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COHORT STUDIES

Evaluation of disease activity in a low-income juvenile idiopathic arthritis cohort

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Abstract

Determine disease activity in a low income juvenile idiopathic arthritis (JIA) cohort. 164 JIA patients from families with less than US$ 4500.00/capita mean annual income followed in Fortaleza-CE, Brazil, were cross-sectionally evaluated between May 2015–April 2016. Mean age was 14 ± 5.1 years (95 female) with 10.31 ± 3.7 years disease duration. Polyarticular category predominated, with 63 (38.4%) patients, followed by 40 (24%) enthesitis-related (ERA), and 36 (22%) oligoarticular. All but 1 out of 84 parents declared less than US$ 10,000.00 annual family income. Eighty-eight (60.7%) were receiving methotrexate and 19 (13%) leflunomide including 12 (63%) using both; 46 (28%) were on biologic DMARD including 20 (43.5%) adalimumab, 17 (41.5) etanercept, 5 (10.8%) tocilizumab, 2 (4.2%) abatacept, and 1 (2.1%) each on infliximab and canakinumab. Mean CHAQ and JADAS27 were 0.36 ± 0.55 and 5.31 ± 8.5, respectively. Thirty-two (20%) out of 159 patients had deformities. A bivariate analysis revealed that polyarticular had more deformities than oligoarticular patients ($p = 0.002$; OR = 2.389; 95% CI 1.37–4.14). Logistic regression showed no association between high JADAS and family income ($p = 0.339$; OR = 1.45; 95% CI 0.67–3.31). A general linear model showed significantly lower CHAQ score in patients from families earning more as compared to those earning less than 300.00 US$ monthly ($p = 0.002$). This study reports JIA disease activity in a low income population. Low income apparently did not influence prognosis given the low mean JADAS27 and CHAQ scores vis-à-vis data from other cohorts.

Keywords Juvenile idiopathic arthritis · Epidemiology · Pediatric rheumatology

Introduction

Juvenile idiopathic arthritis (JIA) is the most frequent chronic arthropathy affecting patients less than 16 years-old and girls are the predominant gender. The prevalence in white Caucasians varies from 0.07 to 4.01/1000 children and there is scant data concerning JIA prevalence in low income patients, including those from Latin America [1, 2]. A study conducted in São Paulo, Brazil estimated that JIA accounts for more than 30% of new cases seeking pediatric rheumatologists [3] and JIA prevalence in a small city in the State of São Paulo, Brazil was estimated at 0.34/1000 children [4]. Environmental factors related to regional differences were shown to influence incidence and prevalence as well as JIA outcome [5]. Health inequities, meaning differences among populations based on economic status, are considered to represent a major factor in disease burden given that low income leads to unfavorable health conditions. Additionally, sick people usually have their socioeconomic status worsened thus creating a vicious cycle particularly in less developed regions [6, 7]. Usually, data concerning Latin-America do not take into account geographical, political, and economic heterogeneity among countries, not to mention differences

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within countries [8]. For instance, the mean GDP/capita in the state of Ceará, northeast of Brazil, where the present study was conducted, is US$ 4398.00 as compared to US$ 13,093.00 in the state of São Paulo, southeast of Brazil [9]. However, studies reporting data of JIA patients seen in São Paulo, Brazil, such as those included in the PRINTO cohort, may inadvertently be considered to reflect the reality of the whole country [10]. Latitude variation in this subcontinent that spans over 60° carries geographic and socioeconomic issues that may impact disease prevalence as well as access to health care [2, 8]. Notwithstanding, there is a paucity of JIA data on patients living in low latitude and recent data have shown that developmental status, geographic and geomagnetic location influence the age of onset of rheumatoid arthritis [10–13]. Treatment strategy aims for disease remission in JIA, an ill-defined and hard to achieve disease state in clinical practice. However, low disease activity (LDA), a state of feasible, clinically acceptable outcome, has been previously defined, using data from international cohorts [14]. To our knowledge, there are no studies measuring disease activity in JIA patients specifically from low income populations. Our objective was to determine disease activity in a JIA cohort followed in Fortaleza, State of Ceará, Brazil.

Methods

Clinical and demographic data from 164 patients with a diagnosis of JIA according to the International League of Associations for Rheumatology (ILAR) [14] seen at the rheumatology outpatient clinics of the Hospital Universitário Walter Cantídio (HUWC) of the Faculty of Medicine of the Universidade Federal do Ceará and Hospital Geral de Fortaleza (HGF), in Fortaleza, CE, Brazil, between May 2015 and April 2016, were cross-sectionally collected. The clinical protocol was approved by both HUWC and HGF Ethics Regulatory Committee that follow the rules of the Brazilian National Ethics Committee on Clinical Research (CAAE 72914316.4.3001.5045). All patients or their responsible relatives signed an informed consent before any intervention.

A clinical chart was filled for each patient registering demographic data, clinical evaluation with complete physical examination, rheumatoid factor, and antinuclear antibody test results, and current Disease Modifying Anti-Rheumatic Drug (DMARD) treatment. Parents or relatives were asked about mean monthly family income using October 2017 as reference for the conversion of Brazilian to US$ currency, as follows: less than 300.00 US$, between 300.00 and 900.00 US$, and above 900.00 US$. BMI was calculated as weight/squared height (kg/m^2). Cross-sectional disease activity measurement was done using the Juvenile Arthritis Disease Activity Score (JADAS) 27 [15] that considers physician global assessment of disease activity [0–10 cm visual analog scale (VAS)], parent global assessment of child's well-being (0–10 cm; VAS), number of joints (0–27) with active disease, and erythrocyte sedimentation rate (ESR), providing a total score of 0 to 57 where high scores mean high disease activity. A Portuguese version of the CHAQ was used for the evaluation of functional status [16]. LDA, moderate disease activity (MDA), and high disease activity (HDA) were determined as defined previously for oligoarthritis and polyarthritis category patients, considering cJADAS meaning JADAS value without the acute phase reactant (ESR) result. Cut-off values were <1.5 and <2.5 for LDA, between 1.51 and 4 and 2.51 and 8.5 for MDA and >4 and >8.5 for HDA in oligoarthritis and polyarthritis, respectively [17]. The number of children with joint deformities, that we defined as an irreversible damage to the anatomic structure and/or function that interfered with joint range of motion that could be attributed to the JIA [11], was also recorded.

Statistics used descriptive analysis for demographics and outcomes using means $\pm$ SD or medians and interquartile range (IQR), as appropriate. Dichotomous variables were expressed as absolute and percent values. Assessment of normality of continuous data was done using the Kolmogorov–Smirnov test. Differences between means were evaluated using Student's *t* test; dichotomous data were evaluated using Chi-square or Fisher's exact (when needed) test. Disease outcome using CHAQ scores were also analyzed using bivariate logistic and linear regression models. A general linear model after adjustment of family income, JADAS and CHAQ scores to natural logarithms was also analyzed. No imputation was done for missing data. The level of significance was set at 0.05. Sample size, entering of data, and data analysis were done using SPSS v17, SPSS Inc.

Results

Table 1 displays demographic and clinical data of 164 JIA patients evaluated. Mean age was 14 ± 5.1 years with predominance of female patients. There were 63 (38.4%), 40 (24%), 36 (22%), 20 (12.1%), 4 (2.5%), and 1 (0.6%) patients classified as belonging to the polyarticular, enthesitis-related (ERA), oligoarticular, systemic, undifferentiated, and psoriatic JIA categories, respectively. Mean disease duration was 10.31 ± 3.7 years. Fifty-seven (70%) out of 81 patients tested for rheumatoid factor were negative. Among the 24 (30% of the tested sample) that tested positive for rheumatoid factor all but 2 were of the polyarticular category meaning that 22 (34.9%) out of the 63 patients pertaining to the polyarticular category were rheumatoid factor positive. Conventional non-biologic DMARD (cDMARD) use comprised 87 (53%) patients receiving methotrexate and 19 (11.6%) on leflunomide. Among those on leflunomide, there were 12 (63%) with concomitant methotrexate. Biologic

Table 1 Clinical characteristics of low income 164 juvenile idiopathic arthritis patients

Demographics	
Female [*n* (%)]	95 (58)
Age (years), mean (SD)	14 (5.12)
BMI, mean (SD)	21.2 (5.07)
Normal [*n* (%)]	58 (58)
Underweight [*n* (%)]	6 (6)
Overweight [*n* (%)]	20 (20)
Obese [*n* (%)]	16 (16)
JIA category [*n* (%)]	
Polyarthritis, RF^-	41 (25)
Polyarthritis, RF^+	22 (13.4)
Oligoarthritis, persistent	29 (17.7)
Oligoarthritis, extended	7 (4.3)
ERA	40 (24.4)
Persistent	29 (80.6)
Extended	7 (19.4)
Systemic	20 (12.1)
Undifferentiated	4 (2.5)
Psoriatic	1 (0.6)
Disease duration (years)	10.31 ± 3.7
JADAS27, mean (SD)	5.31 (8.5)
Disease activity [*n* (%)]	
Low disease activity	51 (58.6)
Moderate disease activity	22 (25.3)
High disease activity	14 (16.1)
CHAQ, mean (σ)	0.36 (0.55)
RF positivity [*n* (%)]	24 (29.6)
ANA positivity [*n* (%)]	5 (16.1)

Data represent mean (%) of 164 patients, except for rheumatoid factor and antinuclear antibodies where data are n(%) of tested patients

ANA antinuclear antibody, *BMI* body mass index, *CHAQ* childhood health assessment questionnaire, *JIA* juvenile idiopathic arthritis, *JADAS* juvenile arthritis disease activity score, *RF* rheumatoid factor, *SD* standard deviation

DMARD (bDMARD) was being used by 46 (28%) of the patients including 20 (43.5%) on adalimumab, 17 (37) on etanercept, 5 (11%) on tocilizumab, 2 (4.3%) abatacept, and 1 (2.1%) each on infliximab and canakinumab. Monthly family income was obtained from 84 (51%) parents or relatives comprising 27 (32%) declaring less than 300.00 US$, 56 (66%) earning between 300.00 and 900.00 US$, and only 1 (1%) declaring more than 900.00 US$ earnings.

Assessment of disease severity at the time of evaluation revealed a mean total CHAQ score of 0.36 ± 0.55 and mean JADAS27 of 5.31 ± 8.5. Specifically, patients classified in the polyarticular category had a nonsignificant trend towards higher mean CHAQ scores (0.55 ± 0.69) as compared to those of the oligoarticular (0.3 ± 0.4) category ($p = 0.12$). Additionally, patients of the polyarticular category displayed significantly higher mean JADAS27 (5.0 ± 5.9) as compared to those of the oligoarticular category (2.96 ± 3.83; $p = 0.038$). Thirty-three (61%) and 18 (54%) of polyarticular and oligoarticular category patients had LDA, respectively ($p = 0.54$), based on previously proposed cut-off values using JADAS data [1]. Seven patients in polyarticular (21.2%) and oligoarticular (13%) categories each were considered with high disease activity ($p = 0.3$).

Table 2 Juvenile idiopathic arthritis activity in a low income population

Variable	Family income < 300.00 US$	Family income > 300.00 US$	OR (95% CI);[!]*p* value
Polyarticular	18 (46.2)	21 (53.8)	0.5 (0.22–1.11); [!]0.09
Oligoarticular	9 (25.7)	26 (74.6)	
CHAQ[a]	0.125 (0–0.625)	0 (0–0.625)	[!]0.002

Bivariate analysis considered presence of permanent deformities and predominant disease categories compared to monthly family income. Data represent *n* (%) of patients

OR odds ratio, *IQR* interquartile range, *CI* confidence interval

[a]*CHAQ* childhood health assessment of questionnaire (median; IQR range) analysed with general linear model after normalization of variables with logarithms

Thirty-two (20%) out of 159 patients evaluated were considered to present permanent deformities, including 18 polyarticular, 5 systemic, 4 oligoarticular, 4 ERA, and 1 of undifferentiated category. Disease severity seemed worse in patients with permanent deformities given that mean CHAQ was 0.721 ± 0.76 as compared to 0.26 ± 0.42 mean CHAQ in those with no deformities ($p = 0.0019$) whilst JADAS-27 scores were 8.17 ± 13.51 in the former as compared to 4.69 ± 6.86 mean in the later group ($p = 0.0259$).

In a bivariate logistic analysis, patients of the polyarticular category had significantly more deformities, as compared to oligoarticular patients (OR = 2.389; 95% CI 1.378–4.141; $p = 0.002$). Table 2 shows a tendency of patients from families earning more than 300.00 US$ monthly to be of the oligoarticular category, but the difference did not reach significance (OR = 0.5; 95% CI 0.22–1.11; $p = 0.09$). Analysis using a general linear model after adjustment of the variables to natural logarithm showed that patients from families earning less than 300 US$ monthly had significantly ($p = 0.002$) higher CHAQ scores (median = 0.125; IQR 0.625) as compared to those from families earning more than 300.00 US$ monthly (median = 0; IQR 0.625), as shown in Table 2. A logistic regression analysis did not find an association between having a high JADAS and family income (OR = 1.45; 95% CI 0.67–3.31; $p = 0.339$).

Discussion

We describe a cohort of low income JIA patients living in a low latitude region of Latin America. Comparing to the Pediatric Rheumatology International Trials Organization (PRINTO) the average age of our patients was very similar to worldwide data with a lower percentage of females (58%) as compared to the 70% prevalence in the PRINTO cohort [10]. Patients classified in the JIA polyarticular category were predominant in our sample, followed by those of ERA and oligoarthritis categories. Compared to the PRINTO cohort, we had more patients classified as being polyarthritis and ERA [10] whilst our predominance of polyarthritis patients is similar to that reported in the Childhood Arthritis and Rheumatology Research Alliance (CARRA) registry [18]. Our increased prevalence of patients classified in polyarthritis category is similar to a recently reported study focusing on mothers' exposure to smoking and air pollution as risk factors in JIA done in São Paulo, Brazil [19].

Concerning disease severity, our data may look surprising as mean CHAQ scores were lower than those reported in the PRINTO cohort [10], particularly if we consider that patients classified as being polyarthritis that usually carry worse prognosis were more prevalent in our cohort. Mean CHAQ scores of 0 were previously associated to children with no disability whereas those with CHAQ below 0.13 would have mild disability [20]. Our cohort has relatively long disease duration and present low mean CHAQ scores. Even when data were split based on number of patients from families earning more or less than 300.00 US$ monthly, median CHAQ scores were either 0 in the former or 0.125 in the later group, meaning that most patients could be considered as presenting mild disability. Thus, despite the predominance of patients classified in the polyarticular category and a very low mean family income one may consider that patients display a favorable prognosis. Recent data from the CARRA registry that includes patients solely from the United States of America reported a median CHAQ value of 0.125 (range 25–75%; 0–0.625) which is slightly higher than our zero (range 25–75%; 0–0.625) median CHAQ score [18]. Income data from the CARRA registry were not reported but the fact that two-thirds of those patients had private insurance suggests a wealthy group as compared to our patients that are served by public health care since they cannot afford private insurance. Although only 51% of the parents of our sample agreed to declare family income, at least half of the patients belong to families earning less than US$ 10,000.00 yearly. Despite our attempt to categorize our patients considering family income, the whole sample actually comprises a very low income population. We are not aware of data on family income in JIA patients. However, juvenile dermatomyositis (JDM) data from the CARRA registry showed that only 13.7% of the families declared annual earnings of less than US$ 25,000.00 and patients from families earning less than US$ 50,000.00 had a tendency to have more calcinosis, used as a marker of JDM morbidity [21].

One may argue that PRINTO covers patients from roughly every region of the globe and, as such, data from underdeveloped countries may have contributed for higher CHAQ scores in that cohort. However, 66% of JIA patients included in PRINTO were from developed countries. Moreover, although 486 (15.3%) Brazilian patients were included in PRINTO, there were no patients from rheumatology services of the northern poorer regions of Brazil [10].

We had only 13% and 21.2% of our patients classified in the oligo and polyarticular categories, respectively, that could be considered in high disease activity [17]. Our relatively low mean JADAS27 scores and the fact that approximately 80% of our patients classified as being oligo and polyarticular did not present high disease activity do also suggest a more benign JIA course.

We had a relatively low percentage (28%) of patients using bDMARD vis-à-vis data from other studies [10, 18], notably when we consider that most of our patients were of classified as being polyarticular category. As recommended [22], it is our current practice to try to achieve disease remission. The predominant health system in Brazil is public and all DMARD compounds are available at no direct cost to the patient, at rheumatologist's scrutiny. Hence, we have no formal limitation to indicate bDMARD [2]. Treatment comparisons among different cohorts are hard to be made but it is worth remarking that 60% of our patients were on isolated methotrexate. As a comparison, 47% of JIA patients from the recently reported CARRA registry were using methotrexate at the time of evaluation. Moreover, those on methotrexate and leflunomide, either isolated or combined, comprised 65% of our cohort as compared to 57% of patients of the CARRA registry treated with those compounds. Additionally, we had 28% of our patients on bDMARD as compared to 50% of patients of the CARRA registry on current bDMARD use, either isolated or combined to conventional DMARD [18].

Our study has some limitations, including the fact that the number of patients, although representing probably the largest cohort of low income JIA patients ever reported, are fairly low as compared to international cohorts. We also did not capture the time of disease evaluation, the proportion of patients with inactive disease as well as other long term damage data such as growth retardation and organ failure that can also be influenced by family income. In addition, we were not able to collect all data from all patients, thus limiting comparisons across JIA categories. However, despite

limitations, our cohort captures patients seen in the two specialized local public services that cover more than 85% of a low-income population of over 8500.000 people living in low latitude, providing the largest report of original JIA data under these circumstances.

The present data add to the larger PRINTO and CARRA cohorts, revealing some singularities of the outcome of JIA patients in this region of the globe. One cannot claim being poor as an advantage. In fact, although all patients can be classified as belonging to low income families, those of lower earnings had significantly higher CHAQ scores. The apparently benign prognosis lead us to speculate that environmental issues yet to be clarified contribute to the low CHAQ values found in this low income cohort.

Author contributions FACR and CNRJ conceived the article. FACR, JIVDL, LNR and HALR performed tabulation of data and statistics. JIVDL, MGA, JPEA, CNL, LHAC, LNR performed data collection, revision of clinical files, interviewed and applied questionnaires to patients/parents. All authors participated in the preparation and revision of the manuscript, read and approved the final version to be submitted.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no competing interests.

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