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Original Article

Long-Term Outcome After Bilateral Perinatal Arterial Ischemic Stroke

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ABSTRACT

Aim: We aimed to characterize the phenotype and outcome of children with bilateral, large vessel perinatal arterial ischemic stroke.
Methods: Patients with bilateral, large vessel perinatal arterial ischemic stroke were identified from a large, population-based cohort (Alberta Perinatal Stroke Project). Subjects were included if stroke involving a major cerebral artery territory was documented in both cerebral hemispheres on magnetic resonance imaging. Standardized variables were extracted from charts including clinical presentations, associated potential risk factors, and outcomes. Outcome measures included the Pediatric Stroke Outcome Measure, Gross Motor Function Classification System, and epilepsy frequency score. Electroencephalographies were reviewed for sleep, epileptiform activity, and background.
Results: Of 174 children with perinatal arterial ischemic stroke, eight (5%) had bilateral large artery infarcts. Patients were followed for a mean of 9.7 years (range 1.8 to 14.6 years). One child died. All children had a total Pediatric Stroke Outcome Measure of $\geq$2 (median 8, range 2 to 10) and Gross Motor Function Classification System $\geq$ II. Seven of eight (88%) children had a history of epilepsy.
Conclusions: Children with bilateral, large vessel perinatal stroke are at high risk of severe cognitive and motor sequelae. Epilepsy may also be more common than unilateral strokes. Cautious discussions with families regarding prognosis are recommended.

Perinatal stroke is the leading cause of hemiparetic cerebral palsy (CP) with lesions typically being unilateral.[1] Modern imaging can now define specific perinatal stroke disease states, the most common of which are large artery occlusions, improving the study of pathogenesis and outcomes.[2] Research on outcomes following perinatal stroke has focused on the "typical" unilateral syndrome where motor deficits are common, but many children do well in other realms of devleopment.[3] Cognitive, behavioral, and other developmental consequences do occur in a minority[4] where they appear to be associated with epilepsy,[5] which itself occurs in about 25% of unilateral cases.[6] Little is known regarding the long-term outcomes of patients with bilateral infarcts. The aim of this study was to describe the long-term outcomes of patients with bilateral, large artery perinatal ischemic stroke.

Methods

Population

Children with bilateral perinatal arterial ischemic stroke were identified through the Alberta Perinatal Stroke Project. This population-based registry has identified all patients with perinatal stroke in southern Alberta from 2008 to 2018 and is described elsewhere.[5] Patients were classified as either having (1) neonatal arterial ischemic stroke if they presented with acute neurological symptoms within 28 days of birth and had an acute infarct within an arterial territory on magnetic resonance imaging (MRI) or (2) arterial presumed perinatal ischemic stroke if presentation occurred later in infancy or childhood with remote arterial infarction on MRI. Patients were included in this study if their stroke involved the territory of a major cerebral artery (internal carotid, anterior or posterior cerebral, or middle cerebral including its two major divisions) in both cerebral

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hemispheres. The study was approved by the institutional ethics review board (ID 21522).

Outcomes

Clinical records were reviewed for demographics, clinical presentation, and associated maternal, pregnancy, and neonatal factors. Standardized outcome measure data were collected from patient records as assessed by the treating physicians. (1) The Pediatric Stroke Outcome Measure (PSOM)[7] is a validated, disease-specific scale that assesses functional domains in areas of sensorimotor impairment, expressive and receptive language, and cognition and behavior. Each of these five domains are scored as no (0), mild (0.5), moderate (1.0), or severe (2) impairment for a maximum total score of 10. Scores greater than 1 are generally considered a poor outcome. (2) The Gross Motor Function Classification System (GMFCS)[8] score was abstracted from clinical records and graded from I to V per standard convention. (3) Electroencephalographic (EEG) data were abstracted from original reports to assess for background, sleep architecture, epileptiform discharges, and signs of epileptic encephalopathy as previously described in this population.[5] Epileptic encephalopathy was considered present if electrical status epilepticus in sleep (ESES), continuous spike wave discharges in sleep, or hypsarrhythmia was reported. Epilepsy data were gathered from charts to determine seizure frequency score as defined by So et al.[9] and number of antiepileptic medications.

Results

From the original registry cohort of 174 subjects with arterial perinatal stroke, eight individuals with bilateral stroke were identified (5%). Population characteristics are summarized in Table. Available MRI findings of seven patients are shown in Fig. Five of the eight patients (63%) had neonatal arterial ischemic stroke and four (50%) were female. Patients were followed to a mean age of 9.7 years (range 1.8 to 14.6 years). One (patient 6) died at 14.6 years of age due to complications of a respiratory illness.

Pregnancy and delivery history were known in six of eight patients. Three (38%) had uncomplicated pregnancies, and five (63%) had uncomplicated deliveries. One pregnancy was complicated by maternal gestational diabetes and hypertension, and the baby had perinatal depression and was treated with therapeutic hypothermia. One pregnancy was complicated by vaginal bleeding and partial placental detachment. One patient was the surviving child of an *in utero* twin demise. One patient, following a normal pregnancy, was delivered urgently due to decreased fetal movements but had a normal transition. Placental pathology was not available for any case.

Four patients (50%) were diagnosed with stroke in the neonatal period after presenting with seizures in the first days of life. Another was diagnosed with stroke prenatally by fetal MRI completed following *in utero* fetal demise of their cotwin. Three patients (38%) were diagnosed with arterial presumed perinatal ischemic stroke in infancy due to emerging motor deficits.

Clinical outcomes at last follow-up are described in Table. All eight (100%) had a total PSOM score of 2 or greater. Four of eight (50%) had the maximum total PSOM score of 10. The patient with the lowest PSOM (patient 2) had a score of 2 representing only motor dysfunction at age 14.5 years. Another patient had a total PSOM score of 5.5 (severe motor dysfunction on one side, mild motor dysfunction on the contralateral side, severe language dysfunction, and moderate cognitive and behavioral dysfunction). Two patients had a PSOM score of 5 (severe motor dysfunction on one side, moderate language dysfunction, and mild cognitive and behavioral dysfunction). GMFCS levels were V in three patients and IV in one patient. The remaining four patients were ambulatory with level II GMFCS scores.

Neuroimaging for patients are shown in Fig. Of the four patients with PSOM scores below 10, two had a unilateral proximal middle cerebral artery (MCA) infarct on one side and a smaller posterior MCA branch infarct on the contralateral side (Fig A and D). Patient 3 (Fig C), with a PSOM score of 5, had bilateral MCA branch infarcts (anterior on the right and posterior on the left). Patient 2 (Fig B), with a PSOM score of 2, had bilateral posterior MCA branch infarcts. Three patients with PSOM scores of 10 (Fig F–H) had larger bilateral infarcts. One patient (Fig E) had a unilateral proximal MCA infarct and a contralateral posterior MCA branch infarct and also had a PSOM score of 10.

A diagnosis or history of epilepsy was present in seven of eight (88%) children. At last follow-up, five remained on one or more antiepileptic medications. The mean seizure frequency score was 2.6 (range 0 to 7, median 1.5). One patient had a hemispherectomy for seizure control. EEG data were available for all eight patients (Table). Patients had a mean of 4.8 EEGs (range 1 to 9; median 6) during their follow-up period for a total of 39 studies (including nine ambulatory and eight telemetry). Seven of eight patients (88%) had abnormal background, frequent epileptiform discharges, and abnormal sleep architecture. Three patients (38%) had a history of ESES recorded on EEG. One patient had a single EEG performed that was normal.

Discussion

Perinatal stroke is the leading cause of hemiparetic CP[1] as lesions are most often unilateral.[10] Previous studies demonstrate that bilateral stroke occurs in 24% to 35% of all perinatal stroke[11] and is associated with a five-fold increased risk of triplegia or quadriplegia.[10] Usually, bilateral infarcts are small.[12] Our study helps define a smaller proportion (5%) of perinatal strokes where large vessel injury has occurred bilaterally. In such cases, risk of quadriparesis and more severe motor outcomes are certainly expected, although half of our subjects were ambulatory. This is certainly not to say that outcomes are favorable as most children also incur major disorders of communication, cognition and behavior, and epilepsy.

Perinatal stroke represents a leading example of how CP research is advancing from a generic syndrome to the study of specific disease states. CP registries provide important epidemiologic data but continue to suffer from limited disease classification systems and a paucity of the original imaging review required to achieve this. Some systems with categories of “focal infarction” are probably capturing many strokes but are not likely specific enough to accurately capture the specific perinatal stroke diseases,[2] let alone explore the effects of lesion number, location, or laterality.[13] Accordingly, the prevalence of bilateral stroke as a cause of CP is unknown. CP registries have also demonstrated an increased number of comorbidities (intellectual, speech, vision, hearing, and epilepsy) in patients with quadriplegic CP compared with hemiplegic CP. Increased number of associated impairments increases with GMFCS level, with 73% of patients with GFMCS level V having two or more severe impairments[14] and 5-fold increase in frequency of comorbidities in quadriplegic compared with hemiplegic CP.[15] Integrating these findings from generic CP studies with those defining specific diseases like perinatal stroke should advance progress.

The incidence of epilepsy in our small cohort was high at 88%. This value appears higher than the expected epilepsy incidence where two recent studies found consistent rates of 25% to 30% in patients with unilateral perinatal stroke.[16,17] Our observed rate also appears higher than all forms of quadriparetic CP where rates again approximate 30%.[15] Given our small sample size, this finding may

TABLE.
Demographics

Patient	Imaging	Diagnosis	Pregnancy/ Delivery	Age at Last F/u	Epilepsy			PSOM				GMFCS
					Seizure Score at F/u	AEDs at F/u	EEG No.	Motor (/4)	Cognitive/ Behavioral (/2)	Language (/4)	Total (/10)	
1/M	Restricted diffusion in the entire L MCA territory and middle R MCA territory	NAIS	GDM, HTN, perinatal depression	1.8	5	Clobazam	2 (1 LTM)	2	1	1	5	II
2/M	Encephalomalacia in bilateral posterior MCA territories	APPIS	n/a	14.5	0	None	1	2	0	0	2	II
3/M	Large area of encephalomalacia in the posterior right frontal lobe and smaller area of encephalomalacia in the superior left parietal lobe	APPIS	Placental detachment	14.2	0	None	1	2	1	1	5	II
4/F	Restricted diffusion in the entire L MCA territory and posterior and middle R MCA territories	NAIS	N	9.6	1	None	9 (2 amb, 1 LTM)	2.5	1	2	5.5	II
5/M	Restricted diffusion in the entire R MCA territory and posterior and middle L MCA territories	NAIS	N	10	1	Clonazepam	7 (2 amb, 2 LTM)	4	2	4	10	IV
6/F	Encephalomalacia of the entire left hemisphere and the middle R MCA territory	NAIS	n/a	14.6	7	LEV TPX Nitrazepam	7 (2 amb, 2 LTM)	4	2	4	10	V
7/F	Encephalomalacia of the middle and posterior R MCA and the posterior L MCA territories	NAIS	*In utero* twin demise	6.6	5	LEV Clonazepam	5 (3 amb)	4	2	4	10	V
8/F	Encephalomalacia in the L ICA and R PCA territories	APPIS	Decreased fetal movements, induced	6.2	2	Nitrazepam	7 (2 LTM)	4	2	4	10	V

Abbreviations:
AED = Antiepileptic drug
Amb = Ambulatory EEG
APPIS = Arterial presumed perinatal ischemic stroke
EEG = Electroencephalography
F = Female
f/u = Follow-up
GDM = Gestational diabetes mellitus
GMFCS = Gross Motor Function Classification System
HTN = Hypertension
ICA = Internal carotid artery
L = Left
LEV = Levetiracetam
LTM = Long-term EEG monitoring
M = Male
MCA = Middle cerebral artery
N = Normal
n/a = Not available
No. = number
NAIS = Neonatal arterial ischemic stroke
PCA = Posterior cerebral artery
PSOM = Pediatric Stroke Outcome Measure
R = Right
TPX = Topiramate

relate to chance. However, other factors may also be considered. All our perinatal stroke subjects had large cortical injuries, which may affect the risk of epilepsy, particularly compared with nonstroke patients with quadriparetic CP where subcortical white matter injuries are common. Epileptic encephalopathy in the form of ESES was also common, observed in 38% of our cohort. A recent study described an overall similar incidence (35%) of ESES[5] and an association with worse cognitive and developmental outcomes in children with perinatal stroke.[4] Our results suggest that patients with bilateral perinatal stroke may have an increased risk of developing epilepsy and require careful surveillance for epileptic encephalopathy.

A major limitation of our study was an inability to assess quality of life for the child and the family. Although we have documented scale scores of neurological and developmental function, this may not be reflective of quality of life. There is no reason to think that the paradox of often marked discrepancies between level of disability and reported quality of life that has been well demonstrated in other CP populations[18] is relevant in bilateral perinatal stroke. Our clinical experience with these families would certainly suggest that many of the children are very happy members of families that report high levels of family well-being. In contrast, we have also documented substantial parental and family mental health morbidities within general perinatal stroke populations

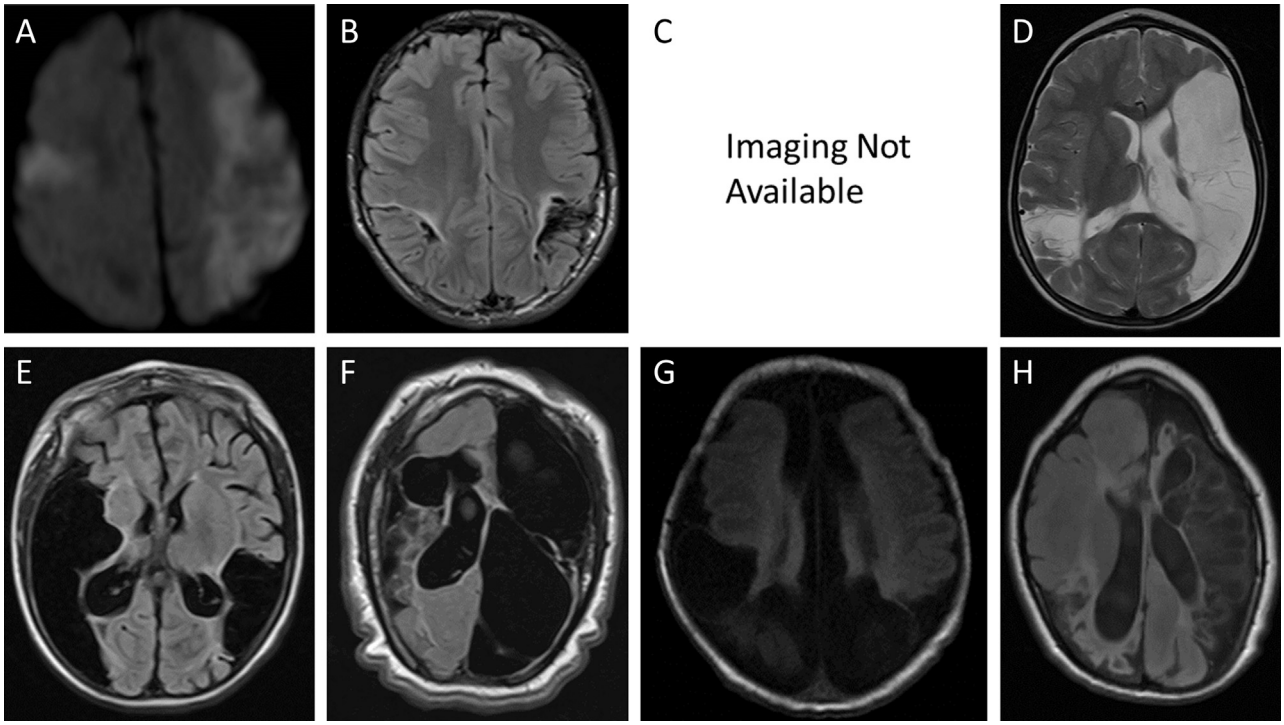

FIGURE. Magnetic resonance imaging of patients with bilateral perinatal stroke. (A) Axial diffusion-weighted image of a 7-day-old boy (Patient 1). (B) Axial T2 fluid-attenuated inversion recovery (FLAIR) image of a 14-year-old boy (Patient 2). (C) Patient 3 images are not available (D) Axial T2-weighted image of a 2-year- and 8-month-old girl (Patient 4). (E) Axial T2 FLAIR image of a 5-year-old boy (Patient 5). (F) Axial T2-weighted image of a 12-year-old girl; axial T2 FLAIR (Patient 6). (G) Axial T1-weighted image of a 2-day-old girl (Patient 7). (H) Axial T2-weighted image of a 4-year-old girl (Patient 8).

where overt measures of disability are much less severe.[19] Better measurement of such factors and outcomes should be emphasized in future studies.

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