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Primary Central Nervous System Vasculitis in Childhood (cPACNS): A Case Series Study

Farhad Salehzadeh MD[1], Adel Ahadi MD[2*], Omid Akbari MD[3]

Abstract

Background: Primary CNS angiitis of childhood (cPACNS) is an autoimmune process of CNS vascular structure. It is considered a novel and challenging clinical problem in pediatric neurology and rheumatology. This study discusses a significant case series study of cPACNS.

Methods: From 1994 to 2021 at pediatric rheumatology clinic, patients <18 years of age were enrolled this study with diagnosis of cPACNS if they had: a clinical symptoms compatible with primary CNS vasculitis, and MRA findings demonstrating arterial stenosis and or aneurism that are not attributable to other disease and background.

Results: There were 22 patients with mean age 10 years, 12 patients (54%) were female. The mean delayed time to diagnosis was 4 years. The most common neurologic symptoms were headache (88%) then seizure and mental disorder in (45%). Fever was in (54%) and positive ANA result in (31%) patients. 14 patients (63 %) showed abnormality in both MCA and ACA, whereas PCA showed this abnormity in 36% (8) patients. Most of patients 86 % (19) had normal EEG findings. Five patients (22%) had severe and permanent neurological damage and sequel.

Conclusion: Although cPACNS seems to be a rare and unfamiliar disorder, however it can be conceptualized much in the same way as pediatric CNS ischemic disorder, and it should be considered in any patient with unexplained headache, seizure and mental disorders.

Keywords: Primary CNS vasculitis**;** Childhood CNS vasculitis; Primary CNS angiitis

Abbreviations: CPACNS: Primary CNS Angiitis of Childhood; CNS: Central Nervous System; MRA: Magnetic Resonance Arteriography; MRI: Magnetic Resonance Imaging; MCA: Middle Cerebral Artery; ACA: Anterior Cerebral Artery; PCA: Posterior Cerebral Artery; HSP: Henoch-Schonlein Purpura; KD: Kawasaki Disease; VZV: Varicella Zoster Virus; ESR: Erythrocyte Sedimentation Rate; CRP: C-Reactive Protein; WBC: white Blood Cell Count; CA: CT-Angiography

Introduction

Vasculitis is a heterogeneous group of blood vessels disorders which characterized by inflammation, necrosis and the obstruction of the inflamed vessels [1]. Central nervous system (CNS) vasculitis of childhood is a novel recognized autoimmune brain disorder with significant diagnostic and therapeutic challenges [2,3]. CNS vasculitis has been reported under a variety of descriptive terms including isolated CNS angiitis, idiopathic angiitis of

Affiliation:

[1]Professor of Pediatric Rheumatology, Pediatric Department, Ardabil University of Medical Sciences (ARUMS), Ardabil, Daneshgah st. Ardabil, Iran

[2]Adel Ahadi Assistant Professor of Pediatric. Pediatric Department, Bouali Children`s Hospital, Ardabil University of Medical Sciences (ARUMS), Ardabil, Iran

[3]Pediatric Department, Bouali Children`s Hospital, Ardabil University of Medical Sciences (ARUMS), Ardabil, Iran

***Corresponding author:**
Adel Ahadi MD, Assistant Professor of Pediatric. Pediatric Department, Bouali Children`s Hospital, Ardabil University of Medical Sciences (ARUMS), Ardabil, Iran

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the CNS, and primary angiitis or vasculitis of the CNS. In a range of inflammatory vascular process, vasculitis may affect the CNS vessels. Not having sensitive and specific laboratory tests and rarity of disorders in one hand, and limitation in access to pathological evaluation of disease, on the other hand considered it as a very challenging clinical problem. Lack of specific signs and symptoms make more difficulty in diagnosis of this disorder [2].

CNS vasculitis can cause brain damage with reversible and or irreversible neurologic involvement, including acute ischemic attack, progressive cognitive decline and seizures often with intractable pattern. Headaches and concentration problems can be leading, to mood changes, significant school problems, personality and behavioral abnormalities [3-5]. Acute and or chronic inflammatory course of vasculitis may causes severe neurological impairment or also death. When the vessels become inflamed as a consequence of less blood flow brain tissue may be damaged. Studies have shown that early diagnosis and aggressive treatment result in improved neurological outcome and reduced mortality [6-8]. If untreated, this condition can lead to permanent damage of the brain tissue [9,10].

In the past, childhood primary angiitis of the CNS (cPACNS) was thought to be a rare disease. [11,12]. More commonly, CNS vessels inflammation had been described in association with an identifiable systemic condition (secondary CNS vasculitis) such as an infectious process [13,14], systemic vasculitis [15,16], a collagen-vascular disease [17,18] a systemic inflammatory disease [15] or specific malignancy [19,20].

Cravioto and Feigin [13] reported a first case of primary CNS vasculitis with “noninfectious granulomatous angiitis with predilection for the nervous system. Calabrese et al. [21] the pioneer of CNS vasculitis, coined the term “primary angiitis of the CNS (PACNS)” in 1987. Calabrese proposed and validated diagnostic criteria for PACNS in adults: an acquired neurological deficit, plus angiographic or histopathology features of angiitis within the CNS, in the absence of a systemic vasculitis or any other condition to which the angiographic or pathologic features could be secondary [22,23]. These criteria have since been adopted for childhood primary angiitis of CNS (cPACNS) by pediatric neurologists and rheumatologists [24-27]. In 2001, Lanthier reported two cases of biopsy-proven cPACNS [2]. The same year, Gallagher et al. [1] reported five children with angiography positive primary CNS vasculitis concomitantly. Since then the recognition of childhood CNS vasculitis in the absence of a systemic vasculitis or disease appears to be increased [27]. This case series work as a single-center study represents 22 cPACNS patients and describe their clinical and imaging characteristics with arteriography evidence of cPACNS.

Methods

From 1994 to 2021 at pediatric rheumatology and FMF clinic, patients <18 years of age were included to this study as having cPACNS if they had: 1) A clinical diagnosis of primary CNS vasculitis on the basis of neurological findings, and 2) Magnetic resonance angiography (MRA) findings demonstrating arterial stenosis, aneurism, lack of vascularity not attributable to other causes. (Calabrese criteria: an acquired neurological deficit, plus angiographic or histopathology features of angiitis within the CNS, in the absence of a systemic vasculitis or any other condition to which the angiographic or pathologic features could be secondary [22,23].)

The study excluded patients and children with systemic vaculities, children with collagen vascular disease, and other defined conditions known to cause vascular involvment.

Clinical symptoms were categorized as headaches, seizures, focal neurologic deficits (hemiparesis, hemifacial weakness, and hemisensory and fine motor deficits), diffuse neurologic deficits (altered concentration, cognition, mood, or personality), and constitutional symptoms (fever, fatigue, and weight loss).Administration of drug therapy was considered on a case by- case basis and condition.

The study is complaint with the Helsinki Declaration and was approved by the local Ethics Committee under number (IR.ARUMS.REC.1393.0476). Informed consent was obtained from all parents individual participants included in the study. Simple statistical method has been done by SPSS Ver.18

Results

22 patients were enrolled this study, 12 patients (54%) were female, the youngest was 3 years old and the oldest one was 17 years old (mean10 yr.). The mean delayed time to diagnosis was 4 years. The most common neurologic symptoms in our series were headaches (88%), seizure and mental disorder in (45%). Systemic symptoms such as fever, decreased energy level and weakness were common findings 54%, 45%, 31% respectively. The main complaint of patients was headache (68%) then fever (54%). Laboratory results in our series showed mild anemia (63%) and leukocytosis (45%). ESR and CRP were in high results in (40%). ANA was positive in (31%) but not in significant high titers. Small vessels involvements were in 14 (63%) patients, four patients had large vessels involvement and in the rest (4 patients) showed both vessels involvement. 14 patients (63 %) showed abnormality in both MCA and ACA, whereas PCA showed this abnormity in 36% (8) patients. Most of patients 86 % (19) had normal EEG findings. Table1 shows some characteristic features of all patients.

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Table 1: Patients' symptoms and signs.

Symptoms and signs	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	no/ %
Headache	+	+	+	+	+		+		+	+		+	+		+	+			+	+	+		15/ 68
Seizures	+	+			+					+	+		+			+			+	+		+	16711
Visual Problems			+							+			+										41334
Motor Problems					+							+	+	+			+						44682
Personality and mood Changes	+	+			+	+		+				+					+					+	13363
Dysarthria	+				+	+		+									+	+				+	11505
Concentration difficulties		+	+			+						+						+		+		+	11505
Mental disorder				+	+	+		+				+	+				+	+		+		+	16711
Weakness				+	+					+	+		+						+			+	11505
Fever	+		+	+	+					+	+		+	+	+	+				+		+	20059
Decreased Energy level	+	+			+				+	+	+		+				+			+		+	16711
Weight loss	+			+			+					+	+	+						+			11505
Loss of appetite	+				+					+				+	+				+	+			11505

Table 2: Comparison of MRI and MRA findings.

MRI Findings	MRA Findings
Mild cerebral atrophy with subarachnoid space dilatation	Micro aneurysms seen in the MCA ,distal branches of the right and left middle cerebral artery
Ventricular dilatation	Micro aneurysms in ACA and MCA
Evidence of peri-ventricular white matter foci with special involvement of occipital area	Beadings in cerebral Arteries in Anterior and Posterior Vessels
Mild hydrocephaly and Occipital Lobe atrophy	Micro aneurysm at PCA and MCA
White matter lesions multifocal	Micro aneurysms seen at MCA and ACA

Discussion and Conclusions

cPACNS is a primary immune mediated inflammatory disorder of CNS vessels. It is hypothesized that reactivated Varicella Zoster virus (VZV) and other neurotropic viruses can induce a post infectious type of CNS vasculitis and it has been proposed that viral infections such as Parvovirus B19 has been reported to trigger CNS vasculitis among immune-suppressed pediatric patients [28] however, these patients usually have a long prodromal period and less constitutional symptoms with few patients presenting so far [29].

Signs and symptoms of systemic vasculitis such as peripheral neuropathy, fever, weight loss or rash are usually absent [30]. In our study Systemic symptoms such as fever, decreased energy level and weakness were common findings 54%, 45%, 31% respectively. The main complaints of patients in this study were headache (68%) then fever (54%) and seizure with mental disorder in (45%). CNS vasculitis is usually suspected when recurrent vascular events occur in young patients with no identifiable risk factors, or in the setting of chronic and progressive unexplained CNS disorder [30]. In one study focal neurologic deficits were the most frequent clinical symptom, including acute hemiparesis (80%), hemi-sensory deficit (79%), and fine motor deficits (73%). Headaches were present in 56% of patients and seizures in 15%. Diffuse neurologic deficits included mood/personality changes in 26%, cognitive dysfunction in 37%, and concentration difficulties in 29% of patients. Concentration difficulties and cognitive dysfunction resulted in decline in school performance and participation [31].

A study conducted by Benseler et al. [7,27] on children with initial diagnosis of cerebral vasculitis (the proof was based on the findings of angiography and MRA) 62 children (38 male, 27 female, mean age 2/7 years) with a diagnosis of primary CNS vasculitis were divided into two groups with progressive disease (20 patients) and non-progressive disease (42 patients). Neurologic symptoms such as cognitive impairment, attention and mood disorders in patients with progressive disease were significantly higher than other groups (p<001/0).

The spectrum of cPACNS includes three distinct disease entities: progressive angiography-positive cPACNS (P-cPACNS); non-progressive angiography-positive cPACNS (NP-cPACNS); and angiography-negative, small-vessel cPACNS (SV-cPACNS) [27,31].

Proximal, large-vessel inflammation with subsequent focal stenosis is the hallmark of non-progressive angiography-

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positive NP-cPACNS. NP-cPACNS patients often present with unilateral MRI lesions predominantly focal deficits, and proximal vessel stenosis on angiography [31]. These patients have a monophasic inflammatory large-vessel disease, which does not progress beyond 3 months. The majority of NP-cPACNS patients present with strokes.

In contrast, Patients with progressive angiography-positive, P-cPACNS frequently present with multifocal MRI lesions and evidence of both proximal and distal vessels stenosis on angiography and both focal and diffuse neurological findings. Untreated patients will progress beyond 3 months [27].

P-cPACNS patients have both large and small-vessel inflammation and will therefore present with overlapping clinical features including cognitive and behavior changes. Distal vessels inflammation is commonly seen in progressive angiography-positive P-cPACNS vasculitis.

Children with angiography-negative, small-vessel SV-cPACNS present with distal vessels stenosis and multifocal MRI lesions with significant diffuse neurological deficits including cognitive decline, behavior changes, school difficulties, and mood/personality changes. Angiography remains normal and brain biopsies confirm the diagnosis of SV-cPACNS [32-35].

Laboratory results although in different reports did not show specific findings, systemic inflammatory markers are frequently normal in children with cPACNS. Some children may have positive antinuclear antibodies (ANA) [11,29].

However, as the inflammation progresses, some children may develop mildly elevated systemic inflammatory markers. [27,29] A normal erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), white blood cell count (WBC), C3 complement, or immunoglobulin levels by no means exclude an active vasculitis process in the CNS. In our series anemia (63%) and leukocytosis (45%) were common abnormalities. ESR and CRP were in high amounts in (40%) patients .ANA was positive in (31%) patients although not in significant and high titers.

Pathological and imaging studies (MRI, MRA, CT-SCAN and CA) are valuable tools for the diagnosis of cerebral vasculitis [36-40].

In this study CT-SCAN showed nonspecific abnormalities in three patients only, however in MRA study small vessels involvements were in 14 (63%) patients, which could be in favor of P-cPACNS. Four patients had large vessels involvement and in the rest (4 patients) both vessels were involved.14 patients (63 %) showed abnormality in both middle cerebral artery (MCA) and anterior cerebral artery (ACA), whereas posterior cerebral artery (PCA) showed this abnormity in 36% (8) patients. In six patients MRI showed some pathologic results and their simultaneous MRA had particular findings. Comparisons of the MRI and MRA findings of these patients have been shown in Table 2.

There is not clear findings about EEG in this disorder, most patients 86 %(19) in our group had normal EEG results.

In children, the choice of treatment depends on the cPACNS classification [41]. Intravenous (IV) monthly cyclophosphamide plus high-dose corticosteroids are the current method in patients with P-cPACNS and SV-cPACNS [25,29]. Induction therapy consists of seven IV cyclophosphamide pulses (500–1000 mg/m^2/month) plus corticosteroids (2 mg/kg/day). Maintenance course follow with oral drugs such as azathioprine or mycophenolate mofetil plus a tapering low dose of corticosteroids for 2 years [41].

Approach of therapy was on a case by- case basis, diseases severity, neurologic handicap, drug tolerance and availability were additional parameter that we considered in therapy. Prednisolone (90%) Cyclophosmide (50%), MMF (50%), Azathioprne (45%), Methotrexate (9%) have been used. In spite of full course therapy, five patients (22%) had sever and permanent neurological sequel such as seizure, mental regress and personality disorders. At recent decade in all refractory cases our first choice of biologic therapy was infliximab (this protocole is under-investigate), most of them in view of subsiding clinical symptoms showed favorable response to this biologic treatment.

There are some limitations in this study such as lack of biopsy proven and tissue pathology that are not available in our centers, on the other hand long term period of study (25 years) made we could not follow accurately our patients because of changing of their follow up clinic by adult one.

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Authors' Contributions

FS: carried out the management and diagnosis of patients. OA and AH Participated in the design of the study and performed the statistical analysis and helped to draft the manuscript. All authors read and approved the final manuscript.

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Ethics approval and consent to participate

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Consent for publication:

Not applicable.

Competing interests:

The authors declare that they have no competing interests.

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