Polyarteritis nodosa: lessons from 25 years of experience

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ABSTRACT

Objective. *Polyarteritis nodosa is a necrotising vasculitis of predominantly medium-sized vessels. The present study aimed to summarise the characteristics of PAN patients, and also analyse the trend of decreasing PAN frequency in the last 25 years.*

Methods. *PAN patients followed up between 1990 and 2015 were included. The demographics, clinical findings and outcomes were retrospectively evaluated.*

Results. *One hundred and thirty-three patients, including 66 children, were enrolled in the study. Among 133 patients, 86 (64.7%) had fever, 108 (81.2%) had skin involvement, 54 (40.6%) had renal involvement, 43 (32.3%) had neurological involvement, 32 (24.1%) had gastrointestinal involvement, 10 (7.5%) had cardiac involvement, 6 (4.5%) had pulmonary involvement. The median (minimum-maximum) leukocyte count, erythrocyte sedimentation rate and C-reactive protein levels at the time of diagnosis were 10400 (6100–32000)/ mm³, 58 (2–132) mm/h and 5.22 (0–46) mg/dL, respectively. All patients were ANCA negative. Hepatitis serology was analysed in 121 patients and found positive in 13 of them. MEFV mutations were screened among 65 patients, 24 of them had mutations in at least one allele. Biopsy was performed in 109 patients and angiography was performed in 92 patients. The number of PAN patients declined significantly after 2010. 9 patients were re-categorised as DADA2 after 2014 and no patient were diagnosed with FMF+PAN after 2008.*

Conclusions. *Our results suggest a decrease in PAN in our country which may be due to improved healthcare and dissecting mimicking diseases. Further prospective studies with prolonged follow-up could help us to better understand the disease characteristics.*

Introduction

Polyarteritis nodosa (PAN) is a necrotising arteritis involving medium and small-sized vessels without the presence of capillaries, venules or arterioles involvement or glomerulonephritis, with a lack of antineutrophil cytoplasmic antibodies (ANCA) positivity (1, 2). Skin, musculoskeletal and gastrointestinal systems are the most frequently affected sites; however, PAN might involve all systems (3, 4). The estimated annual incidence of PAN is 2.0–9.0/ million in adults, but epidemiological studies in childhood are scarce (5). PAN comprises 9% of all childhood vasculitis and is the most common primary vasculitis after IgA vasculitis/ Henoch-Schönlein purpura (IgAV/HSP) and Kawasaki disease in Turkey (6). The age at disease onset is between 25–50 years in adults while it is around 9–10 years of age in children (3, 7). Furthermore, clinical manifestations and outcomes may also vary between children and adults. Previous studies have confirmed that childhood PAN had better outcomes than adults (3, 7).

Although the first cases of PAN were described in the mid-1800s, the classification of the disease has evolved over the years. In 2012, the definition of vasculitis was updated in the Chapel Hill Consensus Conference (CHCC) with the substantial advances in our understanding of vasculitis pathogenesis (1). In CHCC 2012, ANCA negativity was added to the definition of PAN which is a valuable feature for distinguishing PAN from microscopic polyangiitis (MPA). In addition, hepatitis B-related PAN is clearly separated from PAN and classified as "vasculitis associated with the probable aetiology" (2, 8). In 2014, a monogenic disease caused by *CECR1* (cat eye syndrome chromosome region candidate 1) gene mutations, deficiency of adenosine deaminase 2 (DADA2),

was described which could lead to vasculitis mimicking PAN (9, 10). It is accepted that these patients should now be classified under the category of "vasculitis associated with probable aetiology" and not as PAN (2). An increased frequency of PAN among FMF patients has been previously described (11-13). Our common observation suggests that the frequency of PAN in FMF patients has declined. With all these changes, the characteristics and frequency of PAN might have changed over years.

In this study, our aim was to report the characteristics of PAN patients, make a comparison between paediatric and adult PAN patients, and analyse PAN frequency in the last 25 years in Turkey.

Patients and methods

Study population

Two centres from Turkey were enrolled in the study (Hacettepe University and İstanbul University Cerrahpaşa Faculty of Medicine). Patients with PAN who were followed between 1990 and 2015 were included in the study. Demographic data, clinical manifestations, laboratory, radiological, histopathological findings, treatment, and outcome were documented from patient charts retrospectively.

The paediatric patients were classified as having PAN according to the European League Against Rheumatism (EULAR)/Paediatric Rheumatology European Society/Paediatric Rheumatology International Trials Organisation (PRINTO) classification criteria for childhood PAN (4, 14). The adult patients were classified with PAN according to the American College of Rheumatology (ACR) criteria (15).

Paediatric vasculitis activity score (PVAS) (16) and Birmingham Vasculitis Activity Score (BVAS) v. 3 (http://www.vasculitis.org/images/documents/bvas%203.0.pdf) were calculated retrospectively to evaluate the disease activity (17).

MEFV (MEditerranean FeVer) gene variant analysis and *CECR1* gene were performed with Sanger sequencing in Departments of Medical Biology. *MEFV* mutation analysis was performed in patients who had at least one of following findings; 1) history of recurrent fever or serositis, 2) presence of elevated acute phase reactants despite the adequate treatment, 3) presence of relapse.

We also analysed the distribution of patients according to years.

The study was approved by the ethical committee of Hacettepe University. (June 14, 2016; GO 16/386-23). All these patient files were evaluated retrospectively and all patients were anonymous. When the patients admitted to the hospital, the parents gave a general consent approving anonymous data use for academic purpose.

Statistical analysis

Statistical analyses were performed using the SPSS software v. 21. The variables were investigated using visual (histogram, probability plots) and analytic methods (Kolmogorov-Smirnov/Shapiro-Wilk's test) to determine whether or not they are normally distributed. Descriptive analyses were presented using proportions, medians, minimum, and maximum values as appropriate. Differences in proportions between groups were evaluated by the Chi-square test or Fisher's exact and Mann-Whitney U-test where appropriate. A *p*-value of less than 0.05 was considered to show a statistically significant result.

Results

A total of 133 patients were included in the study, and 66 (49.6%) of them were children. 78 patients (58.6%) were from Hacettepe University, and 55 patients (41.4%) were from İstanbul University Cerrahpaşa Faculty of Medicine. Male to female ratio was 1.4. Median (minimum-maximum) age at onset of symptoms and diagnosis were 16 (2–75) and 17 (3–75) years, respectively. The median (minimum-maximum) time of diagnostic delay was 4 (0-144) months. The median (minimum-maximum) duration of follow up was 13 (2–27) years. Among 133 patients, 86 (64.7%) had fever, 79 (59.4%) myalgia, and 65 (48.9%) had weight loss as constitutional symptoms; and 108 patients (81.2%) had skin involvement, 54 (40.6%) had renal involvement, 43 (32.3%) had neurological involvement, 32 (24.1%) had gastrointestinal involvement, 14 (10.5%) had testicular involvement, 10 (7.5%) had cardiac involvement, and 6 (4.5%) had pulmonary involvement.

The laboratory evaluation showed the median (minimum-maximum) leukocyte count, erythrocyte sedimentation rate, and CRP levels at the diagnosis were 10400 (6100–32000)/mm^3, 58 (2–132) mm/h, and 5.22 (0–46) mg/dl, respectively. 130 patients were tested for ANCA, and all were negative. Hepatitis serology results could be obtained in only 121 patients, of which 13 (10.7%) had positive results for Hepatitis B surface antigen (HBsAg). All of them were born before 2000. *MEFV* mutation analysis was performed in 65 patients, and 24 of them had mutations in at least one allele.

109 patients had biopsy results, and 92 patients had computerised tomography angiography results. Angiographic findings were as follows: 69 patients had renal artery microaneurysm, 17 patients had hepatic artery microaneurysm, 3 patients had aneurysm at splenic artery, 3 patients had aneurysms at branches of the superior mesenteric artery, 3 patients had occlusion at superior mesenteric artery (SMA), 2 patients had aneurysms at coeliac trunk, 2 patients had renal subcapsular haematoma, and 1 patient had splenic infarction. Biopsy samples were obtained from kidneys in 9 patients, skin in 94 patients, and muscle in 6 patients. Biopsy samples revealed necrotising vasculitis in medium-sized vessels in all these patients, and panniculitis was also detected in 5 of them. There was no immune deposition in renal biopsies.

Median (minimum-maximum) PVAS was 11 (2–18) in the paediatric patient group, and median BVAS was 4 (2–37) in the adult patient group at the diagnosis.

All patients used corticosteroids for induction therapy, 62 (46.7%) patients also received cyclophosphamide. 20 of these patients received oral while 42 got intravenous (IV) cyclophosphamide. 32 (24%) received azathioprine, and 39 (29.3%) patients were administered mycophenolate mofetil (MMF) for remission induction. 89 (66.9%)

patients were treated with azathioprine, 29 (21.9%) patients used methotrexate, 13 (9.7%) patients used MMF, and 2 (1.5%) patients used anti-tumor necrosis factor (anti-TNF) drug for maintenance therapy. 10 (7.5%) patients received aspirin or dipyridamole and 36 (27%) patients were treated with colchicine in addition to the primary treatment. 54 (40.6%) were administered antihypertensive drugs (nifedipine, enalapril, propranolol). 13 patients were also treated with antiviral agents.

We have reached 102 of these patients for a final evaluation. Among them, 6 (5.9%) patients died, and the cause of death was sepsis in 4 and pneumonia in the other 2. 42 patients (41.1%) experienced relapse at a median of 13 (12–36) months after remission. All of them had at least one episode of relapse after the remission-induction therapy. All of them received pulse methylprednisolone for three consecutive days. Among these 42 patients, 28 (66.7%) were on methotrexate and 14 (33.3%) were on azathioprine. Treatments were switched to MMF in 27 patients and anti-TNF drug in 11 patients and IV cyclophosphamide in 4 patients

The differences between paediatric and adult patients were summarised in Table I. The main significant clinical differences between paediatric and adult patients were as follows; myalgia (p=0.01) and skin involvement (p<0.001) were more common in children, whereas neurological involvement was more frequent in adults (p=0.007). The number of PAN patients decreased significantly after 2010 (Fig. 1).

Table I. Characteristics of paediatric and adult polyarteritis nodosa (PAN) patients.

Features, n (%)	Patients (n=133)	Paediatric patients (n=66)	Adult patients (n=67)	p-value
Gender, female	55 (41.4)	35 (53)	20 (29.8)	0.07
Fever	86 (64.7)	50 (75.7)	36 (53.7)	0.06
Myalgia	79 (59.4)	48 (72.7)	31 (46.2)	0.01
Abdominal pain	65 (48.9)	40 (60.6)	25 (37.3)	0.05
Weight loss	56 (42.1)	20 (30.3)	36 (53.7)	0.06
Arthralgia	87 (65.4)	48 (72.7)	39 (58.2)	0.06
Arthritis	23 (17.3)	11 (16.6)	12 (17.9)	0.58
Skin involvement	108 (81.2)	63 (95.5)	45 (67.2)	<0.001
Raynaud's phenomenon	13 (9.8)	3 (4.5)	10 (14.9)	0.04
Livedo reticularis	48 (36.1)	36 (54.5)	12 (17.9)	<0.001
Panniculitis	23 (17.3)	18 (27.2)	5 (7.5)	0.003
Necrosis	12 (9)	3 (4.5)	9 (13.5)	0.069
Autoamputation	2 (1.5)	0 (0)	2 (2.9)	0.49
GI[a] involvement	32 (24.1)	17 (25.7)	15 (22.3)	0.64
Renal involvement	54 (40.6)	22 (33.3)	32 (47.7)	0.09
Hypertension	54 (40.6)	26 (39.3)	28 (41.7)	0.77
Scrotal involvement	14 (10.5)	4 (6)	10 (14.9)	0.09
Cardiac involvement	10 (7.5)	8 (12)	2 (2.9)	0.04
Pulmonary involvement	6 (4.5)	4 (6)	2 (2.9)	0.4
Neurologic involvement	43 (32.3)	14 (21.2)	29 (43.2)	0.007
WBC[a], x10^3/mm^3	10400 (4200-32000)	11800 (4300-32000)	9850 (4200-21800)	0.02
PLT[a], x10^3/mm^3	365000 (259000-726000	456000 (259000-696000)	300000 (268000-726000)	<0.001
CRP[a], mg/dl	5.22 (0-46)	4.6 (0.1-46)	5.8 (2-29.8)	0.88
ESR[a], mm/h	58 (2-132)	65 (10-132)	56 (2-125)	0.03
Exitus	6 (4.5)	0 (0)	6 (8.9)	0.007

[a]CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; GI: gastrointestinal; PLT: platelet; WBC: white blood cell.

Discussion

The presented study has attempted to analyse the epidemiology of PAN according to decades. Our results suggest a significant decrease in PAN frequency especially in the last 5 years. The two centers that contributed the patient data have remained the main referral centers for these patients in the country throughout these years.

Among the presented PAN patients, the most common findings were constitutional symptoms, skin involvement, renal involvement, neurological involvement, and gastrointestinal involvement. Myalgia and skin involvement were more common in children, whereas neurological involvement was more frequent in adults. The French Vasculitis Study Group Database has reviewed the characteristics of 348 adult PAN patients (225 PAN and 123 HBV-PAN). In this study, the most frequent findings were constitutional symptoms (93.1%), neurologic findings (79%), urologic and renal manifestations (50.6%), skin involvement (49.7%) and gastrointestinal symptoms (37.9%) similar to our results except for urologic findings (18). In the largest multicentre study including 110 children with PAN constitutional features were the most common findings (86.4%), followed by skin involvement in 74.5%, myalgia in 33.6%, and gastrointestinal symptoms in 17.3% (7). However, this study included both systemic (63 patients) and cutaneous (33 patients) and also the patients associated with hepatitis B (5 patients) and the microscopic poliangiitis (9 patients). Recently Eleftheriou *et al*. have reported the largest paediatric cohort of systemic PAN, including 69 patients. The most common clinical findings were as follows; fever (87%), myalgia (83%), skin involvement (88%), gastrointestinal findings 41%, and hypertension 16% (3). Our group have recently compared the differences between adult and paediatric patients and found that arthralgia/arthritis and skin involvement were more common in children while renal and neurologic involvement were more frequent in adult patients (19). Similarly, we have observed that myalgia and skin involvement were more common in children, whereas neurological involvement was more frequent in adults.

Previous studies suggested that PAN had better course among children compared to adult patients (3, 7). The mortality rate was reported as 1–4% in children (3, 7) while it was 14.5–24.6% in adult PAN patients (18, 20-22). In the present study, 6 (5.9%) patients died, and the cause of death was related to infections. All of the infection-related mortality occurred before 2005. All of the patients were adults and there was

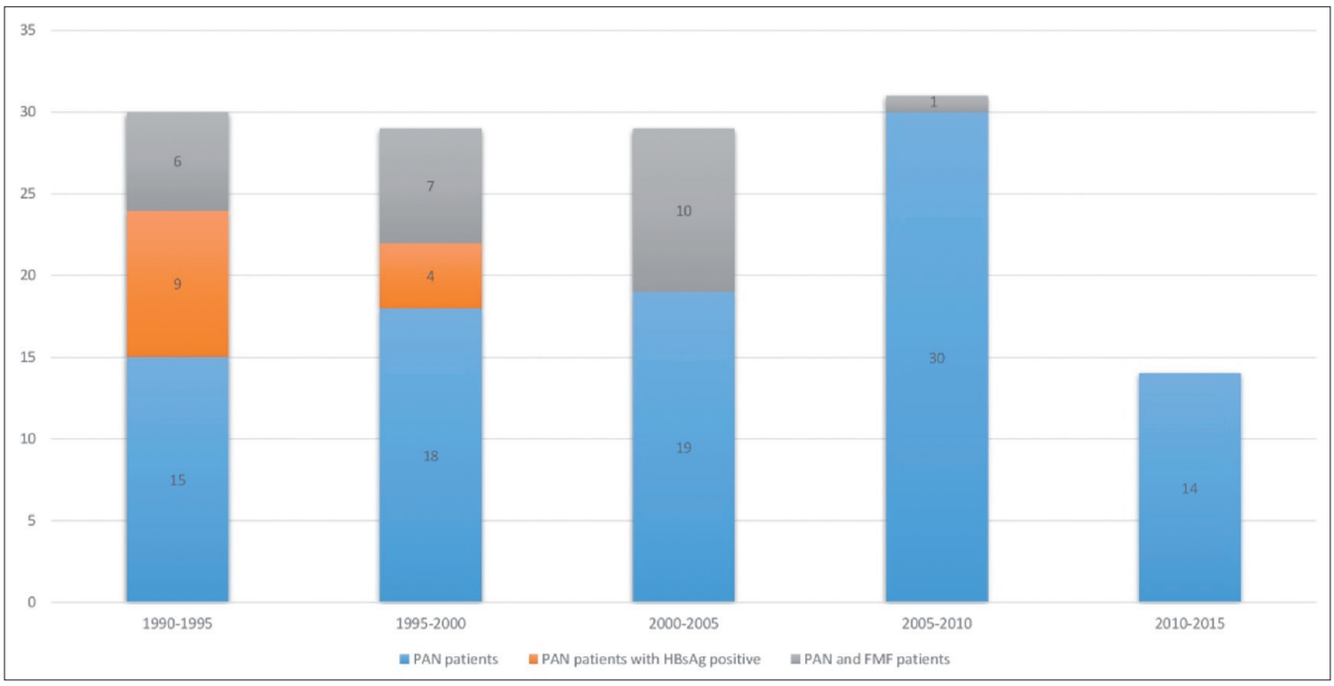

Fig. 1. Distribution of the polyarteritis nodosa (PAN) patients by years.

a major organ involvement in all of them. According to the French Vasculitis study group registry, the incidence of mortality, including infection-related mortality, declined over the years among PAN patients, especially after 2010 (23). Falcini *et al*. (24) have demonstrated worsened outcome among paediatric PAN patients with renal and neurological involvement. However, in the present study, paediatric patients had less neurologic involvement compared to adults.

In recent years, definition of PAN has evolved, and it has become a rarer disorder with the decrease in the prevalence of hepatitis B infection, definition of DADA2, and an effective control of inflammation in FMF patients. The major environmental factor associated with PAN-like vasculitis is hepatitis B infection. However, due to widespread vaccination practices, hepatitis B-related PAN does not exist anymore in children. In our country, hepatitis B vaccination has been included to the national vaccination program after 2000. In the present study, 13 patients were infected by hepatitis B, all born before 2000. With the improvement of the knowledge in pathogenesis, infection-related PAN has been classified as "vasculitis related with a possible aetiology" in the CHCC 2012 classification and it is now known to be an immune complex disease (2).

Two independent groups have described a new monogenic disease called DADA2 in 2014 (9, 10). DADA2 is an autosomal recessively inherited disease, caused by loss of function mutations in the *CECR1* gene, leading to necrotising vasculitis involving medium-sized arteries resembling PAN (9, 10). More than 100 patients with DADA2 have been reported so far and most of these patients had PAN-like vasculitis, most with an unsatisfactory response to conventional treatment or a family history of PAN or were offspring of consanguineous marriage. In our series, 24 patients who had been diagnosed with PAN and followed as such have been screened for this mutation due to family history or the presence of stroke or resistance to therapy: 9 of them had DADA2. Thus, this may be contributing to the decrease in PAN frequency especially after 2014.

Rheumatic diseases such as vasculitis are more common in FMF patients compared to normal population. A nationwide study from Turkey, including almost 3,000 FMF patients, has demonstrated an increased frequency of PAN in these patients (almost 0.9%) (12). An ongoing inflammation involving the innate immune system probably triggers necrotising vasculitis in patients with FMF. Carrying severe *MEFV* mutations such as M694V may also be a predisposing factor for PAN, and again a study from Turkey have reported that 38% of Turkish children with PAN carried at least one mutant *MEFV* allele (25). In the presented study, *MEFV* mutation analysis was performed in 65 patients, and 24 of them had mutations in at least one allele. All of the patients with PAN and FMF were diagnosed before 2006. This coincides with the period in which we had better control of the disease with earlier diagnosis and the use of anakinra (26-28). In Turkey, anti-interleukin 1 drugs were introduced for FMF treatment after 2008, which helped to have a better control of chronic inflammation and to lower the risk of amyloidosis (29). Better control of subclinical inflammation may have caused a decrease in vasculitis frequency in these patients. A drawback of this study is that it was not nationwide, but confined to the two main referral centres in Turkey.

In conclusion, our results suggest a decrease in PAN in our country, which may be due to an improved healthcare and to dissecting mimicking diseases.

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