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Incidence and clinical features of paediatric vasculitis in Eastern China: 14-year retrospective study, 1999–2013

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Abstract

Objectives: To determine the incidence and clinical features of paediatric primary vasculitis in patients from one centre in Eastern China.

Methods: Medical records of paediatric patients diagnosed with primary vasculitis between January 1999 and December 2013 were retrospectively reviewed. For Henoch–Schönlein purpura (HSP) and Kawasaki disease (KD), patients included in the analyses had data available for the previous 5 years.

Results: In total, 1896 patients were identified, of whom 1100 had HSP, 760 had KD, 23 had Takayasu arteritis, five had polyarteritis nodosa, four had cutaneous polyarteritis, three had Behçet's disease and one had microscopic polyangiitis. Of the 615 patients with HSP included in the analyses, 49.8% had HSP nephritis (for 90% of whom it occurred within 1 week of disease onset). Of the 470 patients with KD included in the analyses, 13.8% were diagnosed with incomplete KD and 29.0% had a concurrent coronary artery lesion. For the 23 patients with Takayasu arteritis, the common clinical symptoms were hypertension, asphygmia/weak pulse and heart failure; only one of these patients had been diagnosed at an early disease stage. The five patients with polyarteritis nodosa received immunosuppressant therapy following diagnosis. Other vasculitides were uncommon.

Conclusions: The most common primary vasculitides in this population of children from Eastern China were HSP and KD; other vasculitides were rare. Paediatricians should be suspicious of vasculitis when there is evidence of systemic inflammation and multisystem disease that cannot be explained by one specific disorder.

Keywords

Children, vasculitis, paediatric vasculitis, Henoch–Schönlein purpura, Kawasaki disease

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Introduction

Paediatric primary vasculitides are heterogeneous disorders characterized by blood vessel inflammation leading to tissue or organ injury. The incidence and distribution of paediatric primary vasculitides both vary among different regions and populations.[1] The most common paediatric vasculitides are Henoch–Schönlein purpura (HSP) and Kawasaki disease (KD).[1] Other vasculitides, such as Takayasu arteritis, polyarteritis nodosa and antineutrophil cytoplasmic antibody (ANCA) type vasculitides (e.g. Wegener's granulomatosis, microscopic polyangiitis) are relatively uncommon and often present with nonspecific symptoms, which can lead to diagnostic delay.[1] The diagnosis and therapy for all of these vasculitides are challenging.[2]

The incidence of paediatric primary vasculitides in China is not well characterized. The purpose of this study was to ascertain the incidence and clinical features of these related conditions from data collected at one centre in Eastern China over a 14-year period. Medical records from patients who had been diagnosed with a primary vasculitis at Shanghai Children's Medical Centre between January 1999 and December 2013 were reviewed, and a retrospective analysis of data obtained over the last 5 years was used to ascertain the main features and outcomes of several primary vasculitides.

Patients and methods

Data collection

Paediatric inpatients, aged < 18 years, diagnosed with a primary vasculitis between January 1999 and December 2013, were eligible for study inclusion. Data from relapse cases were excluded. Patients were recruited from the rheumatology, cardiology, respiratory and surgical departments of the Shanghai Children's Medical Centre, which is affiliated to the College Of Medicine, Shanghai Jiaotong University. Patient characteristics, clinical and laboratory data, therapy and prognosis were obtained from the patients' medical histories. Informed consent was obtained from patients' parents or carers and the protocol was approved by the ethics committee of Shanghai Children's Medical Centre.

Diagnosis and classification of childhood primary vasculitis were both made according to European League Against Rheumatism and Pediatric Rheumatology European Society-endorsed consensus criteria.[3,4] Incomplete KD was diagnosed based on echocardiography according to American Heart Association criteria.[5] The diseases were classified as follows: large vessel vasculitis, Takayasu arteritis; medium-sized vessel vasculitis, childhood polyarteritis nodosa, cutaneous polyarteritis, KD; small vessel vasculitis, HSP, microscopic polyangiitis; other vasculitides, Behçet's disease.

Statistical analyses

Descriptive statistics, using SPSS® version 16.0 (SPSS Inc, Chicago, IL, USA), for Windows®, were used to summarize patients' characteristics. Data were presented as mean ± SD or median (interquartile range). For HSP and KD, only patients with data recorded over the previous 5 years were included in the analyses.

Results

Study population

In total, 1896 paediatric patients were hospitalized with a first-time diagnosis of vasculitis over the 14-year study period. The most commonly reported vasculitides were HSP ($n = 1100$; 58%) and KD ($n = 760$; 40%), as shown in Table 1. Other vasculitides (Takayasu arteritis, polyarteritis nodosa, cutaneous polyarteritis, microscopic

Table 1. Newly diagnosed paediatric inpatients with a primary vasculitis; retrospective review of data from Shanghai Children's Medical Centre over a 14-year period (1999–2013); $n = 1896$.

Disease	Patients, *n*	%
Henoch–Schönlein purpura	1100	58
Kawasaki disease	760	40
Other vasculitides		
Takayasu arteritis	23	1
Polyarteritis nodosa	5	
Cutaneous polyarteritis	4	}0.8
Microscopic polyangiitis	1	
Behçet's disease	3	

polyangiitis and Behçet's disease) accounted for the remaining 2% of cases.

Henoch–Schönlein purpura

Of the 1100 patients with HSP, only those with data recorded over the previous 5 years were included in the analysis. For these 615 patients (352 male; 263 female), the male-to-female ratio was 1.3:1.0 (Table 2). Mean ± SD age at the first onset was 6.8 ± 2.8 (range, 2–16 years). All patients developed nonthrombocytopenic palpable purpura during the disease course, most of which were distributed on the lower limbs. Approximately 13.5% patients showed purpura on upper limbs and/or face. Arthralgia occurred in ~57.8% patients and abdominal pain in 49.9% patients. Bloody stools were reported in 6.0% of patients. For the 49.8% patients with renal involvement, presence of haematuria or haematuria with proteinuria is showin in Table 2. Approximately 90% of patients who experienced nephritis did so within 1 week of disease onset; 98.6% of patients who experienced nephritis did so within 1 month of disease onset. The remaining 1.4% of patients developed nephritis between 1 and 6 months after disease onset.

Analysis of laboratory data showed the mean ± SD complete blood cell count was

Table 2. Clinical features of patients with Henoch–Schönlein purpura; data obtained over the previous 5 years.

Clinical features	Value
Patients, *n*	615
Sex, male: female	1.34:1.0
Age, years, mean ± SD	6.8 ± 2.8
Purpura, *n* (%)	615 (100.0)
Arthralgia, *n* (%)	355 (57.8)
Abdominal pain, *n* (%)	307 (49.9)
Nephritis, *n* (%)	306 (49.8)
Isolated haematuria, *n* (%)	16 (5.3)
Mild proteinuria and haematuria, *n* (%)	237 (77.3)
Moderate proteinuria and haematuria, *n* (%)	21 (6.9)
Severe proteinuria and haematuria, *n* (%)	32 (10.5)

Mild, ≤25 mg/kg/day; moderate, 25 mg/kg/day–50 mg/kg/day; severe, ≥50 mg/kg/day.

$12.2 \pm 5.1 \times 10^9$/l, the mean ± SD C-reactive protein (CRP) was 9.5 ± 16.1 mg/l and the mean ± SD erythrocyte sedimentation rate (ESR) was 17.5 ± 16.3 mm/h. Albumin levels were within the normal range.

Kawasaki disease

Data from the previous 5 years were available for 470 of the 760 patients with KD. As shown in Table 3, there were more male than female patients: the male-to-female ratio was 1.7:1.0 and the median age of onset was 15 months (range, 2 months to 10 years). The median fever duration before admission was 6 days (range, 1–30 days). Laboratory data for these patients on admission are shown in Table 3; acute phase reactants were elevated.

Patients with incomplete KD ($n = 65$; 13.8%) were treated with intravenous immunoglobulin (IVIG) 2 g/kg. Although most patients responded to such therapy and their body temperature returned to normal, 28 patients (5.9%) failed to respond

Table 3. Clinical features of patients with Kawasaki disease; data obtained over the previous 5 years.

Clinical feature	Value
Patients, *n*	470
Sex, male:female	1.71:1.0
Age, median (range)	15 (2 months–10 years)
Fever duration, days, median (range)	6 (1–30)
C-reactive protein*, mg/l, median (IQR)	48 (20–87)
White blood cell count*, $\times 10^9$/l, median (IQR)	13.5 (10.5–17.6)
Erythrocyte sediment rate*, mm/h, median (IQR)	75 (50–96)
Pplatelet*, $\times 10^9$/l, median (IQR)	312 (239–410)
Albumin*g/l, median (IQR)	31.6 (28.6–35)
Incomplete Kawasaki disease, *n* (%)	65 (13.8)
Failure to respond to initial IVIG therapy *n* (%)	28 (5.9)
Coronary artery lesion: normal (%); CAD (%); CA (%)	334 (71); 120 (25.6); 16 (3.4)

Data recorded on admission.
IQR, interquartile range; IVIG, intravenous immunoglobulin; CAD, coronary artery dilatation; CA, coronary aneurysm.

to the first course of IVIG (i.e., persistent or recrudescent fever $\geq$36 h after completion of the initial infusion) and so received a second course of IVIG.

Takayasu arteritis

In total, 23 patients (seven male and 16 female) had Takayasu arteritis with a mean $\pm$ SD age at onset of 10.5 ± 4.5 years. Thirteen (56.5%) patients had concomitant hypertension, 10 (43.5%) had concomitant heart failure, 12 (52.2%) had concomitant asphygmia or weak pulse, seven (30.4%) had concomitant weak pulse, seven (30.4%) had concomitant blood pressure asymmetry on both upper limbs, four (17.4%) had concomitant fever, four (17.4%) had concomitant vascular murmur on upper limbs and seven (30.4%) had elevated CRP and ESR levels. Computed tomography (CT) and magnetic resonance imaging (MRI) scans showed that 19 (82.6%) patients had aortic stenosis and five (21.7%) had renal artery stenosis. Overall, five (21.7%) patients had common carotid artery involvement, four (17.4%) had stenosis and one had carotid artery thickening. Three (13.0%) patients had subclavian artery involvement.

Of the 23 patients with Takayasu arteritis, 11 (47.8%) patients had received corticosteroids (either standard oral or intravenous regimens) and immunosuppressants, and four (17.4%) had undergone vascular surgery. Most patients ($n = 22$) were diagnosed with late-stage disease; only one patient was diagnosed with early stage disease: this patient was admitted to hospital because of blood pressure asymmetry on both upper limbs. A CT scan showed common carotid artery thickening with elevated CRP and ESR levels. He received corticosteroids and was stable for the following year with white blood cell (WBC) count and CRP level returning to within the normal range.

Polyarteritis nodosa

Five patients (four boys, one girl) had polyarteritis nodosa. The mean $\pm$ SD age at onset was 13.4 $\pm$ 3.1 years (range 10–16 years). All five patients had fever on admission, three presented with skin involvement (livedo reticularis and/or tender

subcutaneous nodules), one patient had myalgia, two had renal involvement, four had necrotizing vasculitis (as identified on skin biopsy), and one had thickening of the proximal left radial artery, as shown by ultrasound examination. All five patients had negative antinuclear antibody ANA and ANCA blood tests, but four of them had highly elevated CRP and ESR levels. Four patients received corticosteroids and two received mycophenolate mofetil (standard regimens).

Cutaneous polyarteritis

Four patients (two of each sex) had cutaneous polyarteritis. The mean ± SD age at onset was 8 ± 2.8 years (range 4–11 years). All patients were admitted to hospital because of livedo reticularis or subcutaneous nodules, and skin biopsies showed necrotizing nongranulomatous vasculitis. One patient had concomitant tuberculosis. Two patients were treated with standard regimens of corticosteroids; the other two were treated with standard regimens of nonsteroidal anti-inflammatory drugs.

Microscopic polyangiitis

The one patient with microscopic polyangiitis was a 15-year-old girl who presented with repeated cough, polypnea and a history of bloody sputum for the previous 7 months. She was admitted to the respiratory department for a fibrebronchoscopy. The ANCA test was positive for perinuclear ANCA and antimyeloperoxidase antibodies, and negative for cytoplasmic and antiproteinase 3 antibodies. The test for antiglomerular basement membrane antibodies was negative. The peripheral blood cell count was as follows: WBC count 9.3×10^9/l, haemoglobin 98 g/l, platelet count 426×10^9/l. Renal function was within the normal range. Pulmonary function was mildly restrictive with forced expiratory volume in 1 s 73.7% of predicted value.

Behçet's disease

Retrospective review of the data showed that three patients (aged 8, 9 and 10 years) had been diagnosed with Behçet's disease. In two patients, disease onset started as nodular erythema on upper and lower limbs, and on the face. Both patients had oral ulcers and eye involvement (blurred vision, later diagnosed as uveitis). In two patients, ESR was elevated. One patient developed hypertension. Two patients received corticosteroids combined with cyclosporine. The third patient showed atypical Behçet's disease. He was a 9-year-old boy admitted to the cardiology department because of intermittent haemoptysis, which had lasted 18 days, and mass occupation in the right atrium and ventricle as shown by echocardiography. Over the previous year he had experienced repeated bouts of erythema nodosum and oral ulcers, and had received standard corticosteroid treatment. After excluding endocarditis and tumours, this patient underwent surgery for the mass excision. The biopsy showed fibrinoid necrosis and inflammatory cell infiltration and the patient was diagnosed with Behçet's disease. The patient was subsequently prescribed standard courses of corticosteroids and mycophenolate mofetil.

Discussion

As far as we are aware, this is the largest data set describing the incidence and clinical features of paediatric primary vasculitides in a Chinese population. As expected, HSP and KD were the most common of the childhood vasculitides, although other types of vasculitides were observed (in low numbers). This tertiary hospital in Shanghai receives patients from surrounding cities, therefore the distribution of paediatric primary vasculitides observed in this study probably represents the prevalence of these conditions in Eastern China.

Henoch–Schönlein purpura was the most common paediatric primary vasculitis in this retrospective review of data. Age at first onset ranged between 2 and 16 years, and 50% of patients developed renal involvement (most of them within 1 week of disease onset). This finding is in agreement with other research, which showed that the proportion of renal involvement can vary between 20 and 56%.[6] It has been estimated that up to 20% of children with HSP nephritis may develop chronic kidney disease, with up to 2% progressing to end stage renal disease.[6–8] As we previously reported, age ≥ 6 years, presence of purpura other than on lower limbs and a positive faecal occult blood test were independent risk factors for developing HSP nephritis.[9] The prognosis for these patients needs further study. To-date, there are no reports of renal failure or chronic renal insufficiency from the patients involved in the present review.

Kawasaki disease was the second most popular vasculitis observed in the present paediatric population. This observation is different from the results of a 10-year retrospective study of Taiwanese data,[10] which reported more patients with KD than HSP from one centre in Taiwan. However, the prevalence of diseases may differ, based on the population studied. Nevertheless, the age distribution at onset observed in this present study was similar to that found in other reports.[10,11] Although the proportion of coronary artery dilatation and coronary aneurysm was much lower than that reported in the Taiwanese study,[12] the incidence of coronary aneurysm was similar to that reported from patients in the USA.[9,11] Inflammatory markers, CRP and ESR, were highly elevated in patients included in the present study. The proportion of patients with incomplete KD was lower than that observed in studies in Germany and Japan[13,14] and the proportion of patientsretreated with IVIG was lower in the present study than that found in a study of US-based patients.[11]

Takayasu arteritis was the third most common primary vasculitis observed at our centre. Clinical symptoms combined with imaging were used for diagnosis. However, the early manifestation of Takayasu arteritis was unspecific and so most of the patients were not diagnosed until they experienced cardiovascular involvement. At the late stage of Takayasu arteritis, therapy is palliative and patients have a poor prognosis. Importantly, Takayasu arteritis therefore requires early diagnosis for the best outcome. If the condition is diagnosed at an early stage, remission may be induced by high-dose glucocorticoids and immunosuppressive agents.[15] The big challenge is that each child with suspected Takayasu arteritis requires a thorough diagnostic evaluation to exclude other conditions and to confirm the presence of vascualitis.[16] As reported by Dagna et al,[17] pentraxin-3 may be a useful biomarker for defining disease activity in patients with Takayasu arteritis.

There were few reports of polyarteritis nodosa from the present retrospective study in Eastern China. Similar to other surveys, fever and elevated acute phase reactants were commonly found in these patients.[18,19] Corticosteroids were the cornerstone therapies for these patients. As reported by Fernanda et al,[20] mycophenolate mofetil therapy is effective in patients refractory to corticosteroids. Cutaneous polyarteritis was rare and all patients presented with livedo reticularis or subcutaneous nodules. Behçet's disease was also rare: one patient presented with an atypical manifestation of haemoptysis and a mass occupying the right atrium and ventricle.

A limitation of this study is that the data were obtained from only one centre in China. In addition, the data were retrieved from medical records and so not all information was available, particularly that for patients with mild disease. Furthermore, the clinical features were reported at the time of diagnosis, so

long-term follow up of these patients remains to be analysed.

In conclusion, paediatric vasculitides represents a challenging and complex group of conditions. The most common forms are HSP and KD. Other forms are relatively rare in children, but carry significant morbidity and mortality. Paediatricians should be suspicious of vasculitis when there is evidence of systemic inflammation and multisystem disease that cannot be explained by one specific disorder. A priority should be to develop biomarkers to detect paediatric vasculitides at an early stage. Immunosuppressant therapies, such as mycophenolate mofetil, maybe useful in the treatment of vasculitis but there is a need for more research into effective and well-tolerated therapies.

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Declaration of conflicting interest

The authors declare that there are no conflicts of interest.

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