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Case Report

Juvenile rheumatoid arthritis associated with uveitis in a 4-year-old girl

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Juvenile rheumatoid arthritis (JRA) causes disability and blindness, and is considered the most common and important rheumatic disease in childhood. JRA is defined as persistent arthritis in ≥1 joints for at least 6 weeks if certain exclusionary conditions have been eliminated and the onset of the disease occurs before 16 years of age.[1,2] Differential diagnoses include infectious arthritis, osteomyelitis, specific non-rheumatologic abnormalities, such as sarcoidosis, neoplastic disease, acute rheumatic fever, vasculitis, and systemic lupus erythematosus.[3]

The overall prevalence of JRA is approximately 30-150/100,000 children. In the United States, the incidence of JRA has been estimated to be 10-20/100,000 children. This is found more frequent in native Americans.[4] JRA, as a single entity, affects females twice as much as males with a ratio of 2:1. Pauciarticular and polyarticular types occur more often in with a ratio of 2.8:1, although both sexes are affected equally in the systemic type. In children with uveitis accompanying JRA, the ratio of females to males is much higher, 5:1.[1]

The variability of the disease may explain misconceptions that JRA is usually a benign disease. A cohort study in which 506 subjects during the period of 1970-1999 found that approximately one-third of JRA patients achieve disease remission. The visual complications are also important in determining the outcome. Functional disability is common and can be long-lasting. Recognizing JRA symptoms earlier are important to prevent mortality, disability, and long-term complications.[2] Although JRA is the most common rheumatic disease in children, many doctors are not familiar with this disease.[5] The purpose of this paper is to report a case of juvenile rheumatoid arthritis associated with uveitis in a 4-year, 8-month-old girl.

Report of the case

A 4-year, 8-month-old girl was referred to the Outpatient Clinic, Department of Child Health, Sanglah Hospital, Denpasar on February 20, 2004 with blurring of vision as a chief complaint. She was consulted by the Ophthalmology Department with suspected juvenile rheumatoid arthritis. Her father stated that the blurring of vision had occurred since 2 weeks; she could not reach for an object farther than 30 cm and had difficulty in walking. He also noticed white opaque lenses on both her eyes. She had deformities on her right and left hand fingers, elbows, and knees. The

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fourth fingers on both her hands were contracted, yet without swelling, tenderness, redness, nor were they warm. The elbows and knees were in flexion. She was afebrile, had normal bowel habit and urination.

During second years of life, she had low-grade intermittent fever for 2 weeks. Her elbows and knees were swollen and red, which felt painful when she moved and complained of morning stiffness. Six months later, her fingers were also affected. The inflammation had disappeared after 3 months, yet deformity of the fingers, elbows, and knees persist until now. She had no history of rash on the skin or difficulty breathing. Her parents occasionally brought her to a general practitioner and pediatrician when her joints swelled, but the symptoms never disappeared. She was the second child and no other family members had similar history.

On physical examination, the patient was alert, had an equal and regular pulse rate at 110 beats/minute, respiratory rate was 28 times/minute, axillary temperature was 37^0C, and blood pressure was 120/80 mmHg. Her body weight was 12 kg, her body height was 90 cm (Z score weight to height was –0.79 SD: well nourished). There were no signs of anemia or jaundice. She had cataracts, posterior synechia, and uveitis in both her eyes, and band keratopathy on her left eye. An eye examination showed that her right eye could follow objects and light but her left eye could not. Intraocular pressure was normal on her right eye but decreased on her left eye (phthisis bulbi). On chest inspection, there was no precordial bulging, ictus cordis was normal and palpable at fifth intercostal space and left mid-clavicular line.

On auscultation, the first and second heart sounds were normal and no murmur was heard. Breath sounds were vesicular, without rales, friction rub, nor wheezing. Bowel sounds were normal. Liver and spleen were not palpable. Examination of hands showed deformity on her fourth finger of both hands. These fingers were contracted, without swelling, tenderness, nodules, nor redness. The elbows and knees were in flexion. The neck, hips, and ankles were normal. Based on history and clinical manifestation, the patient was diagnosed as juvenile rheumatoid arthritis subtype pauciarticular with associated uveitis.

Laboratory investigations revealed a leukocyte count of 9.3 K/μl, hemoglobin 11.2 g/dl, hematocrit 35.1%, platelet count 327 K/μl, and erythrocyte sedimentation rate (ESR) 12 mm/hr. Examination of rheumatoid factor (RF) showed a negative result and anti nuclear antibody (ANA) was positive. RF and ANA are used as prognostic factors in patients with JRA. ANA positively showed that the prognosis was poor.[2] The sensitivity of RF examination for rheumatoid arthritis was 66% and specificity 87%,[6] while ANA has a sensitivity of 41% and specificity of 56%.[7] HLA (human leukocyte antigen) examination was not performed since laboratory limitations. X-ray examination of metacarpophalangeal joints, elbows, and knees showed normal results. Chest X-ray was normal.

The patient was treated with scopolamine 3x1 drop, polynel (fluorometholone+neomycin sulfate) 6x2 drops, methyl prednisolone 3x4 mg. The patient was consulted to an orthopedic surgeon and physical therapist. She had physiotherapy once a week to improve the range of motion of contracted joints and also received occupational therapy. The orthopedic surgeon planned a soft tissue release, tendon lengthening from contracted interphalangeal distal joints, elbows, and knees if there was no improvement after 6 months of physical therapy. After 1 month of treatment, ranges of motion of contracted joints were improved, yet there were no improvement of the eyes.

Discussion

JRA is the most common rheumatic disease of childhood. It represents up to 70% of arthritis diseases in children.[1] The pathogenesis of JRA remains unknown. Possible causes are infections, autoimmunity, trauma, stress, and immunogenetic predisposition.[1,3] Inflammatory arthritis has been observed with infections of mycoplasma and viruses (rubella and parvovirus). The histopathology of affected tissues, notably synovial tissue, shows chronic inflammation with lymphocytes and plasma cell as chief inflammatory cells.[8] Chronic inflammation may be perpetuated by immune complexes formed by autoantibodies, such as ANA and RF induced by infections.[1] The ANA are a group of antibodies which react with various constituents of the cell nuclei. Both IgM and IgG subtypes are represented among the antinuclear antibodies.[9] RF is a group of antibodies which react with IgG. RF is produced by plasma cells in the rheumatoid synovium and other lymphoid tissues.[3] It is observed frequently

that the onset of JRA may follow physical trauma on the extremities, such as a fall or a sprain ankle. It is also well documented that psychological stress appears to be particularly common.[1]

Although JRA has been rarely observed to occur in siblings or in families with first-degree relatives who have other connective-tissue diseases, histocompatibility antigens point a possible hereditary predisposition to the disease. HLA-DR4 is associated with seropositive rheumatoid arthritis. A decrease in Dw4 and DR4 has been noted principally in young girls with persistent oligoarthritis and seropositive ANA. Increases in the frequency of DR5 and of DRw8 have been associated with pauciarticular diseases in young girls with ANA seropositivity and chronic uveitis.[10] In our case, there was no history of the disease among family members. She had no history of trauma or any psychological problems before the onset of arthritis. HLA examination was not performed because of laboratory limitation.

A child's ability to communicate symptoms of illness varies according to age. A young child with JRA may have increased irritability, anorexia, a posture of guarding the joints, a limp, or absolute refusal to crawl or walk.[1] Frequent symptoms include morning stiffness, gelling following inactivity, and night pains. The cardinal signs of inflammation indicate the presence of arthritis.[5] Swelling results from periarticular soft tissue inflammation, edema, and from intra articular effusion. Involved joints are warm but usually not erythematous. Although tenderness or pain on motion of a joint may be present, the child often does not complain of pain at rest.[3] In our case, the patient had arthritis at 2 years old. Her elbows and knees were swollen, with redness, morning stiffness, and pain when she moved. The fingers were also affected after 6 months. She had low-grade intermittent fever for 2 weeks. Symptoms of arthritis persisted for 3 months. There many criteria for diagnosis and classification of children with JRA, however, the criteria by the American Rheumatism Association (ARA) is most frequently used (**Table 1**).[1]

JRA can be classified as systemic, pauciarticular and polyarticular according to the onset within the first 6 months. (**Table 2**)

In our case, the diagnosis of JRA was established by the ARA criteria. The patient at the onset had arthritis on 4 joints, thus classified as pauciarticular JRA.

Systemic lupus erythematosus (SLE) is the most frequent problem in differential diagnosis of JRA. The child with SLE may have arthritis that mimics JRA. The more specific features of SLE include a butterfly rash, alopecia, nephritis, CNS disease, Raynaud's phenomenon, leukopenia and hemolytic anemia.[1] Our patient had arthritis for 3 months and no clinical sign of SLE, therefore the diagnosis of SLE was ruled out.

Complications of JRA are growth retardation, localized growth disturbance, subcutaneous nodule, muscle disease (atrophy, shortening, contracture, weakness), cardiac involvement (pericarditis, endocarditis), pulmonary disease, lymphadenopathy, splenomegaly, hepatic disease, central nervous system disease, vasculitis, renal and eye involvement.[12] In our case, the patient had complications of the muscles and eyes. The muscle of the 4th fingers on the left and right hand were shorted which gave rise to flexion contracture. Her elbows and knees were in flexion. Flexion contracture of the knees resulted in difficulties in walking. Complications of the eyes were uveitis, cataract, posterior synechia on both her eyes, and band keratopathy on her left eye.

Involvement of the eye is one of the most perplex complications of JRA. The majority of JRA-associated uveitis patients are oligoarticular JRA (78-90%), while 7-14% are the polyarticular variety. JRA associated uveitis is chronic and usually ($\pm$65%) involves both eyes, either simultaneously or within a few months of each other.[9,10] The greatest risk of uveitis occurs within the first 2 years after the onset of JRA, and the risk declines considerably by 8 years after the onset of arthritis. Eye symptoms are non-specific and may include pain, light sensitivity, and blurring of vision.[11] Unfortunately, the disease does not cause obvious symptoms in about 50% of patients and

Table 1. Diagnosis criteria for juvenile rheumatoid arthritis[1,5]

1. Age of onset <16 years
2. Arthritis in one or more joints defined as swelling or effusion, or presence of two or more of following sign: limitation of range of motion, tenderness or pain on motion, and increased heat
3. Duration of disease $\geq$6 weeks
4. Type of onset of disease during the first 6 months classified as:
   a. Polyarticular: 5 or more joints
   b. Pauciarticular disease (oligoarthritis): 4 or fewer joints
   c. Systemic disease: arthritis with intermittent fever
5. Exclusion of other form of juvenile arthritis

TABLE 2. JRA CLASSIFICATION ACCORDING TO TIME OF ONSET [1, 3, 10 , 11]

Classification	Manifestations
1. Systemic	- 20% prominently extra-articular as well as arthritis - fever (typically quotidian pattern with high spike) - rash (evanescent) - lymphadenopathy (often massive) - hepatosplenomegaly - pericarditis (often asymptomatic) - haematological disturbance (anemia, leucocytosis) - features can precede arthritis (4-6 months) - RF and ANA (-) - early onset (1-4 years) - equal sex incidence
2. Pauciarticular/oligoarthritis (=4 joints)	
a. Early onset approximately 25% of all JRA	- predominant in female (2-5 years) - 35% eye involvement: chronic uveitis [may be asymptomatic (white eye) but can cause blindness] - ANA (+) (which occurs in about 50% in this group) increases this risk - joints involved: 1 or 2 large joints (e.g. knees, ankles, elbow); hips and sacroiliac joints are more often spared - arthritis is rarely erosive
b. Late onset approximately 15% of all JRA	- predominant in males of pre-teenage years - lower limb involvement, especially hips and sacroiliac joints - 25% are at risk for uveitis - HLA B-27 (+) in 75% - ANA and RF (-)
3. Polyarticular (=5 or more joints)	
a. RF(-) polyarthropathy	- female predominance and occurs in any age - arthritis is symmetrical - involves both large and small joints of upper and lower limbs - uveitis may occur - ANA (+) in 25%
b. RF(+) polyarthropathy	- female predominance - late onset - resembles adult rheumatoid arthritis - symmetrical polyarthritis of upper (metacarpophalangeal joints most common) and lower limbs - subcutaneous nodules - early erosive changes (radiology) - ANA (+) 50-75% of case

symptoms only appear once the vision robbing complications such as cataract, band keratopathy, glaucoma, and hypotony occurs.[1]

The earliest sign of uveitis on slit-lamp examination are those of cellular exudates of inflammatory cells in the anterior chamber of the eye. A punctate keratic precipate develops later on the posterior corneal surface. Inadequately controlled inflammation leads to progressive damage with the development of posterior synechia. Band kerato-pathy, secondary cataracts, glaucoma, and phthisis bulbi are other late manifestations of uveitis.[10,11]

Factors determining the high risk of uveitis in children with JRA are female gender, age of onset <6 years, oligoarthritis, duration of arthritis <2 years, presentation of ANA, HLA-DR 8.5, and absence of HLA-DR4.[1]

In our case, the patient is of high-risk to suffer from uveitis. She had arthritis at 2 years of age, female, oligoarthritis, and had positive ANA examination. She never complained about her eyes until her father noticed she could not reach an object of more than 30 cm.

Since of the therapeutic program in children with JRA is supportive and not curative, a program of conservative management should attempt to control the clinical manifestations of the disease, preserve function, and prevent deformity. This involves

a multidisciplinary team which consists of pediatric rheumatologist, ophthalmologist, orthopedic surgeon, psychiatrist, physical and occupational therapist, and social worker.[1,2,4]

First-line therapy includes non-steroidal anti-inflammatory drugs (NSAIDs). In addition, intra-articular corticosteroid injections have been shown to be safe and effective and have beneficial effects on growth, and can be administered with little psychological trauma.[4] The philosophy of JRA management is to begin with the safest, simplest, and most conservative measures (**Table 3**). Acute inflammation in JRA leads to transient disability, swelling, pain, and necessitates a different approach with chronic articular inflammation which leads progressively to deformity and destruction of cartilage and bone.[1]

The initial treatment of chronic uveitis consists of corticosteroid eye drops and use of mydriatic drugs to dilate pupil and help prevent posterior synechia.

TABLE 3. OUTLINE OF JRA MANAGEMENT [1]

Basic program
- Acetylsalicylic acid
- Balanced rest/exercise
- Physical and occupational therapy
- Education of patient and family
- Involvement of school and community agencies
Nonsteroidal anti-inflammatory drug
Intra-articular steroid
Hydroxychloroquine
Gold salt
Penicillamine
Sulfasalazine
Prophylactic surgery
Reconstructive surgery
Immunosuppressive drug

Chelation in selected cases of band keratopathy may be successful in decreasing the interference of the opacity with sight. Cataract extraction may be dangerous when operated during inflammation of eye since there are risks of amblyopia development.[10]

The effect of therapy, progression of the disease, complications, and drug toxicity should be monitored continuously which generates long-term follow-up.[12] In our case, the patient was treated with scopolamine 3x1 drop, polynel 6x2 drops, and methyl prednisolone 3x4 mg. She had physiotherapy once every week to improve the range of motion of contracted joints and occupational therapy.

The prognosis of JRA varies from subgroup to subgroup. The mortality rate estimates at 2-4%.[5] Children with systemic onset of JRA accounts for almost two-thirds of all deaths. The cause of death is divided between disease-related causes and treatment-related causes. The disease related causes of death are secondary to cardiac disease or amyloidosis, whereas infection leads the list of treatment-related causes.[12] The morbidity of JRA lies in the amount of joints damaged and disability which occurs. Poor prognostic indicators for patients with JRA are active systemic disease at 6 months, polyarticular onset or disease course, female gender, positive rheumatoid factor, persistent morning stiffness, tenosynovitis, subcutaneous nodules, antinuclear antibody, early involvement of small joints of hands and feet, rapid appearance of erosions, and extended pauciarticular disease course.[2]

The child with oligoarthritis is best from the standpoint of joint disease but worst from the risk of uveitis. Approximately 34% of patients with pauciarticular onset are in remission at 5 years after the onset of the disease and only 15% develop erosions within the first 5 years.[2]

Although prognosis for sight in chronic uveitis has improved, visual outcome still remains far less than satisfactory with estimates of blindness. Blindness was reported approximately 50-70% of children with uveitis. Visual loss may occur when there are complications of uveitis or amblyopia related to suppression of visual images from a cataract.[1,9,10] In our case, the prognosis of the patient is poor since there are delays of treatment and some prognostic factors e.g. female gender, ANA positive, early involvement of small joints of hands and feet, and extended of pauciarticular. She had complications of muscles and eyes. Her fingers, elbows, and knees were contracted and she had uveitis and amblyopia which threatened visual loss.

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