Clin Rheumatol (2007) 26: 196–200
DOI 10.1007/s10067-006-0266-6

ORIGINAL ARTICLE

Seza Ozen · Aysin Bakkaloglu · Ruhan Dusunsel · Oguz Soylemezoglu · Fatih Ozaltin · Hakan Poyrazoglu · Ozgur Kasapcopur · Ozan Ozkaya · Fatos Yalcinkaya · Ayse Balat · Nurdan Kural · Osman Donmez · Harika Alpay · Ali Anarat · Sevgi Mir · Ayfer Gur-Guven · Ferah Sonmez · Faysal Gok · On behalf of Turkish Pediatric Vasculitis Study Group

Childhood vasculitides in Turkey: a nationwide survey

Received: 8 February 2006 / Revised: 22 February 2006 / Accepted: 23 February 2006 / Published online: 4 April 2006

Abstract *Aim:* The aims of this study were to evaluate the characteristics of childhood vasculitides and to establish the first registry in Turkey, an eastern Mediterranean country with a white population. *Patients and methods:* A questionnaire was distributed to the main referral centers asking for the registration of the Henoch-Schönlein purpura (HSP) patients in the last calendar year only and 5 years for other vasculitides. Demographic, clinical, and laboratory data were assessed. *Results:* Vasculitic diseases were registered from 15 pediatric centers. These centers had a fair representation throughout the country. In the last calendar year, incidences were as follows: HSP 81.6%, Kawasaki disease (KD) 9.0%, childhood polyarteritis nodosa (C-PAN) 5.6%, Takayasu arteritis (TA) 1.5%, Wegener's granulomatosis 0.4%, and Behçet disease 1.9%. There was no clear gender dominance. The mean age was 11.05±4.89 years. Acute phase reactants were elevated in almost all, highest figures being in C-PAN. Renal involvement was present in 28.6% of HSP and 53% of the C-PAN patients. Abdominal aorta was involved in all TA patients. Among the C-PAN patients, 25% had microscopic PAN with necrotizing glomerulonephritis; antineutrophil cytoplasmic antibody was positive in those who were studied. Among the patients, 12.5% and 15% had classic PAN and cutaneous PAN, respectively. The remaining majority were classified as systemic C-PAN diagnosed with biopsies and/or angiograms demonstrating small to midsize artery involvement. The overall prognosis was better than reported in adult series. *Conclusion:* This is the largest multicenter study defining the demographic data for

S. Ozen (✉) · A. Bakkaloglu · F. Ozaltin
Department of Pediatrics, Faculty of Medicine,
Hacettepe University,
06100 Ankara, Turkey
e-mail: sezaozen@hacettepe.edu.tr

R. Dusunsel · H. Poyrazoglu
Department of Pediatrics, Erciyes University,
Kayseri, Turkey

O. Soylemezoglu
Department of Pediatrics, Gazi University,
Ankara, Turkey

O. Kasapcopur
Department of Pediatrics, Istanbul University,
Istanbul, Turkey

O. Ozkaya
Department of Pediatrics, Ondokuz Mayis University,
Samsun, Turkey

F. Yalcinkaya
Department of Pediatrics, Ankara University,
Ankara, Turkey

A. Balat
Department of Pediatrics, Gaziantep University,
Gaziantep, Turkey

N. Kural
Department of Pediatrics, Osmangazi University,
Eskisehir, Turkey

O. Donmez
Department of Pediatrics, Uludag University,
Bursa, Turkey

H. Alpay
Department of Pediatrics, Marmara University,
Istanbul, Turkey

A. Anarat
Department of Pediatrics, Cukurova University,
Adana, Turkey

S. Mir
Department of Pediatrics, Ege University,
Izmir, Turkey

A. Gur-Guven
Department of Pediatrics, Akdeniz University,
Antalya, Turkey

F. Sonmez
Department of Pediatrics, Adnan Menderes University,
Aydin, Turkey

F. Gok
Department of Pediatrics,
Gulhane Military Academy and Medical School,
Ankara, Turkey

childhood vasculitides. The distribution of childhood vasculitides was different in our population where KD is much less frequent, whereas HSP constitutes an overwhelming majority. C-PAN was more frequent as well.

Keywords Childhood · Epidemiology · Vasculitis

Introduction

Vasculitis is the inflammation of the blood vessels. The most frequent vasculitides of childhood are Kawasaki disease (KD) and Henoch-Schönlein purpura (HSP). Vasculitides display a somewhat different distribution throughout the world [1]. For adults in Europe, Wegener granulomatosis appears to be more common at high latitudes, whereas microscopic polyangiitis shows the reverse pattern [2]. There are no comparative epidemiologic studies in children. However, KD, which is a characteristic pediatric vasculitis, is very high in Japan and east Asia with incidences reaching as high as 90/100,000 [3]. The incidence in US has been reported as 5.95/100,000 again for children younger than 5 years [4]. On the other hand, HSP is much more frequent than KD in eastern Mediterranean (unpublished data).

Polyarteritis nodosa (PAN) is another vasculitis that has started to be increasingly defined in children. Recent reports have shown that features of juvenile PAN or childhood PAN in children differ from that seen in adults [5]. The main differences were the affect of streptococcal infections, the peak age of the disease, lack of gender difference, some clinical features, and a distinctly better prognosis [5]. In this large international survey, childhood PAN has been stratified into four groups, and it has been suggested that the microscopic polyangiitis of adults was rare in children. The main problem of this study was the low participation of pediatric nephrologists, which was a limitation of this study.

We attempted to survey the main centers in our country caring for childhood vasculitides to define the epidemiology of these diseases in this part of the world. We also designed the study to characterize the main features and outcome of each disease. This represents the largest collection of such pediatric data.

Patients and methods

A questionnaire was distributed to the main referral centers throughout Turkey. The questionnaire had two parts. The first part was for the registry of all the aforementioned childhood vasculitides. This part included questions for demographic features, clinical and a number of laboratory features, and treatment and outcome in a retrospective manner. Since HSP is very frequent in our country, participants were asked to register only the patients of the last calendar year, whereas for the other vasculitides, the 5-year data or for new centers, data since the establishment of that center were asked. Each disease was asked to be classified according to existing criteria [6–11]. The yearly incidences of each disease were also inquired. The diseases were as follows: HSP, childhood polyarteritis nodosa (C-PAN), Takayasu arteritis (TA), Kawasaki disease (KD), and Wegener's granulomatosis (WG), Churg-Strauss syndrome, and Behçet disease (BD), all to be diagnosed before the 18th birthday. The registered patients were expected to meet the ACR criteria for each plus the pediatric criteria suggested for PAN (1992) [6–11].

Questions of classification and diagnostic modalities were included for the childhood polyarteritis patients. On the basis of these data, the patients were stratified into:

1. microscopic polyarteritis with renal involvement and associated with antineutrophil cytoplasmic antibody (ANCA),
2. classic polyarteritis with renal artery involvement associated with HBsAg,
3. cutaneous PAN limited to skin disease,
4. systemic polyarteritis not limited to the above.

The classification of all patients was subsequently reviewed with the newly suggested classification criteria for childhood vascultitides [12].

SPSS 12.0 was used to analyze the data.

Results

General

Children with vasculitis were registered from 15 centers in the country. Of these, 218 HSP patients represented the number for the last calendar year only, whereas the remaining were the figures for the other vasculitides encountered in the last 5 years. These centers were distributed throughout the country and thus had a fair representation. Demographic data were identified based on this total number. There was a dominance of nephrologists among responders. The majority of the non-HSP patients were registered from the two main centers in Ankara and Istanbul.

When the incidence of each vasculitis was analyzed in the last calendar year for 267 patients, HSP patients constituted the majority (Table 1). There were no statistical differences when the centers serving the west of the country were compared with the referral centers in the central of the country.

There was no significant gender difference (Table 1).

The incidence of childhood PAN was more than half of that for KD. When compared, the incidence of SLE in a given year was only 2.3 times more common than that of juvenile PAN (Table 1).

Henoch-Schönlein purpura

Data were available for 218 patients (in a year). Renal disease was reported in 28.6% in spite of the nephrologist

Table 1 Distribution of patients in the last year

Disease	Total (% among vasculitis)	Age (Mean±SD)	Gender, F/M (%)
HSP	81.6	9.36±3.48	46.6/53.4
KD	9	3.05±1.86	43/57
PAN	5.6	15.45±5.50	49/51
TA	1.5	15.48±2.83	50/50
WG	0.4	10	
BD	1.9	12.77±1.97	50/50

predominance among the respondents. Purpura was present in all, arthritis in 62.3%, and gastrointestinal (GIS) involvement in 43.4% of the patients. Thus, arthritis/arthralgia scored higher than GIS involvement.

In two of the patients, HSP was described in a sibling as well. A vast majority of the patients were diagnosed on clinical grounds, whereas about a quarter were diagnosed by skin or renal biopsies. Acute phase reactants were mildly elevated. The mean erythrocyte sedimentation ratio (ESR) and C-reactive protein (CRP) were 32.94±22.38 and 16.23±38.06 (N<6 mg/L), respectively. Complete blood counts were within normal ranges.

Antistreptolysin O (ASO) was elevated in 80% of the patients studied. Prognosis was excellent; no patients progressed to renal failure during the 5 years. A presence of familial cases was reported in 2.1%.

Kawasaki disease

Data were available for 78 patients. There were only 3 atypical cases among the registered 35 yielding a rate of about 10%. Among these, 34.3% had arthritis/arthralgia, whereas renal involvement was present in 5.6%.

All had high acute phase response (APR), with mean ESR and CRP of 93.90±30.90 and 29.60±60.65, respectively. Thrombocyte count was significantly higher than the other groups with a mean of 665,055±182,200.

Mode of diagnosis was on clinical grounds with or without echocardiography findings. Coronary artery disease developed in 1 of the 3 patients and was always associated with a delay in diagnosis.

Takayasu arteritis

Data were available for 14 patients. Among the patients, 71.4% described constitutional symptoms. Hypertension was the leading symptom, and renal artery involvement was present in 86% of the patients. This may reflect a selection bias of the high representation of nephrology centers. There were no patients with thoracic aorta involvement only. Half of the patients had both the thoracic and abdominal aorta involved, whereas half had abdominal aorta involvement only. On the other hand, pulmonary and GIS vasculatures were involved in 28.5% and 57.1%, respectively.

Acute phase reactants were elevated in all: mean ESR and CRP were 50.00±19.07 and 33.20±23.72, respectively. The mode of diagnosis was through conventional or MR angiographies. There was only one death.

Childhood PAN

Data were available for 60 patients. There was no significant gender preference with 51.4% of the patients being male. The mean age of the patients was 15.45±5.50 with a range of 13–18 years. There was no gender difference (51% male). Three patients were also known to have familial Mediterranean fever.

There was a wide range of organ involvement from GIS (33.3%) to central nervous system (CNS) (20%) involvement. Kidney disease was present in 53%. Skin involvement was reported in 59.3%. Arthritis and/or myalgia were present in 57.6% of the patients. Thus, among all vasculitic diseases, pulmonary (except for the one patient with WG) and CNS disease was present only among childhood PAN patients. Pulmonary involvement in microscopic disease was rare (5%).

Acute phase reactants were elevated in all except for four with the cutaneous disease. The mean ESR and CRP levels were 78.11±38.15 and 35.71±35.74, respectively. ASO was elevated in 91.7% of the patients studied.

Two thirds of the participants responded to the second part for detailed evaluation; thus, further classification was possible for 40 patients. The diagnosis of these C-PAN patients was classified as follows:

1. 10/40 (25%) microscopic PAN
2. 6/40 (15%) cutaneous PAN
3. 5/40 (12.5%) classic PAN associated with HBsAg
4. 19/40 (47.5%) systemic PAN

All but two patients were diagnosed by biopsies of the target organ and/or angiograms demonstrating small to midsize artery involvement. All also met the ACR and the pediatric criteria suggested for PAN [8, 9].

ANCA was reported as positive in 5 of the microscopic PAN patients, involving indirect immunofluorescence (IIF) staining or as elevated myeloperoxidase (MPO) titers. However, ANCA was reported as negative in the other 17 childhood PAN patients studied.

Steroids were given to all juvenile PAN patients except for three with cutaneous PAN. For the patients with systemic, microscopic, or classic PAN, the most frequently used immunosuppressive was cyclophosphamide given to 59.5% of the patients. Azathioprine was given to 10%. Classic PAN patients associated with HBsAg received lamivudin or interferon treatment. At follow-up, three progressed to end-stage renal failure. One of these patients had a successful renal transplant. There were no deaths in this cohort. Sixteen percent had relapses, and 51.4% were in remission. Among these patients, 40% were off treatment at the time of evaluation with a median follow-up of 66 months (range, 1–144) and a mean of 62.72± 38.79 months.

Wegener's granulomatosis was reported in only one patient during the 5 years. For Behçet disease, 21 cases of BD patients were registered in these 5 years with only 5 for the last year.

At the time of this registry, the newly suggested childhood criteria for the classification of childhood vasculitides were not available. The classification of the patients was subsequently reevaluated with the new criteria [12]. Seven percent of the HSP patients fell to meet the criteria. All patients with TA, KD, and WG fulfilled the new criteria. Two of the childhood PAN patients did not meet the new childhood criteria since they were diagnosed as PAN without a biopsy or angiography.

Discussion

This is the largest study in the subject providing a considerable data for demographic features of vasculitic diseases and outlines the distribution of these diseases in this part of the world. A striking difference becomes evident in the distribution. When compared to American and west European figures, these data show a difference in the distribution of childhood vasculitides. KD is much less frequent, whereas HSP constitutes an overwhelming majority. WG was almost nil. The presented registry reflects the data of tertiary centers, and thus, it is possible that mild patients of HSP and KD may have been missed. However, we believe that this sample mirrors the overall distribution of these vasculitides.

This series shows that there are no significant gender differences among these diseases. At the time of the set-up of this registry, the recently published childhood criteria were not available [12]. When the patients were reevaluated with the new classification criteria, some patients with HSP failed to meet the new classification criteria since they were defined to have palpable purpura only, and one had an associated viral infection. It is possible that these patients should have been diagnosed as isolated cutaneous leukocytoclastic vasculitis, which is often disregarded in the pediatric practice. Two of the childhood PAN patients did not meet the new childhood criteria since they were diagnosed as PAN without a biopsy or angiography. If for the sake of the study design, the diagnosis of the registering patient is accepted as the gold standard, these patients decrease the sensitivity of the new criteria. However, large-scale studies are needed to define sensitivity and specificity ratios.

The demographic data for HSP were similar to those reported in the literature. This series also confirms that HSP is mainly diagnosed on a clinical basis, and seldom do pediatricians seek a biopsy. Renal involvement was only 28.6%, although most the participants were nephrologists. The features of renal involvement will be evaluated separately.

Another important data were the association of streptococcal infection in HSP and C-PAN. These data support previous clinical publications suggesting the role of streptococci in the pathogenesis of these two pediatric vasculitides. The role of streptococci has previously been referred to in a number of pediatric studies [13].

C-PAN was more frequent than the western figures where it constitutes about 2–3% of the vasculitides [14]. This was evident when the incidence was compared to KD and SLE as well; PAN is only as frequent as 2.7–14.4% of KD in the Canadian and US registry, respectively [14]. When C-PAN was evaluated separately, it was observed that the systemic form constituted the majority of the disease. We believe that the stratification of C-PAN into the assigned four groups is appropriate since the pathogenesis, clinical features, and treatment vary between these four groups [5]. Cutaneous disease is that confined to the skin, and immunosuppressives are usually not used. Microscopic PAN is ANCA-driven and requires heavy immunosuppression with the most guarded prognosis. Classical PAN associated with HBsAg is the only definite immune-complex form of the disease and requires antiviral treatment. The group defined as systemic C-PAN constituted the patients with small and/or midsize artery involvement who had a large range of organ involvement. They were diagnosed either by characteristic biopsy findings and/or angiograms.

Kidney involvement was present in 53% of the overall group, whereas renal disease was always present in microscopic PAN. Microscopic polyangiitis as described for the adult disease was more frequent than that reported in an international registry; however, this was interpreted to be due to the center bias, since the presented Turkish registry had a dominance of nephrology centers. The rate of microscopic PAN patients associated with ANCA was similar in a report from India of 11 patients [15].

The distribution of TA throughout the world shows certain differences in the site of involvement, at least in adult series [16, 17]. In European patients, the brachiocephalic trunk is more frequently involved when compared with that in Asian patients [16]. The Japanese patients were shown to have more thoracic involvement, whereas the abdominal aorta was more frequently involved in Indians who commonly presented with hypertension [17]. The low number in this group of patients prevent us from strict comments; however, it was interesting that half of our patients had both parts of the aorta involved.

Vasculitic diseases are multifactorial and probably multigenetic diseases. Bronstein et al. [18] have designed a study in KD, a pediatric vasculitis, to explore the relationship between climate, ethnicity, socioeconomic status, and susceptibility to KD. They concluded that KD had an infectious etiology and that the disease was influenced by genetic and environmental factors such as the insurance status. These factors are probably effective in all vasculitic diseases of children. Identifying the geographic vs ethnic factors and the environmental factors such as infections will clearly shed light to the pathogenesis of these diseases. The optimal therapy and management protocols lie within this pathway.

References

1. Ozen S (2004) Vasculitis in children. In: Isenberg DA, Maddison PJ, Woo P, Glass D, Breedveld FC (eds) Oxford textbook of rheumatology, 3rd edn. Oxford University Press, Oxford, pp 993–997
2. Watts RA, Lane SE, Scott DG, Koldingsnes W, Nossent H, Gonzalez-Gay MA, Garcia-Porrua C, Bentham GA (2001) Epidemiology of vasculitis in Europe. Ann Rheum Dis 60:1156–1157
3. Yanagawa H, Yashiro M, Nakamura Y et al (1995) Epidemiologic pictures of KD in Japan: from the nationwide incidence survey in 1991 and 1992. Pediatrics 95:475
4. Shulman ST, McAuley JB, Pachman LM et al (1987) Risk of coronary abnormalities due to KD in urban area with small Asian population. Am J Dis Child 141:420
5. Ozen S, Anton J, Arisoy N et al (2004) Juvenile polyarteritis: results of a multicenter survey of 110 children. J Pediatr 145:517–522
6. Mills JA, Michel BA, Bloch DA, Calabrese LH, Hunder GG, Arend WP, Edworthy SM, Fauci AS, Leavitt RY, Lie JT et al (1990) The American College of Rheumatology 1990 criteria for the classification of Henoch-Schönlein purpura. Arthritis Rheum 33:1114–1121
7. Japan Kawasaki Disease Research Committee (1984) In: Diagnostic guidelines of Kawasaki disease, 4th revised edn. Japan Red Cross Medical Centre, Tokyo
8. Lightfoot RW Jr, Michel BA, Bloch DA et al (1990) The ACR 1990 criteria for the classification of polyarteritis nodosa. Arthritis Rheum 33:1088
9. Ozen S, Besbas N, Saatci U, Bakkaloglu A (1992) Diagnostic criteria for polyarteritis nodosa in childhood. J Pediatr 2:206–209
10. Arend WP, Michel BA, Bloch DA et al (1990) The ACR 1990 criteria for the classification of Takayasu arteritis. Arthritis Rheum 33:1129–1134
11. Leavitt RY, Fauci AS, Blach DA et al (1990) The ACR 1990 criteria for the classification of Wegener's granulomatosis. Arthritis Rheum 33:1101
12. Ozen S, Ruperto N, Dillon M, Bagga A, Barron K, Davin JC, Kawasaki T, Lindsley C, Petty R, Prieur AM, Ravelli A, Woo P (2005) EULAR/PRES endorsed consensus criteria* for the classification of childhood vasculitides * under review by the ACR. Ann Rheum Dis Dec 1. DOI 10.1136/ard.2005.046300
13. Falcini F (2004) Vascular and connective tissue diseases in the pediatric world. Lupus 13:77–84
14. Petty RE, Cassidy JT (2001) Vasculitis and its classification. In: Cassidy JT, Petty RE (eds) Textbook of pediatric rheumatology, 4th edn. Saunders, Philadelphia, PA, pp 564–568
15. Handa R, Wali JP, Gupta SD et al (2001) Classical PAN and microscopic polyangiitis—a clinicopathological study. J Assoc Phys India 49:314–319
16. Desiron Q, Zeaiter R (2000) Takayasu's arteritis. Acta Chir Belg 100:1–6
17. Moriwaki R, Noda M, Yajima M, Sharma BK, Numano F (1997) Clinical manifestations of Takayasu arteritis in India and Japan—new classification of angiographic findings. Angiology 48:369–379
18. Bronstein DE, Dille AN, Austin JP, Williams CM, Palinkas LA, Burns JC (2000) Relationship of climate, ethnicity and socioeconomic status to Kawasaki disease in San Diego County, 1994 through 1998. Pediatr Infect Dis J 19:1087–1091