Comparison of posterior and anterior circulation stroke in childhood – Results from the International Pediatric Stroke Study (IPSS)

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Word counts: abstract 235, text 2,479. Character count: title 92.

References: 30. Tables: 4. Figures: 1

Supplemental data:

Figure.e-1: IPSS enrollment flowchart

Appendix 2: List of IPSS Investigators

Table e-1: Predictors of neurological deficit at discharge in Children

Table e-2: Predictors of Recurrent Ischemic Events in Children

Search terms: [2] All Cerebrovascular disease/Stroke; [10] Childhood stroke.; [54] Cohort studies

Disclosures

B Goeggel Simonetti (MD) reports no disclosures relevant to the manuscript.

MF Rafay (MD) reports no disclosures relevant to the manuscript. **M Chung (MD)** reports no disclosures relevant to the manuscript. **WD Lo (MD)** reports no disclosures relevant to the manuscript. **LA Beslow (MD)** reports no disclosures relevant to the manuscript. **LL Billinghurst (MD)** reports no disclosures relevant to the manuscript. **CK Fox (MD)** reports no disclosures relevant to the manuscript. **A Pagnamenta (MD MSc)** reports no disclosures relevant to the manuscript. **M Steinlin (MD)** reports no disclosures relevant to the manuscript. **MT Mackay (MD)** reports no disclosures relevant to the manuscript.

Study Funding

This research was graciously supported by The Auxilium Foundation.

Abstract

Objective: This study compares risk factors, clinical presentation, and outcomes after posterior circulation (PCAIS) and anterior circulation arterial ischemic stroke (ACAIS) in neonates and children.

Methods: International multicenter observational study including neonates and children up to 18 years of age with arterial ischemic stroke (AIS), comparing clinical and radiological features according to stroke location.

Results: Of 2,768 AIS cases, 507 (18%) were located in the posterior circulation, 1,931 (70%) in the anterior circulation, and 330 (12%) involved both. PCAIS was less frequent in neonates compared to children (8.8% versus 22%, $p<0.001$). Children with PCAIS were older than children with anterior circulation arterial ischemic stroke (ACAIS), (median age 7.8 (IQR 3.1-14) versus 5.1 (IQR 1.5-12) years, $p<0.001$), and more often presented with headache (54% versus 32%, $p<0.001$) and a lower PedNIHSS score (4 (IQR 2-8) versus 8 (IQR 3-13), $p=0.001$). Cervicocephalic artery dissections (CCAD) were more frequent (20% versus 8.5%, $p<0.001$), while cardioembolic strokes were less frequent (19% versus 32%, $p<0.001$) in PCAIS. Case fatality rates were equal in both groups (2.9%). PCAIS survivors had a better outcome (normal neurological examination at hospital discharge in 29% versus 21%, $p=0.002$) than ACAIS survivors, although this trend was only observed in children and not in neonates.

Conclusion: PCAIS is less common than ACAIS in both neonates and children. Children with PCAIS are older, have a higher rate of CCAD, lower clinical stroke severity, and better outcome than children with ACAIS.

Introduction

Current knowledge about pediatric posterior circulation arterial ischemic stroke (PCAIS) is largely based on a few, mostly single-center retrospective studies that report PCAIS in 10-43% of cases of childhood arterial ischemic stroke (AIS), and rarely in neonates.[1-7] Cerebral vasculopathies are the most commonly identified etiologies of childhood PCAIS, and recurrence rates are reportedly higher when compared to anterior circulation arterial ischemic stroke (ACAIS).[1, 2, 4, 8] Clinical outcomes for children with PCAIS are available through a limited number of studies and range from a good outcome in 55% of children with no case fatalities , to fatality rates as high as 26% and poor outcome in 45% of survivors.[1-4, 8]

These discrepant reports in the literature and the fact that PCAIS has not been directly compared to ACAIS except for stroke recurrence, led us to review data from a large prospective multicenter study, the International Pediatric Stroke Study (IPSS) over a 10-year period to provide comparative information on risk factors, clinical presenting features, and outcomes following ACAIS and PCAIS in neonates and children. We hypothesized that children with PCAIS frequently have non-specific symptoms such as headache or altered level of consciousness, different risk factors and differ in terms of stroke outcomes and recurrence compared to ACAIS.

Methods

The methods of the IPSS have been described in detail.[9, 10] In brief, the IPSS is an international multicenter observational study prospectively including children and neonates with arterial ischemic stroke or cerebral sinovenous thrombosis since 2003. All participating centers are listed in table e-1. For this analysis, we included all patients (neonates aged 0 days to 28 days of life and children aged 29 days to <19 years at onset) with AIS registered between 2003 and 2014 for

whom stroke location was known. Children with a stroke involving both the anterior and the posterior circulation were excluded.

Variable definitions

AIS was defined as an acute event with clinical and radiological evidence of cerebral ischemia, including 1) a focal neurological deficit of acute onset AND 2) computed tomography (CT) or magnetic resonance imaging (MRI) showing infarct in location consistent with neurological signs and symptoms. Patients with diffuse or bilateral infarction related to hypoxic ischemic events were included only if a definite focal, single arterial infarct in a specified vascular territory was also present. Stroke locations were reported by local site investigators as isolated involvement of the posterior circulation (PCAIS), isolated involvement of the anterior circulation (ACAIS), or involvement of both the anterior and posterior circulations (BCAIS). The anterior circulation was defined as the territory of the internal carotid, middle or anterior cerebral artery, the posterior circulation as the territory of the vertebral, basilar, cerebellar, or posterior cerebral arteries. Clinical stroke severity at diagnosis was assessed with the Pediatric National Institutes of Health Stroke Scale (PedNIHSS).[11] Outcome was assessed with an examination by a pediatric neurologist and a standardized neurologic outcome measure validated for pediatric ischemic stroke, the Pediatric Stroke Outcome Measure (PSOM),.[12] In addition, parents or guardians answered two outcome questions at follow-up: 1) “Has your child recovered completely from the stroke?”, 2) “Does your child need extra help with day-to-day activities compared with other children of the same age?”. Hemorrhagic transformation of AIS was defined according to the European-Australasian Cooperative Acute Stroke Study (ECASS II).[13] Recurrent ischemic events were defined as any clinical or subclinical ischemic event after the index stroke.

Statistical analyses

Statistical analyses were performed using Stata version 15 (StataCorp LP, College Station, TX, USA). Data are reported descriptively as numbers and frequencies. For variables with missing data, the term "valid n" indicates the number of patients for whom information was available. Continuous data are expressed as median and interquartile ranges (IQR). Groups were compared according to stroke location (ACAIS versus PCAIS) using the Mann-Whitney-U test for continuous variables, and Fisher exact or Pearson Chi Square test for categorical variables, as appropriate. A two-sided p-value ≤ 0.05 was considered statistically significant. Multivariable logistic regression analysis was performed to determine predictors of recurrent ischemic events and neurologic deficits at hospital discharge, including variables with a p-value ≤ 0.1 in the univariable logistic regression analysis.

Standard Protocol Approvals, Registrations, and Patient Consents

The study protocols were approved by relevant local authorities in all participating centers and conducted according to national rules concerning ethics committee approval and informed consents. The IPSS is registered with clinicaltrials.gov (NCT00084292).

Data availability statement

All data used for analysis are presented in the tables and figure in this article. Data will be shared after ethics approval if requested by other investigators for purposes of replicating the results.

Results

Stroke location was recorded in 2,768 (87%) of all AIS patients (88% of neonates, 86% of children), with the majority being ACAIS (n=1,931, 70%), followed by PCAIS (n=507, 18%) and

BCAIS (n=330, 12%). After excluding the 330 patients with BCAIS, 2,438 participants were included in this study (703 neonates and 1,735 children). PCAIS was less frequent in neonates than children (8.8% versus 22%, $p<0.001$).

Childhood Stroke

Children with PCAIS were older (median age 7.8 years, IQR 3.1-14 years) than children with ACAIS (median age 5.1 years, IQR 1.5-12 years, $p<0.001$). Age distribution according to stroke territory is displayed in figure 1.

The male preponderance was more marked in PCAIS (64%) than ACAIS (56%) ($p=0.002$). This difference persisted when correcting for preceding head trauma ($p=0.014$), but was not significant when adjusting for cervicocephalic artery dissection (CCAD, $p=0.3$).

The most common presenting signs and symptoms in PCAIS were limb paresis (65%), headache (54%), speech disturbance (48%), and ataxia (47%). Apart from obvious differences due to stroke location, displayed in detail in table 1, children with PCAIS had headache more often at stroke onset ($p<0.001$), while seizures were less frequent than in ACAIS ($p<0.001$). Altered level of consciousness ($p=0.27$) and visual field defects ($p=0.15$) did not differ.

Stroke severity at presentation was reported in 273 patients (16% of ACAIS, 15% of PCAIS) and was lower in PCAIS with a median PedNIHSS of 4 (IQR 2-8) compared to ACAIS (median PedNIHSS 8 (IQR 3-13), $p=0.001$).

Time from symptom onset to radiological confirmation of diagnosis was available in 449 children (25% of ACAIS, 28% of PCAIS), and was similar in both groups with a median of 19.8 (IQR 6.8-48) hours in PCAIS, compared to 13 (IQR 5-28) hours in ACAIS ($p=0.25$). MRI was the

imaging modality most frequently required to diagnose PCAIS (MRI 68%, CT 32%), while a CT scan was sufficient for diagnosis in nearly half of ACAIS (MRI 56%, CT 44%, $p<0.001$). Vasculopathy and chronic illness were the two most common risk factors for both PCAIS and ACAIS. However, the distribution of subtypes within these groups differed with CCAD being more common in PCAIS (20%) than in ACAIS (8.5%, $p<0.001$), while Moyamoya and Transient Cerebral Arteriopathy (TCA) were more frequent in ACAIS than in PCAIS (Moyamoya 14 versus 2.8%, $p<0.001$, TCA 5 vs 2%, $p=0.033$). Hematological disease, including iron deficiency anemia, sickle cell disease, or any kind of prothrombotic state, were less frequent in PCAIS (2%) than ACAIS (7%, $p=0.001$). Cardioembolic conditions and acute systemic illness were less common in PCAIS than in ACAIS, while acute and chronic diseases affecting the head or neck including migraine were more frequent in PCAIS (table 2).

Children with PCAIS more often received an antithrombotic agent during the acute phase than children with ACAIS (84% in PCAIS, 77.1% in ACAIS, $p<0.003$). Thrombolysis was rarely performed for stroke in any location (5.1% in ACAIS, 2% in PCAIS, $p=0.07$), 5 thrombectomies were performed, all in ACAIS. Hemorrhagic transformation of stroke, occurring in 5.5% of PCAIS and 6.6% of ACAIS ($p=0.53$), and the need for neurosurgical procedures, such as decompressive craniectomy or cerebrospinal fluid drainage, performed in 14% of ACAIS and 9.1% of PCAIS patients ($p=0.1$) were similar.

The fatality rate was identical for PCAIS and ACAIS (both 2.9%). In survivors, outcome data were obtained in 92% of PCAIS and 97% of ACAIS patients at discharge, and in 52% of PCAIS and 46% of ACAIS patients after a median follow-up duration of 1.5 (IQR 0.5-3.1) years, which did not differ between the groups ($p=0.5$).

Survivors of PCAIS were more frequently reported to have a normal neurologic examination at hospital discharge than survivors of ACAIS. In the multivariable logistic regression analysis, the risk for a neurological deficit at discharge was decreased in children after PCAIS (OR 0.61; 95% CI 0.45-0.84; *p*=0.002), and cardioembolic stroke (OR 0.67; 95% CI 0.49-0.91; *p*=0.01), and increased after CCAD (OR 1.88; 95% CI 1.11-3.17; *p*=0.02) (table e-1). However, full recovery was reported by parents of roughly a third of children both after PCAIS and ACAIS at the last follow-up visit (table 3).

Recurrent ischemic events were more frequent in PCAIS than ACAIS despite similar rates of secondary preventive antithrombotic treatment. The multivariable logistic regression analysis revealed PCAIS (OR 1.69; 95% CI 1.08-2.65; *p*=0.02), and CCAD (OR 2.39; 95% CI 1.36-4.22; *p*=0.003) as risk factors for recurrent ischemic events (table e-2).

Neonatal stroke

Neonates with PCAIS did not differ from neonates with ACAIS in terms of clinical presentation, distribution of the sexes, risk factors, diagnostic imaging modality, complications such as hemorrhagic transformation, recurrence, and outcome (table 4). Complete recovery from stroke at last follow-up visit (median follow-up 2 years) was reported in more than one third of neonates with PCAIS.

Discussion

This large international observational study comprehensively compares PCAIS with ACAIS throughout the pediatric age groups, demonstrating g that pediatric PCAIS is less frequent than

ACAIS in both neonates and children, and confirming our hypothesis of a distinct clinical presentation, risk factor profile and outcome in children, but not in neonates with PCAIS compared with ACAIS.

PCAIS presenting beyond the newborn period is associated with older age at stroke onset and different risk factor profiles, with higher rates of CCAD, acute/chronic head and neck conditions and migraine, and lower rates of cardioembolic conditions, transient cerebral arteriopathy, moyamoya arteriopathy, acute systemic illnesses, and hematological disease, when compared to ACAIS. In a systematic review of CCAD and stroke in childhood, patients with CCAD leading to PCAIS were younger than those with ACAIS,[14] while CCAD occurred at any age throughout childhood in a more recent prospective study.[15] Lower rates of cardioembolic events in PCAIS are not unexpected as the anterior circulation carries the majority of the cerebral blood supply, and as a consequence emboli from the heart are more likely to travel to the middle or anterior cerebral artery.[16] In children, cardioembolic events often occur in the perioperative period in younger children with complex congenital heart disease.[17] Similarly, involvement of the posterior circulation occurs later in children with moyamoya syndrome.[18]

A marked male preponderance has been reported in PCAIS.[1-4, 8] These previous studies did not correct for potential confounding factors such as preceding trauma and CCAD. In the current study the association between PCAIS and male sex persisted even when correcting for trauma, but not for CCAD. The reason for this association remains to be determined. Higher testosterone levels have been reported in some pediatric stroke patients compared to healthy controls, but these findings were not further analyzed according to stroke location or etiology.[19] A male preponderance has also been noted in adult CCAD patients,[20, 21] but was more marked in the

anterior than in the posterior circulation,[22] and sex differences in putative risk factors, such as hypertension, hypercholesterolemia, or past smoking may explain the higher frequency of CCAD in men.

Clinical presentation did differ, as hypothesized, with non-specific symptoms such as headache, vertigo, nausea and vomiting being more common in PCAIS. However, seizures that may also mislead and delay the diagnosis, were less common in PCAIS than in ACAIS, while altered consciousness was reported equally in both groups. In contrast to a previous report, these differences in clinical presentation did not seem to lead to a longer time to diagnosis.[23]

MRI remains the imaging modality of choice to radiologically confirm diagnosis in PCAIS, as our data and previous studies show. CT has lower sensitivity for detection of acute infarction, particularly for smaller brainstem or cerebellar lesions, due to bony artifacts from the base of the skull.[23-25] This study also highlights the importance of vascular imaging, including sequences for vessel wall pathologies, such as CCAD, which are highly prevalent in PCAIS[26, 27]

Fatality rates were identical for PCAIS and ACAIS. In survivors, outcome was better and the need for inpatient rehabilitation was lower in PCAIS compared with ACAIS at discharge. Similar differences were observed at a median of 1.5 years after the stroke, even though children with PCAIS more often had recurrent ischemic events. Discharge outcomes after CCAD differed for children with PCAIS versus ACAIS. In univariate analysis, CCAD cases with ACAIS were noted to have more neurologic deficits compared to CCAD cases with PCAIS (93% versus 76%, $p<0.001$) .

Relatively good outcome in children compared with adults has already been described after basilar artery stroke.[28] However, recent reports comparing ACAIS and PCAIS in adults show more similarities than differences, not only in initial stroke severity,[29] but also in terms of clinical outcome which was favorable (modified Rankin score 0-2) in a majority of both ACAIS and PCAIS patients.[30]

Previously reported as a rare occurrence in neonates,[5, 6] this study shows that PCAIS accounts for almost 10% of AIS in this age group. No significant differences between neonates with PCAIS and ACAIS were identified. A prior case series described 18 neonates with posterior cerebral artery stroke, 5 of whom did not have concomitant hypoxic ischemic encephalopathy or hypoglycemia.[7] We did not have serum glucose measurements available for cases recruited to the current study but Apgar-scores were similar in all stroke territories; 14% of PCAIS and 10% of ACAIS% had an Apgar score <4 at 1 minute and 1.4% of PCAIS and 2.3% of ACAIS had an Apgar score <4 at 5 minutes.

The main strengths of this study were the prospective international multicenter design, allowing enrollment of a large number of children, data collection according to a predefined standardized protocol, and comparison of neonates and children with PCAIS to ACAIS. However, information on some variables of interest, such as the PedNIHSS which indicates stroke severity, or outcome data after discharge from hospital were missing in a substantial part of the study participants. Furthermore, selection bias towards more severe cases is possible due to the fact that most enrolling sites were tertiary pediatric care centers. The higher recurrence rates observed in the current study, compared to the previous literature, may also be due to selection bias, as

long-term follow-up data beyond discharge were only available for approximately half of the study cohort and the majority of IPSS recruiting sites are tertiary pediatric centers. The IPSS does not provide detailed information on imaging modalities such as the rate of cervical angiographies performed or the MRI sequences used, thus, diagnosis of certain conditions such as vasculopathies may be under recognized or overestimated.

In conclusion, PCAIS is less common than ACAIS in the pediatric population. Children with PCAIS are older, have higher rates of CCAD and other head and neck conditions, lower stroke symptom severity at presentation, increased stroke recurrence risk and better outcome than children with ACAIS.

Tables

Table 1: Clinical presentation stratified by stroke territory in 1,735 children with acute arterial ischemic stroke

Characteristics **n with condition/valid n (%)**	**Posterior Stroke** **(n=436)**	**Anterior Stroke** **(n=1,299)**	***Posterior vs anterior*** ***Two-tailed p-value***
Paresis of extremities, any	268/410 (65)	1093/1265 (86)	<0.001
Quadriparesis	22/410 (5.4)	25/1265 (2)	0.001
Hemiparesis	246/410 (60)	1068/1265 (84)	<0.001
Headache	194/357 (54)	306/969 (32)	<0.001
Speech disturbance, any	189/391 (48)	722/1183 (61)	<0.001
Ataxia, any	22/47 (47)	30/126 (24)	0.005
Visual field defect, any	159/384 (41)	428/1153 (37)	0.15
Nausea/vomiting	25/61 (41)	40/160 (25)	0.03
Altered consciousness	144/372 (39)	465/1105 (42)	0.27
Vertigo	15/51 (29)	10/126 (7.9)	0.01
Seizure	76/408 (19)	396/1222 (32)	<0.001

Table 2: Risk factors stratified by stroke territory in 1,735 children with acute arterial ischemic stroke

Characteristics **n with condition/valid n (%)**	**Posterior Stroke** **(n=436)**	**Anterior Stroke** **(n=1'299)**	***Posterior vs anterior*** ***Two-tailed p***
Vasculopathy*	129/407 (32)	413/1206 (34)	0.36
Cardioembolic conditions	79/417 (19)	403/1263 (32)	<0.001
Acute systemic illness	83/417 (20)	338/1244 (27)	0.003
Underlying chronic illness	131/431 (30)	415/1287 (32)	0.51
Hematological disease	10/431 (2.3)	95/1287 (7.4)	<0.001
Acute head and neck conditions	106/421 (25)	250/1244 (20)	0.03
Head trauma	61/376 (16)	92/1086 (8.5)	<0.001
Meningitis	4/319 (1.3)	46/1040 (4.4)	0.006
Chronic head and neck conditions	51/420 (12)	96/1255 (7.6)	0.007
Migraine	22/391(5.6)	28 /1187 (2.4)	0.002
Family history positive for stroke	67/257 (26)	163/768 (21)	0.12

*Vasculopathy subtypes include focal cerebral arteriopathy (FCA), craniocervical arterial dissection (CCAD), Moyamoya disease/syndrome, small vessel arteriopathy and arteriopathy not otherwise specified.

Table 3: Recurrent ischemic events, and outcome stratified by stroke territory in 1,735 children with acute arterial ischemic stroke

Characteristics **n with condition/valid n (%)**	**Posterior Stroke** **(n=436)**	**Anterior Stroke** **(n=1,299)**	***Posterior vs anterior*** ***Two-tailed p***
Recurrent ischemic event	66/217 (30)	115/522 (22)	0.02
Any antithrombotic medication before recurrence	16/17 (94)	31/36 (86)	0.65
Outcome			
Death	12/410 (2.9)	35/1196 (2.9)	1.0
Normal neurological examination at discharge	111/389 (29)	235/1142 (21)	0.002
Discharge Destination	Valid 376	Valid 1113	<0.001
Home	325 (86)	861 (77)	
Rehabilitation Hospital	46 (12)	205 (18)	
Other Hospital	5 (1.3)	47 (4.2)	
Increased need of help 1 y after stroke	13/65 (20)	52/135 (39)	0.67
Increased need of help at last follow-up visit	51/153 (33)	161/369 (44)	0.03
"Child has recovered completely from the stroke" (as reported by parents at last follow-up visit)	87/220 (40)	176/543 (32)	0.07
PSOM score at last follow-up visit, median (IQR)	0.5 (0-1) Valid 204	1 (0.5-2) Valid 524	<0.001

PSOM = Pediatric Stroke Outcome Measure.

Table 4: Characteristics, treatment and outcome stratified by stroke territory among 703 neonates with acute arterial ischemic stroke

Characteristics **n with condition/valid n (%)**	**Posterior Stroke** **(n=71)**	**Anterior Stroke** **(n=632)**	***Posterior vs anterior*** ***Two-tailed p***
Male	42 (59)	371 (59)	1.0
Clinical Presentation			
Seizures	49/65 (75)	476/606 (79)	0.53
Altered consciousness	23/58 (40)	218/548 (40)	1.0
Time from onset of symptoms to diagnosis, median (IQR) [h]	24 (1-68) Valid 7	32 (12-72) Valid 75	0.47
Maternal risk factors			
Arterial hypertension	5/52 (9.6)	43/503 (8.5)	0.15
Fever	2/52 (3.8)	54/495 (11)	0.80
Age [years]	28 (23-34) Valid 40	29 (25-33) Valid 451	0.4
Neonatal risk factors			
Meningitis	3/63 (4.8)	12/560 (1.2)	0.19
Cardiac disease	13/65 (20)	173/565 (31)	0.09
Vasculopathy	2/66 (3)	11/564 (2)	0.64
Apgar score at 1 min (median (IQR), % with score <4)	7 (4-9), 14% Valid 48	8 (6-9), 10% Valid 466	0.13
Apgar score at 5 min (median (IQR), % with score <4)	9 (8-9), 1.4% Valid 50	9 (8-9), 2.3% Valid 481	0.39
Any antithrombotic therapy	8/64 (12.5)	95/585 (16)	0.59
Hemorrhagic Transformation	7/55 (12.7)	49/467 (11)	0.64
Recurrent ischemic event	1/27 (3.7)	14/261 (5.4)	1.00
Outcome			

Death	0	7/604 (1.2)	1.0
Normal neurological exam at discharge	37/60 (62)	343/572 (60)	0.89
"Child has recovered completely from the stroke" (as reported by parents at last follow-up visit)	11/30 (37)	124/285 (44)	0.56

Figure Legend

Figure 1: Age distribution according to stroke territory

Glossary

AIS = acute arterial ischemic stroke

ACAIS = anterior circulation stroke

BCAIS = AIS in both the anterior and the posterior circulations

CCAD = cervicocephalic artery dissection

IPSS = International Pediatric Stroke Study

IQR = interquartile range

PCAIS = posterior circulation stroke

PedAIS = pediatric arterial ischemic stroke

PedNIHSS = Pediatric National Institutes of Health Stroke Scale

PSOM = Pediatric Stroke Outcome Measure

Acknowledgments

The authors thank the children, their caregivers and staff of all participating centers for their help and valuable contribution to this study.

Appendix 1: Author contributions

BGS designed/conceptualized the study, analyzed/interpreted the data, drafted the manuscript, and collected data. **MFR** designed/conceptualized the study, interpreted the data, collected data and reviewed and edited the manuscript for content. **, MC, WDL, LAB, LLB, CKF:** data collection, critical review of the manuscript, editing manuscript for content. **AP** performed the statistical analyzes/interpreted the data and reviewed the manuscript, editing manuscript for content. **MTM and MS** initiated, designed, conceptualized and supervised the study, analyzed/interpreted the data, revised the manuscript, and collected data. All authors agreed on submission of the present version of the manuscript. IPSS study group collaborators and co-investigators are mentioned in Appendix 2.

References

1. Ganesan V, Chong WK, Cox TC, Chawda SJ, Prengler M, Kirkham FJ. Posterior circulation stroke in childhood: risk factors and recurrence. Neurology 2002;59:1552-1556.
2. Mackay MT, Prabhu SP, Coleman L. Childhood posterior circulation arterial ischemic stroke. Stroke 2010;41:2201-2209.
3. McCrea N, Saunders D, Bagkeris E, Chitre M, Ganesan V. Diagnosis of vertebral artery dissection in childhood posterior circulation arterial ischaemic stroke. Dev Med Child Neurol 2016;58:63-69.
4. Carey S, Wrogemann J, Booth FA, Rafay MF. Epidemiology, Clinical Presentation, and Prognosis of Posterior Circulation Ischemic Stroke in Children. Pediatr Neurol 2017.
5. Grunt S, Mazenauer L, Buerki SE, et al. Incidence and outcomes of symptomatic neonatal arterial ischemic stroke. Pediatrics 2015;135:e1220-1228.
6. Laugesaar R, Kolk A, Tomberg T, et al. Acutely and retrospectively diagnosed perinatal stroke: a population-based study. Stroke 2007;38:2234-2240.
7. van der Aa NE, Dudink J, Benders MJ, et al. Neonatal posterior cerebral artery stroke: clinical presentation, MRI findings, and outcome. Dev Med Child Neurol 2013;55:283-290.
8. Uohara MY, Beslow LA, Billinghurst L, et al. Incidence of Recurrence in Posterior Circulation Childhood Arterial Ischemic Stroke. JAMA Neurol 2017;74:316-323.
9. Golomb MR, Fullerton HJ, Nowak-Gottl U, Deveber G, International Pediatric Stroke Study G. Male predominance in childhood ischemic stroke: findings from the international pediatric stroke study. Stroke 2009;40:52-57.

10. Mackay MT, Wiznitzer M, Benedict SL, et al. Arterial ischemic stroke risk factors: the International Pediatric Stroke Study. Ann Neurol 2011;69:130-140.
11. Ichord RN, Bastian R, Abraham L, et al. Interrater reliability of the Pediatric National Institutes of Health Stroke Scale (PedNIHSS) in a multicenter study. Stroke 2011;42:613-617.
12. Kitchen L, Westmacott R, Friefeld S, et al. The pediatric stroke outcome measure: a validation and reliability study. Stroke 2012;43:1602-1608.
13. Hacke W, Kaste M, Fieschi C, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Second European-Australasian Acute Stroke Study Investigators. Lancet 1998;352:1245-1251.
14. Fullerton HJ, Johnston SC, Smith WS. Arterial dissection and stroke in children. Neurology 2001;57:1155-1160.
15. Wintermark M, Hills NK, DeVeber GA, et al. Clinical and Imaging Characteristics of Arteriopathy Subtypes in Children with Arterial Ischemic Stroke: Results of the VIPS Study. AJNR Am J Neuroradiol 2017;38:2172-2179.
16. Boyajian RA, Schwend RB, Wolfe MM, Bickerton RE, Otis SM. Measurement of anterior and posterior circulation flow contributions to cerebral blood flow. An ultrasound-derived volumetric flow analysis. J Neuroimaging 1995;5:1-3.
17. Dowling MM, Hynan LS, Lo W, et al. International Paediatric Stroke Study: stroke associated with cardiac disorders. Int J Stroke 2013;8 Suppl A100:39-44.
18. Lee JY, Kim SK, Cheon JE, et al. Posterior cerebral artery involvement in moyamoya disease: initial infarction and angle between PCA and basilar artery. Childs Nerv Syst 2013;29:2263-2269.

19. Normann S, de Veber G, Fobker M, et al. Role of endogenous testosterone concentration in pediatric stroke. Ann Neurol 2009;66:754-758.

20. Arnold M, Kappeler L, Georgiadis D, et al. Gender differences in spontaneous cervical artery dissection. Neurology 2006;67:1050-1052.

21. Metso AJ, Metso TM, Debette S, et al. Gender and cervical artery dissection. Eur J Neurol 2012;19:594-602.

22. von Babo M, De Marchis GM, Sarikaya H, et al. Differences and similarities between spontaneous dissections of the internal carotid artery and the vertebral artery. Stroke 2013;44:1537-1542.

23. Rafay MF, Pontigon AM, Chiang J, et al. Delay to diagnosis in acute pediatric arterial ischemic stroke. Stroke 2009;40:58-64.

24. McGlennan C, Ganesan V. Delays in investigation and management of acute arterial ischaemic stroke in children. Dev Med Child Neurol 2008;50:537-540.

25. Srinivasan J, Miller SP, Phan TG, Mackay MT. Delayed recognition of initial stroke in children: need for increased awareness. Pediatrics 2009;124:e227-234.

26. Dlamini N, Yau I, Muthusami P, et al. Arterial Wall Imaging in Pediatric Stroke. Stroke 2018;49:891-898.

27. Tan MA, DeVeber G, Kirton A, Vidarsson L, MacGregor D, Shroff M. Low detection rate of craniocervical arterial dissection in children using time-of-flight magnetic resonance angiography: causes and strategies to improve diagnosis. J Child Neurol 2009;24:1250-1257.

28. Goeggel Simonetti B, Ritter B, Gautschi M, et al. Basilar artery stroke in childhood. Dev Med Child Neurol 2013;55:65-70.

29. von Sarnowski B, Schminke U, Grittner U, et al. Posterior versus Anterior Circulation Stroke in Young Adults: A Comparative Study of Stroke Aetiologies and Risk Factors in Stroke among Young Fabry Patients (sifap1). Cerebrovasc Dis 2017;43:152-160.

30. De Marchis GM, Kohler A, Renz N, et al. Posterior versus anterior circulation strokes: comparison of clinical, radiological and outcome characteristics. J Neurol Neurosurg Psychiatry 2011;82:33-37.