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Research Article

Childhood Primary Angeitis of CNS, Ten Years' Experience in a Pediatric Rheumatology Clinic

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Abstract

Background: CNS vasculitis in children as a primary vascular inflammatory process is considered a novel clinical problem in pediatric rheumatology clinics.

Methods: From 1996 to 2016 at pediatric rheumatology clinic, patients < 18 years of age were included to this study as having childhood primary angeitis of CNS (cPACNS). Including criteria were: clinical diagnosis of primary CNS vasculitis, and MRA findings demonstrating aneurism and or arterial stenosis not attributable to other causes.

Results: 22 patients were enrolled with mean age 10 years, (54%) were female. Headache was in (88%) then mental disorder and seizure in (45%) were the most common neurologic symptoms. The mean delayed to diagnosis was 4 years. Fever was in (54%) and ANA in (31%) was positive. 63 %had abnormality in both MCA and ACA (14 patients), whereas PCA showed abnormity in 36% (8 patients). 86 % had normal EEG results. 22% suffered from severe and permanent neurological damage.

Conclusion: Since cPACNS is unfamiliar and rare disorder, we recommend that in any patient with unexplained neurologic symptoms such as headache, seizure and mental disorder, CNS vasculitis should be considered as a probable background.

Keywords: *CNS Vasculitis; CNS Angeitis; Brain MRI; Brain MRA*

Introduction

Vasculitis is a vessels disorders which characterized by obstruction, necrosis and inflammatory of vessels [1]. It may affect the central nervous system (CNS), and because of the followings considered a very challenging clinical problem: 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 primary angiitis or vasculitis of the CNS, idiopathic granulomatous angiitis of the CNS, and isolated CNS angiitis. CNS vasculitis can cause brain damage with reversible and or irreversible neurologic involvement, including seizures often intractable, cognitive decline and acute ischemic attack [3,4]. Acute and or chronic inflammatory course of CNS primary vasculitis may result in severe neurological impairment and or death [5,6].

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

Early diagnosis and treatment result in improved neurological outcome significantly [8]. If untreated, this process may lead to permanent damage of the CNS [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].

Childhood primary angiitis of the CNS (cPACNS) was thought to be a rare disease, in the past [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].

Cravioto and Feigin reported as a first case of primary CNS vasculitis in 1959, 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 diagnosis of childhood CNS vasculitis in the absence of a systemic vasculitis or disease have increased [27].

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

Methods

During ten years from 1996to 2016, 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 children with systemic vaculities, children with collagen vascular disease, and neonate patients 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). Different therapy was decided on a case by- case basis and simple statistical analysis 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 years. The mean delayed time to diagnosis was four years. The most common neurologic symptoms in this study were headaches (88%), seizure and mental disorder in (45%). Systemic symptoms including fever, decreased energy level and weakness were common findings 54%, 45%, 31% respectively.

The main complaint of patients was headache (68%) and fever (54%). Hematologic findings were anemia (63%) and leukocytosis (45%). ESR and CRP were in high results in (40%).ANA was positive in (31%) but not in high titers.

14 patients (63%) had small vessels involvements, four patients showed large vessels involvement and in 4 patients both vessels have been involved.

63 % (14) patients 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. Table 1 shows some characteristic features of all patients.

Discussion and Conclusion

CPACNS is an immune mediated inflammatory disorder of CNS although reactivated VZV and other neurotropic viruses can induce a post infectious type of CNS vascular inflammation. Parvovirus B19 has been reported to trigger CNS vasculitis among pediatric immune-suppressed patients [28] although with a long prodromal period. Constitutional symptoms are uncommon and signs and symptoms of systemic vasculitis such as peripheral neuropathy, fever, weight loss or rash are usually lacking [29]. In our study, systemic symptoms such as fever, decreased energy level and weakness were common findings 54%, 45%, 31% respectively.

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	
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 1: *Patients' symptoms and signs.*

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 [29].

In one study, focal neurologic deficits were the most frequent clinical symptom, including acute hemiparesis (80%), hemisensory deficit (79%), and fine motor deficits (73%). Headache in 56% of patients and seizures in 15% have been presented.

Diffuse neurologic deficits included cognitive dysfunction in 37%, and concentration difficulties in 29% of patients, mood/personality changes in 26%. Concentration difficulties and cognitive dysfunction resulted in decline in school participation and school work [30].

A study conducted by Benseler., *et al*. on children with initial diagnosis of cerebral vasculitis (the diagnosis 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 non-progressive disease (42 patients) and progressive disease (20 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); non-progressive-angiography- positive cPACNS (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. If untreated, disease progresses beyond 3 months [27].

Proximal, large-vessel inflammation with subsequent focal stenosis is the hallmark of NP-cPACNS. NP-cPACNS patients often present with focal deficits and unilateral MRI lesions and proximal vessel stenosis on angiography. These patients present a monophasic inflammatory large-vessel vasculitis, which does not progress beyond 3 months. The majority patients of NP-cPACNS present with strokes.

Distal vessel inflammation is commonly seen in P-cPACNS and SV-cPACNS and is frequently associated with features of adjacent CNS 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 [30-33].

Laboratory results although in different studies did not show specific findings, acute phase reactants are frequently normal in children with cPACNS. Some children may show positive antinuclear antibodies (ANA) in low titer [11,29]. However, as the inflammation progresses, some patients may develop mildly elevated systemic inflammatory response [27].

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 this study anemia (63%) and leukocytosis (45%) were common hematological abnormalities. ESR and CRP were in (40%) patients in high amounts. 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 [34-37]. Table 2 shows the comparison of those.

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 study but 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 2: *Imaging characteristics of CNS vaculities [30].*

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 CNS MRI showed some pathologic findings and their simultaneous MRA had particular results. Table 3 shows the comparisons of the MRI and MRA findings of these patients.

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 Vessels
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.

Table 3: *Comparison of MRI and MRA findings.*

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

In children, the choice of treatment depends on the cPACNS classification [38]. Intravenous (IV) monthly cyclophosphamide plus high-dose corticosteroids are the current method in patients with P-cPACNS and SV- cPACNS [25].

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 corticosteroids in a tapering low dose 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.

Declarations

Ethics approval and consent to participate

This manuscript dose not contains any individual person's data in any form, (including individual details, images or videos).

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Authors' Contributions

FS as a pediatric rheumatologist carried out diagnosis and management of the patients, FA as child neurologist carried out exclusion of neurologic disorder in the patients. MB as child infectious e specialist carried out exclusion of infectious disease in the patients. All authors read and approved the final manuscript.

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Conflict of Interest

Authors declare no conflict of interest in this study.

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