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ORIGINAL ARTICLE

Clinical characteristics and outcomes of perinatal stroke in Australia: Population-based longitudinal study

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Aim: Perinatal stroke is one of the main causes of hemiplegia and seizure disorder. This study aimed to analyse the clinical characteristics and outcomes of perinatal stroke in a cohort of Australian children for its early detection.

Methods: A population-based prospective longitudinal study on perinatal stroke up to 2 years of age, was conducted from 2017 to 2019.

Results: Eighty-seven children with perinatal stroke included 79% (69/87) acute and 21% (18/87) presumed perinatal stroke. Seventy-four per cent (51/69) acute symptomatic perinatal strokes presented in the first 3 days of life and 78% (14/18) presumed perinatal strokes presented by 6 months of age. 62% had an arterial stroke, 29% had a venous stroke and 5% had a combined arterial and venous stroke. Unexpectedly, 35% (24/69) acute symptomatic perinatal stroke had only respiratory symptoms and 50% (9/18) presumed perinatal stroke were asymptomatic. The incidence of cerebral palsy was 29% (20/69) with acute symptomatic perinatal stroke and 72% (13/18) with presumed perinatal stroke.

Conclusions: The first week of a child's life is the most critical period in terms of lifelong disability from perinatal stroke. Recognising diverse clinical presentations will ensure early diagnosis and timely intervention treatments.

Key words: cerebral palsy; perinatal stroke; seizures.

What is already known on this topic

1 Perinatal stroke in children occurs most frequently in the first month of life.
2 Cerebral palsy is an important consequence of perinatal stroke.

What this paper adds

1 The non-neurological presentations of perinatal stroke can lead to a cascade of adverse outcomes in children due to delayed diagnosis and delayed initiation of interventional therapy.

Perinatal stroke is defined as a clinical syndrome due to focal cerebral interruption of blood supply between 20 weeks of gestation and 28 days of post-natal age.[1] There are two types of perinatal stroke depending on the age of diagnosis: (i) acute symptomatic perinatal stroke – which is diagnosed within the perinatal period (<28 days of age), and (ii) presumed perinatal stroke – which is diagnosed after 28 days of age with presentation of motor abnormalities or delayed milestones.[2]

The aetiology is multifactorial and some of the risk factors are present in healthy children. The known risk factors include infection, fetal distress, hypoglycaemia, congenital heart disease, thrombophilia and prothrombotic disorders. Despite the critical role of the placenta, which is a highly vascular organ between the mother and the fetus, the aetiological role is not completely clear because of infrequent placental histopathology reporting.[3] The other causes include head injury, genetic abnormalities and inborn errors of metabolism. A lower socio-economic status has also been associated with higher risk of stroke.[4]

Seizures are a common symptom of acute symptomatic perinatal stroke.[5] However, the nonspecific presenting symptoms such as poor feeding, respiratory distress, apnoea, cyanosis or lethargy can lead to delayed diagnosis or misdiagnosis.[6,7] Presumed perinatal stroke presents with motor asymmetry, abnormal muscle tone, delayed milestones and/or epilepsy.[8] Most of these

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presentations are in the first 2 years of life when the developmental milestones are emerging.

The gold standard for diagnosis of acute perinatal stroke is magnetic resonance imaging (MRI) of the brain.[9,10] Diagnosis of cerebral palsy (CP) after presumed perinatal stroke includes clinical history and neurological assessments such as Prechtl's qualitative assessment of General Movement Assessment (GMA), Hammersmith Infant Neurological Examination and Hand Assessment in Infants.[11]

In this prospective longitudinal study, we aimed to describe the clinical characteristics and neurodevelopmental outcomes in a cohort of children under 2 years of age with perinatal stroke in Australia. The 2-year follow-up point was prioritised because the first 2 years are critical in ameliorating deficits through appropriate and timely interventions and a conventional time point for confirmation of disability.

An insight into early diagnosis and early intervention strategies are important for ameliorating the deficits through timely and evidence-based interventions such as physiotherapy, occupational therapy, speech pathology, exercise physiology and assistive technology and equipment assistance to improve daily living skills that harness neuroplasticity.

Methods

Study design

This was a 2-year population-based longitudinal prospective follow-up study conducted at the University of Sydney, Australia between 1 July 2017 and 30 June 2019. Data were prospectively collected via physician (neonatologist, paediatrician or neurologist) report of perinatal stroke cases to the Australian Paediatric Surveillance Unit (APSU). APSU is a national body affiliated with The University of Sydney, Australia and is responsible for population surveillance of rare childhood diseases.

Physicians completed a questionnaire designed by the investigators (BR, IN and NB) based on key variables identified from published systematic reviews and large case–control studies.[5,12,13] Data included postal zip code, risk factors of stroke, clinical presentation, investigations, management and outcome of stroke. Results were reported according to the revised STROBE statement.[14]

Participants

Inclusion criteria were –

1 Children less than 2 years of age with perinatal stroke occurring between 2017 and 2019 residing anywhere in Australia.
2 Perinatal stroke diagnosed clinically and/or by MRI of the brain.

Exclusion criteria was –

1 Strokes secondary to head injury.

Analysis

Study data were collected and managed using REDcap electronic data capture tools. Characteristics for mother and children,

Table 1 Perinatal stroke characteristics ($n = 87$)

	n (%) (Total = 87 cases)
Characteristics of mother†	
Maternal age	
20–35 years	57 (66%)
>35 years	11 (13%)
Missing	19 (21%)
Racial background	
Caucasian	54 (62%)
Indigenous	1 (1%)
Pacific Islander	2 (2%)
Asian	10 (12%)
Other	12 (14%)
Missing	8 (9%)
Parity	
Nullipara	44 (54%)
Multiparity (>1)	35 (40%)
Missing	8 (6%)
Miscarriage	7 (8%)
Stillbirth	0
Neonatal death	0
Missing	8 (9%)
Plurality	
Singletons	84 (97%)
Twins and triplets	3 (3%)
Missing	0
Type of conception	
Natural	74 (86%)
In vitro fertilisation	2 (2%)
Other	2 (2%)
Missing	9 (10%)
Pregnancy complications	
Fetal distress	20 (23%)
Group B Streptococcal colonisation	9 (10%)
Gestational diabetes mellitus	10 (11%)
Prolonged rupture of membranes (>24 h)	3 (3%)
Herpes Simplex infection	1 (1%)
Parvovirus infection	1 (1%)
Missing	3 (3%)
Abnormal antenatal ultrasound	14 (16%)
Missing	7 (8%)
Meconium-stained liquor	15 (17%)
Missing	5 (6%)
Placental pathology available	4 (5%)
Chorioamnionitis	3 (3%)
Missing	83 (95%)
Maternal medication (metformin, antidepressant, prednisolone, aspirin, thyroxine, insulin, hydralazine, fluconazole)	20 (23%)
Missing	6 (7%)
Smoking	5 (6%)
Missing	11 (13%)
Alcohol	2 (2%)
Missing	14 (16%)

(*Continues*)

Table 1 (Continued)

	n (%) (Total = 87 cases)
Illicit drugs (methadone, oxycodone, benzodiazepam, quetiapine, buprenorphine, barbiturates)	3 (3%)
Missing	10 (12%)
Family history of stroke	0
Missing	4 (5%)
Mode of delivery	
Normal vaginal delivery	28 (32%)
Instrumental delivery	14 (16%)
Emergency caesarean section	31 (36%)
Elective caesarean section	8 (9%)
Missing	5 (6%)
Difficult delivery	1 (1%)
Missing	10 (12%)
Haematological/genetic tests attended	10 (12%)
Abnormal studies	4/10 (40%)
Characteristics of children†	
Gestational age	
Preterm (<37 weeks)	14 (16%)
Term (37–42 weeks)	65 (75%)
Post-term	2 (2%)
Missing	6 (7%)
Males	48 (55%)
Females	39 (45%)
Missing	0
Apgar scores	
1-min Apgar score <7	26 (30%)
5-min Apgar score <7	11 (13%)
10-min Apgar score <7	4 (5%)
Missing	10 (12%)
Abnormal cord blood gas	19 (22%)
Missing	22 (25%)
Resuscitation at birth	35 (40%)
Missing	6 (7%)
Birthweight	
Normal birthweight	60 (69%)
Low birthweight (<2500 g)	18 (21%)
Small for gestational age (<10th percentile)	16 (18%)
Large for date (>90th percentile)	9 (10%)
Missing	8 (9%)
Head circumference	
<10th or >90th percentile	15 (17%)
Missing	33 (38%)
IM vitamin K	87 (100%)
Oral vitamin K	0
Central vascular catheterisation	10 (12%)
Missing	14 (16%)
Congenital heart disease	15 (17%)
Missing	47 (54%)
Infection	22 (25%)
Positive blood culture	8 (9%)
Positive blood and cerebrospinal fluid culture	1 (1%)
Missing	7 (8%)
Hypoglycaemia (blood sugar level <2.6 mmol/L)	5 (6%)
Haematological/genetic tests attended	23 (26%)
Abnormal studies	11/23 (48%)

† *n* – frequency counts. Note regarding overlapping variables: some babies had more than one characteristic such as with pregnancy complications or birthweight (low birthweight and small for gestational age), which means the count data value does not always total *n* = 87.

clinical presentations and outcomes were reported using descriptive statistics as frequency counts (*N*) and percentages (%). The frequency of missing data was reported for each variable of interest. Differences in long-term outcomes between stroke subtypes were investigated using Fisher's exact tests. A *P* value of 0.05 was considered statistically significant.

Statement on ethics

This study was approved by the Sydney Children's Hospital Network Human Research Ethics Committee (Ethics approval no: 2019/ETH06281).

Results

Patient demographics

Characteristics of 87 children with perinatal stroke (Table 1) were reported prospectively from New South Wales (53%; 46/87), Victoria (33%; 29/87), Queensland (12%; 10/87) and one each from Western Australia and South Australia including the aetiological subtypes and birth prevalence (Fig. 1), clinical presentations (Table 2) and outcomes up to 2 years of age (Table 3).

Clinical presentations

Clinical presentations of perinatal stroke were analysed separately for acute symptomatic ($n = 69$) and presumed perinatal strokes ($n = 18$) (Table 2). Seventy-four per cent (51/69) acute symptomatic perinatal stroke presented in the first 3 days of life, 17% (12/69) between 4 and 7 of age, and 9% (6/69) between 7 and 28 days of age. Eighty-seven per cent (14/18) presumed perinatal stroke presented within 6 months of age and 22% (4/18) between 6 and 24 months of age.

Investigations

Fifty-seven per cent (50/87) had cranial ultrasound (cUS) and all had brain MRI. On brain MRI, 62% of the stroke lesions were diagnosed as arterial and 33% as venous stroke. Electroencephalogram (EEG) was performed in 47% (41/87).

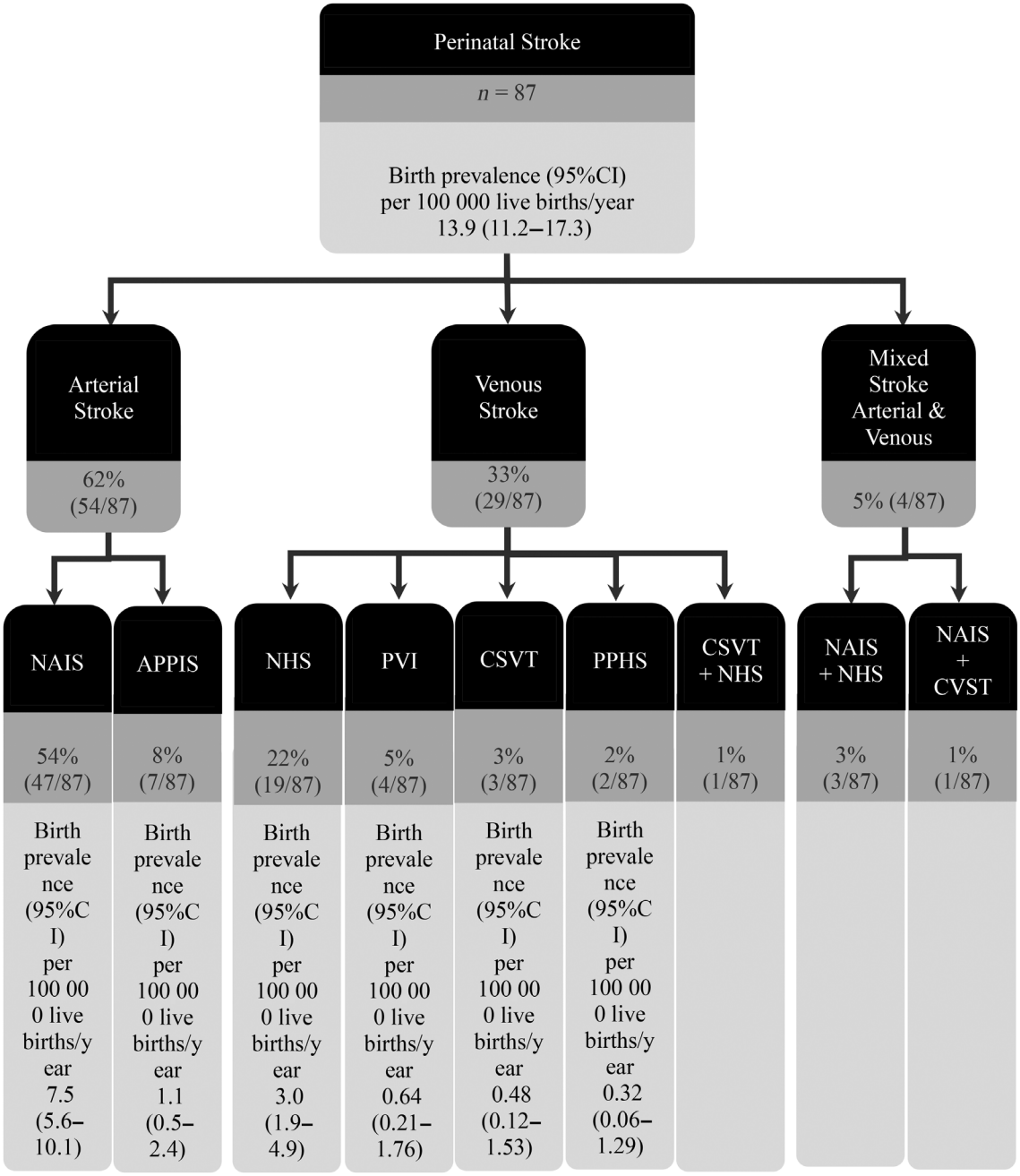

Fig. 1 Perinatal stroke subtypes ($n = 87$) and birth prevalence. APPIS, arterial presumed perinatal stroke; CSVT, cerebral sinovenous thrombosis; NAIS, neonatal arterial ischaemic stroke; NHS, neonatal haemorrhagic stroke; PPHS, presumed perinatal haemorrhagic stroke; PVI, periventricular venous infarction.

Echocardiography was performed in 46% (40/87), of which 38% (15/40) had cardiac abnormalities, which included atrial septal defect (excluding patent foramen ovale), ventricular septal defect, a combination of atrial and ventricular septal defect, and patent ductus arteriosus (two cases each) and patent ductus arteriosus with tricuspid regurgitation and pulmonary hypertension, transposition of great arteries and tetralogy of Fallot (one case each).

Haematological and genetic studies were reported in 12% (10/87) of mothers, of which 40% (4/10) were abnormal and in 26% (23/87) of the children, of which 48% (11/23) were abnormal. The abnormalities were factor V Leiden, Protein C and S, homocysteine, antithrombin III and fibrinogen anomalies.

Acute treatment

Forty-one per cent (36/87) received respiratory support and 7% (6/87) required therapeutic cooling. Eight per cent (7/87) required anticoagulant therapy, such as unfractionated heparin infusion

Table 2 Clinical presentations

Clinical presentations	Acute symptomatic perinatal stroke† ($n = 69$)	Presumed perinatal stroke† ($n = 18$)	*P* value
Seizures	65% (45/69)	0	**<0.001**
Focal seizure on right side	20% (9/45)		
Focal seizure on left side	31% (14/45)		
Multifocal (generalised)	49% (22/45)		
Lethargy/poor feeding/respiratory symptoms	77% (53/69)	44% (8/18)	**0.034**
Only respiratory symptoms	35% (24/69)	0	**0.002**
Asymptomatic	0	50% (9/18)	**<0.001**
Missing	0	1	

† *n* – frequency counts.

(2/87), low molecular weight heparin (2/87), oral aspirin (2/87) and cryoprecipitate (1/87). Three children required ventriculo-peritoneal shunt placement.

Outcomes

The perinatal stroke outcome was analysed separately for acute symptomatic and presumed perinatal strokes (Table 3). There were multiple and overlapping neurodeficit outcomes for presumed perinatal stroke, meaning that the count data is greater than 18 for this group.

Prechtl's GMA was reported in 7% (6/87) of all perinatal strokes.

Discussion

Between 1997 and 2014, the overall rate of CP decreased by 30% in high-income countries, whereas the rate of hemiplegic CP showed no such decrease.[15] There are no studies outlining the cost burden of CP in Australia, but the average estimated cost is AUD 43 431 per person per year.[16] This study analysed a range of clinical presentations to help clinicians (neonatologists and paediatricians) and related health professionals (physiotherapists, occupational therapists and speech pathologists) to recognise the signs and symptoms of perinatal stroke. This will allow timely detection of the onset of the disability, lower the severity of neurodeficit and lessen the burden of cost on the health-care system and families of children with CP.

In this national cohort of 87 children with perinatal stroke (Fig. 1), birth prevalence of perinatal stroke and its subtypes were comparable to the global pooled data.[17]

Perinatal stroke characteristics (Table 1) showed that most were singletons (97%) following a spontaneous pregnancy (85%), from nulliparous (54%), Caucasian (62%) mothers, born by emergency caesarean section (36%) with 1-, 5- or 10-min Apgar score of <7. Some of these characteristics are also found in healthy children, but similar associations have been cited in a meta-analysis study, suggesting careful consideration should be given to suspected children.[18] There were more males (55%) in our study, which was supported by a case–control study (62%),

Table 3 Outcome of perinatal stroke

	Acute symptomatic perinatal stroke† ($n = 69$)	Presumed perinatal stroke† ($n = 18$)	*P* value
Normal	48% (33/69)	17% (3/18)	0.023
Death	1% (1/69)	0	0.999
Neurodeficit	42% (29/69)	72% (13/18)	0.064
Early cerebral palsy (CP) (generalised hyper or hypotonia)	6% (4/69)	0	0.329
Hemiplegic CP	20% (14/69)	72% (13/18)	<0.001
Right hemiplegia	57% (8/14)	69% (9/13)	0.695
Left hemiplegia	43% (6/14)	31% (4/13)	
Diplegic CP	3% (2/69)	0	0.999
Hearing loss	3% (2/69)	6% (1/18)	0.498
Language delay/aphasia	1% (1/69)	6% (1/18)	0.366
Delayed milestones	1% (1/69)	0	0.999
Seizure disorder/epilepsy	0	28% (5/18)	<0.001
Missing	6	2	

† *n* – frequency counts.

although the cause for such correlation was not clear.[19] Placental pathology was reported in only four cases, three of which were intra-uterine infections, similar to the rarity of placental pathology in the literature.[20,21] However, chorioamnionitis has been described as an independent risk factor for arterial ischaemic stroke.[18]

Seizures are one of the most common presentations of perinatal stroke (Table 2), although non-conventional presentations have been described by other authors.[2,21,22] In our study, 65% (45/69) with an acute symptomatic perinatal stroke presented with seizures and unexpectedly 35% (24/69) had only respiratory symptoms, such as tachypnoea, apnoea, cyanosis and/or respiratory distress. We can safely conclude that the cases of presumed perinatal stroke presenting with purely respiratory symptoms are at risk of delayed diagnosis of neurological deficit during infancy.

Fifty per cent (9/18) of presumed perinatal strokes were asymptomatic, and 44% (8/18) had nonspecific signs and symptoms in the perinatal period. It is not clear why some infants are asymptomatic or have non-neurological symptoms. Another likely reason for the occurrence of presumed perinatal stroke is the difficulty in recognising stroke in unwell newborns.

Perinatal stroke has some of the most debilitating lifetime-lasting disabilities, namely CP. Adverse outcomes (Table 3) were present in 42% (29/69) of acute symptomatic perinatal stroke and 78% of presumed perinatal stroke. Additionally, the incidence of CP was higher with presumed perinatal stroke (72% vs. 29%). While motor deficits are the hallmark of hemiparetic CP, children may also experience cognitive and impairments plus epilepsy. In our presumed perinatal stroke cohort, hemiplegia was also associated with hearing loss and aphasia in two children, respectively. Seventy-two per cent (63/87) of all perinatal strokes occurred within the first week of life, demonstrating the importance of this age.

Prechtl's GMA was underreported in our study. Although GMA has a 95% sensitivity to predict CP from a score of 'absent fidgety', this confirmation was lacking in this study because further follow-up data were not available.[23] The underutilisation of the GMA may be due to its lower predictability of hemiplegia, because not all assessors identify hemi-fidgety as absent fidgety, and not all babies with hemiplegia have absent fidgety. Therefore, a combination of tests is recommended to identify hemiplegic CP.[11,24]

The strength of this study is that it is the first prospective national study of perinatal stroke in Australia. It highlights the need for placental pathology investigations and lays the framework for future large studies to improve the outcome of perinatal stroke.

A limitation of this study was the lack of ability to review original MRI images of the brain. The diagnosis of stroke was based on MRI reports and the reporting physicians. However, in Australia, paediatric MRIs are performed in tertiary care hospitals; thus, MRI reporting is done by senior radiologists, which ensures accurate reporting. The second limitation was the lower number of reported cases from some states in Australia, partly due to the small population and ethical constraints of reporting within the jurisdictions.

Conclusions

Given that 72% of perinatal strokes occur during the first week of a child's life, this is the most vulnerable period in terms of acquiring a lifelong disability after stroke. Therefore, to ensure that the diagnosis of perinatal stroke is made and the diagnosis of disability after stroke is made, it is crucial to be aware of its diverse clinical presentations. With an overall disability rate of 48% (42/87) and a disability rate of 72% (13/18) with presumed perinatal stroke, this study highlighted the burden of perinatal stroke and the importance of early intervention therapy in reducing the severity of disability.

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