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ORIGINAL ARTICLE

Comparison of cryoglobulinemia in children and adults

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Background/Purpose: Cryoglobulinemic vasculitis is a systemic vasculitis resulting from circulating immune complex deposition in the small vessels and is characterized by variable clinical features, including purpura, Raynaud's syndrome, ulcerations, arthralgia, glomerulonephritis, and peripheral neuropathy. Cryoglobulinemia can also result from hepatitis C virus (HCV) infection. The clinical spectrum and associated or underlying diseases of cryoglobulinemia in different age groups is not well understood. This study investigated the demographic, clinical, serologic features, and associated or underlying diseases in children and adult patients with cryoglobulinemia.
Methods: The retrospective study included 114 patients (18 children, 96 adults) who presented with cryoglobulinemia between 2000 and 2010 at the Chang Gung Memorial Hospital. Their medical records were reviewed and serological and virologic assessments were analyzed.
Results: In this group of patients, children had a significantly higher prevalence of prolonged fever (16.7% vs. 3.13%; $p = 0.018$), arthralgia (66.67% vs. 16.67%; $p < 0.001$), arthritis (66.67% vs. 15.63%; $p < 0.001$) and cutaneous involvement (77.78% vs. 50%; $p = 0.03$) compared with adults. Both the adult and children groups had a greater frequency of hepatitis B virus (HBV) infection (20.8% and 5.6%, respectively), than HCV infection (12.5% and 0%, respectively).

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Conclusions: Children with cryoglobulinemia had a significantly higher prevalence of prolonged fever, arthralgia, arthritis and cutaneous involvement compared with adults.

Introduction

The presence of one or more immunoglobulins that precipitate below core body temperatures and re-dissolve on re-warming is termed "cryoglobulinemia".[1,2] Cryoglobulinemia has been described in a wide variety of diseases, including malignancies, infections, and systemic autoimmune diseases in adults.[3–6] When there is no demonstrable associated or underlying disease, the condition is called "essential cryoglobulinemia".[7,8] Hepatitis C virus (HCV) is one of the main causative pathogens in Caucasian mixed cryoglobulinemia (MC).[9,10] Hepatitis B virus (HBV) is the major hepatitis virus in the Far East.[11] It is conceivable that the most prevalent infectious etiologies of cryoglobulinemia between the East and West are different.

The clinical manifestations of cryoglobulinemia in Caucasian adults are diverse. Cutaneous features were the most frequent presentations; purpura on lower limbs was the most common symptom (~80–90%).[2,9] Other clinical manifestations included arthralgia (40–98%), muscle weakness (80–90%), peripheral neuropathy (20–84%), liver involvement (58–77%), renal involvement (20–60%), Raynaud phenomenon (25–50%), and ulcers (10–40%) .[2,9,12]

Cryoglobulinemia is rarely reported in the pediatric literature. A few studies investigated the associated or underlying diseases of children's cryoglobulinemia, such as *Schistosoma haematobium* infection[13] and essential cryoglobulinemia.[14,15] The clinical symptoms of children's cryoglobulinemia were fever, arthralgia, rash, membranoproliferative glomerulonephritis in one case report[14] and fever, and bluish black discoloration of hands and feet in another report.[15] According to the literature review, we considered that the different age groups may have distinct clinical features and associated or underlying diseases. To our knowledge, there have been no reports, so far, that have assessed the clinical dissimilarities and associated diseases between children and adults.

The present retrospective study evaluated the characteristics of pediatric cryoglobulinemia and compared the epidemiologic and clinicoserologic features, and associated or underlying diseases between children and adult groups in a large series of patients with cryoglobulinemia in Taiwan.

Materials and methods

Study subjects

We reviewed the medical records and enrolled patients that had cryoglobulinemia and clinical manifestations at Chang Gung Memorial Hospital from January 2000 to October 2010. The definition of the mean age at onset was the age of the patient when they first presented the common clinical symptoms of cryoglobulinemia. The definition of the mean age at diagnosis was the time when the patient had clinical features and had a confirmed serologic diagnosis.

Analysis of associated or underlying factors

In order to explore the relationship between the clinical symptoms and different associated or underlying disorders, we identified the most common clinical features and associated diseases. Viral infection included HBV, HBC, Epstein-Barr virus, and parvovirus. Autoimmune diseases were diagnosed based on the following criteria: (1) primary Sjogren syndrome (SS) according to the preliminary diagnostic criteria for SS proposed by the European Community Study Group[16] before 2002 and the revised diagnostic criteria for SS proposed by the American-European Consensus Group[17] after 2002; (2) systemic lupus erythematosus (SLE) according to the 1997 revised criteria of the American College of Rheumatology;[18] (3) rheumatoid arthritis (RA) using the 1987 criteria of the American College of Rheumatology;[19] (4) juvenile idiopathic arthritis (JIA) as defined by the International League of Associations for Rheumatology criteria;[20] (5) polymyositis-dermatomyositis using the criteria of Bohan and Peter;[21] and (6) primary antiphospholipid syndrome as defined by the revised classification criteria.[22] Hematologic malignancies were confirmed by the clinical findings and biopsies of lymph nodes and/or bone marrow. Essential cryoglobulinemia was considered in those cases in which no infectious, autoimmune, or hematologic disease was found.

Definition of clinical features

The clinical symptoms evaluated in our protocol were defined as follows: (1) prolonged fever meant axillary temperature $< 38^{\circ}C$ for at least 1 week; (2) arthralgia meant joint pain. Arthritis indicated joint swelling or two or more of erythema, local heat, tenderness or a limited range of motion; (3) cutaneous involvement contained papule, macule or gangrene; (4) peripheral neurologic manifestations included paresthesia, numbness, and/or motor defects of the lower extremities; (5) kidney involved proteinuria or altered urinalysis (hematuria, red blood cell casts), or raised serum creatinine. Glomerular injury diagnosed by renal biopsy included membranoproliferative glomerulonephritis, mesangial proliferative glomerulonephritis, and segmentary and focal glomerulonephritis; (6) gastrointestinal involvement covered severe abdominal pain, elevated liver enzymes with/without echographic and/or histologic features of chronic hepatitis, cirrhosis; (7) arterial or venous thrombosis confirmed by clinical and color Doppler or computed tomography angiogram.

Laboratory studies

Cryoglobulin was detected by double immunodiffusion. HCV antigen, anti-HCV, HBV surface antigen (HBsAg), and anti-HBV antibodies were measured by Roche COBAS TaqMan, Mannheim, Germany. Antinuclear antibodies were identified by indirect immunofluorescence using ASP1200, DiaSorin, Stillwater, MN, USA. Anticardiolipid antibodies, anti-extractable nuclear antigen, and antineutrophil cytoplasm antibodies were detected by Uni-CAP 100, Phadia, Uppsala, Sweden. Parvovirus B19 IgM was detected by RIDASCREEN, R-Biopharm AG, Darmstadt, Germany. EBV IgM was detected by LIAISON, DiaSorin, Saluggia, Italy. Rheumatoid factor was measured by nephelometry using the N Latex RF kit, Siemens, Marburg, Germany. Quantitative determinations of complement factor 3 and complement factor 4 in patients' sera were conducted using N antisera to human complement factor reagents with Behring nephelometry (Siemens, Germany).

Statistical analysis

The Chi-square test was applied for categorical variables of demographic data, clinical characteristics and serology. We compared the interval between the onset of symptoms and diagnosis (years) in adults and children by the Mann-Whitney U test. Statistical significance was assumed for $p < 0.05$. Values are expressed as means $\pm$ standard deviation (SD).

Results

General characteristics

The study recruited 114 subjects (18 children, 96 adults). Baseline demographics are summarized in Table 1. In the children's group, female patients were more common than male patients with a ratio of 2.6, but in the adult group, the proportion of females to males was similar. The difference in sex ratio between the children and adult groups was significant ($p < 0.01$). The mean age at onset in the children and adults was 6.69 ± 3.08 years and 51.57 ± 20.88 years, respectively. The mean age at diagnosis in children and adults was 7.34 ± 3.69 and 51.57 ± 20.88 years, respectively. The interval between the onset of symptoms and diagnosis in children was longer than that in adults.

Table 1 Demographic features of 114 cryoglobulinemia patients

	Children, $n = 18$	Adult, $n = 96$	p
Female / male ratio	13/5	47/49	<0.01
Mean (SD) age at onset (yrs)	6.69 ± 3.08	51.5 ± 20.88	
Mean (SD) age at diagnosis (yrs)	7.34 ± 3.69	52.23 ± 18.81	
Interval between the onset of symptoms and diagnosis (yrs)	0.66 ± 1.30	0.37 ± 1.58	0.04

Clinical symptoms

In children versus adults, there was a significantly higher prevalence of prolonged fever (16.7% vs. 3.13%; $p = 0.018$), arthralgia (66.67% vs. 16.67%; $p < 0.001$), arthritis (66.67% vs. 15.63%; $p < 0.001$) and cutaneous involvement (77.78% v. 50%; $p = 0.03$) (Table 2).

Associated or underlying disorders

The most common associated or underlying diseases in the children and adult groups were essential cryoglobulinemia (77.2% vs. 68.8%), followed by infection (16.7% vs. 33.3%) and autoimmune diseases (16.7% vs. 17.7%). For both adults and children, HBV infection (20.8% vs. 5.6%) was greater than HCV (12.5% vs. 0%) infection (Table 3). Some associated diseases were found together. Specifically, it was observed that HBV and hematologic disease (33.3% of non-Hodgkin lymphoma) and autoimmune (5.9% of SS and 5.9% of polymyositis) diseases sometimes affected the same patient. We also found that only a few HBV patients (8.3%) had HCV infection.

Immunologic features

There were no significant variations with regard to C3 and C4 complement fractions and autoantibodies in both children and adult groups (data not shown).

Clinical features between HBV and HCV groups

Among adults, one patient with both HBV and HCV infection was excluded. In adult patients with HBV, the cutaneous (42.11%) and liver (42.11%) were affected most frequently, followed by renal involvement (21.05%) and peripheral neuropathy (21.05%). In patients with HCV, the cutaneous involvement (45.45%) was affected most frequently, followed by leg ulcer (36.36%) and Raynaud phenomenon (36.36%). A higher proportion of patients with HBV

Table 2 Comparisons of clinical characteristics between the children and adult control groups

Event, n (%)	Children group, $n = 18$	Adult group, $n = 96$	p
Prolonged fever	3 (16.67)	3 (3.13)	0.018
Leg ulcer	3 (16.67)	18 (18.75)	0.834
Petechiae/Purpura	5 (27.78)	15 (15.63)	0.213
Arthralgia	12 (66.67)	16 (16.67)	<0.001
Arthritis	12 (66.67)	15 (15.53)	<0.001
Cutaneous involvement	14 (77.78)	48 (50.00)	0.030
Raynaud phenomenon	6 (33.33)	26 (27.08)	0.588
Peripheral neuropathy	3 (16.67)	19 (19.79)	0.758
Renal involvement	2 (11.11)	12 (12.50)	0.869
Liver involvement	3 (16.67)	10 (10.53)	0.454
Muscle weakness	0	9 (9.38)	0.176
DVT, arterial thrombosis	1 (5.56)	7 (8.33)	0.688

DVT = deep vein thrombosis.

Table 3 Comparisons of associated or underlying diseases between the children and adult groups

Event, *n* (%)	Children	Adult	*p*
EC	13 (72.2)	66 (66.8)	0.504
Infection	3 (16.7)	32 (33.3)	0.128
HBV	1 (5.6)	20 (20.8)	0.109
HCV	0	12 (12.5)	0.113
EBV	1 (5.6)	0	0.158
Parvovirus	1 (5.6)	0	0.158
Autoimmune diseases	3 (16.7)	17 (17.7)	0.610
SLE	1 (5.6)	5 (5.2)	0.652
SS	1 (5.6)	5 (5.2)	0.652
JDM/DM	0	1 (1)	0.842
JPM/PM	0	1 (1)	0.842
JRA/RA	0	2 (2)	0.708
Anti-phospholipid syndrome	0	1 (1)	0.842
Henoch-Schonlein disease	1 (5.6)	0	0.158
Autoimmune thyroiditis	0	1 (1)	0.842
Malignancy	0	6 (6.2)	0.348
Leukemia	0	3 (3.1)	0.594
Lymphoma	0	2 (2)	0.708
Multiple myeloma	0	1 (1)	0.842

EC = essential cryoglobulinemia; HBV = hepatitis B virus; HCV = hepatitis C virus; EBV = Epstein-Barr virus; SLE = systemic lupus erythematosus; SS = Sjogren syndrome; JDM = juvenile dematomyositis; DM = dermatomyositis; JPM = juvenile polymyositis; PM = polymyositis; JRA = juvenile rheumatoid arthritis; RA = rheumatoid arthritis.

compared to those with HCV had a leg ulcer (5.26% vs. 36.36%; $p = 0.028$) (Table 4).

Discussion

The clinical profiles were different between the children and adult groups. In the adult group, the most frequent clinical features at onset were cutaneous involvement, followed by Raynaud phenomenon and peripheral neuropathy. In contrast, in Western adults, purpura was the most common presentation, followed by muscle weakness, arthralgia, peripheral neuropathy and liver involvement. The Raynaud phenomenon and arthritis were 36% and 8%, respectively.[2] We also found a low frequency of muscle weakness in our adult cryoglobulinemic patients (9.38%), which is different from that found by Ferri et al (80—98%).[2,23] In previous studies, the classical "Meltzer's triad" of purpura, arthralgias and weakness was seen in 25—30% of patients.[12,24] In our patients, no cryoglobulinemic children had the classical triad, and only one cryoglobulinemic adult (1.04%) had these symptoms.

Table 4 Comparisons of clinical features between HBV and HCV groups in adults

Event, *n* (%)	HBV group	HCV group	*p*
Prolonged fever	2 (10.53)	0 (0.00)	0.265
Leg ulcer	1 (5.26)	4 (36.36)	0.028
Petechiae/purpura	2 (10.53)	3 (27.27)	0.236
Arthralgia	2 (10.53)	1 (9.09)	0.9
Arthritis	2 (10.53)	1 (9.09)	0.9
Cutaneous involvement	8 (42.11)	5 (45.45)	0.858
Raynaud phenomenon	3 (15.79)	4 (36.36)	0.199
Peripheral neuropathy	4 (21.05)	2 (18.18)	0.85
Renal involvement	4 (21.05)	0 (0.00)	0.102
Liver involvement	8 (42.11)	1 (9.09)	0.076
Muscle weakness	2 (10.53)	2 (18.18)	0.552
DVT, arterial thrombosis	1 (5.26)	1 (9.09)	0.685

The HBV group included 19 patients, and the HCV group included 11 patients. HBV group = hepatitis B virus group; HCV group = hepatitis C virus group; DVT = deep vein thrombosis.

In this cohort of children, we found that the most frequent clinical symptoms were cutaneous involvement, followed by arthritis, arthralgia, and Raynaud phenomenon. To date, there has not been a comparable study worldwide. Cryoglobulinemic vasculitis is a multifactorial disease. The causes of clinical diversities between our study group and Caucasians may possibly result from different ethnicity, sex, and mean age at diagnosis.

The most common etiologies were essential cryoglobulinemia, followed by infection and autoimmune diseases in both children and adult groups. In Caucasian adults, infection was the principal etiologic factor identified, followed by autoimmune diseases, essential cryoglobulinemia and hematologic diseases.[10] Another study demonstrated that essential cryoglobulinemia was the chief etiology (71.6%), followed by chronic liver disease (11.7%), lymphoproliferative disease (8.9%) and connective tissue disease (5.4%).[12]

In this study, HBV was more common than HCV in cryoglobulinemic adults. In previous Western literature, the incidence of HCV infection in mixed cryoglobulinemia ranged from 40 to 90% and varied geographically.[25,26] Although most cryoglobulinemia was associated with chronic HCV infection, this association was reported predominantly in countries with a high prevalence of HCV.[27] HCV infection was the main infectious pathogen among infections in 73%, and HBV constituted 3% of cryoglobulinemic patients.[10] HBV infection is also an uncommon cause of cryoglobulinemia in Caucasians.[28] HBV carriers vary from 0.1 to 2% in the United States, Canada, Western Europe, Australia and New Zealand. However, in Taiwan, Southeast Asia, China, and sub-Saharan Africa, there is a high prevalence of HBV (10—20%).[29,30] In a survey conducted among Asian and Pacific island populations living in New York City, 15% were positive for HBsAg, a proportion much higher than the average US.[31] Literature data states that HBV represents an etiological factor of cryoglobulinemic vasculitis in a minority of individuals.[2,10,32] In chronic hepatitis B infections, cryoglobulins which contain virus particles, heterogeneous antigen-antibody complexes which have IgG and IgM, can be detected.[33] By means of the decrease in viral antigen and antibodies against them, the amount of cryoglobulin probably decreases and symptoms of vasculitis regress.[34] In prior studies, the symptoms of vasculitis were resolved in patients with HBV-related cryoglobulinemic vasculitis with the use of lamivudine by itself or by its combination with interferon.[34,35]

The cutaneous involvement, leg ulcer, and Raynaud phenomenon were the most frequent in the HCV group. The

HCV group showed a significantly higher prevalence of leg ulcers compared to the HBV group. The pathogenic mechanisms of cryoglobulinemia may be different in both groups. Even in Caucasians, patients with HCV related cryoglobulinemic vasculitis presented diverse clinical symptoms, including more renal, cutaneous involvement,[10] purpura, arthralgia, peripheral neuropathy,[36] livedo, distal ulcers, gangrenous changes, or higher alanine aminotransferase.[37]

We analyzed the amount of overlap among the different associated or underlying diseases. Specifically, we observed a strong overlap between HBV infection and hematologic (33% non-Hodgkin lymphoma) diseases. HBV infection had few overlaps with HCV infection and autoimmune diseases. In a prior study, there was a strong association between HCV infection and some autoimmune (50% of SS, 67% of polyarteritis nodosa) or hematologic (50% of non-Hodgkin lymphoma) diseases.[10] One study also found that most patients with HBsAg (80%) or HIV infection (76%) also had HCV infection.[10]

There are several limitations in this study. Firstly, our laboratory use of qualitative analysis rather than quantitative analysis.[2] Secondly, few children and adults with cryoglobulinemia had acute nephritis or nephrotic syndrome, so it was not possible to compare these renal diseases between the children and adult groups. Thirdly, 13 adult patients were excluded from our study owing to no overt clinical characters, including positive cryoglobulin serology. This isolated serology may be due to in the early stages of the disease or during clinical remission.[32,38,39]

In conclusion, the clinical manifestation in both children and adult groups were different. Children with cryoglobulinemia had a significantly higher prevalence of prolonged fever, arthralgia, arthritis and cutaneous involvement compared with adults with cryoglobulinemia.

Conflicts of interest statement

The authors had no financial support and have no conflicts of interest to disclose.

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