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Original article

Long-term outcome of children with pediatric-onset cutaneous and visceral polyarteritis nodosa

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ABSTRACT

Objective: To assess the prognostic impact of clinical presentation in children with polyarteritis nodosa (PAN).
Methods: Children diagnosed between 1986 and 2006 in a tertiary care pediatric rheumatology center were classified as "cutaneous PAN" (group 1), "cutaneous PAN with significant extra-cutaneous features" (group 2) or "visceral childhood PAN" (group 3). Outcome measures: (1) clinical remission off-therapy at last follow-up, (2) requirement and length of glucocorticoid therapy, (3) presence of disease-related sequelae.
Results: Twenty-nine children were included. Sixteen met the Ankara criteria for PAN. Nine patients were qualified as group 1, 11 as group 2, and 9 as group 3. At last follow-up, 15 children were in clinical remission off-therapy: 4 from group 1 (44%), 4 from group 2 (36%) and 7 from group 3 (78%). Glucocorticoid therapy was required for 8 (89%), 7 (64%) and 7 (78%) patients from groups 1, 2 and 3, respectively. Seven children did not require any glucocorticoid therapy. Time-dependent probability of achieving glucocorticoid-free clinical remission was similar between the three groups. Three patients (one from each group) had digital ischemia leading to amputation. There were no significant between-group differences in outcome based on the three outcome measures addressed.
Conclusion: Outcome was not strikingly predictable from initial presentation in children with PAN. The organ distribution-based distinction between cutaneous and visceral PAN had little prognostic power in this series.

1. Introduction

Polyarteritis nodosa (PAN) was first described as a lethal condition characterized by diffuse necrotizing vasculitis that predominantly affects medium-sized arteries [1]. A separate distinction was later made for cutaneous PAN, characterized by a chronic relapsing benign course and an absence of systemic involvement [2]. Although the cutaneous features are similar, there is

Abbreviations: CRP, C-reactive protein; ENT, ear-nose-throat; ESR, erythrocyte sedimentation rate; HBV, hepatitis B virus; IVIG, intravenous immunoglobulin; NSAIDs, non-steroidal anti-inflammatory drugs; PAN, polyarteritis nodosa.

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emerging consensus that these two diseases should be considered different, since progression from cutaneous to visceral PAN appears extremely rare [2].

The clinical spectrum of pediatric-onset PAN varies from severe visceral involvement to less aggressive disease with cutaneous and subcutaneous involvement and milder systemic symptoms [3,4]. The 2009 Ankara classification criteria offers a valuable framework to distinguish PAN from other primary vasculitides but is unable to distinguish "cutaneous PAN" from "visceral PAN" [5]. It is unclear whether intermediate forms with predominant cutaneous features associated with mild extra-cutaneous signs (such as marked weight loss, abdominal pain or headaches) are to be considered visceral or cutaneous in terms of prognosis and therapeutic approach.

We therefore conducted a retrospective study designed to assess whether disease characteristics at diagnosis have the power to predict long-term patient outcome.

2. Methods

Retrospective analysis was led on the medical records of patients diagnosed with PAN before age 18 years between January 1986 and December 2006 and followed in a French tertiary care pediatric rheumatology center at Hôpital Necker-Enfants Malades, Paris. Diagnosis of PAN relied on the association of a clinical presentation compatible with a systemic inflammatory process involving ischemic manifestations and histological small or middle-sized-vessel involvement after ruling out other vasculitides. Patients were excluded if they presented with diffuse alveolar hemorrhage, pauci-immune glomerulonephritis, histological evidence of capillary and/or venular vasculitis and presence of anti-neutrophil cytoplasm antibodies (ANCA) specific for proteinase 3 or myeloperoxidase detected by ELISA, granuloma or IgA deposition. The study was approved by the Rhône-Alpes-Auvergne inter-regional institutional review board.

2.1. Data collection

Clinical data collected included fever, constitutional symptoms (general malaise, fatigue, weight loss), evidence of specific organ involvement (as defined in the Ankara criteria) [6] such as high blood pressure, renal involvement, peripheral neuropathy, muscle or skin involvement – for all other organs, we collected clinical symptoms compatible with vasculitis. Ear-Nose-Throat (ENT) manifestations preceding (within 21 days) or accompanying PAN were also recorded. We also recorded what other diagnoses were considered. The laboratory data were: complete blood count and differential, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), cryoglobulins and serological hepatitis B virus (HBV) status. All imaging and/or histological investigations performed during follow-up were collected. Any abnormalities were reviewed by an expert clinician to rule them in or out as PAN-related. All treatments were systematically recorded.

2.2. Definitions

Visceral involvement was defined as involvement of at least one of the following organs: nervous system, gastro-intestinal tract (documented by histology, endoscopy and/or computed tomography scan), testis (clinically or by histology), heart, lungs, kidney, or any other organ. Functional complaints (abdominal pain, headache, myalgia, arthralgia) and arthritis were not considered as visceral involvement. PAN was classified as "cutaneous PAN" in the absence of visceral involvement, marked weight loss ($\geq$ 10% of body weight), abdominal pain or headache (group 1), "cutaneous PAN with significant extra-cutaneous features" if no visceral involvement was proven but marked weight loss, abdominal pain and/or headache was present (group 2), and "visceral childhood PAN" if visceral involvement was present (group 3).

Histology was considered as diagnostic in cases where fibrinoid necrosis of the arterial wall was straightforward, and non-diagnostic in cases where there was an inflammatory infiltrate composed predominantly of polymorphonuclear and lymphocytic cells within the medium-sized artery wall but without clear fibrinoid necrosis.

Based on the data collected, the patients were re-evaluated according to the Ankara criteria [5]. Patient status at the latest follow-up was assessed as follows: clinical remission off-therapy-patients presented neither clinical nor physical symptoms for at least 6 months after discontinuation of therapy; treatment-dependency-patients presented neither clinical nor physical signs but were still under therapy; active-disease-patients presented with clinical evidence of active disease.

Relapse was defined as a resurgence of one or more clinical symptoms in a patient who had previously been free of any manifestation of the disease [7].

2.3. Outcome

Three main outcome measures were considered:

- treatment-free clinical remission at last follow-up;
- requirement and length of glucocorticoid therapy;
- presence of disease-related sequelae.

2.4. Statistics

First, we ran a univariate comparison between the 3 groups. Next, we ran a univariate analysis for each of the five outcome parameters in an attempt to identify prognostic factors. Analyses were led using Fisher's exact test for qualitative variables or a non-parametric Kruskall-Wallis test for quantitative variables. Given the small number of patients, we did not run multivariate analyses. No adjustment was made for analyzing multiple outcomes [8]. All analyses were performed on R software (version 2.13.0) using the Epicalc package.

3. Results

A total 29 children (20 girls and 9 boys) were included in the study. Median age at diagnosis was 6.9 years (range: 2–14).

3.1. Initial features

Eight patients had an ENT infection 5 to 22 days prior the first signs of PAN. At first presentation, all children were febrile. The most frequent features involved: skin (24 children), joints (n = 21), muscles (n = 12), gastro-intestinal tract (n = 10), ENT (n = 9), and nervous system (n = 7). Other features are shown in Table 1.

The delay between first signs and diagnosis ranged from 5 to 1580 days (median: 37 days). Before PAN was diagnosed, four patients were misdiagnosed as systemic-onset juvenile idiopathic arthritis, 3 as acute rheumatoid fever, 3 as Kawasaki disease, and one as systemic lupus erythematosus. Reason for delayed diagnosis > 30 days was: absence of initial cutaneous involvement (7 children), glucocorticoids or IVIG administered before skin biopsy (6 children), or spontaneous transient remission (1 child).

HBV serology was negative in all patients. At least one biopsy was performed in all patients: in 16 cases, histological examination showed diagnostic PAN lesions with destruction of the medium-sized artery walls and fibrinoid necrosis, and in 13 patients the biopsies were non-diagnostic. Angiography was performed in two