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Original Article

Juvenile Idiopathic Arthritis Presenting with Prolonged Fever

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BACKGROUND/PURPOSE: Systemic-onset juvenile idiopathic arthritis (s-JIA) is a systemic disease often accompanied by a fever. We examined 16 patients with s-JIA and reported the clinical manifestations, laboratory data, treatments and outcomes.

METHODS: From 1984 to 2007, 16 children (aged 1–16 years), who were diagnosed as having s-JIA, were admitted to the Mackay Memorial Hospital in Taiwan. We retrospectively reviewed their medical charts.

RESULTS: There were nine boys and seven girls, with mean age of onset of 7.4 ± 5.5 years. Fever (100%), typical rash (63%), and arthritis (75%) were the three most common symptoms. Lymphadenopathy (50%), hepatosplenomegaly (63%), pleural pulmonary manifestations (13%) and myalgia (25%) were also noted. One patient had Epstein-Barr virus-associated hemophagocytic syndrome complications. Neutrophilic leukocytosis was a common feature. Other laboratory data showed elevated C-reactive protein levels (25.1 ± 50.3 mg/dL), and erythrocyte sedimentation rates (69 ± 28 mm/hr) and abnormal liver enzymes. Marked hyperferritinemia (> 2,000 ng/mL) was noted in 57% (4/7) of the patients. The mean time from onset of symptoms to diagnosis was 9.2 weeks. Non-steroidal anti-inflammatory drugs, steroids, disease-modifying anti-rheumatic drugs and anti-tumor necrosis factor agents were used for treatment. Due to prolonged fever, 2.0 ± 1.6 (maximum = 5) different kinds of antibiotics were used before a diagnosis was made. Most cases had satisfactory therapeutic outcomes except one boy, who had permanent joint contracture.

CONCLUSION: The clinical manifestations of s-JIA in Taiwan were often accompanied by a prolonged fever. This results in clinicians often suspecting bacterial infections and prescribing several kinds of antibiotics. In the case of prolonged fever, s-JIA should always be placed on the list of differential diagnoses.

KEYWORDS: clinical manifestation, fever, systemic-onset juvenile idiopathic arthritis

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Introduction

Systemic-onset juvenile idiopathic arthritis (s-JIA), also called Still's disease, systemic-onset juvenile chronic arthritis (s-JCA), or systemic-onset juvenile rheumatoid arthritis (s-JRA) is not a single disease but a term that encompasses all forms of arthritis that begin before the age of 16, persist for more than 6 weeks, and are of unknown cause (according to the 1986 definition criteria).[1,2]

We used to think of joints when we mentioned JIA but, in fact, many s-JIA cases are accompanied by a prolonged fever. Now, this definition is currently being supplanted by the newer International League of Associations for Rheumatology criteria, which more strictly defines the quotidian nature of the fever and requires the presence of at least one of the other four characteristic systemic signs: rash, generalized lymphadenopathy, organomegaly, or serositis.[3] Since the disease is mainly diagnosed by clinical criteria and by exclusion, recognition of the clinical symptoms and signs is important. Much literature regarding the disease has been published in the Western countries. A recent study evaluated the presentation of s-JRA in Pennsylvania.[4]

In Taiwan, one clinical manifestation of adult-onset Still's disease was reported in 2004.[5] There were three other articles published; but none emphasized the clinical manifestrations.[6–8] The clinical characteristics of JIA in Taiwan were reported in 1984,[9] 1993[10] and 2001,[11] but no recent clinical observation data has been reported. Thus, we collected 16 cases and reviewed the clinical features of their presentation.

A prolonged high fever was the most common feature of s-JIA, but was often misdiagnosed as a bacterial infection. Thus, many unnecessary antibiotics were used. To avoid the abuse of antibiotics in future cases, we report the clinical characteristics of 16 cases of s-JIA.

Methods

From 1984 to 2007, 16 children (aged 1–16 years) were admitted to the Mackay Memorial Hospital. They were diagnosed as having s-JIA according to the 1986 definition criteria, or the International League of Associations for Rheumatology criteria. Their medical charts were retrospectively reviewed, and gender, age, clinical manifestations, physical findings, laboratory data, image studies, treatments, and prognosis were all analyzed. This data were collected from medical records on their first admission.

Results

Clinical manifestations

Sixteen patients were enrolled in our study. There were nine boys and seven girls, with a mean age of onset of 7.4 ± 5.5 years (ranging from 10 to 202 months). The mean time from onset of symptoms until diagnosis was 9.2 weeks (ranging from less than 1 week to almost 1 year). The clinical manifestations of the patients diagnosed with s-JIA are shown in Table 1. According to the medical charts, the Aunt's of both Case 3 and Case 13 had arthritis and the sister of Case 15 had human herpesvirus 6-related infantile rheumatoid arthritis when she was 12 years old.

Fever, rash, and arthritis were the three most common symptoms. All patients (16/16) had fever. The mean fever duration was 28.6 days, (ranging from 10 to 90 days) with a temperature of 39–40°C. The typical rash was an evanescent, non-fixed erythematosus rash and characteristically coincided with the fever peak.[2] Sixty-three percent (10/16) of the patients displayed the typical rash. Arthritis is often symmetrical and polyarticular, and may be absent at onset but develop during the course of the disease.[2] Our findings are consistent with previous reports in that the knee, ankle, wrist, proximal interphalangeal, and distal interphalangeal joints were the most commonly involved joints in s-JIA patients.[11]

Seventy-five percent (12/16) of the patients had arthritis (red, swelling, local heat and tenderness). Four patients lacked sufficient data in their retrospective medical charts. The most common sign was swelling and only one patient had morning stiffness. Polyarthritis accounted for 31% (5/16) of cases and oligoarthritis accounted for 44% (7/16). The knee joint was the most commonly affected site (4/12), with the ankle joint ranked second (2/12). Unlike previous studies that indicated significant morbidity in children with s-JIA in Taiwan,[12] most of our patients had a good prognosis; permanent joint contracture and disability were noted in only one patient (1/16, 0.6%; Case 4).

A sore throat is characteristic of adult-onset Still's disease, but was not the main criterion for s-JIA.[13,14] In the three patients who had a sore throat, the local findings revealed an infected throat without exudates.

Of the sixteen cases, lymphadenopathy was present in eight patients (50%). Cervical and axillary areas were the most commonly affected sites. Most of the lymphadenopathies were larger than 1 cm. The largest was 2 × 2 × 1 cm. One patient (Case 16) had a right auxiliary lymph node biopsy performed that showed only reactive hyperplasia. Hepatosplenomegaly (2–3 fingerbreadths below the right costal margin) was seen in 62.4% (10/16) of patients.

Table 1. Clinical manifestations of patients with systemic-onset juvenile idiopathic arthritis

Case	Sex	Age of onset (yr)	Duration from onset to diagnosis (wk)	Family history[a]	Fever (d)	Joint involvement	Rash	Hepatosplenomegaly	Myalgia	LAP site	Comorbidity
1	M	2.2	3	–	21	Polyarthritis	+	+	–	Femoral, cervical	
2	M	1.4	40	–	10	Oligoarthritis: fingers	+	+	–	Cervical	EBV-VAHS
3	M	3.0	–	+	14	Oligoarthritis: leg	+	–	–	–	Thalassemia minor
4	M	3.0	12	–	90	Oligoarthritis: knee and bilateral ankles	+	+	–	–	Pericardial effusion
5	F	4.6	6	–	30	Polyarthritis	+	+	–	Cervical	
6	F	3.6	12	–	90	NA	+	+	–	–	
7	M	6.2	4	–	12	Oligoarthritis: finger and toe	+	+	+	–	
8	F	6.6	5	–	14	NA	–	+	–	–	
9	F	5.8	0.5	–	10	Polyarthritis	–	–	–	+	
10	M	0.8	2	–	14	NA	–	–	–	Cervical	
11	M	8.4	12	–	12	NA	–	+	–	Cervical	
12	M	11.9	16	–	16	Arthralgia: left knee	–	–	–	–	Myocarditis, pericardial effusion
13	F	13.9	2	–	14	Polyarthralgia	+	–	+	–	
14	F	15.5	4	+	30	Oligoarthritis: bilateral knees and hips	+	+	+	Axillary	
15	M	15.1	16	+	60	Oligoarthritis: bilateral knees and right ankle	–	–	–	–	
16	F	16.8	4	–	21	Polyarthralgia	+	+	+	Axillary	

[a]According to the medical charts, the Aunts of both Case 3 and Case 13 had arthritis. The sister of Case 15 had human herpesvirus-6 related infantile rheumatoid arthritis when she was 12 years old. EBV-VAHS=Epstein-Barr virus-associated hemophagocytic syndrome; LAP=lymphadenopathy; NA=not available.

Myalgia was recorded in 4/16 cases (25%). Two patients (2/16, 12.5%) had pleural pulmonary manifestations, such as pleural and pericardial effusion.

Bacterial, or viral, infections such as *Mycoplasma pneumoniae* might have had a role in triggering JIA.[15] Of our cases, four patients had *M. pneumoniae*. One patient (Case 2) had Epstein-Barr virus-associated hemophagocytic syndrome (EBV-VAHS) complications.

Laboratory data

The laboratory results are summarized in Table 2. Neutrophilic leukocytosis was a common feature. White blood counts ranged from 3,500/μL to 44,000/μL (mean=15,932±10,872/μL). Hemoglobin was 10.5±1.2 g/dL. The mean platelet count was 459±234×10^3/μL (range, 91–804×10^3/μL). Other laboratory data revealed elevated C-reactive proteins (25.1±50.3 mg/dL; ranging from 0.01mg/dL to 200 mg/dL), and erythrocyte sedimentation rates (69±28 mm/hr). Impaired liver function was also noted. Glutamate oxaloacetate transaminase was 69±53 IU/L (ranging from 20 IU/L to 169 IU/L). Glutamic pyruvic transaminase was 34.6±35.2 IU/L (ranging from 12 IU/L to 123 IU/L).

Ferritin levels were checked in 10 patients. The mean value for ferritin was 21,061 ng/mL. Markedly hyperferritinemia (>2,000 ng/mL) was noted in 57% (4/7).

Antinuclear antibody titers were checked in 13 patients. Four were negative (31%), seven patients (54%) had a low titer (≤1:80). Of the two patients whose antinuclear antibody titer was higher than 1:80, all had the speckled form. Rheumatoid factor was negative in all except one patient, who had a rheumatoid factor titer of 48.7 IU/mL. Human leukocyte antigen-B27 (HLA-B27) was checked in four patients and only one was positive (25%). Anti-cyclic citrullinated peptide was checked in Case 16 and the result was negative.

C3 and C4 did not decrease. The mean serum C3 concentration was 163±40 mg/dL (ranging from 86 mg/dL to 206 mg/dL; normal range, 79–152 mg/dL). The mean serum C4 concentration was 31±10.4 mg/dL (ranging from 19 mg/dL to 54 mg/dL; normal range, 16–38 mg/dL).

Imaging studies and invasive procedures such as abdominal echogram, computed tomography, magnetic resonance imaging, bone marrow biopsy and Gallium scan were also performed. Most of the examinations were non-diagnostic, or yielded negative results, except that one

Table 2. Laboratory data of patients with systemic-onset juvenile idiopathic arthritis

Case	Hb (g/dL)	WBC (μL)	Neut (%)	Platelet (10^3/μL)	CRP (mg/dL)	ESR (mm/hr)	GOT (IU/L)	GPT (IU/L)	Ferritin (ng/mL)	ANA (<40×+)	RF (IU/mL)	C3/C4 (mg/dL)
1	9.3	31,100	85	536	–	60	169	123	–	–	<20	160/33
2	9.6	11,700	67	91	7.54	–	143	49	5,530	–	<20	193/99
3	8.8	27,900	86	556	32.30	64	46	13	–	–	<20	155/31
4	8.4	22,100	82	623	200.00	70	72	20	–	–	neg	–/–
5	9.0	18,000	72	804	12.06	81	–	–	257	80	<30	206/22
6	11.8	4,900	49	247	1.69	26	29	15	–	80	<20	86/19
7	10.6	44,000	82	758	5.29	50	–	–	480	40	<20	–/–
8	11.2	11,100	53	699	5.78	107	20	18	125	–	<20	205/–
9	10.9	11,800	65	619	26.50	6	–	–	–	80	<20	192/54
10	12.0	14,400	7	642	6.95	113	–	–	–	–	<20	–/–
11	12.5	3,500	45	154	0.01	61	–	–	–	640	48.7	116/25
12	11.2	9,800	42	–	45.00	81	–	–	–	320	neg	154/–
13	10.7	16,300	92	325	11.00	87	69	33	132,222	40	<20	158/20
14	10.9	15,800	83	254	11.20	99	39	28	4,814	40	<20	208/33
15	9.8	8,210	67	350	4.58	60	–	–	–	–	<20	–/–
16	11.2	4,300	67	232	2.00	66	35	12	4,002	40	<20	124/31

Hb=Hemoglobin; WBC=white blood cell; Neut=neutrophils; CRP=C-reactive protein; ESR=erythrocyte sedimentation rates; GOT=glutamate oxaloacetate transaminase; GPT=glutamic pyruvic transaminase; ANA=antinuclear antibody; RF=rheumatoid factor; neg=negative.

patient (Case 8) had a thoracic spinal lesion which was revealed in a bone scan, a Gallium scan and a spinal magnetic resonance imaging. Previous reports often mention the relationship between the cervical spine and JIA,[16,17] but none mention the thoracic spine.

Treatment

One of the 16 patients (6.3%) received acetaminophen, and five patients (31.3%) received aspirin (dose, 80–100 mg/kg/day) before the diagnosis was made. Due to a poor response, non-steroidal anti-inflammatory drugs (NSAIDs) were also given to 13 patients (81.3%). The most common NSAID was naproxen (12/13, 92.3%). Steroids were also added to the treatment regimen if NSAIDs failed, and accounted for 75.0% (12/16) of patients. Steroid was administered in different ways. An oral steroid (11/12, 91.7%) was the most common, although systemic steroids (5/12, 41.7%) or even pulse therapy (2/12, 16.7%) was also used. Nineteen percent (3/16) of patients received disease-modifying antirheumatic drugs. Most of them were given sulfasalazine, hydroxychloroquine and methotrexate. Only Case 3 (1/16) received an anti-tumor necrosis factor agent (etanercept). Most cases showed satisfactory therapeutic outcomes. Only one boy was left with permanent joint contracture. Because one patient had EBV-VAHS complications, intravenous immunoglobulin and chemotherapy were given.

Antibiotics, due to prolonged fever, were used empirically for covering unknown bacterial infections. The mean period of antibiotic usage was 7.3 ± 6.5 days (range, 1–18 days), and 2.0 ± 1.6 (maximum = 5) kinds of antibiotics were used before a diagnosis was made.

Discussion

s-JIA can be difficult to diagnose due to the lack of specific biomarkers, variable presentations, and overlap of symptoms with many other illnesses.

The main limitation of the present study resides in its retrospective design. Furthermore, our analysis was conducted on a limited number of patients. We were able to record a limited number of clinical histories and laboratory data, and this weakened the significance of our statistical analysis.

Our clinical findings are consistent with a report on a cohort of patients from the United Kingdom, France, and Spain[18] and a recent retrospective report from Pennsylvania.[4] In short, the clinical manifestations of s-JIA in Taiwan are similar to those reported worldwide.

In our study, the male to female ratio was 9:7. The previous studies did not find any significant sex bias for s-JIA.[19] The time between onset of symptoms until diagnosis indicates that the disease is difficult to diagnose in the beginning if we do not keep the diagnosis and clinical features in mind. Also, myalgia and abdominal pain can be intense during fever peaks.

The results of our laboratory investigations are similar to those of previous studies, such as neutrophilic leukocytosis, high erythrocyte sedimentation rates, high C-reactive proteins, thrombocytosis and microcytic anemia.[2] The serology for atypical or viral infections were all negative, including serology for EBV, cytomegalovirus, mycoplasma, scrub typhus, Lyme disease, malaria, Q fever and typhoid fever. Thrombocytopenia and abnormal bone marrow changes, such as megakaryocytic or erythroid hyperplasia have been reported in Taiwan, but were not observed in our study.[20]

Macrophage activation syndrome (MAS), or hemophagocytic syndrome, is a severe complication of chronic rheumatic diseases, especially s-JIA.[21] The frequency of MAS in s-JIA was found in one retrospective study from a tertiary pediatric rheumatology unit to be 6.7%.[22] Patients usually present with an acute febrile illness, hepatosplenomegaly, lymphadenopathy, cutaneous and mucosal bleeding, pancytopenia, and central nervous system, cardiac, and renal involvement.[21] MAS is often difficult to recognize because the symptoms and signs are the same as those of active s-JIA. The differences between MAS and s-JIA are discussed in another article.[23]

NSAIDs have been the mainstay of treatment of s-JIA for decades. Intra-articular steroid injections of triamcinolone hexacetonide, moderate or high-dose systemic corticosteroid therapy, anti-tumor necrosis factor agents, physiotherapy, and occupational therapy are the mainstream treatments for s-JIA.[2]

Due to the common initial presentation of a fever of unknown origin and elevated systemic inflammatory laboratory profiles, serial workup and other examinations are often done to include or exclude possible infectious pathogens. Thus, many unnecessary antibiotics are given for non-infectious, rheumatological diseases. Several kinds

of antibiotics are used for 1–2 months on average. The cost, adverse effects, and possible production of resistant strains are all concerns with unnecessary antibiotic treatment. Earlier diagnosis reduces unnecessary antibiotic use.

In conclusion, the clinical manifestations of s-JIA in Taiwan often present alongside a prolonged fever, which causes clinicians to assume bacterial infections are present and to prescribe several kinds of antibiotics. In cases of prolonged fever, s-JIA should always be put on the list of differential diagnoses to avoid abuse of antibiotics.

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