ORIGINAL ARTICLE

Childhood Primary Angiitis of the Central Nervous System

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ABSTRACT

Objective: To analyze the clinical course and magnetic resonance angiographic (MRA) abnormalities in children with primary angiitis of the central nervous system (cPACNS).

Study Design: Cohort study.

Place and Duration of Study: Neurosciences and Neuroradiology Department of the Children's Hospital, Lahore, from January 2009 to December 2010.

Methodology: The cohort comprised consecutive patients diagnosed as having cPACNS based on clinical findings and identification of arterial stenosis on magnetic resonance angiography (MRA) in the absence of an underlying condition that could cause these findings. The treatment protocol for ischaemic infarcts consisted of induction therapy with intravenous steroids pulses and intravenous immunoglobulin followed by maintenance therapy with azathioprine and low dose aspirin. When indicated, they were treated with anticoagulants at least for 4 weeks along with induction therapy. Patients were followed at a single centre and systemically assessed for clinical presentation, classification of disease as progressive or non-progressive, adverse effects of anticoagulants, aspirin, azathioprine and their hospital course.

Results: Sixty-eight children with medium-large vessel cPACNS (62% boys, 38% girls) with mean age of 8.5 ± 3.5 years were enrolled in this study. Motor deficit (70%); headache (64%) and fever (20%) were the commonest symptoms; whereas hemiparesis (60%); seizures 55% (focal 35%, generalized 20%) and decreased conscious level (30%), were the commonest neurological findings. Neuroradiological findings were ischaemic strokes in 50 (73.5%), haemorrhagic strokes in 10 (14.7%) and ischaemic haemorrhagic lesions in 8 cases (11.8%). Angiographically 51 (51/68, 75%) of the cohort had non-progressive (obliterative) and 17 (17/68, 25%) had evidence of progressive arteriopathy at the time of admission. No secondary haemorrhagic lesions were documented among infarcts strokes, which were treated with heparin and oral anticoagulants. Outcome was survival in 56 cases (81.5%) and death in 12 cases (18.5%). All survivors were discharged on long-term oral aspirin; 15 of them were also commenced on azathioprine. Neurological findings among the 56 survivors were; normal 20%, minor disabilities in 25%, moderate disabilities in 20% and severe disabilities in 35%.

Conclusion: The spectrum of cPACNS includes both progressive and non-progressive forms with significant morbidity and mortality. This treatment protocol of immunosuppressive therapy may improve long-term neurological outcome in children with medium-large vessel childhood primary angiitis of the CNS.

Key words: *Primary angiitis. Intracerebral haemorrhage. Aneurysms. Subarachnoid haemorrhage. Central nervous system.*

INTRODUCTION

Childhood primary angiitis of the central nervous system (cPACNS) is a form of idiopathic vasculitis restricted to the brain and spinal cord with an often slow progressive course.[1] The true incidence of cPACNS remains unknown, but as recognition of the condition increases, so does the number of cases that are diagnosed and treated appropriately. Children with the disorder present with a range of neurological symptoms including intractable seizures, hemiparesis, cranial nerve deficits, severe cognitive deficits, and decreased consciousness.[2]

Medium-large vessel disease affects arteries that are large enough to be differentiated by magnetic resonance angiogram (MRA) or conventional angiography. In patients with small vessel childhood primary angiitis of CNS, angiography findings are typically negative and thus diagnosis must be confirmed by brain biopsy. Identification and appropriate diagnosis of children with the disorder is crucial because with standardized treatment good neurological outcome is a realistic goal and early immunosuppressive therapy has improved the prognosis.[3] Therapeutic modalities including anti-platelet agents, corticosteroids, azathioprine, cyclo-phosphamide and other immunomodulatory agents have been used with variable success. While primary angiitis of the central nervous system (cPACNS) remains a rare entity, the poor specificity of the available diagnostic tests and its multiple mimics create a major diagnostic challenge.[4] In children with transient ischaemic strokes (TIAs), prompt evaluation with neuroimaging is important to rule out cPACNS and to initiate preventative antithrombotic treatment without delay. Magnetic resonance angiogram (MRA) is the imaging modality of choice for the investigation of paediatric cPACNS due to its greater sensitivity and specificity in the diagnosis of

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stroke and conditions which may cause stroke-like symptoms, i.e. “stroke mimics”. In an ideal world, immediate access to an MRI unit, able to provide a timely and accurate paediatric service, should be the gold standard.[5] The children with cPACNS have shown neurological recovery after immunosuppressive treatment suggesting that the neurological deficits caused by brain inflammation are reversible. Azathioprine has been used successfully in a few case reports. For cPACNS, the data for immunomodulatory therapies are limited, and further research is required. The improved understanding of cPACNS facilitates a tailored diagnostic approach that results in earlier diagnosis and initiation of therapy for this potentially reversible condition.[6]

There is no treatment protocol or standardized documentation of neurological outcome of children with cPACNS.[7]

The aim of this study was to describe the clinical spectrum of a cohort of children with medium-large vessel childhood primary angiitis of CNS, report the efficacy and safety of a particular treatment regimen.

METHODOLOGY

This study was a retrospective analysis of a prospectively enrolled consecutive cohort of children that were evaluated for medium-large vessel cPACNS at the Children's Hospital, Lahore, a tertiary care centre, from January 2009 to December 2010. Patients with childhood primary angiitis of the CNS who were ≤ 16 years old at diagnosis were included. The inclusion criteria were clinical diagnosis of primary CNS vasculitis of childhood and MRA confirmation of suspected cPACNS. The patients presented with history of acute neurological deficits including 94 children of either gender, with acute hemiparesis, sudden loss of consciousness, seizures, altered sensorium and speech disturbances with infarction or haemorrhage on neuroimaging of the brain. These children were admitted in the Department of Neurosciences. Cases were identified by a detailed history and thorough neurological examination. Children presenting with perinatal strokes, transient ischaemic attacks, traumatic brain injuries and neurological deficits resulting directly from an infective agent were excluded. Children with known conditions causing thromboembolic predisposition were also excluded.

Arteriopathies causing stroke in children were categorized as: non-progressive (non-obliterative) and progressive (obliterative) arteriopathies, based on the findings of CA and/or MRA. Arteriopathies causing ischaemic strokes were treated with anticoagulation according to the protocol approved by the paediatric neurologists of the department in consensus (Table I).

Induction therapy was used for resuscitation and stabilization of the patients with I/V heparin, I/V pulse methylprednisolone or I/V immunoglobulin. Maintenance therapy constituted of low dose aspirin and azathioprine. Haemorrhagic infarcts were treated conservatively but raised intracranial hypertension was treated vigorously to maintain critical cerebral perfusion pressure (more than 40 mmHg in younger children and more than 60 mmHg in older children). All patients with ischaemic infarcts were commenced on long-term aspirin 3 mg/kg/day, started on day 5-30th (depending upon patients' condition), for two years. In addition, patients with obliterative angiopathic stroke were put on oral azathioprine, started on day 5-30th (depending upon patients' condition), for 2 years. The eligible patients were recorded and analyzed for information concerning patient demographics, age, presentation, family history, underlying disease or risk factors, clinical state at presentation, investigations, diagnosis, treatment and follow-up. Initially patients were followed monthly for 3 months, then three monthly afterwards. Based on CT, MRI and/or MRA findings, stroke were classified as ischaemic, ischaemic-haemorrhagic and haemorrhagic-infarcts. Information on inpatient treatment included drugs administered, hospital course, medical therapy and decompressive surgery for raised intracranial pressure. Short-term outcome was measured in terms of mortality and clinical state at discharge as compared to that at presentation determined by neurological examination for the presence of motor, visual and speech difficulties.

Data were analyzed using Statistical Package for Social Sciences (SPSS) version 12.0 (Chicago, IL). Frequencies and percentages were calculated for qualitative data including gender, final outcome (discharge, residual neurological deficit, death) and complications of anticoagulation therapy. Mean ± SD and median were calculated for quantitative variables including age.

Table I: Treatment protocol for childhood arterial ischaemic strokes at the Children's Hospital, Lahore, Pakistan.

Induction therapy: 5-10 days

- Methyl prednisone 25 mg/kg intravenous over 4 hours daily for 3 days and/or intravenous immunoglobulin 400 mg/kg/day over 6 hours for 5 days.
- Oral prednisone 2 mg/kg daily (maximum 60 mg daily) for 30 days, weaning over 30 days.
- Supplementary calcium and vitamin D also given during prednisone treatment.
- Heparin (for ischaemic strokes, infarction size ≤ 50% of cerebral hemisphere size); loading dose 75 units/kg intravenously followed by 20 units/kg/hour for children over one year of age (or 28 units/kg/hour below one year of age) for 3-5 days, followed by oral anticoagulants for 30 days.
- Anticonvulsants and antipsychotics as needed.
- Antibiotics and antiviral and antacids along with other supportive cares as needed.

Maintenance therapy: 24 months

- Aspirin 3 mg/kg daily for all ischaemic strokes.
- Aspirin 3 mg/kg and azathioprine 1 mg/kg daily for progressive arteriopathies.
- Anticonvulsants, antipsychotics, nutrients and other supportive cares as needed.

RESULTS

Sixty-eight patients (72.3%) met the study inclusion criteria of idiopathic large-medium size arterial disease, whereas, 26 (27.7%) had strokes due to conditions other than primary pathology of cerebral arteries. The mean age at diagnosis was 8.5 ± 3.5 years (median age 7.4 years, range 1·5 - 16 years) and the median time between disease onset and diagnosis was 12 days (range 1-18). On the average 46000 children visited the department of the neurosciences each year during the study period, making an annual frequency of childhood primary ischaemic stroke of 0.57% (34/6000, 0.57%) among the admissions in the neurology wards (n = 4800, 80%) and neurosurgery wards (n = 1200, 20%) and 0.07% (34/46000, 0.07%) among the children seeking neurological (n = 35000, 76%) and neurosurgical (n = 11000, 24%) consultations.

There were 50 ischaemic strokes (50/68, 73.5%), 10 haemorrhagic strokes (10/68, 14.7%); 8 patients had ischaemic-haemorrhagic lesions (8/68, 11.8%). Forty two boys (42/68, 61.7%) and 26 girls (26/68, 38.3%) with male to female ratio of 1.6 were diagnosed with childhood primary arterial ischaemic stroke (cPAIS) of medium-large vessel variety. Based on the findings of carotid angiography (CA) or magnetic resonance angiography (MRA), 51 patients (75%) had non-progressive and 17 patients (25%) had progressive arteriopathies. Majority of the patients (62%) were more than 5 years of age. Headache was a common symptom (64%) either before the onset or on presentation of stroke. Detailed neurological examination revealed hemiplegia in 60%, seizure in 55% (focal in 30%, generalized in 25%) and decreased conscious level in 30%.

Fifty-six patients completed induction and received maintenance therapy; 41 with aspirin and 15 with combined aspirin and azathioprine. Twelve patients (17.6%) died (5 in haemorrhage only, 5 in haemorrhagic infarcts and 2 in ischaemic group who had progressive arteriopathy) on their first admission in the hospital. Of the 12 patients who died, 7 were males, 8 had severe bilateral involvement of major cerebral arteries and /or massive parenchymal bleed causing clinically significant raised intracranial pressure and deep coma (Glasgow Coma Scale ≤ 8). No secondary haemorrhage was observed among all the ischaemic-infarcts patients who were treated initially with IV heparin and later on switched over to oral anticoagulants.

DISCUSSION

This 2 years study revealed 68 cases of ischaemic and ischaemic haemorrhagic strokes with medium vessel cPACNS. However, as this study was limited to only one paediatric neurology department in Punjab, the frequency of stroke cannot be extrapolated to the whole population. Studies based on hospital discharge databases have found higher incidences.[8,9] In Asia, studies based on hospital admission database have estimated comparatively higher incidences, ranging from 27.1 to 29.7 per 100,000 children per year.[10] Similarly, in the tertiary care paediatric neurosciences department, it was documented that 0.57% of the admitted children had cPACNS with an annual frequency of 570/100,000 among children admitted in neurology and/or neurosurgery wards, and frequency of 74/100,000 in children visiting hospital for neurological and neurosurgical consultations.

Several studies have found that paediatric ischaemic stroke is more common in boys than in girls.[11] The explanation for the apparent male predominance is unknown. In agreement, male dominance (62.5%) was documented, however, a reason could not be attributed for that. In contrast to this equal gender distribution which has also been documented from India among children with cPACNS.[12]

In this case series, median age at initial presentation was 8.5 years; in agreement, Soman *et al*. have documented median age of 8.8 years, (range 1.5 - 17 years) in 212 patients.[11] DeVeber *et al*. have documented male dominance of 54% and median age of 5 years.[12] Similarly, the median age at presentation of 4.8 years has been reported by Barnes *et al*.[13] This wide variation in anthropometric data indicates the care level of paediatric neurology department receiving referrals.

In this study, fever and headache has been reported in 45% and 30% of the patients, respectively, either before or at the onset of AIS. In this case series, 26.5% children had decreased conscious level (GCS < 14) at the time of admission. Adam *et al*. have documented in their 41 children with AIS; altered mental status 17%, fever 7% and headache in 7%.[14] In contrast to this, seizures were documented in 55% (35% focal and 20% generalized) in these patients, whereas, Jiun-Chang *et al*. from Taiwan have reported seizures in 41.5% of their cAIS patients.[15]

Compared to adults, seizures, fever, lethargy and headache are frequent in children with cPACNS. In the Canadian paediatric ischaemic stroke registry (CPISR), 69% children with AIS presented with focal neurological deficits and 37% with seizures. In this case series, the focal deficits included motor deficits 78%, speech abnormalities 16%, visual deficits 10% and other deficits 32%.[7] Data from Asian countries has also revealed similar figures.[7,9,16,17] Although the majority of childhood PACNS presented with single episode of focal neurological deficit, preceding TIAs are present in about one-third.[18] A preceding history suggestive of TIAs was found in 20.6% patients. Najaraja *et al*. in a study of 43 stroke patients between age 1 - 16 years noted that 10 patients (23%) had preceding history of febrile episode and suggested viral infections may have a triggering

factor for a vascular lesion leading to a thrombosis phenomenon and resulting in vascular occlusion.[19] In the present series, febrile illness was reported in 30% and 20%, preceding and at presentation, respectively. Headache was reported among 34% and seizures in 20% of those patients; either before the onset of stroke or on presentation. Similarly, Braun *et al*. have documented headache and seizures in 45% and 16% respectively.[20]

Neuroradiology of the head documented abnormal imaging in 100% of the patients. In contrast, Makhija *et al*. documented infarction in 91% of their childhood ischaemic stroke patients.[21]

All the patients with haemorrhagic and haemorrhagic-infarct lesions were treated conservatively (no anti-coagulants), but raised intracranial pressure was vigorously treated to maintain the critical cerebral perfusion pressure. Four patients required craniotomy to remove large blood clots to lower intracranial hypertension. Majority (80%) of the patients with infarct strokes were administered heparin, and later these were switched over to oral anticoagulants, where clotting profile monitoring was possible. Ten patients (20%) in ischaemic infarcts group had either very large infarcts (greater than 50% of single hemisphere) or presented later than one week, so they were not treated with heparin and oral anticoagulants but aspirin was commenced.

Azathioprine and mycophenolate mofetil are recommended as maintenance therapy once remission is achieved.[22] At discharge, all patients with infarct strokes were put on oral acetylsalicylic acid (aspirin) 3 mg once a day and patients with progressive arteriopathy were also put on azathioprine 1 mg/kg/day, commenced on 15-30th day. These two agent would be continued for 2 years. The protocol is to treat cPACNS as; non-progressive form for 2 years and progressive form for 5 years but azathioprine would be stopped after 2 years. No secondary haemorrhage due to heparin or oral anticoagulants was observed in these patients. No adverse effects have been observed in children on long term aspirin and azathioprine (follow-up 1 - 18 months). In agreement, in a case series by Barnes *et al*. 26 patients (26%) received anticoagulation without any adverse side-effects.[13] The benefits of anti-platelet (aspirin) therapy are well established in the acute management of AIS in adult patients. However, aspirin, either alone or in combination with some other anti-platelet agents, appears to be a well-justified choice for the prevention of recurrent ischaemic stroke.[21] Long-term neurologic deficits occur in 50 - 85% of infants and children after arterial ischaemic stroke (AIS).[8]

Lanthier *et al*. reported the outcome as asymptomatic in 36%; symptomatic epilepsy or persistent neurologic deficit in 45%; and death in 20%.[18] More than a half of these children with AIS will have neurological sequelae.[18] Eighty percent survivors in the studied group had neurological deficit at the time of discharge; hemiparesis being the most common (55.5%), followed by seizures, visual disturbances, speech difficulties and swallowing difficulties. This high percentage of neurological deficits indicated critical and advance stages of patients being treated at the tertiary care paediatric neurology department. In agreement, DeVeber *et al*.[12] have documented that long-term neurological deficits occur in 50 - 85% of infants and children after arterial ischaemic stroke (AIS).

The present case series demonstrates that childhood AIS is associated with an estimated disease related mortality of 18.4%. In contrast, Barnes *et al*.[13] have recorded a mortality of 8.4% in such patients. Almost 78% of survivors have significant neurological deficits. Infarcts in both hemispheres have been associated with poor outcome, but haemorrhagic infarction, the number of infarcts, and the size of the artery involved were not predictive factors.[23]

Strength of this study was the large number of consecutive cases. Compared with individual cases or smaller previous series, this cohort provided a more complete spectrum of clinical findings. As in any retrospective study, incompleteness of data was a concern. In particular, inflammatory markers were not systematically assessed, and their predictive value for differentiating progressive and non-progressive forms of the disease remained unclear from this study. The use of MRA as compared with conventional angiography at presentation presents additional issues in the study, since 80% patients in this study were investigated with MRA only and brain biopsy was not done in any of these patients.

CONCLUSION

The findings from this study underline the significant mortality and morbidity of childhood strokes, and the importance of having a high index of suspicion, so as to ensure early diagnosis and prompt commencement of specific therapies. MR imaging findings were abnormal in all cases at diagnosis and this remained the most sensitive technique for the detection of cPACNS of large-medium vessel disease. This treatment protocol may improve long-term neurological outcome in these children.

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