected.[19] Association of PVL and significant IVH was reported,[25,26] but cystic PVL was not associated with minor IVH.[26] Previous studies have reported the neurological outcomes of cohorts with either PVL or IVH. Often, these studies did not discriminate isolated from secondary PVL.[20,27] In our report, we aim to compare the neurological outcome of isolated PVL (iPVL) and sIVH in two separate cohorts of patients presenting to a single center in Saudi Arabia.

Methods

We reviewed medical records of all preterm infants with gestational ages from 23 to 32 weeks with birth weights between 501 and 1500 g born at King Abdulaziz Medical City, Riyadh—a tertiary-care medical institute that provides health care to the Saudi National Guard members and their families—and cared for at its neonatal intensive care unit between January 1, 2004, and December 31, 2008. As with our previous study,[28] this patient group included all preterm neonates with iPVL defined as periventricular leukomalacia not associated with significant intraventricular hemorrhage or periventricular hemorrhagic infarction and severe IVH (grades III and IV) documented with at least two imaging modalities. One of these modalities was cranial ultrasound; the other was either cranial computed tomography scan or brain MRI as indicated. According to the standards of our neonatal unit, all very low birth weight infants would undergo at least three cranial ultrasound studies: one during the first week of age, a second study 2 weeks later, and a third study around age 5-6 weeks or at discharge, whichever occurred first. Additional cranial ultrasound studies would have been performed as clinically indicated. The severity of PVL was assessed according to the classification described by de Vries et al.[29]: PVL grade I, periventricular areas of increased echogenicity present for 7 days or more; grade II, periventricular areas of increased echogenicity evolving into small localized frontoparietal cysts; grade III, periventricular areas of increased echogenicity evolving into extensive periventricular cystic lesions involving the occipital and frontoparietal white matter; and grade IV, areas of increased echogenicity in the deep white matter evolving into extensive subcortical cysts (Fig 1 shows example patients).

The severity of IVH was assessed according to the classification described by Papile[30]: grade III IVH, blood filling the ventricular system more than 50% associated with acute dilatation of the ventricular system; and grade IV IVH, parenchymal hemorrhage, associated with an ipsilateral IVH (see Table 4 for comparison with other studies' type and timing of neuroimaging and timing of follow-up).

Exclusion criteria for the study comprised infants born outside the institution, inadequate brain imaging studies, craniofacial dysmorphism, central nervous system congenital anomalies, infants with subadequate neurological follow up, hypoxic-ischemic encephalopathy, and complex congenital heart disease.

Clinical neurological evaluation and developmental assessment were undertaken on all patients presented to our clinics with abnormal neuroimaging with either iPVL or sIVH. Patients with minimum corrected age of 1 year at follow-up were included in the analysis. Clinical neurological evaluation was performed by a pediatric neurologist and included both developmental assessment and a neurological examination. Development was assessed using the Denver Developmental Screening Test and clinical evaluation and was classified as either normal or delayed. When developmental delay was identified, it was classified as either mild, moderate, or severe for patients whose development was considered $\geq$66%, 33%-66%, or $\leq$33% of their chronological ages, respectively. The developmental outcome was considered good if the patient showed normal or mildly delayed development. The developmental outcome was considered bad if the patient showed moderate to severe developmental delay.

The neurological examination assessed head size, cognitive function for age, speech and language, cranial nerve function, motor function, and sensory systems. The results of the examination were considered either normal or abnormal. Abnormality, when present, was identified in the following categories: CP, sensory deficit including vision and hearing, oculomotor anomalies, microcephaly/macrocephaly, speech and language defect, and cognitive and social deficiency. CP was identified if the motor examination showed motor abnormality. This was classified, according to the deficit, as diplegic, hemiplegic, quadriplegic, ataxic, or dyskinetic.

Statistical analysis was performed for both continuous and categorical variables of the group of patients with iPVL and sIVH. Data were entered and analyzed using SPSS for Windows, version 16.0 (Chicago, SPSS Inc). The chi-square, Fisher's exact, and Student t tests were used where appropriate. In all statistical tests, a two-tailed $P < 0.05$ was considered statistically significant.

Results

A total of 776 very low birth weight infants were delivered during the study period. Infants who survived until follow-up at minimum 12 months' corrected age were studied for iPVL and sIVH (grades III and IV). A flow diagram of the population of very low birth weight infants involved in the study is presented in Fig 2. Twenty patients with iPVL and 26 with sIVH were identified. Median ages were 24 months (interquartile range = 19-47) in the iPVL group and 34 months (interquartile range = 24-66) in the sIVH group ($P = 0.08$). The age ranges were 1 year to 7 years, 1 month, in the iPVL group and 1 year, 2 months, to 10 years, 5 months, in the sIVH group. The median gestational age was 28 weeks (interquartile range = 26-29.5) for the iPVL group and 27 weeks (interquartile range = 25.75-28) ($P = 0.28$) for the sIVH group. Female gender was seen in 50% and 42% of the two groups, respectively ($P = 0.60$).