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International Paediatric Stroke Study: stroke associated with cardiac disorders

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Abstract

Background and hypothesis—The aetiologies of arterial ischaemic stroke in children are diverse and often multi-factorial. A large proportion occurs in children with cardiac disorders. We hypothesized that the clinical and radiographic features of children with arterial ischaemic stroke attributed to cardiac disorders would differ from those with other causes.

Methods—Using the large population collected in the prospective International Paediatric Stroke Study, we analysed the characteristics, clinical presentations, imaging findings, and early outcomes of children with and without cardiac disorders.

Results—Aetiological data were available for 667 children with arterial ischaemic stroke (ages 29 days to 19 years). Cardiac disorders were indentified in 204/667 (30·6%), congenital defects in 121/204 (59·3%), acquired in 40/204 (19·6%), and isolated patent foramen ovale in 31/204 (15·2%). Compared to other children with stroke, those with cardiac disorders were younger (median age 3·1 vs. 6·5 years; $P < 0{\cdot}001$) and less likely to present with headache (25·6% vs.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix: Members of the International Paediatric Stroke Study Group.

44·6%; $P < 0·001$), but were similar in terms of gender and presentation with focal deficits, seizures, or recent infection. Analysis of imaging data identified significant differences ($P = 0·005$) in the vascular distribution (anterior vs. posterior circulation or both) between groups. Bilateral strokes and haemorrhagic conversion were more prevalent in the cardiac disorders group.

Conclusions—Cardiac disorders were identified in almost one-third of children with arterial ischaemic stroke. They had similar clinical presentations to those without cardiac disorders but differed in age and headache prevalence. Children with cardiac disorders more frequently had a 'cardioembolic stroke pattern' with a higher prevalence of bilateral strokes in both the anterior and posterior circulations, and a greater tendency to haemorrhagic transformation.

Keywords

arterial ischaemic stroke; cardiac; cardiac disorders; cardioembolic stroke; child neurology; paediatric

Introduction

The incidence of arterial ischaemic stroke (AIS) in children is estimated at 1·2 and 8/100 000/year (1,2). While increasing evidence suggests that many AIS cases have a multifactorial aetiology (3–5), cardiac disorders, either congenital or acquired, are associated with 10% to 29% of strokes in children (4,6–9) while accounting for 25% to 30% of ischaemic stroke in adults (10). The presumed mechanism in most is cardioembolic, but as many congenital or acquired heart lesions can cause chronic hypoxia and polycythaemia, it may be difficult to differentiate the contribution of embolic and thrombotic disease. Additionally, congenital lesions that allow for right-to-left shunting, including single ventricle physiology, septal defects, and isolated patent foramen ovale (PFO), can allow venous blood to enter the systemic circulation, bypassing the pulmonary filter, and cause stroke via paradoxical embolization. Since many cardiac disorders are identified prior to stroke and stroke is a frequent complication of cardiac catheterization or surgery, this subgroup has potential for more rapid recognition and implementation of preventative strategies.

We evaluated the patient characteristics, clinical presentations, stroke characteristics from imaging studies, and early outcomes of children with AIS with reported cardiac disorders and compared them to those of children with other causes of stroke from the large population enrolled in the International Paediatric Stroke Study (IPSS) registry. We hypothesized that these factors would differ between these two groups. We also evaluated the current practice for cardiac evaluation in this large cohort.

Methods

The IPSS is a prospective registry that enrolled 1187 children with AIS and sinovenous thrombosis at 30 hospitals in five continents between 1/2003 and 7/2007. Institutional Review Board approval was obtained at each centre and informed consent was obtained from parents or caregivers. Details of the IPSS network, case identification, data collection, and database management have been previously described (11). Previous reports on this

IPSS cohort have detailed the male predominance, risk factor associations, predictors of cerebral arteriopathy, antithrombotic treatments, and outcomes of childhood AIS (5,11–13). For this analysis, we specifically investigated the subgroup of children with cardiac disorders and AIS. Clinical, laboratory, and radiological data were de-identified, collected on standardized case report forms, and submitted to a centralized database. Our analysis focused on non-neonatal (>28 days old) children (<19 years of age) with AIS, defined as a clinical neurological deficit with acute onset with radiographic imaging [magnetic resonance imaging (MRI) or computed tomography (CT)] showing parenchymal infarcts in an arterial territory corresponding to the clinical symptoms.

Site investigators categorized stroke aetiology in six non-exclusive categories: (1) cardiac; (2) vasculopathy; (3) underlying chronic disorders; (4) associated acute systemic illnesses; (5) underlying chronic head and neck disorders; or (6) acute head and neck disorders. Cardiac disorders included both congenital and acquired heart disease, stroke at the time of cardiac surgery or catheterization, or isolated PFO. Children with abnormalities detected on echocardiogram were included in the cardiac disorders category. The vasculopathy category included dissection, moyamoya, transient cerebral arteriopathy of childhood, postvaricella angiopathy, and other causes of vasculopathy (12). Endocarditis was classified within the cardiac disorders group.

Neuroimaging data were based on the on-site review by the site investigator. Stroke features were reported by lateralization (left, right, or bilateral), location (anterior or posterior circulation or both), and number (single or multiple strokes). Haemorrhagic lesions within the infarct were reported and other types of intracranial haemorrhage were reported as intraventricular, subdural, subarachnoid, or were unspecified. Treatment and early outcome data (status at hospital discharge) for this cohort have been previously described (13). Outcomes were reported as normal, any neurologic deficit, or dead.

Statistical analysis

We compared the characteristics of children with AIS associated with cardiac disorders to those without using chi-square, Fisher's exact, or Mann–Whitney test as appropriate. When chi-square testing was significant, Tukey type multiple comparison test of proportions was used. For all tests, alpha <0·05 was considered significant. Analyses were performed using IBM SPSS Statistics, Version 19·0 (Somers, NY, USA).

Results

Patient characteristics and clinical presentation

Of the 1187 cases enrolled in the IPSS registry, 676 children had AIS and were >28 days old. Data on the presence or absence of cardiac disorders were available for 667. Of these, 204 (30·6%) had cardiac disorders or potential cardiac aetiologies on echocardiography. Compared to children with other stroke aetiologies, the children with cardiac disorders were younger (median 3·1 years vs. 6·5 years; $P < 0·001$) (Table 1). This difference was not present when comparing only the children with acquired heart disease or isolated PFO (median 8·3 years) to those without cardiac disorders (median 6·5 years; $P = 0·210$). Prior

analyses of the IPSS cohort revealed a male predominance for children with AIS (11). There was no significant difference in those with (57·4% male) and those without (60·0%) cardiac disorders ($P = 0·515$).

Congenital heart disease accounted for 121/204 (59·3%) with cardiac disorders, but specific details were not reported (Table 2). Acquired heart disease (e.g. cardiomyopathy or endocarditis) was present in 40/204 (19·6%). The children with congenital heart disease, as expected, tended to be younger at the time of stroke than those with acquired heart disease (median age 1·7 years vs. 8·7 years). Many suffered their strokes within 72 h of cardiac surgery (15·9%) or cardiac catheterization (8·5%).

Isolated PFO was reported in 31/204 (15·2%); however, echocardiogram details were reported for only 85 children as this item was added to the registry near the end of the data collection period. Echocardiogram was transthoracic in 77 and transoesophageal in nine patients. Contrasted echocardiography was performed in only 15 (18%).

Overall, 39·5% of children with AIS reported headache at onset. Of those children old enough to report headache symptoms (>3 years old), 50·0% reported headache at stroke onset. Fewer of the children with cardiac disorders reported headache at presentation (25·6% vs. 44·6%, $P < 0·001$; Table 1). This difference persisted when analysing those >3 years old (38·3% vs. 53·5%; $P = 0·016$). This age cut-off was chosen because headache was rarely reported before that age; only six children <3 years old reported headache. We collected data on the presence or absence of headache at stroke presentation, but not on details of headache location, duration, intensity, or migrainous/vascular features.

Among all children with AIS, recent infection occurred in 15·3%, 31·0% presented with seizure, and 82·6% presented with focal neurological deficits. There were no significant differences in the presence of recent infection prior to stroke ($P = 0·262$) between the groups, and although seizures at presentation were more prevalent in those with cardiac disorders, this did not reach significance ($P = 0·112$). There was a trend ($P = 0·059$) for a lower prevalence of focal findings at onset in children with cardiac disorders.

Imaging findings

Radiographic confirmation of AIS was an inclusion criterion. Imaging modality was MRI in 603/667 (90·4%) with CT only in 64/667(9·6%). Infarction in the territory of the anterior circulation only was noted in 67·6%, posterior circulation only in 21·5%, and both anterior and posterior circulations in 10·9%. Overall, infarcts were bilateral in 25% and multiple in 41·7% (Table 1).

Comparison of the children with cardiac disorders to the others revealed a significant difference in the distribution by circulation ($P = 0·005$) (Table 1). Tukey type multiple comparison testing revealed significant differences ($P < 0·05$) between the proportion with posterior circulation infarcts vs. both anterior and posterior circulation infarcts, as well as between the proportion with anterior vs. posterior circulations. There was also a significantly higher proportion of bilateral strokes in the cardiac disorder group (31·3%) than those without (22·2%; $P = 0·015$), but there were no significant differences in the proportion with

left-sided infarcts ($P = 0{\cdot}993$) or multiple infarcts ($P = 0{\cdot}652$). Overall, vasculopathy was reported in 44·5% of the children with AIS but was present in significantly fewer with cardiac disorders than those without (25·8% vs. 52·1%; $P < 0{\cdot}001$).

Children with haemorrhagic strokes were not included in the IPSS registry, but data on haemorrhagic conversion of AIS and co-incident intracranial haemorrhage were recorded. Children with cardiac disorders had more frequent haemorrhage (15·2%) than those without (6·6%; $P = 0{\cdot}001$). Of all children with AIS, there were a few with other haemorrhagic complications in conjunction, including five with intraventricular, three subarachnoid, and four subdural haemorrhages, and 22 with other uncharacterized haemorrhage.

Outcomes

Outcomes at discharge for this entire cohort have been reported (13). This analysis includes children with isolated PFO, a group separated from the cardiac disorders subgroup in the prior analysis. There was a trend ($P = 0{\cdot}078$) for worse outcome in the cardiac disorders group, with both groups having the same proportion with a normal outcome (22·0%) but a higher mortality for those with cardiac disorders (6·3% vs. 2·6%) (Table 3).

Discussion

In this large prospective international cohort, cardiac disorders were identified in 30·6% of children with AIS outside of the neonatal period. This is at the upper end of the reported range (4,6–9). This includes a relatively small number ($n = 31$ of 204) with isolated PFO, where the causal relationship to stroke is unclear (14). As expected, the majority (59·3%) had congenital heart disease and these children tended to suffer stroke at an earlier age than those without cardiac disorders. One-quarter suffered their stroke within 72 h of cardiac surgery or catheterization. Strategies for primary stroke prevention could be directed at this group.

Data on echocardiography were not systematically collected in the registry until the final year and thus is highly limited. The transthoracic approach was preferred (91%) and only a few children (18%) received contrasted studies. More thorough evaluation for cardiac disorders in children with AIS may be warranted, as recommended (15). The recent consensus and evidence-based guidelines for the treatment of stroke in children (16,17) support different therapy for children with cardiac sources of stroke, and, thus, the identification of cardiac disorders could alter management and improve outcomes.

We found a high overall prevalence of headache at presentation (50·0%) in those >3 years old. This is higher than the 21% to 34% noted in studies of adult AIS (18–23). This suggests that children may be more sensitive or susceptible to vascular changes or have increased vasoreactivity in response to stroke than adults. This elevated headache prevalence could have important ramifications for early detection as well as early treatment of stroke in children and warrants further investigation.

Headaches at presentation were significantly less prevalent in children with cardiac disorders than those without, even when looking only at children >3 years of age. This could be due to

other factors, such as whether they were able to communicate their pain or if this was prevented in the cardiac group by group-specific confounding factors such as intubation or sedation at presentation, as one quarter of the strokes in the cardiac group were procedure-related. While we did not collect specific details of the headache features at presentation, migraine itself as an underlying chronic condition was reported in only 26/667 (3·9%) of children with AIS. All were >3 years old, and thus represents 26/430 (6·0%) of the older children. There was no significant difference in the report of migraine as a potential risk factor between those children >3 years old with and without cardiac disorders ($P = 0·303$). Data on headache prevalence in children with heart disease without stroke would be useful for comparison, but, to our knowledge, have not been published.

Unlike the findings in children with cerebral vasculopathy (12), we found no significant association of stroke with recent infection when comparing the children with cardiac disorders to those without. There was no difference in the presence of seizures and a trend towards a lower prevalence of focal deficits, at presentation.

Neuroimaging studies were not centrally reviewed, but details on the location (anterior vs. posterior circulation), lateralization, and number of strokes were reported. Almost one-third of the children with AIS had posterior circulation involvement. This includes the 10·9% with involvement of both the anterior and posterior circulation. It is difficult to directly compare this to adult studies, especially as the distribution of anterior and posterior strokes in adults has altered with time, with an increase in posterior circulation involvement (24). In general, adult stroke registry data reveal posterior circulation involvement in 17–40% (24–26).

In addition, we found that one-quarter of the children with AIS had bilateral strokes and 47·1% had multiple strokes. The high proportion of children with strokes in multiple arterial distributions rather than single discrete localized lesions will complicate future studies of treatment and outcomes in children. Children may be subject to more complex deficits that will be more difficult to subcategorize for research studies. However, this tendency to multiple strokes also represents an opportunity for prevention, as at least some of these strokes are likely to be recurrent infarcts. Earlier diagnosis and more rapid initiation of antithrombotic treatment may reduce the total stroke burden.

On imaging studies, the classic ‘cardioembolic stroke pattern’ in adults (27,28) is described as multiple, often bilateral, strokes in both the anterior and posterior circulations, with a greater tendency to haemorrhagic transformation. This same pattern is also more prevalent in children with cardiac disorders. We found significant differences in stroke location, in terms of anterior or posterior circulation strokes, with a higher proportion of strokes in the anterior circulation or both the anterior and posterior circulation in the cardiac disorders group. They also had a significantly higher prevalence of bilateral strokes (31·3% vs. 22·2%) compared to those without cardiac disorders, but there was no difference in the proportion reporting single vs. multiple strokes. We also found over twice the rate of haemorrhagic transformation in the cardiac group (15·2% vs. 6·6%). This could relate to treatment differences between the groups, but data on the treatments and the timing of haemorrhage are not available. Haemorrhagic conversion was also associated with cardiac disorders among all presumptive risk factor categories in a multivariate analysis of this group

(5).Unlike the findings reported in neonatal stroke, where a predilection towards left hemisphere strokes is well described (29,30), we found no significant differences in stroke lateralization in this older (>28 day) cardiac group.

While outcome data are limited to death, neurologic deficit, or normal at hospital discharge, we found no significant difference in outcomes between the groups. This is remarkable given the additional morbidity from both congenital and acquired cardiac diseases including more global injury from hypoxia in cyanotic heart disease or low cardiac output states, as well as the increased tendency towards bilateral strokes in children with cardiac disorders, a predictor of worse outcomes. Preconditioning by prior exposure to hypoxia or reduced perfusion may account for this lack of difference in outcomes (31). It is also possible that the younger age of the children with congenital heart disease and the limited follow-up period resulted in an under-recognition of the neurologic deficits in this group.

Our study is limited by the constraints of the IPSS registry. It is an unfunded, prospective study of all children suffering stroke at enrolling institutions. As a voluntary, collaborative study, there is no central review of cases or imaging; however, site investigators (paediatric neurologists or haematologists) identified cases using consensus-based, published clinical and radiographic criteria and submitted data into standardized forms via a web-based data entry system (11). Prior to analysis, the data were reviewed and outliers were identified and the reporting sites were queried for clarification or correction of the data. As the aetiologies of stroke in children are numerous, only limited data on the specific nature of the cardiac disorders were collected. The site investigators classified the cardiac disorders as congenital or acquired without more specific characterization. Specific details of the cardiac diagnosis were not systematically recorded and details on the type of echocardiographic studies performed were only collected late in the study period, limiting the available data and the detail of the analysis.

Another limitation of the prospective IPSS is that children in the registry are not systematically investigated according to a research protocol. Rather, IPSS investigators report their clinical observations and results of clinically indicated testing according to local practice and availability, so not all of the patients underwent cardiac evaluation and children with known cardiac disorders did not all have vascular imaging. In this IPSS cohort, arteriopathy was present in 45/135 (33%) of children who had both cardiac disease and vascular imaging (12). In addition, details of the underlying cardiac disorders were not reported nor was the total number of children with similar disorders or undergoing similar procedures. Thus, we are unable to report on the relative risks of different cardiac disorders or procedures as reported in single-centre studies (32–34).We also excluded children <28 days old, a population where stroke secondary to congenital heart disease may be more common. Furthermore, imaging studies were not centrally reviewed and only limited imaging data were reported. There could also be a bias towards a higher observed prevalence of cardioembolic stroke in our study, due to the possibility of preferential enrolment of children from sites with specialization in children with heart disease. However, this large international study involved 30 centres on five continents and included centres with and without cardiothoracic surgery programs, and hopefully does allow for a wider view of the contribution of cardiac disorders to AIS in children.

Conclusions

Despite inherent limitations, the IPSS registry provides data for a large, geographically diverse group of children with AIS. Cardiac disorders were identified in 30·6%: 59·3% had congenital heart disease, 19·6% had acquired heart disease, and 15·2% reported an isolated PFO. Compared to other children with AIS, the children with cardiac disorders were overall younger and less frequently reported headache at presentation. Imaging results support the concept of a ‘cardioembolic stroke pattern’ in children with cardiac disorders, with involvement of multiple vascular distributions and a higher prevalence of bilateral strokes and haemorrhagic conversion.

Analysis of the limited imaging data available reveals the complexity of paediatric AIS, with a high prevalence of posterior circulation stroke as well as multiple or bilateral strokes. This suggests that clinical presentations can be more difficult to assess and stratification for research studies will require more rigorous imaging evaluation. Our observation that 50% of children over age 3 with AIS report headache at presentation is much higher than reported in adults and suggests a difference in vascular reactivity or sensitivity in children that warrants further investigation.

Many children with stroke have multiple risk factors. In this study, the cardiac evaluation of children presenting with other potential risk factors appears to have been limited. More thorough evaluation of more children with stroke for cardiac risk factors may be warranted, as has been recommended (15). The recent consensus and evidence-based guidelines for the treatment of stroke in children (16,17) support different therapy for children with cardiac sources of stroke. The identification of cardiac risk factors could alter management and hopefully improve outcomes. In our study, one-quarter of the children with stroke and cardiac disorders suffered procedure-related strokes. Children with known cardiac disorders represent a high-risk population for stroke, especially at the time of surgery or catheterization, and thus warrant heightened clinical attention for stroke as well as additional research for prevention, treatment, and neuroprotection.

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Table 1

Patient characteristics and imaging findings

	Cardiac disorders	No cardiac disorders	All AIS	Group comparison
Demographics				
Male	117/204 (57·4%)	278/463 (60·0%)	395/667 (59·2%)	0·515
Age (median, y)	3·1 (IQ 0·8–9·7)	6·5 (IQ 2·3–11·9)	5·7 (IQ 1·7–11·6)	<0·001
Age for those >3 years	9·7 (IQ 6·3–14·9)	9·6 (IQ 5·7–13·8)	9·6 (IQ 6·0–14·0)	0·305
Clinical presentation				
Recent infection	36/204 (17·6%)	66/463 (14·3%)	102/667 (15·3%)	0·262
Focal deficit	160/204 (78·4%)	391/463 (84·4%)	551/667 (82·6%)	0·059
Headache (all)	32/125 (25·6%)	150/336 (44·6%)	182/461 (39·5%)	<0·001
Headache (age >3 years)	31/81 (38·3%)	145/271 (53·5%)	176/352 (50·0%)	0·016
Seizure	70/198 (35·4%)	127/437 (29·1%)	197/635 (31·0%)	0·112
Stroke location				
Anterior circulation	142/198 (71·7%)	298/453 (65·8%)	440/651 (67·6%)	
Posterior circulation	28/198 (14·1%)	112/453 (24·7%)	140/651 (21·5%)	0·005
Both ant and post	28/198 (14·1%)	43/453 (9·5%)	71/651 (10·9%)	
Left	71/134 (53·0%)	180/340 (52·9%)	251/474 (53·0%)	0·993
Bilateral	61/195 (31·3%)	97/437 (22·2%)	158/632 (25·0%)	0·015
Multiple	81/188 (43·1%)	174/423 (41·1%)	255/611 (41·7%)	0·652
Haemorrhagic	26/171 (15·2%)	26/392 (6·6%)	52/563 (9·2%)	0·001
Vasculopathy	47/182 (25·8%)	231/443 (52·1%)	278/625 (44·5%)	<0·001

Differences in dominators reflect the availability of data. Group comparison is for cardiac vs. no cardiac disorder, IQ = interquartile range.

Table 2

Disorders in children with stroke attributed to cardiac cause

Disorder	*n* (%)	Median age in years (interquartile range)
Congenital heart disease	121/204 (59·3%)	1·7 (0·4–7·1)
Acquired heart disease	40/204 (19·6%)	8·7 (2·8–14·1)
Prior surgery for any heart disease	33/204 (16·2%)	3·0 (0·4–8·8)
Isolated patent foramen ovale	31/204 (15·2%)	6·1 (2·5–12·6)
Stroke at cardiac surgery (<72 h)	32/201 (15·9%)	1·5 (0·4–5·9)
Stroke at cardiac catheterization		
Diagnostic catheterization	15/201 (7·5%)	1·8 (0·3–7·3)
Interventional catheterization	2/201 (1·0%)	–
Other cardiac disorders	20/201 (10·0%)	–

Totals greater than 204 as patients can be listed in multiple categories.

Table 3

Outcomes at discharge in children with stroke

Outcome	Cardiac disorders	No cardiac disorders	All AIS	Group comparison
Normal	42/191 (22·0%)	94/427 (22·0%)	136/618 (22·0%)	
Neurologic deficit	137/191 (71·7%)	322/427 (75·4%)	459/618 (74·3%)	0·078
Death	12/191 (6·3%)	11/427 (2·6%)	23/618 (3·7%)	

Group comparison is for cardiac vs. no cardiac disorders.