

Recurrence Prevention of Childhood Primary Angiitis of Central Nervous System by Combination of Azathioprine and Aspirin

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Abstract The objectives of the study were to determine the frequency of various presenting features and its effect on final outcome in childhood primary angiitis of central nervous system (cPACNS). The study also aimed to determine the frequency of complications with use of anticoagulants followed by long term Aspirin and Azathioprine in patients with ischemic infarcts. The study was conducted at the department of the Neurosciences and the Neuroradiology of the Children's Hospital from 1st Jan 2009 to 31st December 2010. 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 ischaemic infarcts were treated with anticoagulants at least for 04 weeks and this was followed by long term use of Aspirin and Azathioprine. Patient were followed in Hospital based cohort study at single center and were systemically assessed for clinical presentation, classification of cPACNS, adverse effects of anticoagulants, aspirin, azathioprine and their hospital course. Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 12.0 (Chicago, IL). 68 children with cAIS (boys 62%, girls 38%) with mean age of 8.5 years (median age 7.4 + 3.5 years), were enrolled in this study. 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, which were treated with heparin and anticoagulants. Hospital outcome was as; survivors 56 (81.5%) and deaths 12 (18.5%). 40 patients discharged on long term oral aspirin, and 14 children of these were commenced also on Azathioprine and are on follow-up. Male sex, deep conscious level and intra cerebral bleed causing severe raised intracranial pressure were the poor prognostic factor. The Neurological findings among 56 survivors were; normal 20%; minor disabilities 25%; moderate disabilities 20% and severe disabilities 35%.

Keywords: primary angiitis, intracerebral hemorrhage, multiple aneurysms, subarachnoid hemorrhage, central nervous system, children

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1. Introduction

Meaningful progress in our understanding and clinical approach to primary angiitis of the CNS (PACNS) has been made in the past three decades. Increased recognition of PACNS 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) childhood 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 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 challenge⁴. CNS vasculitis symptoms and signs are frequently subtle, subacute and often non-specific in nature. These characteristics combined with the fact that confirmation of the diagnosis requires that an invasive procedure (either an angiogram or brain of available diagnostic modalities, pose a challenge for accurate diagnosis. PACNS can be mimicked closely in both its clinical presentation and radiologic manifestations by a number of disorders. Because it has only biopsy, be performed on a delicate organ system, the brain. 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.

2. 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 AIS at the Children's Hospital Lahore between 1st January 2008, to 31st Decembe 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, 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.

2.1. 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 primary cAIS, whereas, 26 (26.6%) had strokes due to conditions other than primary pathology of cerebral arteries. 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 (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 ischaemic (50/68, 73.5%), 10 haemorrhagic (10/68, 14.7%) and 8 had Ischaemic-haemorrhagic lesions (8/6811.8%). Forty two boys (42/68, 62%) and 26 girls (26/68, 38%) with male female ratio of 1.62 were diagnosed with childhood arterial ischaemic stroke (cPAIS). 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. Majority of the patients (62%) in our study group were more than 05 years of age: mean age was 8.5 years (median age 7.4 ± 3.5 years, range 1.5 years to 16 years). Headache was common symptom (64%, either before the onset or on presentation of stroke).Detailed Neurological examination revealed; hemiplegia 60%; seizure 55% (focal 30%, generalized 25 %) and decreased conscious level (30%).

Twelve patients (18.5%) died (5 in haemorrhagic, 5 in haemorrhagic infarcts and 2 in Ischaemic groups) on their first admission in the hospital. Of the 12 patients who died, 7 were males, 8 had sever bilateral involvement of major cerebral arteries and /or massive parenchymal bleed

causing significant raised 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. 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.

3. Results

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). 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 \pm 3.5 (median age 7.4yrs, 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.

4. Discussion

Central nervous system vasculitis in children is a newly recognized inflammatory brain disease, which may develop as a primary condition, or secondary to an underlying systemic disease. 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]. Childhood strokes, though perceived to be relatively rare, have an incidence approximately equal to pediatric brain tumors. 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 the United States, a national study of hospital discharge codes for ischaemic stroke for children, revealed an estimated incidence of 7.8 per 100,000 children per year. 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. Several studies have reported an increased in the overall average annual incidence of AIS in children. 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 from 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]. DeVeber 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, Jiunchang L et al from Taiwan have reported seizures in 41.5% of their 94 cAIS patients [15].

In infants and young children, AIS usually presents with seizures, irritability or altered consciousness. Hemiparesis although not uncommon, is difficult to recognize in this age group. Older children typically present with focal neurological deficit usually hemiparesis and/or facial droop with or without seizures. [15] They can also present with other neurological deficits such as speech, visual, focal sensory or coordination abnormalities. Compared to adults, seizures, fever, lethargy and headache are frequent in children with AIS. In the CPISR, 69% children with AIS presented with focal neurological deficits and 37% with seizures. The focal deficits included motor deficits 78%, speech abnormalities 16%, visual deficits 10% and other deficits 32%. Data from Asian countries has also revealed similar figures. [7,9,16,17] Although the majority of childhood AIS present with single episode of focal neurological deficit, preceding TIAs are present in about one third [18]. In children with transient ischemic strokes (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 unfractionated, 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 than 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. An alternative option is the use of the anti-CD20 antibody Rituximab. Methotrexate, Azathioprine and Mycophenolate mofetil are recommended as alternatives to CYC once remission is achieved.²³At 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.

Azathioprine has been used successfully in a few case reports. Immunosuppressive treatment regimen was effective for reversing neurological deficits and controlling severe neurologic manifestations of small-vessel childhood primary angitis of the central nervous system in a relatively large cohort study of the rare inflammatory brain disease. There is good evidence for the efficacy and tolerability of immunomodulatory therapies in GBS, myasthenia gravis, and acute central nervous system demyelination, though data to establish superiority of one therapeutic regimen over another remains lacking. 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.

No secondary hemorrhage 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 month – 18months). In agreement in a case series by Barnes et al, twenty-six patients (26%) received anticoagulation without any adverse side effects [13]. The benefits of antiplatelet (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 ischemic stroke²¹. Long-term neurologic deficits occur in 50% to 85% of infants and children after arterial ischemic stroke (AIS) [8].

Lanthier et al, in a study of 72 stroke patients reported as follows: asymptomatic, 36%; symptomatic epilepsy or persistent neurologic deficit, 45%; and death, 20%. More than a half of these children with AIS will have neurological sequelae¹⁸. We observed that 80% of our survivals 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 out tertiary care paediatric neurology department. In agreement, DeVeber et al¹², have documented that long-term neurological deficits occur in 50% to 85% of infants and children after arterial ischemic stroke (AIS).

Barnes et al [13], have documented hemiplegia/hemiparesis in 42.0%, developmental delay in 20.0%, ataxia in 15.9% and seizures in 7%. Similarly Cnossen et al demonstrated that 54% of children had severe neurological impairments at 12 months after discharge from hospital [21].

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].

Seizure at stroke onset has been suggested as a negative prognostic factor¹⁸ but a larger study did not support this. Children with altered mental status on presentation and with complete middle cerebral artery cortical strokes have a less favorable prognosis. With modern therapeutic agents, it is possible to implement appropriate therapy but in spite of this, there remains a not inconsequential morbidity and mortality. This encouraging finding emphasizes the need for early diagnosis and initiation of therapy that may help avoid irreversible CNS events.

A strength of this study was the large number of unselected, consecutive cases. Compared with individual cases or smaller previous series, our cohort likely provided a more complete spectrum of clinical findings. 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 nonprogressive disease are needed

4.1. 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. Accesses to 24-hour neuroimaging facilities, dedicated and specialized acute stroke units for managing childhood stroke are of utmost importance. Further studies are required to substantiate our findings.

Keeping these findings in view, we have established the first National Paediatric Stroke Unit in the Children's Hospital Lahore.

Disclosure

The authors have no conflict of interest to declare.

Acknowledgement

Being a retrospective study, the study protocol was granted exemption from review as per guidelines of the Ethical Review Committee of the Children's Hospital Lahore. Similarly informed consent was not needed owing to the anonymous presentation of the patient data.

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