Azathioprine and Aspirin in Childhood Primary Arterial Stroke

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Abstract: *Objectives*: The objectives of the study were to determine the complications of anticoagulants in acute phase, and of low dose Aspirin with and without Azathioprine in remission and maintenance phases in patients with arterial ischemic strokes (AIS).

Study Type: observational and analytic.

Place: The department of the Neurology of the Children's Hospital Lahore-Pakistan.

Setting and Duration: The study was conducted at the department of the Neurology of the Children's Hospital from 1st Jan 2009 to 31st December 2010.

Methods: Over the period of 2 years, 68 patients with acute ischemic strokes were admitted, who presented within 14 days of onset of the symptoms. Patients with AIS were treated with anticoagulants at least for 04 weeks and this was followed by long term use of Aspirin. Patients ais due to progressive arteriopathy were treated with Azathioprine. Patient were followed in Hospital based cohort study at single center and were systemically assessed for clinical presentation, classification of choldhood primary ischaemic stroke (cPIS), adverse effects of anticoagulants, aspirin and azathioprine.

Statistical Analysis: Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 12.0 (Chicago, IL). Frequencies were calculated for categorical data including gender, final outcome and complications of anticoagulation therapy.

Result: 68 children with cPIS (boys 62%, girls 38%) with mean age of 8.5 years (median age 7.4 + 3.5 years), were enrolled in this study.The mean time-interval between the symptoms onset and the patients' admission to the hospital was 5.6 days (range 1 to 14 days). Motor deficit (70%); headache (64%) and fever (20%) were the commonest symptoms, whereas, hemiparesis (60%); seizure 55 % (focal 35%, generalized 20%); and decreased conscious level (30%), were the commonest neurological findings. Neuroradiological findings of head revealed; ischemic strokes 50 (73.5%); hemorrhagic strokes 10 (14.7%) and ischaemic- haemorrhagic lesions 8(11.8%). Conventional angiography and/or MRA revealed that at the time of admission 51 (51/68, 75%) of the cohort had non-progressive (obliterative) and 17 (17/68,25%) had evidence of progressive arteriopathy. No secondary hemorrhagic was documented among infarcts strokes, who were treated with heparin and anticoagulants. Hospital outcome was as; survivors 56 (81.5%) and deaths 12 (18.5%). 40patints discharged on long term oral aspirin, and 14 children of these were commenced also on Azathioprine and are on follow-up. The Neurological findings among 56 survivors were; normal 20%; minor disabilities 25%; moderate disabilities 20% and severe disabilities 35%.

Conclusions and Recommendations: The spectrum of cPIS in children includes both progressive and nonprogressive forms. Characteristic features at diagnosis can be used to predict later progression, and to guide selection of patients for immunosuppressive therapy. Further studies are required to substantiate our findings.

Keywords: Primary angiitis, Intracerebral hemorrhage, Multiple aneurysms, Subarachnoid hemorrhage, Immunosuppressive Therapy, Central nervous system, Children.

INTRODUCTION

Meaningful progress in our understanding and clinical approach to childhood primary ischaemic stroke (cPIS) has been made in the past three decades. Increased recognition of cPIS and general advances in diagnosis of neurological disorders has led to an aggressive diagnostic approach and a proliferation of case reports providing enriched clinical and pathological descriptions. Primary angiitis of the central nervous system (PACNS) is a rare, idiopathic vasculitis diagnosed most frequently in adults. 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 slowly progressive course [1]. 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]. In children, PACNS can result in permanent central nervous system damage, potential for survival to be compromised by delayed diagnosis and treatment. No consistent Laboratory abnormalities are diagnostic. While neuroimaging and lumbar puncture can be helpful, angiography (conventional / MRA) or brain biopsy is necessary of diagnosis. Identification and appropriate diagnosis of children with the disorder is crucial because with standardized treatment good neurological outcome is a realistic goal. Early immunosuppressive therapy has improved the prognosis [3]. Therapeutic modalities including anti

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platelet agents, corticosteroids, Azathioprine, Cyclophosphamide and other immunomodulatory agents have been used with variable success. While primary angiitis of the central nervous system (PACNS) remains a rare entity, the poor specificity of the available diagnostic tests and its multiple mimics create a major diagnostic challenge [4]. CNS vasculitis symptoms and signs are frequently subtle, subacute and often non-specific in nature. The protean manifestations of cPACNS, along with the nonspecific recently been described in case reports and case series, 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. There is no treatment protocol or standardized documentation of neurological outcome of children with PACNS [5]. We aimed to assess clinical features, a treatment regimen and describe short term neurological outcomes in a cohort of children with this disorder.

MATERIALS AND METHODS

This study is a retrospective analysis of a prospectively enrolled consecutive cohort of children aged 6 months to 16 years that were evaluated for cPAS at the Children's Hospital Lahore between 1st January 2008, to 31stDecembe 2010. The patients presented with history of acute neurological deficits including 84 children of either sex, with acute hemiparesis, sudden loss of consciousness, seizures, altered sensorium and speech disturbances with infarction or hemorrhage on neuroimaging of the brain. Children presenting within primary diagnosis of meningitis encephalitis, systemic lupus erythematosis head trauma or stroke caused by other conditions than cerebral arteritis were excluded.

These children were admitted in the department of Neurosciences. Cases were identified by a detailed history and thorough neurological examination. Inclusion criteria comprised (as described for adults by Calbrese *et al.,*) [1, 6]. Children presenting with perinatal strokes, transient ischemic attacks, traumatic brain injuries and neurological deficits resulting directly from an infective agent were excluded. Children with known conditions causing thromboembolic predisposition were 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 published protocols. Hemorrhagic infarcts were treated conservatively but raised intracranial hypertension was treated vigorously to maintain critical cerebral perfusion pressure (more than 40mmHg in younger children and more than 60mmHg in older children). All patients with ischaemic infarcts were commenced on long term aspirin 3mg/kg/day, started on day 5-30th (depending upon patients' condition), for two years and obliterative angiopathic patients were put on oral Azathioprine, started on day 30th, 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 would be followed monthly for 3 months, then three monthly afterward. Based on CT, MRI and/or MRA findings, stroke were classified as ischemic, 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.

RESULT

Between 1st January 2008 and 31st December 2010, 94 patients, aged 6 months to 16 years with clinical diagnosis of cAIS were identified from the 6000 admissions in the Department of the Neuroscience. Of these 94 children, 68(73.4%) met the study inclusion criteria, as they had childhood primary acute ischemic stroke (cPAIS). All patients presented with headache and/or focal neurologic deficits and exhibited clinical and/or radiographic evidence of disease progression. Twenty six patients (26.6%) had strokes due to conditions other than primary pathology of cerebral arteries and were excluded from the study. Among the enrolled patients, 42 boys (42/68, 62%) and 26 girls (26/68, 38%) with male female ratio of 1.62 were diagnosed with cPAIS. Majority of the patients (62%) in our study group were more than 05 years of age: mean age was 8.5 yrs (median age 7.4 yr±3.5 range 1.5 yrs to 16yrs). On the average 46000 children visited the department of the neurosciences each year during the study period, making an annual frequency of cPAIS of 0.55 % (68/6000, 0.55%) among the admissions in the Neurology (4800, 80%) and Neurosurgery (1200, 20%) wards, and 0.05% (68/46000, 0.05%) among the children seeking neurological (35000) and neurosurgical (11000) consultations. There were 50 ischemic (50/68, 73.5%), 10 hemorrhagic (10/68, 14.7%) and 8 had Ischemic hemorrhagic lesions (8/68,

11.8%). Based on the findings of carotid angiography (CA) and/or magnetic resonance carotid angiography (MRCA) 51patients (75%) had non-progressive and 17patients (25%) had progressive arteriopathies. Headache was common symptom (64%, either before the onset or on presentation of stroke), followed by hemiplegia 60%; seizure 55% (focal 30%, generalized 25 %) and decreased conscious level (30%). Twelve patients (18.5%) died (5 in hemorrhagic, 5 in hemorrhagic infarcts and 2 in Ischemic groups) 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 significantly elevated intracranial pressure and deep coma (Glasgow Coma Scale < 8). No significant differences were found for age, localization of AIS and occurrence of seizures for morbidity and mortality among these patients (p=0.24 – 0.78). No secondary hemorrhage was observed among all the ischemic-infarcts patients who were treated initially with IV heparin and later on switched over to oral anticoagulants

DISCUSSION

Primary angiitis of the central nervous system of childhood (cPACNS) is a reversible cause of severe neurological impairment, including acute ischemic stroke, intractable seizures and cognitive decline. Once clinically suspected, angiography and /or MRA are key imaging modalities [7]. Epidemiological studies have revealed an annual incidence of 2.5-2.7 pediatric strokes per 100,000 children. This figure comprises ischemic and hemorrhagic events, and excludes strokes from trauma or birth-related complications [1]. Our 2-year retrospective review revealed 68 cases of ischaemic and haemorrhagic strokes. 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]. These studies were reported from two large hospitals in Saudi Arabia. The reason for the increased incidence is likely related to the fact that both hospitals serve as tertiary care centers and provide services to several regions of the country. Similarly, In our tertiary care paediatric neurosciences department, we documented that 0.55% of the admitted children had cPAIS with an annual frequency of 550/100,000 among children admitted in neurology and / or neurosurgery wards, and frequency of 149/100,000 in children visiting hospital for neurological and neurosurgical consultations. Like most of the Asian studies, our increased incidence of cAIS among the hospitalized patients, similar to other studies [10], is likely related to the fact that our hospital serves as tertiary care center and provides services to several regions of the country and receives referrals from other teaching hospitals.

Several studies have found that pediatric ischemic stroke is more common in boys than in girls [11]. The explanation for the apparent male predominance is unknown. In agreement we have documented male dominance (62.5%) and could not explain reason for that. In contrast to this equal sex distribution also, has been documented form India among children with AIS [12].

In our case series, mean age at initial presentation was 8.5 years; in agreement, Soman *et al*. have documented mean age of 8.8 years, (range 1.5 to 17 years) in two hundred twelve patients [11]. De Veber *et al.,* have documented male dominance of 54% and median age of 5 years 12, similarly, the mean age at presentation of 4.8 years has been reported by Barnes *et al*. [13]. This great variation in anthropometric data indicates the care level of paediatric neurology department receiving referrals.

The clinical manifestations of stroke in children are diverse and often non-specific. In our study fever and headache has been reported in 45% and 30% of the patients, respectively, either before or at the onset of AIS. In our 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 our patients, whereas, Jiun-chang L *et al.* from Taiwan have reported seizures in 41.5% of their 94 cAIS patients [15].

They can also present with other neurological deficits such as speech, visual, focal sensory or coordination abnormalities. The focal deficits include 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 transient ischemic strokes (cAIS) present with single episode of focal neurological deficit, preceding TIAs are present in about one third [18]. In children with TIAs, prompt evaluation with neuroimaging is important to rule out AIS and to initiate preventative antithrombotic

treatment without delay. We documented preceding history suggestive of TIAs in 20.6% patients. Najaraja *et al.,* in a study of 43 stroke patients between age 1 to 16 years noted that 10 (23 %) patients had preceding history of febrile episode and suggested viral infections may a triggering factor for a vascular lesion leading to a thrombosis phenomenon and resulting in vascular occlusion [19]. In our case series febrile illness was reported in 30% and 20%, preceding and at presentation, respectively. This high percentage may be explained due to poor documentation of preceding fever or prevalence of high infections in our society. We documented headache among 34% and seizures in 20% of our 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].

Magnetic resonance imaging (MRI) is the imaging modality of choice for the investigation of paediatric AIS due to its greater sensitivity and specificity in the diagnosis of 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 [7]. Neuroradiology of the head in our case series documented abnormal imaging in 100% of the patients and the classification of stroke was; ischaemic infarcts 73.5%; hemorrhagic strokes 14.7% and haemorrhage-ischemic infarcts 11.8. In contrast, Makhija *et al*. [21] documented infarction in 91 % of their childhood stroke patients.

Antithrombotic and anticoagulants are used in the treatment of pediatric stroke; however, there are no established guidelines for the use of these agents in children. Adult studies, pediatric case studies and expert opinion form the basis for these treatment strategies. Current treatment strategies for treating cAIS are to treat with anticoagulants (IV heparin or unfractioned, oral anticoagulants) and aspirin. Although the pathophysiology and outcomes of adult AIS differ significantly from those in childhood AIS, therapeutic management remains similar, largely because of the paucity of evidence from devoted pediatric observational studies and clinical trials [22]. All patients in our case series with haemorrhagic and haemorrhagic- infarct lesions were treated conservatively 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 (20% patients in ischaemic infarcts group had either very large infarcts (greater than 50% of single hemisphere) or presented later then one week, so were not treated with heparin and oral anticoagulants but aspirin was commenced.

Treatment recommendations for cerebral angitis are derived from protocols for systemic vasculitides. In general, a combination of steroids and pulse cyclophosphamide (CYC) is recommended for induction treatment [23]. At discharge all patients with infarct strokes were put on oral acetylsalicylic acid (aspirin) 3mg once a day and patients with progressive arteriopathy were also put on Azathioprine 1mg/kg/day, commenced on 30th day. These two drugs would be continued for 2 years.

For cPACNS, the data for immunomodulatory therapies are limited, and further research is required. Our improved understanding of cPACNS facilitates a tailored diagnostic approach that results in earlier diagnosis and initiation of therapy for this potentially reversible condition [24]. Our protocol is to treat cPACNS as; non-progressive form for two years and progressive form for five years. We will monitor the response and side effects over this time period but till now we have not documented any serious side effects of Azathioprine in these patients.

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 and almost 78% of survivors have significant neurological deficits. Infarcts in both hemispheres have been associated with poor outcome, but hemorrhagic infarction, the number of infarcts, and the size of the artery involved were not predictive factors [25]. A strength of this study was the large number of unselected, consecutive cases. Compared with individual cases or smaller previous series.

CONCLUSION

In summary, our study defined progressive and nonprogressive forms of cPACNS. Further studies to assess additional markers of inflammatory activity and biopsy results as well as clinical trials to assess immunosuppressive therapy for children who exhibit features of progressive disease are needed. 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.

DISCLOSURE

The authors have no conflict of interest to declare.

ETHICAL CONSIDERATIONS

The study protocol was granted ehical approval from as per guidelines of the Ethical Review Committee of the Children's Hospital Lahore. The informed consent was not needed owing to the anonymous presentation of the patient data.

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