

Change of diagnosis and diagnostic category in patients with juvenile idiopathic arthritis

Cambio de diagnóstico y de categoría diagnóstica en pacientes con artritis idiopática juvenil

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What do we know about the subject matter of this study?

Juvenile idiopathic arthritis (JIA) with onset before the age of 16 can progress into adulthood presenting flare-ups and sequelae, even with timely and effective treatment, requiring organized transition, monitoring, and regular therapy adjustments.

What does this study contribute to what is already known?

JIA can be associated with other autoimmune diseases. There are different risk factors between rural and urban populations, individuals, and places with different access to specialized health care. Frequent monitoring of pediatric and post-transition management is essential.

Abstract

At least 50% of pediatric patients with Juvenile Idiopathic Arthritis (JIA) will require continued follow-up in adult rheumatology. The present International League of Associations for Rheumatology (ILAR) classification, currently under revision, differs from its classification of inflammatory arthritis in adults. Category changes have been reported in 10.8% of patients during follow-up. **Objective:** To analyze JIA patients in follow-up for at least 7 years to detect diagnosis changes during transition to adult care, identifying factors of poor functional prognosis. **Patients and Method:** Retrospective study based on medical records of JIA patients seen at the pediatric polyclinic of the Puerto Montt

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Hospital between 2005 and 2017, who were monitored for at least 7 years. Descriptive analysis was performed according to clinical variables: diagnostic category, evolution before diagnosis, clinical and serological activity, and evolution before starting drug therapy. **Results:** We evaluated 18 patients, corresponding to 3 patients with persistent oligoarticular arthritis (OA), 1 with extended OA, 4 with polyarticular arthritis (PA) rheumatoid factor (RF) negative, 4 with PA RF positive, 5 with systemic JIA, and 1 with psoriatic arthritis, all have had follow-up more than 7 years. 11 out of 18 patients transitioned to adult care. Three out of 11 patients changed diagnosis to Rheumatoid Arthritis (RA) plus another autoimmune disease such as Sjögren's Syndrome + Systemic Lupus Erythematosus, Immune thrombocytopenia, or unclassified autoimmune disease, and 5 out of 11 children changed ILAR category from OA to Juvenile Rheumatoid Arthritis, extended OA to PA RF negative, and 3 from Systemic arthritis to PA RF negative. Age of onset, polyarticular forms, delay in diagnosis, and the start of therapy were associated with sequelae and persistent inflammation. **Conclusions:** Eight of the eleven JIA patients who transitioned to adult care changed their diagnosis or presented other autoimmune diseases. Some factors of poor prognosis must improve.

Introduction

Juvenile idiopathic arthritis (JIA) is the most common pediatric rheumatic disease. It is characterized by joint inflammation of more than 6 weeks, of unknown cause, and onset before age 16. The following are the 7 mutually exclusive categories: Persistent or extended oligo-articular arthritis (OA), rheumatoid factor-positive, or -negative (RF) poly-articular arthritis (PA), psoriatic arthritis, enthesitis-related arthritis (ERA), systemic JIA, and undifferentiated. These categories are defined in the first 6 months of evolution, based on clinical parameters such as the number of affected joints, presence of specific antibodies, enthesal involvement, and association with psoriasis and systemic inflammation¹⁻³, which are partially related to joint prognosis and it is believed that they would have different etiopathogenesis and genetic basis⁴. Its incidence is between 2 and 20 cases per 100,000 children, with wide geographical distribution¹⁻⁴. In Chile, it presents an estimated prevalence of 10 cases per 100,000 children under 16 years of age. The 2010 International League of Associations for Rheumatology (ILAR) classification is currently under review both in the number of categories and the clinical characteristics that define them, and in matters related to adult autoimmune arthropathies such as seropositive or seronegative rheumatoid arthritis (RA), Still's disease, and spondyloarthropathies, including psoriatic arthritis.

The objective of this work is to present the data related to the initial classification of patients with JIA under follow-up for more than 7 years, to detect the change in diagnostic after transfer to adult rheumatology, and to analyze the factors of inflammation and sequelae persistence in our cohort, which will contribute to designing strategies to improve our clinical procedures and the transition process.

Patients and Method

Design

A retrospective study based on clinical records. We included all patients with JIA seen at the pediatric polyclinic of the *Hospital de Puerto Montt* (HPM) between 2005 and 2017, who completed seven or more years of follow-up (18 patients).

Variables analyzed

A descriptive analysis based on clinical variables such as diagnostic category, time to diagnosis, clinical and serological activity, and time to evolution at the beginning of drug therapy.

Statistical analysis

The qualitative variable (diagnostic category) was expressed in absolute numbers and the quantitative one (time of evolution at the beginning of treatment) was expressed by its mean and standard deviation. The groups were compared through mean differences using the Student's T-test with a $p < 0.05$ value considered as significant.

Ethics

The study was approved by an accredited scientific ethics committee and informed consent was applied.

Results

18 out of 42 patients aged 7 years and older (range 8-14 years) diagnosed between 1998 and 2011, seen at the HPM between 2005 and 2017, were followed-up at the HPM. According to the ILAR classification, 3 patients presented OA, 1 patient extended OA, 4 patients RF-negative PA, 4 patients RF-positive PA, 5 patients

Table 1. Distribution according to diagnosis

Initial diagnosis		Diagnosis after 7 years	
Category	n	Category	n
Persistent OA JIA	3	OA JIA	2
		JRA	1
Extended OA JIA	1	PA JIA RF negative	1
PA JIA RF positive	4	PA JIA RF positive	3
		RA + Sjödren Syndrome + SLE	1
PA JIA FR negative	4	PA JI ARF negative	3
		RA + ITP	1
Systemic JIA	5	Systemic JIA	1
		JIA PA RF negative	3
		RA + Unspecified Autoimmune Disease	1
Psoriatic JIA	1	Psoriatic JIA	1
Undifferentiated JIA	0		
Total	18	Total	18

JIA: Juvenile Idiopathic Arthritis, OA: Oligoarticular, PA: Polyarticular, RF: Rheumatoid Factor, JRA: Juvenile Rheumatoid Arthritis, RA: Rheumatoid Arthritis, SLE: Systemic Lupus Erythematosus, ITP: Immune Thrombocytopenic Purpura.

systemic JIA, and 1 patient psoriatic arthritis. There were no patients with undifferentiated JIA. Only one of the three patients with OA presented uveitis.

Of the 18 patients with follow-up, 11 were transferred to adult health care. Eight of these patients under follow-up in adult rheumatology changed their classification, three of them to RA plus another autoimmune pathology, and five of them to a category of the ILAR classification (Table 1).

Four out of 7 non-transferred patients presented full remission before transition age, two children under 15 years old presented clinical and serological remission using Tocilizumab (TCZ) after non-response to 2 previously administered anti-TNF (Etanercept and Adalimumab), and a 19-year-old patient who continued in follow-up with pediatric immune-rheumatologist of the referral center due to parental refusal to transition and with approval from the treating physician.

Regarding the initial classification, the current clinical status of the 18 patients is as follows: 5 are in remission without treatment and sequelae; 3 with OA, 1 of them with psoriatic arthritis, and the other one with pure systemic arthritis. One patient diagnosed with systemic arthritis associated with unclassified autoimmune disease is in remission without treatment but with sequelae. Three patients with systemic arthritis and polyarticular involvement are in remission with treatment but with chronic joint damage. Three patients with RF-negative PA are in remission with

Table 2. Current condition of 18 patients after 7 years of evolution

Remission	Without treatment	Without sequelae	5
		With sequelae	1
	With treatment	Without sequelae	3
		With sequelae	3
Active	Without sequelae	3	
	With sequelae	3	
Total			18

treatment and no sequelae to date. Out of the 18 patients, 3 presented RF-positive PA, one of them with Sjödren's syndrome, and 3 with RF-negative PA, one of them with idiopathic thrombocytopenic purpura (ITP), all with active disease and treatment. Seven of the 18 patients have arthrosis (Table 2).

Factors associated with activity and presence of sequelae were: polyarticular forms and excessive time of evolution (longer than 3 months) before methotrexate (MTX) and biological therapy. However, considering the late administration of treatment and the small number of patients, these differences did not prove to be statistically significant (Table 3).

Table 3. Current condition after 7 years according time of evolution from the start of pharmacological therapy

Start of Methotrexate: 14 months (SD ± 12 m)	p = 0,3	Start of Methotrexate: 22 months (SD ± 28 m)	p = 0,3
Start of Biologics: 5,8 years (SD ± 3,3 y)	p = 0,8	Start of Biologics: 5,4 years (SD ± 3,9 y)	p = 0,8
REMISSION (n = 12)		ACTIVITY (n = 6)	
Start of Methotrexate: 11 months (SD ± 11 m)	p = 0,3	Start of Methotrexate: 22 months (SD ± 24 m)	p = 0,3
Start of Biologics: 4 years (SD ± 2,1y)	p = 0,4	Start of Biologics: 7 years (SD ± 3,8 y)	p = 0,4
WITHOUT SEQUELAE (n = 11)		WITH SEQUELAE (n = 7)	
SD: Standard dev			

In the case of the patient with a positive OA anti-nuclear antibody (ANA) form who developed uveitis and its complications, the factors that influenced were the age of onset (under 2 years), delay in diagnosis and start of disease-modifying therapy (DMARD), initiation and continuity of biological therapy before the GES program, and the lack of response to 3 anti-TNF (Etanercept, Adalimumab, and Infliximab) and a selective T lymphocyte co-stimulation modulator (Abatacept).

Discussion

Knowing the evolution of our patients with JIA and the risk factors of sequelae, such as the current subtypes, including the diagnosis made after the transition to adult rheumatology, is important to improve our care processes, along with systematically including advances in knowledge and earlier and more effective therapies.

Before the clinical guidelines and the country health benefit program called “Explicit Health Guarantees” (*garantías explícitas de salud*, GES), juvenile rheumatoid arthritis (JRA) was the generic diagnosis. There were few specialist physicians, concentrated in the regions of Valparaíso, O’Higgins, El Maule, Bío-Bío, Araucanía and the Metropolitan Region of the country⁵, and some patients were probably treated too late, inadequately or not considering the most modern therapy options, a situation described in other countries⁶.

In November 1998 the US Federal Drug Administration (FDA) approved the use of Etanercept for treating RA, and in May 1999 for polyarticular JIA. Other biological drugs have subsequently appeared, with the potential for improvement and/or total or partial remission of the disease⁶⁻¹⁰.

In Chile since 2010, patients with JIA in the public and private health systems access the GES program

with the pathology No. 63 which adopts the name of JIA, classification ILAR, clinical guide, and biological drugs. In 2014, this guide was updated by pediatric rheumatologists¹¹. Based on this classification, which is still in force, we had already demonstrated that in our HPM total JIA population reported in 2018, the RF-negative PA phenotype was the most frequent (33%) and the RF-positive PA category reached 17%¹², unlike other regions of Chile and western countries where the OA form predominates^{11,13}, but similar to other countries such as Sweden, South Africa, Germany, India, and New Zealand^{7,14}. However, this difference from national data may be due to underdiagnosis of the OA forms.

Our estimated incidence between 2005 and 2015 ranges from 0-4.9 cases in 100,000 children per year, which also suggests underdiagnosis in our region. It would be important to know the current national incidence and prevalence, along with the most frequent phenotypes in different regions of the country, which may differ the phenotypes previously reported, preferably based on the population of the Metropolitan Region^{11,13}.

In 2011, Nordal et al. in a long-term follow-up of patients with JIA reported 10.8% of changes in the initial category in their cohort and persistence of inflammatory activity¹⁵, which motivated us to study our cohort.

The subtype of JIA has been associated, among other factors, with difficulty in achieving remission, where the RF-positive or -negative PA, ERA, and systemic forms with polyarticular involvement persisting with inflammation. 50%-60% of the patients with some of these subtypes are transferred to adult rheumatology¹⁵⁻¹⁷. It has also been described that the clinical evolution of patients with JIA is variable and unpredictable, even within the same subtype¹⁵. The OA forms have the best evolution and the highest remission rate¹⁵⁻¹⁸, as we can see in this group of patients. The exception is the patient with early-onset, aged 1

year and 6 months, positive ANA, late diagnosis due to no specialist physician, early development of uveitis, and access to late and irregular biological therapy at the beginning when the GES program did not exist, which conditioned poor functional joint and ocular prognosis.

Regarding the functional prognosis, Wallace et al. in 2012 and Albers et al. in 2010 have proposed as ideal management of JIA, to achieve remission or at least minimal inflammation before the first two years of the disease, avoiding chronic pain and reducing functional disability¹⁹⁻²⁰, which has not been met in the HPM-followed cohort. In 2010, Albers et al. have indicated that the most significant factor predicting disease activity in subsequent years is the time with active disease during the first 2 years with the disease, where predictors of flare-ups are increased PCR or ESR, polyarticular development, and no response to methotrexate therapy²⁰.

Before 2010, as in other reported cases, our patients were treated with different schemes and the delay in both diagnosis and the start of treatment as identified in the results (Table 3) conditioned a high rate of sequelae resulting from poor knowledge of the disease in pediatrics, lack of clinical guidelines with access to effective therapies, and no local pediatric rheumatologist or immunologist.

In different countries, access to biological medicines has not been equal, nor has the form of use⁶, which has also been the case in Chile, especially in regions. Since 2010, some patients have had access to effective, relatively timely therapy, including biological drugs, however, others have not received it or have started late (Table 3).

Other non-biological factors detected in our population are poor knowledge of the disease in primary health, delay in diagnosis due to demographic and organizational reasons, accessibility to specialized physicians, delay in immune-rheumatological and imaging tests such as ultrasound, delay of immunizations before starting disease-modifying anti-rheumatic drugs (DMARDs) administration, availability and timeliness of DMARDs including biologicals ones, and access, quality and persistence of rehabilitation. All these factors were specified in the 2018 report¹² which can be modified with education and planning.

Our casuistry is small compared with international publications, and the number of patients who meet the transition age and live in a given geographical area is even lesser, therefore, we cannot collect results of statistical significance. However, the follow-up of our patients shows that a significant number of them present inflammation, treatment, and/or sequelae at the age of transfer to adult rheumatology.

Despite the extensive international experience in structured transition programs that address this and

other particular issues of adolescence such as pregnancy prevention, tobacco, alcohol, and other substance use, exercise and sports, normal or abnormal psychological changes and peer relationships²¹⁻²⁷, to our knowledge, there is no data on a transition program of JIA in Chile and, in our region, we have not yet implemented a formal transition program. The only criteria used in our hospital for transfer are the persistence of symptoms or absence of remission, age over 17 years, and lack of rheumatologist or immunologist or pediatrician trained in rheumatology in some periods. The transfer has been carried out in the consultation, without prior knowledge of patients and adult rheumatologists, which contrasts with the European League Against Rheumatism (EULAR) recommendations published by Foster et al. 2016²⁶ and updated by Conti et al. 2018²⁷.

Some adult rheumatologists have not previously seen patients with JIA, which is also the case in other countries, thus some patients are diagnosed immediately after transfer according to the adult classification of inflammatory arthropathies, mainly RA²⁸⁻²⁹. This, plus the evolution towards other autoimmune diseases, has changed the diagnosis of 8 out of 11 transferred patients. Some of these changes were expected, such as other autoimmune diseases, and others evidenced the lack of a structured transition program that contemplates the conjoint health care of patients during the transition period, maintaining the JIA classification after the transition to adult care, as reported in published transition experiences, which means maintaining the benefits of access, timeliness, and treatment of a pathology guaranteed by law in our country.

The JIA drug set of the GES program has progressively incorporated biological drugs such as etanercept in 2010, adalimumab and infliximab in 2012, and tocilizumab in 2019 for systemic and PA forms that do not respond to treatment with methotrexate and anti-TNF.

Since 2007 (last update MINSAL 2014), RA is the 52nd pathology of the GES program. The national clinical guidelines for JIA and RA differ in the type of patients included, since RA only considers PA forms with high/strong or low/weak positive or negative RF or anti-citrullinated protein antibody (ACPA), and does not include enthesitis-related arthritis, OA, systemic, and psoriatic forms which are considered within the differential diagnosis, categories that are included in the ILAR classification of JIA. The time and type of biologics used also differ in the treatment schemes, especially DMARDs (guidelines 52 and 63 GES MINSAL).

Despite that adult psoriatic arthritis and spondyloarthritis are not included in the GES program, there are biologics drugs available through the high-cost

drug law. Regarding the different therapy guidelines for chronic inflammatory joint diseases in adults and children under 17 years of age, differences in drug use have been detected between the populations with JIA classification RF-positive or -negative PA and RA, systemic JIA and Still's disease, psoriatic JIA, and adult psoriatic arthritis, and between enthesitis-related arthritis and spondyloarthritis, with a higher prevalence of TNF, IL-1 and IL-6 inhibitor use in the pediatric population and exceptional use of hydroxychloroquine and azulfidine in children^{6,28,29}, which is reflected in the pediatric care of our patients and in the transition. Therefore, it is important to maintain the name JIA and the corresponding phenotypes after the transition, thus patients can access therapies for JIA assured by the GES program throughout their evolution.

Different researchers highlight the lack of agreed treatment guidelines for JIA adult arthropathies²⁶⁻²⁹. Recent publications critically analyze the ILAR classification of JIA and the adult arthropathies, pointing out that it is necessary to review and update this classification, considering advances in genetic and pathophysiological knowledge, as well as clinical follow-up studies of JIA patients. These studies have shown great concordance between JIA RF-positive PA and seropositive RA, so they would be the same chronic autoimmune arthropathy manifested since childhood^{30,31}. In addition, similarities in symptoms and systemic signs of inflammation and absence of autoantibodies between systemic JIA and Still's disease have been reported, therefore suggesting that both are the same inflammatory disease at different stages of development^{32,33}. Also, the common factors, enthesal involvement, and association with HLA-B27 antigen between ERA and spondyloarthritis have been analyzed as well as the differences related to the predominance of JIA of the axial or peripheral joints, where the latter is more frequent in pediatric age³⁴.

Despite some researchers maintain that positive JIA OA ANA form would be an exclusive or preferential phenotype of childhood³⁵, in 2018, Nigrovic et al. questioned this idea³⁶. It has been suggested that, in the absence of dactylitis or enthesal involvement, psoriasis in the patient or her/his immediate family members as the only element would not be a useful tool to designate the phenotype of psoriatic arthritis according to the ILAR classification of JIA³⁷.

Recent publications on A, including juvenile PA, confirm the link with adult spondyloarthritis³⁸. Therefore, it has been proposed to decrease the ILAR classification from 7 to 4 subtypes^{36,39}, and even to 3 categories⁴⁰ which would allow to standardize therapy and follow-up criteria from the pediatric age onwards, decrease diagnostic changes and probably optimize treatment and follow-up. At the moment, we should

maintain the current JIA classification and transfer our patients to adult rheumatology with the respective denomination, in the best possible conditions regarding the persistence of inflammation and sequelae, in a structured transition process according to the recommendations of EULAR²⁶.

Finally, it seems fundamental the presence and equitable distribution of pediatric rheumatology specialists in the regions of the country, training on these diseases in the primary health, the standardization of treatment guidelines that timely incorporate advances in their non-pharmacological and pharmacological management, and the periodic evaluation of inflammation activity with the available tools such as the visual analog scale for pain, inflammation and sense of well-being for the patient, her/his family and physician, the juvenile arthritis disease activity score (JADAS) or the disease activity score (DAS), specific quality of life questionnaires (CHAQ), HSV and PCR tests, and a patient-centered approach from childhood onwards, in order to consider the personal risk factors for early indication and change of available therapies and to implement the transition program in cooperation with adult rheumatology according to EULAR criteria, which consider joint care for a specified period, facilitating continuity of care in this special patient population.

In conclusion, in our case study, there were changes in diagnosis and category according to what has been described internationally and the transition process was not appropriate. By identifying the risk factors of sequelae in our population and periodically reviewing the management carried out, will allow us to plan actions to avoid or minimize them, in order to transfer adolescents with a better quality of life and to organize an adequate and complete transition to adult rheumatology.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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