

# Profile of Indian Patients with Juvenile Onset Chronic Inflammatory Joint Disease Using the ILAR Classification Criteria for JIA: A Community-based Cohort Study

VINAYA KUNJIR, ANURADHA VENUGOPALAN, and ARVIND CHOPRA

**ABSTRACT. Objective.** To assess the current International League of Associations for Rheumatology (ILAR) classification criteria (Edmonton, 2001) for juvenile idiopathic arthritis (JIA) in Indian patients.

**Methods.** Out of 441 children, 330 with chronic joint pains were diagnosed with juvenile onset chronic inflammatory arthritis and followed in an observational cohort. Our study was carried out from 1994 to 2006 in a community rheumatology clinic. Emphasis was placed on obtaining data required by the ILAR system. Of the original group, 235 children were eventually classified as having JIA; 108 were examined during the first year of illness.

**Results.** We assigned 224 children (95%) to discrete JIA categories: enthesitis-related arthritis (ERA; 36%), oligoarthritis (OLA-persistent; 17%), polyarthritis rheumatoid factor (RF)-negative (17%), polyarthritis RF-positive (12%), systemic arthritis (8%), OLA-extended (4%), and psoriatic arthritis (1%). The remaining 11 children (5%) were classified with undifferentiated arthritis (mostly an overlap due to seropositive RF and/or HLA-B27). The prevalence of ERA (89% HLA-B27-positive) and seropositive RF was unexpectedly high. Although agreement ( $\kappa > 0.79$ ) with the American College of Rheumatology criteria and the European Spondylarthropathy Study Group criteria was good to excellent, the ILAR system was found to be more comprehensive and clinically homogeneous. However, some problems appear unique in our scenario.

**Conclusion.** A wide-spectrum phenotype of JIA is demonstrated by an Indian cohort. Although useful, RF and HLA-B27 in this population proved problematic to the ILAR classification. (First Release June 1 2010; J Rheumatol 2010;37:1756–62; doi:10.3899/jrheum.090937)

*Key Indexing Terms:*

JUVENILE RHEUMATOID ARTHRITIS

PEDIATRIC RHEUMATIC DISEASES

CLASSIFICATION CRITERIA

Juvenile idiopathic arthritis (JIA)<sup>1</sup> is a heterogeneous group of disorders with a childhood onset of chronic idiopathic inflammatory arthritis. The current nomenclature of JIA is meant to encompass the descriptions of juvenile chronic arthritis (JCA), juvenile ankylosing spondylitis, juvenile-onset seronegative spondyloarthritis (SSA), and psoriatic arthritis (PsA). The qualifying age of onset (disorder) for juvenile forms of chronic immune inflammatory arthritis in all classification systems remains arbitrarily fixed at prior to age 16 years.

The European League Against Rheumatism (EULAR)<sup>2</sup>

and the American College of Rheumatology (ACR)<sup>3,4</sup> criteria have been most frequently used to classify children with chronic arthritis. The ACR system for diagnosis of JRA is more bedside-oriented but requires several time-consuming and cumbersome exclusions. To complicate matters, the EULAR system includes JRA (to represent rheumatoid factor-seropositive arthritis) among its 6 categories. The ACR cautions against using the diagnostic terms JRA, JCA, or juvenile arthritis synonymously or interchangeably, which often has been the case<sup>1,3</sup>. Better understanding of HLA-B27-related SSA disorders and psoriasis has led to newer discrete criteria<sup>5,6</sup>.

To clarify differences and develop a uniform standard approach, the International League of Associations for Rheumatology (ILAR) developed a new set of classification criteria for childhood-onset idiopathic inflammatory arthritis and called it JIA<sup>7</sup>. The latter system was revised several times to improve its usefulness. First proposed in 1994 (Santiago criteria)<sup>7</sup>, the classification system was twice revised: in 1997 (Durban)<sup>8</sup> and in 2001 (Edmonton)<sup>9</sup>. Broadly speaking, the current ILAR system (Edmonton ver-

*From the Center for Rheumatic Diseases (CRD), Pune, India.*

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*V. Kunjir, MBBS, Rheumatology Associate; A. Venugopalan, MSc, In-charge, Immunology and Microbiology; A. Chopra, MD, Director, Chief Rheumatologist, Center for Rheumatic Diseases.*

*Address correspondence to Dr. A. Chopra, Center for Rheumatic Diseases, Hermes Doctor House/Hermes Elegance, 1988 Convent St., Camp 411001, Pune, India. E-mail: crdp@vsnl.net*

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sion) recognizes 7 categories of JIA: systemic arthritis, oligoarthritis, polyarthritis [rheumatoid factor (RF)-negative], polyarthritis (RF-positive), enthesitis-related arthritis (ERA), PsA, and undifferentiated arthritis (UnA). Oligoarthritis is divided into 2 subcategories: persistent and extended.

Our aim was to describe a cohort of Indian patients with juvenile onset chronic inflammatory joint disease using the current ILAR classification criteria for JRA. The emphasis was to identify the early phenotype of the disease. We also intended to compare this classification system with the ACR<sup>4</sup> and the European Spondylarthropathy Study Group (ESSG)<sup>5</sup> classification systems that are often used worldwide and in our region.

## MATERIALS AND METHODS

The study was carried out in the Center for Rheumatic Diseases (CRD), Pune (State of Maharashtra, West India), which runs an outpatient community referral clinic<sup>10</sup> for both adults and children. Sixty to 70 patients, including 3–6 children, are examined daily in the clinic. Almost half the children live in villages and small towns all over the state. CRD is also the nodal center for several ongoing World Health Organization (WHO) ILAR Community-oriented Program for Control of Rheumatic Diseases (COPCORD) population survey sites in the Pune region<sup>11</sup>. Although there are several pediatric outpatient and inpatient facilities in the region, there are no other dedicated rheumatology centers treating pediatric patients.

**Design and selection.** This was a cross-sectional observational study. During the period 1994–2005, 441 children with chronic joint pains were referred to CRD. Of them, 330 children were suspected of having chronic inflammatory arthritis [other diagnoses: nonspecific arthralgias (70), other connective tissue disorders (36), rheumatic fever (5)]. Beginning from January 1999, we began to classify the patients as per the ILAR classification system and followed them in a longitudinal observation cohort. Detailed clinical profiles during the first year of illness and investigation results were recorded. In addition, the ILAR classification system inventory was used to prepare a classification questionnaire for each child and a concerted effort was made to fulfill the requirements. Several children examined prior to 1999 were especially recalled along with their guardians to the clinic for the latter purpose. Initially using the ILAR DURBAN version, we upgraded the questionnaire once the Edmonton version was made available. In December 2006, we carried out a final retrospective cross-sectional analysis of all clinical case records and classification questionnaires to confirm JIA as per the current ILAR system. We excluded 57 children examined prior to 1997 who had incomplete clinical records and could not be interviewed during the study period. Another 38 children were excluded who could not be tested for serum RF during the initial 6 months of illness. We found that 235 children satisfied the current ILAR classification criteria for JIA.

**Respondents.** Several children were recalled for free evaluations to confirm the archival data and complete the classification questionnaire. In our study cohort, 108 children were evaluated during the first year of illness (0–3 months = 51 children, 3–6 months = 21 children, and 6–12 months = 36 children). In the remaining 127 patients, the median time interval from the onset of illness to the first referral was 8.5 yrs (range 1.1–16 yrs). Only children with obvious symptomatic eye disease were examined by an ophthalmologist and in several instances it was after the clinical episode.

Although they represented many religions, the children in the cohort were predominantly Hindu and mostly from families of low-middle socioeconomic status (annual family income < US \$2000). Although the children in the cohort made several followup visits during the study period, all had been followed for at least 18 months.

**Case record forms.** Every patient was evaluated systematically by trained personnel and findings were recorded in standard rheumatology case record forms. Evaluations included general demographics, anthropometric measurements, patient narrative (complaints, comorbidity, and drug use/toxicity), disease activity (global assessments by patient and doctor), and physical and rheumatology examination (including joint counts for pain/tenderness and swelling). Data in case record forms were entered into a referral database program.

**Classification inventory.** The final inventory used in this study contained all the items required by the current ILAR system (2001) and was similar to that used by the Swiss investigators<sup>12</sup>. The inventory was transformed into a computer questionnaire for recording patient data. This questionnaire was specifically designed to gather data from 2 successive 6-month periods following the onset of illness.

**Variables.** Each joint was counted individually. Cervical spine, lumbar spine, thoracic spine, carpal joints of each hand, and tarsal joints of each foot were counted as 1 joint each. Each metacarpophalangeal, metatarsophalangeal, and proximal interphalangeal joint was counted as a separate joint. Enthesitis was defined by a history of moderately severe persistent pain and demonstration of tenderness at 1 or more bony insertion sites of ligaments/tendons/fascia, especially around the heel and knee region. The latter pain/tenderness should have been nontraumatic in origin, lasting for at least a couple of days. The children were especially questioned about early-morning painful gait or a limp due to pain in the heel-foot region.

**Investigations.** IgM-RF and antinuclear antibody (ANA) were detected by nephelometry and ELISA, respectively, and measured using standard controls (cutoff values for RF and ANA were 40 IU/ml and 1 index unit, respectively). All children in this cohort were required by the ILAR system to have been tested for RF. However, we allowed the confirmatory second positive RF test any time during the first 9 months of illness. HLA-B27 was detected using the standard polymerase chain reaction technique. All male patients in the cohort with onset of arthritis at 6 years of age and beyond were required to be tested for HLA-B27. There was no charge to the patients for any investigations.

**Classification diagnosis.** Every child in the cohort was evaluated by a rheumatology associate who was exclusively dedicated to examining children in the clinic, and by a rheumatologist. All children were classified for JIA as per the current ILAR system. Based on longterm data, oligoarthritis cases were further subclassified into persistent or extended. We also reclassified all children using the ACR<sup>4</sup> and the ESSG<sup>5</sup> classification system for purposes of comparison.

**Regulatory and ethical issues.** We were not required to seek informed consent from the patients or clearance from the ethics committee because the data pertained to standard-of-care diagnosis and management. However, all patients were informed about our research.

**Statistics.** Kappa ( $\kappa$ ) coefficient was calculated to estimate the level of agreement between the classification systems using a statistical software package (EpiInfo v 6.04; Centers for Disease Control and WHO, 2001).

## RESULTS

Two hundred thirty-five children (137 male, 98 female) were classified as having JIA. The diagnostic breakdown is shown in Figure 1. ERA was the single largest category (36%), followed by oligoarthritis (21%) and RF-negative polyarthritis (17%). Table 1 shows features as per the ILAR classification system during the initial 6 months of illness (except for an extended followup period in the case of oligoarthritis).

**Systemic arthritis.** Twelve patients showed polyarticular (> 4 joints) joint involvement and 6 patients showed oligoarticular joint involvement. One child did not have arthritis

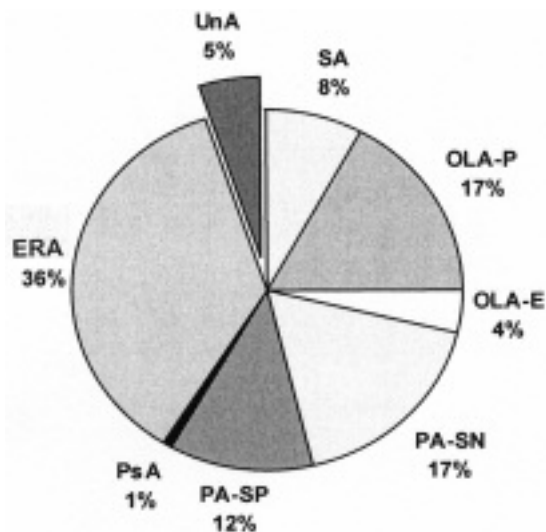


Figure 1. Distribution (%) of categories in 235 Indian children with juvenile idiopathic arthritis as per the ILAR classification system (Edmonton, 2001). SA: systemic arthritis; OLA: oligoarthritis; P: persistent; E: extended; PA: polyarthritis; SP: seropositive rheumatoid factor; SN: seronegative rheumatoid factor; PsA: psoriatic arthritis; ERA: enthesitis-related arthritis; UnA: undifferentiated arthritis.

during the initial 6 months of febrile illness. All children described a typical intermittent high fever at the onset of illness that generally lasted for more than 2 weeks. However, a proper body temperature record was often missing, even when the child had been under pediatric care or admitted to a pediatric facility. Rash, hepatosplenomegaly, ocular manifestations, and polyserositis were clinically recorded in 3, 5, 2, and 2 patients, respectively; hepatic and/or spleen enlargement (3 cases) and serositis (pleural effusion 2 cases, pericarditis 1

case) were initially demonstrated by imaging (ultrasonography and echocardiography). In 1 child the ocular manifestation was vitreitis while the other child showed keratitis.

**Oligoarthritis.** Forty-nine children (21%), predominantly girls, were classified as having oligoarthritis. Ten children showed an extended pattern of arthritis. Only 1 male child had symptomatic ocular involvement diagnosed as chronic anterior uveitis. Overall, seropositive ANA was found in 3 children (2 girls). Three (12.5%) of the 24 children tested for HLA-B27 were found positive.

**Polyarthritis.** Twenty-eight of the 69 children (40.6%; predominantly girls) tested seropositive for RF. The overall clinical articular profile of seropositive polyarthritis and seronegative polyarthritis was similar. Two children with RF-negative polyarthritis were also found to have clinical sacroiliitis but were negative for any of the discriminative features of ERA including HLA-B27.

**ERA.** Seven children (8.3%) in the group reported symptomatic ocular manifestation, which was predominantly anterior uveitis. Acute and chronic anterior uveitis was diagnosed in 5 and 2 children, respectively. Sixteen children (19%) provided a family history of HLA-B27-associated disease. Nineteen percent of patients showed sacroiliitis (clinical and/or radiological); 37% showed inflammatory spine manifestations (predominantly thoracic/lumbar spine), and 37% showed enthesitis (predominantly heel and Achilles tendon). Eighty-nine percent of the patients tested positive for HLA-B27.

**PsA.** Three children fulfilled the ILAR criteria of PsA and manifested typical scattered scaly skin lesions; none had nail lesions. Two patients, both girls, had polyarticular arthritis.

Table 1. Distribution (percentages) of selected features by category in 235 Indian children with juvenile idiopathic arthritis, classified by the ILAR classification system (Edmonton, 2001).

| Features/Subset               | Systemic Arthritis, n = 19 | OLA-P, n = 39 | OLA-E, n = 10 | Polyarthritis, RF-, n = 41 | Polyarthritis RF+, n = 28 | Psoriatic Arthritis, n = 3 | Enthesitis-related Arthritis, n = 84 | UnA, n = 11 | All Patients, n = 235 |
|-------------------------------|----------------------------|---------------|---------------|----------------------------|---------------------------|----------------------------|--------------------------------------|-------------|-----------------------|
| Median onset age, yrs         | 5.25                       | 10            | 9.75          | 11.5                       | 13                        | 12                         | 13                                   | 11          | 12                    |
| Range for onset age, yrs      | 1.5–13                     | 1–16          | 1–14          | 1–15.5                     | 2–16                      | 5–12                       | 7–16                                 | 2–15.5      | 1–16                  |
| Female                        | 42.1                       | 59            | 70            | 61                         | 88.9                      | 66.7                       | 9.5                                  | 45.5        | 41.7                  |
| Cervical spine                | 16.7                       | 2.5           | 20            | 14.6                       | 11.1                      | 0                          | 7.2                                  | 13.3        | 9.8                   |
| Thoracic spine                | 0                          | 0             | 0             | 2.4                        | 0                         | 0                          | 6                                    | 0           | 2.6                   |
| Lumbar spine                  | 5.5                        | 7.7           | 0             | 7.3                        | 14.8                      | 0                          | 33.7                                 | 20          | 17.4                  |
| Sacroiliac joint              | 0                          | 0             | 0             | 4.9                        | 0                         | 0                          | 19                                   | 18.1        | 8.5                   |
| Enthesitis                    | 5.2                        | 0             | 0             | 0                          | 3.6                       | 0                          | 36.9                                 | 27.2        | 15.3                  |
| Eye                           | 5.2                        | 2.6           | 0             | 0                          | 0                         | 0                          | 8.3                                  | 0           | 3.8                   |
| Liver/spleen                  | 26.3                       | 0             | 0             | 0                          | 0                         | 0                          | 0                                    | 9.1         | 2.6                   |
| RF-positive                   | 0                          | 0             | 0             | 0                          | 100                       | 0                          | 0                                    | 82          | 15.7                  |
| ANA (positive/no. tested)     | 11.8 (2/17)                | 8 (2/25)      | 10 (1/10)     | 16.7 (5/30)                | 27.3 (6/22)               | 0 (0/2)                    | 7.4 (5/68)                           | 20 (2/10)   | 12.5 (23/184)         |
| HLA-B27 (positive/no. tested) | 0 (0/8)                    | 16.7 (3/18)   | 0 (0/6)       | 15.8 (3/19)                | 15.8 (3/19)               | 100 (1/1)                  | 88.7 (55/62)                         | 40 (4/10)   | 48.3 (69/143)         |

UnA: undifferentiated arthritis; RF: rheumatoid factor; ANA: antinuclear antibody; ILAR: International League of Associations for Rheumatology.

**Undifferentiated arthritis.** Eleven children were classified as undifferentiated JIA because they failed to satisfy the inclusion criteria of any discrete category. Table 2 provides an overview of this subgroup. Nine children (6 girls) with oligoarticular onset tested seropositive for RF. Three boys from the latter group, with onset of illness after 6 years of age, also tested positive for HLA-B27. One boy, aged 6 years, with an otherwise typical profile of systemic arthritis, developed polyarthritis and tested seropositive for RF. A 13-year-old boy, with seronegative RF oligoarthritis and dactylitis, tested positive for HLA-B27 (and thereby fulfilled the criteria for ERA), but recalled a history of skin psoriasis in a first-degree cousin; this patient was finally classified as UnA.

**Exclusions (failed strict ILAR criteria).** We classified 38 children from the observational study who failed the study cohort because of a lack of appropriate RF testing. The distribution of JIA categories (ERA 37%, polyarthritis 12.5%, oligoarthritis 12.5%, and UnA 10.5%) in this group was similar to that of the study cohort.

**HLA-B27.** In the absence of B27 testing, 63 children (75%) out of a cohort of 84 (Table 1) would still satisfy the criteria for ERA; the remaining would then be classified as oligoarthritis and polyarthritis (RF-seronegative) in 13 and 8 children, respectively. In our study, HLA-B27 testing made no difference to the classification of children into other categories (Table 1) except that of UnA. If the HLA-B27 result were ignored, 1 male child in the undifferentiated category would be classified as having PsA (Table 2).

**ACR classification system<sup>3</sup> (Table 3).** One hundred sixty children (68%) in the JIA cohort fulfilled the ACR criteria of JRA (systemic arthritis 19, oligoarticular 65, polyarticular 76). Polyarthritis was the single largest JRA subgroup (47.5%). Seventy-five children belonged to the “exclusion” group that included ankylosing spondylitis (20 patients), PsA (3 patients), reactive arthritis (1 patient), and unclassifiable seronegative inflammatory arthritis (51 patients). We compared the 2 systems (Table 3) for corresponding categories. There were no differences with reference to systemic

arthritis. Twenty-six percent of the JRA-oligoarthritis and 14.5% of the JRA-polyarthritis subtypes could not be classified into corresponding named categories in the ILAR system, and the majority of them fulfilled the criteria for ERA (ILAR). It may be added that the ACR system allows RF positivity in the oligoarthritis category, which is otherwise a strict exclusion in the corresponding category of the ILAR system. Seven children (5.6%) in the ACR cohort, including the child with systemic JRA, were classifiable as UnA by the ILAR system.

However, the  $\kappa$  statistic showed good-excellent agreement between the 2 systems for classifying oligoarthritis ( $\kappa = 0.79$ ,  $p < 0.001$ ) and polyarthritis ( $\kappa = 0.87$ ,  $p < 0.001$ ).

**ESSG criteria<sup>5</sup>.** Eighty-seven children from the JIA cohort fulfilled the criteria of juvenile SSA (ESSG); 79% tested positive for HLA-B27. Only 74 children (85%) of the latter group were otherwise classifiable as ERA (ILAR), while those remaining fulfilled the requirement of other ILAR categories (persistent oligoarthritis 2, RF-negative polyarthritis 2, UnA 7, PsA 2). Nine children (11%) with ERA (Table 1) did not meet the ESSG criteria. However, there was good agreement ( $\kappa = 0.79$ ,  $p < 0.001$ ) between the 2 systems.

**The “second” 6-month period (postillness onset).** This period of illness was pivotal in subclassifying 4 children with oligoarthritis (Table 1); in the remainder, the extended pattern became visible much later (1–7 yrs). However, data collected during this period did not change the earlier classification category or clinical profile of the large majority of patients. The results of repeat serological testing (RF, ANA) in several children remained unchanged (data not shown). However, 3 children (2 boys) with an oligoarthritis pattern (and seropositive for RF) in the UnA group developed polyarthritis. Both boys in the latter group tested positive for HLA-B27 and recalled having chronic heel pains.

## DISCUSSION

In our study, 95% of the Indian children with chronic idiopathic inflammatory arthritis were classified into discrete JIA categories using the current ILAR classification system

**Table 2.** Reasons for failure to classify 11 patients out of a cohort of 235 with juvenile idiopathic arthritis into a discrete (possible) category and further classifying as undifferentiated arthritis, as per the ILAR classification system (Edmonton, 2001).

| Possible Category   | No. Patients | Cause of Exclusion/<br>Second Category    | No. Patients | Remarks                      |
|---------------------|--------------|---|--------------|------------------------------|
| OLA-P               | 4            | RF+                                       | 3            | All females                  |
|                     |              | RF+, HLA-B27+                             | 1            | Male, onset age $\geq 6$ yrs |
| OLA-E               | 5            | RF+                                       | 3            | All females                  |
|                     |              | RF+, HLA-B27+                             | 2            | Male                         |
| Systemic arthritis  | 1            | RF+                                       | 1            | Male                         |
| Psoriatic arthritis | 1            | HLA-B27+,<br>enthesitis-related arthritis | 1            | Male                         |

OLA: oligoarthritis; P: persistent; E: extended; ILAR: Internal League of Associations for Rheumatology.

Table 3. Comparing the subcategories in 160 children who met the classification criteria of juvenile rheumatoid arthritis (JRA; American College of Rheumatology criteria) from a cohort of 235 Indian children with juvenile idiopathic arthritis (ILAR classification system, Edmonton, 2001) with their earlier ILAR classification categories; 75 children from the cohort did not meet the criteria for JRA.

| Features/Subset               | Systemic Arthritis, n = 19 | OLA-P, n = 39 | OLA-E, n = 10 | Polyarthritis, RF-, n = 41 | Polyarthritis, RF+, n = 28 | Psoriatic Arthritis, n = 3 | Enthesitis-related Arthritis, n = 84 | UnA, n = 11 |
|-------------------------------|----------------------------|---------------|---------------|----------------------------|----------------------------|----------------------------|--------------------------------------|-------------|
| JRA systemic arthritis n = 19 | 18                         | 0             | 0             | 0                          | 0                          | 0                          | 0                                    | 1           |
| JRA OLA, n = 65               | 0                          | 38            | 10            | 0                          | 0                          | 0                          | 11                                   | 6           |
| JRA-polyarthritis, n = 76     | 1                          | 0             | 0             | 39                         | 27                         | 0                          | 9                                    | 0           |

UnA: undifferentiated arthritis; ACR: American College of Rheumatology; ILAR: International League of Associations for Rheumatology.

(Edmonton, 2001). This success was certainly more than what had been achieved earlier (80%–88%) by investigators using the ILAR Durban version<sup>12-17</sup>. This is probably the first report of a systematic evaluation of the current ILAR system in a large number of children with JIA in a community setting. We also report a wide phenotypic spectrum of Indian JIA, which also shows some unique clinical-immunogenetic features.

The earlier studies<sup>12-17</sup>, predominantly of people with white ethnicity, were mostly carried out retrospectively in tertiary hospitals several years after the onset of illness. Although not strictly comparable, we selected the Canadian<sup>13</sup> and the Spanish<sup>16</sup> studies to compare our results (Table 4) and highlight some differences that are likely to affect the utility of the ILAR system in our setting and may affect the current understanding of JIA.

ERA (current prevalence 35% vs 7%–13% reported earlier<sup>12-18</sup>) was the commonest JIA category in the current cohort. The age of onset of illness in the Indian cohort appeared comparatively higher for all ILAR categories except systemic arthritis. Whether this was a reflection of referral bias or a true difference was difficult to confirm. The children in the cohort with systemic arthritis showed few extraarticular features. The infrequent occurrence of ocular involvement in our cohort was consistent with some earlier Indian reports<sup>19-21</sup>, but for reasons described, could

be an underestimate. The frequency of seropositive RF in our patients was unexpectedly high. JIA subtype distribution may vary in different ethnic populations, and RF-positive JIA and ERA are likely to be more common in non-European populations<sup>22</sup>. The association of HLA-DRB1 with JIA may also differ in only this population<sup>23</sup>. In contrast, the frequency of seropositive ANA (by ELISA) in our cohort was strikingly low, as in earlier reports<sup>19</sup>. However, a recent prospective study<sup>24</sup> of children with early JIA has shown that chronic uveitis was associated with seropositive ANA, demonstrated by immunofluorescence and not ELISA, and that ANA by ELISA had no clinical significance. The incidence of HLA-B27 in each of the ILAR categories in our cohort (Table 1) was remarkably similar to that reported by Merino, *et al*<sup>16</sup>.

Intriguingly, 82% of the Indian children classified as UnA in this report also tested seropositive for RF. A higher proportion of children with ERA in the cohort were positive for HLA-B27. Infections, often subclinical, are rampant in our community and are linked with RF; they are also triggers for B27-related arthritis. It has also been postulated that childhood infections may be protective against inflammatory arthritis<sup>25</sup>. However, we have found a high prevalence of inflammatory arthritis in our community-based COPCORD studies<sup>11,26</sup>. The incidence of RF (cutoff value 40 IU/ml) in healthy adult urban and rural controls in our earlier studies

Table 4. A study of juvenile idiopathic arthritis classified by the ILAR classification system: comparing distribution (percentages) and selected features by category of 235 Indian children with Spanish<sup>16</sup> and Canadian<sup>13</sup> studies.

| Category                     | Indian study, n = 235<br>ILAR Edmonton 2001 |       |                |        | Spanish Study, n = 125<br>ILAR Durban 1997 |      |                |        | Canadian Study, n = 69<br>ILAR Durban 1997 |      |                |        |
|------------------------------|---|-------|----------------|--------|--|------|----------------|--------|--|------|----------------|--------|
|                              | Freq  | M:F   | Onset Age, yrs | ANA, % | Freq                                       | M:F  | Onset Age, yrs | ANA, % | Freq                                       | M:F  | Onset Age, yrs | ANA, % |
| Systemic arthritis           | 7.7   | 1.5:1 | 5.3            | 11.8   | 14.4                                       | 1:1  | 11.8           | 6      | 4.4  | 1:2  | 6.3            | 0      |
| Oligoarthritis, persistent   | 16.5  | 1:1.4 | 10             | 8      | 37.6                                       | 7:40 | 7.4            | 81     | 20.3                                       | 4:10 | 4.3            | 67     |
| Oligoarthritis extended      | 4.3   | 1:2   | 9.75           | 10     | —  | —    | —              | —      | 13   | 2:7  | 4.4            | 71     |
| Polyarthritis, RF-           | 17.4  | 1:1.6 | 11.5           | 16.7   | 22.4                                       | 6:22 | 9.2            | 57     | 21.7                                       | 1:2  | 6.5            | 54     |
| Polyarthritis, RF+           | 11.5  | 1:8   | 13             | 27.3   | 1.6  | 0:2  | 18.0           | 100    | 5.8  | 0:4  | 10.5           | 75     |
| Psoriatic arthritis          | 1   | 1:1   | 12             | 0      | 1.6  | 1:1  | 15.5           | 100    | 11.6                                       | 1:3  | 4.8            | 20     |
| Enthesitis-related arthritis | 35.3  | 9.4:1 | 13             | 7.4    | 7.2  | 8:1  | 16.6           | 0      | 11.6                                       | 3:1  | 11.8           | 0      |
| Undifferentiated arthritis   | 6.3   | 1:1   | 11             | 20     | 15.2                                       | 9:10 | 10.6           | 42     | 11.6                                       | 1:1  | 8.4            | 57     |

ILAR: International League of Associations for Rheumatology.

was 1.3% and 3.9%, respectively<sup>27,28</sup>. We do not have RF data on healthy children in our community.

Onset of arthritis after age 6 in a boy with HLA-B27 is a strong indicator for ERA in the current ILAR system and an exclusion for other categories. But HLA-B27 *per se* is not mandatory to classify ERA. We have reported HLA-B27 in 9% of healthy Indian subjects<sup>29</sup>. However, 16% of the children (either female or with onset of illness prior to age 6 yrs) in each of the ILAR categories of polyarthritis and oligoarthritis in our cohort tested positive for B27 (Table 1), but had very little if any enthesitis, inflammatory spine, and/or sacroiliitis. In a similar North American study of JRA, Cassidy, *et al* found no increased incidence of HLA-B27 in children with oligoarthritis and polyarthritis<sup>4</sup>. However, the logistics and value of testing serum RF and HLA-B27 in our setting do not seem to fit well into the current ILAR classification scheme.

The high level of statistical agreement between the ILAR system and other classification systems in our report is somewhat misleading. Although clinically oriented, the ACR system does not seem to suitably handle oligoarthritis, seronegative spondyloarthropathy, RF, and HLA-B27. Although the ESSG system is conceptually developed on an SSA platform, we were surprised to find mismatch with at least 10% of the children classified as ERA in the cohort. We found the ILAR system clinically more homogeneous. But a longer term of followup is required to assess the usefulness of the current ILAR system regarding therapeutic response and prognosis.

Several limitations in our study have bearing on the feasibility and application of the ILAR system. It was challenging, if not impossible, to pinpoint the precise date of onset of illness, including in the cases of children examined with early illness. Often we were frustrated by the insufficient case records and/or poor recall of the patient/parent. Several of the children lived in distant rural/underdeveloped areas with scanty medical facilities and poor access. We excluded several cases from the cohort because of lack of appropriate RF testing as required by the ILAR system, but it made little difference to the distribution of JIA categories in our community. A more recent European study reported that < 50% of cases of polyarthritis and < 35% of cases of oligoarthritis could achieve 2 RF reports, as the ILAR system specifies<sup>17</sup>. Eliciting family history of a HLA-B27-related disorder in our patients was problematic. Confirming the quotidian pattern of fever was more a matter of clinical judgment. We obtained firsthand evidence of serositis and/or organomegaly on imaging studies (e.g., ultrasonography) which is not part of the ILAR system. Detecting rash in dark-complexioned skin can be difficult.

A WHO ILAR COPCORD survey of 5998 people in a rural area recorded 774 cases of musculoskeletal aches and pains, with 28 cases (3.6%) belonging to the age group < 16 years (32% of the population were aged < 16 years)<sup>30</sup>. Five

cases (3 adults with childhood-onset) in that survey were clinically diagnosed as JCA<sup>30</sup>, which suggested a rural prevalence of about 1 per 1000 children. This compares well with the global situation<sup>31</sup> and is likely to mean a high burden of JIA in the Indian population.

We need larger population surveys and a classification system that predominantly depends upon clinical manifestations (systemic fever profile, pattern of peripheral arthritis, enthesitis, axial spine and/or sacroiliac joint involvement, extraarticular systemic features, and psoriasis) and routine laboratory discriminators (such as RF). We propose a 1-year observation period post-onset to confirm the JIA category. In a context of persistent arthritis more than 6 weeks beyond the onset of illness, a single seropositive RF result with a cutoff value of 80 IU/ml (at least in our community setting) within 1 year of onset may be considered sufficient for classification. We do not believe that HLA-B27 is mandatory to classify JIA, but it should be considered if the clinical profile, along with the RF results, do not support the diagnosis of systemic arthritis and polyarthritis. We propose that HLA-B27 be considered in a setting of oligoarthritis with overlapping features of ERA. HLA-B27 may not be a discriminator in a setting of PsA. It is also prudent to add that we still do not have longterm data to show the prognostic value of using HLA-B27 as a classification marker. This lack of data is also true of the role of RF and the current classification system.

In our community-based Indian cohort study, HLA-B27-related ERA was the most common disorder. Overall, a high incidence of RF also led to several cases being classified as UnA. We found the current ILAR system relevant and comprehensive, but several practice issues regarding the period of observation for diagnosis, RF (in particular seronegative inflammatory arthritis), ANA, and HLA-B27 need attention. The growing pains with the ILAR system are likely to last a little longer as it finds application worldwide<sup>32</sup>.

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