Arterial ischaemic stroke in children

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Objective: Arterial ischaemic stroke (AIS) in childhood is a serious disorder about which little is published. The aim of this study is to determine the epidemiology and outcome of AIS in Australian children.

Methods: Cases of childhood AIS occurring at the Royal Children’s Hospital, Melbourne 1993–2001, were identified by medical record search using International Classification of Disease Codes. Information was collected on demographics, risk factors, arterial distribution, results of thrombophilic testing, management and outcome.

Results: During the 8 years of review 95 patients presented with 98 cases of AIS calculating an incidence of 1.8 per 100 000 children per year. Children less than 12 months of age represented greater than one third of all cases. Identifiable risk factors were present in 64% of cases with congenital heart disease the major risk factor. Thrombophilic testing was incomplete with initial abnormalities present in 18% of cases tested. The estimated stroke-related mortality was 8.4%. Of the patients who survived and who had follow-up details available, 78% had a neurological deficit. Twenty-six patients (26%) received anticoagulation. There was no statistically significant association between treatment with anticoagulation and normal neurological outcome.

Conclusion: AIS is over-represented in children under 12 months of age and results in death or residual neurological impairment in the majority of cases. Further prospective studies are needed to identify risk factors for poor outcome. The recently established Australian and New Zealand Stroke and Thrombophilia Registry should provide important information on clinical and laboratory based risk factors and create a basis for international clinical trials to improve the outcome of childhood AIS.

Key words: arterial ischaemic stroke; children; stroke; thrombophilia.

Arterial ischaemic stroke (AIS) in neonates and children is a major cause of significant morbidity and mortality.¹–⁴ Although considered rare, estimates place the incidence of AIS at 2.7 per 100 000 children, which is comparable to the incidence of brain tumours in children.⁵ Unlike brain tumours however, there is no comprehensive, multi-institutional approach to understanding the pathophysiology and improving the management of childhood AIS. Our understanding of the epidemiology of childhood AIS in Australia is limited.

Judging by the largest cohort of childhood stroke available, the majority of children with AIS present in association with a recognized risk factor.⁶ However, over one third of cases occur in otherwise well children.⁶ Recent interest has focused on thrombophilia as a cause of AIS in these children. Thrombophilic states may lead to a reduced threshold for pathological thrombus formation in cerebral vessels presenting with AIS in children. An association between thrombophilia and AIS may warrant development of primary and secondary thromboprophylactic strategies as prevention of childhood AIS.

To gain a greater understanding of epidemiology, risk factors including thrombophilic abnormalities, and outcome of childhood AIS in Australia, we reviewed all cases of AIS presenting to Royal Children’s Hospital (RCH), Melbourne from 1993 to 2001.

METHODS

Cases were identified by a medical record search. Medical records computer searches were conducted by International Classification of Disease (ICD) codes version 9 for cases diagnosed before 1998 and version 10 for cases diagnosed after 1998. Medical records were reviewed identifying eligible patients. Eligibility required a radiological diagnosis of arterial ischaemic stroke or lesion consistent with arterial ischaemic stroke. Cases that did not have radiological demonstration of arterial ischaemic stroke were excluded. Medical records of eligible patients were analysed and data collected on the following; demographics, risk factors, arterial distribution, thrombophilic investigations, treatment and outcome.

RESULTS

Patient population and demographics

One hundred and forty-four patients were identified using the ICD codes. After medical record review, 98 episodes (95 patients) met the eligibility criteria of radiographic proven AIS (35 females and 60 males). Three patients had a recurrent episode of AIS. Using data from the Australian Bureau of Statistics (http://www.abs.gov.au) this calculates an approximate incidence of AIS in Victoria of 1.8 per 100 000 children per year.

The mean age of presentation was 4.8 years (range 1 day to 19.25 years). Thirty-six episodes (36%) of AIS occurred in children less than 12 months of age with 8% of total episodes occurring in the perinatal period (Fig. 1).
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Risk factors

Risk factors for AIS were identified in 61 patients (64%). Almost one third of all strokes were associated with congenital heart disease (Table 1).

Arterial distribution

The anterior cerebral circulation was involved in 83 episodes (55 episodes involving a single vessel distribution, 29 episodes involving multiple vessel distributions). The posterior circulation was the site of involvement in 16 episodes.

Thrombophilic testing

Thrombophilic testing was performed in 33 patients (35%) at a mean duration of 44 days (range 0–690 days) after presentation. Results of thrombophilic markers were abnormal in six of these patients (18% of those patients tested).

One patient had combined protein S and protein C deficiency and was heterozygous for factor V Leiden mutation. One patient had isolated protein C deficiency and one patient had isolated factor V Leiden mutation. Three patients were positive for the anticardiolipin antibodies.

No retesting or family testing was performed on any patients with positive results.

Anticoagulation and outcome

Patients were admitted to Royal Children’s Hospital for an average duration of 18.25 days (range 0–98 days).

Twenty-six patients had management that included anticoagulation. Sixteen patients were treated with antiplatelet medication, nine patients were treated with antithrombotic medication, two patients were treated with both antiplatelet and antithrombotic medication and one patient received a single dose of lytic therapy followed by antithrombotic medication.

Fourteen patients died. Cause of death was attributed to AIS in eight cases (estimated stroke related mortality of 8.4%). Other causes of death included overwhelming sepsis, cardio-respiratory arrest, and recurrent tumour. Cause of death could not be determined in two patients.

DISCUSSION

Our study confirms the significant morbidity and mortality associated with childhood AIS in Australia. A large proportion of childhood AIS occurs in children less than 12 months of age. Most children survive but with significant neurological deficits. Our results provide basic epidemiological data and support the establishment of prospective, multi-institutional stroke registries aimed at identifying important regional differences and prognostic factors in children presenting with AIS. Stroke registries are in turn necessary to provide information and assess feasibility for future multinational intervention trials aimed at improving the outcome and prevention of childhood AIS.

Of the remainder, follow-up details were available for 69 patients (88%) with a median follow-up period of 1.6 years (range 11 days to 7.2 years). Fifteen patients (21.7%) were considered normal. Fifty-four patients (78.3%) had an identifiable neurological deficit as shown in Table 2.

Of the patients assessed as neurologically normal at follow-up, six were managed with anticoagulation (three antiplatelet, one antithrombotic and two antiplatelet and antithrombotic). This compared to 20 patients who had neurological deficits who were treated with anticoagulation. A c2 test showed no statistically significant relationship between treatment with anticoagulation and normal neurological outcome ($P = 0.84$).

Table 1 Risk factors for arterial ischaemic stroke (AIS)

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Number of children (%)</th>
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<tr>
<td>Congenital heart disease</td>
<td>28 (29.4)</td>
</tr>
<tr>
<td>No risk factor</td>
<td>27 (28)</td>
</tr>
<tr>
<td>CNS vascular malformation (total)</td>
<td>12 (12.4)</td>
</tr>
<tr>
<td>Moya moya</td>
<td>8 (8.4)</td>
</tr>
<tr>
<td>Head trauma</td>
<td>10 (10.5)</td>
</tr>
<tr>
<td>CNS or ENT infection</td>
<td>10 (10.5)</td>
</tr>
<tr>
<td>Indwelling central venous line</td>
<td>6 (6.3)</td>
</tr>
<tr>
<td>Extracorporeal support</td>
<td>6 (6.3)</td>
</tr>
<tr>
<td>Recent intracranial surgery</td>
<td>5 (5.2)</td>
</tr>
<tr>
<td>Intracranial tumour</td>
<td>4 (4.2)</td>
</tr>
<tr>
<td>Recent varicella infection</td>
<td>3 (3.1)</td>
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</tbody>
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CNS, central nervous system; ENT, ear nose throat.

Table 2 Neurological morbidity of childhood arterial ischaemic stroke (AIS)

<table>
<thead>
<tr>
<th>Neurological deficit</th>
<th>Patients (%)</th>
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<tbody>
<tr>
<td>Hemiplegia/hemiparesis</td>
<td>29 (42.0)</td>
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<tr>
<td>Developmental delay</td>
<td>14 (20.0)</td>
</tr>
<tr>
<td>Ataxia</td>
<td>11 (15.9)</td>
</tr>
<tr>
<td>Seizures</td>
<td>5 (7.0)</td>
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and 28 days postnatal age) in our study is only 8% compared to 25% of cases in the Canadian Paediatric Stroke Registry. The Royal Children’s Hospital is not an obstetric hospital and perinatal cases will be under represented in our series. An accurate number of cases of perinatal stroke may be difficult to ascertain since symptoms in neonates are non-specific and investigations may not be initiated until specific motor symptoms develop at 4–6 months of age. Identifiable risk factors were present in two thirds of our cases. Almost one third of cases presented with AIS in association with cardiac disease, which is a well-recognized risk factor and reflects the large number of cardiac procedures performed at RCH. None of the cases identified had sickle cell disease, a common association with AIS, and is consistent with the relatively low incidence of sickle cell disease in Australian children. Three cases of AIS occurred in children with recent varicella infection but no indication of the number of cases in which this association was specifically excluded could be made from the chart review. Sebire et al. was able to show a highly significant relationship between recent varicella infection (median 6 weeks) of 7 of 11 children presenting with AIS compared to controls. The mechanism by which varicella infection causes AIS remains unknown but possibly involves a focal inflammatory arteriopathy secondary to intraneural migration of the virus along the trigeminal nerve to the cerebral vasculature. Six patients in our series developed AIS in the setting of extracorporeal membrane oxygenation (ECMO). Cerebral thromboembolism is a well-recognized and unfortunate cause of neurological impairment following extra-corporeal support.

No clinically significant conclusion can be drawn from the results of thrombophilic testing in our case series. Testing was incomplete with only one third of patients tested. The testing was performed at different times following the episode of AIS. Six patients were initially deemed to have a thrombophilic abnormality present but patients with results suggestive of protein C and S deficiencies were not retested nor was family testing performed. Patients in whom antiphospholipid antibodies were identified were not retested as recommended by published guidelines. Only two patients with heterozygosity for the factor V Leiden mutation were identified. Based on a recent review of case-controlled studies in childhood stroke, the odds ratio of developing AIS in children with factor V Leiden mutation compared with controls is 4.3 (95% confidence interval 2.8–6.5). However the clinical significance of this association is not known and no evidence on the risk of recurrence, or on the risk to family members, of children with AIS and factor V Leiden mutation, or other thrombophilic markers, is available.

Management of AIS in our case series included anticoagulation for a significant proportion of cases. There are no evidence-based guidelines on the treatment of AIS in children, and the use of anticoagulation or lytic therapy is controversial. The benefits of antiplatelet (aspirin) therapy are well established in the acute management of AIS in adult patients. The function of platelets is significantly different in neonates and children and direct extrapolation of these results may be inappropriate. The use of antithrombotic therapy in adult patients with AIS has also been extensively investigated. The benefits of antithrombotic therapy in AIS are matched with an increase in intracranial haemorrhage in the older population such that anticoagulation with heparin is no longer recommended for the acute management of AIS. However, the adult cerebral circulation may be at greater risk of haemorrhage compared to that of children and antithrombotic medication may be useful to improve the outcome of children with AIS. Finally, lytic therapy offers a potentially effective form of therapy for acute AIS with early reperfusion of cerebral tissue. Experience from adult studies shows lytic therapy needs to be given within the first 6 h of symptoms and children often present significantly later.

The present case series demonstrates that childhood AIS is associated with an estimated disease related mortality of 8% and almost 80% of survivors have significant neurological deficits. However, no clinical trials have been attempted to improve stroke outcome in children. Our results also confirm that thrombophilic testing in this population is problematic and the clinical significance of the screening is unknown. The Australian and New Zealand Stroke and Thrombophilia Registry has been established and incorporates most major tertiary paediatric hospitals in Australia and New Zealand. The registry is prospectively collecting clinical and laboratory information on childhood AIS and cerebral sinus venous thrombosis (SVT) and will perform centralized thrombophilic testing on all children enrolled. The registry will provide baseline information on risk factors and prognostic information on Australian and New Zealand children and importantly establish a platform to instigate future, international clinical trials aimed at improving the outcome of childhood stroke. Further information on the registry is available by contacting the registry co-ordinator via janine.furmedge@rch.org.au.

ACKNOWLEDGEMENTS

Chris Barnes is supported by a National Health and Research Medical Council Scholarship. Dr Paul Monagle is supported by Murdoch Children’s Research Institute Part-time salary Grant. Fiona Newall is supported by the Quality Use of Medicines division of the Commonwealth Department of Health and Ageing.

REFERENCES