

POLYARTERITIS NODOSA - A FEW UNUSUAL FINDINGS

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Objective: To report the clinical spectrum of polyarteritis nodosa (PAN) from North India and highlight some unusual findings. **Design:** Retrospective study. **Setting:** Hospital based. **Subjects:** Eight children with PAN. **Intervention:** Treatment with prednisolone and cyclophosphamide. **Results:** One child had spontaneous remission while another started deteriorating rapidly in spite of treatment and died within 2 weeks. Six children went into remission-of these one died, two were lost to follow-up and the remaining three are on regular follow-up for periods ranging from 3-5 years. **Conclusions:** Prednisolone and cyclophosphamide can significantly improve the outcome in childhood PAN.

Key words: Polyarteritis nodosa, Cyclophosphamide, Prednisolone.

POLYARTERITIS nodosa (PAN) is a vasculitic syndrome involving the medium sized muscular arteries. It is a rare disorder and has been infrequently reported in the Indian literature(1). Childhood presentation of the disease is rarer still and there have only been occasional case reports from India (2,3). The present communication documents our experience with this condition.

Patients

Eight children with PAN were seen between February 1990 to May 1992 in the Department of Pediatrics, Postgraduate Institute of Medical Education and Research, Chandigarh. The diagnosis was based on the American College of Rheumatology (1990) criteria for the

classification of polyarteritis nodosa(4) (Table I).

These children were between 3.5 to 12 years of age (mean 8.7 years) with male to female ratio of 5:3. All children had fever, anorexia and weight loss. The duration of symptoms prior to hospitalization varied from 2-10 weeks. Hypertension was a universal finding. Aches and pains were present in 5 patients, maculopapular rashes in 6, generalized tonic clonic seizures in 5, mononeuritis multiplex in 1, pain abdomen in 5, gangrene of finger tips in 1, dystrophic nails in 1 and nephrotic syndrome in 2 patients. One child had cardiomegaly and an ejection systolic murmur secondary to hypertension.

Raised erythrocyte sedimentation rate

(ESR) was seen in all which decreased to normal levels on therapy. Anti-neutrophil cytoplasmic autoantibodies (ANCA) were positive transiently in 1 child, negative in 5 and could not be done in 2 children due to the non-availability of test at that time. Serum complement levels were normal in all 8 children (Table I). The only patient who was HBsAg positive had an episode of jaundice 8 weeks prior to the onset of symptoms.

Renal involvement was seen in 5

patients; all had nephrotic range proteinuria, 2 had hematuria, while 1 subject had granular casts in the urine. Kidney biopsy was done in 3 patients. Microscopy showed membranoproliferative glomerulonephritis with crescents in 2 and focal sclerosing glomerulonephritis in 1 biopsy sample.

Ultrasonographic examination revealed interesting findings in 2 children; spontaneous perinephric hematoma was

TABLE I—Important Clinical and Laboratory Parameters in Children with PAN

Patients	1	2	3	4	5	6	7	8
<i>Symptoms</i>								
Fever	+	+	+	+	+	+	+	+
Hypertension	+	+	+	+	+	+	+	+
<i>Organ Involvement</i>								
Renal	+	+	+	+	+	-	-	-
Musculoskeletal	+	-	-	-	+	+	+	+
GIT	+	-	+	-	+	+	-	+
Nervous system	+	+	-	+	+	-	+	+
Cutaneous	+	-	+	+	-	+	+	+
<i>Investigations</i>								
ESR	↑	↑	↑	↑	↑	↑	↑	↑
ANCA	-	-	+	-	-	-	ND	ND
C ₃	N	N	N	N	N	N	N	N
Rh factor	-	-	-	-	-	-	-	-
LE cell	-	-	-	-	-	-	-	-
ANF	-	-	+	-	-	-	-	-
HBsAg	+	-	-	-	-	-	-	-
<i>Evidence of Vasculitis</i>								
Kidney biopsy	+	+	+	ND	ND	ND	ND	ND
	PM							
Muscle biopsy	-	ND	-	ND	-	+	ND	-
Skin biopsy	-	ND	ND	ND	ND	ND	+	+
Aneurysm on angiography (renal/abdominal)	ND	+	+	-	+	+	ND	-
Infarcts on CT scan head	ND	+	ND	+	ND	ND	ND	ND
Outcome	D	D	AW	LF	SR	LF	AW	AW

ND = not done; PM = post mortem; D = died; AW = alive and well; LF = lost to follow-up; SR = spontaneous remission.

noted in one subject while in the other case both kidneys were enlarged in the longitudinal axis. The pyramids were hyperechoic and the sinus echogenicity could not be observed separately. This type of dotted hyperechogenicity was also observed in the spleen and the pancreas. Abdominal angiography was performed on 6 patients and revealed aneurysms in renal vessels in 4 children. In addition mesenteric, hepatic and splenic medium and small artery aneurysms were also seen. Cranial CT scans revealed bilateral cerebral infarcts in 3 patients. Fibrinoid necrosis of medium and small vessels was seen in skin/muscle biopsies in 4 patients where these were done and similar involvement in vessels of many organs was noted in postmortem specimens of 1 child.

Therapeutic regimen consisting of prednisolone and cyclophosphamide as described by Fauci *et al.*(5) was used to treat 7 of the 8 children. One girl died after 2 weeks of therapy and the boy who had focal sclerosing glomerulonephritis showed rapidly deteriorating renal functions after some initial improvement over a year and is now presumed dead. Five children achieved remissions after 2-6 months of starting treatment. Of these 2 were lost to follow-up after achieving initial remission. One of the patients went into spontaneous remission even without treatment and has remained well for the last 5 years. The remaining three patients have maintained their remission and have been on follow-up for periods ranging 3-5 years. All children required drugs (enalapril, nifedipine, propranolol) for control of hypertension.

Discussion

Histology and /or angiography should confirm the diagnosis of PAN, although evaluation is tricky due to segmental nature of the disease(6). The clinical picture is diverse but the constellation of

clinical features seen in PAN is well established(7-10). Our experience with these children confirms the frequent involvement of the nervous system, skin, kidneys and the musculoskeletal system(7,10). Hyper-tension was a universal feature in our patients. Fink *et al.* reported it in 96% of the children in their series(10). Generalized tonic clonic seizures were the presenting feature in 5 of our patients. Though cerebral angiography was not done, bilateral infarcts were detected in 2 children on CAT scan of the head and on autopsy of the brain in one patient. The patients with bilateral infarcts seen on CT scan of the brain also had histopathological evidence of vasculitis in the kidneys. Fauci *et al.*(5) considered an organ involved if vasculitis was seen in the biopsy specimen or if there was angiographic evidence of vessel involvement or functional impairment was documented in an organ in the presence of biopsy or angiographic, evidence of vasculitis in another organ. Mononeuritis multiplex is uncommon in children though it is a well known complication of systemic vasculitis in adults(5,11,12) and was seen in only one child in our series.

Although on histology, kidney is involved in 70-80% patients of PAN, overt clinical manifestations may be infrequent(13,14). There may be considerable morphological heterogeneity within the same biopsy specimen and this can result in a diagnostic dilemma. Glomeruli may show ischemic wrinkling, focal glomerulitis with necrosis and epithelial crescents or diffuse proliferative glomerulo-nephritis (13,14). Interstitial nephritis has also been described. Well developed membrano-proliferative glomerulonephritis has been rarely reported and its presence should prompt a search for associated conditions such as cryoglobulinemia or hepatitis B infection (13)

None of the two children who had membrano-proliferative glomerulonephritis had any of these.

Conclusions and proposals made at the Chapel Hill Consensus Conference on the nomenclature of systemic vasculitis, defines PAN as arteritis in the medium sized and small arteries without the involvement of the smaller vessels(15). Therefore, patients with vasculitis affecting arterioles, venules or capillaries, including glomerular capillaries (*i.e.*, with glomerulonephritis) are excluded from this category. The entity of "microscopic polyarteritis" connotes *pauci* immune necrotizing vasculitis affecting small vessels with or without involvement of the medium sized arteries (after exclusion of cryoglobulinemic vasculitis, Henoch Schonlein purpura and other forms of immune complex mediated vasculitis). In light of these classifications it can be argued that our patients with glomerulonephritis should be labelled as 'microscopic polyarteritis'(15). However, it must be emphasized that universal consensus on nomenclature in systemic vasculitis has still not been reached. The heterogeneity in features of vasculitic syndromes would necessarily lead to some overlap and thereby create difficulties in rigid categorization.

Interesting abdominal ultrasound finding in the form of hyperechoic areas in both kidneys, spleen and pancreas seen in a child have not been reported in PAN. Similar ultrasound findings in the corticomedullary junction of kidneys were reported in 6 children (aged 3-12 years) suffering from renovascular hypertension due to causes other than PAN. Where histopathology of the vessels was available, calcification of laminae elastica of the intra renal arteries was noted. Renal angiography done in 4 of these children was normal(16). A host of etiologic factors have been incriminated

in triggering off immunological reactions resulting in vasculitis. Hepatitis B virus, parvovirus B19, streptococcus, human immunodeficiency virus, enterovirus, as well as basic genetic predisposition are some of them(17-22). Only one of our patients was HBsAg positive but even in this case it would be presumptuous to categorically implicate the presence of this virus in the pathogenesis of disease.

Various therapeutic modalities have been tried in patients with PAN but a combination of cyclophosphamide and prednisolone has proved most effective(5). Six of our patients went into remission with the above treatment. One of our patients went into spontaneous remission by the time the diagnosis was confirmed. We were in a clinical and ethical dilemma whether to treat or not to treat. We only treated his hypertension. He continues to be in remission for the last 5 years. Spontaneous remissions in childhood PAN are unusual and were not seen in any of the patients described by Ozen *et al.*(7).

Immunomodulatory agents as well as specific agents targeted against the associated etiological factors are beginning to be tested in the clinical setting. Antiviral therapy in the form of interferon alpha 2b in combination with plasma exchanges have been tried in PAN related to hepatitis B virus with some degree of success(17). In patients with parvovirus infection and systemic vasculitis, intravenous immunoglobulin therapy led to rapid improvement where a combination of corticosteroids and cyclophosphamide had failed in this disease(23). However, till these futuristic approaches are thoroughly evaluated Fauci's regime will continue to be used.

In a study in children with vasculitis syndromes, the von Willebrand factor antigen has been shown to be a useful marker for monitoring disease activity(24).

However, laboratory tests are generally unhelpful in predicting relapse(25). Anticipation of events in long term follow up is so far the only way to record relapses.

Our experience of PAN in a short span of 27 months has led us to believe that this condition may not be rare in Indian children, the clinical spectrum being similar to that reported in literature. Early diagnosis and rapid institution of therapy is essential to reduce mortality and morbidity.

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