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Infants at very high risk of cerebral palsy

Hielkema, Tjitske

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MOTOR AND COGNITIVE OUTCOME AFTER SPECIFIC EARLY LESIONS OF THE BRAIN - A SYSTEMATIC REVIEW

T. Hielkema
M. Hadders-Algra

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ABSTRACT

The aim of this systematic review was to study motor and cognitive outcome in infants with severe early brain lesions and to evaluate effects of side of the lesion, sex, and social economic status on outcome. A literature search was performed using the databases Pubmed and Embase. Included studies involved infants with either cystic periventricular leukomalacia (cPVL), preterm, or term stroke (i.e. parenchymal lesion of the brain). Outcome was expressed as cerebral palsy (CP) and intellectual disability (mental retardation). Median prevalence rates of CP after cPVL, preterm, and term stroke were 86%, 71%, and 29% respectively; of intellectual disability 50%, 27%, and 33%. Most infants with cPVL developed bilateral CP, those with term stroke unilateral CP, whereas after preterm stroke bilateral and unilateral CP occurred equally often. Information on the effects of sex and social economic status on outcome after specific brain lesions was very limited. Our findings show that the risk for CP is high after cPVL, moderate after preterm stroke, and lowest after term stroke. The risk for intellectual disability after an early brain lesion is lower than that for CP. Predicting outcome at individual level remains difficult; new imaging techniques may improve predicting developmental trajectories.

WHAT THIS PAPER ADDS

- Severe brain lesions in preterm infants are associated with a high risk for cerebral palsy (median prevalence >70%); the risk is highest in infants with cystic periventricular leukomalacia (median prevalence 86%).
- About 30% of infants with term stroke is diagnosed with cerebral palsy.
- An early lesion of the brain is in 27-50% (median prevalence) of infants associated with intellectual disability.

It is well established that infants with a prenatal, perinatal, or neonatal lesion of the brain are at risk for neurodevelopmental disorders. In general, infants with the most extensive lesions are at highest risk for neuromotor disabilities, such as CP, and cognitive impairments.¹ However, some infants with an extensive brain lesion develop quite well, whereas some infants in whom brain imaging showed the presence of only a relatively small or no lesion may develop severe neurodevelopmental problems.² Little is known on the neurodevelopmental sequelae of specific brain lesions. In addition, it has not been systematically studied whether an early lesion of the brain affects the motor and cognitive domains similarly. Neither is it clear whether the child's sex and social class affect the developmental sequelae of a lesion. In general, male sex and low social class are associated with a higher risk of adverse outcome,²⁻⁴ but whether these factors modify the developmental effect of a lesion of the brain is uncertain.

The aim of this systematic review is to assess developmental outcome in infants with the following specific lesions of the brain: cystic periventricular leukomalacia (cPVL) and neonatal stroke. For the latter lesion, we differentiated between lesions occurring at preterm age and those occurring around term age.⁵ Outcome will be specified as CP, including unilateral and bilateral forms, and as impaired cognitive outcome, expressed as intellectual disability (mental retardation). Specific attention will be paid to a potentially modifying effect of sex, social class, and the side of the lesion.

METHOD

A literature search was performed to identify studies published from 1970 to April 2014. Electronic databases searched were PubMed and Embase. Reference lists in original studies and reviews were examined for appropriate articles. For details of the search string see Table 1.

Inclusion criteria for the studies were: a follow-up at least until the age of 18 months; brain imaging was available (cranial ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI)); outcome expressed in either CP or a developmental or intelligence quotient; peer-reviewed articles with full text published in English, German, or French. Studies were excluded if they dealt with traumatic brain injury or severe congenital disorders, if they were review studies or retrospective imaging studies in children with clinical problems, or if they included fewer than three participants. For studies that described outcome of infants with various types of brain lesion, we studied outcome for each lesion group separately.

For the definition of cPVL we followed de Vries et al.⁶ If a study did not use the classification of de Vries et al, we determined whether the lesions reported resembled grade 2 or higher cPVL according to de Vries et al. Studies were excluded if imaging information was insufficiently detailed for such classification, or if lesions were milder. Haemorrhagic

or ischaemic parenchymal lesions of the brain with a preterm origin will be referred to as 'preterm stroke'; neonatal parenchymal lesions occurring at or within 28 days after term age will be referred to as 'term stroke'. For the definition of stroke we used the American Heart Association/American Stroke Association Expert Consensus Document.⁷ This consensus document is mainly based on adult stroke. Preterm parenchymal lesions usually have a different origin than term or adult stroke. In preterm infants, intracerebral lesions often originate from haemorrhages caused by impaired drainage of the veins in the white matter. For brevity's sake, we labelled both haemorrhagic and ischaemic parenchymal lesions as 'stroke' and differentiated between preterm and term origin. Therefore, both preterm and term parenchymal lesions are described as stroke, notwithstanding their different pathophysiology. Cognitive outcome was classified as intellectual disability if developmental quotient or IQ was under 70.

Table 1: Search string and key words

Brain lesion	AND	Outcome	AND	Study group
leukomalacia OR (periventricular OR parenchymal OR cerebral AND cysts) OR (cerebral OR brain OR cortical OR parenchymal OR periventricular) AND (stroke OR ischemia OR hemorrhage OR bleeding OR infarction OR lesion) OR (sinovenous AND thrombosis) OR (cerebrosinovenous AND thrombosis) OR (intraventricular AND (bleeding OR hemorrhage)		motor AND outcome OR cognition OR (motor AND development) OR (cognitive AND development) OR (cerebral AND palsy)		infant OR neonate OR newborn OR infancy

RESULTS

The literature search resulted in 3818 unique hits (see Figure 1). After screening titles and abstracts, 111 articles were left that reported some aspect of developmental outcome for infants with cPVL and 238 for infants with preterm or term intraparenchymal haemorrhage or infarction. Eventually, 29 articles on cPVL (28 with outcome CP, 11 reported on intellectual disability (mental retardation), 23 articles on preterm stroke (22 with outcome CP, 13 with outcome intellectual disability (mental retardation), and 18 articles on term stroke (15 with outcome of CP; 9 with outcome of intellectual disability (mental retardation) met our inclusion criteria.

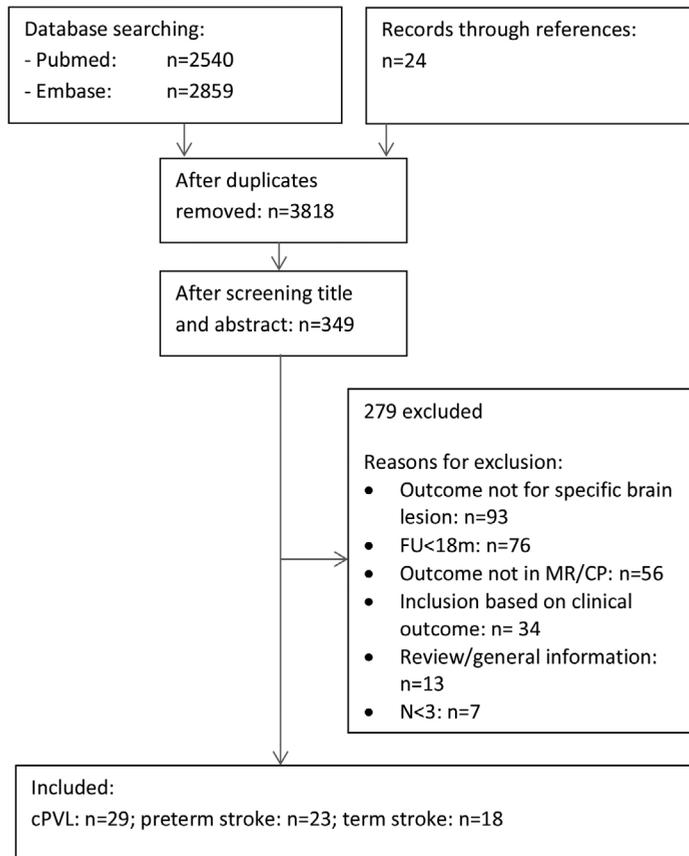


Figure 1: Literature search for outcome

Cystic periventricular leukomalacia

Most of the infants with cPVL developed CP, that is, CP was diagnosed in 474 out of the 607 (78%) infants assessed (median 86%; range in the 28 studies 52–100%; see Fig. 2).^{8–35} In studies that presented the severity of the lesion in terms of the grades of periventricular leukomalacia according to de Vries et al. (n=8), the prevalence of CP was higher in infants with a grade 3 and 4 lesion (95% (110/116) and 78% (7/9) respectively) than in infants with grade 2 periventricular leukomalacia (59% (67/113)). Note that studies on infants with grade 1 periventricular leukomalacia were excluded from the review. Fifteen out of the 28 studies classified CP into unilateral or bilateral forms; 92% of the infants with cPVL who were diagnosed with CP had the bilateral form (232/253). Ten studies (n=266) reported whether cPVL was unilateral (n=65; 24%) or bilateral (n=201; 76%). Of the infants with bilateral cPVL, 81% developed CP (163/201); of those with unilateral cPVL, 42% (27/65) developed CP. Five

studies (n=59; 18 unilateral cPVL, 41 bilateral cPVL) specified whether CP was unilateral or bilateral. Four of the 18 infants with unilateral cPVL developed a unilateral CP (two contralateral, two not specified); seven infants developed a bilateral CP and seven infants did not develop CP. Thirty-nine of the 41 infants with a bilateral cPVL developed a bilateral CP, two did not develop CP.

Eleven studies reported on cognitive outcome (Figure 2);^{8-11,13,14,16,19,21,22,26,27,36} the overall rate of children diagnosed with intellectual disability was 47% (106/224; range of individual studies 25–100%; median 50%). Five studies reported the sex of the infants with cPVL (n=51); 30 (59%) were male. Four studies reported outcome per sex (n=27; 21 males, six females): 20 males and six females developed CP. The search string did not reveal studies that addressed social status in relation to outcome in infants with cPVL.

Preterm stroke

Sixty-two percent (297/479) of infants with preterm stroke was diagnosed with CP (median 71%; range 25–100%; see Fig. 2).^{8,16,26,29,37-53} Thirteen studies (n=132) classified CP as unilateral or bilateral; half (66/132=50%) of the infants developed a bilateral CP. Six studies (n=127) described the localization of the lesion in terms of unilateral (106/127=83%) or bilateral distribution (21/127=17%). Five of the latter studies also reported outcome for unilateral (n=87) and bilateral (n=19) lesions separately. Twentyseven of the 87 (31%) infants with a unilateral brain lesion developed a unilateral CP; 28 (32%) developed a bilateral CP and 32 (37%) had no CP. Twelve of the 19 infants with a bilateral brain lesion developed a bilateral CP; three developed a unilateral CP and four had no CP. In three studies (n=22), outcome was described per side of the lesion. Eight infants had a right-sided brain lesion: one developed a unilateral left-sided CP, one a unilateral rightsided CP, and four a bilateral CP; two infants had no CP. Thirteen infants had a left-sided brain lesion, five developed a unilateral right-sided CP, five a bilateral CP, and three had no CP.

Cognitive outcome varied largely (Figure 2);^{8,16,26,37-42,44,46,49,54} 25% (57/231) of the infants developed intellectual disability, with a range from 0% to 100% (median 26.5%). Three studies (n=98) described cognitive outcome for unilateral and bilateral lesions separately. Twenty-nine of the 79 infants with a unilateral lesion had intellectual disability (37%); 17 of the 19 infants with a bilateral lesion had intellectual disability (89%).

Four studies reported the sex of the infants (n=97); 59 infants (61%) were male. Three studies reported outcome per sex (n=12): 7/8 of the male infants developed CP and 4/4 female infants. No studies reported relations between social status and outcome for infants with preterm stroke.

Term stroke

Of the term infants with neonatal stroke, 34% (range 7–83; median 29%) developed CP (102/296; see Fig. 2).^{52,55–68} Eleven studies (n=204) classified CP (n=61) as unilateral (58/61=95%) or bilateral (3/61=5%).

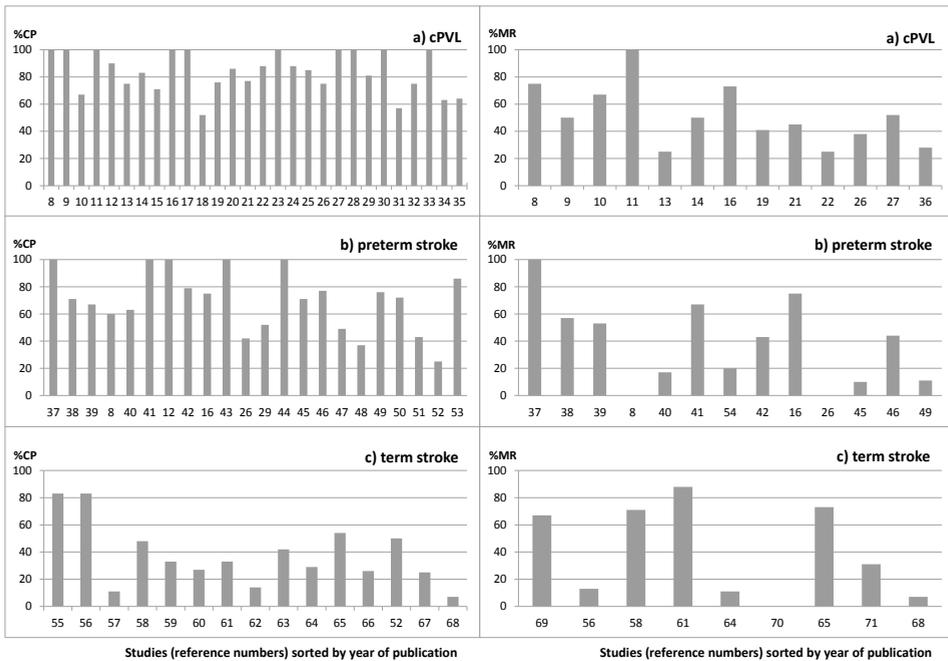


Figure 2: Outcome (percentages CP (Cerebral Palsy) and MR) (Mental Retardation) for infants with a) cPVL, b) preterm stroke and c) term stroke

Fourteen studies described whether brain lesions were unilateral (n=253; 88%) or bilateral (n=36; 12%). The unilateral lesions were more left-sided (n=173; 68%) than right-sided. Seven studies (n=57; n=47 unilateral, n=10 bilateral lesion) described outcome in left-or right-sided CP per side of the lesion. Nine of the 32 infants with a left-sided brain lesion developed a unilateral, right-sided CP; one developed a unilateral left-sided CP; 22 had no CP. Six of the 15 infants with a right-sided brain lesion developed a unilateral, left-sided CP; one developed a bilateral CP; eight had no CP. Thus, children with CP on the basis of a unilateral brain lesion usually had unilateral CP (16/17). Two of the six infants with a bilateral lesion had right-sided CP and four infants had no CP.

Nine studies reported on intellectual disability after term stroke.^{56,58,61,64,65,68–71} The prevalence of intellectual disability was 0% to 88% (median 32.5%). Overall, 61 out of 174 infants (35%) were diagnosed with intellectual disability.

Twelve studies provided information about sex (n=191); 57% of the infants was male. Six studies (n=65) reported motor outcome per sex: 12/42 (29%) males and 13/33 (39%) females developed CP. Another six studies (n=94) described cognitive outcome for males and females; 8/59 (14%) males and 6/35 (17%) females had intellectual disability. One study⁶⁴ (n=26) reported about social class by means of maternal educational level; educational level was not related to outcome.

DISCUSSION

Our systematic review indicated that cPVL is followed by median high rates of CP (86%), preterm stroke with lower rates of CP (71%), and term stroke with the lowest rates (29%). Also highest median rates of intellectual disability were observed in infants with cPVL (50%). About a quarter of the infants with preterm stroke and about one-third of the infants with term stroke developed intellectual disability. It should be noted, however, that fewer studies reported cognitive outcome than motor outcome. This may be due to the difficulty measuring cognitive outcome in children with a severe brain lesion; it is easier to assess whether a child developed CP than to measure the developmental quotient or IQ of a child with severe impairments, as motor and speech impairments may interfere with cognitive testing.

Infants with cPVL are at very high risk for CP, usually a bilateral form; this is especially true for the infants with grades 3 and 4 cPVL.^{25,72,73} The reported prevalence of CP in children with grade 4 cPVL seemed lower than that in children with grade 3 cPVL. This may be a chance finding as the number of infants with cPVL grade 4 was very small (n=9; grade 3: n=116). Alternatively, surviving after grade 4 cPVL may be an indication of 'fitness' and may be associated with relatively better outcome. The risk for intellectual disability after cPVL is substantially less than the risk for CP. However, the absence of intellectual disability does not automatically imply the absence of cognitive impairment. CPVL may result in specific cognitive impairments such as impaired perception attention deficit and impaired social cognition, with or without a reduction in overall IQ.⁷³ Nevertheless, the finding that, in infants with cPVL, intellectual disability occurred less often than CP is interesting, as early intervention in infants at risk for developmental problems has a stronger effect on cognitive than on motor development.⁷⁴ It is conceivable that in infants with cPVL the potential for functional improvement also mainly pertains to the cognitive domain – the domain that predicts later functioning in daily life.^{75,76}

Outcome after perinatal stroke is primarily affected by the age at the insult: the risk for CP after preterm stroke is about twice as high as the one after term stroke. Only a minority of infants with perinatal stroke develop intellectual disability (one out of four infants with preterm stroke; one out of three infants with term stroke). Here, the same caveat as above is valid: the absence of intellectual disability does not preclude the presence of specific

cognitive impairment. The difference in outcome for preterm and term stroke may be attributed especially to the neural substrate of lesion. In our review, preterm stroke denoted preterm parenchymal lesions and periventricular haemorrhagic infarction, caused by impaired drainage of the veins in the white matter. The latter is frequently accompanied by hydrocephalus and periventricular leukomalacia and often results in damage of the periventricular and subplate zone. This zone plays a pivotal role in the development of the cortex.^{5,77} The localization of term stroke in general resembles that of adult stroke, with focal or cortical involvement, usually without involvement of the periventricular zone. It is less often associated with CP. In addition, the sequelae in terms of the type of CP differed for unilateral preterm and term stroke. After preterm stroke half of the children who were diagnosed with CP had a unilateral form, the other half had a bilateral form. After term stroke, children diagnosed with CP in general (94%) had a unilateral form, a minority (6%) a bilateral CP. Conceivably, the higher prevalence of bilateral CP after preterm stroke, results from a different pathophysiology and suggests that preterm stroke often is an expression of a more general encephalopathy, similar to the one associated with cPVL.⁷⁷ If a unilateral lesion resulted in unilateral CP, the contralesional side usually was the most affected side. However, occasionally the ipsilesional side was the most affected side. This was observed both after preterm stroke and term stroke. It should be mentioned that we only included infants with stroke who had imaging before the age of 28 days. Unnoticed stroke during pregnancy and asymptomatic perinatal stroke are common causes of later CP, but are usually not diagnosed in an early stage⁷⁸ and are therefore beyond the scope of our study. The asymptomatic early strokes may have been missed especially in term infants, who – in contrast to preterm infants – do not receive standard neuroimaging.

In preterm infants no differences in the prevalence of right-sided and left-sided lesions were reported. However, in term infants perinatal stroke occurs more often on the left side than on the right side. It has been hypothesized that this difference is due to an asymmetry of the vascularity of the middle cerebral artery and the hemisphere it serves.^{79,80}

Golomb et al.⁸¹ reported that males are more affected by perinatal arterial ischaemic stroke and cerebrosinovenous thrombosis than females. This corresponds to the slight surplus of males in our cases with preterm and term stroke. The few studies that provided information on outcome per sex did not suggest the presence of a clear sex difference. Specification of outcome per social status was virtually absent, with the study of Westmacott⁷⁰ being the exception to the rule. This is disappointing as social economic status is known to have a large impact on development in general, and may be considered as a potential effect modifier of outcome.⁴ In addition, it may be an effect modifier that may be affected by intervention.

One of the strengths of our study is the systematic search and presentation of results. To the best of our knowledge it is the first study that provides an overview of motor and

cognitive outcome of infants with a specific early lesion of the brain, from the 1970s onwards. Followup was at least until the age that CP can be diagnosed, that is, 18 months; however, follow-up at 18 months is relatively short for a good interpretation of cognitive outcome. The relatively low age of 18 months may have caused an underestimation of intellectual disability in our study, particularly since the literature indicates that, especially in very preterm infants, cognitive problems are a major problem.⁸² The time period involved in our review is long, extending over almost 40 years. During that period, neonatal care improved substantially,⁸³ which might have affected the outcome after an early lesion of the brain. However, Figure 2 does not suggest the presence of a time trend. This may reflect that better neonatal care not only improved developmental outcome, but also resulted in higher survival rates of infants with lower gestational age and birthweight, well known risk factors for developmental disorders.⁸⁴ Another consequence of the long study period is that brain lesions were diagnosed with a variety of imaging techniques (ultrasound, CT, conventional MRI), resulting in heterogeneity in diagnostics – a limitation of our study. It is conceivable that during the next decade, the application of novel imaging techniques will assist in the prediction of outcome of specific lesions. In fact, first steps have been taken already; for example, lesions of the posterior limb of the internal capsule, shown on MRI, are a relatively good predictor of adverse outcome.⁸⁵ Another limitation of our study is a possible overlap between study populations, for example, this may be the case for the studies from the Hammersmith Hospital^{8,32,60,62,64} and those of de Vries et al.^{9,16,19,24,26,29,34,35,47,63,68} If overlap was clear, we excluded one of the overlapping studies, that is, the one that provided least details.

The focus on infants with severe brain lesions is another limitation; it often resulted in small numbers per study, which were often small subgroups of larger studies. Background characteristics, such as social economic status and sex, were generally described for the larger study group, but not for the subgroups of infants with a specific lesion of the brain.

In conclusion, infants with cPVL have a high risk for CP, infants with preterm stroke a moderate risk, and those with term stroke the lowest risk. The risk for intellectual disability after an early lesion of the brain is less than that for CP. Novel imaging techniques in combination with improved knowledge about the developmental trajectories of infants with an early lesion of the brain may help to predict and interpret outcome. A better predicting of outcome is an essential tool in family counselling and the planning of intervention. Therefore, we suggest that future research addresses the significance of novel imaging and developmental trajectories in infants with an early lesion of the brain in order to improve prediction of outcome in individual infants.

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