DISSERTATIONES MEDICINAE UNIVERSITATIS TARTUENSIS
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JUVENILE IDIOPATHIC ARTHRITIS IN CHILDREN IN ESTONIA

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In memory of my grandfather,
Jaan Riiv
(1919–1995)

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ABBREVIATIONS

ANA	antinuclear antibodies
ACR	American College for Rheumatology
ARA	American Rheumatism Association
ASCT	autologous stem cell transplantation
ASPs	affected sibling pairs
CD	cluster of differentiation
CI	confidence interval
CRP	C-reactive protein
DMARD	disease modifying antirheumatic drug
DZ	dizygotic
ESR	erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
HC	hydroxychloroquine
HLA	human leukocyte antigen
Hsp	heat shock protein
IgA	immunoglobulin class A
IgG	immunoglobulin class G
IgM	immunoglobulin class M
IL	interleukin
ILAR	International League of Associations for Rheumatology
IR	incidence rate
JCA	juvenile chronic arthritis
JIA	juvenile idiopathic arthritis
JRA	juvenile rheumatoid arthritis
NIAMS	National Institute of Arthritis and Musculosceletal and Skin Diseases
NSAID	non-steroidal antiinflammatory drug
MTX	methotrexate
MZ	monozygotic
PIP joints	proximal interphalangeal joints
PR	prevalence rate
RF	rheumatoid factor
SD	standard deviation
SE	standard error
TNF-α	tumor necrosis factor alpha
TNFR	tumor necrosis factor alpha receptor
US	ultrasound

INTRODUCTION

Nowadays it has become clear that rheumatic or joint diseases are not solely the problem of elderly people. Rheumatic diseases affect 0.1–0.3% of children aged 0–15 years and can cause longterm morbidity. Juvenile idiopathic arthritis (JIA) begins before the 16th birthday and is defined as sterile inflammation in at least one joint that is persistent for at least six weeks, and for which there is no defined diagnosis (Fink 1995). JIA is the most frequent among rheumatic diseases in childhood (Rosenberg 1990; Denardo *et al.* 1994; Symmons *et al.* 1996; Malleson *et al.* 1996; Bowyer and Roettcher 1996; Huemer *et al.* 2001; Rosenberg 2005).

JIA is by clinical presentation a heterogeneous disease lacking specific diagnostic criteria. Over 30 years the classification of juvenile arthritis has changed quite a lot making interpreting the literature concerning the epidemiology of JIA complicated. There exist only a few population-based studies worldwide that can reflect the real prevalence rate of JIA.

Due to the heterogeneity of JIA, the course of the disease is individually quite variable; the majority of children with mild forms of oligoarthritis have a rather favourable outcome, but at the same time they may be left undiagnosed in the population if not seen by specialists.

Since the year 2000 approximately 100 children per year have fallen ill with JIA in Estonia. Therefore, concerning the small population of a country of only 1.3 million, JIA patients form a large group with special demands on society.

REVIEW OF THE LITERATURE

1. Historical background

Historical findings about rheumatic diseases in adult persons go back to ancient times. Skeletons from the Stone Age with changes compatible with the description of chronic arthritis have been found in several places over the world — in Egypt (May 1897), in the United States (Rothschild *et al.* 1992) and in Nordic countries as well (Leden *et al.* 1988). In 1979, Alexandersen *et al.* described a hypoplastic jaw from a medieval Polish skull, which could refer to chronic arthritis in childhood. The "Portrait of a Youth" painted in 1483 by the Florentine artist Sandro Botticelli has features of rheumatoid arthritis in the hand of the subject, who would be young enough to be considered as having juvenile arthritis (Alarcon-Segovia *et al.* 1983).

According to Bywaters (1977) the first clinical description of the disease was given by Thomas Phaire in the first book on pediatrics published in English (in 1545) *The Book of Chyldren*, where a section described "the stifness or starckeness of limmes"; the cause of this was thought to have been getting cold. Cornil is considered to have given the first description of the disease; in 1864 he described a chronic polyarthritis in a 29-year-old woman, in whom the disease had begun at the age of 12 (cited by Andersson Gäre 1994).

By the turn of the nineteenth century, Diament–Berger (1891) had reviewed 38 case reports of chronic arthritis with a start in childhood. He recognized that the childhood form of arthritis was distinct from adult arthritis (and carried a better prognosis), and he also attempted the first classification into acute, slow, and partial groups (cited by Andersson Gäre 1994).

"The father of pediatric rheumatology" — George Frederic Still — described in 1897 in London 12 cases known nowadays as systemic arthritis. The patients had fever, enlarged lymphatic glands and spleen and pericarditis in addition to arthritis, but no rash. In 1901, Hirschsprung confirmed Still´s observations that a chronic articular disease was associated with lymphadenopathy, splenomegaly and hepatomegaly in young children (cited by Cassidy and Petty 2005). "Still's disease" was for many years a term used for the whole group of chronic arthritis conditions in childhood. In pediatric rheumatology, the term "Still's disease" has become a historical one, while the systemic disease as it occurs in adults is referred to as "adult onset Still's disease" even today (Gupta and Mills 1975; Bywaters 1977).

Coss and Boots proposed in 1946 that the term juvenile rheumatoid arthritis (JRA) should be used to refer to all cases of idiopathic inflammatory arthritis (cited by Cassidy and Petty 2005).

Colver was the first one to publish follow-up studies of JRA in 1937; until this time the prognosis of the disease was considered to be poor (cited by Cassidy and Petty 2005).

For a long time, children with chronic arthritis were taken care of by the departments for adult rheumatological patients. The first special unit for pediatric rheumatology patients was opened at Taplow in England by Bywaters in the late 1940s. As in those days children with arthritis stayed in the hospital for a long period of time, the main large epidemiological studies from the 1960s and 1970s are based on the data of these centres (Laaksonen 1966; Ansell and Wood 1976; Stoeber 1981).

2. Classification of JIA

The problem of classifying chronic arthritis in childhood has been dealt with for more than three decades. In the 1970s, two sets of classification criteria were proposed. In 1973, the criteria for JRA were developed and validated by the JRA Criteria Subcommittee of the American Rheumatism Association (ARA), currently the American College of Rheumatology (ACR) (Brewer *et al.* 1972). These criteria were revised in 1977 by Brewer *et al.*, and three different onset types were introduced for the first time: polyarticular (five or more joints involved), pauciarticular or oligoarticular (1–4 joints) and systemic. The clinical signs present during the first six months of illness defined the onset type of JRA. The age at onset was required to be less than 16 years and the duration of arthritis a minimum of six weeks in at least one joint. The criteria excluded other diseases, such as spondyloarthropathies.

The Taplow criteria for the diagnosis of Still's disease were evaluated in a 15-year follow-up study (Bywaters 1968). These criteria were modified and formed the basis of the classification of juvenile chronic arthritis (JCA), proposed by the European League Against Rheumatism (EULAR) (Wood 1978). ARA and EULAR classifications differ considerably, considering the duration of symptoms needed for diagnosis and inclusion of spondylarthropathies, making comparative international research complicated (Table 1). In 1982 the syndrome of seronegative enthesitis and arthritis was defined by Rosenberg and Petty, and further studies by Cabral *et al.* (1992) suggested that it could be the initial phase of later spondylarthritis. Separate criteria have also been proposed for psoriatic arthritis by Southwood *et al.* (1989).

In 1994, the International League of Associations for Rheumatology (ILAR) convened an international classification task force of pediatric rheumatologists with the aim of working out a consensus classification for improving international research and communication among physicians and scientists. In 1994 in Santiago (Chile) a proposal was made by the Task Force

of the Pediatric Standing Committee of ILAR to introduce new classification criteria for childhood arthritides and a new term, "juvenile idiopathic arthritis, JIA" (Fink 1995). The term JIA was adopted as an umbrella term to indicate a disease of childhood onset characterized primarly by arthritis persisting for at least six weeks and currently having no known cause. This classification was revised in 1997 and 2001 (Petty *et al.* 1998; Petty *et al.* 2004) (Table 1). JIA has seven clinical subtypes (Table 2).

Table 1. Classification of JRA, JCA and JIA (Brewer *et al*. 1972; Wood 1978; Petty *et al.* 1998)

	Juvenile rheumatoid arthritis ARA	**Juvenile chronic arthritis EULAR**	**Juvenile idiopathic arthritis ILAR-97**
Duration of symptoms needed for diagnosis	6 weeks	3 months	6 weeks
Age at onset of the disease	0–15 years	0–15 years	0–15 years
Subtypes	Oligo-, poly-, systemic arthritis	Oligo-, poly-, systemic arthritis	Oligoarthritis (persistent, extended), polyarthritis seropositive, polyarthritis seronegative, systemic arthritis
Seronegative spondylarthro-pathies	Not included	Juvenile ankylosing spondylitis, Arthritis associated with in-flammatory bowel diseases, psoriatic arthritis	Enthesitis related arthritis, psoriatic arthritis
Non-classifiable arthritis			Other arthritis

Table 2. Subtypes of JIA (ILAR, 1997)

1. Oligoarthritis — a) Persistent: affects no more than 1–4 joints throughout the course of the disease; b) Extended: involvement of 1–4 joints during the first six months of the disease, with a cumulative total of five or more joints after the first six months of the disease;
2. Polyarthritis (Rheumatoid Factor (RF) Negative) — affects five or more joints during the first six months of disease; tests for RF are negative;
3. Polyarthritis (RF Positive) — affects five or more joints during the first six months of disease; associated with positive RF tests on two occasions at least three months apart;
4. Systemic arthritis — arthritis with or preceded by daily fever of at least two weeks` duration, which is documented to be quotidian for at least three days, and accompanied by at least one of the following: (a) evanescent, non-fixed, erythematous rash, (b) generalized lymph node enlargement, (c) hepatomegaly/splenomegaly and (d) serositis;
5. Enthesitis related arthritis — arthritis and enthesitis or arthritis or enthesitis with at least two of the following: (a) sacroiliac joint tenderness and/or inflammatory spinal pain, (b) the presence of human leucocyte antigen (HLA) B27, (c) family history in at least one first or second degree relative of medically confirmed HLA B27 associated disease, (d) anterior uveitis that is usually associated with pain, redness, or photophobia, or (e) onset of arthritis in a boy after the age of eight years;
6. Psoriatic arthritis — arthritis and psoriasis, or arthritis and at least two of the following: (a) dactylitis, (b) nail abnormalities (pitting and onycholysis), or (c) family history of psoriasis in at least one first degree relative;
7. Other arthritis — arthritis which does not fulfill the criteria for any of the other categories or fulfills the criteria for more than one of the other categories.

The principle of the classification is that all subtypes of JIA are mutually exclusive and each category has a special list of exclusions (Table 3).

Table 3. Exclusions of the subtypes in the ILAR 1997 revision

Oligoarthritis:

a) family history of psoriasis confirmed by a dermatologist in at least one first or second degree relative; b) family history consistent with medically confirmed HLA B27 associated disease in at least one first or second degree relative; c) positive RF test; d) HLA B27 positive male with an onset of arthritis after eight years of age; e) presence of systemic arthritis by the definition;

Polyarthritis (RF negative):

a) presence of RF; b) presence of systemic arthritis by the definition;

Polyarthritis (RF positive):

a) absence of positive tests for RF on two occasions at least three months apart; b) presence of systemic arthritis by the definition;

Psoriatic arthritis:

a) presence of RF; b) presence of systemic arthritis by the definition;

Enthesitis related arthritis:

a) psoriasis confirmed by a dermatologist in at least one first or second degree relative; b) presence of systemic arthritis by the definition;

Other arthritis:

Patients who meet the criteria for other categories.

Additionally, a number of descriptors have been proposed to gather more information about the clinical expressions of the disease, making future reclassification possible. These include: age at onset; a more detailed description of the arthritis (large joints, small joints, symmetry, upper or lower limb predominance and individual joint involvement); disease course (number of joints); presence of antinuclear antibodies (ANA); chronic or acute anterior uveitis; and associations with HLA (Fink 1995; Petty *et al*. 1998; Petty *et al*. 2004).

The 1997 or Durban (South Africa) revision of the ILAR criteria differ from the Santiago version in the following points: a) a new category — other arthritis — was added to include patients with idiopathic arthritis who fit either into none of the categories or into two or more categories; b) in the subtype systemic arthritis the category of "probable systemic arthritis" was left out — meaning children with fever and/or typical rash should not be diagnosed as having systemic arthritis until arthritis is present; c) persistent and extended oligoarthritis are grouped together under the name oligoarthritis due to the fact that the patients in the two subdivisions are indistinguishable within the first six months of the disease; d) in the enthesitis related arthritis subtype the criterion — the onset of arthritis in a boy after the age of eight years — was added (Petty *et al.* 1998).

The 2001 or Edmonton (Canada) revision made the definitions of each category more clear and instituted the following minor changes: a) no further need for a dermatologist to make the diagnosis of psoriasis; b) removal of the requirement for the medical confirmation of HLA B27 associated disease in a relative; c) that the requirement regarding the age at the onset of arthritis in a boy with enthesitis related arthritis be reduced from eight years to six (Petty *et al.* 2004).

The working group supposes that further revisions concerning classification will be needed in accordance with new available information.

3. Epidemiology of JIA

3.1. Incidence of JIA

In epidemiological studies published in the field of JIA, the incidence rate (IR) ranges from 0.8 to 22.6 per 100 000 children (Manners and Bower 2002). The main reasons for the variation in these rates are: 1) different study designs (hospital-based, population-based, questionnaires, data of registries); 2) the size and completion of study groups; and 3) different classification criteria used.

Several authors have noted that the IR of JIA rises and decreases periodically and shows geographical differences, which emphasizes the triggering role of environmental factors or may reflect differences on the basis of genetic

factors (Andersson Gäre and Fasth 1992; Peterson *et al.* 1996; Kaipiainen-Seppanen and Savolainen 1996). In population-based studies (Towner *et al.* 1983; Berntson *et al.* 2003) the IR is usually higher than in hospital-based studies or in the surveys of medical practitioners (Sullivan *et al.* 1975; Rosenberg *et al.* 1990; Oen *et al.* 1995; Malleson *et al.* 1996).

The study by Kunnamo *et al.* (1986) illustrates the effect of the inclusion criteria, specifically the duration of arthritis — when six weeks of duration was required, the IR was 19.6 per 100 000 compared to 18.2 for the series of patients in whom the arthritis was required to have lasted for at least three months. In a study by Towner *et al.* (1983), the application of the ARA and EULAR criteria resulted in IRs of 13.9 and 10.8 respectively. In the latest study covering all the Nordic countries by Berntson *et al.* (2003), the application of the ILAR criteria, demanding shorter disease duration (6 weeks), resulted in slightly higher IRs, compared to the EULAR criteria (needed disease duration 3 months).

Reports from the Nordic countries present the highest ever published IRs — in addition to data reported from Finland by Kunnamo *et al.* (1986), Moe and Rygg (1998) found the IR in Norway to be 22.6 per 100 000. In a recent study by Berntson *et al.* (2003), the highest incidence figures were also found in Finland (Uusimaa County) — 21 per 100 000, and in two regions of Norway (19 and 23 per 100 000 respectively).

3.2. Prevalence of JIA

Similar to the incidence figures, the prevalence rate (PR) of juvenile idiopathic arthritis ranges in wide limits — according to several authors from seven to 401 per 100 000 children aged 0–15 years (Manners and Bower 2002). The reasons for this variation are the same as those for the IRs (see above).

In the first hospital-based study by Bywaters (1968), the prevalence of Still' s disease in English schoolchildren was 65 per 100 000.

Having observed two large samples — the 1978 National Ambulatory Medical Care Survey and the 1979 Monroe County Pediatrician Survey — using the ACR criteria, Gewanter (1983) estimated the prevalence of JRA to be between 16 to 43 per 100 000; after analysing other studies performed in the United States, he estimated the prevalence to be about 0.5 cases per 1000 children.

Many of the studies are hospital-based and according to these the PR ranges from seven to 200 per 100 000 (Rodary *et al.* 1977; Rosenberg *et al.* 1982; Hochberg *et al.* 1983; Andersson Gäre and Fasth 1992; Kiessling *et al.* 1998). In the community-based studies, which include in addition to hospital records cases diagnosed by primary care practitioners, the figure ranges from 34.9 to

401 per 100 000 (Towner *et al.* 1983; Khuffash *et al.* 1990; Steven 1992; Arguedas *et al.* 1998; Ozen *et al.* 1998). The lowest PR of JRA — seven per 100 000 — was found by Arendarczyk (1977) in Poland in a study based on clinical case records (cited by Manners and Bower 2002). A suprisingly high figure (401 per 100 000) was published by Manners and Diepeveen in 1996 in a community-based study of 12-year-old Australian schoolchildren, in which every participating child was examined by pediatric rheumatologists.

The study by Towner *et al.* (1983) illustrates once again the influence of used criteria on the results. The prevalence rate was 113 per 100 000 when the ARA criteria were used and 84 according to the EULAR criteria. A duration of the disease of six weeks is probably not enough to make the right diagnosis — some cases may turn out to not be "real" ones. In a meta-analysis Oen and Cheang (1996) showed that population surveys yielded the highest prevalence, followed by practitioner surveys, while the lowest values were obtained from clinic-based studies.

3.3. Age distribution at onset

According to the terminology, "juvenile" means the onset of the disease in children aged 0–15 years. Age at the onset of JIA can vary a lot, but onset in the first six months of life is rare. According to several authors the disease begins with high frequency between one and three years of age, but the median age at onset depends heavily on the onset subtype (Peterson *et al.* 1996; Moe and Rygg 1998; Berntson *et al.* 2003). A bimodal distribution of onset age with peaks in the 0–3 year age group and in puberty has been described by several authors (Peterson *et al.* 1996; Moe and Rygg 1998; Dracou *et al.* 1998). Andersson-Gäre and Fasth (1992) found the bimodal distribution for girls only. The mean age at onset has been found to range from 6.8 to 9.2 years (Berntson *et al,* 2003; Peterson *et al,* 1996; Moe and Rygg 1998; Kaipiainen-Seppänen and Savolainen 1996). Berntson *et al.* (2003) found the two peaks of onset age in both oligo- and polyarthritis subtypes.

3.4. Sex ratio

Girls are generally affected by JIA more often than boys, but the sex distribution also varies in different JIA subtypes. Schaller (1977) suggested dividing the oligoarthritis subtype into an early onset type dominant in girls, and a late onset type dominant in boys. In the oligoarthritis subtype the sex ratio of girls to boys — is 5:1; in the polyarthritis and systemic sybtypes the numbers are 3:1 and 1:1 respectively (Cassidy and Petty 2005). In the published studies on

epidemiology, the percentage of girls in the whole series is 57.8–63.3% (Andersson Gäre and Fasth 1992; Moe and Rygg 1998; Berntson *et al.* 2003). HLA B27 positive late onset oligoarthritis is more common in boys (Friis *et al.* 1985; Murray *et al.* 1999).

3.5. Geographic and racial distribution and differences

Most of the epidemiological studies on childhood arthritis are derived from North Europe and America. In a study by Haffejee *et al.* (1984) on Black and Indian South African children with JCA, the main peculiarities were high prevalences of polyarticular onset and seropositivity, an equal sex ratio and the absence of a specific subgroup with oligoarthritis and a positive antinuclear factor test. Chandrasekaran *et al.* (1996) have also reported a higher frequency of polyarthritis in India, compared with oligoarthritis or systemic arthritis. In 1977 Hill found the incidence of JRA in aboriginal children in British Columbia (Canada) to be much higher compared to that in Caucasian children, 7:100 000 compared to 3:100 000. In a retrospective study of pediatric rheumatic diseases in a multi-ethnic area, Hawaii, lower risks for developing of JRA were calculated for children of Filipino, Japanese and Samoan origin, over a six-year-period, when compared to Caucasians (Kurahara *et al.* 2002). In Japanese children the incidence of JRA has also been found to be low — 0.83 per 100 000 (Fujikawa and Okuni 1997). Oen *et al.* (1986) reported a high frequency of seronegative spondylarthropathies (annual incidence 60.1 per 100 000), with an annual IR for JRA also being high at 23.6 per 100 000, in Inuit children in a Northwestern district of Canada. In a meta-analysis of studies on epidemiology, Oen and Cheang (1996) detected that the geographic origin and race of the study population were among modifier variables. Analyzing the effect of race in the distribution of patients among onset subtypes, the same authors revealed that oligoarthritis was more frequent and polyarthritis presented with lower frequency in series of North American and European Caucasian patients, when compared with series of East Indian, Native North American Indian and other races. The PR was statistically different between Europe and North America, in clinic studies, 32 and eight per 100 000 respectively.

4. Etiology of JIA

To this date a clear understanding concerning the complicated mechanisms involved in the initiating and perpetuating of chronic inflammation in joints is still missing. It has been discussed whether the various subgroups of JIA represent different disease entities with different etiologies, as each of the subgroups

is characterized by specific immunological specificities and genetic associations (Hall *et al.* 1986; Fernandez-Vina *et al.* 1994; Prakken *et al.* 1997; Murray *et al.* 1999; van Rossum *et al.* 2003; Grom *et al.* 2003; de Kleer *et al.* 2004).

So far it is clear that JIA is an autoimmune disease with complex genetic trait — oligo- or polygenic (Glass and Giannini, 1999). Both genetic and environmental factors play important roles in the etiopathogenesis of JIA (Ansell *et al.* 1969; Clemens *et al.* 1985; Kunnamo 1987; Maximov *et al.* 1992; Sieper *et al.* 1992; Braun *et al.* 1993; Crawley *et al.* 1999; Saila *et al.* 2001; Oguz *et al.* 2002; Donn *et al.* 2002; Postepski *et al.* 2003; Ogilvie *et al.* 2003; Thompson *et al.* 2004; Moroldo *et al.* 2004; Jaakkola and Gissler 2005; Thompson *et al.* 2006; Hinks *et al.* 2006).

Environmental factors. Nielsen *et al.* (1999) studied the socioeconomic background of children with JCA in Denmark. Three socioeconomic variables were identified as independent risk factors for the development of JCA: a single child in the family, high parental income and living in an urban flat.

In a recent study Jaakkola and Gissler (2005) found a relation between foetal exposure to tobacco smoke and the risk of a later development of JRA in girls.

No evidence-based associations have yet been found between nutrition and JIA — so far there do not exist any special dietary recommendations.

Physical trauma. Traumas to an extremity can also trigger arthritis or draw attention to an already inflamed joint (Cassidy and Petty 2005).

Infection. According to many authors, infectious agents can have a triggering role in the initiation of JIA (Kunnamo 1987; Maximov *et al.* 1992; Sieper *et al.* 1992; Braun *et al* 1993; Oguz *et al.* 2002; Postepski *et al.* 2003).

In a case-control study by Kunnamo (1987) in which a parent-completed questionnaire to record the clinical signs of infections preceding the onset of joint symptoms by one month or less in 334 children with arthritis was done, patients with JRA had more signs of mainly upper respiratory tract infections than did controls.

There are studies which examine the possible role of the Parvovirus B19 (Oguz *et al.* 2002; Szumera *et al.* 2004) and *Mycoplasma pneumoniae* (Postepski *et al.* 2003) in the etiology of JIA.

Some works support the causative role of the bacteria associated with reactive arthritis and *Chlamydia trachomatis* in late-onset oligoarthritis (Sieper *et al.* 1992; Braun *et al.* 1993).

Experimental animal models give support for the initiating role of a microbial agent (Cohen *et al.* 1985; Ronaghy *et al.* 2002). Adjuvant arthritis can be induced in rats by an intracutaneous injection of Complete Freund's Adjuvant (heat-killed mycobacteria are added to Incomplete Freund's Adjuvant). Ronaghy *et al.* (2002) described the correlation of the arthritis-promoting effect of the *Mycobacterium tuberculosis* DNA or of the synthetic immunostimulatory segments — oligodeoxynucleotides — with an increased T-helper 1 response.

Some works have been dedicated to an investigation of the protective role of heat shock proteins (hsps) against arthritis (Van de Broek *et al.* 1989; Prakken *et al.* 1997). Hsps are so-called stress proteins and their production increases in stress situations (Young 1990). Self-hsps are upregulated at sites of inflammation. Bacterial hsps are recognized by the immune system, which leads to a cross-recognition of self-hsp and autoimmunity (Lamb *et al.* 1989). Immunization with *Mycobacterium* hsp65 protects rats against a subsequent induction of arthritis (Van de Broek *et al.* 1989). Most T cell responses to hsps are found in oligoarthritis, which has the best prognosis (Prakken *et al.* 1997). The basis of this suggestion is that the self-hsp reactive cells, T regulatory cells, which produce interleukin (IL)-10, are induced (de Kleer *et al.* 2003).

The role of T-cells. T-cells play a central role in the persisting of inflammation. The T-cells found in the synovial fluid are highly activated, expressing rapidly upregulated (cluster of differentiation (CD) 69) and persistent activation markers (Black *et al.* 2002), and are oligoclonal (CD4+ in oligoarthritis, CD8+ in enthesitis related arthritis). This supports the concept that the recognition of Major Histocompatibility Complex-peptide complexes by T-cells has an important role in the pathogenesis of JIA (Wedderburn *et al.* 2001). Synovial T-cells are actually hyporesponsive to T-cell receptor mediated signals (Patel *et al.* 2003), which has been thought to be due to the presence of a subset of regulatory CD4+CD25+ T-cells (de Kleer *et al.* 2004). These cells do have a suppressive ability and have been found in high numbers in those children in whom oligoarthritis remains persistent. In addition, in persistent oligoarthritis the balance of interferon γ: IL-4 (IL-10) production is towards the production of the latter one(s), which possess(es) an anti-inflammatory influence. The situation differs in extended oligoarthritis (de Kleer *et al.* 2004).

Finally, defective apoptosis has been suggested to have a role in the perpetuating of inflammation; this has been discovered in Natural Killer cells, which can lead to macrophage activation syndrome in systemic arthritis (Grom *et al.* 2003).

The role of B cells is not so clear, but the fact is that there exist certain autoantibodies — for instance ANA — that point to their activity. Anti-cyclic citrullinated peptide antibodies have been reported, especially in seropositive polyarthritis, but less frequently than in adults with rheumatoid arthritis (van Rossum *et al.* 2003).

Hormonal factors. As girls dominate in the whole JIA group and the disease has certain age peaks, certain hormone levels have been investigated. Da Silva *et al.* (1993) found that low androgen levels may contribute to the pathogenesis of JIA, as they do have a protective effect against cartilage destruction. In addition, elevated serum prolactin levels have been detected in ANA-positive girls with JIA (McMurray *et al.* 1995).

Genetic factors. Evidence for the genetic component comes from family and twin studies. As JIA is not a homogenous disease, there have been many

studies on the possible genetic heterogeneity (Stastny and Fink 1979; Oen *et al.* 1982; Morling *et al.* 1985; Friis *et al.* 1985; Hall *et al.* 1986; Barron *et al.* 1992; Bedford *et al.* 1992; Haas *et al.* 1994; Albert and Scholz 1998; Murray *et al.* 1999; Crawley E *et al.* 1999; Thomson *et al.* 2002; Ogilvie *et al.* 2003).

Twin studies. Already in 1969, Ansell *et al.* reported on 11 twin pairs — five monozygotic (MZ) and six dizygotic (DZ). Two of the five MZ pairs were concordant for the disease. The largest study so far has been done by Prahalad *et al.* (2000), who presented data of the National Institute of Arthritis and Musculosceletal and Skin Diseases (NIAMS) sponsored Research Registry for JRA Affected Sibling Pairs (ASPs). Of the 118 ASPs on the register, there were 14 pairs (11 of them MZ) of twins where both twins had arthritis. Thirteen of the 14 were concordant for disease onset and disease course. In a Finnish study by Saila *et al.* (2001), eight sets of twins were identified, two of them were concordant for arthritis. An earlier onset of disease was found in familial cases when compared to sporadic ones. A concordance rate of 25% for a disease with a population prevalence of one per 1000 gives a relative risk of JIA of 250 for a MZ twin.

ASPs studies. There are only few studies reporting on ASPs. Studies by Clemens *et al.* (1985) in more than 2000 children with JCA found a remarkable concordance between siblings for onset, manifestations and course of the disease. Ten of the 12 ASPs with the same onset subtype shared two HLA-DR antigens; the other two pairs shared one HLA-DR antigen. In a finnish study, 49 ASPs from 37 families were reported on by Saila *et al.* (2001), with a concordance of 57% in onset type and 61% in disease course within the ASPs. A study on the data of the NIAMS sponsored registry for JRA ASPs in the United States has been published by Moroldo *et al.* (2004). The registry contained 183 ASPs from 164 families. The concordance for the disease onset type between the ASPs was 53% for pauciarticular onset and 19% for polyarticular onset. The difference in age at JRA onset within sibpairs (sibling one versus sibling two) was not significantly different.

HLA and JIA. There are both HLA class I and class II associations with JIA. Some HLA associations are common to all JIA subtypes, while some are subtype specific. The earliest finding concerning HLA was the association between HLA-B27 and older boys (teenagers) with oligoarthritis (Friis *et al.* 1985). Many of these boys later develope sacroiliitis and belong to the enthesitis related arthritis subgroup in the ILAR classification. Another HLA I class association has been found between HLA-A2 and early onset oligoarthritis in girls; but no significant correlation was found with chronic asymptomatic uveitis (Oen *et al.* 1982). Some studies (Forre *et al.* 1983; Schuchmann *et al.* 1984) have found HLA-B27 with an increased frequency in all the subtypes of JIA. Among HLA class II associations, an increased frequency of HLA-DR 5 (its subtype HLA-DRB1*11), DR8 (HLA-DRB1*08) and HLA-DPB1*0201 and a decreased frequency of HLA-DRB1*04 and HLA-DRB1*07 in early

onset oligoarthritis has been found (Stastny and Fink 1979; Hall *et al.* 1986; Haas *et al.* 1994; Albert and Scholz 1998; Murray *et al.* 1999). In oligoarthritis HLA-DR6 (subtype DRB1*1301) is not present in the extended type (Cerna *et al.* 1994); the latter has an association with DR1 (it's subtype DRB1*0101), which predicts a progression to more joints and the development of erosions (Flato *et al.* 2003). In RF negative polyarthritis associations have been reported with HLA-DR8 — these patients are typically characterized by an early age at onset, positive ANA and uveitis — and HLA-DQ4 (Thomson *et al.* 2002; Fernandez-Vina *et al.* 1990; Barron *et al.* 1992). An increased frequency of DR4 has been found in extended oligoarthritis, seropositive polyarthritis and systemic arthritis (Bedford *et al.* 1992; Thomson *et al.* 2002). Systemic arthritis has the most limited associations with the HLA antigens — associations have been found with HLA-DR4, -DR5 and -DR8 (Morling *et al.* 1985; Bedford *et al.* 1992).

Linkage has been shown to both HLA class I and II in oligoarthritis — HLA-A2, -B27, -B35, and HLA-DR5 and -DR8 showed excess transmission, while at the same time HLA-DR4 was under-transmitted (Zeggini *et al.* 2002).

Recently, the results of the first whole genome scan have been published. The study identified five putative JRA regions — 1p36, 1q31, 15q21, 19p13 and 20q13; four of them overlapped with other autoimmune diseases, and only the one on chromosome 15q was JRA-specific (Thompson *et al.* 2004). Also, an association between the protein tyrosine phosphatase N22 (PTPN22) gene and JIA has been found in a large population of JIA patients in the United Kingdom (Hinks *et al.* 2006).

5. Subtypes of JIA

5.1. Systemic arthritis

In this unique form of JIA, the extraarticular manifestations dominate at the beginning of the disease and arthritis usually develops after an interval of some time (Schneider and Laxer, 1998). The disease can start in all age groups, including adults (Bywaters 1971), but most frequently occurs under the age of five years (Ansell 1987). Both sexes are equally affected (Ansell 1987; Schneider and Laxer 1998). For all JIA cases the frequency of systemic arthritis ranges from 4–13.1% (Malleson *et al.* 1996; Peterson *et al.* 1996; Berntson *et al.* 2003; Bowyer *et al.* 1996; Symmons *et al.* 1996).

Annual IRs of systemic arthritis vary from 0.49 per 100 000 (95% CI 0.32;0.77) to 1.3 per 100 000 (95% CI 0.3;2.3) (Malleson *et al.* 1996; Peterson *et al.* 1996; Berntson *et al.* 2003).

The etiology of systemic arthritis is unknown; the onset is similar to several infections, but no clear association with any certain infection has been established (Schneider and Laxer 1998; Prieur *et al.* 2006).

Seasonal variation has been noticed, with the predominance of disease onset in early spring and early autumn (Lindsley 1987).

Systemic arthritis is diagnosed by its clinical features, which are given in Table 2, p. 8. Arthritis with an onset at the same time as systemic features, or often weeks or even months later, is usually symmetrical and can continue for years (Schneider and Laxer 1998).

The course of the disease can be: a) monocyclic (remits completely) in about 11% of cases; b) polycyclic (relapses of the disease with intervals of remission which can last for years) in approximately 34% of cases; and c) unremitting (no remission achieved) in about 55% of cases (Lomater *et al.* 2000; Wallace *et al.* 2004).

Changes in the levels of circulating cytokines and their inhibitors correlate with rises and falls in fever (Peterson *et al.* 1996).

Complications. Growth retardation and osteoporosis can also be complications of systemic arthritis due to several factors, such as the chronic inflammation itself, poor nutritional status, reduced activity and glucocorticoid treatment. Macrophage activation syndrome is a rare life-threatening haemophagocytic syndrome (Schneider and Laxer 1998). Secondary amyloidosis has become very rare as more aggressive treatment is used nowadays. Diffuse interstitial pulmonary fibrosis can occur in a small number of children (Athreya *et al*, 1980).

5.2. Oligoarthritis

Oligoarthritis is the most common subtype of JIA, accounting for 50–75% of all cases (Towner *et al.* 1983; Andersson Gäre and Fasth 1992; Peterson *et al.* 1996; Moe and Rygg 1998; Kaipiainen-Seppänen and Savolainen 2001; Hofer *et al.* 2001; Berntson et al. 2003). According to the ILAR criteria this subtype has been subsequently divided into persistent and extended oligoarthritis (Table 2). The age at onset and sex ratios are the same for persistent and extended oligoarthritis (Hofer *et al.* 2001). Many of the subtypes of JIA can begin with oligoarthritis, such as enthesitis related arthritis and psoriatic arthritis (Huemer *et al.* 2002). Progression to extended oligoarthritis has been reported in 20–50% of children (Sharma and Sherry 1999; Guillaume *et al.* 2000; Hofer *et al.* 2001; Packham *et al.* 2002; Al-Matar *et al.* 2002; Flato *et al.* 2003; Bowyer *et al.* 2003).

The most common joints involved at presentation of the disease are knee and ankle (Sharma and Sherry 1999; Guillaume *et al.* 2000). Hips are rarely involved, while temporomandibular joints and the cervical spine can become

involved later in the course of the disease (Miller and Malleson 2006). The involvement of wrists and elbows can predict a progression to polyarticular disease during the course (Guillaume *et al.* 2000).

The main complications in patients with oligoarthritis are: a) muscle atrophy and weakness around inflamed joints, often accompanied by a shortening of the muscles and tendons resulting in flexion contractures; b) an overgrowth of the bone and cartilage of affected joints; and c) uveitis (Miller and Malleson 2006).

Uveitis. The presence of uveitis occurs in about 30% of patients with oligoarthritis (Petty *et al.* 2003) and can begin insidiously and painlessly. Uveitis in enthesitis related arthritis is more acute and painful. In chronic uveitis of JIA oligoarthritis the earliest change — exudate in the anterior chamber — is visible only by using a slit lamp, so all children with oligoarthritis should be examined by an ophthalmologist (Yancey *et al.* 1993). Late changes include pericorneal vascular dilatation, keratic precipitates in the anterior chamber, synechiae and band keratopathy. Glaucoma and cataracts may develop. The course can vary from mild and self-limited to persistent inflammation, which can progress to blindness (Cabral *et al.* 1994; Dana *et al.* 1997; Miller and Malleson 2006).

5.3. RF positive polyarthritis

There are no specific data on the epidemiology of RF positive polyarthritis alone. This subtype includes about 5–10% of all JIA cases in Caucasian series, being most common in teenage girls (Gardner-Medwin 2006). The mean age of onset for this subtype is around 9–12 years (Symmons *et al.* 1994; Bowyer and Roettcher 1996; Denardo *et al.* 1994).

The course of this subtype is rather often characterized by a symmetrical involvement of both large and small joints — frequently these are wrists, metacarpophalangeal, proximal interphalangeal joints and hips. In addition, fever, moderate hepatosplenomegaly and lymphadenopathy are seen in this subtype. Usually the course of this subtype is characterized by a quite rapid development of joint erosions, and rheumatoid nodules can also be seen, though not very often (Bywaters and Cardoe 1972; Oen *et al.* 2003).

Complications include growth and pubertal development problems and osteoporosis related to chronic inflammation, medications and poor nutritional status (Gardner-Medwin 2006). Atlanto-axial subluxation can appear; in addition, aortic valve involvement (Delgado *et al.* 1988) and Felty syndrome have been described (Bloom *et al.* 1998).

5.4. RF negative polyarthritis

This subtype of JIA is considered to be the most heterogeneous. In epidemiological studies, about 17–29% of patients are described as having this subtype of JIA (Symmons *et al.* 1996; Andersson Gäre and Fasth 1992).

This subtype has two onset peaks — one period is during the toddler to preschool age and the other in the pre-adolescence age (Fink *et al.* 1995). In the British Paediatric Rheumatology National Diagnostic Register, the mean age at onset was 6.5 years (Symmons *et al.* 1996). RF negative polyarthritis is more common in girls, with a female to male ratio of about 3:1 (Symmons *et al.* 1996; Bowyer *et al.* 1996).

The onset of RF negative polyarthritis can be acute or insidious, but the course is progressive. The arthritis may be symmetric or asymmetric with the involvement of both large and small joints (Fink and Fernandez-Vina 1995). Knees, ankles, wrists, elbows, the cervical spine, the small joints of the hands and feet, shoulders and the temporomandibular joint (the latter being often unilateral) can all be involved. Tenosynovitis, especially in wrists, ankles and the flexor tendons of the hands is common (Fink and Fernandez-Vina 1995). Approximately 10% of children who develop chronic anterior uveitis have this form of disease (Fink and Fernandez-Vina 1995).

Martini (2006) has divided the subgroup into three clinically distinguishable groups:

a) Early (before six years of age) onset, ANA positive, asymmetric arthritis, affecting both large and small joints, more common in girls, with a high risk of chronic anterior uveitis; HLA-DRB1*0801 often positive. About one-third of patients are affected with this subgroup.
b) Prolific symmetric synovitis, which has a later onset (7–9 years), symmetric arthritis, affecting both large and small joints, ANA negative, elevated erythrocyte sedimentation rate (ESR), with a low risk of anterior uveitis. This is the most classic form of this subgroup.
c) Dry synovitis — little palpable synovial thickening, a late onset (seven years and later), destructive course, poor response to treatment, ANA negative. Progressive loss of function, poor outcome. An uncommon type, it has been suggested that it could be a separate disease, with a probable genetic origin (Ansell 1987).

Complications. Uveitis in ANA-positive patients can develop. Growth retardation can appear due to low levels of circulating insulin-like growth factor-1 and can be local or generalized. The involvement of temporomandibular joints can cause micro- and retrognathia. There is decreased bone mineral content (Allen *et al.* 1991).

5.5. Psoriatic arthritis

It has been speculated whether there does indeed exist such a disease entity as psoriatic arthritis at all, or whether the components of the disease appear coincidentally in a person, as both psoriasis and inflammatory arthritis do occur in about 3% of the general population (Bruce and Silman 2001). It includes about 2–15% of all children with JIA (Berntson *et al.* 2003; Andersson Gäre and Fasth 1992; Malleson *et al.* 1996; Symmons *et al.* 1996). The IR of this subgroup is 0.23–0.4 per 100 000 children, and the PR is 10–16 per 100 000 children (Berntson *et al.* 2003; Andersson Gäre and Fasth 1992; Southwood *et al.* 1989).

The mean age at onset is about six years and girls are affected twice as frequently as boys (Southwood *et al.* 1989).

Genetic predisposition has been suggested. According to Southwood *et al.* (1989), a family history of psoriasis in a first or second degree relative was noted in about half of the children with juvenile psoriatic arthritis, compared to 21% of children with other forms of arthritis.

In children this type of arthritis affects asymmetrically both large and small joints; but sacroiliitis is uncommon. Dactylitis is found frequently (Roberton *et al.* 1996). According to the ILAR classification, patients with enthesitis do not belong to this subgroup and are grouped as undifferentiated arthritis (Petty *et al.* 1998; Petty *et al.* 2004).

Arthritis precedes psoriasis in about 33–67% of cases. About 25% develop psoriasis within two years from the onset of arthritis (Roberton *et al.* 1996). Clinically the psoriasis vulgaris is characteristic; the rash can be found in the hairline, behind the ears, in the navel and the groin. The nail lesions include pitting, onycholysis and subungual hyperkeratosis (Cabral 2006).

Complications. Uveitis is frequent (in about 20% of patients), being insidious at onset, asymptomatic, chronic and anterior, often found in young girls with positive ANA (Southwood *et al.* 1989).

5.6. Enthesitis related arthritis

This subtype accounts for 5–25% of JIA (Malleson *et al.* 1996), is more frequent in boys than girls (7–9:1), and is very uncommon before the age of seven or eight years. The onset can be abrupt or insidious. The arthritis affects most commonly the joints of the lower extremities, both large and small joints, including the hip, and can be symmetrical or asymmetrical. Morning stiffness is frequent and night pain is possible. The most important clinical characteristic is enthesitis. Enthesitis usually occurs around the foot and the knee. In children, the involvement of a sacroiliac or lumbosacral spine is typically not present at

onset and may not appear until years later, when the patient has reached adult age. Schober measurement is used as a diagnostic tool to ascertain the restriction of range of motion of the lumbosacral spine. In addition, cervical spine inflammation can occur (Petty 2006).

Complications. Acute anterior uveitis is usually painful, the eye is red and photophobia is present. Uveitis is often unilateral and recurrent, appearing in 10–15% of cases (Petty 2006). Spinal fusion is more common in adulthood (Burgos-Vargas and Clark 1989); so is aortic valve insufficiency, the frequency of which increases with age (Stamato *et al.* 1995).

5.7. Other arthritis

It has become evident that increasing the homogeneity of other subtypes increases the numbers in the other arthritis group (Southwood and Kimura 2006). In various studies the frequency of this subtype ranges from 8–21.2% (Krumrey-Langkammerer and Hafner 2001; Berntson *et al.* 2003; Merino *et al.* 2005).

Into this subtype are grouped, in addition to those with an overlapping syndrome, patients in whom some required data is lacking, e.g. family history or the result of a laboratory investigation. There are many reasons for a patient to fall into this category, the most common being an overlap between oligoarthritis and psoriatic arthritis. There are patients with a positive RF without polyarthritis. Oligoarthritis can, for instance, be erosive at an early stage (Sailer *et al.* 1997). Relatively common is the co-existence of a positive family history of psoriasis or HLA-B27-related disease together with polyarthritis (Walker *et al.* 1990; Sailer *et al.* 1997; Cleary *et al.* 2000) (Table 3, page 10).

Some authors would still make changes to the ILAR criteria (Ramsey *et al.* 2000; Hofer *et al.* 2001; Krumrey-Langkammerer and Hafner 2001; Fantini *et al.* 2001). It has been suggested that a family history of psoriasis be excluded as an exclusion criteria for oligoarthritis (Ramsey *et al.* 2000; Fantini 2001), or that replacing RF positive polyarthritis with RF-positive arthritis be considered (Hofer *et al.* 2001). Krumrey-Langkammerer and Hafner (2001) introduced a new category: extended oligoarthritis at onset, including children with five to eight joints affected during the first six months of the disease, in the absence of exclusion criteria for oligoarthritis. This subtype would even include RF negative polyarthritis clinically close to extended oligoarthritis.

6. Laboratory tests

There is no specific laboratory test to confirm the diagnosis of JIA.

Blood count. Mild normocytic hypochromic anaemia is present quite often (Calabro *et al.* 1977). In severe cases, anaemia can be more expressed. Serum ferritin level increases parallely with systemic activity of the disease (Pelkonen *et al.* 1986). Leukocytosis, with polymorphonuclear cells dominating, is prevalent in patients with systemic onset. Platelet count reflects activity of the disease; it can be especially marked in systemic onset.

Acute phase response. Involves levels of ESR and C-reactive protein (CRP). Assessment of ESR is known to be a poor indicator of inflammation in JIA (Giannini and Brewer 1987). Hussein *et al.* (1987) found that ESR and CRP were significantly more elevated in active disease than in moderately active or inactive disease. Neither parameter, however, could differentiate between moderately active and inactive disease. In active systemic JRA without articular involvement, ESR and CRP were more useful for assessing disease activity. In 1982, Dequeker and Mardjuadi noted that persistently elevated ESR is a strong indicator of poor prognosis (Steinbrocker's functional class III and IV).

Levels of immunoglobulins correlate with disease activity. Persistent hypergammaglobulinaemia is considered to predict poor prognosis (Cassidy *et al.* 1973). Selective immunoglobulin class A (IgA) deficiency can be found in about five per cent of the patients, but it does not have prognostic value (Savilahti *et al.* 1985).

Rheumatoid factors. RF is not a very specific and sensitive test; it can also be found in infections, other autoimmune diseases and following immunization. Low-titre RF is found in 0.5–4% of healthy children (Martini *et al.* 1989; Kanakoudi-Tsakalidou *et al.* 1995). RFs are common in a type of polyarthritis found mainly in girls, and are associated with the presence of HLA-Dw4 and -Dw14 (Stastny and Fink 1979). Several authors have found a positive RF with a frequency of 3–10.6% in patients with polyarthritis (Arguedas *et al.* 1998; Moe and Rygg 1998; Berntson *et al.* 2003). Moore and associates (1986) found "hidden" RFs in 59% of children, and their presence correlated with disease activity. Walker *et al.* published their first study on IgA RF in 1990 and found that, measured in active polyarthritis, the presence of this RF correlated with the degree of later functional disability. In the second study (Walker *et al.* 1990) the immunoglobulin class M (IgM) RF was found mainly in polyarthritis and in high concentration in severe disease. A positive RF is an exclusion criterion in the classification of oligoarthritis (Petty *et al.* 1998), but RF positivity in oligoarthritis has been published (Sailer *et al.* 1997). In enthesitis related arthritis RF should be negative (Petty *et al.* 1998). Recently, it has been shown that the presence of anti-cyclic citrullinated peptide antibodies in RF positive polyarthritis patients can predict the development of a more severe destructive

disease, similar to rheumatoid arthritis in adults (van Rossum *et al.* 2003; Kwok *et al.* 2005).

Antinuclear antibodies. Positive ANA have been found in 25–34% of all JIA cases (Moe and Rygg 1998; Berntson *et al.* 2003) and 65–85% of these are found with early onset oligoarthritis and uveitis (Petty *et al.* 1973; Schaller *et al.* 1974). The presence of ANA and uveitis does not differ between persistent and extended oligoarthritis (Packham and Hall 2002). In RF negative polyarthritis ANA is positive in about 20–40% (Hall *et al.* 1989; Barron *et al.* 1992; Andersson Gäre and Fasth 1992), but in enthesitis related arthritis ANA is not found (Petty *et al.* 1998).

HLA antigens. Different JIA subtypes have associations with different HLA antigens and their combinations. An increased frequency of HLA-B27 has been found in the subgroup with enthesitis related arthritis and in the total group of JIA, as well when comparing with a control group (Schuchmann *et al.* 1984). It is present in 21–52% of all JIA patients (Forre *et al.* 1983; Friis *et al.* 1985; Moe and Rygg 1998). HLA-B27 antigen is most frequently found in boys with pauciarticular onset disease, lower limb involvement, sacroiliitis, an older age at onset and negative tests for RF and ANA (Friis *et al.* 1985). Some of these boys later develop ankylosing spondylitis. The presence of HLA-B27 antigen is also considered to be a prognostic marker in JIA patients concerning the involvement of internal organs and responsiveness to treatment, and has been associated with the failure of first remission (Hsu *et al.* 2004) and the development of cardiac involvement (Savolainen *et al.* 1998; Huppertz *et al.* 2000).

7. Radiologic examination

At the diagnosis the main role of x-ray pictures is to exclude other causes like trauma, and bone tumours.

Early radiographic changes of JIA include periarticular soft tissue swelling (the most common finding in oligoarthritis) and a widening of joint space due to increased intraarticular fluid or synovial hypertrophy, juxta-articular osteoporosis and growth-arrest lines (Reed and Wilmot 1991). In polyarticular disease, widening of the midportions of the phalanges from periosteal new-bone formation and generalized osteoporosis can be seen (Cassidy and Hilman 1997). Periosteal new bone can also be found in psoriatic arthritis in digits affected by dactylitis, and in the systemic subtype (Cabral 2006).

Later radiographic changes include joint-space narrowing, erosions, subluxations and ankylosis. Erosions are usually not seen in the first two years and are found more often in polyarticular and systemic forms. It has been speculated by Levinson and Wallace (1992) that children have thicker cartilage and better repair processes together with growth, and this may play a role in their having

fewer erosions compared to adults. Ankylosis develops in children earlier than in adults and is typically found in the carpal and tarsal joints and in the cervical spine. Microfractures are described in growth plates related to abnormal mechanical stress caused by inflammation, joint deformities and subluxations (Cassidy and Petty 2005).

Ultrasonography (US) is often the best method for identifying intra-articular fluid and synovial hypertrophy (El Miedany *et al.* 2001; Friedman and Gruber 2002). It is suggested to perform US in the initial phase of the disease (El Miedany *et al.* 2001). US is most useful in hip disease (Lamer and Sebag 2000).

Magnetic resonance imaging can demonstrate articular cartilage, joint effusion, synovial hypertrophy, cortical and medullary bone, cartilage and bone perfusion, and fibrocartilaginous structures (menisci and ligaments). The method is particularly useful in the early detection of small erosions, for instance in sacroiliac joints in the enthesitis related arthritis (Bollow *et al.* 2002). In addition, it is of major importance in the evaluation of response to local therapy (especially steroids) and the detection of complications (Lamer and Sebag 2000). Magnetic resonance imaging is indicated in cases of uncertain monoarthritis (Cassidy and Petty 2005).

Localized growth disturbances due to inflammation are frequent skeletal changes. Accelerated epiphyseal maturation occurs, which can be associated with a future stunting of growth of the affected bones (Cassidy and Petty 2005).

8. Treatment of JIA

The aims of the treatment of chronic joint inflammation are to control pain and preserve range of motion, muscle strength, and function; to manage systemic complications; and to facilitate normal nutrition, growth, and physical and psychological development (Cassidy and Petty 2005).

The treatment usually begins with the safest and most conservative measures; if this is not sufficient, other modalities are selected (Schaller 1993; Ilowite 2002).

Physical and occupational therapy. In the management of chronic arthritis it is crucial to maintain and restore the function of joints. After the diagnosis has been established, the family and the child should meet a physiotherapist together with the doctor. The latter will describe the physiotherapist the child's situation. Then the visit is continued with the family and the physiotherapist. She shows the parents/the child how the training is done and preferably gives a written description of the program including the frequency of the training. She should also tell the aim of each movement/training. If needed, the occupational therapist will also be consulted right in the beginning. The child may need supportive splints already at this point, and also guidance in e.g. walking,

handling things, writing and using other tools may be necessary. Everyday gymnastics at home following the instructions given by a physiotherapist is of great importance (Cassidy and Petty, 2005).

Nonsteroidal anti-inflammatory drugs (NSAIDs). NSAIDs are used in the initial phase of the treatment in nearly all cases, but their effectiveness is quite individual (Giannini *et al.* 1993). The efficacy and safety — with mainly mild gastrointestinal adverse events — of ibuprofen, naproxen, and diclofenac have been shown by several authors (Haapasaari *et al.* 1983; Laxer *et al.* 1988; Giannini *et al.* 1990; Steans *et al.* 1990; Minisola *et al.* 1990; Flato *et al.* 1998). NSAIDs should be continued as long as any stiffness or pain is discernible.

Disease modifying antirheumatic drugs (DMARDs). Methotrexate (MTX). Methotrexate is to-day the initial second-line agent for many patients, because of its efficacy and relatively low toxicity (Giannini *et al.* 1992). MTX has become a golden standard for the management of moderate to severe polyarthritis (Murray and Lovell 2002). Clinical improvement has been achieved particularly in the ANA positive polyarticular course group (Halle and Prieur 1991). Woo *et al.* (2000) described the efficacy of MTX in both systemic and extended oligoarticular subtypes. Ravelli *et al.* (1999) found the extended oligoarticular subtype to be the best predictor for the short-term clinical response; these patients tended to have earlier and more frequent disease relapses after MTX discontinuation.

Hydroxychloroquine (HC). The therapeutic effect of HC is mild, and evolves over 2–3 months from the beginning of treatment. Fries *et al.* (1990) showed that the addition of HC to MTX essentially eliminated the toxicity of MTX at the liver.

Other DMARDs such as gold compounds (auranofin) (Kvien *et al.* 1986, Giannini *et al.* 1990) and sulfasalazine (Huang and Chen 1998; Van Rossum *et al.* 1998) have been used with little side-effects and some efficacy.

Glucocorticoid drugs. Systemic glucocorticoids are used mainly to control systemic manifestations. A low-dose — 0.1–0.2 mg/kg (Michels 2000) — or alternate-day orally administered prednisolone is widely accepted in the initial treatment of a moderately to severely affected child; it has a supportive effect until the effect of another, slower-acting drug develops.

Intravenous pulse glucocorticoid therapy, with its immediate effect, has an important role in the approach to serious, unresponsive disease, for controlling systemic features without special serious side-effects (Adebajo and Hall 1998). Methylprednisolone is the drug of choice.

Intra-articular corticosteroid injection in children is a safe and effective mode of therapy, used successfully in all the subtypes (Breit *et al.* 2000) in preventing e.g. leg length discrepancies and correcting joint deformities. A must is that every pediatric rheumatologist acquires a good knowledge of the intra-articular injection techniques and uses this treatment often and nearly without limitations. It can be used in every joint, even in the temporomandibular joint,

but this injection may be followed by complications, if the doctor is not experienced. The benefit of this form of corticosteroid therapy is seen within a day or two. The drug to be recommended is triamcinolone hexacetonide, which has a longer effect than methyprednisolone (Honkanen *et al.* 1993). However, in any joint where an injection may result in leakage into the surrounding tissues, methylprednisolone is safer than triamcinolone hexacetonide, as the latter may produce profound atrophy of the fat and other tissues in the proximity of the joint.

Cytotoxic and immunosuppressive drugs like azathioprine (Savolainen *et al.* 1997; Lin *et al.* 2000), cyclophosphamide (Wallace and Sherry 1997; Shaikov *et al.* 1992) and cyclosporine A (Ostensen *et al.* 1988; Gerloni *et al.* 2001) are an alternative choice in serious situations, e.g. nonresponsive systemic arthritis. Leflunomide is a new drug which inhibits lymphocyte proliferation, and has been studied very recently by Silverman *et al.* (2005) in refractory polyarticular patients, with good effect in nearly half of the patients. In another study, the efficacy of leflunomide was compared with MTX in patients with polyarthritis, showing high rates of clinical improvement with both drugs, but with the rate slightly higher for MTX (Silverman *et al.* (2005).

Biological agents. With the introduction of these drugs targeted at cytokines or their receptors, a complete breakthrough came in the treatment of JIA resistant to MTX (Lovell *et al.* 2000; Lovell *et al.* 2003).

Tumor necrosis factor alpha (TNF-α) inhibitors. Etanercept — soluble TNF-α receptor (TNFR) p75 fusion protein — is so far the only biological agent approved for use in children. It is given subcutaneously twice a week in a minimum dose of 0.4 mg/kg (maximum 25 mg per injection), with a continuation of previous medications, such as MTX and an NSAID (Schmeling *et al.* 2001; Haapasaari *et al.* 2002). There exists the risk of a reactivation of tuberculosis (Mohan *et al.* 2004) or the development of granulomatous or fungal disease (Wallis *et al.* 2004). In the first published extensive clinical trial (Lovell *et al.* 2000), etanercept proved to be effective in polyarthritis patients resistant or intolerant to MTX; the drug was well tolerated with only mild to moderate upper respiratory infections or injection-site reactions. In 2003 Lovell *et al.* reported the good effect of etanercept in patients with polyarthritis with more than two years of treatment. Etanercept has not shown sustained efficacy in systemic arthritis (Schmeling *et al.* 2001; Russo *et al.* 2002; Quartier *et al.* 2003) and has been associated with the development of macrophage activation syndrome in some cases (Kimura *et al.* 2005). In addition to the suppression of inflammation, etanercept restores growth velocity in polyarticular course arthritis (Tynjala *et al.* 2006).

Infliximab — a chimeric human-mouse monoclonal antibody to TNF-α.

Ruperto *et al.* (2005) has shown promising results in polyarticular arthritis with infliximab, administered using either three or six mg/kg in combination with MTX. Lahdenne *et al.* (2003) compared etanercept (10 patients) with

infliximab (14) in refractory polyarthritis; 23 were taking MTX in addition. After 12 months, 89% in the etanercept group achieved an ACR 50% response, compared with 75% in the infliximab group.

Since 1997, **autologous stem cell transplantation (ASCT)** has been applied to a number of children in whom the control of severe active disease has not been achieved by other modalities, including anti-TNF therapy. De Kleer *et al.* (2004) reported about 34 children treated with ASCT in nine different European transplant centres. Eighteen of the 34 patients (53%) with a follow up of 12 to 60 months achieved complete drug-free remission. Although promising, the procedure carries a significant mortality risk.

Orthopedic surgery. **Synovectomy.** The reported results of this operation are quite controversial. Jacobsen *et al.* (1985) found not considerable benefit from the operation with reference to pain or improvement of range of motion, but it did seem to provide permanent relief of joint swelling. A reduction in signs of inflammation after synovectomy has been described by Kvien *et al.* (1987) with the effect lasting at least two years; there have also been Hafner and Pieper (1995) and Pahle (1996) — in the latter study, over a period of 13 years 528 synovectomies were performed, with a very low recurrence rate of inflammation.

Promising results in **total hip and knee arthroplasty** have been reported in young patients (Chmell *et al.* 1997; Parvizi *et al.* 2003), although the authors stress that these operations should be used as a last resort and only in the most severe cases. Every effort should be done to minimize the need for these interventions in children.

9. Course of the disease and prognosis

JIA is not a benign disease, since a considerable number of patients still enter to the adulthood with a persistently active disease, and a significant proportion of them may develop a severe physical disability (Ravelli, 2004). Many studies on the outcome and prognosis of JIA concentrate on the early and long-term prognosis of the different onset subtypes (Oen *et al.* 2002; Fantini *et al.* 2003; Oen *et al.* 2003; Flato *et al.* 2006). Although the course of the disease can vary from child to child, common predictors of certain course types and outcome have been searched for by many authors (Ruperto *et al.* 1997; Guillaume *et al.* 2000; Al-Matar *et al.* 2002, Flato *et al.* 2003; Flato *et al.* 2006). Certain variables — involvement of upper limb (especially wrist), hip or ankle and elevated ESR — as present during the first six months of the disease forecast the long-term prognosis (Guillaume et *al.* 2000; Al-Matar *et al.* 2002, Felici *et al.* 2005; Flato et *al.* 2006).

Referring the patients in time and providing adequate initial treatment are of crucial importance (Flato *et al.* 1998; Fantini *et al.* 2003).

In general, in persistent oligoarthritis and systemic arthritis (monocyclic course type), the prognosis rate is the best and remission rate is the highest (Minden *et al.* 2000; Oen *et al.* 2002; Bowyer *et al.* 2003; Wallace *et al.* 2005, Selvaag *et al.* 2005). Bowyer *et al.* (2003) found that at one year after diagnosis, half of the oligoarticular and systemic patients no longer required medication, compared to 78% of the polyarthritis patients. According to Wallace *et al.* (2005), RF positive patients are the least likely (only 5% of patients) to achieve clinical remission off of medication. An unfavourable course in polyarthritis has also been shown by Minden *et al.* (2000); complete remission within 10 years is seen in only 15% of patients (Guillaume *et al.* 2000 and Oen *et al.* 2002).

Patients with enthesitis related arthritis have a poorer physical outcome when compared to oligoarticular or polyarticular cases (Selvaag *et al.* 2005; Flato *et al.* 2006), but the outcome is better in juvenile onset spondyloarthropathy when compared to adult onset ankylosing spondylitis, having a less severe spinal disease (Baek *et al.* 2002). On the other hand, an impairment of functional capacity has been found to be more severe in the juvenile onset group (Garcia-Morteo *et al.* 1983; Stone *et al.* 2005). Only 44% of patients had achieved remission after a mean course of 15.3 years, and reduced spinal flexion was present in 75% and sacroiliitis in 35% (Flato *et al.* 2006). In a case controlled study the predictors of not attaining remission were: ankylosing spondylitis in a first-degree relative, the presence of HLA-DRB1*08, and ankle arthritis in the first six months (Flato *et al.* 2006).

In systemic arthritis, the functional outcome can be poor in patients with polycyclic and persistently active course. The severity of disability evaluated according to Steinbrocker classes is dependent upon the cumulative duration of the active periods of the disease (Lomater *et al.* 2000). Onset before the age of five years and the presence of active systemic disease at six months strongly predicts the development of a poor functional outcome (Schneider *et al.* 1992; Spiegel *et al.* 2000). On the other hand, the absence of active arthritis, an ESR of <26 mm/hour, and no requirement for corticosteroid therapy at three and six months are predictors of an earlier remission (Singh-Grewal *et al.* 2006). Woo reported recently (2006) that up to 30% of systemic patients had active disease after 10 years, and morbidity within this group was high. These patients had serious developmental and social problems.

According to Southwood *et al.* (1989) polyarticular course was examined in 65.7% of 35 patients with psoriatic arthritis. In a study by Hochberg *et al.* (1992), after a mean follow-up of seven years 40% of 63 patients with psoriatic arthritis had persistently active disease. In the series presented by Roberton *et al.* (1996), active disease was present in 70% of 63 patients after a minimum follow-up of 5 years; 30% of the patients were in the functional class III-IV. Progression to polyarticular disease is more common in younger children; older

patients tend to manifest enthesitis, axial joint disease and persistent oligo-arthritis. Younger children with psoriatic arthritis require a longer period of treatment to achieve clinical remission (Stoll *et al.* 2006).

Long-term prognosis. In publications with a follow-up of patients of least five years (5–14.9 years), the remission rate has been found to be in the range of 23–60% for the whole patient group (Michels *et al.* 1987; Flato *et al.* 1998; Guillaume *et al.* 2000; Flato *et al.* 2003; Fantini *et al.* 2003). Joint erosions developed in 24–35% of cases (Flato *et al.* 1998, Flato *et al.* 2003; Guillaume *et al.* 2000). Predictors of unfavourable course are RF positivity (Michels *et al.* 1987; Flato *et al.* 1998; Flato *et al.* 2003); polyarticular course (Michels *et al.* 1987, Selvaag *et al.* 2006), a long duration of elevated ESR (Flato *et al.* 1998; Flato *et al.* 2003); symmetric arthritis (Al-Matar *et al.* 2002; Flato *et al.* 2003); HLA-DRB1*08, -DRB1*01, HLA-B27 and -DRB1*08 in combination; early onset; and female sex (Flato *et al.* 2003).

Ruperto *et al.* (1997) evaluated long-term outcomes in 227 patients with a mean duration of disease of 15 years. The best predictor of long-term disability present during the first six months was the articular severity score, followed by early hand involvement. ANA positivity was associated with less disability.

Progression to polyarthritis in patients with oligoarticular onset has been described in 20%–50% of patients with oligoarticular onset with a mean duration of the disease of 3.9–16.5 years (Guillaume *et al.* 2000; Oen *et al.* 2002; Minden *et al.* 2002; Al-Matar *et al.* 2002; Fantini *et al.* 2003; Felici *et al.* 2005). The early predictors of disease progression are ankle and/or wrist involvement (Al-Matar *et al.* 2002, Felici *et al.* 2005) and elevated ESR during the first six months (Al-Matar *et al.* 2002; Guillaume *et al.* 2000). Symmetric joint involvement (Al-Matar *et al.* 2002) and an involvement of more than one joint or of an upper limb at disease onset (Guillaume *et al.* 2000) have also been found to be predictors of disease extension. The course of extended oligoarthritis is more complicated (Guillaume *et al.* 2000; Minden *et al.* 2002; Flato *et al.* 2003). In the series presented by Minden *et al.* (2002) only 3/26 (12%) patients with extended oligoarthritis were in remission after a mean follow-up of 16.5 years. In the whole series two of those three who had developed amyloidosis belonged to the extended oligoarticular subgroup. Joint erosions are more frequent in those with extended oligoarthritis when compared to persistent oligoarthritis (Guillaume *et al.* 2000; Flato *et al.* 2003).

According to Oen *et al.* (2003), the most important early predictors of outcome were age at onset and sex. Male sex predicted worse disability in systemic onset, but less disability in RF negative polyarthritis, and shorter active disease duration in RF positive polyarthritis. ANA positivity correlated with longer active disease duration in oligoarthritis. A younger age at onset predicted longer active disease duration in oligoarthritis and RF negative polyarthritis, and a shorter one in systemic onset.

10. Disease activity and remission criteria

Common criteria concerning disease activity and remission in JIA do not exist. Different authors have used different definitions and different time periods needed for "remission off the drugs".

As suggested by the EULAR Standing Committee on Paediatric Rheumatology (Moscow 1983) (cited by Andersson Gäre), the activity of disease is divided into four groups: a) active — i.e. increasing number of active joints irrespective of drug therapy; b) stable — i.e. stable number of joints but requiring drug therapy; c) inactive — i.e. no evidence of active synovitis and/or active extra-articular features and without drugs for less than two years; d) remission — i.e. no signs of active synovitis and/or active extra-articular features, and blood inflammatory markers within normal limits and at least two years without drugs (Andersson Gäre and Fasth 1992).

A definition of improvement for juvenile arthritis, based on a core set of outcome variables, was developed with the participation of 21 pediatric rheumatologists from 14 countries, using consensus formation techniques and scoring 72 patient profiles as improved or not improved. Variables in the core set consisted of: 1) physician global assessment of disease activity; 2) parent/ patient assessment of overall well-being; 3) functional ability; 4) number of joints with active arthritis; 5) number of joints with limited range of motion; and 6) erythrocyte sedimentation rate. The definition of improvement with the highest final score was as follows: at least 30% improvement from the baseline in three of any six variables in the core set, with no more than one of the remaining variables worsening by more than 30%, known in the literature as the ACR Pedi 30% response criteria (Giannini *et al.* 1997).

In 2004, Wallace *et al.* reported the results of a consensus vote (130 pediatric rheumatologists from 34 countries responded to the questionnaire and 20 from nine countries attended a nominal group technique conference). Draft criteria for inactive disease include the following: no active arthritis; no fever, rash, serositis, splenomegaly, or generalized lymphadenopathy attributable to JIA; no active uveitis; normal ESR or CRP; and a physician's global assessment of disease activity rated at the best score possible for the instrument used. Six continuous months of inactive disease on medication defines clinical remission on medication, while 12 months of inactive disease off all anti-arthritis (and anti-uveitis) medications defines clinical remission off medication. Having used these criteria in the following study, the results revealed that 36% of episodes of clinical remission off medication persisted for at least two years, and only 6% of such episodes persisted for five years (Wallace *et al.* 2005). Among patients with persistent oligoarthritis, most of the disease course was characterized by inactive disease; in most other patients the majority of the disease course involved active disease. Only one-fourth of 878 episodes of inactive disease resulted in clinical remission off medication during follow-up of at least four years.

11. Physical and psychosocial impacts of JIA

A significant portion of patients enter adulthood with still active disease or problems related to the disease that started in childhood (Minden *et al.* 2000).

As reviewed above, quite a proportion of JIA patients suffer from long-lasting disease resulting in more or less pronounced disability. They have to experience many unpleasant events such as pain, painful procedures, taking medicines and obligatory exercises in childhood. All of this can affect their personality. According to Miller (1993) most children cope with chronic painful or disabling disease rather well. Yet in a proportion of children psychosocial dysfunction is evident (Baildam *et al.* 1995). In adolescence important physical and psychological changes take place. Visible physical defects may affect body image and self-esteem; in this vulnerable age differences in appearance are often exaggerated. Pubertal development can be delayed. The adolescent may need continuous support from the family.

In their follow-up study of an average length of 24.7 years, Peterson *et al.* (1997) evaluated the impacts of JRA in a cohort of 44 adults in whom the disease had begun in childhood, and found greater disability, more bodily pain, increased fatigue, poorer health perception, and decreased physical functioning compared with the controls. JRA cases reported significantly lower rates of employment and lower levels of exercise than did controls. Levels of educational achievement, annual income, health insurance status, and rate of pregnancy and childbirth were similar for both cases and controls.

According to Minden *et al.* (2002), even though approximately half of the JIA patients had more or less distinctive changes in body function and/or structure after disease duration of more than 15 years, fewer than 10% were severely disabled or handicapped. On the other hand, Flato *et al.* (2003) found that after a median follow-up of 14.9 years, 36% of the patients had impaired physical functioning and a lower employment rate compared with healthy controls.

Selvaag *et al.* (2005) followed up 197 patients for 3.1 years and found that predictors of reduced physical function were a high Child Health Assessment Questionnaire disability index and a poor sense of well-being assessed during the first six months.

Arkela-Kautiainen *et al.* (2005) found that patients with extended oligoarthritis attained significantly lower scores in the physical and mental components of a health- related quality of life than persistent oligo- or polyarthritis patients.

12. Death

In earlier studies the overall death rate was 1–4% (Baum and Gutowska 1977; Bernstein 1977). Nowadays it is less than 1% in Europe and less than 0.3% in North America. Stoeber (1981) reported on 433 children followed on average for 15 years; in this group the mortality rate was 13.8% in the systemic polyarticular group, 1% in the non-systemic polyarticular and 0% in the oligoarticular arthritis group. In a study from England, the standardized mortality ratio was 3.4 for males and 5.1 for females (Thomas *et al.* 2003). The majority of deaths was previously related to amyloidosis, peri/myocarditis and infections in systemic arthritis.

THE PRESENT STUDY

Reasons for undertaking the present study

Epidemiological data — the number of new cases per year, the number of active cases at a certain point in time in the population, requiring some kind of drug therapy and team management — and knowledge concerning course and outcome are valuable for forecasting the costs a disease causes to society and for planning health care services.

Until the present study no population-based epidemiological studies on JIA had been performed in Estonia or other previous Soviet countries. Before 1995, diagnosis had not been made on a unified and common basis and standardized classification criteria had not been used; therefore it was difficult to identify the number of JIA cases, since other causes of arthritis had been grouped with great probability together with JIA.

The serological diagnosis of infectious diseases has become available since 1995, and thereafter it has been possible to differentiate infectious arthritis from other childhood arthritides in a more reliable way.

For the reasons mentioned above it was the time and need for a population-based study involving the whole country.

The treatment of JIA nowadays includes very promising new — biological — drugs. These are very expensive: one month treatment with etanercept costs 7936.75 Estonian crowns and one intravenous course of infliximab costs 9332.17 Estonian crowns for a small child. Therefore, reliable number of patients is needed for determining those who will benefit from these treatments and for counting the cost of the treatment.

AIMS OF THE STUDY

- To study the incidence rate of JIA and its clinical subtypes in Estonia for the years 1998–2000;
- To study the point prevalence of JIA in children in Estonia on December 31, 2000;
- To examine the course and short-term clinical outcome of JIA.

PATIENTS AND METHODS

1. Study area and population

Estonia is the northernmost of the Baltic States, with 15 counties, a population of 1.3 million, and an area of 45 square kilometres. Fourteen of the 15 counties participated, and only the eastern part of Virumaa was not included, due to a lack of feedback from the doctors of the region.

Figure 1. The upper picture shows the location of Estonia and the Nordic countries. The lower picture depicts a regional map of Estonia. One county — Eastern Virumaa (depicted on the map using a darker shade) was left out of the study.

The population at risk in the study area was 262 284 children, all Caucasian, aged 0–15 years at the onset of the incidence study (January 1, 1998) and 231 778 at closure (December 31, 2000) (Statistical Office of Estonia, www.stat.ee). The mean population in the study period was 248 624 (127 187 boys and 121 437 girls). The mean population of the county which was left out — Eastern Virumaa — was 35 393 (18 111 boys and 17 282 girls).

The mean population at risk in the year 2000, used in calculating the point prevalence, was 235 395 (120 676 boys and 114 719 girls). The mean population of the county which was left out — Eastern Virumaa — was 33 219 (17 083 boys and 16 136 girls) for the same year.

Health care in Estonia is universally available. Family doctors serve as a first level and county hospitals form a second level. Patients with chronic diseases such as JIA are referred according to the consensus document to the two tertiary level children hospitals for investigations and special care — i.e. pediatricians specialized in pediatric rheumatology. There are two tertiary level hospitals for children in Estonia — Tallinn Children's Hospital for the northern part of Estonia and the Children's Clinic of Tartu University Hospitals for the southern part.

2. Study period

The incidence study (papers 1 and 2) was performed prospectively from January 1, 1998 to December 31, 2000. In addition, all cases in which the onset of the disease occured during the study period (before Dec. 31, 2000), but for which the diagnosis was made in the first half of 2001 (last date Jun. 30, 2001), were also included in the study. The follow-up period was two years for each case after diagnosis, ending June 30, 2003 for the last enrolled patients diagnosed in the first half of 2001.

The study period for the prevalence study (paper 3) covered the years 1995–2000. Active patient and data collection began from January 1, 1998 and was carried out between 1998–2000 in parallel fashion with the incidence study.

3. Patients

Criteria for inclusion. The ILAR criteria (the revision of 1997) were used for the recruitment and classification of patients (Tables 1–3).

In the incidence study (papers 1 and 2) were included children aged 0–15 years who had arthritis (a swollen joint or two of the following three: 1) limitation of movement; 2) warmth; and 3) pain on passive or active movement) of an unknown cause for at least six weeks, inflammatory back pain and enthesitis or spiking fever together with other symptoms suggestive of systemic arthritis with an onset of the disease during the study period.

Children with infectious arthritis, postinfectious arthritis, traumatic arthritis and systemic connective tissue diseases were excluded.

The prevalence study (paper 3) included two populations of patients: a) children aged 0–15 years (born Dec. 31, 1984 and afterwards), living in the study area and having an onset of arthritis between 1995–1997, the early JIA series; and b) children with an onset of arthritis during 1998–2000 and diagnosed during the incidence study, the incidence series. Of these patients were included, on Dec. 31, 2000, into this study only those in whom JIA was: (1) active, i.e. the number of active joints increasing irrespective of drug therapy; (2) stable, i.e. a stable number of joints but requiring drug therapy; or (3) inactive, i.e. no evidence of active arthritis and/or active extrarticular features and without drug therapy for less than two years on the date given above. For estimating the disease activity the definitions suggested by the EULAR Standing Committee on Paediatric Rheumatology (Moscow 1983) (cited by Andersson Gäre and Fasth 1992) were used. Patients diagnosed during the study period but in remission — i.e. those with no signs of active synovitis and/or active extraarticular features, blood inflammatory markers within normal limits and at least two years without drugs — were excluded.

4. Study design

4.1. Patient retrieval and data collection

Both of the two tertiary children's hospitals in Tartu and Tallinn participated in the study.

Before the beginning of the study, a meeting to confirm the study design, inclusion/exclusion criteria, and a consensus document was held, with the presence of the administrations of the two hospitals and of all the pediatric rheumatologists participating in the study. Additionally, a couple of meetings were held with local pediatricians of the counties and family doctors during the study period through teaching seminars and advanced courses, where the inclusion criteria and classification of JIA were introduced and discussed with the purpose of improving collaboration and getting all patients having or suspected of having JIA in the region included. According to the guidelines for the first level practitioners approved by the Estonian Association of Paediatricians, the diagnosis of JIA should be confirmed and the treatment started in the third-level centre by a pediatric rheumatologist.

Before starting the incidence study, all the pediatricians in charge of the 14 counties, and family practitioners were informed by mail about the beginning of the study, and the list of important symptoms and diagnostic criteria for JIA were added to the letters. All the doctors were asked to send all new patients

with JIA, and those they suspected of having JIA, to one of the two tertiary children's hospitals. In addition the doctors were asked to report to either of the tertiary hospitals for the prevalence study on all patients meeting the JIA criteria and diagnosed since Jan. 1, 1995 in their region. Altogether 50 separate family doctors and family medicine centres (with more than one family doctor) were practising at the beginning of the study; they were all contacted by mail. There are only few orthopaedic surgeons and physical therapists consulting children in Estonia and they work in these two centres which participated in the study.

In addition to the abovementioned doctors county hospitals, county outpatient clinics and medical and health care centres (altogether 47) were informed by mail about the beginning of the study, and the criteria for JIA were added to the letters.

During the study period, in the beginning of the year 2000, all the doctors were contacted again by mail and were asked for JIA patients diagnosed in their area during the study period. The received information was compared with the data of the two hospitals. Finally, in the middle of 2001 the doctors were contacted once more in order to include in the study, in addition to all the patients for whom a diagnosis had been made in the second half of 2000, even those in whom the disease onset was before Dec. 31, 2000, but for whom the diagnosis was made in the first half of 2001. The primary care system was at the same time rapidly developing and the number of family doctors practising in the counties examined increased significantly during the study period. In the end of the study already 412 family doctors and family medicine centres were contacted.

The active collection of patients and data for the prevalence study started concurrently with the incidence study on Jan. 1, 1998. Part of it was a retrospective analysis of the medical records of patients with an onset of JIA between 1995–1997 for including and classifying the cases and for the data needed for analysis.

4.2. Follow-up

Clinical and laboratory investigations. In the incidence study the patients were followed up according to the study protocol for two years after the diagnosis was made. For the prevalence study, medical records were analysed retrospectively.

Joint status was fixed at the time diagnosis was made, at six months, at one year and at two years later.

Eyes were examined during the first six months after the diagnosis in most cases; a slit lamp was used for examination. After the first examination the patients were seen by an ophthalmologist at least once a year; those with eye involvement as often as needed.

The heart was examined in all the cases of systemic arthritis, in HLA-B27 positive patients and in patients with complaints suggestive of cardiac involvement.

Laboratory investigation was undertaken to study the markers of inflammation, i.e. ESR (normal value 4–12 mm/h), CRP (normal below 5 mg/l), and counts of white blood cells and platelets. RF was measured using a semiquantitative latex test, with a titre of 20 IU/ml or more considered as positive. ANA were determined by an indirect immunofluorescence method, with positive titres in children from 1:10; in Tallinn nearly half of the analyses were done with enzyme-linked immunosorbent assay. For positive RF and ANA, both of them should be positive at least two times during the first six months of observation, with an interval between separate analyses of at least three months. These laboratory tests and serum levels of immunoglobulins (S-IgG, S-IgA and S-IgM) were studied at the time of diagnosis, and at six months, at one and at two years after the diagnosis. HLA-B27, -DR1 and -DR4 antigens were detected by using polymerase chain reaction. HLA-B27 antigen was studied in 98 patients and -DR1 and -DR4 antigens in 27 of these 98 patients. Ultrasound and x-ray investigations of affected joints were performed at the time the diagnosis was made. X-ray investigation was repeated in case of clinical indication mostly at one year and at two years later. Ultrasound investigation of joint(s) was repeated as often as needed.

Ethics. The study was approved by the Ethics Review Committee on Human Research of the University of Tartu. All the parents or the patients gave informed consent for participation in the study.

5. Statistical analysis

The statistical analysis was performed using the statistical package SAS Version 8.02. Continuous variables are presented as mean values (95% confidence interval, CI), while qualitative variables are presented as absolute and relative frequencies. To compare proportions (qualitative variables) the Chi-square test or the Fisher's Exact test (when expected values were <5%) were used.

Kolmogorov-Smirnov criterion was used for the assessment of normality. Comparisons between groups were performed using a non-parametric test — the Wilcoxon-Mann-Whitney test.

The mean population at risk for the incidence study was calculated using the numbers of 0–15 year old children at the beginning of 1998, 1999, 2000 and 2001 (leaving out the 15th county). The mean incidence rate is based on the number of children included during the study period, divided by the estimated population at risk and divided by three. The PR per 100 000 was calculated using the number of 0–15 year old children in the year 2000. Ninety-five percent CI for IR and PR were calculated based on the Poisson distribution. Statistical significance was set at the 95% level ($p<0.05$).

RESULTS

1. Incidence of JIA (papers 1 and 2)

One hundred and sixty two (162) children (76 boys and 86 girls) had an onset of JIA during the years 1998 to 2000. In 1998, JIA was diagnosed in 26 children aged 0–15 years. Forty-five children were diagnosed in 1999, and 85 in 2000. Six children with an onset of the disease in the second half of 2000 were diagnosed with JIA in the first half of 2001 (Figure 2).

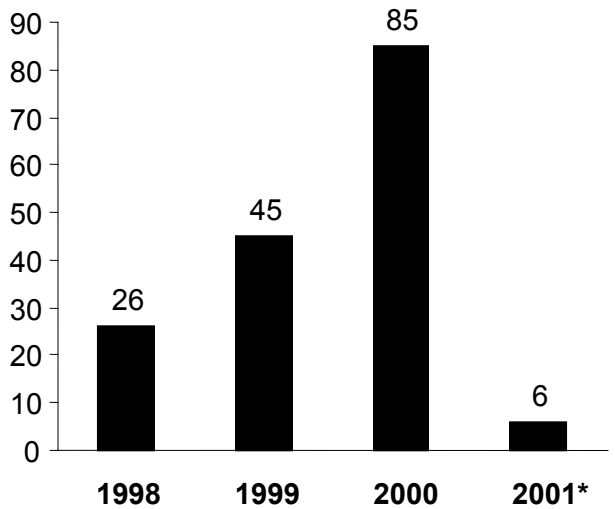

Figure 2. New cases of JIA in 1998–2000.
* Six children who had an onset of the disease in the second half of 2000 were diagnosed with JIA in the first half of 2001.

Table 4. Mean annual IR per 100 000 children aged 0–15 years according to age at onset of the disease

Age at onset of the disease (years)	Number of new cases	Mean annual IR; (95% CI)	Mean annual IR; girls (95% CI)	Mean annual IR; boys (95% CI)
0–3	17	12.7 (2.2; 23.1)	12.3 (0; 27.0)	13.1 (0; 27.8)
4–6	22	18.7 (5.2; 32.3)	15.8 (0; 33.7)	21.6 (1.3; 41.9)
7–10	50	23.8 (12.4; 35.3)	25.6 (8.5; 42.6)	22.3 (6,9; 37.8)
11–15	62	21.8 (12.4; 31.2)	26.8 (11.8; 41.7)	17.2 (5.5; 29.0)
0–15	151*	21.7 (15.4; 26.7)	22.9 (14,5; 31.3)	19.3 (11.8; 26.8)

* The exact time of the onset of the disease could be determined in 151 of 162 cases (93.2%).

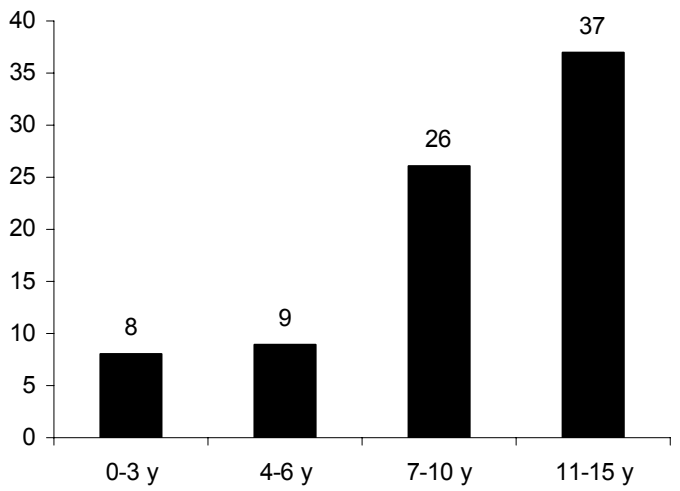

Figure 3. Age distribution in girls at time of onset of JIA, incidence study. The exact time of the onset of the disease is known in 80 patients.

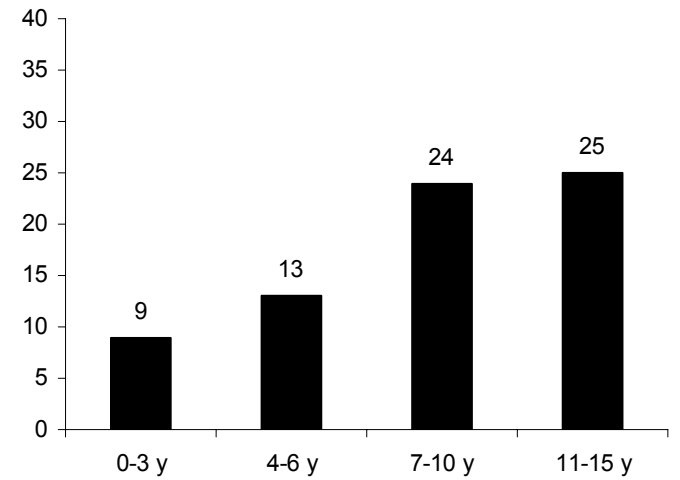

Figure 4. Age distribution in boys at time of onset of JIA, incidence study. The exact time of the onset of the disease is known in 71 patients.

In the first phase, nearly 100 letters were sent to first level practitioners, county hospitals, county outpatient clinics and medical and health care centres. Ten per

cent of the contacted doctors answered, including all the pediatricians in charge of the 14 counties (practising at the county hospitals). The chief pediatricians had contacted the local pediatricians in their county and answered in the name of all of them. At that time the system of first level medical aid was under quick development process. Family doctors did not answer separately in this phase as many of them were former pediatricians undergoing specializing in family medicine.

In the second phase 385 letters were sent to family doctors, family medicine centres, county hospitals and county outpatient clinics; 95 answers were received (25%). At that time 370 family doctors were practising. Family medicine centres with more than one doctor practising sent usually one answer in the name of all the doctors.

In the final phase already 412 family doctors or family medicine centres were contacted, like as county hospitals and outpatient clinics. One hundred and sixty-five (40%) of them answered.

Fourteen patients were reported by family doctors, but as they were never sent to the participating centres to confirm the diagnosis by a specialist to be sure that they were real JIA cases, they were not included in the study.

The mean annual IR was 21.7 per 100 000 children aged 0–15 years; 22.9 per 100 000 girls and 19.3 per 100 000 boys (Table 4).

The mean annual IR was the highest in the 7–10 years age group. Girls were affected most often between the ages of 7–15 years and boys between 4–10 years (Figures 3 and 4).

The mean age at the onset of JIA symptoms was 9 years 6 months (standard error (SE) 0.3); 10 years and 1 month (SE 0.4) for girls and 8 years and 10 months (SE 0.5) for boys. It was lowest in the systemic subtype ─ 4 years and 3 months and highest in the enthesitis related arthritis subtype ─ 12 years and 6 months (Table 5).

An infection was documented prior to the onset of the disease in 31% of the patients. Preceding infections were mainly viral: 23/45 (51.1%) were respiratory infections, 6/45 (13.3%) were unspecified gastrointestinal infections and 18/45 (40%) were, according to the records, unspecified viral infections. The number of preceding infections increased from 11 cases in 1998 to 26 cases in 2000.

Table 5. Subtypes of JIA: mean annual IR, mean age at the onset of the disease, proportion of girls

Subtype	Number of new cases (girls)	Percentage of new cases in which the subtype is known (160)	Mean annual IR per 100 000 children aged 0–15 years (95% CI)	Mean age at the onset of the disease (SE)
Oligoarthritis Persistent Extended	87 (43) 70 (33) 17 (10)	54.4 43.8 10.6	11.7 (7.4; 5.9) 9.4 (5.6; 13.2) 2.3 (0.4; 4.2)	9y 2mo (0.4) 8y 11mo (0.5) 10y 3mo (0.8)
Polyarthritis RF neg	33 (22)	20.6	4.4 (1.8; 7.0)	9y 11mo (0.6)
Polyarthritis RF pos	7 (6)	4.4	0.9 (0; 2.1)	11y 6mo (0.8)
Systemic arthritis	7 (2)	4.4	0.9 (0; 2.1)	4y 3mo (1.2)
Enthesitis related arthritis	11 (3)	6.9	1.5 (0; 3.0)	12y 6mo (0.7)
Psoriatic arthritis	5 (2)	3.1	0.7 (0; 1.7)	9y 8mo (2.3)
Other arthritis	10 (7)	6.3	1.3 (0; 2.8)	9y 1mo (1.2)
Total	162 (86)		21.7 (15.4; 26.7)	9 y 6 mo (0.3)

1.1. Distribution of subtypes (paper 2)

In the incidence group oligoarthritis was the most frequent subtype (87 cases (54.4%) followed by seronegative polyarthritis (33 cases, 20.4%). Thirteen (14.9%) of the oligoarthritis cases had monoarthritis. All the polyarthritis cases formed 20.3% of the incidence cases (Table 5).

The mean annual IR for oligoarthritis was 11.7 per 100 000 children aged 0–15 years. A systemic subtype was more often diagnosed in boys (five cases) compared to two cases in girls. Polyarthritis (both seronegative and seropositive) was more often found in girls (28 cases compared to 12 cases in boys). For other arthritis cases 7 cases out of 10 were girls in the incidence study.

2. Prevalence of JIA (paper 3)

On Dec. 31, 2000 there were 197 children (94 boys and 103 girls) aged 0–15 years and living in the 14 counties of Estonia in whom JIA, with an onset between 1995–2000, was active, stable or inactive. Thirty (30) patients had an onset of the disease between 1995–1997 and 167 patients between 1998–2000.

The point prevalence was 83.7 (95% CI 72.4; 95.8) per 100 000 children aged 0–15 years, 77.1 (95% CI 62.2; 93.5) for boys and 90.7 (95% CI 74.1; 108.9) for girls (Table 6). Seventeen patients with an onset of the disease occurring during 1995–2000 were classified as being in remission on Dec. 31, 2000. Including these patients as well would have given a point prevalence of 91 per 100 000 children aged 0–15 years (95% CI 79.1; 103.5); 85.4 for boys (95% CI 69.7; 102.6) and 96.8 for girls (95% CI 79.6; 115.6).

Table 6. PRs according to sex and age groups (Dec. 31, 2000)

Age groups (y)	Number of cases	All cases (95% CI)	Girls (95% CI)	Boys (95% CI)
0–3	7	16.3 (6.6; 30.4)	9.6 (1.2; 26.7)	22.6 (7.3; 46.2)
4–6	27	76.4 (50.4; 107.8)	92.6 (52.9; 143.2)	60.9 (30.4; 101.9)
7–10	53	82.8 (62; 106.5)	80.3 (52; 114.7)	85.2 (56.6; 119.5)
11–15	107	115 (94.2; 137.7)	132 (100.7; 167.4)	98.7 (72.6; 128.9)
0–15	194*	83.7 (72.4; 95.8)	90.7 (74.1; 108.9)	77.1 (62.2; 93.5)

* In three patients the exact birth date was not found in records.

The PR was the highest among 11–15 year old girls (132: 100 000) and the lowest in 0–3 year old girls (9.6: 100 000). Twenty-one patients were reported by family doctors, but as they were never sent to either of the participating centres to confirm the diagnosis by a specialist to be sure that they were real JIA cases, they were not included in the study.

The mean age at the onset of JIA symptoms in the prevalence study was 8 years and 8 months (95% CI: 8y 2mo; 9y 4mo) (Table 7); 9 years and 1 month for girls and 8 years and 4 months for boys (Figures 5 and 6).

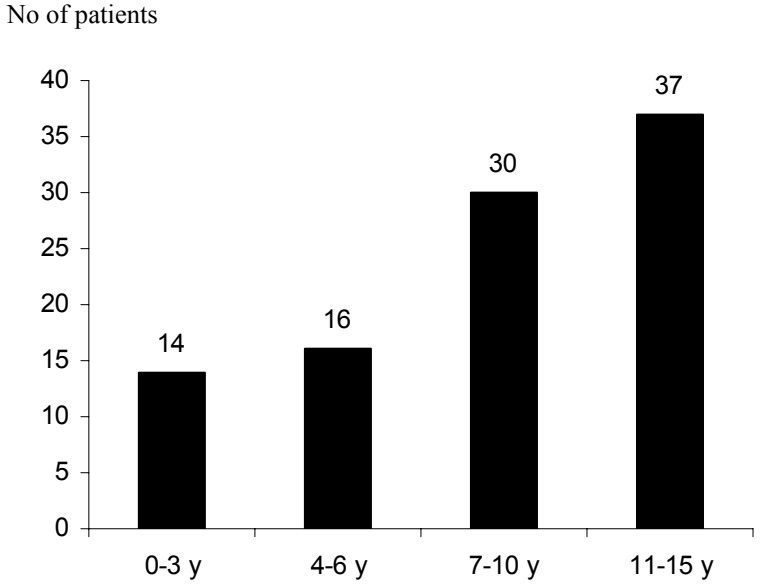

Figure 5. Age distribution in girls at time of onset of JIA, prevalence study. In 6 patients the birth date or exact time of onset of symptoms is not known.

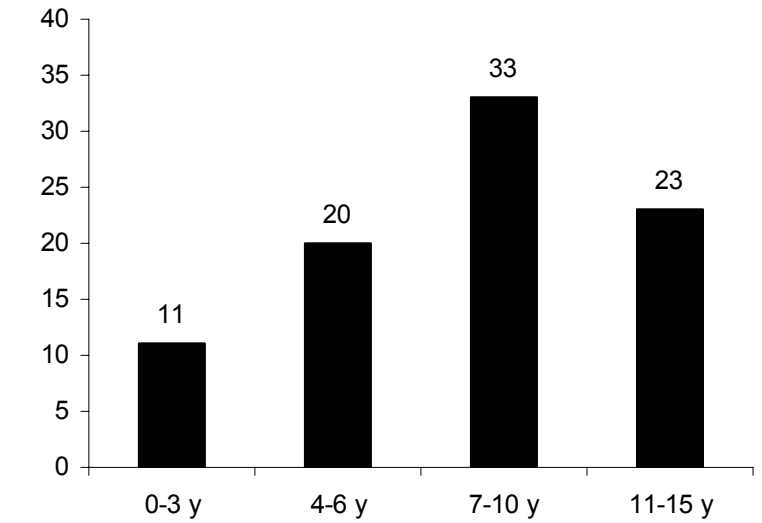

Figure 6. Age distribution in boys at time of onset of JIA, prevalence study. In 7 patients the birth date or exact time of onset of symptoms is not known.

2.1. Distribution of subtypes

A part of the incidence and prevalence series constituted of the same patients. Oligoarthritis was the most frequent subtype in the prevalence series as well — 111 cases (56.3%), followed by seronegative polyarthritis — 39 cases (19.5%). Thirty two (28.8%) of the oligoarthritis cases had monoarthritis. All the polyarthritis cases formed 24.9% of the prevalence cases (Table 7).

Table 7. Subtypes of JIA at onset, proportion of girls, proportional distribution of subtypes, mean age at the onset of the disease. Prevalence study

Subtype	Number of cases (girls)	Percentage of all cases	Mean age at the onset of the disease (95% CI)
Oligoarthritis	111 (56)	56.3	8y 2mo (7y 5mo; 8y 11 mo)
Persistent	88 (40)	44.7	7y 11mo (7y 1mo; 8y 10mo)
Extended	23 (16)	11.7	9y 1mo (7y 4mo; 10y 11mo)
Polyarthritis RF neg	39 (25)	19.5	9y 8mo (8y 8mo; 10y 10mo)
Polyarthritis RF pos	9 (8)	4.5	10y 2mo (7y 4mo; 13y)
Systemic arthritis	8 (2)	4	4y 8mo (2y; 7y 4mo)
Enthesitis related arthritis	11 (2)	5.5	11y 1mo (10y; 12y 2mo)
Psoriatic arthritis	5 (2)	2.5	9y 8mo (3y 4mo; 16y)
Other arthritis	13 (8)	6.5	8y 6mo (6y 2mo; 10y 10mo)
All JIA	196/197*	100	8y 8mo (8y 2mo; 9y 4mo)

* In one patient with polyarthritis the exact classification was not possible, as the RF analysis was not performed.

A systemic subtype was more often diagnosed in boys (six cases compared to two cases in girls). Polyarthritis (both seronegative and seropositive) was more often found in girls (33 cases compared to 16 cases in boys). For other arthritis cases 8 out of 13 were girls.

The systemic subtype was diagnosed earlier (the mean age was 4 years and 8 months and the enthesitis related arthritis subtype started later — the mean age was 11 years and 1 month.

The mean interval between the onset of the disease and the time the diagnosis was made was seven months; it was longest for extended oligoarthritis and psoriatic arthritis (one year for both) and shortest for systemic arthritis (one month).

3. Follow-up

3.1. Clinical characteristics (papers 1–3)

Joint involvement. The knee was the most common first-affected joint, followed by the right hip joint and the ankle joints (Table 8).

Table 8. Joints affected at the onset of the disease

First-affected joint	Number of cases	% of all cases
Left knee	23	14.2
Right knee	22	13.6
Both knees	12	7.4
Right hip	8	4.9
Left ankle	5	3.1
Both ankle joints	5	3.1
Right ankle	4	2.5
Left hip	3	1.9
Bilateral PIP* joints of fingers	3	1.9

* PIP joints — proximal interphalangeal joints

All 7/197 patients with systemic onset had high spiking fever and arthralgia and/or arthritis, three had a typical rash, two had hepato- and/or splenomegaly, and one had pleuritis.

Uveitis. Four patients (2.5%) in the incidence group and five patients (2.5%) in the prevalence group (the four from the incidence study plus one) had chronic uveitis and in three of them it was the initial manifestation of the disease. Cataract secondary to iridocyclitis was present in two patients and one had episcleritis. Three of the patients had oligoarthritis, one enthesitis related arthritis and one systemic arthritis. All five of these patients were ANA negative at the diagnosis; in 1 patient the titer was 1:100 positive a year after the onset of the disease.

3.2. Laboratory tests (papers 1–3)

Incidence study. ESR was elevated at diagnosis in 73/144 patients (50.7%), CRP in 32/144 patients (22.2%), and the count of platelets in 18/144 patients (12.5%). ESR remained elevated in 33 of those 112 patients (29.5%) for whom at least one repeated analysis was performed and CRP in 8/144 patients (5.6%).

ESR was elevated for the whole follow-up period in nine patients (among them three with extended oligoarthritis and three with seronegative polyarthritis).

The titre of ANA was positive at diagnosis for 20/126 (15.9%) patients; 10/20 were with oligoarthritis (among them four with extended oligoarthritis), nine with polyarthritis and one with other arthritis. ANA remained positive for the whole follow-up period in six patients (four extended oligoarthritis). RF was positive in 22/136 (16.2%) patients; eight patients had oligoarthritis, two extended oligoarthritis, seven polyarthritis and five other arthritis. Deviations from normal age-related values in Ig levels were found in 55/162 patients (34%). The most frequent finding was an increase in the value of IgG in 28/131 patients (21.4%) at the diagnosis. Neither hypogammaglobulinemia nor selective IgA deficiency were encountered.

Prevalence study. ESR was elevated at diagnosis in 77/176 patients (43.8% of those for whom the analysis was performed), CRP in 36/168 patients (21.4%), and the count of platelets in 25/169 patients (14.8%). ESR was elevated after six months had passed in 21 patients of those 77 in whom it had been elevated at diagnosis (27.3%), and CRP in 4/36 (11.1%). ESR was elevated for the whole follow-up period in five patients (among them two with extended oligoarthritis, one oligoarthritis, one enthesitis related arthritis and one with seronegative polyarthritis).

The titre of ANA was positive at diagnosis in 26/146 (17.8%) patients; 13 of them had oligoarthritis (among them five with extended oligoarthritis), 11 polyarthritis, one with psoriatic arthritis and one with other arthritis. ANA remained positive for the whole follow-up period in nine patients (four with extended oligoarthritis, four with seronegative polyarthritis and one with psoriatic arthritis). RF was positive in 24/158 (15.2%) patients; nine patients had oligoarthritis, three extended oligoarthritis, seven polyarthritis and five other arthritis. Deviations from normal age-related values in Ig levels were found in 70/152 patients (46.1%).

3.3. HLA antigens (paper 2)

HLA-B27 was determined in 98 patients and -DR1 and -DR4 antigens in 27 of these 98 patients in the incidence series. HLA-B27 antigen was present in 28 (15 boys, 13 girls) out of 98 patients (28.6%). HLA-DR1 was present in 12 patients (44.4%) and -DR4 in three patients (11.1%).

When comparing HLA-B27 positive patients with -B27 negative patients, statistically significant differences were found in the frequency of enthesitis related arthritis, which was diagnosed in eight of 28 HLA-B27 positive patients and in three of 70 HLA-B27 negative patients ($p=0.002$; OR=8.9; 95% CI 2.2; 36.9), and in the persistence of high inflammatory markers (ESR or CRP or both for at least six months in 11 of 28 HLA-B27 positive patients and in 14 of

70 HLA-B27 negative patients (p=0.085; OR = 2.6; 95% CI 1.0; 6.8). No difference was found in the presence of spinal involvement between HLA-B27 positive and negative groups. The mean age at the onset of JIA symptoms was 10 years (95% CI 8 y 6 mo; 11 y 7 mo) in HLA-B27 positive and 9 y 7 mo (95% CI 8 y 7 mo; 10 y 7 mo) in HLA-B27 negative patients. No difference was found between HLA-B27 positive boys and girls considering the mean age at the onset of the disease.

3.4. X-ray investigation. Prevalence study

An X-ray investigation was performed in 146/197 of patients (74.1%) at diagnosis. Of those examined, 87/146 (59.6%) showed no changes and 59/146 (40.4%) had some kind of change in at least 1 joint. The main changes were: periarticular soft tissue swelling in 27/59 (45.8%) patients, waved bone contours in 25/59 (42.4%), periarticular osteoporosis in 8/59 (13.6%), and bone destruction in 5/59 (8.5%). Among the patients with detectable changes there were 26 with persistent oligoarthritis, 9 with extended oligoarthritis, 9 with seronegative polyarthritis, 4 with seropositive polyarthritis, and 4 with other arthritis. After 1 year changes were found in 18 of 59 (30.5%) patients for whom the investigation was performed. Periarticular osteoporosis was present in 8 of 18 patients (44.4%), waved bone contours in 6/18 (33.3%), and bone destruction in 4/18 (22.2%). At 2 years the data are available for 51 patients. The following changes were present in 15 (29.4%) of these patients: periarticular osteoporosis in 5, waved bone contours in 8 and bone destruction in 2. Bone destruction was found in 13 patients during the 2-year follow-up period; 6 patients had oligoarthritis, 4 seronegative polyarthritis, 1 seropositive polyarthritis, 1 extended oligoarthritis, and 1 other arthritis. In 9 of those 13 with bone destruction the disease was still active clinically or according to the inflammatory markers at two years from the onset of the disease. Pathologic changes persisted for at least 1 year in 21 patients. Progression towards more severe changes was found at 1 year in 6/51 of those patients for whom the investigation was performed at diagnosis and after one year. At 2 years the progression was documented in 10 patients, among them 4 with RF negative polyarthritis and one with extended oligoarthritis.

3.5. US investigation of joints. Prevalence study

An US investigation was performed in 152/197 (77.2%) patients at diagnosis. Ninety-five of those 152 (62.5%) showed either a thickening of the synovial layer or an increase in the volume of intraarticular fluid, or both, in at least one joint involved. Intraarticular fluid was found in 77/152 cases (50.7%) and synovial thickening in 52/152 (34.2%).

In cases of synovial thickening no special predilection concerning the subtype was found.

At one and two years respectively one or both of the pathological findings were present in 62.5% (40/64) and 71.7% (38/53) of those in whom the investigation was performed. In six patients synovial thickening was present each time joints were investigated.

4. Course of the disease. Short-term clinical outcome (papers 2 and 3)

The incidence study. For the follow-up, the data of 125/162 patients were available. There were 37 patients (22.8%, 27 with oligoarthritis) for whom there were no data after the first hospitalization or outpatient visit. In all of these cases, however, the duration of symptoms had been so long that the subtype could be determined. In 51/162 patients (31.9%, 31 of them with oligoarhritis), the disease subtype remained the same during the follow-up period. During the follow-up 17 of the 87 patients with oligoarthritis (19.5%) changed subtype to extended oligoarthritis.

The prevalence study. Data for the follow-up were available for 120/197 patients (Table 9).

There were 49/197 patients (24.9%, 35 with oligoarthritis) for whom the follow-up extended to only 6 months following the diagnosis, but their subtype could be determined. For 76/197 patients (38.6%), among them 46 with persistent oligoarthritis and 10 with seronegative polyarthritis, there were no data at two years as they were no longer seen by doctors. In 63 patients (32%, 25 of them with persistent oligoarthritis), the disease subtype remained the same during the follow-up period. During the follow-up, 23 of the 111 patients with oligoarthritis (20.7%) changed subtype to extended oligoarthritis.

Table 9. Course of the disease during the first two years following the onset of JIA. Prevalence study

Onset subtype	No. of patients	Patients with inactive disease**	Active or stable cases at 2 yrs	Same pattern of joint involve-ment at 2 yrs	Changes in course during 2 yrs	Patients for whom there are no data at 2 yrs
Oligo	111	22	37	37	23 – extended oligo	52
Persistent oligo	88	17	25	25		46
Extended oligo	23	5	12	12		6
Seropos poly	9		8	5	3 – oligo	1
Seroneg poly	39	14	15	8	7 – oligo	10
Systemic	8	4	3	1	2 – oligo	1
Enthesitis related	11	1	5	5		5
Psoriatic	5	1	3	3		1
Other	13	2	5	4	1 – oligo	6
All JIA	196*	44	76	63	36	76

* In one patient with polyarthritis the exact classification was not possible, as the RF analysis was not performed.
** "Inactive" includes patients in whom the disease is inactive and who have been off drugs for less than two years as well some patients who are still on drug therapy.

4.1. Disease activity (paper 3)

Disease activity was studied in the patients of prevalence study. For estimating the disease activity the definitions suggested by the EULAR Standing Committee on Paediatric Rheumatology (Moscow 1983) were used (see above the chapter patients).

On the prevalence date — Dec. 31, 2000 — the state could be determined for 158/197 patients. The mean duration of the disease (from the very first symptoms) at follow-up was two years and four months. There were 37/197 (18.8%) patients for whom the disease had become inactive. Eighty-seven patients of 197 (44.2%) were taking DMARDs; among them there were 20/87 with active disease and 54/87 with a stable state of the disease. Fifteen patients of 197 (7.6%) were taking other drugs, mainly NSAIDs (Table 10). In

addition there were 39/197 for whom there is no information, among them 24 (61.5%) with oligoarthritis; this group includes children in whom the disease was with great probability inactive on Dec. 31, 2000 and who were already without drugs, but for less than two years.

At 2 years following diagnosis, 44/197 patients (22.3%) had inactive disease; in 76/197 patients (38.6%), the disease was active or in a stable state after 2 years.

Table 10. Taking drugs on December 31, 2000, the prevalence day (197 patients)

State on December 31, 2000	Number (%) of patients
No information	39 (19.8)
Taking DMARDs	87 (44.2)
Drugs other than DMARDs (NSAIDs mainly)	15 (7.6)
Treatment just started, just diagnosed	8 (4.1)
Treatment not started yet*	5 (2.5)
Parents refused treatment	1 (0.5)
Alternative medicine	1 (0.5)
Without drugs for a while, started again afterwards	4 (2)
Disease inactive**	37 (18.8)

* In five cases the treatment was started after Dec 31, 2000.

** Without drugs, no articular nor extraarticular signs, for less than two years

DISCUSSION

1. Incidence and prevalence

This study is the first population based study in Estonia and in the Baltic region on the epidemiology of JIA.

According to our study, in the years 1998–2000 the mean annual IR of JIA in Estonia was 21.7 per 100 000 children aged 0–15 years. The point prevalence on Dec. 31, 2000 for children aged 0–15 years with an onset of JIA during 1995–2000 in the 14 counties of Estonia was 83.7 per 100 000.

In epidemiological studies published in the field of juvenile arthritis, the IR is extremely variable, ranging from 0.8 to 22.6 per 100 000, and the PR from 7 to 401 per 100 000 children (Manners and Bower, 2002). The main reasons for the variation in these great limits are: 1) different study designs (hospital-based, population-based, questionnaires, data of registries); 2) the size and completion of study groups; 3) different classification criteria used; and 4) different genetic backgound of the nations. This great variation in IRs and PRs once again underlies the need for well-planned population-based epidemiological studies.

Epidemiological studies are important for every country, making possible to forecast the costs of the disease to the society, to compare the data with that of other countries, and to help in seeking possible etiologic and prognostic factors. Epidemiological studies are also utmost important for planning health care services to people, specially to children with a disease as JIA which is by nature a chronic disease with progressive course and with great risk for longterm disability. JIA can cause disability during the first years of the disease. On one hand, it is very important to register new cases of the disease every year and to have a database of these patients for a better follow-up their natural course. On the other hand there is a need to have a survey regarding the average duration of the disease and the total number of patients requiring any therapy; in this sense the PR reflects even better the socio-economic influence of the disease on society.

Several authors have noted that the IR of JIA rises and decreases periodically and shows geographical differences, which emphazises the triggering role of environmental factors or may reflect true differences on the basis of genetic factors (Andersson Gäre and Fasth 1992; Peterson *et al.* 1996; Kaipiainen-Seppanen and Savolainen 1996). The fluctuation of IR with tendency to increase was found also in our study (Figure 2).

Comparing the results of our study with the data of other studies is, however, difficult due to methodological differences and continuous developments in classification. The mean annual IR in our study — 21.7 per 100 000 children aged 0–15 — is close to those found in the Nordic countries of Finland (19.6: 100 000 children aged 0–15 years when using the ARA classification and 18.2 for arthritis with a duration of three months) (Kunnamo *et al.* 1986) and

Norway (22.6: 100 000) (Moe and Rygg 1998). According to the latest study by Berntson *et al.* (2003) the incidence rates in Finland (Uusimaa County) and in two regions in Norway were 21, 19 and 23 per 100 000 respectively. Those studies are population-based, as is our study. Population-based studies are more complicated to carry out, but are more exact, as they also include mild cases diagnosed in the study area during the study period. IRs calculated in population-based studies are therefore higher than in hospital-based studies (Manners and Bower 2002; Kaipiainen-Seppanen and Savolainen 1996; Moe and Rygg 1998; Berntson *et al.* 2003) (Table 11). Hospital-based studies are easier to carry out and cheaper, but some mild cases may be left out.

Table 11. Incidence of JRA, JCA or JIA per 100 000 children aged 0–15 years according to epidemiological studies and in Estonia

Author	Year	Country	Study type	Criteria	Incidence
Sullivan *et al.*	1975	USA	Hospital	JRA	9.2
Towner	1983	USA	Population	JRA, JCA	10.8–13.9
Kunnamo *et al.*	1986	Finland	Medical practitioners	JRA	18.2
Prieur *et al.*	1987	France	Medical practitioners	JCA	1.3–1.9
Rosenberg	1990	Canada	Hospital	JRA	5–8
Andersson Gäre	1992	Sweden	Population	JCA	10.9
Denardo *et al.*	1994	USA	Hospital	JRA	4
Oen *et al.*	1995	Canada	Hospital	JRA	5.3
Malleson *et al.*	1996	Canada	Hospital	JRA	2.39
Symmons *et al.*	1996	UK	Hospital	JCA	10
Peterson *et al.*	1996	USA	Population	JRA	11.7
Kaipiainen-Seppänen & Savolainen	1996	Finland	Population	JRA	14
Fujikawa & Okuni	1997	Japan	Hospital	JRA	0.83
Moe & Rygg	1998	Norway	Hospital	JCA	22.6
Kiessling *et al.*	1998	Germany	Hospital	JCA	3.5
Arguedas *et al.*	1998	Costa Rica	Medical practitioners	JCA	6.8
Berntson *et al.*	2003	Nordic countries Sweden Finland (Helsingi) Denmark, East Denmark, Århus Norway, Trondheim Norway, Tromsø Island	population	JCA/JIA	14/15 14/15 18/21 9/9 15/16 21/23 18/19 7/7
Pruunsild *et al.*	2007	Estonia	population	JIA	21.7

In our study an effort was made to receive the data of all patients meeting the inclusion criteria, and for this purpose in addition to cases registered at the two children's hospitals, a continuous surveying of first-level doctors, county hospitals and county outpatient clinics took place. The patients were sent by family doctors to the two centres in order to make a diagnosis and start treatment. This type of study design and good cooperation between the first level doctors and pediatric rheumatologists could be one reason for the higher IR in Estonia when compared with other studies.

The mean annual IR in our study was only somewhat higher in girls, 22.8 per 100 000, than in boys, 19.3 per 100 000.

During the study period, the incidence of JIA increased 3-and-a-half fold (from 9.5 cases per 100 000 children aged 0–15 years in 1998 to 33.7 cases in 2000). At the same time, no changes were obvious in the proportional distribution of different JIA subtypes. The reasons for the increase in the IR are not clear, but they may be influenced by both genetic and environmental factors, such as seasonal variations and triggering infections. Although in the whole series an infection (mainly viral, with respiratory infections dominating) was documented prior to the onset of the disease in nearly one-third of the patients, no direct conclusion about the role of infections can be drawn.

An increase in the awareness and knowledge during the study period of first level doctors is crucial and can be one of the reasons of the increased IR of JIA in children in Estonia. The primary care system was at the same time rapidly developing and the number of family doctors practising in the counties examined increased significantly during the study period and reached the number of 412 in the end of the study. Reporting about the patients living in their district grew significantly better during the study period. More patients were referred to the third-level centres. An increase in IR has also been reported in Sweden: according to Berntson *et al.* (2003) the IR was 14:100 000, while the number was 10.9 according to Andersson Gäre and Fasth (1992); in both studies the EULAR criteria were used.

The point prevalence on Dec. 31, 2000 for children aged 0–15 years with an onset of JIA as of Jan. 1, 1995 in the 14 counties of Estonia was 83.7 per 100 000; 90.7 for girls and 77.1 for boys. The lowest prevalence figure published in literature — seven per 100 000 — was found by Arendarczyk (cited by Manners and Bower 2002) in a study based on clinical case records, and the highest — 401 per 100 000 — by Manners and Diepeveen (1996) in a community-based study among 12-year-old schoolchildren. The PR reported in the last study can be explained by the methods used in this study — after questioning the patients and their parents, case ascertainment was done on the basis of an examination by a rheumatologist; as a result of 9 JCA cases were identified out of a population of 2241 12-year-old children, among them 7 who had not been diagnosed earlier. The PR in Estonia (83.7 per 100 000) is close to that published by Towner *et al.* (1983) (in 1970, it was 86 for JCA and 96 for

JRA, and in 1980 the numbers were 84 and 113 respectively), for which the authors included both active and inactive cases. In the study by Andresson-Gäre and Fasth (1992) the PR was 86.3 for all of the cases and 64.1 for the cases with recent or active disease. Peterson *et al.* (1996) included all the cases with JRA and calculated the PRs for 1980 and 1990, those being 94 and 86 per 100 000 respectively. Similar to IRs, apart from methodological differences, the variable PRs may also reflect geographic differences, e.g. the high rates in the Nordic countries (Andersson Gäre and Fasth 1992; Moe and Rygg 1998; Kunnamo *et al.*1986; Berntson *et al.* 2003) (Table 12).

Table 12. Prevalence of JRA, JCA or JIA per 100 000 children aged 0–15 years according to epidemiological studies and in Estonia

Author	Year	Country	Study type	Criteria	Prevalence
Laaksonen	1966	Country	Hospital	English	75–100
Bywaters	1968	UK	Hospital	English	60–70
Sullivan *et al.*	1975	USA	Hospital	JRA	65
Gewanter *et al.*	1983	USA	Medical practitioners	JRA	16–43
Towner *et al.*	1983	USA	population	JCA, JRA	83.7–113.4
Prieur *et al.*	1987	France	Medical practitioners	JCA	7.7–10
Rosenberg	1990	Canada	Hospital	JRA	39.7
Mielants *et al.*	1993	Belgium	population	JCA	167
Andersson Gäre	1994	Sweden	population	JCA	86.3
Oen *et al.*	1995	Canada	Hospital	JRA	32
Malleson *et al.*	1996	Canada	Hospital	JRA	40
Peterson *et al.*	1996	USA	population	JRA	86.1–94.3
Manners & Diepeveen	1996	Australia	population	JCA	401
Arguedas et al	1998	Costa Rica	Medical practitioners	JCA	34.9
Moe & Rygg	1998	Norway	Hospital	JCA	148.1
Ozen *et al.*	1998	Turkey	population	JCA	64
Kiessling *et al.*	1998	Germany	population	JCA	20
Pruunsild *et al.*		Estonia	population	JIA	83.7

Taking into account patients with an onset of JIA during the study period who were in remission on Dec 31, 2000 results in a higher point prevalence (91 per 100 000 children aged 0–15 years). We have not included patients fullfilling the inclusion criteria but diagnosed before 1995. Due to this selection effect, we assume that the real PR could be even higher.

Combining the data of the two centres where specialists in pediatric rheumatology practice with the data reported by county and family doctors gave us quite realistic results in comparison with those from hospital-based studies. A strong aspect of our study is that all of the cases were discussed with the study team to ensure that they were real JIA cases and to avoid the risk of overestimating the diagnosis rates of JIA by local doctors. As well, the follow-up was performed by specialists in pediatric rheumatology.

The patients reported by family doctors who were not sent to the participating centres to confirm the diagnosis by a specialist to be sure that they were real JIA cases were not included in the study. These patients had with great probability other reasons causing arthralgia or arthritis in children or mild self-remitting oligoarthritis. The reason for not including them was the try to avoid overdiagnosis by doctors not specialized in pediatric rheumatology.

2. Onset of JIA and sex distribution

The mean age at the onset of JIA symptoms was 9 years 6 months in the incidence series and 8 years and 8 months in the prevalence group.

The age distribution of our patients in both series was different from that published by other authors (Peterson *et al.* 1996; Moe and Rygg 1998; Berntson *et al.* 2003). Figures 7 and 8 show the differences in the distribution of age at onset in girls and boys between our and Berntson's study. In the distribution of girls and boys according to age at the time of onset, we did not find a peak incidence for girls in the first three years of life when comparing to Berntson's study. The latter is the latest epidemiological study based on ILAR criteria like ours. The difference (re: not finding an early peak) is probably due to possible cases of oligoarthritis with mild activity that begin in the age group of 0–3 years and which may remain undiagnosed and unreported by family doctors. The further development of the Estonian primary health care system and educational work carried out among family doctors during the study period has likely changed the situation by now. The diagnosis of JIA in a young child can be easily missed by a doctor needing more experience with the disease. The same has also been reported by Kiessling *et al*. (1998). Manners and Diepeveen (1996) stressed the possible ignorance of childhood rheumatic complaints in the community and among first-level practitioners; due to this, physicians other than rheumatologists may fail to diagnose rheumatic diseases correctly. The numbers for girls were highest between 12 and 14 years of age in our study and between 10 and 13 years in the Nordic study; in both studies the second peak in the pubertal period was not observed. The number of girls showed a tendency to rise from the age of eight in our study and from the age of nine in the Nordic study. The number of boys also showed a slight tendency to rise from the age of eight in our study; in the Nordic study the number of boys decreased slowly

after the age of five. In both studies no obvious peak was found in the age distribution of boys.

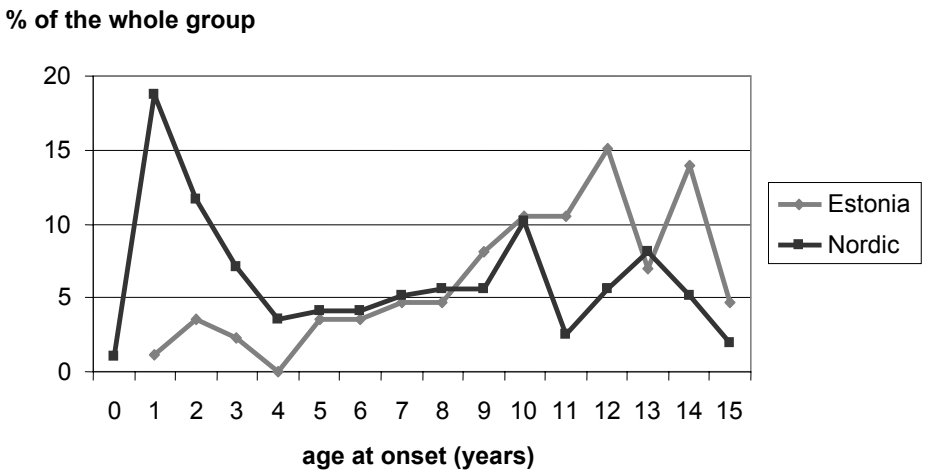

Figure 7. Age distribution in girls at time of onset of arthritis. Comparison between the Estonian incidence study (n=86) and the Nordic incidence study by Berntson *et al.* (2003) (n=197).

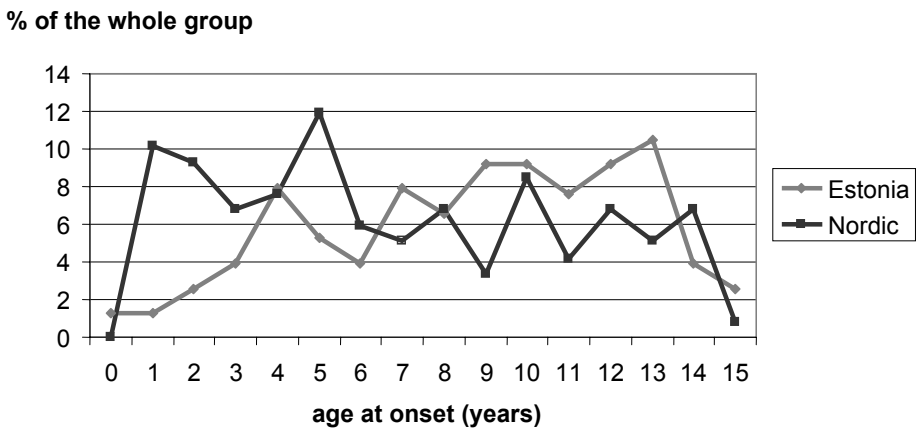

Figure 8. Age distribution in boys at time of onset of arthritis. Comparison between the Estonian incidence study (n=76) and the Nordic incidence study by Berntson *et al.* (2003) (n=118).

Kaipiainen-Seppänen and Savolainen (2001) found the mean age at diagnosis to be 9.2 years in 1995; earlier it had been in the range of 6.6–7.9 years.

The percentage of girls was 53.1 in the incidence study and 52.3 in the prevalence study; these figures do not differ statistically from a proportion of girls of 60–65% reported by other similar studies (Andersson Gäre and Fasth 1992; Berntson *et al.* 2003).

The prevalence was highest among 11–15 year old girls (132:100 000), and lowest in 0–3 year old girls (9.6: 100 000) showing a tendency to rise with increasing age (Table 7). The explanation here could be the short duration of the (active) disease among small girls with oligoarthritis. Oligoarthritis was the main subgroup in those patients for whom there exist no documented data on the prevalence date and for two years after the onset of the disease (12.2% and 23.4% of all cases respectively); in these cases the disease had probably become inactive.

Girls dominated in polyarthritis subgroup. A systemic subtype was more often diagnosed in boys; this result differs from ratio of boys to girls of 1:1 given by others (Cassidy and Petty 2005).

The mean interval between the onset of the disease and the time the diagnosis was made was seven months; it was longest for extended oligoarthritis and psoriatic arthritis (one year for both) and shortest for systemic arthritis (one month). In regards to this, the continuous educating of first-level doctors concerning the initial manifestations of the disease is of crucial importance in order to shorten the above-mentioned interval and to start adequate treatment as early as possible.

3. Distribution of subtypes

In both incidence and prevalence groups oligoarthritis was the most frequent subtype (87 cases, 54.4%) and 111 cases (56.3%) in the incidence study and in the prevalence study respectively)) followed by seronegative polyarthritis (33 cases, 20.4%) and 39 cases (19.5%) (Tables 5 and 6). All the polyarthritis cases formed 20.3% and 24.9% of the incidence and prevalence cases respectively. Our results are similar to those of published epidemiological studies, according to which the frequency of oligoarthritis is 50–75% (Towner *et al.* 1983; Andersson Gäre and Fasth 1992; Peterson *et al.* 1996; Moe and Rygg 1998; Kaipiainen-Seppänen and Savolainen 2001; Hofer *et al.* 2001, Berntson *et al.* 2003) and the frequency of polyarthritis is 17–29% of all the cases (Andersson Gäre and Fasth 1992; Peterson *et al.* 1996; Moe and Rygg 1998; Kaipiainen-Seppänen and Savolainen 2001; Hofer *et al.* 2001, Berntson *et al.* 2003).

4. Clinical characteristics

4.1. Extraarticular manifestations

The most common extraarticular manifestation of JIA is chronic anterior uveitis. Oligoarticular onset, female gender, ANA positivity, and a young age are risk factors for developing uveitis in JIA (Berk *et al.* 2001). However, eye involvement was present in only four (2.5%) patients in our incidence study group and 5 (2.5%) of the prevalence group. All they were ANA negative. It has been stressed that chronic anterior uveitis can often be asymptomatic (Berk *et al.* 2001; Petty *et al.* 2003), and therefore it is suggested that one perform a split-lamp examination in all cases. As a split-lamp investigation was done for most (about 4/5) of our study group cases, the low incidence of eye involvement is difficult to explain.

4.2. Laboratory tests

In the incidence group RF positivity at the onset of the disease was found in 22 (16.2% of those in whom the analysis was performed) of the patients, eight of them were with oligoarthritis, two with extended oligoarthritis, seven with polyarthritis and five with other arthritis. Our data differ from those of other authors who have found positive RF mainly in polyarthritis patients (Andersson Gäre and Fasth 1992). The sensitivity of the method used by the laboratory of the Tallinn Children's Hospital is probably the explanation, as 83% of the positive cases were reported from this hospital. RF remained positive through the whole follow-up period in five patients (four polyarthritis, one other arthritis). In six patients with oligoarthritis, the analysis was performed only once, so there are no data as to whether the RF remained positive; and in one patient with oligoarthritis and one patient with extended oligoarthritis the repeated analysis was negative. There are limited data on RF positivity in extended oligoarthritis, which is completely different from persistent oligoarthritis and has a more complicated prognosis (Sailer *et al.* 1997).

Positive ANA at the onset of the disease was found in 20 (15.9%) of the patients in whom the analysis was performed; the figure is lower than in other published studies — 25–34% (Andersson Gäre and Fasth 1992; Moe and Rygg 1998; Berntson *et al.* 2003) — and may be partialy due to the fact that a repeated analysis was not performed on all patients in order to define an ANA positive case. In addition there were patients in whom positive ANA was detected later in the course of the disease (after the first six months) and they were not included. An explanation for the lower ANA positivity could be it's detecting in different

laboratories with very low presence among the patients diagnosed in Tallinn — only 3/20 patients with positive ANA at onset came from there.

In the prevalence group we also found a rather high incidence of RF-positivity (24 patients, 15.3%) and low ANA-positivity (26 patients, 17.8%) when compared to other reported populations of JIA patients.

4.3. HLA antigens

HLA-DR4 is associated with an unfavourable prognosis in JIA, and has been found to be increased in patients with a systemic subtype (Førre *et al.* 1983; Bedford *et al.* 1992). In our incidence series there were only seven patients with systemic arthritis and all of them were HLA-DR4 negative. According to several authors, HLA-B27 antigen is positive in 21–52% of JIA patients (Førre *et al.* 1983; Friis *et al.* 1985; Moe and Rygg 1998) and a clear difference in the frequency of this antigen has been found when comparing with control groups (Førre *et al.* 1983; Schuchmann *et al.* 1984; Friis *et al.* 1985). In a former work by our study group, HLA-B27 antigen was present in 31.6% of 60 JCA patients and in 16.4% of 110 controls ($p<0.05$) (Pruunsild *et al.* 2000).

HLA-B27 was present in 28 of our 98 patients (28.6%). HLA-B27 is considered to be a marker for a chronicity of inflammation and a prognostic factor (Savolainen *et al.* 1998); the presence of the antigen has been associated with the failure of first remission (Hsu *et al.* 2004) and the development of cardiac involvement (Huppertz *et al.* 2000). In our study group three from the 28 HLA-B27 positive patients (two with systemic arthritis and one with seronegative polyarthritis) had signs of cardiac involvement. HLA-B27 was present in eight of 11 (72.7%) patients with enthesitis related arthritis and in the B27 positive patients the inflammation markers remained on a high level for at least 6 months (in 39.3% of B27 positive versus 20% of B27 negative patients). Although no difference was found regarding the presence of spinal involvement in the HLA-B27 positive and negative groups, that does not mean that the presence of this antigen has no relation with the development of spinal involvement. An explanation here could be the age structure of our study group. In addition there was no difference between HLA-B27 positive boys and girls considering the mean age at the onset of the disease.

4.4. X-ray and US investigation of joints

At diagnosis 87/146 patients (59.6%) showed no changes and 59 (40.4%) had some kind of change in at least 1 joint. Change in at least 1 joint has been found in 48–88% of patients with polyarthritis and juvenile ankylosing spondylitis groups dominating (Williams and Ansell 1985; Andersson Gäre and Fasth

1995; Mason *et al.* 2002; van Rossum *et al.* 2003; Selvaag *et al.* 2006). In our study group there were 35 patients with oligoarthritis and 9 with seronegative polyarthritis; the other subtypes were represented less frequently. Nine of the 20 cases (45%) of extended oligoarthritis for whom the investigation was performed had some kind of radiologic changes. The main changes reported by others are similar to our results — periarticular soft tissue swelling, periarticular osteoporosis, and erosions. For 3/6 patients with erosions at diagnosis, the symptoms of the disease had lasted for 11 months to 5 years already. In addition, growth abnormalities and joint space narrowing have been found with a high frequency (Reed and Wilmot 1991; Mason *et al*. 2003; van Rossum et al. 2003; Selvaag et al. 2006). After 1 year changes were found in 18/59 (30.5%) patients and at 2 years in 15/51 (29.4%) patients. In a recent work by Selvaag *et al.* (2006) changes were documented in 88% of patients at the diagnosis and in 81% at 3 years after the diagnosis; periarticular soft tissue swelling and osteoporosis showed a tendency to decrease and growth abnormalities showed a tendency to increase over time. Bone destruction was present in 13 patients during the whole follow-up period. Van Rossum *et al.* (2003) found erosions in 15% of their patients; the mean duration of the disease was 24 months. Usually erosions are not seen in the first two years in children (Levinson and Wallace 1992). The follow-up period for our patients was too short to evaluate the progression of radiologic changes.

More than half of the patients exhibited some pathological finding in the US investigation of joints; synovial thickening was present in a third of the patients examined at diagnosis. No association between the findings and separate subtypes was found, and this has also not been reported by others.

5. Course of the disease. Short-term outcome

Among epidemiologic studies, there are only a few that, in addition to IRs and/or PRs, present the findings of a clinical follow-up as well.

Two years after the onset the disease was still active or stable in 76 patients of the prevalence series, among them 8/9 seropositive polyarthritis, 3/5 psoriatic arthritis and 12/23 extended oligoarthritis (Table 10). We assume that with great probability the disease had become inactive also for those 49 patients (24.9%, 35 with oligoarthritis) for whom there are no data after the first six months following the diagnosis, as they were not referred to tertiary centres afterwards and were also not reported by first-level practitioners. At the same time we don't have an overview what proportion of our patients will actually reach remission. The observation period in our study is too short in order to compare it with other studies in which the course of the disease was followed. In earlier studies, the division of oligoarthritis between persistent and extended and their

separate follow-up has not been done. An extended oligoarticular course has been described in 20–40% of patients with oligoarticular onset, with a mean duration of the disease of 3.9–16.5 years (Oen *et al.* 2002; Minden *et al.* 2002; Al-Matar *et al.* 2002; Fantini *et al.* 2003). According to our results the percentage is 20.7%.

On the prevalence day, when the disease had lasted on average for two years and four months, the disease had become inactive for 37 (18.8%) patients. At least 22% of the patients were inactive after two years. One hundred and two patients (51.8%) were taking some types of drugs, meaning that in most of these cases the disease was still active or stable (Table 11).

Nowadays, most children with JIA do not need hospitalization. Much has changed as access to doctors becomes easier, the subspeciality of pediatric rheumatology develops all over the world, diagnoses are made earlier and treatment schemes become more aggressive. Today the approach to patients with JIA involves a multi-disciplinary team led by pediatric rheumatologist involving nurses, social workers, physical therapists, occupational therapists and psychologists. The involvement of the family in the treatment program is crucial in terms of supporting and continuously educating them regarding the character of the disease and the need for long-term treatment. The need for experienced specialists in pediatric rheumatology is obvious.

The new promising biological treatments give the pediatric rheumatologists an opportunity to alleviate the chronic disease process for a child in order to enable normal growth and development.

FINALLY

The field of epidemiology of this complicated heterogeneous disease — JIA — still remains a challenge for researches. Some cases may present as mild oligoarthritis and may remain undiagnosed in community-based studies; on the other hand, in hospital-based series more serious cases are represented — in both study types the incidence and prevalence figures are most likely underestimated, and do not reflect actual numbers. With the use of the new JIA classification system the common understanding between scientists and practitioners has significantly improved.

Manners and Bower (2002) have made an interesting supposition that an ideal study on the prevalence of childhood arthritis could involve large numbers of children in homes or schools in the months before their 16th birthday, with a history taken of possible active or inactive arthritis in the previous 16 years, followed by a clinical examination by experienced pediatric rheumatologists using standardized diagnostic criteria. In the evidence of clinical joint inflammation, in order to fulfil the diagnostic criteria for JIA, a second clinical examination would be undertaken to ensure that inflammation remained for at least six weeks and that other conditions were excluded.

CONCLUSIONS

1. A total of 162 new cases of JIA (76 boys and 86 girls) with an onset of JIA during the years 1998 to 2000 were diagnosed in the incidence study. The mean annual IR was 21.7 per 100 000 children aged 0–15 years; 22.9 per 100 000 girls and 19.3 per 100 000 boys. The mean annual IR was the highest — 23.8 per 100 000 — in the age group of 7–10 years. Girls were affected most often between the ages of 7–15 years and boys between 4–10 years. The mean age at the onset of JIA symptoms was 9 years 6 months; 10 years and 1 month for girls and 8 years and 10 months for boys. It was lowest in the systemic subtype — 4 years 3 months — and highest in the enthesitis related arthritis subtype — 12 years and 6 months. The mean annual IR is well in accord with the results of population studies from other Nordic countries like Finland and Norway.
2. Oligoarthritis was the most frequent subtype in the study on IR (87 cases, 54.4%). Thirteen of them (14.9%) had monoarthritis. The mean annual IR for oligoarthritis was 11.7 per 100 000 children aged 0–15 years. Oligoarthritis was followed by seronegative polyarthritis (33 cases, an annual IR of 4.4 per 100 000).
3. During the study period, the incidence of JIA increased three and a half fold (from 9.5 cases per 100 000 children aged 0–15 years in 1998 to 33.7 cases in 2000), with no changes in the proportional distribution of different JIA subtypes. One possible reason is an increase in the awareness and knowledge of first-level doctors.
4. On the prevalence day, December 31, 2000, there were 197 children (94 boys and 103 girls) aged 0–15 years and living in the 14 counties of Estonia in whom JIA diagnosed in 1995–2000 was active, stable or inactive. The point prevalence was 83.7 (95% CI 72.4; 95.8) per 100 000 children aged 0–15 years, 77.1 (95% CI 62.2; 93.5) for boys and 90.7 (95% CI 74.1; 108.9) for girls. The prevalence was highest among 11–15 year old girls, (132: 100 000) and the lowest in 0–3 year old girls (9.6: 100 000) The mean age at the onset of JIA symptoms in the prevalence study was 8 years and 8 months (95% CI: 8y 2mo; 9y 4mo); 9 years and 1 month for girls and 8 years and 4 months for boys. The distribution of subtypes in the prevalence series was similar to the incidence series.
5. The mean interval between the onset of the disease and the time the diagnosis was made was seven months; it was longest for extended oligoarthritis and psoriatic arthritis, (one year for both) and shortest for systemic arthritis (one month). The continuos educating of first level doctors about the initial manifestations of the disease is of crucial importance to shorten the interval and start adequate treatment as early as possible.
6. HLA-B27 antigen was present in 28 (15 boys, 13 girls) out of 98 patients (28.6%). Among HLA-B27 positive patients, enthesitis related arthritis was

more frequent (in eight of 28 B27 positive patients and in three of 70 B27 negative patients) and rise in the inflammatory markers persisted for a longer period (ESR or CRP or both for at least six months in 11 of 28 HLA-B27 positive patients and in 14 of 70 HLA-B27 negative patients).

7. At two years since diagnosis 44 of the 197 patients (22.3%) had inactive disease. For 76 patients (38.6%) the disease was active or stable after two years.
8. On the prevalence date — December 31, 2000 — the mean duration of the disease was two years and four months. For 37 (18.8%) patients the disease had become inactive. Eighty-seven patients (44.2%) were taking DMARDs. Fifteen patients (7.6%) were taking other drugs, mainly NSAIDs.
9. A longer follow-up of JIA patients studied using the ILAR 1997 criteria is needed in order to have a better overview of the course of the disease, to know the proportion of patients reaching remission and the actual prognosis of the patients.

REFERENCES

Adebajo AO, Hall MA. The use of intravenous pulsed methylprednisolone in the treatment of systemic onset juvenile chronic arthritis. Br J Rheumatol 1998; 37: 1240–2.

Alarcon-Segovia D, Laffon A, Alcocer-Varela J. Probable depiction of juvenile arthritis by Sandro Botticelli. Arthritis Rheum 1983; 26: 1266–8.

Albert ED and Scholz S. Juvenile arthritis: genetic update. Ballieres Clin Rheumatol 1998; 12: 209–18.

Alexandersen V, Szlachetko K, Wiercinska A. Bilateral hypoplasia of the mandibular condyles in an ancient Polish skull. OSSA 1979; 6: 7.

Allen RC, Jimenez M, Cowell CT. Insulin-like growth factor and growth hormone secretion in juvenile chronic arthritis. Ann Rheum Dis 1991; 50: 602–6.

Al-Matar MJ, Petty RE, Tucker LB, Malleson PN, Schroeder ML, Cabral DA. The early pattern of joint involvement predicts disease progression in children with oligo-articular (pauciarticular) juvenile rheumatoid arthritis. Arthritis Rheum 2002; 46: 2708–15.

Andersson Gäre B, Fasth A. Epidemiology of juvenile chronic arthritis in southwestern Sweden: a 5-year prospective population study. Pediatrics 1992; 90: 950–8.

Andersson Gäre B. Juvenile chronic arthritis. A Population based study on epidemiology, natural history and outcome. Göteborg 1994; 12–40, 57.

Ansell BM, Bywaters EGL and Lawrence JS. Familial aggregation and twin studies in Still's disease: juvenile chronic polyarthritis. Rheumatology 1969; 2: 37–61.

Ansell BM, Wood PH. Prognosis in juvenile chronic polyarthritis. Clin Rheum Dis 1976; 2: 397–412.

Ansell BM. Juvenile chronic arthritis. Scand J Rheumatol 1987; 66 (Suppl): 47–50.

Arendarczyk Z. Rheumatoid arthritis in children up to the age of 15 in Poland. Pediatr Pol 1977; 52: 73–8.

Arguedas O, Fasth A, Andersson-Gäre B, Porras O. Juvenile chronic arthritis in urban San Jose, Costa Rica: a 2 year prospective study. J Rheumatol 1998; 25: 1844–50.

Arkela-Kautiainen M, Haapasaari J, Kautiainen H, Vilkkumaa I, Malkia E, Leirisalo-Repo M. Favourable social functioning and health related quality of life of patients with JIA in early adulthood. Ann Rheum Dis 2005; 64: 875–80.

Athreya BH, Doughty RA, Bookspan M, Schumacher HR, Sewell EM, Chatten J. Pulmonary manifestations of juvenile rheumatoid arthritis. A report of eight cases and review. Clin Chest Med 1980; 1: 361–74.

Baek HJ, Shin KC, Lee YJ, Kang SW, Lee EB, Yoo CD, Song YW. Juvenile onset ankylosing spondylitis (JAS) has less severe spinal disease course than adult onset ankylosing spondylitis (AAS): clinical comparison between JAS and AAS in Korea. J Rheumatol 2002; 29: 1780–5.

Baildam EM, Holt PJL, Conway SC, Morton MJS. The association between physical function and psychological problems in children with juvenile chronic arthritis. Br J Rheumatol 1995; 34: 470–7.

Barron KS, Silvermann ED, Gonzales JC, Owerbach D, Reveille JD. DNA analysis of HLA-DR, DQ and DP alleles in children with polyarticular juvenile rheumatoid arthritis. J Rheumatol 1992; 19: 1611–6.

Baum J, Gutowska G. Death in juvenile rheumatoid arthritis. Arthritis Rheum 1977, Suppl 20: 253.

Bedford PA, Ansell BM, Hall PJ, Woo P. Increased frequency of DR4 in systemic onset juvenile chronic arthritis. Clin Exp Rheumatol 1992; 10: 189–93.

Berk AT, Kocak N, Unsal E. Uveitis in juvenile arthritis. Ocul Immunol Inflamm 2001; 9: 243–51.

Bernstein B. Death in juvenile rheumatoid arthritis. Arthritis Rheum 1977, Suppl 20: 256.

Berntson L, Andersson Gäre B, Fasth A, Herlin T, Kristinsson J, Lahdenne P, Marhaug G, Nielsen S, Pelkonen P, Rygg M; Nordic Study Group. Incidence of juvenile idiopathic arthritis in the Nordic countries. A population based study with special reference to the validity of the ILAR and EULAR criteria. Rheumatol 2003; 30: 2275–82.

Black AP, Bhayani H, Ryder CA, Gardner-Medwin JM, Southwood TR. T-cell activation without proliferation in juvenile idiopathic arthritis. Arthritis Res 2002; 4: 177–83.

Bloom BJ, Smith P, Alario AJ. Felty syndrome complicating juvenile rheumatoid arthritis. J Pediatr Hematol Oncol 1998; 20: 511–3.

Bollow M, Enzweiler C, Taupitz M,Golder W, Hamm B, Use of contrast enhanced magnetic resonance imaging to detect spinal inflammation in patients with spondyloarthritides. Clin Exp Rheumatol 2002; 20 (Suppl 28): S1, 67–74.

Bowyer S, Roettcher P. Pediatric rheumatology clinic population in the United States: results of a 3 year survey. Pediatric Rheumatology Database Research Group. J Rheumatol 1996; 23: 1968–74.

Bowyer SL, Roettcher PA, Higgins GC, Adams B, Myers LK, Wallace C et al. Health status of patients with juvenile rheumatoid arthritis at 1 and 5 years after diagnosis. J Rheumatol 2003; 30: 394–400.

Braun J, Doring E, Wu P, Heesemann J, Treharne J, Eggens U et al. Synovial cellular immune response to bacterial pathogens in patients with chronic juvenile arthritis. Z Rheumatol 1993; 52: 201–9.

Breit W, Frosch M, Meyer U, Heinecke A, Ganser G. A subgroup-specific evaluation of the efficacy of intraarticular triamcinolone hexacetonide in juvenile chronic arthritis. J Rheumatol 2000; 27: 2696–702.

Brewer EJ, Bass JC, Cassidy JT et al. Criteria for the Classification of Juvenile Rheumatoid Arthritis. Bull Rheum Dis 1972; 23: 712–19.

Brewer EJ Jr, Bass J, Baum J, Cassidy JT, Fink C, Jacobs J, Hanson V, Levinson JE, Schaller J, Stillmann JS. Current proposed revision of JRA criteria. JRA Criteria Subcommittee of the Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Section of The Arthritis Foundation. Arthritis Rheum 1977; 20 (Suppl): 195–99.

Bruce IN and Silman AJ. The aetiology of psoriatic arthritis. Rheumatology (Oxford) 2001; 40: 363–6.

Bywaters EGL. Diagnostic criteria for Still's disease (juvenile, RA). In P.H. Bennett and P.N.H. Wood, eds. Population studies of the rheumatic diseases, proceedings of the Third International Symposium. New York: Excerpta Medica Foundation, 1968, pp. 235–40.

Bywaters EG. Still's disease in the adult. Ann Rheum Dis 1971; 30: 121–33.

Bywaters EG, Cardoe N. Multiple nodules in juvenile chronic arthritis. Ann Rheum Dis 1972; 31: 421.
Bywaters EGL. The history of pediatric rheumatology. Arthritis Rheum 1977; 20 (Suppl): 145–52.
Burgos-Vargas R, Clark P. Axial involvement in the seronegative enthesopathy and arthropathy syndrome and its progression to ankylosing spondylitis. J Rheumatol 1989; 16: 192–7.
Bywaters EG. Pathologic aspects of juvenile chronic polyarthritis. Arthritis Rheum 2003; 48: 642–50.
Cabral DA, Oen KG, Petty RE. SEA syndrome revisited: a longterm followup of children with a syndrome of seronegative enthesopathy and arthropathy. J Rheumatol 1992; 19: 1282–5.
Cabral DA, Petty RE, Malleson PN, Ensworth S, McCormick AQ, Shroeder ML. Visual prognosis in children with chronic anterior uveitis and arthritis. J Rheumatol 1994; 21: 2370–5.
Calabro JJ, Staley HL, Burnstein SL, Leb L. Laboratory findings in juvenile chronic arthritis. Arthritis Rheum 1977; 20 (Suppl): 268–9.
Cassidy JT, Petty RE, Sullivan DB. Abnormalities in the distribution of serum immunoglobulin concentrations in juvenile rheumatoid arthritis. J Clin Invest 1973; 52: 1931–6.
Cassidy JT, Hillman LS. Abnormalities in skeletal growth in children with juvenile rheumatoid arthritis. Rheum Dis Clin North Am 1997; 23: 499–522.
Cassidy JT, Petty RE, Laxer RM, Lindsley CB. Textbook of pediatric rheumatology. Elsevier Saunders 2005: 206–45.
Cerna M, Vavrincova P, Havelka S, Ivaskova E, Stastny P. Class II alleles in juvenile arthritis in Czech children. J Rheumatol 1994; 21: 159–64.
Chandrasekaran AN, Rajendran CP, Madhavan R. Juvenile rheumatoid arthritis — Madras experience. Indian J Pediatr 1996; 63: 501–10.
Chmell MJ, Scott RD, Thomas WH, Sledge CB. Total hip arthroplasty with cement for juvenile rheumatoid arthritis. Results at a minimum of ten years in patients less than thirty years old. J Bone Joint Surg Am 1997; 79: 44–52.
Cleary AG, Sills JA, Davidson JE. Revision of the proposed classification criteria for juvenile idiopathic arthritis: Durban, 1997. J Rheumatol 2000; 27: 1568.
Clemens LE, Albert E, Ansell BM. Sibling pairs affected by chronic arthritis of childhood: evidence for a genetic predisposition. J Rheumatol 1985; 12: 108–13.
Cohen IR, Holoshitz J, van Eden W, Frenkel A. T lymphocyte clones illuminate pathogenesis and affect therapy of experimental arthritis. Arthritis Rheum 1985; 28: 841–5.
Colver T. The prognosis in rheumatoid arthritis in childhood. Arch Dis Child 1937; 12: 253.
Coss JA., Boots RH. Juvenile rheumatoid arthritis. J Pediatr 1946; 29: 143.
Crawley E, Kay R, Sillibourne J, Patel P, Hutchinson I, Woo P. Polymorphic haplotypes of the interleukin-10 5' flanking region determine variable interleukin-10 transcription and are associated with particular phenotypes of juvenile rheumatoid arthritis. Arthritis Rheum 1999; 42: 1101–8.
Dana MR, Merayo-Lloves J, Schaumberg DA, Foster CS. Visual oucomes prognosticators in juvenile rheumatoid arthritis-associated uveitis. Ophthalmology 1997; 104: 236–44.

Delgado EA, Petty RE, Malleson PN, Patterson MW, D`Orsogna L, LeBlanc J. Aortic valve insufficiency and coronary artery narrowing in a child with polyarticular juvenile rheumatoid arthritis. J Rheumatol 1988; 15: 144–7.

Da Silva JA, Larbre JP, Spector TD, Perry LA, Scott DL, Willoughby DA. Protective effect of androgens against inflammation induced cartilage degradation in male rodents. Ann Rheum Dis 1993; 52: 285–91.

Denardo BA, Tucker LB, Miller LC, Szer IS, Schaller JG. Demography of a regional pediatric rheumatology patient population. Affiliated Children's Arthritis Centers of New England. J Rheumatol 1994; 21: 1553–61.

De Kleer IM, Kamphuis SM, Rijkers GT, Scholtens L, Gordon G, De Jager W et al. The spontaneous remission of juvenile idiopathic arthritis is characterized by CD30+ T cells directed to human heat-shock protein 60 capable of producing the regulatory cytokine interleukin-10. Arthritis Rheum 2003; 48: 2001–10.

De Kleer IM, Brinkman DM, Ferster A, Abinun M, Quartier P, Van Der Net J, Ten Cate R, Wedderburn LR, Horneff G, Oppermann J, Zintl F, Foster HE, Prieur AM, Fasth A, Van Rossum MA, Kuis W, Wulffraat NM. Autologous stem cell transplantation for refractory juvenile idiopathic arthritis: analysis of clinical effects, mortality, and transplant related morbidity. Ann Rheum Dis 2004; 63: 1318–26.

De Kleer IM, Wedderburn LR, Taams LS, Patel A, Varsani H, Klein M et al. CD4+CD25+ (bright) regulatory T cells actively regulate inflammation in the joints of patients with the remitting form of juvenile idiopathic arthritis. J Immunol 2004; 172: 6435–43.

Dequeker J, Mardjuadi A. Prognostic factors in juvenile chronic arthritis. J Rheumatol 1982; 9: 909–15.

Diamantberger MS. Du rhumatisme Chronigue noueux (polyarthrite déformante) chez l´enfants. Thése por le doctorat en médicine. Lecrosnier et Babe Livraires Editeurs, Paris 1890.

Donn RP, Davies EJ, Holt PL, Thomson W, Ollier W. Increased frequency of TAP2B in early onset pauciarticular juvenile chronic arthritis. Arthritis Rheum Dis 1994; 53: 261–4.

Donn R, Alourfi Z, De Benedetti F, Meazza C, Zeggini E, Lunt M et al. Mutation screening of the macrophage migration inhibitory factor gene: positive association of a functional polymorphism of macrophage migration inhibitory factor with juvenile idiopathic arthritis. Arthritis Rheum 2002; 46: 2402–9.

Dracou C, Constantinidou N, Constantopoulos A. Juvenile chronic arthritis profile in Greek children. Acta Paediatr Jpn 1998; 40: 558–63.

El-Miedany YM, Housny IH, Mansour HM, Mourad HG, Mehanna AM, Megeed MA. Ultrasound versus MRI in the evaluation of juvenile idiopathic arthritis of the knee. Joint Bone Spine 2001; 68: 222–30.

Fantini F. Classification of chronic arthritides of childhood (juvenile idiopathic arthritis): criticisms and suggestions to improve the efficacy of the Santiago-Durban criteria. J Rheumatol 2001; 28: 456–9.

Fantini F, Gerloni V, Gattinara M, Cimaz R, Arnoldi C, Lupi E. Remission in juvenile chronic arthritis. J Rheumatol 2003; 30: 579–84.

Felici E, Novarini C, Magni-Manzoni S, Pistorio A, Magnani A, Bozzola E, Buoncompagni A, Martini A, Ravelli A. Course of joint disease in patients with antinuclear antibody-positive juvenile idiopathic arthritis. J Rheumatol 2005; 32: 1805–10.

Fernandez-Vina M, Fink CW, Stastny P. HLA antigens in juvenile arthritis. Pauciarticular and polyarticular juvenile arthritis are immunogenetically distinct. Arthritis Rheum 1990; 33: 1787–94.

Fernandez-Vina M, Fink CW, Stastny P. HLA associations in juvenile arthritis. Clin Exp Reumatol 1994; 12: 205–14.

Fink CW, Fernandez-Vina M, Stastny P. Clinical and genetic evidence that juvenile arthritis is not a single disease. Pediatr Clin North Am 1995; 42: 1155–69.

Fink CW. Proposal for the development of classification criteria for idiopathic arthritides of childhood. J Rheumatol 1995; 22:1566–69.

Flato B, Vinje O, Forre O. Toxicity of antirheumatic and anti-inflammatory drugs in children. Clin Rheumatol 1998; 17: 505–10.

Flato B, Lien G, Smerdal A, Vinje O, Dale K, Johnston V et al. Prognostic factors in juvenile rheumatoid arthritis: a case-control study revealing early predictors and outcome after 14.9 years. J Rheumatol 2003; 30: 386–93.

Flato B, Hoffmann-Vold AM, Reiff A, Forre O,Lien G, Vinje O. Long-term outcome and prognostic factors in enthesitis-related arthritis. Arthritis Rheum 2006; 30: 3573–3582.

Forre O, Dobloug JH, Hoyeraal HM, Thorsby E. HLA antigens in juvenile arthritis: genetic basis for the different subtypes. Arthritis Rheum 1983; 26: 35–8.

Friedman S, Gruber MA. Ultrasonography of the hip in the evaluation of children with seronegative juvenile rheumatoid arthritis. J Rheumatol 2002; 29: 629–32.

Fries JF, Singh G, Lenert L, Furst DE. Aspirin, hydroxychloroquine, and hepatic enzyme abnormalities with methotrexate in rheumatoid arthritis. Arthritis Rheum 1990; 33: 1611–9.

Friis J, Morling N, Pedersen FK, Heilmann C, Jorgensen B, Svejgaard A et al. HLA-B27 in juvenile chronic arthritis. J Rheumatol 1985; 12: 119–22.

Fujikawa S, Okuni M. Clinical analysis of 570 cases with juvenile rheumatoid arthritis: results of a nationwide retrospective survey in Japan. Acta Paediatr Jpn 1997; 39: 245–9.

Garcia-Morteo O, Maldonado-Cocco JA, Suarez-Almazor ME, Garay E. Ankylosing spondylitis of juvenile onset: comparison with adult onset disease. Scand J Rheumatol 1983; 12: 246–8.

Gerloni V, Cimaz R, Gattinara M, Arnoldi C, Pontikaki I, Fantini F. Efficacy and safety profile of cyclosporine A in the treatment of juvenile chronic arthritis. Results of a 10-year prospective study. Rheumatology (Oxford) 2001; 40: 907–13.

Gewanter HL, Roghmann KJ, Baum J. The prevalence of juvenile arthritis. Arthritis Rheum 1983; 26: 599–603.

Giannini EH, Brewer EJ. Poor correlation between the erythrocyte sedimentation rate and clinical activity in juvenile rheumatoid arthritis. Clin Rheumatol 1987; 6: 197–201.

Giannini EH, Brewer EJ Jr, Kuzmina N, Shaikov A, Wallin B. Auranofin in the treatment of juvenile rheumatoid arthritis. Results of the USA-USSR double-blind, placebo-controlled trial. The USA Pediatric Rheumatology Collaborative Study Group. The USSR Cooperative Children's Study Group. Arthritis Rheum 1990; 33: 466–76.

Giannini EH, Brewer EJ, Kuzmina N, Shaikov A, Maximov A, Vorontsov I, Fink CW, Newman AJ, Cassidy JT, Zemel LS. Methotrexate in resistant juvenile rheumatoid

arthritis. Results of the U.S.A.-U.S.S.R. double-blind, placebo-controlled trial. The Pediatric Rheumatology Collaborative Study Group and The Cooperative Children's Study Group. N Engl J Med 1992; 326: 1043–9.
Giannini EH, Cassidy JT, Brewer EJ, Shaikov A, Maximov A, Kuzmina N. Comparative efficacy and safety of advanced drug therapy in children with juvenile rheumatoid arthritis. Semin Arthritis Rheum 1993; 23: 34–46.
Giannini EH, Ruperto N, Ravelli A, Lovell DJ, Felson DT, Martini A. Preliminary definition of improvement in juvenile arthritis. Arthritis Rheum 1997; 40: 1202–9.
Glass DN, Giannini EH. Juvenile rheumatoid arthritis as a complex genetic trait. Arthritis Rheum, 1999; 42: 2261–68.
Grom AA, Villanueva J, Lee S, Goldmuntz EA, Passo MH and Filipovich A. Natural killer cell dysfunction in patients with systemic onset juvenile rheumatoid arthritis and macrophage activation syndrome. J Pediatr 2003; 142: 292–6.
Guillaume S, Prieur AM, Coste J, Job-Deslandre C. Long-term outcome and prognosis in oligoarticular-onset juvenile idiopathic arthritis. Arthritis Rheum 2000; 43: 1858–65.
Gupta RC, Mills DM. Still's disease in an adult: A link between juvenile and adult rheumatoid arthritis. Am J Med Sci 1975; 269: 137–44.
Haapasaari J, Wuolijoki E, Ylijoki H. Treatment of juvenile rheumatoid arthritis with diclofenac sodium. Scand J Rheumatol 1983; 12: 325–30.
Haapasaari J, Kautiainen H, Hannula S, Pohjankoski H, Hakala M. Good results from combining etanercept to prevailing DMARD therapy in refractory juvenile idiopathic arthritis. Clin Exp Rheumatol 2002; 20: 867–70.
Haas JP, Nevinny-Stickel C, Schoenwald U, Truckenbrodt H, Suschke J, Albert ED. Susceptible and protective major histocompatibility complex class II alleles in early-onset pauciarticular juvenile chronic arthritis. Hum Immunol 1994; 41: 225–33.
Haffejee IE, Raga J, Coovadia HM. Juvenile chronic arthritis in black and Indian South African children. S Afr Med J, 1984; 65: 510–14.
Hafner R, Pieper M. Arthroscopic synovectomy of the knee joint in chronic juvenile arthritis. Z Rheumatol 1995; 54: 165–70.
Hall PJ, Burman SJ, Laurent MR, Briggs DC, Venning HE, Leak AM, Bedford BA, Ansell BM. Genetic susceptibility to early onset pauciarticular juvenile chronic arthritis: a study of HLA and complement markers in 158 British patients. Ann Rheum Dis 1986; 45: 464–74.
Hall PJ, Burman SJ, Barash J, Briggs DC, Ansell BM. HLA and complement C4 antigens in polyarticular onset seronegative juvenile chronic arthritis: association of early onset with HLA-DRw8. J Rheumatol 1989; 16: 55–9.
Halle F, Prieur AM. Evaluation of methotrexate in the treatment of juvenile chronic arthritis according to the subtype. Clin Exp Rheumatol 1991; 9: 297–302.
Hill RH. Juvenile arthritis in various racial groups in British Columbia. Arthritis Rheum 1977; 20: 162.
Hinks A, Worthington J, Thomson W. The association of PTPN22 with rheumatoid arthritis and juvenile idiopathic arthritis. Rheumatology 2006: 45: 365–8.
Hirschsprung H. Multipel, kronisk, infektios Ledsygdom I Barnealderen. Hospitalstid 1901; 421.

Hochberg MC, Linet MS, Sills EM. The prevalence and incidence of juvenile rheumatoid arthritis in urban Black population. Am J Public Health 1983; 73: 1202–3.
Hochberg MC. Influencing mortality outcomes in RA. Bull Rheum Dis 1992; 41: 4–5.
Hofer MF, Mouy R, Prieur AM. Juvenile idiopathic arthritides evaluated prospectively in a single center according to the Durban criteria. J Rheumatol 2001; 28: 1083–90.
Honkanen VE, Rautonen JK, Pelkonen PM. Intra-articular glucocorticoids in early juvenile chronic arthritis. Acta Paediatr 1993; 82: 1072–4.
Hsu CT, Lin YT, Yang YH, Chiang BL. Factors affecting clinical and therapeutic outcomes of patients with juvenile rheumatoid arthritis. Scand J Rheumatol 2004; 33: 312–17.
Huang JL, Chen LC. Sulfasalazine in the treatment of children with chronic arthritis. Clin Rheumatol. 1998; 17: 359–63.
Huemer C, Malleson PN, Cabral DA, Huemer M, Falger J, Zidek T, Petty RE. Patterns of joint involvement at onset differentiate oligoarticular juvenile psoriatic arthritis from pauciarticular juvenile rheumatoid arthritis. J Rheumatol 2002; 29: 1531–5.
Huppertz H, Voigt I, Muller-Scholden J, Sandhage K. Cardiac manifestations in patients with HLA B27-associated juvenile arthritis. Pediatr Cardiol 2000; 21: 141–7.
Hussein A, Stein J, Ehrich JH. C-reactive protein in the assessment of disease activity in juvenile rheumatoid arthritis and juvenile spondyloarthritis. Scand J Rheumatol 1987; 16: 101–5.
Ilowite NT. Current treatment of juvenile rheumatoid arthritis. Pediatrics 2002; 109: 109–15.
Jaakkola JJ and Gissler M. Maternal smoking in pregnancy as a determinant of rheumatoid arthritis and other inflammatory polyarthritis during the first 7 years of life. Int J Epidemiology 2005; 34: 664–71.
Jacobsen ST, Levinson JE, Crawford AH. Late results of synovectomy in juvenile rheumatoid arthritis. J Bone Joint Surg Am 1985; 67: 8–15.
Kaipiainen-Seppanen O, Savolainen A. Incidence of chronic juvenile rheumatic diseases in Finland during 1980–1990. Clin Exp Rheumatol 1996; 14: 441–4.
Kanakoudi-Tsakalidou F, Tzimouli V, Kapsahili O, Dadalian M, Pardalos G. Detection of rheumatoid factor and antinuclear antibodies in 1500 healthy and 625 hospitalized children. Clin Exp Rheumatol 1995; 13: 557.
Khuffash FA, Majeed HA, Lubani MM, Najdi KN, Gunawardana SS, Bushnaq R. Epidemiology of juvenile chronic arthritis and other connective tissue diseases among children in Kuwait. Ann Trop Paediatr 1990; 10: 255–9.
Kiessling U, Döring E, Listing J, Meincke J, Schöntube M, Strangfeld A, Zink A. Incidence and prevalence of juvenile chronic arthritis in East Berlin 1980–88. J Rheumatol 1998; 25: 1837–43.
Kimura Y, Pinho P, Walco G, Higgins G, Hummell D, Szer I, Henrickson M, Watcher S, Reiff A. Etanercept treatment in patients with refractory systemic onset juvenile rheumatoid arthritis. J Rheumatol 2005; 32: 935–42.
Krumrey-Langkammerer M, Hafner R. Evaluation of the ILAR criteria for juvenile idiopathic arthritis. J Rheumatol 2001; 28: 2544–7.
Kunnamo I, Kallio P, Pelkonen P. Incidence of arthritis in urban Finnish children. A prospective study. Arthritis Rheum 1986; 29: 1232–8.
Kunnamo I. Infections and related risk factors of arthritis in children. A case control study. Scand J Rheumatol 1987; 16: 93–9.

Kurahara D, Tokuda A, Grandinetti A, Najita J, Ho C, Yamamoto K, Reddy DV, Macpherson K, Iwamuro M, Yamaga K. Ethnic differences in risk for pediatric rheumatic illness in a culturally diverse population. J Rheumatol 2002; 29: 379–83.

Kvien TK, Hoyeraal HM, Sandstad B, Kass E. Auranofin therapy in juvenile rheumatoid arthritis: a 48-week phase II study. Scand J Rheumatol Suppl 1986; 63: 79–83.

Kvien TK, Pahle JA, Hoyeraal HM, Sandstad B. Comparison of synovectomy and no synovectomy in patients with juvenile rheumatoid arthritis. A 24-month controlled study. Scand J Rheumatol 1987; 16: 81–91.

Kwok JSY, Hui KH, Lee TL, Wong W, Lau YL, Wong RWS, Kim DL, Jones BM. Anti-cyclic citrullinated peptide: diagnostic and prognostic values in juvenile idiopathic arthritis and rheumatoid arthritis in a Chinese population. Scand J Rheumatol 2005; 34: 359–66.

Laaksonen AL. A prognostic study of juvenile rheumatoid arthritis. Analysis of 544 cases. Acta Paediatr Scand 1966; 1–163.

Lahdenne P, Vahasalo P, Honkanen V. Infliximab or etanercept in the treatment of children with refractory juvenile idiopathic arthritis: an open label study. Ann Rheum Dis 2003; 62: 245–7.

Lamb JR, Bal V, Mendez-Samperio P, Mehlert A, So A, Rothbard J et al. Stress proteins may provide a link between the immune response to infection and autoimmunity. Int Immunol 1989; 1: 191–6.

Lamer S, Sebag GH. MRI and ultrasound in children with juvenile chronic arthritis. Eur J Radiol 2000; 33: 85–93.

Laxer RM, Silverman ED, St-Cyr C, Tran MT, Lingam G. A six-month open safety assessment of a naproxen suspension formulation in the therapy of juvenile rheumatoid arthritis. Clin Ther 1988; 10: 381–7.

Leden I, Persson E, Perrson O. Aspects of the history of rheumatoid arthritis in the light of osteo-archeological finds. Scand J Rheumatol 1988; 17: 341–52.

Levinson JE, Wallace CA. Dismantling the pyramid. J Rheumatol Suppl 1992; 33: 6–10.

Lin YT, Yang YH, Tsai MJ, Chiang BL. Long-term effects of azathioprine therapy for juvenile rheumatoid arthritis. J Formos Med Assoc 2000; 99: 330–5.

Lindsley CB. Seasonal variation in systemic onset juvenile rheumatoid arthritis. Arthritis Rheum 1987; 30: 838–9.

Lomater C, Gerloni V, Gattinara M, Mazzotti J, Cimaz R, Fantini F. Systemic onset juvenile idiopathic arthritis: a retrospective study of 80 consecutive patients followed for 10 years. J Rheumatol 2000; 27: 491–6.

Lovell DJ, Giannini EH, Reiff A, Cawkwell GD, Silverman ED, Nocton JJ, Stein LD, Gedalia A, Ilowite NT, Wallace CA, Whitmore J, Finck BK. Etanercept in children with polyarticular juvenile rheumatoid arthritis. Pediatric Rheumatology Collaborative Study Group. N Engl J Med 2000; 342: 763–9.

Lovell DJ, Giannini EH, Reiff A, Jones OY, Schneider R, Olson JC, Stein LD, Gedalia A, Ilowite NT, Wallace CA, Lange M, Finck BK, Burge DJ; Pediatric Rheumatology Collaborative Study Group. Arthritis Rheum 2003; 48: 218–26.

Malleson PN, Fung MY, Rosenberg AM for the Canadian Pediatric Rheumatology Association. The incidence of pediatric rheumatic diseases: results from the Canadian Pediatric Rheumatology Association Disease Registry. J Rheumatol 1996; 23: 1981–7.

Manners PJ, Diepeveen DA. Prevalence of juvenile chronic arthritis in a population of 12-year-old children in urban Australia. Pediatrics 1996; 98: 84–90.
Manners PJ, Bower C. Worldwide prevalence of juvenile arthritis — why does it vary so much? J Rheumatol 2002; 29: 1520–30.
Manners P, Lesslie J, Speldewinde D, Tunbridge D. Classification of juvenile idiopathic arthritis: should family history be included in the criteria? J Rheumatol 2003; 30: 1857–63.
Martini A, Lorini R, Zanaboni D, Ravelli A, Burgio RG. Frequency of autoantibodies in normal children. Am J Dis Child 1989; 143: 493–6.
Mason T, Reed AM, Nelson AM, Thomas KB, Patton A, Hoffman AD, Achenbach S, O'Fallon WM. Frequency of abnormal hand and wrist radiographs at time of diagnosis of polyarticular juvenile rheumatoid arthritis. J Rheumatol 2002; 29: 2214–8.
Maximov AA, Shaikov AV, Lovell DJ, Giannini EH, Soldatova SI. Chlamydial associated syndrome of arthritis and eye involvement in young children. J Rheumatol 1992; 19: 1794–7.
May P. Rheumatoid arthritis (osteitis deformans) affecting bones 5500 years old. Br Med J 1897; 2: 1631.
McMurray RW, Allen SH, Pepmueller PH, Keisler D, Cassidy JT. Elevated serum prolactin levels in children with juvenile rheumatoid arthritis and antinuclear antibody seropositivity. J Rheumatol 1995; 22: 1577–80.
Merino R, De Inocencio J, Garcia-Consuegra J. Evaluation of ILAR classification criteria for juvenile idiopathic arthritis in Spanish children. J Rheumatol 2001; 28: 2731–6.
Merino R, de Inocencio J, Garcia-Consuegra J. Evaluation of revised International League of Associations for Rheumatology classification criteria for juvenile idiopathic arthritis in Spanish children (Edmonton 2001). J Rheumatol 2005; 32: 559–61.
Michels H, Hafner R, Morhart R, Schuchmann L, Truckenbrodt H. Rheumatic Children's Hospital, Garmisch-Partenkirschen. Five year follow-up of a prospective cohort of juvenile chronic arthritis with recent onset. Clin Rheumatol 1987; 6 Suppl 2: 87–92.
Michels H. What is low-dose corticosteroid therapy in juvenile idiopathic arthritis? A worldwide, questionnaire-based survey. Z Rheumatol 2000; 59 (Suppl 2): 127–30.
Mielants H, Veys EM, Maertens M, Goemaere S, De Clerq L, Castro S, Praet J. Prevalence of inflammatory rheumatic diseases in an adolescent urban student population, age 12 to 18, in Belgium. Clin Exp Rheumatol 1993; 11: 563–7.
Miller JJ. Psychosocial factors related to rheumatic diseases in childhood. J Rheumatol 1993; (Suppl 38)20: 1–11.
Minden K, Kiessling U, Listing J, Niewerth M, Doring E, Meincke J, Schontube M, Zink A. Prognosis of patients with juvenile chronic arthritis and juvenile spondyloarthropathy. J Rheumatol 2000; 27: 2256–63.
Minden K, Niewerth M, Listing J, Biedermann T, Bollow M, Schontube M, Zink A. Long-term outcome in patients with juvenile idiopathic arthritis. Arthritis Rheum 2002; 46: 2392–401.
Minisola G, Dardano B, Calderazzo L, Avola E. Clinical efficacy of sodium diclofenac in chronic juvenile polyarthritis. Pediatr Med Chir 1990; 12: 169–73.

Moe N, Rygg M. Epidemiology of juvenile chronic arthritis in northern Norway: a ten-year retrospective study. Clin Exp Rheumatol 1998; 16: 99–101.
Mohan AK, Cote TR, Block JA, Manadan AM, Siegel JN, Braun MM. Tuberculosis following the use of etanercept, a tumor necrosis factor inhibitor. Clin Infect Dis 2004; 39: 295–9.
Moore TL, Osborn TG, Dorner RW. 19S IgM rheumatoid factor-7S IgG rheumatoid factor-7S immune complexes isolated in sera of patients with juvenile rheumatoid arthritis. Pediatr Res 1986; 20: 977–81.
Morling N, Friis J, Heilmann C, Hellesen C, Jakobsen BK, Jorgensen B, Karup Pedersen F, Svejgaard A, Thomsen K. HLA antigen frequencies in juvenile chronic arthritis. Scand J Rheumatol 1985; 14: 209–16.
Moroldo MB, Chaudhari M, Shear E, Thompson SD, Glass DN, Giannini EH. Juvenile rheumatoid arthritis affected sibpairs: extent of clinical phenotype concordance. Arthritis Rheum 2004; 50: 1928–34.
Murray KJ, Moroldo MB, Donnelly P, Prahalad S, Passo MH, Giannini EH, Glass DN. Age-specific effects of juvenile rheumatoid arthritis-associated HLA alleles. Arthritis Rheum 1999; 42: 1843–53.
Murray KJ, Lovell DJ. Advanced therapy for juvenile arthritis. Best Pract Res Clin Rheumatol 2002; 16: 361–78.
Nielsen HE, Dorup J, Herlin T, Larsen K, Nielsen S, Pedersen FK. Epidemiology of juvenile chronic arthritis: risk dependent on sibship, parental income, and housing. J Rheumatol 1999; 26: 1600–5.
Oen K, Petty RE, Schroeder ML. An association between HLA-A2 and juvenile rheumatoid arthritis in girls. J Rheumatol 1982; 9: 916–20.
Oen K, Postl B, Chalmers IM, Ling N, Schroeder ML, Baragar FD et al. Rheumatic diseases in an Inuit population. Arthritis Rheum 1986; 29: 65–74.
Oen K, Fast M, Postl B. Epidemiology of juvenile rheumatoid arthritis in Manitoba, Canada, 1975–1992: cycles in incidence. J Rheumatol 1995; 22: 745–50.
Oen KG, Cheang M. Epidemiology of chronic arthritis in childhood. Semin in Arthritis Rheum 1996; 26: 575–91.
Oen K, Malleson PN, Cabral DA, Rosenberg AM, Petty RE, Cheang M. Disease course and outcome of juvenile rheumatoid arthritis in a multicenter cohort. J Rheumatol 2002; 29: 1989–99.
Oen K, Malleson PN, Cabral DA, Rosenberg AM, Petty RE, Reed M, Schroeder ML, Cheang M. Early predictors of longterm outcome in patients with juvenile rheumatoid arthritis: subset-specific correlations. J Rheumatol 2003; 30: 585–93.
Ogilvie EM, Fife MS, Thompson SD, Twine N, Tsoras M, Moroldo M, Fisher SA, Lewis CM, Prieur AM, Glass DN, Woo P. The -174G allele of the interleukin-6 gene confers susceptibility to systemic arthritis in children: a multicenter study using simplex and multiplex juvenile idiopathic arthritis families. Arthritis Rheum 2003; 48: 3202–6.
Oguz F, Akdeniz C, Unuvar E, Kucukbasmaci O, Sidal M. Parvovirus B19 in the acute arthropathies and juvenile rheumatoid arthritis. J Paediatr Child Health 2002; 38: 358–62.
Ostensen M, Hoyeraal HM, Kass E. Tolerance of cyclosporine A in children with refractory juvenile rheumatoid arthritis. J Rheumatol 1988; 15: 1536–8.

Ozen S, Karaaslan Y, Ozdemir O, Saatci U, Bakkaloglu A, Koroglu E, Tezcan S. Prevalence of juvenile chronic arthritis and familial Mediterranean fever in Turkey: A field study. J Rheumatol 1998; 25: 2445–9.

Packham JC, Hall MA, Pimm TJ. Long-term follow-up of 246 adults with juvenile idiopathic arthritis: predictive factors for mood and pain. Rheumatology 2002; 41: 1444–9.

Pagan TM, Arroyo IL. Juvenile rheumatoid arthritis in Caribbean children: a clinical characterization. Bol Asoc Med P R 1991; 83: 527–9.

Pahle JA. Orthopaedic management of juvenile chronic arthritis (JCA). Z Rheumatol 1996; 55: 376–87.

Parvizi J, Lajam CM, Trousdale RT, Shaughnessy WJ, Cabanela ME. Total knee arthroplasty in young patients with juvenile rheumatoid arthritis. J Bone Joint Surg Am 2003; 85-A: 1090–4.

Patel A, Varsani H and Wedderburn LR. The hyporesponsiveness of synovial T cells in JIA is a property of CD4+CD25+ T cells: evidence for regulatory T cells in juvenile arthritis. Rheumatol 2003; 42(S1): 11.

Pelkonen PM, Swanljung K, Siimes MA. Ferritinemia as an indicator of systemic disease activity in children with systemic juvenile rheumatoid arthritis. Acta Paediatr Scand 1986; 75: 64–8.

Peterson LS, Mason T, Nelson AM, O´Fallon WM, Gabriel SE. Juvenile rheumatoid arthritis in Rochester, Minnesota 1960–1993. Is the epidemiology changing? Arthritis Rheum 1996; 39: 1385–90.

Peterson LS, Mason T, Nelson AM, O'Fallon WM, Gabriel SE. Psychosocial outcomes and health status of adults who have had juvenile rheumatoid arthritis: a controlled, population-based study. Arthritis Rheum 1997; 40: 2235–40.

Petty RE, Cassidy JT, Sullivan DB. Clinical correlates of antinuclear antibodies in juvenile rheumatoid arthritis. J Pediatr 1973; 83: 386–9.

Petty RE, Southwood TR, Baum J, Bhettay E, Glass DN, Manners P, Maldonado-Cocco J, Suarez-Alamzor M, Orozco-Alcala J, Prieur AM. Revision of the proposed classification criteria for juvenile idiopathic arthritis: Durban, 1997. J Rheumatol 1998; 25: 1991–94.

Petty RE, Smith JR, Rosenbaum JT. Arthritis and uveitis in children. A pediatric rheumatology perspective. Am J Ophthalmol 2003; 135: 879–84.

Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, He X, Maldonado-Cocco J, Orozco-Alcala J, Prieur AM, Suarez-Alamzor M, Woo P; International League of Associations for Rheumatology. International League of Associations for Rheumatology Classification of Juvenile Idiopathic Arthritis: Second Revision, Edmonton, 2001. J Rheumatol 2004; 31: 390–2.

Postepski J, Opoka-Winiarska V, Koziol-Montewka M, Korobowicz A, Tuszkiewicz-Misztal E. Role of mycoplasma pneumonia infection in aetiopathogenesis of juvenile idiopathic arthritis. Med wieku Rozwoj 2003; 7: 271–7.

Prahalad S, Ryan MH, Shear ES, Thompson SD, Glass DN and Giannini EH. Twins concordant for juvenile rheumatoid arthritis. Arthritis Rheum 2000; 43: 2611–2.

Prakken ABJ, van Hoeij MJ, Kuis W, Kavelaars A, Heijnen CJ, Scholtens E et al. T-cell reactivity to human hsp60 in oligoarticular juvenile chronic arthritis is associated with a favourable prognosis and the generation of regulatory cytokines in the inflamed joint. Immunol Lett 1997; 57: 139–42.

Prieur AM, Le Gall LE, Karman F, Edan C, Lasserre O, Goujard J. Epidemiologic survey of juvenile chronic arthritis in France. Comparison of data obtained from two different regions. Clin Exp Rheumatol 1987; 5: 217–23.

Pruunsild C, Uibo K, Liivamägi H, Tarraste S, Urb J. HLA B27 antigen in Estonian children with Juvenile Chronic Arthritis. Scand J Rheumatol 2000, Suppl 114. Abstracts of 28th Scandinavian Congress of Rheumatology.

Quartier P, Taupin P, Bourdeaut F, Lemelle I, Pillet P, Bost M, Sibilia J, Kone-Paut I, Gandon-Laloum S, LeBideau M, Bader-Meunier B, Mouy R, Debre M, Landais P, Prieur AM. Efficacy of etanercept for the treatment of juvenile idiopathic arthritis according to the onset type. Arthritis Rheum 2003; 48: 1093–101.

Ramsey SE, Bolaria RK, Cabral DA, Malleson PN, Petty RE. Comparison of criteria for the classification of childhood arthritis. J Rheumatol 2000; 27: 1283–6.

Ravelli A, Viola S, Ramenghi B, Aramini L, Ruperto N, Martini A. Frequency of relapse after discontinuation of methotrexate therapy for clinical remission in juvenile rheumatoid arthritis. J Rheumatol 1995; 22: 1574–6.

Ravelli A, Viola S, Migliavacca, Ruperto N, Pistorio A, Martini A. The extended oligoarticular subtype is the best predictor of methotrexate efficacy in juvenile idiopathic arthritis. J Pediatr 1999; 135: 316–20.

Ravelli A. Toward an understanding of the long-term outcome of juvenile idiopathic arthritis. Clin Exp Rheumatol 2004; 223: 271–5.

Reed MH, Wilmot DM. The radiology of juvenile rheumatoid arthritis. A review of the English language literature. J Rheumatol Suppl 1991; 31: 2–22.

Roberton DM, Cabral DA, Malleson PN, Petty RE. Juvenile psoriatic arthritis: followup and evaluation of diagnostic criteria. J Rheumatol 1996; 23: 166–70.

Rodary C, Hayem F, Mozziconacci P. Essai d'enquete concernant l'incidence de l'arthrite chronique juvenile en France (annee 1972). Ann Pediatr 1977; 3: 429.

Ronaghy A, Prakken BJ, Takabayashi K, Firestein GS, Boyle D, Zvailfler NJ, Roord ST, Albani S, Carson DA, Raz E. Immunostimulatory DNA sequences influence the course of adjuvant arthritis. J Immunol 2002; 168: 51–6.

Rosenberg AM, Petty RE. A syndrome of seronegative enthesopathy and arthropathy in children. Arthritis Rheum 1982; 25: 1041–46.

Rosenberg AM, Petty RE, Oen KG, Schroeder ML. Rheumatic diseases in Western Canadian Indian children. J Rheumatol 1982; 9: 589–92.

Rosenberg AM. Analysis of a pediatric rheumatology clinic population. J Rheumatol 1990; 17: 827–30.

Rosenberg AM. Longitudinal analysis of a pediatric rheumatology clinic population. J Rheumatol 2005; 32: 1992–2001.

Rothschild BM, Woods RJ, Rothschild C, Sebes JI. Geographic distribution of rheumatoid arthritis in ancient North America: implications for pathogenesis. Semin Arthritis Rheum 1992; 22: 181–7.

Ruperto N, Ravelli A, Levinson JE, Shear ES, Murray K, Link Tague B, Martini A, Glass DN, Giannini EH. Long-term health outcomes and quality of life in American and Italian inception cohorts of patients with juvenile rheumatoid arthritis. II. Early predictors of outcome. J Rheumatol 1997; 24: 952–8.

Ruperto N, Lovell DJ, Cuttica R, Wilkinson N, Espada G, Wouters C, Silverman E, Balogh Z, Henrickson M, Lahdenne P, Prieur AM, Gerloni V, Fasth A, Saurenmann R, Baildam E, Apaz MT, Joos R, Marodi L, Zulian F, Wulffraat N,

Gamir ML, Petty RE, Woo P, Beutler A, Clark J, Chuang E, Giannini EH, Martini A for PRINTO and PRCSG. Randomized trial of infliximab (IFX) plus methotrexate (MTX) for the treatment of polyarticular juvenile rheumatoid arthritis (JRA). Ann Rheum Dis 2005; 64: 34.

Russo RA, Katsicas MM, Zelazko M. Etanercept in systemic juvenile idiopathic arthritis. Clin Exp Rheumatol 2002; 20: 723–6.

Saila HM, Savolainen HA, Kotaniemi KM, Kaipiainen-Seppanen OA, Leirisalo-Repo MT, Aho KV. Juvenile idiopathic arthritis in multicase families. Clin Exp Rheumatol 2001; 19: 218–20.

Sailer M, Cabral D, Petty RE, Malleson PN. Rheumatoid factor positive, oligoarticular onset juvenile rheumatoid arthritis. J Rheumatol 1997; 24: 586–8.

Savilahti E, Pelkonen P, Verkasalo M, Koskimies S. Selective deficiency of immunoglobulin A in children. Klin Padiatr 1985; 197: 336–40.

Savolainen HA, Kautiainen H, Isomaki H, Aho K, Verronen P. Azathioprine in patients with juvenile chronic arthritis: a longterm followup study. J Rheumatol 1997; 24: 2444–50.

Savolainen HA, Lehtimaki M, Kautiainen H, Aho K, Anttila P. HLA B27: a prognostic factor in juvenile chronic arthritis. Clin Rheumatol 1998; 17: 121–4.

Schaller JG, Johnson GD, Holborow EJ, Ansell BM, Smiley WK. The association of antinuclear antibodies with the chronic iridocyclitis of juvenile rheumatoid arthritis (Still's disease). Arthritis Rheum 1974; 17: 409–16.

Schaller J. Juvenile rheumatoid arthritis. Series 1. Arthritis Rheum 1977; 20(Suppl): 165–70.

Schaller JG. Therapy for childhood rheumatic diseases. Have we been doing enough? Arthritis Rheum 1993; 36: 65–70.

Schmeling H, Mathony K, John V, Keysser G, Burdach S, Horneff G. A combination of etanercept and methotrexate for the treatment of refractory juvenile idiopathic arthritis: a pilot study. Ann Rheum Dis 2001; 60: 410–2.

Schneider R, Lang BA, Reilly BJ, Laxer RM, Silvermann ED, Ibanez D et al. Prognostic indicators of joint destruction in systemic-onset juvenile rheumatoid arthritis. J Pediatr 1992; 120: 200–5.

Schneider R, Laxer RM. Systemic onset juvenile rheumatoid arthritis. Baillieres Clin Rheumatol. 1998; 12: 245–71.

Schuchmann L, Albert ED, Michels H, Renz K. Differentiation of juvenile chronic arthritis — diagnostic significance of HLA associations. Klin Padiatr 1984; 196: 355–9.

Schwartz MM, Simpson P, Kerr KL, Jarvis JN. Juvenile rheumatoid arthritis in African Americans. J Rheumatol 1997; 24: 1826–9.

Selvaag AM, Lien G, Sorskaar D, Vinje O, Forre O, Flato B. Early disease course and predictors of disability in juvenile rheumatoid arthritis and juvenile spondyloarthropathy: a 3-year prospective study. J Rheumatol 2005; 32: 1122–30.

Selvaag AM, Flato B, Dale K, Lien G, Vinje O, Smerdel-Ramoya A, Forre O. Radiographic and clinical outcome in early juvenile rheumatoid arthritis and juvenile spondyloarthropathy: a 3-year prospective study. J Rheumatol 2006; 33: 1382–91.

Shaikov AV, Maximov AA, Speransky AI, Lovell DJ, Giannini EH, Solovyev SK. Repetitive use of pulse therapy with methylprednisolone and cyclophosphamide in

addition to oral methotrexate in children with systemic juvenile rheumatoid arthritis-preliminary results of a longterm study. J Rheumatol 1992; 19: 612–6.
Sharma S and Sherry DD. Joint distribution at presentation in children with pauciarticular arthritis. J Pediatr 1999; 134: 642–3.
Sieper J, Braun J, Doring E, Wu P, Heesemann J, Treharne J, Kingsley G. Aetiological role of bacteria associated with reactive arthritis in pauciarticular juvenile chronic arthritis. Ann Rheum Dis 1992; 51: 1208–14.
Silverman E, Spiegel IR, Hawkins D, Petty RE, Goldsmith D, Schanberg L et al. Long-term open-label preliminary study of the safety and efficacy of leflunomide in patients with polyarticular-course juvenile rheumatoid arthritis. Arthritis and Rheum 2005; 52: 554–562.
Singh-Grewal D, Schneider R, Bayer N, Feldman BM. Predictors of disease course and remission in systemic juvenile idiopathic arthritis: significance of early clinical and laboratory features. Arthritis Rheum 2006; 54: 1595–601.
Southwood TR, Petty RE, Malleson PN, Delgado EA, Hunt DW, Wood B, Schroeder ML. Psoriatic arthritis in children. Arthritis Rheum 1989; 32: 1007–13.
Spiegel LR, Schneider R, Lang BA, Birdi N, Silverman ED, Laxer RM, Stephens D, Feldman BM. Early predictors of poor functional outcome in systemic-onset juvenile rheumatoid arthritis: a multicenter cohort study. Arthritis Rheum 2000; 43: 2402–9.
Stamato T, Laxer RM, de Freitas C, Gow R, Silverman ED, Luy L, Smallhorn JF. Prevalence of cardiac manifestations of juvenile ankylosing spondylitis. Am J Cardiol 1995; 75: 744–6.
Stastny P, Fink CW. Different HLA-D associations in adult and juvenile rheumatoid arthritis. J Clin Invest 1979; 63: 124–30.
Steans A, Manners PJ, Robinson IG. A multicentre, long-term evaluation of the safety and the efficacy of ibuprofen syrup in children with juvenile chronic arthritis. Br J Clin Pract 1990; 44: 172–5.
Steven MM. Prevalence of chronic arthritis in four geographical areas of the Scottish Highlands. Ann Rheum Dis 1992; 51: 195–7.
Still GF. On a form of chronic joint disease in children. Med Chir Trans 1897; 80:47 (Reprinted in Am J Dis Child 1978; 132: 195–200).
Stoeber E. Prognosis in juvenile chronic arthritis. Follow-up of 433 chronic rheumatic children. Eur J Pediatr 1981 Feb;135(3):225–8.
Stoll ML. Zurakowski D, Nigrovic LE, Nichols DP, Sundel RP, Nigrovic PA. Patients with juvenile psoriatic arthritis comprise two distinct populations. Arthritis Rheum 2006; 54: 3564–72.
Stone M, Warren RW, Bruckel J, Cooper D, Cortinovis D, Inman RD. Juvenile-onset ankylosing spondylitis is associated with worse functional outcomes than adult-onset ankylosing spondylitis. Arthritis Rheum 2005; 15: 445–51.
Sullivan DB, Cassidy JT, Petty RE. Pathogenic implications of age at onset in juvenile rheumatoid arthritis. Arthritis Rheum 1975; 18: 251–5.
Symmons DP, Barrett EM, Bankhead CR, Scott DG, Silman AJ. The incidence of rheumatoid arthritis in the United Kingdom: results from the Norfolk Arthritis Register. Br J Rheumatol 1994; 33: 735–9.

Symmons DP, Jones M, Osborne J, Sills J, Sothwood TR, Woo P. Pediatric rheumatology in the United Kingdom: data from the British Pediatric rheumatology Group national Diagnostic Register. J Rheumatol 1996; 23: 1975–80.

Szer IS, Kimura Y, Malleson PN, Southwood TR. Arthritis in children and adolescents. Oxford University Press 2006: 205–98.

Szumera M, Sikorska-Wisniewska G, Szweda P, Korzon M. Role of parvovirus B19 as a causative agent for arthritis in children — preliminary studies. Med Wieku Rozwoj 2004; 8: 425–32.

Thomas E, Symmons DP, Brewster DH, Black RJ, Macfarlane GJ. National study of cause-specific mortality in rheumatoid arthritis, juvenile chronic arthritis, and other rheumatic conditions: a 20 year followup study. J Rheumatol 2003; 30: 958–65.

Thompson SD, Moroldo MB, Guyer L, Ryan M, Tombragel EM, Shear ES, Prahalad S, Sudman M, Keddache MA, Brown WM, Giannini EH, Langefeld CD, Rich SS, Nichols WC, Glass DN. A genome-wide scan for juvenile rheumatoid arthritis in affected sibpair families provides evidence of linkage. Arthritis Rheum 2004; 50: 2920–30.

Thomson W, Barrett JH, Donn R, Pepper L, Kennedy LJ, Ollier WE, Silman AJ, Woo P, Southwood T; British Paediatric Rheumatology Study Group. Juvenile idiopathic arthritis classified by the ILAR criteria: HLA associations in UK patients. Rheumatology (Oxford) 2002; 41: 1183–9.

Towner SR, Michet CJ Jr, O' Fallon WM, Nelson AM. The epidemiology of juvenile arthritis in Rochester, Minnesota 1960–1979. Arthritis Rheum 1983; 26: 599–603.

Tynjala P, Lahdenne P, Vahasalo P, Kautiainen H, Honkanen V. Impact of anti-TNF-treatment on growth in severe juvenile idiopathic arthritis. Ann Rheum Dis 2006; 65: 1044–9.

Van den Broek MF, Hogervorst EJ, Van Bruggen MC, Van Eden W, Van der Zee R, Van den Berg WB. Protection against streptococcal cell wall-induced arthritis by pretreatment with the 65-kD mycobacterial heat shock protein. J Exp Med 1989; 170: 449–66.

van Rossum MA, Fiselier TJ, Franssen MJ, Zwinderman AH, ten Cate R, van Suijlekom-Smit LW, van Luijk WH, van Soesbergen RM, Wulffraat NM, Oostveen JC, Kuis W, Dijkstra PF, van Ede CF, Dijkmans BA. Sulfasalazine in the treatment of juvenile chronic arthritis: a randomized, double-blind, placebo-controlled, multicenter study. Dutch Juvenile Chronic Arthritis Study Group. Arthritis Rheum 1998; 41: 808–16.

van Rossum M, van Soesbergen R, de Kort S, ten Cate R, Zwinderman AH, de Jong B, Dijkmans B, van Venrooij WJ. Anti-cyclic citrullinated peptide (anti-CCP) antibodies in children with juvenile idiopathic arthritis. J Rheumatol 2003; 30: 825–8.

Van Rossum MA, Zwinderman AH, Boers M, Dijkmans BA, van Soesbergen RM, Fiselier TJ, Franssen MJ, ten Cate R, van Suijlekom-Smit LW, Wulffraat NM, Kuis W, van Luijk WH, Oostveen JC, Dijkstra PF, Dutch Juvenile Idiopathic Arthritis Study Group. Radiologic features in juvenile idiopathic arthritis: a first step in the development of a standardized assessment method. Arthritis Rheum 2003; 48: 507–15.

Walker SM, Shaham B, McCrudy DK, Wietting H, Arora YK, Hanson V, Bernstein B. Prevalence and concentration of IgM rheumatoid factor in polyarticular onset disease as compared to systemic or pauciarticular onset disease in active juvenile rheumatoid arthritis as measured by ELSA. J Rheumatol 1990; 17: 936–40.

Walker SM, McCurdy DK, Shaham B, Brik R, Wietting H, Arora Y, Lehman TJ, Hanson V, Bernstein B. High prevalence of IgA rheumatoid factor in severe polyarticular-onset juvenile rheumatoid arthritis, but not in systemic-onset or pauciarticular-onset disease. Arthritis Rheum 1990; 33: 199–204.

Wallace CA, Sherry DD. Trial of intravenous pulse cyclophosphamide and methylprednisolone in the treatment of severe systemic-onset juvenile rheumatoid arthritis. Arthritis Rheum 1997; 40: 1852–5.

Wallace CA, Ruperto N, Giannini EH. Childhood Arthritis and Rheumatology Research Alliance; Pediatric Rheumatology International Trials Organisation: Pediatric Rheumatology Collaborative Study Group. Preliminary criteria for clinical remission for select categories of juvenile idiopathic arthritis. J Rheumatol 2004; 31: 2290–4.

Wallace CA, Huang B, Bandeira M, Ravelli A, Giannini EH. Patterns of clinical remission in select categories of juvenile idiopathic arthritis. Arthritis Rheum 2005; 52: 3554–62.

Wallis RS, Broder MS, Wong JY, Hanson ME, Beenhouwer DO. Granulomatous infectious diseases associated with tumor necrosis factor antagonists. Clin Infect Dis 2004; 38: 1261–5.

Wedderburn LR, Patel A, Varsani H, Woo P. Divergence in the degree of clonal expansions in inflammatory T cell subpopulations mirrors HLA-associated risk alleles in genetically and clinically distinct subtypes of childhood arthritis. Int Immunol 2001; 13: 1541–50.

Williams RA, Ansell BM. Radiological findings in seropositive juvenile chronic arthritis (juvenile rheumatoid arthritis) with particular reference to progression. Ann Rheum Dis 1985; 44: 685–93.

Woo P, Southwood TR, Prieur AM, Dore CJ, Grainger J, David J, Ryder C, Hasson N, Hall A, Lemelle I. Randomized, placebo-controlled, crossover trial of low-dose oral methotrexate in children with extended oligoarticular or systemic arthritis. Arthritis Rheum 2000; 43: 1849–57.

Woo P. Systemic juvenile idiopathic arthritis: diagnosis, management and outcome. Nat Clin Prct Rheumatol 2006; 2: 28–34.

Wood PHN. Special Meeting on: nomenclature and classification of arthritis in children. In E. Munthe, ed. The Care of Rheumatic Children. Basel: EULAR, 1978, pp. 47–50.

Yancey C, White P, Magilavy D et al. Guidelines for ophthalmologic examinations in children with juvenile rheumatoid arthritis. Pediatrics 1993; 92: 295–6.

Young DB. Stress proteins and the immune response. Antonie Van Leeuwenhoek 1990; 58: 203–8.

Zeggini E, Donn RP, Ollier WER, The BPRG Study Group, Thomson W. Genetic Dissection of the major histocompatibility complex in juvenile oligoarthritis. Arthritis Rheum 2002; 46: S272.

SUMMARY IN ESTONIAN

JUVENIILNE IDIOPAATILINE ARTRIIT EESTI LASTEL

1. Metoodika

Juveniilse idiopaatilise artriidi (JIA) keskmist haigestumust ja levimust uuriti 14-s Eesti maakonnas. Uuringust jäi välja Ida-Virumaa — seda vähese tagasiside tõttu antud piirkonna esmatasandi arstidelt. Haigestumust uuriti aastatel 1998–2000. Eesti Statistikaameti andmetel (www.stat.ee) oli 0–15-aastaste laste keskmine arv nimetatud perioodil 248 624, neist 121 437 olid tüdrukud ja 127 187 poisid.

Levimuspäeval, 31. detsembril 2000. aastal oli 0–15-aastaste laste koguarv uuringu piirkonnas 235 395, neist 114 719 tüdrukud ja 120 676 poisid.

Levimusuuringusse hõlmati lisaks aastatel 1998–2000 haigestunutele ka aastatel 1995–1997 haigestunud ja uuringukriteeriumitele vastavad JIA haiged, sealhulgas jäeti välja haiged, kes seisuga 31. detsember 2000.a. olid remissioonis.

JIA haigete uurimine ja ravi Eesti Vabariigis toimub III etapi haiglates — SATÜK lastekliinikus ja SA Tallinna Lastehaiglas; mõlemad keskused osalesid andmete kogumises. Enne uuringut toimus nõupidamine, millel osalesid mõlema haigla juhtkonnad ja spetsialistid ja kus lepiti kokku uuringu protokoll. Lisaks toimus enne uuringu algust uuringu protokolli tutvustamine ja uuringu põhimõtete läbiarutamine mõlema haigla arstide koosolekutel. Haigestumuse leidmiseks registreeriti haigeid prospektiivselt ajavahemikus 1. jaanuar 1998 kuni 31.detsember 2000. Lisaks küsitleti 14 maakonna esmatasandi arste uuringuperioodi jooksul korduvalt kirja teel; saadud andmeid võrreldi III etapi haiglate andmetega. Levimusuuringu jaoks töötati läbi keskuste statsionaarse ja ambulatoorse vastuvõtu dokumendid perioodil 1995–1997. Lühiajalise prognoosi uurimiseks jälgiti perioodil 1998–2000 diagnoositud JIA-ga haigeid kahe aasta vältel alates haiguse diagnoosimisest. Dokumenteeriti uuringus osalevate haigete kliinilised ja laboratoorsed näitajad ning ravimite kasutamine. Aastatel 1995–1997 diagnoositud JIA haigete vastavad andmed saadi lastehaiglate haiguslugudest ja ambulatoorsetest kaartidest.

JIA diagnoosimisel ja klassifitseerimisel võeti aluseks Rahvusvahelise Reumatoloogia Seltside Ühenduse (International League of Associations for Rheumatology, ILAR) Alalise Pediaatrilise Komitee töörühma poolt aktsepteeritud kriteeriumid (1997. a. täiendatud versioon). Haiguse aktiivsuse hindamise aluseks olid Euroopa Reumavastase Liiga (European League Against Rheumatism, EULAR) Alalise Pediaatrilise Reumatoloogia Komitee (Standing Committee on Pediatric Rheumatology) poolt 1983.a. Moskvas soovitatud kriteeriumid.

Uuringu läbiviimiseks saadi luba Tartu Ülikooli Inimuuringute Eetika Komiteelt.

2. Tulemused

2.1. Haigestumus

Aastatel 1998–2000 esines 14-s Eesti maakonnas 162 uut JIA juhtu, kellest 76 olid poisid ja 86 tüdrukud. Keskmine haigestumus oli 21,7 juhtu 100 000 kuni 16aastase lapse kohta, tüdrukutel vastavalt 22,9 ja poistel 19,3. Keskmine haigestumus oli suurim 11–15-aastaste tüdrukute hulgas — 26,8 juhtu 100 000 kohta. Keskmine vanus haigestumisel oli 9a6k; poistel 8a10k ja tüdrukutel 10a1k. Poisid haigestusid kõige sagedamini vanuses 4–10 aastat ja tüdrukud vanuses 7–15 aastat.

Alatüüpidest oli sagedaseim püsiv oligoartriit (43,8%), keskmine esmashaigestumus 9,4 juhtu 100 000 kuni 16aastase lapse kohta, järgnesid RF-negatiivne polüartriit (20,6%) ja laienev oligoartriit (12,7%). Süsteemset alatüüpi esines enam poistel, polüartriiti tüdrukutel.

2.2. Levimus

Levimusuuringus registreeriti kokku 197 JIA haiget, neist 103 tüdrukut ja 94 poissi, vanuses 0–15 aastat, kes elasid 14-s maakonnas levimuspäeval, 31. detsembril 2000. aastal. JIA oli alanud perioodil 1995–2000 ja levimuspäeval oli uuringugrupi haigetel haigus aktiivne (püsivad põletikutunnused liiges(t)es ja uute liigeste lisandumine), stabiilne (püsivad põletikutunnused liiges(t)es ilma uute liigeste lisandumiseta) või inaktiivne (kliiniliselt sümptomitevaba, vähem kui kaks aastat ilma ravita). Levimus oli 83,7 100 000 kuni 16aastase lapse kohta, 90,7 tüdrukutel ja 77,1 poistel. Levimus oli suurim 11–15-aastaste tüdrukute hulgas (132: 100 000) ja väikseim 0–3-aastaste tüdrukute grupis (9,6: 100 000).

Keskmine aeg haiguse avaldumisest diagnoosimiseni oli 7 kuud; periood oli kõige pikem laieneva oligoartriidi ja psoriaatilise artriidi korral (mõlemal juhul üks aasta) ja lühim süsteemse artriidi korral (üks kuu).

2.3. Haiguse kulg. Lühiajaline prognoos

Kahe aasta möödumisel JIA diagnoosimisest oli haigus aktiivne või stabiilne 76/197 (38,6%) haigest. Ligikaudu neljandikul haigetest (23%) oli haigus inaktiivne. Jälgimisperioodi jooksul jäi haiguse alatüüp samaks 63 haigel (32%, neist 25 püsiva oligoartriidiga); 23/111 (20,7%) püsiva oligoartriidiga haigel muutus haiguse kulg esimese kuue haiguskuu järel polüartikulaarseks.

Levimuspäeval olid andmed olemas 158/197 haige kohta; keskmine haiguse kestus oli 2 aastat ja 4 kuud. Kahekümne neljal 39-st haigest, kelle kohta puudusid andmed, oli diagnoositud püsiv oligoartriit. Haigus oli inaktiivne 18,8%-l haigetest. Haiguskulgu modifitseerivaid ravimeid tarvitas 87 haiget (44,2%), teisi ravimeid (peamiselt mittesteroidseid põletikuvastaseid aineid) 15 haiget (7,6%).

Haigetel, kellel leiti HLA-B27 antigeen, esines võrrelduna HLA-B27-negatiivsete haigetega sagedamini entesiidiga artriiti (p=0,002) ja põletikunäitajate püsimine normiväärtustest kõrgemal tasemel (p=0,085) vähemalt kuue esimese kuu jooksul haiguse diagnoosimisest.

3. Diskussioon

Käesolev uuring on esimene Eestis, milles on uuritud JIA epidemioloogilisi näitajaid. Epidemioloogiliste uuringute andmetel on JIA haigestumus 0,8–22,6 juhtu 100 000 lapse kohta ja levimus 7–401 juhtu 100 000 lapse kohta. Näitajate kõikumine suurtes piirides on tingitud erinevatest uuringutüüpidest (haiglapõhine, rahvastikupõhine, küsimustikud, esmatasandi arstide ja/või eriarstide vastuvõtu andmed, haigekassa andmed kindlustatute kohta, haiguste registrite andmed), uuringugrupi koostamisest (uuritavate vanus kõigub 12–18 aastani) ja suurusest, kasutatud klassifikatsioonist, uurijate kvalifikatsioonist ning teadlikkusest. Haiglaandmetel põhinevate uuringute eeliseks on nende kerge teostatavus ja odavus, puuduseks aga aladiagnostika, kuna paljud kergema haiguskuluga haiged ei pruugi esmatasandi arstiabist eriarsti vaatevälja ja/või kõrgemasse etappi jõuda. Rahvastikupõhised uuringud on raskemini teostatavad, kuid täpsemad, sest hõlmavad rohkem uuringu piirkonnas uuringuperioodil diagnoositud juhte, sealhulgas ka neid, kellel haigus on kergema kuluga. Rahvastikupõhistes uuringutes saadud haigestumuse näitajad on seega alati mõnevõrra suuremad. Aastatel 1998–2000 Eestis teostatud JIA haigestumuse uuring on rahvastikupõhine; lisaks lastehaiglates diagnoositud juhtude registreerimisele toimus pidev esmatasandi arstide informeerimine, nende teadlikkuse suurendamine ja neilt patsientide kohta informatsiooni laekumine.

Mitmete uuringute andmetel on JIA haigestumuses täheldatavad perioodiline tõus ja langus ja geograafilised erinevused, mis viitavad keskkonnategurite ja/või geneetiliste faktorite osatähtsusele. Käesolevas uuringus ilmnes uuringuperioodi jooksul 3,5kordne haigestumuse tõus (1998. a. 9,5 ja 2000. a. 33,7 juhtu 100 000 kuni 16aastase lapse kohta). Lisaks võimalikele keskkonnafaktoritele avaldas tulemustele mõju esmatasandi arstide teadlikkuse kasv. Uuringu toimumise ajal toimus Eestis esmatasandi arstiabi reform, perearstideks õppisid ümber ka paljud lastearstid. Uuringu lõpuks oli uuringu piirkonnas 412 perearsti; paralleelselt kasvas ka haigetest teatamine ja nende suunamine III etappi.

JIA haigestumusmäär eesti lastel — 21,7 100 000 kuni 16aastase lapse kohta — on võrreldav teistes põhjamaades tehtud rahvastikupõhiste uuringute tulemustega. Soomes on JIA haigestumus 19,6 ARA klassifikatsiooni järgi ja 18,2 kolm kuud kestnud artriidi korral (Kunnamo *et al.* 1986), Norras 22,6 EULAR-i klassifikatsiooni järgi (Moe ja Rygg 1998). Sarnaselt Eestile on Rootsis leitud viimasel kümnendil haigestumuse tõusu — 1992. a. oli haigestumus 10,9 (Andersson Gäre ja Fasth) ja 2003.a 14 (Berntson *et al.* 2003).

JIA levimus eesti lastel (83,7 100 000 kuni 16aastase lapse kohta) on võrreldav USAs tehtud rahvastikupõhise uuringu tulemustega — 83,7–113,4 erinevate klassifikatsioonide alusel. Käesolevast uuringust olid välja jäetud remissioonis haiged ja enne 1995.a. diagnoositud JIA juhud, mistõttu tegelik levimus võib olla mõnevõrra kõrgem. Sarnaselt haigestumusele on ka kõrgeimad levimuse näitajad avaldatud põhjamaades tehtud uuringute põhjal.

Tüdrukute osakaal haigestumuse ja levimuse grupis oli vastavalt 53,1% ja 52,3%, võrreldes kirjanduses avaldatud 60–65%-ga ei ilmnenud statistilist erinevust. Sarnaselt teistele avaldatud uuringutele oli eesti lastel kõige sagedasem JIA alatüüp püsiv oligoartriit.

Antud haigete grupis ei ilmnenud sarnaselt avaldatud epidemioloogilistele uuringutele haigestumuse tippu 0–3aastaste tüdrukute hulgas, mille üheks arvatavaks põhjuseks võib olla uuringuperioodi esimesel aastal (1998) esmatasandi arstide poolt suunatud väga väike haigete arv (26); kuni 3-aastaste hulgas sageli esinev oligoartriit võib kulgeda väga tagasihoidliku kliinilise leiuga ja jääda esmatasandil diagnoosimata. Uuringuperioodi jooksul kasvas oluliselt III etappi suunatud haigete arv. Välistada ei saa ka geneetilistel faktoritel baseeruvaid iseärasusi.

Levimuse osas ilmnes tõus paralleelselt haigete vanuse kasvuga, mille aluseks on tõenäoliselt lühike haiguse kestvus oligoartriidiga väikelapseeas olevate tüdrukute hulgas. Oligoartriit oli peamiseks alatüübiks nende haigete hulgas, kelle kohta ei olnud andmeid kaks aastat peale haiguse diagnoosimist; neil haigetel oli haigus suure tõenäosusega muutunud inaktiivseks.

Kaks aastat peale JIA diagnoosimist oli haigus inaktiivne 23%-l haigetest, lisaks sellele tõenäoliselt ka 24,9%-l haigetest, kes peale haiguse diagnoosimist ja ravi alustamist ei olnud enam arsti juurde pöördunud. Antud uuringu jälgimisperiood on liiga lühike, et objektiivselt hinnata, kui suur osa haigeid tegelikult remissiooni jõuab.

Varasemates epidemioloogilistes töödes ei ole eraldi hinnatud haiguse kulgu püsiva ja laieneva oligoartriidi korral; viimane on üks raskemini ravile alluvaid JIA alatüüpe. Polüartikulaarset haiguse kulgu kirjeldatakse 20–50% algselt oligoartriidina alanud JIA korral. Eesti lastel esines laienevat oligoartriiti 20,7%-l oligoartriidi juhtudest; pooled neist haigetest vajasid kahe aasta möödudes haiguse diagnoosimisest jätkuvalt ravi. Kogugrupis vajas kahe aasta möödudes ravi 51,8% haigetest.

JIA haigete käsitluse aluseks on tänapäeval eriväljaõppe saanud spetsialistide — lastereumatoloog, reumaõde, füsioterapeut, psühholoog, tegelusterapeut ja sotsiaaltöötaja — meeskonnatöö. Enamus JIA haigetest ei vaja haiglaravi, ambulatoorse ravi osakaal on tõusutendentsiga.

Epidemioloogilised andmed on aluseks tervishoiu rahastamise planeerimisel. Uute efektiivsete, ent kulukate bioloogiliste ravimite ajastul on eriti oluline jaotada ressursse selliselt, et võimaldada ravi neile, kes seda tõeliselt vajavad.

4. Järeldused

1. Keskmine haigestumus JIA-sse oli uuringu perioodil 21,7 100 000 kuni 16-aastase lapse kohta (22,9 tüdrukutel ja 19,3 poistel). Keskmine haigestumus oli kõrgeim lastel vanuses 7–10-aastat — 23,8: 100 000 kohta. Tüdrukud haigestusid kõige sagedamini vanuses 7–15 aastat ja poisid 4–10 aastat. Laste keskmine vanus haiguse avaldumisel oli 9 aastat ja 6 kuud; tüdrukutel 10 aastat ja 1 kuu ja poistel 8 aaastat ja 10 kuud. Keskmine vanus haigestumisel oli madalaim süsteemse artriidi korral ─ 4 aaastat ja 3 kuud ─ ja kõrgeim entesiidiga seotud artriidi korral ─ 12 aastat ja 6 kuud. JIA haigestumusmäär ja erinevate haiguse alatüüpide proportsionaalne jaotus Eestis on sarnane Põhjamaades saadud tulemustega.
2. Haigestumusuuringusse kuulunud lastel esines JIA alatüüpidest kõige sagedamini oligoartriiti (87-l juhul, 54,4%, keskmine haigestumus aastas 11,7: 100 000). Sageduselt järgmisena esines seronegatiivset polüartriiti (33-l juhul, aasta keskmine haigestumus 4,4: 100 000).
3. Uuringuperioodi jooksul ilmnes 3,5 kordne haigestumuse tõus (9,5-lt juhult 100 000 kuni 16-aastase lapse kohta 1998. aastal 33,7-le juhule 100 000 kohta 2000. aastal). Erinevate alatüüpide proportsionaalne jaotus sealjuures ei muutunud. Haigestumuse tõusu põhjusena tuleb arvesse esmatasandi arstide teadlikkuse kasv uuringuperioodi jooksul.
4. Levimuspäeval, 31. detsembril 2000. a., oli 14-s maakonnas 197 last (94 poissi ja 103 tüdrukut) vanuses 0–15 aastat, kellel oli JIA alanud ajavahemikul 1995–2000 ja kellel haigus oli aktiivne, stabiilne või inaktiivne. Levimus oli 83,7: 100 000 kuni 16aastase lapse kohta, 90,7: 100 000 tüdrukutel ja 77,1: 100 000 poistel. Levimus oli suurim 11–15-aastaste tüdrukute hulgas (132: 100 000) ja väikseim 0–3-aastaste tüdrukute grupis (9,6: 100 000). Keskmine vanus haigestumisel oli levimusuuringus osalenute hulgas 8 aastat ja 8 kuud; tüdrukutel 9 aastat ja 1 kuu ja poistel 8 aastat ja 4 kuud. Alatüüpide proportsionaalne jaotus oli levimusuuringus sarnane haigestumusuuringule. JIA levimusmäär on kooskõlas teiste avaldatud epidemioloogiliste tööde tulemustega.

5. Keskmine ajavahemik haiguse algusest (esmastest kaebustest / tunnustest) kuni haiguse diagnoosimiseni oli seitse kuud. Nimetatud ajavahemik oli kõige pikem laieneva oligoartriidi ja psoriaatilise artriidi korral (mõlemal juhul üks aasta) ja lühim süsteemse artriidi korral (üks kuu). JIA võimalikult varaseks diagnoosimiseks ja adekvaatse ravi alustamiseks on vajalik pidev koostöö esmatasandi arstidega ja nende teadlikkuse tõstmine.
6. HLA-B27 antigeen leiti 28/98 (28,6%-l) haigestumusuuringus osalenuil (15 poisil ja 13 tüdrukul). Haigetel, kellel leiti HLA-B27 antigeen, esines võrrelduna HLA-B27-negatiivsete haigetega sagedamini entesiidiga artriiti (p=0,002) ja põletikunäitajate püsimine normiväärtustest kõrgemal tasemel (p=0,085) vähemalt kuue esimese kuu jooksul haiguse diagnoosimisest.
7. Kahe aasta möödumisel JIA diagnoosimisest oli haigus aktiivne või stabiilne 76/197 (38,6%-l) haigetest. Ligikaudu neljandikul haigetest (23%-l) oli haigus inaktiivne. Jälgimisperioodi jooksul muutus 20,7%-l püsiva oligoartriidiga haigel haiguse kulg esimese kuue haiguskuu järel polüartikulaarseks.
8. Levimuspäeval, 31.detsembril 2000. a. oli haigus kestnud keskmiselt 2a4k. Haigus oli muutunud inaktiivseks 18,8%-l haigetest. Haiguskulgu modifitseerivaid ravimeid tarvitas 87 haiget (44,2%), teisi ravimeid (peamiselt mittesteroidseid põletikuvastaseid aineid) 15 haiget (7,6%).
9. JIA kulu ja prognoosi objektiivsemaks hindamiseks on vajalik levimusuuringus osalenud haigete pikaajaline uuring.

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PUBLICATIONS

III

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Prevalence and Short-term Outcome of Juvenile Idiopathic Arthritis: a Population-based Study in Estonia

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ABSTRACT

Objectives. To study the point prevalence of juvenile idiopathic arthritis (JIA) in children in Estonia on December 31, 2000. To examine short-term clinical outcome of the disease.

Method. Identification of patients diagnosed with JIA between 1995–2000. Prospective follow-up of new cases diagnosed between 1998–2000 for two years. Retrospective analysis of the medical records of patients diagnosed between 1995–1997. The study was population-based.

Results. One hundred and ninety seven (197) patients fulfilled the study criteria. On December 31, 2000 the point prevalence of JIA was 83.7 (95% CI: 72.4;95.8) per 100 000 children aged 0–15 years, 90.7 (95% CI: 74.1;108.9) for girls and 77.1 (95% CI: 62.2; 93.5) for boys. The prevalence was the highest among 11–15 year old girls (132; 95% CI: 100.7;167.4) and the lowest in 0–3 year old girls (9.6; 95% CI: 1.2; 26.7). For 44 patients (22.3%), the disease was inactive after 2 years since the onset of the disease. For 76 patients (38.6%) the disease was active or stable after 2 years.

Conclusions. This is the first population-based study on the prevalence and outcome of JIA in Estonia in which the new ILAR criteria have been used. A longer follow-up of JIA patients is needed to have a better overview of the course of the disease. A good cooperation between family doctors and specialists is crucial for diagnosing JIA as early as possible.

Key words: juvenile idiopathic arthritis, prevalence rate

INTRODUCTION

Juvenile idiopathic arthritis (JIA), previously also known as juvenile rheumatoid arthritis (JRA) and juvenile chronic arthritis (JCA), begins before the 16th birthday and is defined as sterile inflammation in at least one joint that is persistent for at least six weeks, and in which there is no defined diagnosis (1). The term "juvenile idiopathic arthritis, or JIA" was introduced by the Task Force of Pediatric Standing Committee of the International League of Associations for Rheumatology (ILAR) in 1995 (1); this classification was revised in 1997 (2) and in 2001 (3). JIA is by nature a heterogeneous disease with a chronic course which can cause disability already in early childhood. JIA has seven clinical subtypes. The course of the disease and outcome vary between different subtypes (4–6).

The incidence rate and the prevalence rate of JIA vary in different geographic areas and can be influenced by environmental and/or genetic factors (7,8). The prevalence of juvenile arthritis ranges according to several authors from 7 to 401 per 100 000 children aged 0–15 years (9). The reasons for the variation in these wide limits are most likely connected to different classification criteria used, different study designs (hospital and community-based studies), and varied patient selection.

The aim of this study was to investigate the prevalence of JIA in Estonia on Dec 31, 2000 using the ILAR criteria (the 1997 revision) and to examine short-term clinical outcome of the disease.

MATERIALS AND METHODS

The study area. Estonia is the northernmost of the three Baltic States, with a population of 1.3 million. Fourteen of the 15 counties of Estonia participated, and only the eastern part of Virumaa was not included, due to a lack of feedback from the doctors of the region.

The study population. According to the Statistical Office of Estonia (www.stat.ee) the mean population at risk (children aged 0–15 years) in the year 2000 was 235 396 (120 676 boys and 114 719 girls).

The study period. The study period covered the years 1995–2000. Active patient and data collection was started on Jan 1, 1998 and carried out between 1998–2000.

Study design. Before starting the collection of the series, in late 1997, a meeting to confirm the study design and inclusion/exclusion criteria was held, with the presence of the administrations of the two tertiary hospitals - Tallinn Children's Hospital and Children's Clinic of Tartu University Hospital - and of all pediatricians participating in the study. A couple of meetings were held with local pediatricians in charge of the 14 counties (one in each) and family doctors

via teaching seminars, where the inclusion criteria and classification of JIA were introduced (10). Altogether 50 separate family doctors and family medicine centres (with more than one family doctor) were practising at the beginning of the study; they were all contacted by mail. There are only few orthopaedic surgeons and physical therapists consulting children in Estonia and they work in these two centres which participated in the study.

In addition to the abovementioned doctors county hospitals, county outpatient clinics and medical and health care centres (altogether 47) were informed by mail about the beginning of the study, and the criteria for JIA were added to the letters.

The doctors were asked to send all the new patients with JIA (and those they suspected of having JIA) to the two children's hospitals. In addition the doctors were asked to report on all patients meeting the JIA criteria and diagnosed since Jan 1, 1995 in their region.

The active collection of patients and data started on Jan 1, 1998 and consisted of two parts which were carried out in a parallel fashion. The first was a prospective population-based study, during the years 1998–2000, in which the mean annual incidence rate of JIA was determined (10); and the second was a retrospective analysis of the medical records of patients diagnosed between 1995–1997. The short-term clinical outcome was determined following the incidence group prospectively. The follow-up of the early JIA series was accomplished using the data from patients' records.

All the doctors were reminded about ongoing study twice by mail. The primary care system was at the same time rapidly developing and the number of family doctors practising in the counties examined increased significantly during the study period. In the end of the study already 412 family doctors and family medicine centres were contacted. The received information was compared with the data of the two hospitals.

The patients. We included into the study two populations of patients: a) children under the age of 16 years (born on Dec 31, 1984 and afterwards), living in the study area, fullfilling the ILAR criteria of JIA (the revised version of 1997) and having an onset of arthritis between 1995–1997, the early JIA series, and b) children with onset of arthritis during 1998–2000 and diagnosed during the incidence study (10), the incidence series. Of the abovementioned two groups of patients were included, on Dec 31, 2000, into this study only those in whom JIA was: (1) active, i.e. the number of active joints increasing irrespective of drug therapy; (2) stable, i.e. a stable number of joints but requiring drug therapy, or; (3) inactive, i.e. no evidence of active arthritis and/or active extra-articular features and without drug therapy for less than 2 years on the date given above. For estimating the disease activity we used the definitions suggested by the EULAR Standing Committee on Paediatric Rheumatology in Moscow, 1983, (cited in 11). Patients diagnosed during the study period but in remission — i.e. those with no signs of active synovitis and/or active extra-

articular features, blood inflammatory markers within normal limits and at least two years without drugs were excluded.

One of the authors (CP) visited the second centre ─ Tallinn Children's Hospital ─ regularly, and all cases in which there was doubt in the diagnosis or classification were discussed with the team (CP, KU, HL, ST). The final determination of the subgroups was determined by CP, taking into account all the inclusion and exclusion criteria of the ILAR classification, the revision of 1997.

Statistical analysis. The statistical analysis was performed using the statistical package SAS Version 8.02. Continuous variables are presented as mean values (95% CI), while qualitative variables are presented as absolute and relative frequencies. The prevalence rate for children under 16 years of age per 100 000 was calculated using the data given by the Estonian Statistical Office. Kolmogorov-Smirnov criterion was used for the assessment of normality. Comparisons between groups were performed using the nonparametric test — the Wilcoxon-Mann-Whitney test. Ninety-five percent confidence intervals (CI) for the prevalence rate were calculated based on the Poisson distribution.

The study was approved by the Ethics Committee of Tartu University. All the parents or the patients were asked to give informed consent for participation in the study.

RESULTS

Prevalence. On Dec 31, 2000, there were, 197 children (93 boys and 104 girls) aged 0–15 years and living in the 14 counties of Estonia in whom JIA, diagnosed in 1995–2000, was active, stable or inactive. Thirty (30) patients were diagnosed between 1995–1997 and 167 patients between 1998–2000.

The point prevalence for children under 16 years of age was 83.7 (95% CI: 72.4;95.8) per 100 000, for boys it was 77.1 (95% CI: 62.2;93.5) and for girls 90.7 (95% CI: 74.1;108.9) (Table 1). The prevalence was the highest among 11–15 year old girls, 132 and the lowest in 0–3 year old girls, 9.6.

Of the 412 final reminding letters sent, 165 (40%) were answered by primary care practitioners. Nineteen additional patients were seen only by family doctors; they were not referred to the centres and therefore were not included in the study.

The mean age at the onset of JIA symptoms was 8.7 years (95% CI: 8.2;9.3) (Table 2); 9.1 years (95% CI: 8.3;9.8) for girls and 8.3 years (95% CI: 7.5;9.1) for boys. It was the lowest in the systemic subtype — 4.7 years — and the highest in the enthesitis related arthritis subtype — 11.1 years. The mean interval between the onset of the disease and the time the diagnosis was made was 7 months; it was the longest in extended oligoarthritis and psoriatic arthritis, 1 year for both, and the shortest for systemic arthritis, 1 month. The mean duration of JIA in the group was 2.3 years (95% CI: 2.0; 2.6).

Oligoarthritis was the most frequent subtype (111 cases (56.3%) (Table 2). Thirty-two (28.8%) of those had monoarthritis. Oligoarthritis was followed by seronegative polyarthritis — 39 cases (19.5%). Systemic subtype was more frequent in boys (6 cases compared to 2 cases in girls). Polyarthritis (both seronegative and seropositive) was more often found in girls (33 cases compared to 16 cases in boys).

Clinical outcome at two years. The course of the disease was followed up for two years after the diagnosis was made (Table 3). Data are available of 120/197 patients. Fourty four of the patients (22.3%) had inactive disease at this point. For 76 patients (38.6%) the disease was active or stable after 2 years. There are 49/197 patients (24.9%, 35 with oligoarthritis) for whom the follow-up extended only to 6 months since the diagnosis, but their subtype could be determined. For 76 patients (38.6%), among them 46 with persistent oligoarthritis and 10 with seronegative polyarthritis, there are no data at 2 years as they were not seen by doctors any more. In 63 patients (32%, 25 of them with persistent oligoarthritis), the disease subtype remained the same during the follow-up period. During the follow-up 23 of the 111 patients with oligoarthritis (20.7%) changed subtype to extended oligoarthritis.

Use of drugs on the prevalence date. On Dec. 31, 2000, when the prevalence was calculated, the state could be determined for 158 patients. The mean duration of follow-up was 1.7 years. There were 37 (18.8%) patients for whom there exist documented data that the disease had become inactive. Eighty seven patients (44.2%) were taking disease modifying antirheumatic drugs; among them there were 20 for whom the disease was active and 54 for whom the disease was stable. Fifteen patients (7.6%) were taking other drugs, mainly non-steroid antiinflammatory drugs. Among those 39 for whom there is no information, 24 (61.5%) had oligoarthritis; this group includes children in whom the disease was with great probability inactive on Dec 31, 2000 and who were already without drugs, but for less than 2 years.

DISCUSSION

This is the first population-based study on the prevalence of juvenile idiopathic arthritis in Estonia in which the new ILAR criteria have been used.

According to our earlier findings, the incidence rate of JIA per 100 000 children aged 0–15 years in 14 counties of Estonia was 21.7 between 1998–2000; 22.9 for girls and 19.3 for boys (10). The point prevalence on Dec. 31, 2000 for the children under 16 years of age diagnosed with JIA as of Jan. 1, 1995 in the same area was 83.7 per 100 000.

In the published studies the prevalence rate varies extremely — ranging from 7 to 401 per 100 000 (9, 11–21). In the study by Andresson Gäre and

Fasth the rate was 86.3 for all the cases and 64.1 for the cases with recent or active disease (11). Peterson et al has included all the cases diagnosed with JRA and calculated the prevalence rates for 1980 and 1990, those being 94 and 86 per 100 000 respectively (8). In our study we have not included patients for whom the disease was in remission by Dec. 31, 2000 and those diagnosed before 1995; due to that selection effect our figure can be somewhat lower than in other community-based studies. Apart from methodological differences, the variable incidence and prevalence rates may also reflect geographic differences, as e.g. the high rates in Finland and Northern Norway, found by Kunnamo and Moe and Rygg and confirmed later on by Berntson et al. (11, 22–24).

Since active data collection was started in 1998 there is a discrepancy between the numbers of patients in 1995–1997 compared to that of 1998–2000. The reason for this could be the fact that active data collection was started in 1998 in a prospective fashion. Also, patients from the 1995–1997 series over 16 years of age on the prevalence date were not included.

In Estonia it is common to see native pediatric rheumatologist, not to seek for medical care in neighbouring countries; due to the fact we assume that practically all new JIA cases are captured by Estonian clinics. In addition to those primary care practitioners who answered the letters, there were many of them who did not answer but just referred the patients directly to the two hospitals. All the cases were discussed with the study team to ensure that they were real JIA cases and to avoid the risk of overestimation by local doctors. The follow-up was performed by specialists in pediatric rheumatology.

In our study the prevalence rate was lowest in girls, aged 0–3 years. Oligoarthritis with mild activity is usually frequent in this age group. These cases may remain undiagnosed by family doctors with little experience in JIA. The same has been reported also by Kiessling et al (14). Tendency of prevalence to rise with increasing age could be explained by the short duration of the (active) disease among small girls with oligoarthritis (Table 2); the latter was also the main subgroup among these patients who did not see the doctor any more at two years.

We could estimate the short term prognosis in two thirds of our patients. Two years after the onset the disease was still active or stable in 76 patients (63.3%). We assume that with great probability, the disease had become inactive for those 49 patients (24.9%) for whom we have no data after the first six months following the diagnosis. At present, we cannot say what proportion of the patients will actually reach remission. The follow-up of two years is much too short for this and for comparing our results with other studies on outcome. All we know is that 21 per cent of the oligoarthritis patients changed subgroup to extended oligoarthritis.

On prevalence day, when the disease had lasted on the average for 2.3 years, there were 102 patients (51.8%) taking nonsteroidal or longacting anti-

rheumatic drugs, which means that in many of them the disease was still active or stable.

The prevalence rate in our study is well in accord with those of several other series although the different criteria make comparison difficult. At least 22% of the patients were inactive after two years. A longer follow-up of JIA patients studied using the ILAR 1997 criteria, is needed in order to have a better overview of the course of the disease, to know the proportion of patients reaching remission and the actual prognosis of the patients.

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References

1. Fink CW. Proposal for the development of classification criteria for idiopathic arthritides of childhood. J Rheumatol 1995; 22: 1566–69.
2. Petty RE, Southwood TR, Baum J, Bhettay E, Glass DN, Manners P et al. Revision of the proposed classification criteria for juvenile idiopathic arthritis: Durban, 1997. J Rheumatol 1998; 25: 1991–94.
3. Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J et al. International League of Associations for Rheumatology Classification of Juvenile Idiopathic Arthritis: Second Revision, Edmonton, 2001. J Rheumatol 2004; 31:2: 390–92.
4. Bowyer SL, Roettcher PA, Higgins GC, Adams B, Myers LK, Wallace CA et al. Health status of patients with juvenile rheumatoid arthritis at 1 and 5 years after diagnosis. J Rheumatol 2003; 30: 394–400.
5. Wallace CA, Huang B, Bandeira M, Ravelli A, Giannini EH. Patterns of clinical remission in select categories of juvenile idiopathic arthritis. Arthritis Rheum 2005; 52: 3554–62.
6. Selvaag AM, Lien G, Sorskaar D, Vinje O, Forre O, Flato B. Early course and predictors of disability in juvenile rheumatoid arthritis and juvenile spondylo-arthropathy: a 3 year prospective study. J Rheumatol 2005; 32: 1122–30.
7. Oen KG, Cheang M. Epidemiology of chronic arthritis in childhood. Semin Arthritis Rheum 1996; 26: 576–92.
8. Peterson LS, Mason T, Nelson AM, O'Fallon WM, Gabriel SE. Juvenile rheumatoid arthritis in Rochester, Minnesota 1960–1993. Is the epidemiology changing? Arthritis Rheum 1996; 39: 1385–90.
9. Manners PJ, Bower C. Worldwide prevalence of juvenile arthritis — why does it vary so much? J Rheumatol 2002; 29: 1520–30.

10. Pruunsild C, Uibo K, Liivamägi H, Tarraste S, Talvik T, Pelkonen P. Incidence of juvenile idiopathic arthritis in children in Estonia — a prospective population-based study. Scand J Rheumatol, in press.
11. Andersson Gäre B, Fasth A. Epidemiology of juvenile chronic arthritis in south-western Sweden: a 5-year prospective population study. Pediatrics 1992; 90: 950–8.
12. Rodary C, Hayem F, Mozziconacci P. Essai d`enquete concernant l'incidence de l'arthrite chronique juvenile en France (annee 1972). Ann Pediatr 1977; 3: 429.
13. Rosenberg AM, Petty RE, Oen KG, Schroeder ML. Rheumatic diseases in Western Canadian Indian children. J Rheumatol 1982; 9: 589–92.
14. Kiessling U, Döring E, Listing J, Meincke J, Schöntube M, Strangfeld A et al. Incidence and prevalence of juvenile chronic arthritis in East Berlin 1980–88. J Rheumatol 1998; 25: 1837–43.
15. Hochberg MC, Linet MS, Sills EM. The prevalence and incidence of juvenile rheumatoid arthritis in urban Black population. Am J Public Health 1983; 73: 1202–3.
16. Khuffash FA, Majeed HA, Lubani MM, Najdi KN, Gunawardana SS, Bushnaq R. Epidemiology of juvenile chronic arthritis and other connective tissue diseases among children in Kuwait. Ann Trop Paediatr 1990; 10: 255–9.
17. Steven MM. Prevalence of chronic arthritis in four geographical areas of the Scottish Highlands. Ann Rheum Dis 1992; 51: 195–7.
18. Arguedas O, Fasth A, Andersson-Gäre B, Porras O. Juvenile chronic arthritis in urban San Jose, Costa Rica: a 2 year prospective study. J Rheumatol 1998; 25: 1844–50.
19. Ozen S, Karaaslan Y, Ozdemir O, Saatci U, Bakkaloglu A, Koroglu E et al. Prevalence of juvenile chronic arthritis and familial Mediterranean fever in Turkey: A field study. J Rheumatol 1998; 25: 2445–9.
20. Towner SR, Michet CJ Jr, O' Fallon WM, Nelson AM. The epidemiology of juvenile arthritis in Rochester, Minnesota 1960–1979. Arthritis Rheum 1983; 26: 599–603.
21. Manners PJ, Diepeveen DA. Prevalence of juvenile chronic arthritis in a population of 12-year-old children in urban Australia. Pediatrics 1996; 98: 84–90.
22. Moe N, Rygg M. Epidemiology of juvenile chronic arthritis in northern Norway: a ten-year retrospective study. Clin Exp Rheumatol 1998; 16: 99–101.
23. Kunnamo I, Kallio P, Pelkonen P. Incidence of arthritis in urban Finnish children. A prospective study. Arthritis Rheum 1986; 29: 1232–8.
24. Berntson L, Andersson Gäre B, Fasth A, Herlin T, Kristinsson J, Lahdenne P et al. Incidence of juvenile idiopathic arthritis in the Nordic countries. A population based study with special reference to the validity of the ILAR and EULAR criteria. J Rheumatol 2003; 30: 2275–82.

Table 1. Prevalence rates according to sex and age groups (Dec 31, 2000).

Age groups (y)	Number of cases	All cases (95% CI)	Girls (95% CI)	Boys (95% CI)
0–3	7	16.3 (6.6;30.4)	9.6 (1.2;26.7)	22.6 (7.3;46.2)
4–6	27	76.4 (50.4;107.8)	92.6 (52.9;143.2)	60.9 (30.4;101.9)
7–10	53	82.8 (62;106.5)	80.3 (52;114.7)	85.2 (56.6;119.5)
11–15	107	115 (94.2;137.7)	132 (100.7;167.4)	98.7 (72.6;128.9)
0 –15	194*	83.7 (72.4;95.8)	90.7 (74.1;108.9)	77.1 (62.2;93.5)

* in 3 patients the exact birth date was not found in records

Table 2. Subtypes of JIA at onset, proportion of girls, proportional distribution of subtypes, mean age at the onset of the disease.

Subtype	Number of cases (girls)	Percentage of all cases	Mean age at the onset of the disease, years (95% CI)
Oligoarthritis	111 (56)	56.3	8.2 (7.4;8.9)
Persistent	88 (40)	44.7	7.9 (7.1;8.8)
Extended	23 (16)	11,7	9.1 (7.3;10.9)
Polyarthritis RF neg	39 (25)	19,5	9.7 (8.7;10.8)
Polyarthritis RF pos	9 (8)	4,5	10.2 (7.3;13.0)
Systemic arthritis	8 (2)	4	4.7 (2.0;7.3)
Enthesitis related arthritis	11 (2)	5,5	11.1 (10.0;12.2)
Psoriatic arthritis	5 (2)	2,5	9.7 (3.3;16.0)
Other arthritis	13 (8)	6,5	8.5 (6.2;10.8)
All JIA	196/197*	100	8.7 (8.2;9.3)

* In 1 patient with polyarthritis the exact classification was not possible, as the RF analysis was not performed

Table 3. Two-years outcome of JIA

Onset subtype	No. of patients	Patients with inactive disease**	Active or stable cases at 2 yrs	Same pattern of joint involve-ment at 2 yrs	Changes in course during 2 yrs	Patients for whom there are no data at 2 yrs
Oligo	111	22	37	37	23 — extended oligo	52
Persistent oligo	88	17	25	25		46
Extended oligo	23	5	12	12		6
Seropos poly	9		8	5	3 — oligo	1
Seroneg poly	39	14	15	8	7 — oligo	10
Systemic	8	4	3	1	2 — oligo	1
Enthesitis related	11	1	5	5		5
Psoriatic	5	1	3	3		1
Other	13	2	5	4	1 — oligo	6
All JIA	196*	44	76	63	36	76

* In 1 patient with polyarthritis the exact classification was not possible, as the RF analysis was not performed

** "Inactive" includes patients in whom the disease is inactive and who have been off drugs for less than 2 years as well some patients who are still on drug therapy

CURRICULUM VITAE

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Education

1976–1987	Tartu Miina Härma Secondary School No 2., silver medal
1987–1993	Medical Faculty of Tartu University, department of pediatrics (*cum laude*)
1993–1995	Medical Faculty of Tartu University, internship in pediatrics
1995–2002	Medical Faculty of Tartu University, postgraduate student
2002–	Medical Faculty of Tartu University, residency in pediatrics

Special courses

1998	Pediatric Rheumatology, Hospital for Children and Adolescents, University of Helsingi
2000	Pediatric Rheumatology, Hospital for Children and Adolescents, University of Helsingi
2001	Autoimmunity: molecular and clinical aspects, Tartu, Estonia
2004	International Research Seminar, Heinola Rheumatism Foundation Hospital, Finland
2006	Pediatric Rheumatology, Genova, Italy

Scientific work

Research fields:
Epidemiology of juvenile idiopathic arthritis in children in Estonia.
Pain in 10–15-year-old schoolchildren in Tartu and County of Tartu.
Total: 7 publications, 3 oral and 6 poster presentations in international scientific conferences

Membership of professional societies

- Estonian Society for Rheumatology, member of board 2000–, general secretary 2000–2007
- Bone and Joint Decade, Estonian national coordinator 2000–2004
- Estonian Pediatric Association, department of Tartu, member of board
- Estonian Society for Immunology and Allergology
- Pediatric Rheumatology European Society, Education and Training Committee, representative of Estonia
- Pediatric Rheumatology International Trials Organization, Director of National Coordinating Centre of Estonia

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1993–1995	Tartu Ülikool, pediaatria internatuur
1995–2002	Tartu Ülikool, doktorantuur
2002–	Pediaatria resident

Erialane täiendus

1998	Lastereumatoloogia, Helsingi Ülikooli Laste ja Noorukite Haigla
2002	Lastereumatoloogia, Helsingi Ülikooli Laste ja Noorukite Haigla
2003	Autoimmuunsus: molekulaarsed ja kliinilised aspektid, Tartu, Eesti
2005	Rahvusvaheline Teadustöö Seminar, Heinola Reumakeskus, Soome
2006	Lastereumatoloogia, Genova, Itaalia

Teadustegevus

Uurimisvaldkonnad: juveniilse idiopaatilise artriidi epidemioloogia Eesti lastel. Valu 10–15-aastastel Tartu linna ja maakonna koolilastel.
Kokku 7 publikatsiooni, 3 suulist ja 6 posterettekannet rahvusvahelistel konverentsidel

Kuulumine erialaorganisatsioonidesse

- Eesti Reumatoloogide Selts, alates 2000 juhatuse liige, sekretär 2000–2007
- Luu- ja Liigese Dekaad, Eesti rahvuslik koordinaator 2000–2004
- Eesti Lastearstide Selts, Tartu osakonna juhatuse liige
- Eesti Immunoloogide ja Allergoloogide Selts
- Euroopa Lastereumatoloogia Ühendus, Õppe- ja koolituskomitee, Eesti esindaja
- Rahvusvaheline Lastereumatoloogiliste Uuringute Organisatsioon, Rahvusliku Koordineerimiskeskuse direktor

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