Published in final edited form as:
Pediatr Neurol. 2007 October ; 37(4): 245–249. doi:10.1016/j.pediatrneurol.2007.06.003.

The Association of Cerebral Palsy with Other Disability in Children with Perinatal Arterial Ischemic Stroke

Meredith R. Golomb, MD, MSc[1], **Chandan Saha, PhD**[2], **Bhuwan P. Garg, MBBS**[1], **Faouzi Azzouz, MSc**[2], and **Linda S. Williams, MD**[3,4,5]

1*Division of Pediatric Neurology, Indiana University School of Medicine, Indianapolis, Indiana*

2*Division of Biostatistics, Indiana University School of Medicine, Indianapolis, Indiana*

3*Department of Neurology, Indiana University School of Medicine, Indianapolis, Indiana*

4*Roudebush Veterans' Affairs Medical Center Health Services Research and Development Service, Indianapolis, Indiana*

5*Regenstrief Institute, Indianapolis, Indiana*

Abstract

The association of cerebral palsy with other disability in children with perinatal stroke has not been well-studied. We examined this association in 111 children with perinatal stroke, 67 with neonatal presentation and 44 with delayed presentation. Seventy-six children (68%) had cerebral palsy, which was hemiplegic in 66 and tri- or quadriplegic in 10. Fifty-five (72%) of the children with cerebral palsy had at least one other disability: 45 (59%) had cognitive/speech impairment which was moderate-severe in 20, and 36 (47%) had epilepsy which was moderate-severe in 11. In children with neonatal presentation, cerebral palsy was associated with epilepsy (0.0076) and cognitive impairment (0.0001); these associations could not be tested in children with delayed presentation because almost all children in this group had cerebral palsy. In another analysis with multivariate logistic regression for children with cerebral palsy, children who had both neonatal presentation and a history of cesarean section delivery were more likely to have epilepsy (p=0.001). Children with cerebral palsy after perinatal stroke who had neonatal presentation were more likely to have severe cognitive impairment (OR 7.78; 95% CI 1.80–47.32) or severe epilepsy (OR 6.64; 95% CI 1.21–69.21) than children with delayed presentation. Children with cerebral palsy after perinatal stroke are likely to have additional disability; those with neonatal presentation are more likely to have severe disability. These findings will help pediatricians in planning long-term rehabilitative care.

Introduction

Children with perinatal arterial ischemic stroke are at risk for long-term motor impairment (cerebral palsy), cognitive impairment, and epilepsy. Some children suffer all three impairments, some children experience none of them. The association of cerebral palsy with other impairments in children with perinatal stroke has not been extensively studied.

Corresponding author: Meredith R. Golomb MD, MSc, Indiana University School of Medicine, Building XE 040, 575 West Dr., Indianapolis, IN 46202, Email: mgolomb@iupui.edu Phone: 317-278-5450, Fax: 317-274-3622.

Understanding the association of cerebral palsy with other disabilities in these children will aid physicians and parents in planning long-term rehabilitative therapy.

Methods

Subjects

Children were identified from the Riley Hospital perinatal stroke database. All children in this database had radiographic evidence of an ischemic infarct in an arterial territory occurring during the perinatal period, defined as the period between the 20th week of gestation and the 28th day of life.[1] Children in this database were identified by a combination of neurology clinic record review from September 1989-September 2006, patient referral during this period, and ICD-9 code searches using codes 342, 433–438. and 767 from May 1 1999-May 1 2004. Further ICD-9 searches covering additional years were not performed after we discovered the limitations of these searches; the methodology and rationale behind these searches has been previously described[2]. Inclusion criteria for this study were: 36 weeks or greater gestational age at birth, age of at least 12 months at last neurology clinic visit, presentation with neurological symptoms in the neonatal period with cranial imaging confirming arterial territory ischemic infarction (*"neonatal presentation"*), or presentation with neurological symptoms past the neonatal period with cranial imaging suggesting remote infarct and no events or risk factors past the perinatal period that may have precipitated infarction, and at least 6 months of neurological follow up (*"delayed presentation"; known in previous publications as "presumed perinatal stroke"*[3]). Children with radiographic evidence of generalized hypoxic ischemic injury or dysmorphic features that suggested a genetic syndrome were excluded because hypoxic-ischemic injury and genetic syndromes can cause cerebral palsy in the absence of focal arterial ischemic stroke.

Outcome Definitions

"Cerebral palsy" was defined as any static motor impairment affecting function that could be attributed to cerebral injury. Cerebral palsy was divided into two types: hemiplegia and tri/quadriplegia. Tri- and quadriplegia were grouped together because in our clinical experience, children with triplegia usually have some degree of involvement of all four limbs, but one limb is relatively spared when compared with the other three. None of the children in the database had spastic diplegia, severe generalized hypotonia, or ataxia without focal weakness. Children with mild abnormalities of tone or reflexes that did not interfere with function were defined as *"mild motor abnormalities"*; they were grouped with children who did not have cerebral palsy for the statistical analyses. Cognitive/language impairment was defined as the presence of mental or speech impairment requiring modified classes, or meeting the Indiana State requirements for providing developmental therapy or speech therapy; moderate-severe cognitive/speech impairment was defined as impairment that was likely to prevent the child from ever living fully independently. Epilepsy was defined as the presence of clinical and/or electrographic seizures, with fewer than 6 months seizure-free off medication, or moderate-severe, which was defined as more than one seizure per month while on medication.

Statistical analysis

Proportions were used to describe the clinical features of the population. Epilepsy and cognitive impairment, the primary outcomes of interest, were analyzed in two categories, yes vs. no as well as no/mild vs. moderate to severe. We first assessed the risk factors that might be associated with epilepsy and/or cognitive impairment in children with neonatal presentation of perinatal stroke, comparing children with and without cerebral palsy; this could not be done in children with delayed presentation because almost all children with delayed presentation had cerebral palsy (91%). We then assessed risk factors associated with disability in all children with cerebral palsy after perinatal stroke (both neonatal and delayed presentation). The risk

factors assessed were: gender, maternal preeclampsia, delivery by cesarean section, delivery by emergent cesarean section, bilateral infarction, hemorrhagic infarction, cardiac complications, any involvement of middle cerebral artery territory, and presence of perinatal co-morbidity. For children with neonatal presentation, we considered cerebral palsy (in three categories, no, hemiplegia, tri/quadriplegia) for assessing an association with the primary outcomes. As stated above, no such analysis was performed for children with delayed presentation because almost everyone had cerebral palsy (91%); also, none of the children with delayed presentation had tri- or quadriplegia. In the univariate analysis, contingency tables with Fisher exact statistics were used to detect general association between the primary outcomes and all the other categorical variables. All tests were two-sided using a 5% level of significance.

The overall logistic regression model linked the odds of having epilepsy or cognitive impairment to the covariates. We used exact logistic regression analysis because of small sample size. The standard asymptotic maximum likelihood methods for small samples are not reliable. Covariates as listed previously were included in the multivariate analyses and stepwise method was used to select the significant covariates. Age was always included in the logistic regression model to adjust for age effect on the primary outcomes. We used Cytel (version 6, Cambridge, MA) and SAS (version 9.1, Cary, NC) for all statistical analyses. More detailed cerebral palsy and epilepsy outcomes have been described previously[4–6].

Results

Patient population

The database included 111 children with perinatal arterial ischemic stroke (AIS) who had their last follow-up exam when they were at least 12 months of age. Sixty-seven children presented in the neonatal period, and 44 had delayed presentation. Median age at last follow-up was 56 months (range 12–269). Seventy-six children (68%) had cerebral palsy, 13 (12%) had mild motor abnormalities that did not interfere with function, and 22 (20%) had normal motor exams. Of the 76 children with cerebral palsy, 66 (87%) had hemiplegia and 10 (13%) had tri/quadriplegia. (Table 1)

Radiographic findings

Ninety-three children (84%) had single unilateral strokes in the following territories: anterior cerebral artery (2; 1 left, 1 right), middle cerebral artery (81; 51 left, 30 right), posterior cerebral artery (4; 3 left, 1 right), anterior choroidal (4; 3 left, 1 right), entire internal carotid territory (1) and brainstem (1). Four patients (4%) had multiple unilateral strokes in multiple territories; all included the middle cerebral artery territory. Fourteen children (13%) had bilateral infarctions; 11 of the 14 included the middle cerebral artery territory. All of the children with delayed presentation had unilateral infarctions. Eighteen of the 67 (27%) children with neonatal presentation had hemorrhagic transformation of their infarctions; this could not be assessed in children with delayed presentation because imaging was performed months after the presumed infarction date and MRI sequences necessary for detection of old blood products were not always performed.

Presence of other disability in children with cerebral palsy

Data on cognitive/speech impairment was available for 72 of the 76 children with cerebral palsy; 45 had cognitive or speech impairment (63% of 72) which was moderate-severe in 20 (28%). Epilepsy data was available for all children with cerebral palsy; 36 (50%) had epilepsy and 11 of these had moderate-severe epilepsy (14%). Thirty (42%) of the children with cerebral palsy had both cognitive/speech impairment and epilepsy. (Table 1)

For children with neonatal presentation, cerebral palsy was significantly associated with epilepsy of any type ($p<0.01$), severe epilepsy ($p=0.01$), cognitive impairment of any type ($p<0.001$) and severe cognitive impairment ($p<0.001$) (Table 2). Children with tri/quadriplegic cerebral palsy had the highest risk of having epilepsy or cognitive impairment, followed by the children with hemiplegic cerebral palsy. Children with tri/quadriplegic cerebral palsy after perinatal stroke had 9.2 times higher odds of having epilepsy and 18 times higher odds of having severe epilepsy when compared with children who had perinatal stroke but no cerebral palsy. (Table 3)

The multivariate logistic regression analysis for the children who had cerebral palsy showed a significant interaction effect between cesarean section and presentation type on having epilepsy (any severity) ($p=0.045$). The proportions of children of having epilepsy for four groups: neonatal presentation and cesarean section (n=17), delayed presentation and cesarean section (n=13), neonatal presentation and no cesarean section (n=19), and delayed presentation and no cesarean section (n=27) were 88%, 23%, 42% and 37%, respectively. Children with neonatal presentation and cesarean section had 14.3 times higher odds of having epilepsy than children with delayed presentation and no cesarean section. The other two groups, children with neonatal presentation and no cesarean section, and children with delayed presentation and cesarean section had similar odds when compared with children with delayed presentation and no cesarean section. Presentation type was the only identified risk factor for having severe impairments; among children with cerebral palsy after perinatal stroke, children with neonatal presentation were much more likely than children with delayed presentation to have severe cognitive impairment (OR 7.78; $p=0.0027$) or severe epilepsy (OR 6.64; $p= 0.0240$) (Table 4).

Discussion

Children who have cerebral palsy after perinatal stroke are likely to have additional disabilities, particularly if they presented during the neonatal period. Over 70% of children with cerebral palsy after perinatal stroke have at least one additional disability. Almost 40% of children with cerebral palsy after perinatal stroke have both cognitive/speech disability and epilepsy.

There is a large literature on the association of cerebral palsy with other disability, but in this literature, cerebral palsy is usually subdivided by disability type rather than etiology. Carlsson et al reported epilepsy in 38% of 146 Swedish children with cerebral palsy, and found that epilepsy was more common in children with cognitive disability[7]. Bruck et al looked at 100 children with cerebral palsy with at least 2 years of follow-up data, and found an overall epilepsy rate of 62%, with a rate of 71% in children with hemiplegic cerebral palsy[8]. Zafeiriou et al found an overall epilepsy rate of 36% in 178 consecutive patients with cerebral palsy, with a rate of 42% in patients with hemiplegic cerebral palsy[9]. We did find that in our cohort, children with tri/quadriplegia after perinatal stroke had higher rates of co-disability than children with hemiplegia, probably because children with tri/quadriplegia tend to have more cerebral injury than children with hemiplegia[5].

There have been attempts to determine what factors influence the development of multiple disabilities in children with cerebral palsy. Large areas of cerebral tissue loss on cranial imaging which, by description, are consistent with infarction have been a consistent predictor of multiple impairments. Uvebrant reported disabilities including cognitive impairment and epilepsy in 42% of 169 Swedish children with cerebral palsy, and found that “cortical and subcortical cavities” (possibly infarction) were associated with more severe disabilities[10]. Humphreys et al looked at 41 children with hemiplegic cerebral palsy, and found that arm-dominant cerebral palsy was associated with cognitive impairment, and that cortical involvement (abnormality) on radiographic imaging was associated with both cognitive impairment and epilepsy[11]. We have previously reported that in children with unilateral

middle cerebral artery perinatal stroke, large-branch infarction was predictive of later cerebral palsy[5], but we did not find that large-branch infarction predicted epilepsy in children with neonatal[4] or delayed[6] presentation. We thought that middle cerebral artery infarction might be associated with cognitive/speech impairment in children with cerebral palsy because the left middle cerebral artery supplies language areas, or that bilateral infarcts would raise the risk of both cognitive impairment and epilepsy by striking multiple pathways and limiting plasticity, but we were unable to demonstrate this with our model. We may revisit this when our cohort is larger.

We were somewhat surprised when delivery by cesarean section together with neonatal presentation was associated with childhood epilepsy in children with cerebral palsy. This group included both routine and emergent cesarean sections. It is possible that this group still includes children who were in distress before delivery; we did not have access to birth records on all children. We suspect that neonatal presentation contributed to the risk of later epilepsy because these were sicker children in the neonatal period; almost half of the children with neonatal presentation had respiratory difficulties, 15% had sepsis, and 15% had cardiac abnormalities [5], while none of the children with delayed presentation had these issues.

The fact that children with neonatal presentation were sicker in the neonatal period may also explain why children with cerebral palsy and neonatal presentation were more likely than children with delayed presentation to have severe cognitive impairment or severe epilepsy. Their illnesses in the newborn period may have compounded the initial cerebral injury by compromising cerebral blood flow. Or, it is possible that children with cerebral with perinatal cerebral injury significant enough to cause multiple severe chronic disabilities are more likely to present in the neonatal period, due to seizures, abnormalities in tone, or feeding difficulties.

This study has several limitations. Although we used multiple techniques to locate all possible patients with perinatal stroke, it is possible we missed some patients. We are a tertiary care center, and our data may be biased toward sicker and more disabled patients. This was primarily a retrospective cohort study, and we were unable to locate cognitive outcome data on 4 patients.

In children with perinatal stroke, cerebral palsy is often accompanied by additional disability. Children with neonatal presentation and cerebral palsy are more likely to experience severe cognitive impairment or epilepsy than children with delayed presentation and cerebral palsy. These data will aid pediatric neurologists in counseling families about the outcomes of perinatal stroke and planning long-term care.

Acknowledgement

The authors would like to thank Ms. Nina Talib for technical assistance.

Dr. Golomb is supported by grants from NIH NINDS (K23 NS 048024) and Clarian Values Fund (grant #VFR-171). Dr. Williams is supported by NINDS R01 NS 39571 and Veterans' Administration Stroke QUERI STR 03-168.

References

1. Friel, JP., editor. Dorland's illustrated medical dictionary. 26th ed. W.B. Saunders Company; 1974. p. 1485
2. Golomb MR, Garg BP, Saha C, Williams LS. Accuracy and yield of ICD-9 codes for identifying children with ischemic stroke. Neurology 2006;67:2053–2055. [PubMed: 17159120]
3. Golomb MR, MacGregor DL, Domi T, Armstrong DC, McCrindle BW, Mayank S, deVeber GA. Presumed pre- and perinatal stroke: risk factors and outcomes. Annals of Neurology 2001;50:163–168. [PubMed: 11506398]

4. Golomb MR, Garg BP, Carvalho KS, Williams LS. Perinatal stroke and the risk of epilepsy after 6 months of age. J Peds. In Press

5. Golomb MR, Garg BP, Saha C, Azzouz F, Williams LS. Cerebral palsy after perinatal arterial ischemic stroke. Under Review

6. Fitzgerald KC, Williams LS, Garg BP, Golomb MR. Epilepsy in children with delayed presentation of perinatal stroke. J Child Neuro. In Press

7. Carlsson M, Hagberg G, Olsson I. Clinical and aetiological aspects of epilepsy in children with cerebral palsy. Dev Med Child Neurol 2003;45(6):371–376. [PubMed: 12785437]

8. Bruck I, Antoniuk SA, Spessatto A, Bem RS, Hausberger R, Pacheco CG. Epilepsy in children with cerebral palsy. Arq Neuropsiquiatr 2001;59(1):35–39. [PubMed: 11299428]

9. Zafeiriou DI, Kontopoulos EE, Tsikoulas I. Characteristics and prognosis of epilepsy in children with cerebral palsy. J Child Neurol 1999;14(5):289–294. [PubMed: 10342595]

10. Uvebrant P. Hemiplegic cerebral palsy. Aetiology and outcome. Acta Paediatrica Scandinavica - Supplement 1988;345:1–100. [PubMed: 3201989]

11. Humphreys P, Whiting S, Pham B. Hemiparetic cerebral palsy: clinical pattern and imaging in prediction of outcome. Can J Neurol Sci 2000;27(3):210–219. [PubMed: 10975533]

Table 1

Disability in children with cerebral palsy and perinatal stroke

	No CP N=35	CP N=76	Hemiplegia-neonatal presentation N=26	Hemiplegia-delayed presentation N=40	Tri/Quadriplegia-neonatal presentation N=10
No other disability	17 (49%)	21 (28%)	7 (27%)	14 (39%)*	0 (0%)
Cognitive/speech disability (any)	11 (31%)	45 (59%)	16 (62%)	19 (53%)*	10 (100%)
Moderate-severe cognitive disability	0	20 (26%)	5 (19%)	5 (14%)*	10 (100%)
Epilepsy (any)	11 (31%)	36 (47%)	15 (58%)	13 (33%)	8 (80%)
Moderate-severe epilepsy	1 (3%)	11 (14%)	5 (19%)	2 (5%)	4 (40%)
Cognitive disability (any) and Epilepsy (any)	4 (11%)	30 (39%)	12 (46%)	10 (25%)	8 (80%)
Mod-Sev cognitive disability and mod-sev epilepsy	0	8 (11%)	3 (12%)	1 (3%)	4 (40%)

*Percentages reflect data on 36 delayed presentation children with hemiplegia and both cognitive and epilepsy data; 4 children with delayed presentation of perinatal stroke have missing cognitive data; these children did not have epilepsy but cognitive status is unknown CP= cerebral palsy; mod-sev= moderate-severe

Table 2

Association of CP with other disability in children with neonatal presentation

Risk	No CP N=31	Hemiplegia N=26	Tri/Quadriplegia N=10	Fisher's exact test p-value
Any Epilepsy	9	15	8	.0076
	29.0 %	57.7 %	80.0 %	
Moderate-severe Epilepsy	1	5	4	.0120
	3.2 %	19.2 %	40.0 %	
Any Cognitive Impairment	9	16	10	.0001
	29.0 %	61.5 %	100 %	
Moderate-severe Cognitive Impairment	0	5	10	.0000
	0 %	19.2 %	100 %	

Table 3

Logistic Regression Analysis for Children with Neonatal Presentation (N=67)

	Risk Factors	OR	95% Confidence Interval		P-value
Epilepsy	Hemiplegia	3.26	(0.98	11.57)	0.055
	Tri/Quadriplegia	9.18	(1.45	105.23)	0.013
	Reference: No CP	1.00	_	_	_
Moderate-severe Epilepsy	Hemiplegia	6.92	(0.70	348.82)	0.125
	Tri/Quadriplegia	17.97	(1.47	1016.05)	0.018
	Reference: No CP	1.00	_	_	_

* Exact logistic regression adjusting for age. No logistic regression analysis was performed for any congnitive impairment or moderate to severe impairment outcome since everyone in the tri/quadriplegia group had cognitive impairment.

Table 4

Multivarate logistic regression model- association of variables with other disabilties in children with CP

	Risk Factors	OR	95% Confidence Interval		P-value
Any Epilepsy	Neonatal Presentation and C-section	14.29	(2.40	162.23)	.0010
	Neonatal Presentation and No C-section	1.56	(0.38	6.69)	.6904
	Delayed Presentation and C-section	0.58	(0.08	3.19)	.7413
	Reference: Delayed Presentation and No C-section	1.00	_	_	_
Severe Epilepsy	Neonatal Presentation	6.64	(1.21	69.21)	.0240
	Reference: Delayed Presentation	1.00	_	_	_
Severe Cognitive Impairment	Neonatal Presentation	7.78	(1.80	47.32)	.0027
	Reference: Delayed Presentation	1.00	_	_	_

*Exact logistic regression adjusting for age