

Clinical overview and outcome in a cohort of children with polyarteritis nodosa

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ABSTRACT

Objective. Polyarteritis nodosa (PAN) is a rare vasculitis in childhood and poor information is known about its long-term outcome. Our aim was to describe the clinical features, at onset and during the disease course, of childhood-onset PAN and identify a potential correlation with persistent organ damage and worse outcome in a cohort of paediatric patients with a confirmed diagnosis of PAN.

Methods. A retrospective collection of demographic and clinical data of 52 Caucasian children diagnosed with PAN, fulfilling the EULAR/PRES diagnostic criteria, recruited from eight paediatric rheumatologic centres and one transition unit, was performed. A statistical correlation was made between clinical involvement at onset or during the overall disease course and patients' final outcome.

Results. Data from 52 patients (31 males, 21 females) were collected: their mean age at onset was 7.9 years (median 6.3) and mean follow-up period was 6.2 years (median 5.4). At the last follow-up visit, 27 patients (51.9%) were off therapy in clinical remission, 17 (32.7%) were in clinical remission while on medication, and 6 (11.6%) had a persistent or relapsing disease course. Two patients (3.8%) deceased because of severe cerebral involvement. Cranial nerve palsy during the disease course was significantly correlated with a worse prognosis ($p=0.011$). The presence of nephrogenic hypertension at onset and seizures during the disease course were significantly associated with the development of irreversible organ damage ($p=0.040$ and 0.011 , respectively).

Conclusion. Childhood PAN is a se-

vere disease with substantial risk of long-term morbidities. In our cohort of patients the worst outcome was significantly correlated with renal and neurological involvement.

Introduction

Polyarteritis nodosa (PAN) is a necrotising vasculitis mainly defined by aneurysmal nodules along the walls of small and medium-sized muscular arteries, leading to subsequent multi-organ damage (1). While management recommendations are available for Kawasaki disease (2), no guidelines, and few evidence-based studies are available in the medical literature for PAN occurring in childhood. Although complete remission may be obtained in children and adolescents with PAN, various complications due to the severity of the vasculitic process may develop during the disease course, mainly if treatment is delayed or inappropriate. Late morbidity can also occur years after the onset of vascular injury, resulting in a precocious diffuse atherosclerosis (3). PAN clinical course is often characterised by improvements and relapses, frequently triggered by viral or streptococcal infections (4-5). To date, very few outcome studies have been published with controversial results. A recent large multicentre study from tertiary referral centres, including around one third of cutaneous forms, reported 1.1% of mortality rate for PAN (6). Another study from a major tertiary referral centre mainly following children with aggressive advanced disease reported a 10% mortality rate (1). These discordant results, probably related to the heterogeneous classification criteria used and possible selection bias can explain the difficulty in identifying po-

tential predictors of disease outcome. Aim of our study was to retrospectively evaluate demographic and clinical data of 52 Caucasian children with a definite diagnosis of PAN either at their disease onset or during the disease course, and to define any potential correlation with their final outcome.

Patients and methods

Demographic and clinical data of paediatric patients diagnosed with PAN, defined according to EULAR/PRES diagnostic criteria (7) and recruited in eight paediatric rheumatologic centres and one transition clinic in Italy, were retrospectively collected. According to these criteria, a patient was classified as having PAN in the presence of a mandatory criterion – a systemic illness characterised by either a biopsy showing small and mid-size artery necrotising vasculitis (*i.e.* granulocyte or mixed leucocyte infiltrate in an arterial wall) or confirmed angiographic abnormalities (in terms of vascular aneurysms and occlusions) – plus at least one of the following five clinical items: skin signs, myalgia or muscle tenderness, peripheral neuropathy, hypertension, or renal vascular disease. Patients with an initial diagnosis of cutaneous PAN were also included in our evaluation: this necrotising vasculitis of medium-sized arteries occurs within the skin, with no involvement of internal organs, and a clinical picture characterised by fever, painful subcutaneous nodules, livedo reticularis, arthralgias, or myalgias (8). Demographic information included gender, age at disease onset, age at diagnosis, and disease duration at the time of the last follow-up visit for at least one year. Clinical data included signs and symptoms at disease onset and after follow-up, which were grouped in eight categories according

to the organ involvement: constitutional symptoms, cutaneous, musculoskeletal, renal, neurological (central or peripheral), cardiac, gastrointestinal, and respiratory. Information on the treatment approach was also collected. Patients' outcome was classified as *Clinical Remission* (CR) if they were symptom-free after stopping treatment for at least 6 months; *Clinical Remission on Medication* (CRM) if they maintained the remission status on one or more immune-modulating drugs; *Refractory-Relapsing disease* (RR) in the case of persistently uncontrolled disease, notwithstanding any treatment, or death. *Disease damage* was classified into two entities: *irreversible organ damage or death* and *absence of damage*.

Statistical analysis

A descriptive analysis of all clinical features of PAN at onset and during its course was performed. Qualitative variables were expressed as numbers and percentages. Outcome was measured with respect to baseline demographic/general and clinical data using Student's *t*-test, chi-square test, and Fisher's exact test, where appropriate. Bivariate analysis was carried out by comparing signs and symptoms at disease onset and during the disease course with patients' final outcome, defined as remitted disease (CR groupe) and unremitting disease (CRM and RR groups). All data were processed using the statistical software SPSS 14.0 (SPSS Inc., Chicago IL). A *p*-value <0.05 (2-tailed test) was considered as significant.

Results

The charts of 52 Caucasian patients, 31 males (59.6%) and 21 females (40.4%), with PAN were carefully evaluated (Table I). The mean age at disease onset was 7.9 years (range 2–16 years),

the mean age at diagnosis was 8.9 years (range 3.6–16.2), the mean duration of follow-up was 6.2 years (range 1.0–16.4). Two patients were siblings. All patients were vaccinated against hepatitis B, and had antibody protective levels against the virus. The clinical manifestations at onset and during the disease course are summarised in Table II. Fever, painful subcutaneous nodules, arthralgia, and myalgia were the most frequent symptoms at disease onset. Skin and systemic signs were the most frequent initial manifestations of disease, followed by musculoskeletal, renal, and neurological involvement; cardiac and gastrointestinal signs have been less reported. Among the clinical manifestations during the overall course of the disease, constitutional, musculoskeletal and cutaneous symptoms were the most frequently reported (in around 80% of the patients) while one third had renal or neurological signs. Cutaneous manifestations were present at disease onset in 27 patients (51.9%). Later on, 11 presented other clinical signs that prompted a diagnosis of systemic PAN. The remaining 16 patients persisted as cutaneous PAN during the course of the disease (Table II). The additional systemic manifestations of the 11 patients who shifted from the cutaneous to the systemic subtype were cranial nerve palsy (1 patient), motor mononeuritis multiplex (1), sensory peripheral neuropathy (2), renal involvement (3), visual impairment (2) abdominal pain (2). As shown in Table III, all patients were treated with oral or intravenous (IV) corticosteroids, 16 (30.8%) with azathioprine, 15 (28.8%) with oral and 5 (9.6%) with IV cyclophosphamide, 9 (17.3%) with thalidomide, 7 (13.5%) with IV immunoglobulins, 5 (9.6%), with methotrexate, 4 (7.7%) with mycophenolate mofetil and 2 (3.8%) with

Table I. Demographic characteristics of childhood-onset polyarteritis nodosa.

Gender (F : M)	Cutaneous PAN 6 : 10			Systemic PAN 15 : 21			Overall 21 : 31		
	Mean	Median	Std. Dev.	Mean	Median	Std. Dev.	Mean	Median	Std. Dev.
Age at onset (years)	7.7	6.1	3.8	7.9	6.7	3.8	7.9	6.3	3.8
Age at diagnosis (years)	7.8	6.3	3.7	9.4	9.4	3.2	8.9	8.0	3.4
Follow-up (years)	4.5	2.8	4.5	7.0	6.4	4.6	6.2	5.4	4.7

anti-tumour necrosis factor agents (etanercept or infliximab). At the time of the last evaluation, 27 patients (51.9%) were off-therapy in CR, 17 (32.7%) were in CRM and 6 (11.6%) still had a RR course. Final outcome was not evaluable for 2 patients who were lost to follow-up (3.8%). Two patients died because of severe central nervous system involvement, dramatically complicated by cerebral infarction.

As for organ damage, 8 patients (15.4%) reported nephrogenic hypertension, 2 (3.8%) underwent digital amputation due to necrotising vasculitis, 1 underwent hemicolectomy, and another developed diabetes insipidus, due to cerebral vasculitis. During the disease course, central nervous system involvement, and in particular cranial nerve palsy, was significantly associated with a severe disease course ($p=0.011$). The presence of nephrogenic hypertension at disease onset and the occurrence of seizures during the disease course were the only two parameters that significantly correlated with the development of irreversible organ damage ($p=0.040$ and 0.011 , respectively).

Discussion

Skin, the musculo-skeletal system, kidneys, and gastrointestinal tract are the most frequently affected organs in PAN, while cardiac, neurological and respiratory manifestations occur less frequently both in children and adolescents (9). The exact etiology of PAN remains unknown, although many data support the role of hepatitis B virus, parvovirus B19, and cytomegalovirus in the disease pathogenesis (10). Also group A streptococcal infections may generate a subset of poststreptococcal PAN, requiring both penicillin prophylaxis and steroid treatment for effective disease control in the long term (11). It is widely established that a permanent remission can be achieved in most paediatric patients with PAN, but the possibility of relapses is likewise documented (12). Actually, long-term evaluation studies related to outcome of PAN in paediatrics are poor.

Our data confirm that juvenile PAN, although managed in tertiary paediatric rheumatology centres, is a severe

Table II. Organ involvement and signs or symptoms at onset and during the overall disease course.

Organ involvement	Type	At onset (%)	Overall course (%)	Signs or symptoms	At onset (%)	Overall course (%)
Constitutional	Cut	43.8	68.8	Fever	67.3	78.8
	Syst	86.1	83.3	Fatigue	15.4	19.2
	All	73.1	78.8	Weight loss	9.6	7.7
Cutaneous	All	73.1	78.8	Testicular pain	3.8	1.9
				Painful nodules	42.3	48.1
				Purpuric rash	28.8	32.7
	Cut	100	93.8	Maculo-papular rash	9.6	7.7
	Syst	63.9	77.8	Livedo reticularis	9.6	17.3
All	75.0	82.7	Other (digital ulcers, desquamation)	3.8	11.5	
Musculoskeletal	Cut	37.5	68.8	Arthralgia	48.1	63.5
	Syst	61.1	83.3	Myalgia	21.2	28.8
	All	53.8	78.8	Arthritis	7.7	5.8
Renal	Cut	-	6.3	Hypertension	11.5	25.5
	Syst	16.7	41.7	Haematuria	1.9	5.8
	All	11.5	30.8			
Central nervous system	Cut	6.3	6.3	Headache	5.8	9.6
				Seizure	3.8	7.7
	Syst	22.2	44.4	Cranial nerve palsy	3.8	15.4
				Ataxia	1.9	-
	All	17.3	32.7	Stroke	-	5.8
			Visual impairment	1.9	9.6	
Peripheral nervous system	Cut	-	-	Motor mononeuritis multiplex	6	12
	Syst	8.3	25.0	Sensory peripheral neuropathy	-	6
	All	5.8	17.3			
Cardiac	Cut	0.0	0.0	Coronary artery disease	3.8	3.8
	Syst	8.3	5.6	Pericarditis	1.9	1.9
	All	5.8	3.8			
Gastrointestinal	Cut	-	-	Abdominal pain	3.8	17.3
	Syst	5.6	25.0			
	All	3.8	17.3			

and life-threatening disease. We found a slightly higher prevalence in males, and the mortality rate was 3.8%, much lower than that reported in adult PAN, where it can be as high as 20% (13). A "cutaneous" presentation was observed in around half of the patients but later on, 40% of them developed other features of systemic PAN. This high percentage of cutaneous forms might be explained by the prompt clinical identification of patients, which were earlier referred to tertiary care centres. We also found a high rate of complete remission, up to 52% of cases. This was not related to a milder onset since only 16 patients had a "cutaneous" onset and complete remission was found only in less than half of them (7 patients). This paradigm can be applied for CRM

patients (32.7% of the whole cohort), who had an initial cutaneous onset in 41% of cases. We may also speculate that this good outcome was related to the aggressive treatment, as the majority of patients (80%) was treated with at least one immunosuppressive drug in combination with corticosteroids (Table III). A similar remission rate was recently reported in a cohort of 12 patients with juvenile PAN in whom, however, the mortality rate was higher than in our series (17%), probably because immunosuppressive drugs were used in only half of them (14). Unfortunately, 24% of patients in our series had various degree of organ damage, ranging from chronic hypertension (15.4%) to cerebral infarction (3.8%). Neurological involvement during the

Table III. Treatment, clinical course and organ damage.

		Cutaneous PAN n=16		Systemic PAN n=36		Overall n=52	
Treatment	Corticosteroids	16	100%	36	100%	52	100%
	Cyclophosphamide	6	37.5%	15	41.7%	21	40.4%
	Azathioprine	6	37.5%	10	27.8%	16	30.8%
	Thalidomide	2	12.5%	7	19.4%	9	17.3%
	Intravenous immunoglobulins	2	12.5%	5	13.9%	7	13.5%
	Methotrexate	–	–	5	13.9%	5	9.6%
	Biological agents	–	–	2	5.6%	2	3.8%
Clinical course	Clinical remission (CR)	9	56.2%	18	50.0%	27	51.9%
	Clinical remission on medication (CRM)	7	43.8%	10	27.8%	17	32.7%
	Refractory-relapsing course (RR)	–	–	6	16.7%	6	11.6%
	Lost to follow-up	–	–	2	5.6%	2	3.8%
	Death	–	–	2	5.6%	2	3.8%
Organ damage	Hypertension	–	–	8	22.2%	8	15.4%
	Digital amputation	–	–	2	5.6%	2	3.8%
	Hemicholecystomy	–	–	1	2.8%	1	1.9%
	Diabetes insipidus	–	–	1	2.8%	1	1.9%

disease course significantly correlated with a more aggressive disease course; indeed, the onset of seizures, as a manifestation of central nervous system vasculitis, was significantly correlated with the development of irreversible organ damage. The same can be said for the renal involvement, as the presence of nephrogenic hypertension at disease onset significantly correlated with the development of irreversible organ damage. These findings are similar to what has been reported in adult PAN, as both renal and neurological manifestations, especially at disease onset, are closely related with both a severe disease course and irreversible organ damage (15, 16).

Our data have some limitations as the retrospective analysis did not allow us to find any correlation between the various treatment approaches and the final outcome. In addition, the small size of our cohort has limited a comprehensive multivariate analysis.

In conclusion, childhood-onset PAN is a rare disease and remains a severe condition despite the use of immunosuppressive treatment for the majority of patients. Renal and central nervous system involvement, either at onset or during the disease course, correlate definitely with the worst outcome. Therefore an aggressive approach has to be applied from the very early onset of the disease.

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