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Case Report Open Access

Maintenance Treatment of Childhood Primary Angiitis of Central Nervous System with Aspirin and Azathioprine

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Abstract

Objectives: We aimed to assess the efficacy and safety of Aspirin and Azathioprine in prevention of recurrence of childhood primary angiitis of central nervous system (cPACNS) after induction therapy with intravenous pulse Methylprednisolone/ Immunoglobulin, and describe long-term neurological outcomes in a cohort of children with this disorder.

Study type: Case series

Methods: The cohort comprised of consecutive patients diagnosed as having childhood primary angiitis of central nervous system (cPACNS), based on clinical and vascular imaging findings, including identification of arterial stenosis on conventional angiography or Magnetic Resonance (MR) angiography. Over the period of 2 years, 68 children with cPACNS were admitted, who presented within 14 days of onset of the symptoms. Patients with ischemic infarcts were initially treated in conjunction with Heparin/ Oral Anticoagulant and IV Methylprednisolone and/or Immunoglobulin, and this was followed by long term use of Aspirin and Azathioprine. Patient were followed in the out patients clinics and were systemically assessed for clinical presentation, hospital course, adverse effects of anticoagulants, aspirin and Azathioprine. The primary outcomes were 1) morbidity and mortality, 2) Paediatric Stroke Outcome Measure (PSOM) scores after the median follow-up of 34 months.

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. Mean with 95% SD was calculated for nominal variables including age. Fisher's exact test or chi squared test were used, where appropriate to determine any significant difference in outcome with different presenting features, taking $p<0.05$ as significant.

Results: From January 2008, to December 2010, 94 patients with cPACNS were enrolled, 68 of whom met the inclusion criteria and were given induction therapy. The median age at diagnosis was 8.5 years (range 1·6-16 years). 56 patients (boys 35/56, 62%, girls 21/56, 38%) completed induction therapy (with acute mortality of 12/68, 18.5%) and received maintenance therapy with aspirin (n=40) or aspirin and azathioprine (n=16). At the median follow-up of 34 months, of the total 56 patients is; total 30 (30/56, 53.5%) had relapse/flare: first relapse within 24 months after discharge 35.7%: 20 (20/56, 35.7%) died, 15 (15/56, 26.7%) in association with relapse of cPACNS, 5 (5/56, 9%) died due to other causes:14 (14/56, 25%) were receiving Aspirin only: 11 (11/56, 19.6%) were off any medication : 7 (7/56, 12.3%) were receiving both Azathioprine and Aspirin and 4 (4/56, 7.2%) were lost in follow-up. The Neurological findings among 32 patients available to be assessed at last follow up by Paediatric Stroke Outcome Measurement (PSOM) were; normal 8 (8/32, 25%); minor disabilities 10 (10/32, 31.25%; moderate disabilities 10 (10/32, 31.25%) and severe disabilities 4 (4/32, 12.5%). No serious side effects were documented due to low dose aspirin and azathioprine therapy.

Conclusion: The spectrum of cPACNS in children includes both progressive and non-progressive forms. Recurrence of cPACNS was high within six months after discharge with high mortality, more among the patients treated with Aspirin than with Azathioprine in conjunction with Aspirin, after initial treatment with IV Methylprednisolone / Immunoglobulin and heparin/ oral anticoagulants.

Keywords: Primary angiitis; Intracerebral haemorrhage; Azathioprine; Aspirin; Central nervous system; Children; Headache; Stroke; Magnetic resonance; Angiography; Immunosuppressive therapy

Introduction

Childhood primary angiitis of central nervous system (cPACNS) is a form of vasculitis of unknown etiology primarily affecting small and medium-large sized vessels supplying the brain parenchyma, spinal cord and leptomeninges with an often slowly progressive course [1,2]. Children with this disorder present with a range of neurological symptoms including intractable seizures, hemiparesis, cranial nerve deficits, severe cognitive deficits, and decreased consciousness [3]. While cPACNS remains a rare entity, the poor specificity of the available diagnostic tests and its multiple mimics create a major diagnostic challenge [4]. No consistent laboratory abnormalities are diagnostic. While neuroimaging and lumbar puncture can be helpful, Conventional Angiography (CA)/Magnetic Resonance Angiography (MRA) or brain biopsy is necessary of diagnosis. Identification and appropriate diagnosis of children with the disorder is crucial because with standardized

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treatment good neurological outcome is a realistic goal. Therapeutic modalities including anti platelet agents, corticosteroids, Azathioprine, Cyclophosphamide and other immunomodulatory agents have been used with variable success [5].

There is no treatment protocol and standardized documentation of neurological outcome of children with PACNS [6]. The optimal duration of treatment for children with PACNS remains unknown. Outcome is variable; some children experience permanent neurological damage, whereas others have full recovery [7]. We aimed to assess safety and efficacy of Aspirin and Azathioprine in prevention of recurrence of cPACNS after induction therapy, and describe the long-term neurological outcomes in a cohort of children with this disorder.

Materials and Methods

We did an open-label cohort study at The Children's Hospital Lahore-Pakistan, a tertiary care paediatric neurology centre, from 1st January 2008, to 31st December 2010. After successful induction therapy these patients were started on maintenance therapy and were followed in outpatient department of the hospital. Since February 2011, these patients were followed and monitored in the outpatient clinics at the Brain Associates Lahore. Patients with childhood primary angiitis of the CNS who were ≤ 16 years old at diagnosis were included. Childhood primary angiitis of the CNS was defined according to Calabrese criteria [7], a newly acquired neurological deficit plus angiographic features consistent with CNS vasculitis and absence of evidence of an underlying condition that could explain these findings. Inclusion criteria comprised also, of the confirmation of stroke on the neuroimaging of brain, so only large -medium size arteriopathies were included because small vessel angiitis is diagnosed on brain biopsy that was not available at our centre.

Transient ischaemic attaches were defined as presence of symptoms/signs of stroke which improved within 24 hours after onset. Arteriopathies causing stroke in children were reported in consultation with neuroradiologist and were categorized as: 1) non-progressive cPACNS, a monophasic inflammatory vessel wall disease and brain parenchymal lesion of the same duration, 2) progressive cPACNS as an ongoing inflammatory disease of the CNS vessels frequently affecting both proximal and distal vessel segments or had new vessel segments affected on repeat vascular imaging with evidence of different time of occurrence of these lesions. Standardized assessments, including clinical and neurological examination, quality of life measures, and laboratory markers were done in the CNS vasculitis clinic at baseline, monthly for three months after discharge from hospital, then three-six monthly till the final follow up.

The patients presented with history of acute neurological deficits including 94 children of either sex, with acute hemiparesis, sudden reduced conscious level (defined as a modified Glasgow Coma Score of 14 or less) [8], seizures, altered sensorium and speech disturbances with infarction or haemorrhage on neuroimaging of the brain. Brain imaging was done in all patients at baseline, and when clinically required. Laboratory values, including complete blood count; erythrocyte sedimentation rate; concentrations of C-reactive protein, complement C3, von Willebrand factor antigen, and IgG; and presence of lupus anticoagulant, antinuclear antibody, antineutrophil cytoplasmic antibody, and anticardiolipin antibody, were taken at diagnosis and at follow-up visits, when clinically indicated. We did a standardised series of infectious assessments as required from the clinical presentation.

Each patient had a comprehensive evaluation to exclude alternative pathological causes for their presentation. Neonates, patients with incomplete imaging, imaging suggestive of arterial dissection and Moya/moya, as well as those with other identifiable causes of childhood arterial ischaemic stroke as evaluated using a standardized stroke investigation protocol, were excluded from the study. Children presenting within primary diagnosis of meningitis, encephalitis, head trauma or stroke caused by other conditions than primary cerebral arteritis were excluded. 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 thrombophilic predisposition (haemoglobinopathies, protein C, protein S and anti-thrombin 111 etc.) were investigated when clinically required and such patients were excluded from the study cohort.

These children were admitted in the department of Neurosciences were initially treated with anticoagulation according to the published protocols, combined with intravenous pulse Methylprednisolone/ Immunoglobulin. Hemorrhagic infarcts were treated conservatively (without anticoagulants) 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-recommended in published protocols). Ischemic events that occurred shortly after initiating immunosuppressive therapy may have reflect residual thrombogenicity or residual inflammation of recently affected vessels, which supports the use of antiplatelet agents and potential benefits of stronger immunosuppressive therapy. All patients with cPACNS were commenced on long term aspirin 3 mg/kg/day, started on day 30th (depending upon patients' condition), for two years. Patients with obliterative angiopathies were put on oral Azathioprine in conjunction with Aspirin, started on about day 30th, Azathioprine for 2 years and Aspirin for 5 years, according to the consensus protocol (Table 1). Aspirin and heparin/oral anticoagulants were not used at the same time. The eligible patients were recorded and analyzed for information concerning patient demographics, age, presentation, family history, underlying disease or risk factors, clinical

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.

Table 1: Treatment protocol for childhood arterial ischaemic strokes at the Children's Hospital, Lahore, Pakistan.

state at presentation, investigations, diagnosis, treatment and follow-up. Initially patients were followed monthly for 3 months, then three monthly afterward.

Based on Conventional Angiography (CA), Magnetic Resonance Imaging (MRI) and/or Magnetic Resonance Angiography (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, clinical state at discharge determined by neurological examination for the presence of motor, visual and, speech difficulties. After discharge, Patients with suspicion of recurrence/flare were admitted, fully investigated, categorized and were treated in the hospital for provision of optimal care tailored according to the needs of the individual patient. Remission was defined as complete absence of disease activity in clinical symptoms, examination findings, laboratory markers, and imaging for at least 3 months. Recurrences/relapses were defined as emergence of signs and symptoms of stroke confirmed with neuroimaging (CA and/or MRA) of brain after remission.

The primary long term outcome was the paediatric stroke outcome measure (PSOM) [8] score at last follow up. This measure objectively rates deficit severity (likert-scaled from 0-2) in each of 5 domains: sensorimotor right, sensorimotor left, language expression, language reception, and cognitive/psychological, with total possible deficit severity score 10. Each domain 'subscale' is scored as 0=no deficit, 0.5=mild deficit normal function, 1=moderate deficit, slow function or 2=severe deficit, missing function.

Treatment safety secondary outcomes were mortality; serious infection requiring hospital admission; presence of peptic ulcer disease: deranged hepatic enzymes: clinical manifestations of Rye's syndrome and pancytopenia. Complete blood counts, renal functions and hepatic enzymes were measured regularly to monitor for aspirin and azathioprine toxicity.

Results

Between 1st January 2008 and 31st December 2010, 94 patients, aged ≥ 6 months to ≤ 16 years with clinical and radiological diagnosis of cPACNS were identified from the 6000 admissions in the Department of the Neuroscience of the Children's Hospital Lahore. Of these 94 children, 68 (73.4%) met the study inclusion criteria, as they had childhood primary angiitis of nervous system (cPACNS) and constituted the study cohort. Twenty six patients (26.6%) had strokes due to conditions other than cPACNS or had small vessel CNS vasculitis (negative angiography but presence of clinical evidence of cPACNS), and were excluded from the study.

We documented preceding history suggestive of TIAs in 13 patients (13/64, 20.6%) at presentation.

Among the enrolled patients, 42 boys (42/68, 62%) and 26 girls (26/68, 38%) with male: female ratio of 1:1.62 was diagnosed with cPACNS. Majority of the patients (62%) in our study group were more than 05 years of age: mean age was 8.5 yrs ± 3.5 (median age 7.4 yrs, range 1.5 yrs to 16 yrs). On the average 46000 children visited the department of the neurosciences each year during the study period, making an annual frequency of cPACNS 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 Conventional Angiography (CA) and/or Magnetic Resonance Angiography (MRA), 51patients (51/68, 75%) had non-progressive and 17 patients (17/68, 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) during 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 cPACNS and occurrence of seizures for morbidity and mortality among these patients (p=0.24–0.78). No secondary haemorrhage was observed among all the ischemic-infarcts patients who were treated initially with IV heparin and/or oral anticoagulants. Male sex, deep conscious level and intra cerebral bleed causing severe raised intracranial pressure were the poor prognostic factor.

Fifty six patients successfully completed the induction phase of the treatment, were discharged in stable condition and constituted the cohort for maintenance therapy. Of the 56 survivors, 40 patients were discharged on long term oral aspirin (for two years), and 16 children were commenced on Azathioprine in conjunction with Aspirin (Aspirin for 5 years and Azathioprine for 2 years). The Neurological findings among 56 survivors assessed at the time of discharge from hospital by the Paediatric Stroke Outcome Measurement (PSOM) [7] were; normal 20%; minor disabilities 25%; moderate disabilities 20% and severe disabilities 35%.

Two of the 16 (2/16=12.5%) patients being treated with combined Azathioprine and Aspirin, had recurrence/progression of vasculitis from the base line disease at presentation between 3 to 4 months after first discharge from the hospital and both survived. Three patients died to due to massive cerebral hemorrhage from collateral cerebral arteries after 20 months of commencing the therapy. Three patients got relapse/flare after 4-6 months of successfully completing 2 years of Azathioprine. Of these, two patients died and the third was re-started on Azathioprine along with Aspirin after initial stabilization and was clinically stable on last follow-up. Azathioprine was successfully stopped in the remaining 10 patients were continued on Aspirin only and this would be continued for 5 years and will be monitored outpatients clinics.

In contrast, of the 40 patients treated with aspirin only, 18(18/40, 45%) had recurrence/progression of angiitis within 24 months of commencing Aspirin, 22 (55%) patients were off Aspirin after 24 months. First relapse occurred in 8 (46.6%) patients within 6 months after discharge from hospital with mortality of 4 (4/8, 50%). Ten patients had first relapse/flare, after 6 months of discharge from hospital with mortality of 3 (3/10, 30%) with an overall morality of 7 (7/18, 38.8%), during first relapse. Eleven survivals after first relapse were started on Azathioprine (for 2 years) along with Aspirin (for 5 years) after stabilization. Of these, 5 patients had second relapse with mortality of 2 patients and one patient died in the subsequent attach, with overall morality of 55.5% (10/18) among the patients who suffer from relapse/progression of cPACNS, who were commenced on Aspirin only on their first presentation. Azathioprine was stopped in 4 patients after completing 2 years and aspirin was commenced to be

continued for 5 years since the date of their relapse. Four patients of this group were continued on Azathioprine along with Aspirin after stabilization and were neurologically stable on last follow-up. Among the 22 patients in whom Aspirin was stopped, 4 were lost in follow-up, 5 got relapse within 12 months of being off the Aspirin with mortality of 3 patients and 2 patients were started on Azathioprine and aspirin. Two patients died due to infectious diseases during recurrence/flare, while 11 patients were neurologically stable and off any medication on last follow up.

In summary after the median follow-up of 34 months, of the total 56 patients is; first relapse within 24 months after discharge 35.7% (2/16, 12.5% aspirin and azathioprine group, and 18/40, 45% aspirin only): total 30 (53.5%) had relapse/flare: 20 (20/56, 35.7%) died, 15 (15/56, 26.7%) in association with relapse of cPACNS, 5 (5/56, 9%) died due to other causes: 14 (14/56, 25%) were receiving Aspirin only: 11(11/56, 19.6%) were off any medication: 7 (7/56, 12.3%) were receiving both Azathioprine and Aspirin and 4 (4/56, 7.2%) were lost in follow-up. The Neurological findings among 32 patients available to be assessed at last follow up by Paediatric Stroke Outcome Measurement (PSOM) [7] were; normal 8 (8/32, 25%); minor disabilities 10 (10/32, 31.25%) moderate disabilities 10 (10/32, 31.25%) and severe disabilities 4 (4/32, 12.5%).

The most common serious side effects observed in patients being treated with low doses of Azathioprine and Aspirin involved blood elements (pancytopenia in 5 patients), the GI system (e.g., nausea, vomiting, and loss of appetite), and liver toxicity whereas, less frequently included fatigue, hair loss, joint pain, and diarrhoea. No serious side effects like aplastic anaemia, malignancy, overt hepatic and renal failure were observed. These side effects were successfully managed except for 2 patients (among 5 patients with pancytopenia, 1 on combination of azathioprine and aspirin, and the other on aspirin only), who had pancytopenia but died due to overwhelming bacterial infections and presented late in the hospital.

Discussion

Once clinically suspected, conventional angiography (CA) and /or magnetic resonance angiography (MRA) are key imaging modalities for the diagnosis of cPACNS [9]. Our 2-year retrospective review revealed 68 cases of 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 [10,11]. 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. These studies were reported from two large hospitals in Saudi Arabia [11]. The reason for the increased incidence is likely related to the fact that both hospitals serve as tertiary care centres 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 cPACNS 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 cPACNS among the hospitalized patients is likely related to the fact that our hospital serves as tertiary care centre and provides services to several regions of the country and receives referrals from other teaching hospitals.

Several studies have found that cPACNS is more common in boys than in girls [12]. 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 our case series, mean age at initial presentation was 8.5 years; in agreement Soman et al. [13]. Have documented mean age of 8.8 years, (range 1.5 to 17 years) in two hundred twelve patients [13]. deVeber et al. [14], have documented male dominance of 54% and median age of 5 years [14], similarly, the mean age at presentation of 4.8 years has been reported by Barnes et al. [15]. This great variation in anthropometry in data indicates the care level of paediatric neurology department receiving referrals.

The clinical manifestations of cPACNS 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 (MGCS<14) [7] at the time of admission. Adam et al. [16]. Have documented in their 41 children with cPACNS; altered mental status 17%, fever 7% and headache in 7% [16]. In contrast to this, seizures were documented in 55% (35% focal and 20% generalized) in our patients, whereas, Lee JC et al. [17] from Taiwan have reported seizures in 41.5% of their 94 cAIS patients [17]. Although the majority of childhood cPACNS present with single episode of focal neurological deficit, preceding transient ischaemic atachs (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 13 (13/64, 20.6%) patients. Nagaraja et al. [19], 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 thrombotic 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. [20], have documented headache and seizures in 45% and 16% respectively [20].

Neuroradiology of the head in our case series documented abnormal imaging in 100% of the patients (inclusion criteria) 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. Current treatment strategies for treating cPACNS are to treat with anticoagulants (IV heparin or with low molecular weight heparin (LMWH) or unfractionated heparin and/or 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 paediatric observational studies and clinical trials [22]. Untreated, PACNS follows a progressive and relapsing course that leads to severe disability or death, with exceptional spontaneous remissions [23]. There are few controlled studies on the treatment of cPACNS. Usually a combination of steroids and cytotoxic drugs is used, but there is considerable variation between centres on current therapeutic regimens [24]. Recent descriptions of cPACNS vasculitis support the use of cytotoxics in addition to corticosteroids, but fall short of precisely how regimens should be managed in the longer term [25]. The optimal duration of immunosuppressive therapy is unknown. Some authors recommend treating most cases for 12–18 months [9]. Others recommend prolong treatment to two to three years following remission [26].

Hutchinson et al. [4,5], used a treatment protocol consisting of induction therapy with steroids and pulses of intravenous Cyclophosphamide followed by maintenance therapy with either azathioprine or Mycophenolate mofetil. We used a slightly different Conesus- based protocol in our case series, consisting of intensive resuscitation and stabilization, induction and maintenance phase (Table 1). Overall, 56 patents (81.5%) had induction successfully and could be started on maintenance therapy, whereas, 12 (18.5%) patients died during to the resuscitation and stabilization phase. 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 low dose aspirin was commenced. No secondary haemorrhage due to heparin or oral anticoagulants was observed in these patients. In agreement in a case series by Barnes et al. [15], twenty-six patients (26%) received anticoagulation without any adverse side effects [15]. At discharge all patients in with cPACNS in our study were put on oral acetylsalicylic acid (aspirin) 3 mg once a day for two years and patients with progressive cPACNS were also put on Azathioprine 1 mg/kg/day for two years, commenced on 30th day, depending upon the patient's condition, but aspirin would be continued for 5 years in this category. Lanthier et al. [27], 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 cPACNS will have neurological sequelae [27]. 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 al. [14] have documented that long-term neurological deficits occur in 50% to 85% of infants and children after PACNS. Barnes et al. [15]. Have documented hemiplegia/ hemiparesis in 42%), developmental delay in 20.0, ataxia in 15.9% and seizures in 7%. Similarly Cnossen et al. [28] demonstrated that 54% of children had severe neurological impairments at 12 months after discharge from hospital [28]. The optimal duration of treatment for children with PACNS remains unknown. Outcome is variable; some children experience permanent neurological damage, whereas others have full recovery [7]. Our experience shows that long term follow up of children with medium-large vessel disease is not very promising in children with cPACNS. Relapses or recurrences were recorded in only 26% of the Mayo Clinic series [9]. Patients with relapsing disease required longer therapy but otherwise had outcomes similar to those without re lapses. In contrast to this after the median follow-up of 34 months, our follow-up of the total 56 patients is 30(53.5%) had relapse/ flare, 20 (35.7%) died, 14 (25%) were receiving Aspirin only, 11 (19.6%) were off any medication and were neurologically sable, 7 (12.3%) were receiving both Azathioprine and Aspirin, whereas, 4 (7.2%) were lost in follow-up. This indicates that recurrence and mortality is very high in these patients, when follow-up done with meticulous monitoring for the prolonged period. If relapses occur the diagnosis and the treatment regimen must be reconsidered. With a relapse rate of 25% and a reduced survival rate a close follow up of suspected PACNS is mandatory [29]. Our findings of high mortality among patients who had relapsed are different from those of MacLaren et al. [30] (patients with relapse required longer therapy but otherwise had similar outcomes to those without relapse).

The present case series demonstrates that cPACNS is associated with an estimated disease related mortality of 18.5% on first presentation* in contrast, Barnes et al. [15], have recorded a mortality of 8.4% in such patients and almost 78% of survivors have significant neurological deficits. Many authors [31] have stressed advantages of multicentre prospective studies on cPACNS and we also, recommend the same. No serious side effects like aplastic anaemia, malignancy, overt hepatic and renal failure were observed. The side effects were successfully managed (according to the standard published protocols), except for 2 patients, who had pancytopenia but died due to overwhelming bacterial infections and presented late in the hospital. Whereas, up to 80% of patients with cPACNS when treated for prolonged period, experience complications related to steroid therapy. These include diabetes mellitus, osteoporosis with vertebral compression fractures and Cushing syndrome [32]. The addition of steroid sparing immunosuppressive agents like Methotrexate (MTX) and Azathioprine may be tried, but has not been proven to be clearly beneficial.

Whether combination of Azathioprine and aspirin is superior to Mycophenolate and Cyclophosphamide remains unknown because no comparison was done in this study design. The strengths of the study are the sample size and the authors used a standard treatment protocol, but conclusions are difficult because of the study design, small number of participants, and limited follow-up. Although the optimal treatment for childhood CNS angiitis remains unknown, these descriptive data are a valuable contribution. Findings in our series of cPACNS, and knowledge of its natural history, also strongly support the case for alternative maintenance immunosuppressive, extending at least to 2 years after presentation.

We conclude that our treatment regimen was effective for reversing neurological deficits and controlling severe neurologic manifestations of cPACNS in a relatively large cohort study of the rare inflammatory brain disease, as there was high relapse rate and mortality among the patients who being were treated with aspirin only. This encouraging finding emphasizes the need for early diagnosis and initiation of therapy that may help avoid irreversible CNS events. Further studies are required to substantiate our findings (Table 1).

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