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CHILDHOOD CNS VASCULITIS A NOVEL CHALLENGE IN PEDIATRIC RHEUMATOLOGY CLINIC, A CASE SERIES STUDY

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ABSTRACT
Primary CNS vasculitis of childhood (cPACNS) is an inflammatory vascular process of CNS. It is considered a very novel and challenging clinical problem in pediatric rheumatology and neurology clinic. From 1994 to 2014 at pediatric rheumatology clinic, patients <18 years of age were included to this study as having cPACNS if they had: a clinical diagnosis of primary CNS vasculitis, and MRA findings demonstrating arterial stenosis and or aneurism not attributable to other causes. 22 patients were enrolled this study 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 sequel. It seems cPACNS is unfamiliar disorder and we recommend that in any patient with unexplained headache, seizure and mental disorder CNS vasculitis should be considered.

INTRODUCTION

Vasculitis is a heterogeneous group of blood vessels disorders which characterized by inflammation, necrosis and the obstruction of the inflamed vessels. [1] In a range of inflammatory vascular process, vasculitis affects the central nervous system (CNS), and considered a very challenging clinical problem. The reasons include the following: the lack of specific signs and symptoms, lack of sensitive and specific laboratory tests and relatively rare disorders of CNS, and limitation in access to tissue for pathological evaluation. [2]

CNS vasculitis has been reported under a variety of descriptive terms including isolated CNS angiitis, idiopathic granulomatous angiitis of the CNS, and primary angiitis or vasculitis of the CNS.CNS vasculitis can cause brain damage with reversible and or irreversible neurologic involvement, including acute ischemic attack, seizures often intractable and cognitive decline. [3,4] Acute and or chronic inflammatory course of vasculitis may causes severe neurological impairment or death [5,6].

When the blood vessels become inflamed less blood flows through those, subsequently brain tissue around the inflamed blood vessels may be damaged. Headaches and concentration problems can be leading, to mood changes, severe school problems, personality and behavioral abnormalities. [7]

Studies have shown that early diagnosis and aggressive treatment result in improved neurological outcome and reduced mortality.[8] If untreated, this condition can lead to permanent damage of the brain tissue.[9]

Apart from relatively common vasculitides such as Henoch-Schonlein purpura (HSP) and Kawasaki disease (KD), most of the primary vasculitic syndromes are rare in childhood, but with a significant attendant morbidity and mortality. [10]Central nervous system (CNS) vasculitis of

childhood is a newly recognized inflammatory brain and spine disease with significant diagnostic and therapeutic challenges. [11]

In the past, childhood primary angiitis of the CNS (cPACNS) was thought to be a rare disease. [1, 2,12].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 a malignancy[19,20].

As a first case of primary CNS vasculitis in 1959, Cravioto and Feigin reported a case with "noninfectious granulomatous angiitis with predilection for the nervous system [13].

Leonard Calabrese [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. These criteria [22, 23] have since been adopted for childhood primary angiitis of CNS (cPACNS) by pediatric neurologists and rheumatologists [24-27].

In 2001, Lanthier [2] reported two cases of biopsy-positive cPACNS. The same year, Gallagher [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 have increased. [27]

This case series study represents 22 cPACNS patients and the aim of that is to analyze the clinical and imaging characteristics of a large group, single-center pediatric patients having arteriographic evidence of probable cPACNS.

METHODS

From 1994 to 2014 at pediatric rheumatology 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, and
2) Magnetic resonance angiography (MRA) findings demonstrating arterial stenosis not attributable to other causes.

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

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 decided on a case by- case basis. 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). 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 anemia (63%) and leukocytosis (45%).

ESR and CRP were in high results in (40%).ANA was positive in (31%) but not in very 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. Tables 1 and 2 show some characteristic features of all patients.

Table 1. Patients' findings (demographic and neurologic)

S.No.	age	sex	ID	MRA	MRI	CT Scan	EEG
1	3Y	F	He .R	Beading is seen at all cerebral vessels with micro aneurysm.	There is evidence of periventricular WM foci with special involvement of occipital area.	Hypo dense is seen lesion in the left temporal lobe. Herpetic encephalitis can be considered. Ventricles are Normal.	normal
2	15Y	F	Ha .R	All cerebral vessels showed microaneurysm.	No space occupying lesion. White and gray matter, ventricles are Normal.	Old hemorrhage and ventricular bleeding is	Dysrhythmia

					Nerves are Normal in shape and signal	considered.	
3	14Y	M	M.H	There is evidence of microaneurysm at Distal ACA and Left MCA	No space occupying lesion. White and gray matter, ventricles are Normal. Nerves are Normal in shape and signal	normal	normal
4	7Y	M	A.F	Beading is seen at all cerebral vessel with microaneurysm. (MCA,PCA,ACA)	No space occupying lesion. White and gray matter, ventricles are Normal. Nerves are Normal in shape and signal	normal	Mild Abnormal EEG due to mild dysrhythmia plus abnormal reactivity
5	5Y	M	J.Kh	Microaneurysms can be seen in the MCA ,distal branches of the right and left middle cerebral artery	There is mild cerebral atrophy with sub arachnoid space dilatation. Nonspecific deep white matter bright foci are seen in periventricular regions and centrome semiovale at long TR images. Pansinusitis is seen	normal	normal
6	4Y	M	M.A	1: Micro Image proximal artery aneurysm in the MCA and it is evident at Bifurcation. AFTER TREATMENT 2: The arteries are normal without evidence of AVM or aneurysm no displacement of vessels is seen. All visible vessels are patent.	No space occupying lesion. White and gray matter, ventricles are Normal. Nerves are Normal in shape and signal	normal	normal
7	9Y	M	A.S	Multiple beadings are seen at cerebral arteries in Favor of microaneurysm .(MCA,PCA,ACA)	No space occupying lesion. White and gray matter, ventricles are Normal. Nerves are Normal in shape and signal	normal	normal
8	3Y	F	M.H	Multiple microaneurysm are seen at ACA and MCA in favor of vasculitis	No space occupying lesion. White and gray matter, ventricles are Normal. Nerves are Normal in shape and signal	normal	normal
9	6Y	M	A.T	Beadings are seen in All cerebral arteries in Favor of micro aneurysm.(MCA,ACA,PCA)	No space occupying lesion. White and gray matter, ventricles are Normal. Nerves are Normal in shape and signal	normal	normal
10	14Y	F	E.H	There is small aneurismal dilatation in distal	No space occupying lesion. White and gray matter, ventricles are Normal.	Sulci and ventricles have normal	normal

				end of MCA.	Nerves are Normal in shape and signal	appearance. Posterior fossa is involved. No midline shift.	
11	8Y	F	Z.H		No space occupying lesion. White and gray matter, ventricles are Normal. Nerves are Normal in shape and signal	normal	normal
12	6Y	F	R.F	The Arteries are normal without Evidence of AVM. Small Microaneurysms are seen at left PCA.	No space occupying lesion. White and gray matter, ventricles are Normal. Nerves are normal in shape and signal	normal	normal
13	6Y	F	A.CH	There is microaneurysm at PCA and MCA	Mild Hydrocephaly and Occipital Lobe atrophy.	normal	normal
14	8Y	F	F.F	Microaneurysms are seen at MCA and ACA. Left ACA is derived from Anterior Communicating Artery.	1: The Size and Signal Intensity of Both Cerebellar Hemisphere are Normal. Bilateral White matter Plaques are seen at Occipital Horns. 2: High Signal Periventricular white matter Lesions Are seen. The Size and Signal Intensity of Both Cerebellar Hemisphere are Normal. White matter lesions are evidence of vasculitis.	normal	normal
15	8Y	F	R.S	There is evidence of Multiple Microaneurysms at MCA and ACA.	No space occupying lesion. White and gray matter, ventricles are Normal. Nerves are Normal in shape and signal	normal	normal
16	6Y	M	R.H	Multiple microaneurysms are seen in all arteries in Favor of vasculitis.(ACA,PCA,MCA)	No space occupying lesion. White and gray matter, ventricles are Normal. Nerves are Normal in shape and signal	normal	normal
17	4Y	F	F.P	There are beadings in cerebral Arteries in Anterior and Posterior circulation and Willis Circulation.(ACA, PCA) No evidence of ateriovenous Malformation and blockage is seen.	Small focal lesions with fluid intensity signal in right. These findings are in favor of Cerebral Vasculitis.	normal	Dysrhythmia
18	8Y	M	S.N	Multiple beading and microaneurysms	No space occupying lesion. White and gray matter, ventricles are Normal.	normal	normal

				are seen at ACA. Conclusion : vasculitis	Nerves are Normal in shape and signal		
19	9Y	M	M.S	There are Beadings in ACA and Ophthalmic arteries in Favor of Vasculitis.	No space occupying lesion. White and gray matter, ventricles are Normal. Nerves are Normal in shape and signal	normal	normal
20	17Y	F	R.D	The arteries are normal without evidence of A.V.M or aneurysm. Small nonspecific microaneurysms are seen at ACA which may be due to vascular kink.	No space occupying lesion. White and gray matter, ventricles are Normal. Nerves are Normal in shape and signal	normal	normal
21	6Y	F	N.S	There are symptoms of beading and microaneurysms in main cerebral arteries.(MCA,ACA,PCA)	No space occupying lesion. White and gray matter, ventricles are Normal. Nerves are Normal in shape and signal	normal	normal
22	11Y	M	A.M	Microaneurysms in ACA and MCA	Mild dilatation and rounding at occipitalhorns of lateral ventricles. Dilatation in temporal horn of right lateral ventricle associated with signal change and volume loss at right hippocampal gyrus inkeeping with mild mesial temporal sclerosis is seen.	normal	normal

Table 2. 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	T
Headache	+	+	+	+	+		+		+	+		+	+		+	+			+	+	+		15
Seizures	+	+			+					+	+		+			+			+	+		+	10
Visual Problems			+							+			+										3
Motor Problems					+							+	+	+			+						5
Personality and mood Changes	+	+			+	+		+				+					+					+	8
Dysarthria	+				+	+		+									+	+				+	7
Concentration difficulties		+	+			+						+						+		+		+	7
Mental disorder				+	+	+		+				+	+				+	+		+		+	10
Weakness				+	+					+	+		+						+			+	7
Fever	+		+	+	+					+	+		+	+	+	+				+		+	12
Decreased Energy level	+	+			+				+	+	+		+				+			+		+	10
Weight loss	+			+			+					+	+	+						+			7
Loss of appetite	+				+					+				+	+				+	+			7

Table 3.Imaging characteristics of CNS vaculities [30]

Test	Sensitivity	Estimated specificity
CT	33-50% (Even in biopsy-proven cases)	Data not available (no pathognomonic findings)
MRI	50-100% (It approaches 100%in histologically confirmed cases and is lowest in those diagnosed only by angiography)	Data not available (no pathognomonic findings)
Angiography	30-100% (It is less than 40%in histologically confirmed cases, and 100% in reports not supposed by histology.)	22% (Assessed in only one studybut may be higher if vasculitis secondary to other causes are excluded)
Biopsy	75% (The negativity can be due to the patchy nature of the disease and small tissue sample)	80% (The same pattern inflammation can be due to other causes)

Table 4. comparison of MRI and MRA findings

MRI Findings	MRA Findings
Mild cerebral atrophy with subarachnoid space dilatation	Microaneurysms can be seen in the MCA ,distal branches of the right and left middle cerebral artery
Ventricular dilatation	Microaneurysms in ACA and MCA
Evidence of peri- ventricular WM foci with special involvement of occipital area	There are beadings in cerebral Arteries in Anterior and Posterior Vesseles
Mild hydrocephaly and Occipital Lobe atrophy	There is microaneurysm at PCA and MCA
White matter lesions	Microaneurysms are seen at MCA and ACA. Left ACA is derived from Anterior Communicating Artery.
Small focal lesions with fluid intensity signal in right	There are beadings in cerebral Arteries in Anterior and Posterior circulation and Willis Circulation. (ACA,PCA) No evidence of arteriovenous Malformation and blockage is seen.

DISCUSSION AND CONLUSION

CPACNS is an immune mediated inflammatory disorder of CNS although it is hypothesizing that reactivated VZV and other neurotropic viruses can induce a post infectious type of CNS vasculitis. Viral infections such as Parvovirus B19 have been reported to trigger CNS vasculitis amoung immune-suppressed pediatric patients. [28] These patients usually have a long prodromal period, with few patients presenting acutely. [29]Constitutional symptoms are uncommon. Signs and symptoms of systemic vasculitis such as peripheral neuropathy, fever, weight loss or rash are usually lacking. [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%), hemisensory 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 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. ($p<001/0$) [27]. The spectrum of cPACNS includes three distinct disease entities: progressive angiography-positive cPACNS (P-cPACNS); nonprogressive-angiography-positive cPAC NS (NP-cPACNS); and angiography-negative, small-vessel cPACNS (SV-cPACNS). [25]. Patients with angiography-positive, P-cPACNS frequently present with multifocal MRI lesions and evidence of both proximal and distal vessel stenosis on angiography and both focal and diffuse neurological findings. Untreated patients progress beyond 3 months[27].

Proximal, large-vessel inflammation with subsequent focal stenosis is the hallmark of NP-cPACNS. In contrast, NP-cPACNS patients often present with unilateral MRI lesions predominantly focal deficits, and proximal vessel stenosis on angiography. 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.

Distal vessel inflammation is commonly seen in P-cPACNS and SV-cPACNS and is frequently associated with features of adjacent parenchymal inflammation. P-cPACNS patients have both large- and small-vessel inflammation and will therefore present with overlapping clinical features.

Children with SV-cPACNS present with distal vessels stenoses 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 immunoglobulins level by no means exclude an active vasculitic 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 imagings studies (MRI, MRA, CT-SCAN and CA) are valuable tools for the diagnosis of cerebral vasculitis. [36-39] Table 3 shows the comparison of these tools.

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 MCA and ACA, whereas 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 4.

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. [40] 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/m2/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. [11]

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. Most of them showed favorable response to treatment. Authors declare no conflict of interest in this study.

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