

School-age outcomes following intraventricular haemorrhage in infants born extremely preterm

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ABSTRACT

Objective To determine the associations of different grades of intraventricular haemorrhage (IVH), particularly grades 1 and 2, with neurodevelopmental outcomes at 8 years of age in children born extremely preterm.

Design Population-based cohort study.

Setting State of Victoria, Australia.

Patients Survivors born at <28 weeks' gestational age (n=546) and matched term-born controls (n=679) from three distinct eras, namely, those born in 1991–1992, 1997 and 2005.

Exposure Worst grade of IVH detected on serial neonatal cranial ultrasound.

Outcome measures Intellectual ability, executive function, academic skills, cerebral palsy and motor function at 8 years.

Results There was a trend for increased motor dysfunction with increasing severity of all grades of IVH, from 24% with no IVH, rising to 92% with grade 4 IVH. Children with grade 1 or 2 IVH were at higher risk of developing cerebral palsy than those without IVH (OR 2.24, 95% CI 1.21 to 4.16). Increased rates of impairment in intellectual ability and academic skills were observed with higher grades of IVH, but not for grade 1 and 2 IVH. Parent-rated executive functioning was not related to IVH.

Conclusion While low-grade IVH is generally considered benign, it was associated with higher rates of cerebral palsy in school-aged children born EP, but not with intellectual ability, executive function, academic skills or overall motor function. Higher grades of IVH were associated with higher rates and risks of impairment in motor function, intellectual ability and some academic skills, but not parental ratings of executive function.

INTRODUCTION

Children born extremely preterm (EP; <28 weeks of gestational age (GA)) are at risk of intraventricular haemorrhage (IVH). In recent years, there has been a decrease in the incidence of IVH; in one large study from 24% in 1995 to 21% in 2012.¹ However, since IVH continues to affect many EP infants it is important to understand its long-term effects.²

Grade 3 or 4 IVH reflects more severe pathology and is associated with subsequent neurodevelopmental impairments.^{3,4} The long-term neurodevelopment of infants with grade 1 or 2 IVH is less clear, with conflicting results reported to date.^{5–9} Moreover, most studies have only associated IVH with early outcomes in the first few years of life, an age when it is not possible to measure outcomes such as executive functioning (EF) or academic skills, which emerge across childhood.¹⁰

What is already known on this topic?

- Children born extremely preterm (EP) are at risk for developing intraventricular haemorrhage (IVH) and adverse neurodevelopmental outcomes.
- Grade 3 and 4 IVH is associated with impaired neurodevelopmental follow-up in children born EP.
- The long-term impact of lower grades of IVH is unclear as few studies with school-age follow-up have been conducted.

What this study adds?

- Lower grades of IVH are associated with higher rates of cerebral palsy at school-age, but not with intellectual, academic or executive functioning.
- Further insight on the association of higher grades of IVH and impaired neurodevelopment at school-age including impaired academic skills.
- Parent-rated executive functioning in daily life is not affected by any degree of IVH.

Glial and neuronal cells arise from the germinal matrix during development. In preterm infants, the germinal matrix undergoes changes after birth involving reduction in size and migration of glial and neuronal cells. Additionally, several studies showed white matter abnormalities on MRI in infants born EP with lower grade IVH.^{11–13} It is therefore hypothesised that even lower grades of IVH might affect the maturation of the brain and thereby result in later neurodevelopmental impairment.^{4,8}

Several studies into school-age have reported minimal influence of IVH grade 1 and 2 on neurodevelopmental outcomes.^{5,6} However, other studies up to 5.5 years of age have found significant associations of IVH grade 1 and 2 with cerebral palsy (CP) and neurosensory outcomes.^{7,8} Given the prevalence of low-grade IVH and the uncertainty of its long-term consequences, more research with large sample sizes assessing outcomes beyond early childhood is needed.

The aim of this study was to determine the associations of different grades of IVH with neurodevelopmental outcome at 8 years in EP survivors, particularly of grades 1 and 2.² It was hypothesised that grades 3 and 4 IVH would be related to impaired



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Table 1 Perinatal and sociodemographic characteristics of the EP children assessed at 8 years of age

	No IVH n=331 (66%)	Grade of IVH*				P value†
		1 n=80 (16%)	2 n=53 (11%)	3 n=23 (5%)	4 n=12 (2%)	
<i>Perinatal variables</i>						
Antenatal corticosteroids	279 (84%)	60 (75%)	39 (74%)	14 (61%)	8 (67%)	0.001
Multiple birth	105 (32%)	18 (22%)	7 (13%)	0 (0%)	3 (25%)	<0.001
GA at birth, weeks, mean (SD)	25.8 (1.1)	25.7 (1.2)	25.5 (1.2)	25.7 (1.2)	25.5 (1.4)	0.20‡
Birth weight, g, mean (SD)	865 (182)	848 (192)	848 (169)	899 (190)	853 (150)	0.76‡
Male	164 (50%)	39 (49%)	26 (49%)	16 (70%)	10 (83%)	0.032
Surfactant	221 (67%)	53 (66%)	37 (70%)	17 (74%)	7 (58%)	0.80
Indomethacin for PDA	159 (48%)	47 (59%)	31 (58%)	10 (43%)	9 (75%)	0.08
Postnatal corticosteroids	105 (32%)	38 (48%)	23 (43%)	9 (39%)	7 (58%)	0.09
Bronchopulmonary dysplasia	146 (44%)	48 (60%)	27 (51%)	12 (52%)	9 (75%)	0.016
NEC	26 (8%)	4 (5%)	3 (6%)	3 (13%)	3 (25%)	0.23
Cystic PVL	11 (3%)	5 (6%)	2 (4%)	3 (13%)	3 (25%)	0.001
Surgery in newborn period	93 (28%)	23 (29%)	17 (32%)	9 (39%)	7 (58%)	0.037
<i>Sociodemographic variables</i>						
Mothers age at birth, years, mean (SD)	29.7 (5.7)	29.9 (5.6)	29.6 (6.1)	29.0 (7.3)	26.9 (5.1)	0.53‡
Lower social class at 8 years	104/320 (32%)	23/78 (29%)	14/51 (27%)	11 (48%)	7 (58%)	0.17
Lower maternal education	155/329 (47%)	38/78 (49%)	28/52 (54%)	15/22 (68%)	6/11 (55%)	0.08

Data are n (%), unless otherwise specified.

*According to Papile.³

†From χ^2 trend unless otherwise stated.

‡From one-way ANOVA.

ANOVA, analysis of variance; EP, extremely preterm; GA, gestational age; IVH, intraventricular haemorrhage; NEC, necrotising enterocolitis; PDA, patent ductus arteriosus; PVL, periventricular leukomalacia.

neurodevelopment in all domains, and that grades 1 and 2 IVH would be associated with impaired motor outcomes and milder impairments in intellectual, academic and executive function.

Materials and methods

Participants comprised three cohorts of children born EP in the state of Victoria in 1991–1992, 1997 and 2005. All survivors were admitted to one of the four tertiary neonatal units in the state. Term-born controls were matched with the EP survivors for the expected date of delivery, child sex, mother's health insurance status (private or public) and country of birth (primarily English speaking or not). Expected due date was based on obstetric ultrasound prior to 20 weeks' gestation and was available for >90% of the cohort, otherwise menstrual history was used. Together the EP cohorts comprised 546 survivors over the three eras.¹⁴

Perinatal data, outlined in table 1, were collected during the newborn period. Cranial ultrasounds of EP infants were performed at least once during the first week of life, at 28 days and prior to discharge from the tertiary level nursery, as part of standard clinical care. IVH was graded according to Papile, with the worst grade of IVH (1 to 4) on either side recorded.³ Additionally, the presence of cystic periventricular leukomalacia (PVL) was recorded.

Children were assessed at 8 years of age, corrected for prematurity to avoid a known bias in cognitive test scores.¹⁵ Social variables were collected, including lower social class (unskilled occupation of the main income earner in the family, or unemployed) and lower maternal education (<12 years of education for the 1991–1992 and 1997 cohorts and \leq 12 years of education for the 2005 cohort). Intellectual, executive, academic and motor outcomes were assessed by psychologists and paediatricians blinded to perinatal details and group status. Cognitive ability was assessed using the Wechsler Intelligence Scale for Children (WISC)—Third Edition (1991–1992 cohort), WISC—Fourth Edition (1997 cohort) and the Differential Ability Scales—Second Edition (2005 cohort). Academic achievement was evaluated using the Wide Range

Achievement Test: version 3 (1991–1992 and 1997 cohorts) or version 4 (2005 cohort). IQ and academic performance z-scores were generated by standardising scores against the mean values of the respective term-born control groups, adjusted for social variables.¹⁴ Impaired intellectual ability was defined as a z-score <−2. Impaired academic skills were defined as any z-score (reading, spelling and/or arithmetic) <−2. To assess EF in everyday life, the parent-completed Behaviour Rating Inventory of Executive Functioning was administered,¹⁶ with impaired EF defined as a standard score \geq 65 on the Global Executive Composite, Behavioural Regulation Index or the Metacognition Index.

To assess motor skills, the Movement Assessment Battery for Children (MABC) first edition (1991–1992 and 1997 cohorts) or second edition (2005 cohort) was used. CP was diagnosed in children with loss of motor function along with abnormal tone and tendon reflexes, with severity determined by a functional classification (1991–1992 cohort) or the Gross Motor Function Classification System (1997 and 2005 cohorts).¹⁷ Motor dysfunction was defined as CP or MABC first edition <5th percentile or MABC second edition \leq 5th percentile.

Data on survival rates, intellectual ability, academic performance, motor function and executive function from these cohorts have been reported previously, but not in relation to grades of IVH.^{16 18 19}

Data were analysed using IBM SPSS Statistics 22 and STATA/IC 15.1. The associations between different grades of IVH and dichotomous variables, such as rates of impairment at 8 years of age, were assessed using χ^2 tests for trend, and between grades of IVH and continuous variables by analysis of variance. Data were then analysed by logistic regression, using generalised estimating equations to account for lack of independence in multiples within the same family. ORs for impairment were computed for IVH grades 1–2 and IVH grades 3–4, compared with the no IVH group as baseline. We added an interaction term between grade of IVH and era to the regression models to assess if any relationships between IVH and

outcomes differed across eras. We did not consider imputation for missing data at 8 years was necessary because the follow-up rates were high for both cohorts: EP 91.4% and controls 85%.

Ethical approval for the different cohorts was obtained through the various Human Research Ethics Committees at the four neonatal units in the state of Victoria, Australia. Written informed consent was obtained from parents of all controls and for children born EP in 2005. In earlier cohorts, the follow-up of children born EP was considered routine clinical care.

RESULTS

There were 915 EP live births without lethal anomalies over the three eras, 546 (59.7%) of whom survived to the age of 8 years. Of those, 499 (91.4%) were assessed at the age of 8 years. Children lost to follow-up had similar characteristics to those who were assessed at 8 years except for a higher GA at birth (mean difference 0.38 weeks (95% CI 0.01 to 0.75), $p=0.03$) and lower age of the mother at birth (mean difference -1.94 years (95% CI -3.71 to 0.16), $p=0.03$) (online supplementary table 1). Characteristics of the children were similar across IVH subgroups for GA, birth weight, surfactant treatment and all social variables (table 1). There were decreasing trends with worsening grade of IVH for multiple birth and antenatal corticosteroid treatment, and increasing trends for male sex, receiving surgery, postnatal corticosteroids, bronchopulmonary dysplasia and cystic PVL. More than 50% of all infants were treated with indomethacin for a symptomatic patent ductus arteriosus, but there was little evidence for a trend in indomethacin rates across the IVH subgroups. Ten infants with either grade 3 or 4 IVH developed posthaemorrhagic ventriculomegaly and required surgery for ventricular drainage.

Intellectual ability and EF

There was weak evidence for more intellectual impairment with increasing severity of IVH (table 2). The increase was most in those with IVH grades 3 and 4 (table 3). Children with IVH showed no increased risk in impaired EF, whether the comparisons were

Table 3 Risks of abnormal outcomes in categories of IVH relative to no IVH

	IVH 1 or 2		IVH 3 or 4	
	OR (95% CI)	P value	OR (95% CI)	P value
IQ score <-2 SD	0.78 (0.41 to 1.48)	0.45	2.68 (1.21 to 5.94)	0.01
EF GEC ≥ 65	1.06 (0.60 to 1.87)	0.84	1.17 (0.46 to 2.97)	0.75
EF BRI ≥ 65	1.12 (0.64 to 1.95)	0.69	1.76 (0.75 to 4.11)	0.20
EF MI ≥ 65	1.66 (0.98 to 2.82)	0.06	1.73 (0.74 to 4.06)	0.21
Any academic skill <-2 SD	0.70 (0.39 to 1.27)	0.24	2.91 (1.35 to 6.27)	0.006
Reading <-2 SD	0.85 (0.44 to 1.66)	1.64	3.62 (1.59 to 8.24)	0.002
Spelling <-2 SD	0.46 (0.16 to 1.29)	0.14	4.48 (1.80 to 11.2)	0.001
Arithmetic <-2 SD	0.61 (0.30 to 1.27)	0.19	2.79 (1.20 to 6.48)	0.017
Motor dysfunction	1.45 (0.93 to 2.26)	0.11	4.45 (2.18 to 9.08)	<0.001
Cerebral palsy	2.24 (1.21 to 4.16)	0.011	8.80 (4.03 to 19.2)	<0.001
M-ABC	1.38 (0.87 to 2.19)	0.17	4.70 (2.21 to 9.97)	<0.001

BRI, Behavioural Regulation Index; EF, executive functioning; GEC, Global Executive Composite; IVH, intraventricular haemorrhage; MABC, Movement Assessment Battery for Children; MI, Metacognition Index.

across all grades of IVH (table 2) or grouped into grades 1–2 and 3–4 (table 3).

Academic skills

There was strong evidence for increasing trends in impaired academic skills, particularly for reading and spelling, with increasing grade of IVH. Compared with those with no IVH,

Table 2 Impaired cognitive and executive performance related to the grade of IVH

Outcome	No IVH n=331	Grade of IVH*				P value†
		1 n=80	2 n=53	3 n=23	4 n=12	
Impaired intellectual ability						
IQ score <-2 SD	41 (12%)	9 (11%)	4 (8%)	5 (22%)	5 (42%)	0.08
Impaired executive functioning						
GEC ≥ 65	49/309 (16%)	13/73 (18%)	7/46 (15%)	4/22 (18%)	2/11 (18%)	0.78
BRI ≥ 65	46/310 (15%)	12/73 (16%)	8/46 (17%)	6/22 (27%)	2/11 (18%)	0.21
MI ≥ 65	48/309 (16%)	19/73 (26%)	9/46 (20%)	5/22 (23%)	3/11 (27%)	0.10
Impaired academic skills						
Any academic skill <-2 SD	50/311 (16%)	7/75 (9%)	8/52 (15%)	5/21 (24%)	7/11 (64%)	<0.001
Reading <-2 SD	32/313 (10%)	5/75 (7%)	6/52 (12%)	4/21 (19%)	6/11 (55%)	0.002
Spelling <-2 SD	21/312 (7%)	3/75 (4%)	1/51 (2%)	3/21 (14%)	5/11 (45%)	0.011
Arithmetic <-2 SD	38/309 (12%)	5/74 (1%)	5/52 (10%)	4/21 (19%)	5/11 (45%)	0.09
Motor dysfunction						
Any motor dysfunction‡	81 (24%)	22 (28%)	20/52 (38%)	10 (43%)	11 (92%)	<0.001
Cerebral palsy	26/330 (8%)	12/80 (15%)	9/51 (18%)	6/23 (26%)	9 (75%)	<0.001
MABC <5 th percentile§	79/309 (26%)	21/74 (28%)	18/47 (38%)	9/20 (45%)	11 (92%)	<0.001

Data are n (%).

*According to Papile.³

†From χ^2 trend.

‡Either cerebral palsy or MABC <5 th centile.

§MABC ≤ 5 for the 2005 cohort.

BRI, Behavioural Regulation Index; GEC, Global Executive Composite; IVH, intraventricular haemorrhage; MABC, Movement Assessment Battery for Children; MI, Metacognition Index.

however, only those with grade 3 or 4 IVH were at higher risk of impaired academic scores (table 3).

Motor function

There was evidence of an increasing trend of motor dysfunction with increasing severity of IVH (table 2). This trend was contributed to by increasing numbers of children with both CP and low scores on the MABC. There was strong evidence for an increased risk of CP in those with grade 1 or 2 IVH compared with no IVH, with little evidence for low motor scores on the MABC alone (table 3). Those with grades 3 or 4 IVH had an increased risk of developing motor impairment compared with no IVH, with strong evidence for both CP and low scores on the MABC. Of the 62 children with CP, severity was mild in 29, moderate in 18 and severe in 15. There was no evidence that CP was less severe in children with lower grades of IVH than those with more severe IVH (χ^2 trend; $p=0.29$). Of the 12 children who had a grade 4 IVH, 3 were bilateral. Nine of the 12 children with grade 4 IVH developed CP (table 2). The CP was mild in two cases, moderate in four and severe in three.

There was no evidence that relationships between IVH and outcomes differed across eras (all p -values for interaction terms were >0.05). Consistent with the findings when outcomes were dichotomised, continuous z -scores for IQ and academic performance deteriorated with increasing severity of IVH, but there was no substantial change in scores for EF across IVH grades (online supplementary table 2).

DISCUSSION

In our cohort, 27.7% of the infants who survived to the age 8 years and 33.7% of those assessed were diagnosed with IVH. Infants with grade 1 or 2 IVH had a higher risk of having a diagnosis of CP at school-age compared with those without IVH. However, grades 1 and 2 IVH were not associated with impaired intellectual, academic or executive function. Higher grade IVH (3 or 4) was associated with poorer intellectual, academic and motor impairment, but not parent-rated EF compared with no IVH.

There are several other studies, with follow-up beyond 2 years of age, that reported absence of significant differences in intellectual outcomes in those with IVH grade 1 or 2 compared with those without IVH.⁵⁻⁷ However, results have been inconsistent in studies with a follow-up until 2 years of age.^{20 21} Few studies have reported outcomes on academic skills specifically; our current and previous studies show similar findings regarding increased risks of impaired academic outcomes only in those with grade 3 or 4 IVH.⁵

EF includes higher-order cognitive skills supporting goal-directed behaviour and independent problem solving.^{22 23} The absence of associations between the grade of IVH and parent-rated EF in our sample was surprising. Several studies have reported poor EF in children born EP compared with term-born controls,^{16 24-26} but few studies have specifically related EF to the severity of IVH. Vohr *et al* reported that children at 16 years of age with IVH grade 2 had significantly greater odds of low scores on cognitive flexibility, verbal memory and efficient retrieval of phonological information compared with children without IVH and IVH grade 1.²⁷ In the current study, we used parental ratings of behavioural EF rather than direct assessment, which can yield different results. Hence, more extensive research, complementing parental reports with performance-based measurements, is needed. As EF skills continue to develop until early adulthood, assessing EF beyond school-age is essential.

Several other studies have reported associations between IVH grade 1 to 2 and motor impairment.^{7 8 18 26} An Australian study

($n=1472$) reported higher rates of CP at 2 to 3 years in those with grade 1 or 2 IVH (10.4%) compared with those without IVH (6.5%).⁸ Klebermass-Schrehof *et al* reported rates of CP at 5.5 years of age in children born <28 weeks' gestation with IVH grade 1 (34.8%) and IVH grade 2 (55%) compared with 14.3% in children with no IVH.⁷ Additionally, the French EPIPAGE study showed a higher prevalence of CP at 5 years of age in children born <33 weeks' GA with IVH grades 1 (8%) and 2 (11%) compared with those with no IVH (4%).²⁸ However, contrary results have also been reported. An American study of 1472 infants born <27 weeks' GA at 18 to 22 months did not show any differences of CP rates in those with grades 1 and 2 IVH compared with those without IVH.²¹ We have previously reported a trend in CP from no IVH to IVH grade 3,⁵ but the current study in which we added additional cohorts to the first cohort increased the power to find stronger evidence of relationships of lower grade IVH with CP. Grade 3 or 4 IVH was an independent risk factor for developing CP and motor dysfunction in our study, consistent with recent research.⁴ Strengths of our study include the recruitment of three cohorts over distinct time periods from the same geographic region with contemporaneous term-born matched controls. Outcomes were determined at school-age, which are more meaningful for later life functioning than are outcomes assessed only in the first few years of life. Follow-up rates to school-age were high across the cohorts. Neurodevelopment in several important clinical areas was assessed, and paediatricians and psychologists were blinded to group allocation or previous history to avoid any bias in the assessments.

There are, however, several limitations. Our ultrasound protocols did not include cerebellar or mastoid views across all sites and across all eras, and hence we may have missed some important early pathologies. We did not adjust for later pathology, such as cystic PVL, because it may lie along the causal pathway between IVH and adverse outcomes. Redirection of care might influence the ultimate rates of adverse neurodevelopmental outcomes, but we do not have precise data on how often redirection of care followed a diagnosis of major cranial ultrasound abnormality. Outcome measurements were not identical for the cohorts as different versions were used for the cognitive, academic and motor assessments, but we addressed this problem by computing z -scores relative to contemporaneous controls. To assess executive dysfunction, only parental report was used. However, parents' observations are clinically relevant, since performance within the highly structured neuropsychological testing environment does not perfectly reflect problems faced by children in complex everyday settings.²³

CONCLUSIONS

Grades 1 and 2 IVH were associated with a higher risk of CP at 8 years of age. Grades 3 and 4 IVH were associated with poorer intellectual, academic and motor impairment, but not parent-rated EF compared with no IVH. Our study adds to a growing understanding of the negative impact of low-grade IVH on motor development. This emphasises the importance of long-term follow-up and early intervention in children with IVH, as well as parental counselling.

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Contributors NLH conceptualised and designed the study, conducted the initial analyses, drafted the initial manuscript, and reviewed and revised the manuscript; AJS conceptualised and designed the study, contributed to data analyses and critically reviewed the manuscript; GR, ACB and PJA contributed to interpretation of data and critical revisions of the manuscript; LWD and JLYC conceptualised and designed the study, designed the data collection and study protocol, coordinated and supervised data collection, contributed to data analyses and critically reviewed the manuscript.

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