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ADVANCES IN PEDIATRIC RESEARCH

Childhood primary angiitis of the central nervous system: poor neurologic outcome despite treatment

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Abstract

Background: Childhood primary angiitis of the central nervous system (cPACNS) is one of the most formidable diagnostic and therapeutic challenges to pediatric neurologists. Understanding the long-term outcomes related to cPACNS in children is important in the development of secondary prevention strategies.

Methods: A prospective, long-term, follow-up study was performed at the Brain Associates Institute Lahore. Children with cPACNS were reviewed every 12 months and neuropsychological assessment was done with the Pediatric Stroke Assessment Outcome Measurement (PSOM) between January 2008-June 2014.

Results: Among 56 survivors assessed by PSOM at the time of discharge from hospital, 11 (20%) were normal; 14 (25%) had minor disabilities; 11 (20%) had moderate disabilities and 20 (35%) had severe disabilities. These patients were analyzed every 12 months and the final follow-up was at 60 months after discharge. At the final follow-up, a very high mortality rate of 39% was observed, with the highest mortality (54%), during the first 12 months post-discharge. Of the 22 patients who died, 16 (73%) died directly due to cPACNS, 6 (23%) patients died from other causes. At the final follow-up, only 28 (50%) of the discharged cPACNS were available, as 6 (11%) patients were lost in follow-up. Of these, 19 (37%) had independent lives, 7 (12.5%) required some help and 2 (3.5%) were totally care dependent.

Conclusions: Long-term neurological, neuropsychological and functional impairments are common in cPACNS survivors. Outcome improvement should focus on minimizing complications and evolution of the disease should be monitored with meticulous neurorehabilitation.

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Introduction

Childhood primary angiitis of the central nervous system (cPACNS) is an idiopathic vasculitis confined to the central nervous system. It is a relatively rare disease in children, but not yet clearly understood and has a multifactorial etiology [1]. Patients with cPACNS present with severe neurological deficits, which may include hemiplegia, vision abnormalities, speech deficits, seizures, cognitive dysfunction, and behavioral problems [2]. Central nervous system (CNS) vasculitis is an increasingly recognized inflammatory brain disease in children. Inflammation of the cerebral blood vessels may be idiopathic, as in cPACNS, which affects previously healthy children [3]. The impact of childhood PACNS may be devastating, with <50% survival and long-term brain damage in >50% of survivors (4). However, recent studies have suggested that early diagnosis and treatment improve morbidity and mortality in CNS vasculitis [5-7]. A combination of magnetic resonance imaging (MRI) and carotid angiography

(CA) are commonly used to assess parenchymal and vascular abnormalities. Studies have reported the high sensitivity of MRI in a large pediatric cohort of PACNS [8]. In children, PACNS can result in permanent central nervous system (CNS) damage, and the potential for survival can be compromised by delayed diagnosis and treatment. There is no treatment protocol or standardized documentation of neurological outcomes in children with PACNS [9]. In time, the arteriopathy stabilizes, improves or even completely resolves, sometimes after initial worsening during the first few months [10]. In children, PACNS can reoccur several years after discontinuation of combination therapy. Long-term relapses may reflect intrinsic predispositions to cPACNS rather than treatment failure. These cases highlight different chronological patterns of neurologic deterioration despite immunosuppressive therapy, which supports the relevance of monitoring clinical, laboratory, and radiologic responses to treatment and of long-term follow-up of patients with cPACNS [9]. Little is known about long-term physical sequelae, cognitive functioning, and quality of life in children who have experienced stroke due to cPACNS. Knowledge of the consequences of the cerebral damage with respect to cognition, behaviur, emotions, and relationships is necessitated. Moreover, parents will benefit from information about long-term prognosis. This study focused on the long-term sequelae of stroke due to cPACNS that occurred in children younger than 16 years of age. Surviving patients were followed prospectively, including physical check-up, and final outcome was assessed by modified pediatric stroke outcome measure (PSOM) at median follow-up of 60 months.

Methods

A single-center cohort study of consecutive children diagnosed with cPACNS based on Calabrese criteria [11] was performed between January 2008 and June 2014. The primary outcomes for the study were neurologic outcome and survival. Neurological deficits were measured with the PSOM, which was developed and validated by the neurology team at the Hospital for Sick Children to follow up survivors of stroke [12]. The PSOM is scored on a Likert scale based on the clinician's assessment of neurologic deficits in five domains: motor, sensory, cognitive-behavioral, speech, and language comprehension. A PSOM summary score of zero corresponds to complete recovery. A persistent neurologic deficit of at least moderate severity is denoted by a score of ≥1 in any domain. The PSOM was also scored prospectively at the end of each standardized clinic visit by a single physician (Malik). We did an open-label cohort study at the Brain Associates Institute Lahore, where patients diagnosed with cPACNS, were followed for 5 years; from January 1, 2008 to June 30, 2014. After successful induction therapy, these patients were started on maintenance therapy and were followed in the outpatient department of the hospital. Since February 2011, these patients were followed and monitored in the outpatient clinics of the Brain Associates Institute Lahore. Patients with cPACNS who were ≤ 16 years age at diagnosis were included. Childhood primary angiitis of the CNS was defined according to the Calabrese [11] criteria, which define a newly acquired neurological deficit plus angiographic features consistent with CNS vasculitis and an absence of evidence to indicate an underlying condition that could explain these findings. Other inclusion criteria consisted of the confirmation of stroke by brain neuroimaging, so that only large-medium size arteriopathies were included, because small vessel angiitis is diagnosed by brain biopsy and these were not available to us.

Transient ischemic attacks were defined as the presence of symptoms/signs of stroke that improved within 24 hours after onset. Arteriopathies causing stroke in children were reported in consultation with a neuroradiologist and were categorized as: 1) non-progressive cPACNS, a monophasic inflammatory vessel wall disease and brain parenchymal lesion of the same duration; or 2) progressive cPACNS as an ongoing inflammatory disease of the CNS vessels frequently affecting both proximal and distal vessel segments or new vessel segments affected on repeat vascular imaging with evidence of different times 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 every six to twelve months until the final follow up.

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 ischemic stroke as evaluated using a standardized stroke investigation protocol, were excluded from the study. Children presenting with a 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 (hemoglobinopathies, 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 followed and communication was accomplished via telephone for the final follow-up; they were provided with free pediatric neurology consultations. The eligible patients were investigated for information concerning patient demographics, age, presentation, family history, underlying disease or risk factors, clinical state at presentation, investigations, diagnosis, treatment and follow-up, and these data were recorded. Initially patients were followed monthly for 3 months, then every six to twelve months afterward.

Short-term outcome was measured in terms of mortality and clinical state at discharge as 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 the brain after remission.

Results

Demographics

Between January 1, 2008 and June 30, 2010, 68 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. Among the enrolled patients, 42 boys (62%) and 26 girls (38%) with male:female ratio of 1:1.62 were diagnosed with cPACNS. The majority of the patients (62%) in our study group were more than 5 years of age: mean age was 8.5 yrs ± 3.5 (median age 7.4 yrs, range 1.5 yrs to 16 yrs). Twelve patients (18%) died during their first admission to the hospital, whereas 56 cPACNS patients successfully completed the induction phase of treatment, were discharged in stable condition and constituted the cohort for maintenance therapy and follow-up.

Clinical state at discharge

The neurological findings among 56 survivors assessed at the time of discharge from hospital by the PSOM [7] were: 11 (20%) normal; 14 (25%) minor disabilities; 11 (20%) moderate disabilities and 20 (35%) severe disabilities (Table 1).

Long-term outcomes

Short-term outcome was measured in terms of mortality and clinical state at discharge. These patients were followed and analyzed every 12 months and the final follow-up was at 60 months after discharge from the hospital. At the end of this follow-up, a very high mortality of 39% (22 patients) was observed, with the highest mortality of 54% (12 patients) occurring during the first 12 months after discharge (Table 1). Of the total 22 patients who died, 16 (73%) died due to direct effects of cPACNS; 6(23%) patients died due to the other causes At the final follow-up, only 28 (50%) of the discharged cPACNS were available for analysis, as 6 (11%) patients were lost in follow-up. Of these 28 cPACNS patients, 19 (37%) had independent lives, 7 (12.5%) were requiring some help and 2 (3.5%) were totally care dependent (Table 1).

Table 1. Neurological findings by Pediatric Stroke Outcome Measurement (PSOM) ≥ 60 Months after Discharge

Follow-up Duration	Total Patients	PSOM				Lost in Follow-up	Deaths
		Normal	Minor Disabilities	Moderate Disabilities	Severe Disabilities		
At Discharge	56(100%)	11(20%)	14(25%)	11(20%)	20(35%)	0	0
12 Mon	42(100%)	10	12	12	8	2	12
24 Mon	37(100%)	8	13	10	6	1	4
36Mon	32(100%)	6	14	10	2	1	4
48Mon	31(100%)	6	15	8	2	0	1
60 Mon	28(100%)	6	13	7	2	2	1
At 60 Mon: Available for analysis 28(100%)		6(11%)	13(23%)	7(12.5%)	2(3.5%)	6(11%)	22(39%)

Discussion

The strength of our study is the analysis of a single, rare pediatric disease, long-term follow-up and assessment performed by the same pediatric neurologist. Our study had several limitations. The study cohort included a small number of patients, although 56 patients is a reasonable sample size when dealing with a rare disease such as cPACNS. In addition, the wide range of age distribution required the use of different neuropsychological tests; therefore comparison of results was limited. As recognition of this condition increases, the number of cases that are diagnosed and treated appropriately will also increase. Our 5-year, prospective follow-up study revealed grave long-term prognosis of childhood ischemic/hemorrhagic stroke due to cPACNS. Previously, a small number of case reports have described fatalities resulting from this disease [13]. However, although the neurological compromise observed at initial presentation may be very formidable and even life-threatening, most children survive. Despite therapy, which sometimes can be aggressive and multimodal [14], PACNS remains fatal in approximately one-sixth of patients [7]. In agreement with this, we have documented acute mortality at 18%, with survival rate of 82%. Morbidity is not uncommon, and includes a wide variety of diffuse and focal neurological deficits. The impact of untreated childhood PACNS may be devastating, with 50% survival and long-term brain damage in 50% of survivors [4]. Folk *et al*., have documented that neuromotor impairment was evident in 62% of children with neonatal strokes, and in 70% of children with childhood strokes when followed long-term (>7years) and PSOM was used for neurologic outcomes [15]. In current studies, positive neurological outcome has been reported in 45% of patients with progressive large-medium vessel disease and in 31% of patients with nonprogressive large-medium vessel disease [1]. Similarly, in a cohort of mixed large-medium vessel cPACNS, we documented that at 5 years after discharge from the hospital, 34 had a good, functional life (minimal or no psychomotor impairment) and 16% had moderate to severe neurodisability when assessed by PSOM (Tabe 1). In our study, 11% were lost in follow-up, but in contrast to all other studies, we documented very high mortality (39%) at >5 years of follow-up. Of the total 22 deaths, 12 (54%) died during the first 12 months after discharge from the hospital, indicating severity in these patients, as well a scarcity of health care facilities available for such patients in our set-up and referral delay to the tertiary care neurology center.

Patients with angiography-positive cPACNS were more likely to present with motor deficits. There was also a trend toward more speech abnormalities in this group. These findings confirm the clinical patterns that were described in previous studies of cPACNS [1-4]. Ongoing, close follow-up with a multidisciplinary team is important in primary CNS vasculitis of childhood. The particular needs of each patient should be identified and addressed as they arise during treatment. In the 2007 study by Salvarani *et al*. involving 101 North American adult patients with PCNSV diagnosed between 1983 and 2001,

mortality and relapse rates after a mean follow-up of 13 months were 17% and 26%, respectively [7]. Differences between PCNSV in children and adults remains to be further studied. None of the 62 children reported by Benseler *et al*. died within a mean follow-up of 20 months, but only 34% recovered without any neurological damage, which is in contrast to our findings [1]. This large variation in morbidity and mortality indicates diversity of the nature of PACNS. In agreement, Salvarani *et al*. identified several disease subgroups with some outcome differences finding that patients with focal neurological deficits, multiple bilateral cerebral infarction and/or large-vessel involvement had increased risk of death. We await similar studies from other groups [16, 17]. It has been suggested that PACNS is clinically more heterogeneous than previously appreciated and may include both relatively benign subsets and very aggressive varieties [18].

The longer period of follow-up helped us to confirm the diagnoses and provided time to assess response to treatment and determine outcomes. Our findings confirm that cPACNS is a rare disease associated with increased morbidity and mortality. Although our findings were not definitive, these data suggest that cPACNS is composed of more than one entity. In recent studies, positive neurological outcome has been reported in 45% of patients with progressive large-medium vessel disease, in 31% of patients with non-progressive large-medium vessel disease, and in 69% of patients with small vessel disease [1, 19]. Tools such as the PSOM can be used to quantify neurological deficits on serial clinical assessments. Some children with cPACNS stabilize or improve even without specific treatment, often in the context of a self-limiting or treated infection. Distinguishing between transient or non-progressive and progressive arteriopathies at presentation is not straightforward [1, 19] and currently is the subject of active research [10, 20]. Cerebrovascular disorders occur relatively often among children and adolescents, and stroke in children is now a common topic in the literature. Nevertheless, the incidence of stroke among children is low enough that it is difficult to plan clinical trials designed to improve therapy for long-term prognosis. There are enough age-specific differences in the cause, manifestations, treatment responses and long-term prognosis in individual children with stroke that we must be cautious when attempting to apply our knowledge of stroke in adults to children [21]. In fact, large-scale clinical trials will be difficult to perform with children with stroke, but continued research and additional experience are imperative if we are to better understand this important group of conditions [22,23].

Conclusions

Raising awareness in families that stroke can occur in childhood and encouraging clinicians to always consider it as a possible cause in children with acute neurologic deficits may allow for a more timely diagnosis and treatment of this devastating event and facilitate the planning of long-term follow-up and therapy. This report emphasizes the potential for neurologic deterioration despite immunosuppressive therapy in patients with cPACNS when followed for long-term, which underlines the importance of monitoring response to treatment. Long-term follow-up and neurorehabilitation is recommended after discontinuation of immunosuppressive treatment because of possible recurrences, sometimes even after several years of clinical quiescence.

References

1. Benseler SM, Silverman E, Aviv RI, Schneider R, Armstrong D, Tyrrell PN, et al. Primary central nervous system vasculitis in children. Arthritis Rheum 2006;54:1291-7.
2. Benseler SM, deVeber G, Hawkins C, Schneider R, Tyrrell PN, Aviv RI, et al. Angiography-negative primary central nervous system vasculitis in children: a newly recognized inflammatory central nervous system disease. Arthritis Rheum. 2005;52:2159-67.
3. Cellucci T, Benseler SM. Central nervous system vasculitis in children. Curr Opin Rheumatol 2010; 22:590-7.
4. Lanthier S, Lortie A, Michaud J, Laxer R, Jay V, deVeber G. Isolated angiitis of the CNS in children. Neurology. 2001;56:837-42.
5. Bitter KJ, Epstein LG, Melin-Aldana H, Curran JG, Miller ML. Cyclophosphamide treatment of primary angiitis of the central nervous system in children: report of 2 cases. J Rheumatol. 2006;33:2078-80.
6. Gallagher KT, Shaham B, Reiff A, Tournay A, Villablanca JP, Curran J, et al. Primary angiitis of the

central nervous system in children: 5 cases. J Rheumatol. 2001;28:616-23.

7. Salvarani C, Brown RD Jr, Calamia KT, Christianson TJ, Weigand SD, Miller DV, et al. Primary central nervous system vasculitis: analysis of 101 patients. Ann Neurol. 2007; 62:442-51.
8. Aviv RI, Benseler SM, Silverman ED, Tyrrell PN, Deveber G, Tsang LM, et al. MR imaging and angiography of primary CNS vasculitis of childhood. AJNR Am J Neuroradiol. 2006;27:192-99.
9. Hutchison C, Elibers I, Halliday W, Brasen H, Langtion S, Arnistrong D, et al. Treatment of primary CNS vasculitis in children: an open label cohort study. The Lancet Neurology. 2010; 9:1078-84.
10. Sébire G, Fullerton H, Riou E, deVeber G. Toward the definition of cerebral arteriopathies of childhood. Curr Opin Pediatr. 2004;16:617-22.
11. Calabrese, L.H. and Mallek, J.A. Primary angiitis of the CNS: report of 8 new cases, review of the literature, and proposal for diagnostic criteria. Medicine. 1987l67:20-37.
12. DeVeber GA, McGregor D, Curtis R, Mayank S. Neurologic outcome in survivors of childhood arterial ischemic stroke and sinovenous thrombosis. J Child Neurol. 2000;15:316-24.
13. Matsell DG, Keene DL, Jimenez C, Humphreys P. Isolated angiitis of the central nervous system in childhood. Can J Neurol Sci. May 1990;17:151-4.
14. Salvarani C, Brown RD Jr, Calamia KT, Christianson TJ, Huston J 3rd, Meschia JF, et al., Rapidly progressive primary central nervous system vasculitis, Rheumatology. 2011;50:349-58.
15. Kolk A , Ennok M, Laugesaar R, Kaldoja ML, Talvik T. Long-term cognitive outcomes after pediatric stroke. Pediatr Neurol. 2011;44:101-9.
16. Salvarani C., Brown R.D., Hunder G.G. Adult primary central nervous system vasculitis Lancet. 2012;380:767-77.
17. Salvarani C., Brown R.D., Calamia K.T., Christianson T.J., Huston J., Meschia J.F., et al. Primary central nervous system vasculitis: comparison of patients with and without cerebral amyloid angiopathy. Rheumatology (Oxford). 2008; 47:1671-7.
18. Calabrese LH. Vasculitis of the central nervous system. Rheum Dis Clin North Am. 1995;21:1059-76.
19. Danchaivijitr N, Cox TC, Saunders DE, Ganesan V. Evolution of cerebral arteriopathies in childhood arterial ischemic stroke. Ann Neurol. 2006;59:620-6.
20. Kirkham F. Improvement or progression in childhood cerebral arteriopathies: Current difficulties in prediction and suggestions for research. Ann Neurol. 2006;59:580-2.
21. Sébire G. Transient cerebral arteriopathy in childhood. Lancet. 2006; 368:8-10.
22. Biller J, Mathews KD, Love BB. Stroke in Children and Young Adults. Boston, MA: Butterworth-Heinemann, 1994.
23. Michelson AD, Bovill E, Andrew M. Antithrombotic therapy in children. Chest. 1995;108:506S-22S.