



HEINI POHJANKOSKI

Juvenile Idiopathic Arthritis

Studies on associated autoimmune diseases
and drug therapy



ACADEMIC DISSERTATION

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for public discussion in the Päijät-Häme District Central Hospital,
Lecture room 1, Keskussairaalankatu 7, Lahti,
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UNIVERSITY OF TAMPERE



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**To my family
and to my patients**

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ORIGINAL PUBLICATIONS

LIST OF ORIGINAL PAPERS

This thesis is based on the following original papers referred to in the text by their Roman numerals I-IV. In addition, the thesis contains unpublished data.

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- I. Pohjankoski H, Kautiainen H, Kotaniemi K, Korppi M, Savolainen A.
Autoimmune diseases in children with juvenile idiopathic arthritis. *Scand J Rheumatol* 2010;39:435-6.
- II. Pohjankoski H, Kautiainen H, Kotaniemi K, Korppi M, Savolainen A.
Diabetes, coeliac disease, multiple sclerosis and chronic arthritis in first-degree relatives of patients with juvenile idiopathic arthritis. *Acta Paediatr* 2012;101:767-71
- III. Pohjankoski H, Kautiainen H, Korppi M, Savolainen A. Simultaneous juvenile idiopathic arthritis and diabetes mellitus type 1 - a Finnish nationwide study. *J Rheumatol* 2012;39:377-81.
- IV. Pohjankoski H, Latva K, Kautiainen H, Säilä H, Klaukka T, Virta L, Puolakka K, Pohjolainen T, Savolainen A. First-year purchases of disease modifying drugs of incident patients with chronic juvenile arthritis in Finland. *Clin Exp Rheumatol* 2011;29:878-81.

ABSTRACT

Autoimmune diseases (AIDs) are chronic conditions that involve an immune attack on one or more organ systems. Juvenile idiopathic arthritis (JIA) belongs to AIDs with an unknown specific aetiology, with some evidence referring to genetic and environmental factors. Over the recent years, several studies have revealed that the prevalence of AIDs is higher among JIA patients than in controls.

The occurrence of other AIDs was studied in 417 children referred to the Rheumatism Foundation Hospital (RFH) because of JIA during years 1992-2000. Children with JIA had approximately over 5-fold occurrence of diabetes mellitus type 1 (DM1), celiac disease (CD) or hypothyreosis (HT) compared to the population data available.

The occurrence of AIDs was studied by questionnaires addressed to the families of the 362 JIA patients referred to the RFH in years 1996-2001. The questions concerned the AID diagnoses in these families: chronic arthritis (CA), DM1, CD and multiple sclerosis (MS). The families were also asked whether the patients or their first-degree relatives were entitled to a special reimbursement for medicines for diabetes or chronic arthritis by the Social Insurance Institution (SII), and what their exact diagnosis was. The diagnoses ultimately made by a physician and recorded as per the ICD-10 classification were then gathered. Almost a quarter, 21.4%, of the families had a member with another AID. The occurrence of JIA and DM1 among the JIA patients' relatives was clearly higher than in the previously published studies.

The characteristics of JIA were studied in 82 patients with both JIA and DM1 identified from the SII registers in years 1976-2005. The simultaneous occurrence of JIA and DM1 had increased over 5-fold as the first ten-year period (1976-1985) was compared with the last ten-year period (1996-2005). A quarter of these patients (22%) had a third AI disease. Seropositivity was recorded more often than expected and the proportion of uveitis was low. Almost a fifth of children in this group (16%) had serious psychiatric problems.

The data on prescribed medication for JIA, reimbursed by SII for the first time in years 2000-2007, were collected from the SII registers. The number of identified patients younger than 16 years was 1970. The use of methotrexate (mtx) increased significantly whereas the use of prednisolone decreased during the study period.

The influence of simultaneous DM1 to the drug treatment for JIA was studied in 1970 JIA patients identified in the SII registers from years 2000-2007. The diagnosis of DM1 was already made in 23 children. Mtx was introduced to 83% of these children during the first 3 disease months, compared to 59% in all Finnish JIA patients.

TIIVISTELMÄ

Autoimmuunitaudit ovat kroonisia sairauksia, joissa elimistön oma poikkeavasti toimiva puolustusmekanismi kohdistuu yhteen tai useampaan elimeen tai kudokseen. Lastenreuma on autoimmuunitauti, jonka syy on edelleen avoin. Tutkimukset viittaavat sekä perimän että ympäristön vaikutukseen taudin synnyssä. Geneettiset että epidemiologiset tutkimukset eri puolilta maailmaa ovat vahvistaneet, että normaaliväestöön verrattuna autoimmuunitauteja on enemmän sekä lastenreumapotilailla että heidän sukulaisillaan.

Tutkimme kaikkien vuosina 1992-2000 Reumasäätiön Sairaalaan tutkimuksiin ja hoitoon ensi kertaa lähetettyjen lastenreumapotilaiden (417) sairauskertomukset. Totesimme, että potilailla oli keskimäärin yli 5-kertainen todennäköisyys saada joko nuoruusiän diabetes, keliakia tai hypothyreoosi.

Lisäksi selvitimme lastenreumapotilaiden ensimmäisen asteen sukulaisten (isä, äiti ja täyssisar) autoimmuunitaudit. Vuosina 1996-2001 Reumasäätiön sairaalaan lähetettyjen 432 potilaan perheille postitettiin kyselylomake, jossa tiedustelimme perheen autoimmuunitauteja: krooninen reumatauti, keliakia, MS-tauti ja nuoruusiän diabetes. Kroonisesta reumataudista ja nuoruusiän diabeteksestä halusimme tietää, milloin erityiskorvattavat lääkkeet oli myönnetty, ja muista taudeista halusimme varmistua, että diagnoosin oli tehnyt lääkäri. Saimme vastauksen 355 perheeltä, joissa oli yhteensä 362 potilasta. Noin viidesosassa (21,4 %) perheistä oli lastenreuman lisäksi joku muu autoimmuunitauti. Lastenreuman ja nuoruusiän diabeteksen esiintyvyys oli selvästi suurempi kuin aikaisemmissa väestötutkimuksissa.

Väitöskirjatyössä tarkastettiin valtakunnallisesti vuosilta 1976-2005 kaikkien lastenreumaa ja samanaikaista nuoruusiän diabetesta sairastavien potilaiden sairauskertomukset. Tutkimuksessa selvitettiin näiden tapausten ilmaantuvuus ja lastenreuman taudinkuva. Ilmaantuvuus oli noussut yli viisinkertaiseksi kolmen vuosikymmenen aikana. Tutkituista potilaista useampi kuin lastenreumapotilaista yleensä sairasti taudin reumafaktoripositiivista muotoa ja heillä esiintyi vähemmän

kroonista reumaattista silmätulehdusta. Lähes neljäsosalla (22 %) oli joku kolmas autoimmuunitauti. Heillä oli myös huomattavasti enemmän (16 %) vaikeita psykiatrisia ongelmia muuhun väestöön verrattuna.

Kansaeläkelaitoksen (KELA) tiedostoista kerättiin tiedot erityiskorvattavista lääkkeistä, jotka oli myönnetty kroonisen niveltulehduksen hoitoon alle 16-vuotiaille lapsille vuosina 2000-2007 ja samanaikaisista reseptiostoista. Seurantajakson aikana metotreksaatin käyttö lisääntyi merkittävästi samalla kun kortisonin käyttö väheni.

Selvitimme myös, miten samanaikainen nuoruusiän diabeteksen sairastaminen vaikutti lastenreuman lääkitykseen. KELAn tiedostoista löytyi 23 potilasta, joilla oli jo diagnosoitu DM1 ja joille myönnettiin korvattavuus kroonista artriittia hoitaviin lääkkeisiin. Näistä 19:lle (83 %) aloitettiin metotreksaatti ensimmäisen kolmen kuukauden aikana. Vastaava luku kaikilla lastenreumaa sairastavilla potilailla (1970) valtakunnallisesti oli 59 %.

ABBREVIATIONS

ACR	American College of Rheumatology
AID	autoimmune disease
AIT	autoimmune thyroid disease
ANA	antinuclear antibodies
ARA	American Rheumatoid Association
AS	ankylosing spondylitis
CD	celiac disease
CA	chronic arthritis
CJA	chronic juvenile arthritis
CI	confidence interval
CRP	C-reactive protein
DM1	diabetes mellitus type 1
DMARD	disease modifying antirheumatic drugs
ERA	enthesitis-related arthritis
ESR	erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
HLA	human leukocyte antigen
HT	hypothyreosis,
HRQL	health related quality of life
IgM	immunoglobulin M
IL	interleukin
ILAR	International League of Associations for Rheumatology
JAIT	juvenile autoimmune thyroiditis
JCA	juvenile chronic arthritis
JIA	juvenile idiopathic arthritis
JRA	juvenile rheumatoid arthritis
mtx	methotrexate
MS	multiple sclerosis
NSAID	non-steroidal anti-inflammatory drug
PRR	prevalence rate ratio
PsA	psoriatic arthritis
RA	rheumatoid arthritis
RFH	Rheumatism Foundation Hospital
RF	IgM rheumatoid factor
RR	relative risk
SI	sacroiliac
SII	Social Insurance Institution
SD	standard deviation
Th1	T-helper 1 cell

LITERATURE REVIEW

I. JUVENILE IDIOPATHIC ARTHRITIS

Juvenile idiopathic arthritis (JIA), previously also called juvenile chronic arthritis (JCA) and juvenile rheumatoid arthritis (JRA) belongs to autoimmune diseases (AID) and is the most common cause of chronic arthritis (CA) in children. JIA is not a single disease, but merely an umbrella term for various clinical entities of CA in children and adolescents, forming a complex group of diseases where other reasons for arthritis are excluded. According to the current concept, system-onset JIA is rather an autoinflammatory than autoimmune disease.

JIA has various phenotypes, which refer to the involvement of multiple susceptibility genes. Genetic studies have identified both general autoimmune genes and JIA-specific genes, explaining the variability of different phenotypes (Phelan et al 2006, Angeles-Han and Prahalad 2010).

The balance of immune system, including both innate and acquired immunity, is disturbed in JIA patients. There is evidence that inflammatory cells are trafficking to the synovium causing local inflammation and further progressive joint damage. Inflammation includes T-cell and macrophage infiltrations, Th1-oriented cytokine predominance in inflamed tissues, evidence of T-cell clonality and by inference, antigen presentation (Phelan et al 2006).

1.1. Classification and diagnostic criteria

JIA is defined as a CA in a child aged less than 16 years and lasting more than six weeks in the absence of any known cause. There are no specific diagnostic tests for JIA.

During the past decades, rheumatologists have struggled to identify and classify the disease in order to understand the disease more clearly (Haines 2007). The oldest classification made by the American Rheumatoid Association (ARA) in 1973 used

the term juvenile rheumatoid arthritis (JRA). In 1977 the European League Against Rheumatism (EULAR) recommended the term juvenile chronic arthritis (JCA). The latest classification from 1995 was proposed by the task force of the Pediatric Standing Committee of the International League of Associations of Rheumatology (ILAR). In this proposition, further revised in 1997, 2001 and 2004, earlier chronic juvenile arthritis, is called JIA, juvenile idiopathic arthritis (Petty et al 1998 and 2004). The purpose was to change the classification better suited for clinical work and to help the research on the etiology, pathogenesis, epidemiology, outcome and treatment of the disease (Ravelli and Martini 2007).

The ILAR criteria of JIA demand on over 6-week duration of the disease and the patient must be younger than 16 years at the disease onset. The onset-type is the type of JIA defined 6 months after the onset of the disease, and course-type is the type which the disease develops later.

The current classification of JIA is presented in Table 1 and the exclusion criteria in Table 2.

Table 1. Classification of juvenile idiopathic arthritis (Petty et al 2004)

Oligoarthritis

Persistent

affecting four or fewer joints throughout the disease course

Exclusion criteria: 1-5

Extended

affecting more than four joints after the first six months following the onset of the disease

Exclusion criteria: 1-5

Polyarthritis

Rheumatoid factor negative

arthritis affecting five or more joints during the first six months following the onset of the disease

rheumatoid factor negative

Exclusion criteria: 1-5

Rheumatoid factor positive

arthritis affecting five or more joints during the first six months of the disease

rheumatoid factor positive two or more times at least three months apart

Exclusion criteria: 1,2,3,5

Systemic arthritis

arthritis in one or more joints

fever for two weeks (at least 3 days with a daily pattern)

plus one or more systemic manifestations

erythematous rash

generalized lymphadenopathy

hepato- and/or splenomegaly

Exclusion criteria: 1-4

Seronegative spondyloarthropathies

Psoriatic arthritis

Arthritis and psoriasis – or

Arthritis and two of the following

dactylitis

nail pitting or onycholysis

psoriasis in a first-degree relative

Enthesitis-related arthritis

Arthritis and enthesitis – or

Arthritis or enthesitis and two of the following

sacroiliac-joint tenderness and/or inflammatory lumbosacral pain

HLA-B27 positivity

arthritis in a male over six years of age

acute anterior uveitis

history of ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome or acute uveitis

in a first-degree relative

Exclusion criteria: 1,4,5,

Non-classified and/or other arthritis

Fulfills criteria in none of the above categories

Fulfills criteria in more than one of the above criteria

Table 2. Exclusion criteria for JIA categories

1. Psoriasis or history of psoriasis in a first-degree relative
 2. Arthritis in a HLA-B27 positive male beginning at 6 years of age or older
 3. History of ankylosing spondylitis, enthesitis-related arthritis, sacroilitis with inflammatory bowel disease, Reiter's syndrome or acute anterior uveitis in a first-degree relative
 4. IgM rheumatoid factor on two or more occasions, three months apart
 5. Systemic JIA in the patient
-

Enthesitis-related arthritis was not included in JRA by the ARA criteria, and the duration of symptoms should then have lasted over three months instead of the current six weeks.

Recently, a discussion has arisen regarding a new classification including a category of patients with antinuclear antibodies (ANA) and whether they should be classified as a separate group. The Italian findings substantiate the hypothesis that ANA-positive patients constitute a homogeneous patient group (Ravelli et al 2011).

The proportion of ANA-positive cases has been 39% in Scandinavia, 16% in Estonia and 33% in Finland (Berntson et al 2003, Pruunsild et al 2007b, Kaipainen-Seppänen and Savolainen 2001). Whereas in India, only one of the 89 patients was ANA-positive (Aggarwal and Misra 1994).

1.2. Clinical features

The symptoms and presentations vary a lot both between and within the JIA subtypes. Chronic synovitis is an obligatory clinical manifestation in all patients. Some patients may only have stiffness in one or more joints in the morning (oligoarticular JIA), whereas some others suffer from stiffness and pain in almost every joint and have problems with walking and sleeping (polyarticular JIA). Small children cannot express their symptoms and may therefore only seem irritable and/or find it difficult to move. Patients with Still's disease can be seriously ill with high

fever and inner organ manifestations like pericarditis or myocarditis and sometimes need intensive care (Ravelli and Martini 2007).

1.2.1. Oligoarthritis, persistent

In the oligoarticular-type of JIA patients suffer from an inflammation in four or fewer joints during the first six months of the disease as well as during the whole disease course. This subtype is more frequent in girls than boys, and the onset is most common in young children (peak age 2-4 years). Patients are often ANA-positive (70-80%) and have chronic uveitis (Kotaniemi et al 2003, Petty et al 2003). The involvement of joints is generally asymmetric and mostly affects knees and ankles.

1.2.2 .Oligoarthritis, extended

In this subtype, patients first have oligoarthritis, but they develop a polyarticular course.

Persistent and extended oligoarthritis types form a clinically homogenous group, except that the outcome is more severe in the extended oligoarthritis (Ravelli and Martini 2007).

1.2.3. Polyarthritis seronegative

This subtype is defined as an arthritis affecting five or more joints during the first six months of the disease in the absence of IgM rheumatoid factor (RF). Some patients in this group resemble the adult-onset, seronegative rheumatoid arthritis (RA) with symmetric synovitis of large and small joints. Some patients have dry synovitis which causes flexion contractures (Ravelli and Martini 2007).

1.2.4. Polyarthritis seropositive

Patients with RF resemble adult-onset RA. Adolescent girls are dominant in this group, and their arthritis affects small and large joints symmetrically with an increased risk for erosive changes.

1.2.5. Systemic arthritis

This subgroup, also called Still's disease, presents with daily, spiking fever for at least two weeks and arthritis. Patients may have hepato- and/or splenomegaly, lymphadenopathy, serositis and a typical rash, appearing simultaneously with the fever spikes. Laboratory findings consist of elevated acute-phase reactants, such as thrombocytosis, leukocytosis and increased ferritin level. Systemic arthritis is equally common in boys and girls.

1.2.6. Seronegative spondyloarthropathies

Psoriatic arthritis: Arthritis and psoriasis rash can appear separately many years apart.

Enthesitis-related arthritis: Enthesitis most commonly affects the achilles tendon, plantar fascia or tarsal area. Synovitis often affects joints of lower extremities. Some patients have inflammation in SI and spinal joints, thus producing clinically ankylosing spondylitis (AS). Most patients are HLA-B27 positive boys.

Finally, because of the wide heterogeneity in the symptom presentation of the disease it is difficult to reach a 100% valid classification.

1.3. Epidemiology

JIA is the most common cause of CA in children. The published incidence figures of JIA vary depending on geographical factors, ethnicity of the target population and patient selection, and also on the difference in community-based and hospital-based studies. The highest prevalence was reported in an Australian community-based study, which included children with previously diagnosed JIA and with JIA diagnosed during the study (Manners and Diepeveen 1996). Differences in epidemiology have been found between various ethnic groups. In a Canadian study, children of European descent had an increased risk of developing JIA (Saurenmann et al 2007). Studies on environmental influences show seasonal trends suggesting highly plausible, possible etiological factors, such as infections (Oen et al 1995). The

classification of JIA, from ARA and EULAR criteria to ILAR criteria, caused a change in the epidemiological figures for decades, because e.g. enthesitis-related arthritis was not included in JIA by the ARA criteria. Therefore the year of the publication and the criteria used must be born in mind when looking at the figures in Table 3.

Table 3. Incidence (1/100 000) and prevalence (1/10 000) of juvenile idiopathic arthritis

3a. Figures from Asia, Australia and North America

Country/Year	Classification	Incidence	ERA*	Prevalence	Reference
Japan 1994	ARA	0.83	no		Fujikawa and Okuni 1997
Kuwait 1988	EULAR	2.84*	no	1.87**	Khuffash et al 1990
Australia	EULAR		yes	4.0***	Manners et al 1996
Canada 1975-92	ARA	5.34	no		Oen et al 1995
Canada 2000	ARA	17.8	no		Feldman et al 2009

*ERA enthesitis related arthritis

**under 12 years old, including patients in remission

***12 years old, including cases diagnosed before and during the study

3b. Figures from Europe

Country/Year	Classification	Incidence	Prevalence	Reference
Germany 1995	EULAR	6.6	1.48	von Koskull et al 2001
France 2001	ILAR	3.2	1.98	Danner S et al 2006
Spain 2004-6	ILAR	6.9	3.97	Modesto C et al 2010
France 2006	ILAR		1.57	Solau-Gervais et al 2010

In Japan (ARA criteria) and Kuwait (EULAR criteria), the incidence of JIA is lower than the respective incidences in North America (ARA criteria) or in Europe

(EULAR criteria or ILAR criteria). The prevalence figures are not comparable due to the different age limits and research strategies.

Berntson et al (2003) compared the incidence rates of JIA by the ILAR criteria and of JCA by the EULAR criteria in the Nordic countries. The conclusion was that the rates by the ILAR criteria were slightly higher, obviously due to two reasons: a shorter duration of symptoms required for the diagnosis and the inclusion of children with enthesitis-related arthritis.

3c. Figures from Scandinavia and Estonia

Country	Year	Classification	Incidence	Prevalence	Reference
Finland	1980	ARA	13.8		Kaipiainen-Seppänen et al 1996
Finland	1985	ARA	15.1		Kaipiainen-Seppänen et al 1996
Finland	1990	ARA	13.5		Kaipiainen-Seppänen et al 1996
Finland	1986	ARA	19.6		Kunnamo et al 1986
Sweden	84-88	EULAR	10.9	6.41	Andersson-Gäre and Fasth 1992
Norway	85-94	EULAR	22.6		Moe and Rygg 1998
Finland	1995	ARA	22.7		Kaipiainen-Seppänen et al 2001
Finland	1997-8	ILAR	21		Berntson et al 2003
Sweden	1997-8	ILAR	15		Berntson et al 2003
Norway	1997-8	ILAR	19-23		Berntson et al 2003
Estonia	98-00	ILAR	21.7	8.37	Pruunsild et al 2007 and 2007
Norway	2004-5	ILAR	14		Riise et al 2008

The incidence of JIA is higher in Northern Europe than in other countries regardless of the classification criteria applied. However, there are only two prevalence studies, one from Sweden (EULAR criteria) and one from Estonia (ILAR criteria).

Until recently, Finland has been a closed area from a genetic point of view due to the relatively small immigration into the country. In Scandinavia in general, the incidence and prevalence of JIA has remained rather stable. In Finland, however, the

incidence of another AID, DM1, is the highest in the world and still on the increase (Harjutsalo et al 2008).

1.4. Uveitis

Approximately 20% of JIA patients will develop chronic uveitis during a longer follow-up period. Uveitis is particularly common in ANA-positive girls with an early-onset (before 4 years of age) oligoarthritis during the first years of the disease (Kotaniemi et al 2001). Patients with JIA need regular ophthalmologist's consultations because chronic uveitis is usually asymptomatic.

The prevalence and incidence of uveitis also seem to vary in different countries. Among 89 Indian JIA patients, the median duration of JIA was 3.5 years, and only one had uveitis and only one was ANA-positive (Aggarwal and Misra 1996). In Sweden, 15% developed uveitis during a 4-year follow-up (Andersson- Gäre and Fasth 1992). Overall, 8.6% of JIA patients developed uveitis during the first six months of the disease in the Scandinavian countries (Berntsson et al 2003). In Finland, the presence of uveitis was 5% among patients at the time of the JIA diagnosis, when 33% of the patients were ANA-positive (Kaipiainen-Seppänen and Savolainen 2001). In previous Finnish studies the proportion of JIA patients with uveitis has been 21%, 16% and 24%, respectively (Kunnamo et al 1986, Kotaniemi et al 1999 and 2001).

1.5. Drug treatment

The treatment of JIA has been somewhat experimental and has undergone significant changes in the past. In the 1970s in Finland, intramuscular gold, glucocorticoids, chloroquine preparations and non-steroidal anti-inflammatory drugs (NSAID) dominated the therapy (Immonen et al 2007). In the early 1980s, azathioprine (Savolainen et al 1997, Kvien et al 1986, Dale 1972 and Kölle et al 1972) and in the late 1980s methotrexate (mtx) (Giannini et al 1992) were introduced into the treatment of JIA. In the early 1990s, the superiority of mtx became widely recognized

(Giannini et al 1992, Haapasaari 2006). Thereafter, mtx gained position as the second-line drug in JIA medication and the gold standard in therapeutic trials replacing gold proper (Ruperto et al 2004, Ortiz-Alvarez et al 2004).

Among other disease modifying drugs (DMARDs) used for JIA, both sulphasalazine, which was initially used to treat juvenile spondyloarthropathies (van Rossum et al 1998 and 2007), and an oral gold preparation auranofin are safe but their clinical effect is poor or only modest (Giannini et al 1990). D-penicillamine and cyclosporin A have some effect on JIA (van Kerckhove et al 1988, Prieur et al 1985, Gerloni et al 2001, Ruperto et al 2006). Leflunomide has been nearly as efficient and equally well tolerated as mtx (Silverman et al 2005). Chlorambucil, a potent, established and historical drug, has only been used in the most severe JIA cases (Savolainen 1999). Mtx and cyclosporin A are used for severe uveitis (Kotaniemi et al 2003, Petty et al 2003).

In the late 1990s and early 2000s biologic agents, gradually became more widely used for JIA patients in Finland (Haapasaari 2006). Anti TNFalfa therapy: etanercept, adalimumab and infliximab, is commonly used in combination with mtx in cases resistant to mtx alone (Horneff et al 2009, Beukelman 2011). Etanercept has a history of numeral studies demonstrating its efficacy and safety in JIA (Giannini et al 2009). Adalimumab has been effective in polyarticular JIA with some effect on uveitis, too (Lovell et al 2008, Kotaniemi et al 2011).

In the most recent study on a very early drug therapy for JIA from Finland, infliximab and mtx combined were superior to a combination of three DMARDs and strikingly superior to mtx alone (Tynjälä et al 2011).

Abatacept blocks T-cell activation. It is recommended for JIA patients who are resistant to mtx (or other DMARDs) and TNF alpha inhibitors (Beukelman et al 2011).

Rituximab, a CD-20-cell blocker, can be introduced to JIA patients with a high disease activity after receiving mtx, TNFalpha and abatacept therapy.

Anakinra, IL-1-receptor antagonist, and tocilizumab, an antibody against IL-6-receptor, are especially indicated in systemic JIA (Ilowhite et al 2003, Beukelman 2011).

However, side effects, even rare, should be considered (Scheinfeld 2005). They are most commonly connected with abnormal laboratory measurements (blood cell counts, liver enzymes and/or serum creatinine) or infections. Therefore all patients need regular laboratory monitoring and pediatric rheumatologist screening (Beukelman et al 2011). The possible long-term side-effects of biologic drugs need consideration. In Sweden, biologics-naïve patients with JIA, who had been followed up for 40 years, did not have an increased risk of cancer. In stratified analyses, patients with JIA diagnosed 20-40 years ago did not have an elevated risk, whereas patients with JIA diagnosed within the past 20 years had an elevated risk of lymphoproliferative cancers (Simard et al 2010). In a study from the USA, children with JIA had an increased rate of incident malignancy compared to children without JIA. The treatment for JIA, including TNF inhibitors, did not appear to be significantly associated with the development of malignancy, but as for TNF inhibitors, the follow-up was only two years (Beukelman et al 2012). Until now respective data have not been available regarding the long-term users of biologic drugs, and any possible connection between malignancies and biologic medication needs both register monitoring and controlled studies (Ruperto and Martini 2011). Biologic medication may also have other rare side-effects, such as lupus or demyelinating disorders, but any evidence of this is only preliminary (Kahn 2011).

The data gained from adult patients with RA show that an early aggressive intervention even with conventional medication or by combining the drugs (Korpela et al 2004, Möttönen et al 1999) helps to achieve clinical remission.

Regarding JIA, recent studies recommend an early introduction of mtx to achieve maximal effect on rheumatic inflammation (Albers et al 2009b, Cespedes-Cruz et al 2008). The time from symptom onset to diagnosis and treatment was a significant predictor for inactive disease at 6 months in 356 prospectively studied patients

(Oen et al 2009). Inactive disease at 1 year from the disease onset was associated with the use of mtx and/or oral corticosteroids within the first 6 months in polyarticular JIA patients (Ringold et al 2009). Remission, even in the short term, may prevent later joint damage and consequently also functional impairment (Albers et al 2009). Patients responding favorably to mtx at 6 months from the disease onset had an improved outcome (Bartoli et al 2008). The improvement was seen in the physical domain of health-related quality of life (HRQL) and responses in the ACR pediatric 70 definition (Cespedes-Cruz et al 2008, Giannini et al 1997).

1.6. Outcome

The outcome of JIA has varied depending on the study period. Laaksonen studied 544 JIA patients treated at the RFH in 1951-1961. The disease was active in 42% of the patients depending on the duration of the disease: in 41%, 46% and 41%, if the duration was 3-7, 8-15 or 16 or more years, respectively. Only 30.1% of the patients had preserved complete functional capacity: 51%, 34.5% and 9.6%, if the duration was 3-7, 8-15, 16 or more years, respectively (Laaksonen 1966).

Ylijoki studied 174 JIA patients at 15 years after the onset of the disease in 1965-1974. The functional capacity was normal in two-thirds of the patients, and severe or moderate lack of functional capacity was present in only 10%. Thus, the outcome was significantly better than in the earlier study of Laaksonen (Ylijoki 1998).

Arkela-Kautiainen et al studied 123 JIA patients, born in 1976-1980 diagnosed and treated at the RFH, at the age of 21-26. Spousal relationship, educational level and employment status were similar to those of the controls. Their HRQL results were similar to those in the controls with only one exception, the physical functions scale. As expected, patients with an active disease had poorer HRQL when weighted against the physical component. The extended oligoarthritis group had the lowest physical and mental scores in HRQL among all JIA subgroups

(Arkela-Kautiainen et al 2005). The authors concluded that JIA patients' outcome has improved with better diagnostic methods and improved treatment.

An early introduction of mtx improves the long-term outcome in JIA patients (Albers et al 2009b, Cespedes-Cruz et al 2008), but mtx alone is not sufficient for all patients. Therefore, it is very important to recognize the prognostic factors or indicators of this poor outcome. The known risk factors for the poor outcome are the disease duration, the presence of RF and HLAB-27 positivity (Savolainen et al 1998). In a population-based, long-term Nordic cohort study the remission rate was highest in the oligoarticular persistent and systemic JIA subgroups (Nordal et al 2011). The outcome of juvenile psoriatic arthritis seems to be associated with an unfavorable outcome compared to oligo- or polyarthritis (Flato et al 2009).

1.6.1. Psychological outcome

In general, children and adolescents with a chronic illness face a greater risk to develop internalizing problems (e.g. anxiety, depression, social withdrawal), but there are individual differences in their responses to life stress caused by the illness (LeBovidge et al 2003).

In 1974, a study from the USA revealed that children with CA had more psychological difficulties than their healthy peers (McArney et al 1974). In 1988, 363 Australian JIA patients filled out a questionnaire aimed at assessing disease activity, psychosocial functioning and adjustment with the disease. Psychological function and disease activity scores associated with adjustment scores in both elementary and high school groups, whereas social scores associated with adjustment only in the high school group. The associations between the measures of psychological functioning, social relationships, severity of the disease and adjustment to the disease were minor in young adults. The authors emphasized the importance of using a developmental model to understand the adjustment of patients to JIA (Ungerer et al 1988).

In Finland, the rate of suicides among young people between 15 and 24 years of age

has increased in the 1980s, being about 22/100 000. The incidence among patients with JIA was two-fold which is alarming (Savolainen and Isomäki 1993).

In 82 adults with JIA from the UK with an average of 21 year disease duration and 30 years of age, mental summation scores were lower than in controls. The result was similar in all subtypes of JIA and independent of the degree of functional disability. Furthermore, despite an excellent educational attainment, there was a high rate of unemployment among the patients (Foster et al 2003).

In view of the recent studies from western countries, JIA patients seem to have quite a normal psychosocial outcome. This is shown in a study from the UK regarding 60 polyarthritis type of JIA patients aged 7-18 (Ding et al 2008). A similar result was found in a Finnish study of 123 JIA patients aged 21-26 (Arkela-Kautiainen et al 2005). Another Finnish study showed that 142 JIA patients aged 8-15 with their disease lasting for at least one year seemed to cope quite well despite the disease. The level of pain was not alarmingly high, self-efficacy was good and no severe depression or anxiety was detected (Vuorimaa 2010).

In Norway, 55 young adults with JIA, in mean 18.3 years after the onset of the disease, did not differ in their psychosocial health compared to the general Norwegian population. The level of education was even higher, and there was no difference in their employment status (Ostle et al 2010).

In every aspect, the outcome of JIA has shown radical improvement over the past decades.

2. OTHER AUTOIMMUNE DISEASES

2.1. Diabetes mellitus type 1

2.1.1. Definition, diagnostic criteria, clinical characteristics

DM1 is perceived as a chronic immune-mediated disease with a subclinical asymptomatic, prodromal period of highly variable duration. The pathological process causes selective loss of insulin-producing beta-cells in the pancreatic islets in genetically susceptible subjects (Knip and Siljander 2008). DM1 is characterised by chronic hyperglycemia resulting from defective insulin secretion. Diagnostic criteria are based on blood glucose measurements, and when required also on an oral glucose tolerance test. Serological markers of an autoimmune pathological process, including islet cell antibodies (ICA), or insulin antibodies (IAA), are present in 85-90% of the patients when fasting hyperglycemia is detected.

DM1 in children usually presents itself with characteristic symptoms such as polyuria, polydipsia, fatigue and weight loss in association with glucosuria and ketonuria (Craig et al 2009).

2.1.2. Epidemiology,

The incidence of DM1 varies greatly between different countries and ethnic groups. Based on several studies, DM1 is more common in Finland than in any other country. In 1996, the incidence was 45/100 000 children aged 14 years or younger (Tuomilehto et al 1999). In fact, the incidence is the world's highest in Finland and still growing. During 1980-2005, the average age-standardized incidence was 42.9/100 000, increasing from 31.3/100 000 in 1980 to 64.2/100 000 in 2005 (Harjutsalo et al 2008, Myers et al 2008). In the most recent study, the prevalence of pediatric DM1 in the Helsinki region was 3.7/1000 (Oilinki et al 2012).

2.2. Celiac disease, juvenile autoimmune thyroiditis and multiple sclerosis

Celiac disease (CD) is an AID triggered by wheat, barley and rye proteins in genetically susceptible individuals and is known to have classic symptoms caused by malabsorption and failure to thrive. CD may remain non-symptomatic for years. In an extensive population-based study, the prevalence of CD was 1% in Finnish schoolchildren (Mäki et al 2003).

Juvenile autoimmune thyroiditis (JAiT), also called chronic lymphocytic thyroiditis or Hashimoto's disease, is the most common cause of thyroid enlargement in children and adolescents. No population-based data are available on the occurrence of autoimmune thyroiditis in Finland. In the USA, the incidence has varied from 5 to 6.5/1000 children (Rallison et al 1975). In Finland and Israel, JAiT was leading to hypothyroidism (HT) in about 70% of the cases (Mäenpää et al 1985, de Vries et al 2009).

Multiple sclerosis (MS) is an AID with a complex aetiology with involvement of both genetic and environmental factors. MS is very rare in children; less than 10% of all cases occur under 18 years of age (Chabas et al 2008). The estimated MS prevalence in Finland is 1.0/1000, in the over 10-year-old population, with pronounced regional variations (Sumelahti et al 2001). In the UK, the prevalence was 1.46/1000 in 2005 in the total population (Hirst et al 2008).

2. CONNECTION BETWEEN JUVENILE IDIOPATHIC ARTHRITIS AND OTHER AUTOIMMUNE DISEASES

AIDs are chronic conditions, where the immunological environmental and genetic factors are involved (Becker et al 1998). In the USA, the overall prevalence of autoimmunity is estimated at 5% (Jacobson et al 1997). JIA has been described as a complex genetic trait where multiple genes interact and result in a specific phenotype (Angeles-Han and Prahalad 2010). Therefore, genetic studies of JIA, including those

regarding the link to other AIDs, are difficult. Many presenting phenotypes resulting from different and complex pathogenetic mechanisms are likely to involve different susceptibility genes (Phelan et al 2006).

The autoimmune regulatory (AIRE) gene mutations result in a defective AIRE protein. This protein is essential for self-tolerance. AIRE gene mutations are associated with multiple autoimmune diseases and e.g. systemic type of JIA (Podkrajsek et al 2008). Autoimmune polyendocrine syndromes (APS) are rare autosomal recessive disorders characterized by autoimmune multiorgan attack (Weiler et al 2012).

3.1. Autoimmune diseases in children with JIA

The identification of genes behind JIA and other AIDs has improved over the recent years (Albers et al 2009a, Hinks et al 2009, Hinks et al 2010). There is increasing evidence that AIDs, such as JIA and DM1, share the same susceptibility genes. For example, PTPN22 SNP has been strongly associated with both JIA and DM1 (Hinks et al 2005). In addition, IL2RA/CD25, which regulates interleukin-2 receptor expression, bears a connection with JIA and DM1 inheritance and represents a susceptibility locus for both diseases (Hinks et al 2009). Albers et al recently confirmed that autoimmunity locus 4q27 previously associated with DM1 was also associated with the polyarticular JIA (Albers et al 2009a).

3.1.1. DM 1 in children with JIA

The incidence of JIA in Finnish children is quite similar to that in other Nordic populations (Berntsson et al 2003). Instead, the incidence of DM1 in Finland is the world's highest and still on the increase (Harjutsalo et al 2008).

The few publications on patients having both JIA and DM1 are mostly case reports (Castleman and McNeely 1968, Fisher et al 1980, Aggarwal and Meena 2003, Nagy et al 2010).

The first pediatric patient with arthritis and diabetes whom we found in the literature

was a 7-year-old girl reported in 1968 (Castleman and McNeely 1968). Since then, ten patients with JIA and DM1 have been reported, and nine of them also had thyroiditis (Fisher et al 1980, Rudolf et al 1981, Aggarwal and Meena 2003, Nagy et al 2010).

In the USA, seven patients with JIA were found among 200 diabetic children. Six of them had polyarthritis with RF and/or ANAs and evidence of thyroid problems (Rudolf et al 1981).

When 66 Italian JIA patients were screened for pre-diabetic autoantibodies, only 3% showed any positivity (Alpigiani et al 2002). On the other hand, children with JIA in the USA had a 6-fold prevalence of DM1 compared to the population prevalence (Prahalad et al 2004).

3.1.2 Other autoimmune diseases in children with JIA

Studies in adults have shown that AIDs cluster in the same patients (Viljamaa et al 2005). There is preliminary evidence that a similar clustering may also take place in children. In Finland, CD was discovered in 3 out of 150 JIA patients (Mäki et al 1988). In line, the prevalence of HT in Italian JIA patients was 4-fold (Stagi et al 2005) and the prevalence of CD 8-11-fold compared with the control group (Lepore et al 1996, Stagi et al 2005). As many as 44 % of the Bulgarian (Mihailova et al 1999), 14% of the Italian (Stagi et al 2005), 7-11% of the Israeli (Harel et al 2006), and 5% of the Turkish (Unsal et al 2008) JIA patients had laboratory findings suggestive of JAIT, although nearly all patients were euthyroid.

3.2. Autoimmune diseases in JIA children's first-degree relatives

AIDs seem to cluster in children with JIA (Lepore et al 1996, Prahalad et al 2002, Stagi et al 2005, Alpigiani et al 2008). Reports suggesting that AIDs, such as CA, may also cluster in JIA children's families have been published since the 1950s (Wittinghill et al 1958, Ansell et al 1962, Andersson-Gäre and Fasth 1995, Säilä et al

2003). JIA itself has a tendency to cluster in families (Säilä et al 2003, Prahalad et al 2004 and 2010). The approximate effect of familial factors attributing to the risk for JIA was recently calculated to be 13% in a study from the USA (Prahalad et al 2010). In Finland, the sibling occurrence risk in JIA families is approximately 15-20-fold (Säilä 2006).

The occurrence of AIDs in JIA families has been rarely compared with the population data. The prevalence of spondyloarthropathy in parents of 70 children with JIA was 16-fold in the Netherlands (Hertzberger-ten and Dijkmans 1993). In the USA, the population prevalence of AIDs is about 5%, and the figure was 16.1% among JIA patients' first-degree relatives (Prahalad et al 2002). In Taiwan, there was a family member with AID in 4.5% of the 110 JIA patients' families. Of individual family members, 6.4% had an AID (Huang et al 2004).

There are two previous controlled studies from the USA regarding the clustering of AIDs in families with JIA children (Prahalad et al 2002 and 2004). In an interview study of 110 JIA families, the prevalence of AIDs was increased as compared to 45 control families. Among individual AIDs, the difference was statistically significant only for thyroiditis (Prahalad et al 2002).

PURPOSES OF THE PRESENT STUDY

The main purposes of the thesis were to evaluate the clustering of AIDs in children with JIA and in their family members, as well as the recent trends in medical treatment of JIA.

The specific aims were

- 1) to assess the prevalence of AIDs, including DM1, CD and HT in JIA patients (I)
- 2) to evaluate the occurrence of AIDs, including DM1, CD, CA and MS in families of children with JIA (II)
- 3) to establish the prevalence and to describe the clinical characteristics of patients with simultaneous JIA and DM1 (III)
- 4) to establish the trends in medical treatment of JIA in years 2000-2007, with a special focus on early treatment during the first 3 and 12 months after disease onset, respectively (IV)
- 5) to estimate what effect DM1 has on the drug treatment for JIA (unpublished data)

PATIENTS AND METHODS

The Rheumatism Foundation Hospital (RFH) in Heinola, Finland, was a tertiary centre for patients with chronic inflammatory articular diseases. Approximately 60-70% of JIA patients were referred to the RFH from the early 1950s onwards. Two original articles of the present thesis are based on the medical and family histories and clinical characteristics of JIA patients who for the first time were admitted to the RFH (I, II).

The Social Insurance Institution (SII) in Finland maintains registers on individuals who are granted a special reimbursement for medication for defined chronic diseases. To establish this entitlement, a doctor's certificate based on clinical examination is required. In the case of JIA and AIDs, the diagnoses must have been made by paediatricians (DM1) according to the ICD-10 classification, and the treatment plan must follow good clinical practice. The certificates are checked by an expert physician at the SII, before any special reimbursement is granted. In addition, the SII keeps a register of the prescription drugs which are entirely or partly free of charge. Access to the SII registers to collect information from the patient files requires an authorization from the Ministry of Social Affairs and Health. Two original articles (III, IV) and the presented unpublished data are based on the data collected from the SII registers.

1. Autoimmune diseases in children with JIA (I)

All children aged under 16 years admitted to the RFH during 1992-2000 and diagnosed with JIA were recruited into the study. All diagnoses were revised from the patient files according to the ILAR criteria (Petty et al 2004). The study subjects were identified from the ophthalmologist's register, because all patients admitted to the RFH for the first time underwent an ophthalmologist's evaluation. Patients admitted solely for eye problems were excluded. Clinical data were collected, including the age at JIA diagnosis, course type of JIA and the presence of uveitis,

from the patient registers by using a structured form. The number of patients was 417, consisting of 283 girls and 134 boys.

There were 5 sibling pairs, including one set of twins and one family with 3 affected daughters. The follow-up of 191 patients lasted until their 16th birthday. The rest, 226 patients, were followed-up until 31st January 2006.

The population data were collected from the Official Statistics of Finland. Children with DM1, CD and HT were identified from the SII registers. The average numbers of children of 16 years or younger at the end of the years 2003, 2004, 2005 and 2006 were calculated from both population and SII registers, and the figures were then compared with the respective figures of the 417 study patients.

2. Autoimmune diseases in JIA children's first-degree relatives (II)

The families of all consecutive JIA patients admitted first time to the RFH in 1996-2001 were identified by using the hospital registers. All diagnoses were revised by HP from the patient files in March 2007 according to the ILAR criteria (Petty et al 2004).

In winter 2003-2004, a questionnaire was posted to 432 patients. In case they did not reply, a new one was sent out within a year. No response was received from 46 patients, 15 letters were returned marked as "address unknown", and nine patients were excluded because of incomplete information (e.g. adoption, paternal information unavailable). Complete data were thus obtained from 362 (84%) patients.

The questions concerned CA, CD, DM1 and MS diagnoses of the index patients' first-degree relatives (mothers, fathers, full siblings). The diagnoses (recorded according the ICD-10 classification) had to be made by a physician.

3. Simultaneous occurrence of JIA and DM1 in a same patient (III)

Starting from 1965, the SII has provided reimbursement for prescription drugs for DM and from 1966 also for chronic rheumatic diseases including JIA. Injectable

drugs, e.g. intra-articular glucocorticoids are not reimbursed for and therefore not registered since they are administered free in inpatient and outpatient clinics.

Biologic agents are administered in outpatient or inpatient clinics, or require specific certificates when administered at home; data on these drugs were not collected.

The patients were identified from the SII registers on the basis of reimbursement for medication for both CA and DM1 granted for the first time between 1 January 1976 and 31 December 2005. The register files of the SII provide basic data like the patients' birth date, gender and residential area and the date of the reimbursement decision. In Finland, according to an established practice, certain chronic diseases in children like DM1 and JIA are treated in the secondary-level central hospitals.

During the 30-year surveillance period, a total of 240 patients were reimbursed for both CA and DM. The 112 patients who were reimbursed for arthritis at 21 years or older were excluded. The age limit of 20 for JIA was chosen because of the possibility that the application for reimbursement had been filed with delay, which for DM is unlikely. The files of the remaining 128 patients were further checked to ascertain the diagnoses and the patients' exact age at the onset of the diseases. Twenty had adult onset RA, three had DM secondary to glucocorticoids and five had DM type 2. Thirteen patients had later been re-diagnosed as having another disease than JIA. Four potential patients were excluded because their files could not be located and one patient was not included in the study period and was thus excluded. The remaining 82 patients who met the study criteria were classified according to the ILAR criteria. Data on laboratory markers, radiological changes, uveitis, and the use of intra-articular and systemic glucocorticoids, were collected by charting the patients' hospital records.

The study patients were divided into two groups depending on which disease, JIA or DM1, had started first. The activity of JIA was assessed on the basis of inflammatory parameters, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), at the onset of the disease, on the presence of erosions in native radiology and on the use of systemic glucocorticoids. The need of systemic glucocorticoids or the need of

six or more intra-articular injections in any one year was set as criteria for an active disease.

4. Trends in the medical treatment practice of JIA in years 2000-2007 (IV)

Patients with certain chronic and severe diseases, such as idiopathic inflammatory rheumatic diseases, are entitled to a special (72% or 100%) reimbursement for medication from the SII if their condition meets the defined criteria. In JIA, the special reimbursement covers DMARDs and glucocorticoids but not NSAIDs. The new biologic agents are granted separately with stringent criteria, and they are not intended for the first-line use. The reimbursement decisions are gathered in a register maintained by the SII, as are all reimbursable drugs purchased on doctor's prescription. From this database, the patients aged 16 years or younger, who were first granted a special reimbursement for drugs for JIA in years 2000- 2007, were identified.

Children with the following ICD-10 diagnoses were included: M08 (prolonged childhood arthritis) either with a more specific subcategory (n=458) or without (n=1316), L40.5 psoriatic arthritis (n=33), M45 spondyloarthropathies (n=13), M46.1 sacroiliitis of no obvious other cause (n=6), M05 seropositive RA (n=24), M06 seronegative or non-specified RA (n= 36), and M13.9 non-specified arthritis (n= 22). A total of 1970 children with CJA (ICD10 M08) were thus identified.

We collected the data on prescribed medication purchased by JIA patients in 2000-2007. The introduction of DMARDs, whether single or combined, was the primary interest of the study, with a special focus on mtx.

Intra-articular and intravenous glucocorticoids like all the intravenous medications are not included in this study, because these are provided at inpatient and outpatient clinics without any written prescription. With the exception of glucocorticoids, intravenous medications were practically never given during the first year. The use of oral glucocorticoids was not analyzed during 2006-2007 because of a temporary change in the reimbursement system.

5. The effect of simultaneous DM1 on the drug treatment for JIA (unpublished data)

As described above, patients with simultaneous JIA and DM1 were identified from the SII registers from 1 January 2000 to 31 December 2007. Among the 1970 patients who were granted a special reimbursement for drugs to treat CJA were patients who were already reimbursed for the treatment of DM with insulin, were selected. Twenty patients were reimbursed for drugs to treat CJA and DM1 and 3 to treat CJA, DM and HT.

We collected the same data as in the study above on prescribed medication purchased for JIA patients in 2000-2007 (IV). In addition, data were collected on prescribed medication purchased by those 23 patients who already received reimbursement for insulin to treat DM1 and for drugs to treat CJA.

The treatment of the 23 JIA patients with simultaneous DM1 was compared to the treatment of all the 1970 JIA patients. Our primary interest was to check the possible delay in the introduction of mtx, with a focus on treatment in the first 3 and 12 months of the disease.

6. Statistical methods

The results are expressed as mean figures with standard deviations (SD), medians with interquartile ranges (IQR) or counts with percentages. Descriptive values were expressed with 95% CI. Statistical comparison between groups was made by t-test, Chi-Square test, Fisher exact test or permutation test (Monte Carlo p-value) where appropriate. In the study, the occurrence of the common AI diseases DM1, CD and HT as diagnosed by clinical criteria in children with JIA, their families and in the general population was compared, the results were expressed as prevalence rate ratios (PRR) with 95% CI. Gender- and age- matched samples of the general population were obtained from data in the Official Statistics of Finland (I,II).

In the third study, the estimates of occurrence rate ratios (ORR) were calculated by using Poisson regression models (III).

In the fourth and fifth study statistical significance for hypotheses of linearity was evaluated by using Cochran-Armitage test (IV,V).

RESULTS

1. Autoimmune diseases in children with JIA (I)

The median age of the 417 patients admitted to the RFH in 1996-2000 and eligible to the study was 7 years (range 12 months to 15 years). At the end of the study in 2006, the median follow-up time from the JIA diagnosis was 7.5 years (range 5.5 - 9.5 years).

The course type of JIA was oligoarthritis in 22%, extended oligoarthritis in 36%, and seronegative polyarthritis in 33%. All other course types each formed less than 5%. Nine patients had DM1 [2.2% (95 CI 1.0 to 4.1)] (Table 4). DM1 preceded JIA in 7/9 (78%) cases. The PRR for DM1 between the JIA patients and the general population was 5.0 (95% CI 2.3 to 9.5).

Three patients, all with seronegative polyarthritis, had CD [0.7% (0.1-2.1)] (Table 4). All the 3 CD diagnoses were confirmed by a small bowel biopsy from children with intestinal symptoms. CD was diagnosed before JIA in 1/3 cases. Gluten-free diet did not improve their joint symptoms. The PRR for CD between the JIA patients and general population was 5.6 (95% CI 1.2 to 16.5).

Three patients had HT [0.7% (0.1 to 2.1)], and they were all on thyroxin substitution (Table 4). The JIA diagnosis was either extended oligoarthritis or seronegative polyarthritis, and DM1 and CD were present in 2 cases. HT was diagnosed before JIA in 2/3 (67%) cases. The PRR for HT between the JIA patients and the general population was 5.6 (1.2 to 16.5).

In summary, 13/417 (3.1%) of the children with JIA had another AID. Only one (7.7%) of them, a girl with seronegative polyarthritis and CD, had uveitis, compared with 90 uveitis cases (22%) in the group of JIA patients without another AID ($p=0.18$).

Table 4. Clinical diabetes mellitus type 1, celiac disease and hypothyreosis in 417 children with juvenile idiopathic arthritis and their relative risk compared to general population.

Autoimmune disease	Number (%)	RR (95% CI)
Diabetes mellitus type 1	9 (22)	5.0 (2.3 to 9.5)
Celiac disease	3 (0.7)	5.6 (1.2 to 16.5)
Autoimmune hypothyreosis	3 (0.7)	5.6 (1.2 to 16.5)

2. Autoimmune diseases in JIA children's first-degree relatives (II)

Since JIA patients were five times more likely to have another AID than their age mates, the link between JIA and AIDs was evaluated by sending a questionnaire concerning AIDs to the families of JIA patients. The eligible 432 patients had been admitted to the RFH in 1996-2001, and by the end of the year 2007, 355 families had answered.

The 355 families consisted of 24 (5.8%) multiple-JIA families; 6 JIA cases were diagnosed in siblings during the study period at the RFH and 18 siblings were either diagnosed elsewhere or in the RFH outside the study period. All of the 710 parents were of Finnish origin. The mean age of the mothers was 45 years (range 28-66) and that of the fathers 47 years (31-74). The mean child count per family was 2.6 (range 1-18), including the index-JIA patients. The total number of the index patients was 362, their siblings 528, totalling 890 children and 1600 study subjects.

Of the 362 index JIA patients, 241 (67%) were girls and 121 (33%) boys, and 331 (91%) belonged to single-JIA and 31 (9%) to multiple-JIA families. At the end of the

study, the mean age of the girls was 15.5 years (range 7-27) and that of the boys 15.7 years (range 7-26). The index patients' course types of JIA are given in Table 5.

Table 5. Course type* of JIA in 362 index patients

Course type	Girls (N=241) N (%)	Boys (N=121) N (%)	All (N=362) N (%)
Oligoarthritis	47 (19.5)	32 (26.5)	79 (21.8)
Oligoarthritis, extended	84 (34.8)	42 (34.7)	126 (34.8)
Polyarthritis seronegative	88 (36.5)	33 (27.3)	121 (33.4)
Polyarthritis seropositive	15 (6.2)	2 (1.6)	17 (4.7)
Systemic onset JIA	4 (1.7)	4 (3.3)	8 (2.2)
Psoriatic arthritis	1 (0.4)	4 (3.3)	5 (1.4)
Enthesitis related arthritis	1 (0.4)	4 (3.3)	5 (1.4)
Undefined arthritis	1 (0.4)	0 (0)	1 (0.3)

*ILAR criteria (International League of Associations of Rheumatology)

2.1. Prevalence of autoimmune diseases in the index-patients' families

DM1, CD, MS or CA were present in 76 families [21.4% (95% CI 17.3 to 26.0)], with no significant difference between multiple-JIA and single-JIA families (data not shown). Thirty-three mothers [9.3% (6.5 to 12.8)] and 23 fathers [6.5% (4.2 to 9.6)] had DM1, CD, MS or CA (Table 6). There were no cases where both parents had been diagnosed with AID. In 56 families [15.8% (12.1 to 20.0)] either the father or mother had AID (Table 6).

CA formed 62.5% of the AID cases in fathers and 71.9% in mothers (Table 6). Fathers and mothers did not differ for the types of CA, but JIA was the only CA diagnosis in siblings (Table 7). In 6.8% of the families, at least one sibling had JIA. AIDs were present in 2.7% (95% CI 1.8 to 3.7) of the 1238 family members of the

children with JIA when CA was not included and in 7.0% (5.6 to 8.5) when CA was included (Table 6).

Table 6. Autoimmune diseases in families of index-JIA patients

Autoimmune disease diagnosis	Fathers (N=355) n (%)	Mothers (N=355) n (%)	Siblings (N=528) n (%)	Family members* (N=1238) n (%)	Index JIA patients (N=362) n (%)
DM1	3 (0.8)	2 (0.6)	6 (1.1)	11 (0.9)	8 (2.2)
CD	4 (1.1)	6 (1.7)	7 (1.3)	17 (1.4)	3 (0.8)
MS	2 (0.6)	3 (0.8)	0 (0)	5 (0.5)	0 (0)
Total (CA excluded)	9 (2.5)	11 (3.1)	13 (2.5)	33 (2.7)	11 (3.0)
CA	15 (4.2)	23 (7.0)	18 (3.0)	56 (4.5)	---
Total (CA included)	23 (6.5)	32 (9.7)	31 (5.9)	86 (7.0)	---

For abbreviations, see text

*Index-JIA patients not included. There were 2 AIDs in 2 mothers (CD+CA, DM+MS), in 1 father (CD+CA) and in 2 siblings (DM1+CD). There were 2 index-JIA patients in 1 family.

Table 7. Chronic arthritis by specific diagnoses in index-JIA patients' family members

Diagnosis	Fathers (N=355) n (%)	Mothers (N=355) n (%)	Siblings (N=528) n (%)	Family members (N=1238) n (%)
RA	6 (1.7)	10 (2.8)	0 (0)	16 (1.3)
SPA	4 (1.1)	2 (0.6)	0 (0)	6 (0.5)
PSA	2 (0.6)	2 (0.6)	0 (0)	4 (0.3)
JIA	2 (0.6)	4 (1.1)	18 (3.4)	24 (1.9)
Reactive Arthritis	1 (0.3)	4 (1.1)	0 (0)	5 (0.4)
Others*	0 (0)	1 (0.3)	0 (0)	1 (0.1)

For abbreviations, see text.

*Arthritis with non-specified collagenosis

The numbers of AID patients were too small for statistical tests in relation to the course types of JIA in the index patients and in relation to any specific AID in the family.

When the data on age, sex and course type of JIA were compared between the 70 eligible families who did not attend the study and the 355 families who did, no statistically significant differences were found.

The prevalence of AIDs in the present study and in the previous studies available are given in Table 8. The parental RA prevalence was 22.5/1000, AS prevalence 8.5/1000, PsA prevalence 5.6/1000 and MS prevalence 3.1/1000, and the JIA prevalence in children was 34.1/1000. Except for MS, the prevalence of the study exceeded the published population prevalence (Table 8). The prevalence of CD has been well documented both in Finland and elsewhere, and our figures were quite similar to the published prevalence (Table 8).

Table 8. Prevalence (per 1000) of autoimmune diseases in JIA patients' first-degree relatives in the present and other available studies

Disease	Present prevalence (95% confidence interval) in first-degree relatives	Prevalence (reference) in the population Finland	Prevalence (country, reference) in the population Other countries
CA (parents)	45.2 (34.3 to 58.3)	NA	NA
RA (parents)	22.5 (12.9 to 36.3)	8.0 (Hakala et al 1993)	6.6 (Sweden, Englund et al 2010)
AS (parents)	8.5 (3.1 to 18.3)	1.5 (Kaipiainen-Seppänen et al 1997)	2.1 (Norway, Backland et al 2005)
PsA (parents)	5.6 (1.5 to 1.4)	NA	1.3 (Norway, Nossent and Grant 2009)
JIA (parents) JIA (children [^])	8.5 (3.1 to 18.3) 34.1 (20.3 to 53.3)	NA 0.8 (Lantto et al 1985)*	NA 0.9 (Sweden, Andersson-Gäre and Fasth 1992)** 1.5 (Norway, Moe and Rygg 1998)** 1.2 (USA, Prahalad et al 2010)**
DM1 (parents) DM1 (children ^{^^})	7.0 (2.3 to 16.4) 15.7 (8.6 to 26.3)	NA 3.7 (Oilinki et al 2012)	NA 1.9 (US, Jacobson et al 1996)
CD (parents) CD (children ^{^^})	14.1 (6.8 to 25.7) 11.2 (5.4 to 20.6)	19.9 (Lohi et al 2007) 10.0 (Mäki et al 2003)	9.5 (USA, Fasano et al 2003) 4.8 (Sweden, Lagerqvist et al 2001) 3.1 (USA, Fasano et al 2003) 1.3 (Sweden, Carlsson et al 2001)
MS (parents)	3.1 (1.0 to 7.3)	1.0 (Sumelahti et al 2001)	1.5 (UK, Hirst et al 2009)

For abbreviations, see text

NA, not available

[^] 528 siblings included; ^{^^}528 siblings and 362 index JIA children combined

* ARA criteria; **EULAR criteria

3. Simultaneous occurrence of JIA and DM1 in the same patient (III)

JIA patients and their first-degree relatives have a higher risk for AIDs than the general population. This association was studied more accurately in terms of JIA and DM1.

The SII statistics from 1976-2005 identified 82 patients with simultaneous JIA and DM1, consisting of 55 (67%) girls and 27 (33%) boys. The subtypes of the patients, classified according to the ILAR criteria, are presented in Table 9.

Table 9. Subtypes of JIA in 82 patients with both JIA and DM1.

JIA	Onset type N (%)	Course type N (%)
Systemic onset arthritis	1 (1.2)	1 (1.2)
Oligoarthritis	45 (55)	33 (40)
Oligoarthritis, extended		11 (13)
Polyarthritis seropositive	12 (15)	12 (15)
Polyarthritis seronegative	22 (27)	22 (27)
Enthesitis related arthritis	2 (2)	2 (2)
Psoriatic arthritis	0 (0)	1 (1.2)

3.1. Occurrence

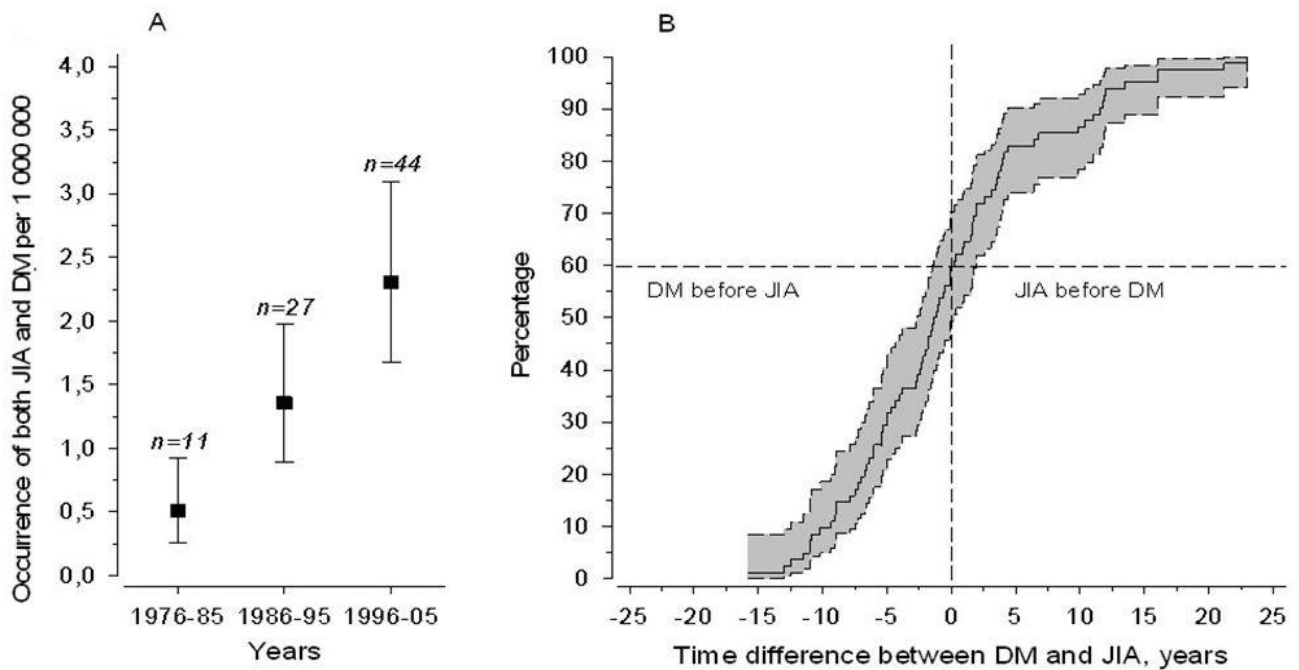
Simultaneous JIA and DM1 occurrence during the 30-year period is shown in Figure 1A. There was a statistically significant increase in this occurrence (age and sex adjusted p for linearity <0.001): 4.49-fold [95% CI (2.32 to 8.69)] between the first (1976-1985) and last (1996-2005) periods.

3.2. JIA or DM1 onset first

Forty-nine (60%) patients (71% girls, 29% boys) had DM1 prior to JIA and 33 (61% girls, 39% boys) had JIA prior to DM1 (Figure 1B).

Figure 1A. Simultaneous occurrence of JIA and DM1 during 30 years in 10-year episodes. The year of onset of the second disease was used as an end point. The error bars give 95% confidence intervals.

Figure 1B. Cumulative distribution of the difference between the onset age of DM1 and JIA. The gray band shows the 95% confidence interval.



3.3. Age at onset

The mean onset age of JIA in all the 82 patients was 8.5 years (SD 5.2) and that of DM1 8.1 years (SD 6.4) ($p=0.61$). The age at the onset of JIA and DM1 remained fairly constant over the three surveillance decades.

3.4. Laboratory findings

There were no significant differences in ESR and CRP between the DM-first and JIA-first groups at the time of the disease onset. ANAs were found in 18 (22%) patients, with no difference between the groups. The only difference was RF positivity in those who had got DM1 first.

Table 10. Laboratory findings at disease onset in two patient groups.

	DM1-first (N=49)	JIA-first (N=33)	p value
ESR, median (IQR)	26 (12, 45)	27 (12, 45)	0.62
CRP, median (IQR)	7 (3, 26)	10 (5, 16)	0.90
ANA+ (%)	11 (22)	7 (21)	0.97
RF+ (%)	11 (22)	1 (3)	0.023

3.5 Erosions

Erosions in native radiographs were present in 21 (43%) in the DM-first and in 13 (39%) in the JIA-first group ($p=0.75$).

3.6. Use of glucocorticoids

Nine (27%) of the 33 patients with JIA-first had been on systemic glucocorticoids once or more, and nine (27%) had received six or more intra-articular injections in some year. The respective figures for the 49 children with DM1-first were 14 (29%) and 26 (53%, $p=0.021$)

3.7. Use of biologic agents

Seventeen (21%) out of the 82 patients had received biologic agents (etanercept was first introduced to 11 patients and infliximab to 6 patients), All of them had DM1 before any biologic agent was introduced.

3.8. Uveitis

Six patients (7%) had chronic uveitis. Five of them had JIA before DM1, four had oligoarthritis (one with extended arthritis) and one had seronegative polyarthritis. The patient with seronegative polyarthritis had DM1 before JIA. Five patients with chronic uveitis were ANA-negative. The seventh patient, a boy with oligoarthritis (ANA -/HLA-B27+), had experienced several bouts of acute uveitis.

3.9 Additional autoimmune diseases

Eighteen (22%) out of 82 patients had a third AID, which in 12 cases was HT. Three were RF-seropositive and all 12 were ANA-negative. Six had CD.

3.10. Psychiatric diseases

Thirteen (16%) patients, three male and 10 females, had psychiatric disorders demanding regular or longstanding therapy or medication or even admittance to a psychiatric hospital (five depressions necessitating drug therapy and psychiatric therapy, one psychosis and drug abuse, one alcohol abuse, one had severe compliance problems as a teenager, two anorexia and one bulimia with depression, one ADHD and compliance problems).

4. Trends in the medical treatment practice of JIA in years 2000-2007 (IV)

The data were limited to the drug treatment during the early disease months, defined in two ways: the first 3 months and first 12 months after the JIA diagnosis.

4.1. Drug treatment

Mtx and hydroxychloroquine were the most commonly purchased first-year drugs over the whole study period (Table 11). The use of mtx increased significantly (p for linearity < 0.001) during the follow-up period, which meant 71.5 % of the patients in 2007. The use of hydroxychloroquine decreased ($p < 0.001$), and a declining trend

was also seen in the use of prednisolone (Table 11). The increased use of mtx was on the same level as during the first 3 months in both single and combination therapies (Figure 2).

4.2. Early treatment strategy

The most common early treatment (3-month) strategy was DMARD monotherapy. The proportion of patients on a single DMARD remained constant, approx. 50%. The number of patients receiving combination therapy increased between years 2000-2003 ($p < 0.001$), but remained rather stable thereafter (Table 11).

Almost 20% of all patients received neither a DMARD nor a biologic agent during the immediate 3 months after the disease onset, the proportion being rather stable between 2000-2007.

Figure 2. Methotrexate used as single therapy and in combination with other DMARDs during the first 3 disease months in patients with JIA in 2000-2007.

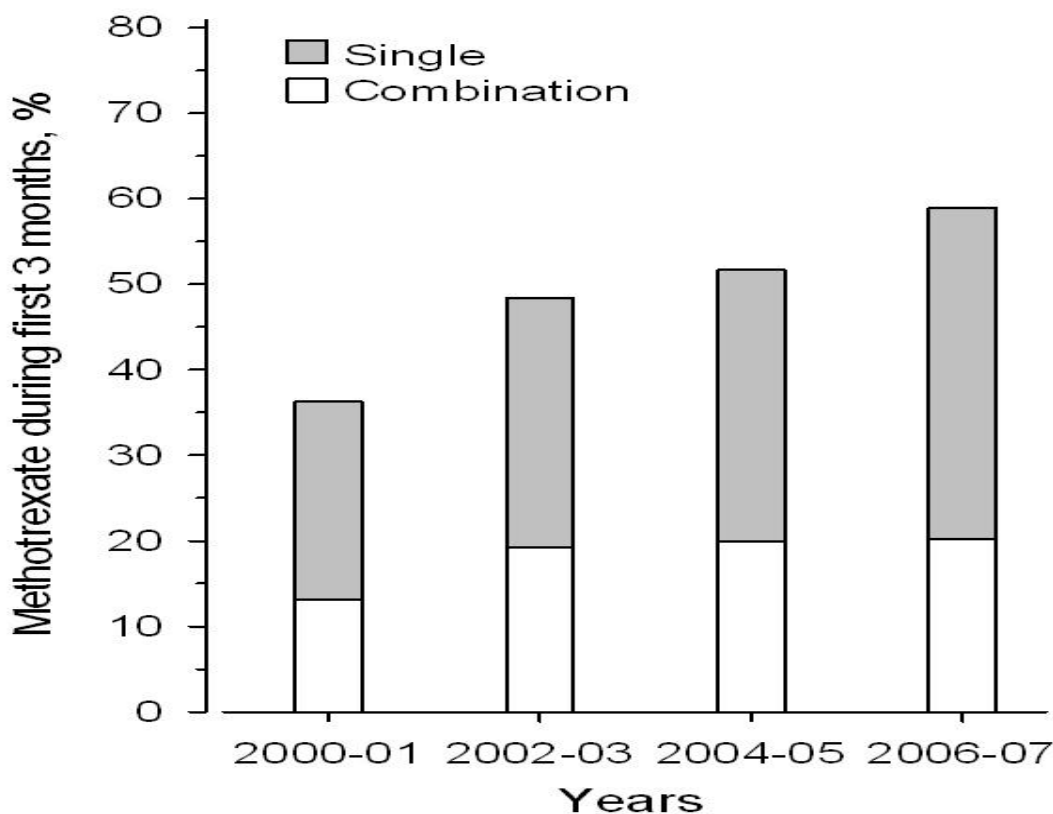


Table 11. Medication of chronic juvenile arthritis in the first 3 and 12 months in 2000-2007.

Medication	Years				p for linearity
	2000-01 N=449	2002-03 N=477	2004-05 N=515	2006-07 N=529	
Drugs, first 12 months					
Methotrexate	241 (53.7)	321 (67.3)	353 (68.5)	378 (71.5)	<0.001
Hydroxychloroquine	276 (61.5)	288 (60.4)	296 (57.5)	239 (45.2)	<0.001
Prednisolone	127 (28.3)	151 (31.7)	103 (20.0)	NA	
Sulphasalazine	69 (15.4)	68 (14.3)	86 (16.7)	61 (11.5)	0.19
Leflunomide	2 (0.4)	8 (1.7)	5 (1.0)	11 (2.1)	0.08
Gold sodium thiomalate	6 (1.3)	0 (0.0)	0 (0.0)	1 (0.2)	0.01
Auranofin	2 (0.4)	1 (0.2)	1 (0.2)	0 (0.0)	0.18
Azathioprine	3 (0.7)	2 (0.4)	3 (0.6)	4 (0.8)	0.80
Cyclosporine	2 (0.4)	5 (1.0)	2 (0.4)	0 (0.0)	0.14
TNF-inhibitor	0 (0.0)	8 (1.7)	32 (6.2)	25 (4.7)	<0.001
Podophyllotoxin	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0.55

Medication	Years				p for linearity
	2000-01 N=449	2002-03 N=477	2004-05 N=515	2006-07 N=529	
No DMARD or biologic agent	75 (16.7)	84 (17.6)	90 (17.5)	103 (19.5)	0.29
Single DMARD therapy	245 (54.6)	236 (49.7)	286 (55.5)	298 (56.3)	0.24
Single DMARD therapy with prednisolone	50 (11.1)	45 (9.4)	22 (4.3)	NA	<0.001
Combination* therapy	46 (10.2)	67 (14.0)	83 (16.1)	105 (19.8)	<0.001
Combination therapy with prednisolone	24 (5.3)	33 (6.9)	23 (4.5)	NA	
Prednisolone alone	9 (2.0)	10 (2.1)	7 (1.4)	NA	
only TNF-inhibitor	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0.37

*Two or more DMARDs

**all TNF-inhibitors as one entity

5. The effect of simultaneous DM1 on the drug treatment for JIA (unpublished data)

During the years 2000-2007, 23 patients with simultaneous reimbursement for the treatment for CJA and diabetes were identified from the SII registers. Their drug treatment was compared with the 1970 JIA patients' treatment which was recorded in the nationwide study (IV). Mtx was introduced in 19 (83%) patients during the first 3 disease months vs. 59% in the 1970 control JIA patients (p=0.002). The difference was significant.

DISCUSSION

1. *Background research*

1.1. *Connection between different autoimmune diseases*

The epidemiology of autoimmune diseases is a topic of growing focus. AIDs are considered having a complex etiology with a risk conferred by both genes and environment (Ellis et al 2010).

A number of recent studies show evidence that AIDs, such as JIA, DM1, CD, HT and MS, share some common genetic factors (Lettre et al 2008, Mysliwiec et al 2008, Albers et al 2009a, Hinks et al 2005 and 2010). Studies regarding the pathogenesis of different AIDs e.g. the pathogenesis of CD and JIA show that they may have several features in common. The lymphocyte cytotoxicity is abnormally increased in the intestinal mucosa in patients with JIA. The same phenomenon is also seen in patients with CD (Arvonien et al 2010). CD and HT also have a connection in their pathogenesis. Serum transglutaminase-2 autoantibodies, which are very common in patients with active CD, can react with transglutaminase-2 in thyroid tissue and thereby contribute to the development of thyroid disease (Duntas 2009). Environmental factors, an infection for example, may have a role in triggering CA, such as JIA (Oen et al 1995, Ravelli and Martini 2007).

The occurrence of both JIA and DM1 have a seasonality trend (Levy et al 2008). It is widely recognized that viral infections and low levels of vitamin D in children, follow the same seasonal variation as the onset of DM1 and MS (Handel et al 2009). Vitamin D has a role in regulating innate and adaptive immunity which may provide a link between vitamin D and AIDs. Vitamin D regulates T and B cells, macrophages, dendritic cells and ceratinocytes (Hewison 2010, Maruotti and Cantatore 2010). In 2001, a Finnish study showed that vitamin D supplementation may have a protective effect against the development of DM1 (Hyppönen et al 2001). In a more recent Finnish study, low levels of vitamin D were also linked to some incident cases of

DM1 (Oilinki et al 2011). It is worth noting, that according to another Finnish study vitamin D supplements are not used as per to the dietary recommendations in a substantial proportion of children (Räsänen et al 2006). Furthermore, vitamin D may have a protective role in the pathogenesis of MS (Mirzaei F et al 2011). The studies suggesting that low levels of vitamin D could be an etiological factor for JIA are few, but the idea is fascinating (Ellis et al 2010).

1.2. Autoimmune diseases' response to drug treatment

Similar responses to the same drugs in different AIDs have evidenced that there are common mechanisms. In animal models on RA, DM1 and MS, certain potassium channel blockers have eased the disease (Rangaraju et al 2009). Type 1 interferons contribute to autoimmune pathogenesis, but they can also control inflammation and as a therapeutic agent, have had favourable effects to RA, DM1 and MS. Some positive effect, such as a trend toward preservation of pancreatic beta-cell function, was observed in the recent-onset DM1 patients, who received oral recombinant INF-alpha (Crow 2010). On the other hand, biologic agents, e.g. TNF blockers, may contribute as a cause of triggering chronic rheumatoid diseases, systemic lupus erythematosus, and another AID, MS (Kahn 2011).

1.3. Epidemiological aspects

In epidemiological studies the connection between DM1 and CD seems to be obvious. The prevalence of CD was 7% in DM1 patients in Italy (Valetta et al 2007). In another Italian study, the prevalence of CD was 5.7% among DM1 patients and 1.9% among the first-degree relatives of DM1 patients (Not et al 2001). All figures differed significantly from the controls. In two recent studies, the consumption of gluten resulted in an altered gut permeability and mucosal immunity, which may predispose the patient to the development of DM1 (Sud et al 2010, Vaarala et al 2008). In patients with CD, a gluten-free diet may also reduce joint symptoms

(Alpigiani et al 2008), which was not, however, observed in the patients of the present study.

A register-based study from the UK, made among an adult population regarding AIDs in the same patient, found a connection between RA, AIT and DM1 at a higher rate than expected, but was not found between RA and MS (Somers et al 2009)

In a Finnish study based on SII registers, 596 children and adolescents were identified to have inflammatory bowel disease. The presence of CD, epilepsy, JIA and DM1 in these patients was calculated. These children had more chronic diseases than their controls. CD was associated with later development of ulcerative colitis. Clear association was seen only with epilepsy and ulcerative colitis (Virta and Kolho 2012).

The present study showed that Finnish JIA patients and their families had AIDs more often than the general population. This clustering offers indirect evidence that AIDs may have similar mechanisms. Moreover, the simultaneous occurrence of JIA and DM1 has increased significantly during the past 30 years.

2. Autoimmune diseases in children with JIA

The patients with JIA had more than 5-fold risk of getting another AID, such as DM1, CD or HT a sequel of autoimmune thyroiditis. The results are in line with the evidence obtained from adults (Viljamaa et al 2005). Compared with the population data, the 1.1% prevalence of DM1 was 6-fold in 443 American children (Prahalad et al 2004), and the 2.5% prevalence of CD was 8-fold in 119 Italian children with JIA (Lepore et al 1996). Based on active screening, the 1.3% prevalence of subclinical HT was 4-fold and the 6.7% prevalence of CD was 11-fold in 151 Italian children with JIA, as compared with age- and sex-matched controls (Stagi et al 2005). In our study, the 2.2% figure for DM1 was 2-fold compared with the American JIA patients, probably due to the higher prevalence of DM1 in the Finnish population (Harjutsalo

et al 2008). The numbers of children with CD and HT were so small, i.e. less than 1% of the JIA patients that to compare them with other results is not justified.

Three earlier studies give strong laboratory evidence for the connection between JIA and AIT in children (Mihailova et al 1999, Stagi et al 2005, Harel et al 2006). Since we did not use any systematic screening, only three clinically obvious cases were diagnosed, and thus transient JAIT cases and probably also some mild HT cases were missed.

An untreated autoimmune disease, such as CD, which often remains non-symptomatic for years, may predispose the patient to another autoimmune disease (Lepore et al 1996). In patients with CD, a gluten-free diet may also reduce joint symptoms (Alpigiani et al 2008). In the present study, all three CD diagnoses were based on histological findings in symptomatic patients, and thus represent an end-stage of the autoimmune process. Therefore, a gluten-free diet reduced intestinal symptoms, but did not reduce joint symptoms in patients with JIA. The connection between JIA and CD should be evaluated according to studies which include systematic laboratory screening for CD in both JIA patients and controls. There also seems to be a connection between DM1 and CD. The prevalence of anti-tTG IgA positivity among children and adolescents with DM1 was 8.6% (Kakleas et al 2010). The present results provide preliminary evidence that the presence of multiple AIDs may even protect a patient from uveitis, which commonly occurs jointly with seronegative polyarthritis and extended oligoarthritis. This suggests that the mechanisms leading to autoimmune disorders and uveitis are different. The conclusion is based on an active over 5 year monitoring of the eye status of more than 400 JIA patients, mainly consisting of seronegative polyarthritis or extended oligoarthritis cases.

3. Autoimmune diseases in JIA children's first-degree relatives

Two conclusions can be drawn from the present retrospective study on the prevalence of AIDs in 355 families with a JIA child. First, as many as 21.4% of the families had at least one member with DM1, CD, MS or CA. This figure is high when compared with the 4.5% prevalence in 110 JIA families in Taiwan (Huang et al 2004) and with the 16.1% prevalence in 110 JIA patients families in the USA (Prahalad et al 2002). The prevalence figures of AIDs were high, although we did not collect data on thyroiditis, which has been a major AID in several previous studies (Prahalad et al 2002, Huang et al 2004, Zeff et al 2008).

Second, when compared with the population data available (Oilinki et al 2012, Hakala et al 1993, Kaipiainen-Seppänen et al 1997, Sumelahti et al 2001), the prevalence of DM1, RA, AS and MS was increased in JIA families. CD was as prevalent as in the general population (Mäki et al 2003). However, there were no significant differences in the occurrence or distribution of AIDs between the single-JIA and multiple-JIA families, which disagreed with the previous US study (Prahalad et al 2002).

CA formed over half of the AIDs in JIA families and occurred only in parents. The parental 9.7% occurrence in single-JIA and 25% occurrence in multi-JIA families are in line with the previously found 18% in Finnish multiple-JIA families (Säilä et al 2003). In the present study, RA was the most common specific diagnosis in parents, especially mothers. The 23/1000 prevalence of RA was 3.5-fold (Hakala et al 1993) and the 8/1000 prevalence of AS was 6.7-fold compared with the national population data (Kaipiainen-Seppänen et al 1997). Surprisingly, the parents with AS had no sons with juvenile AS, and 3 of the 4 index-JIA patients with a parent with AS were girls. The prevalence of PsA in the Finnish adult population is not known; the present 6/1000 prevalence was 4.6-fold compared with the prevalence in Norway (Nossent et al 2009).

The prevalence of JIA was found to be 0.8/1000 in northern Finland when the ARA criteria was used in 1985 (Lantto and von Wendt 1985). In the present study, the 34.1/1000 prevalence of JIA in siblings was 42.6-fold, but the real difference must be lower because ARA criteria excluded juvenile SPA. The prevalence in our study was 22.7- to 28.4-fold when compared with the figures by the EULAR criteria from the USA, Sweden and Norway (Andersson-Gäre and Fasth 1995, Moe and Rygg 1998, Andersson-Gäre 1999). The JIA prevalence in parents was 8.5/1000, but no population data are available for JIA in adults. Since the prevalence of JIA in children in the Nordic countries is about 1/1000 and the mean age of onset is 7-8 years, the cumulative incidence of JIA in adults can be estimated at 2/1000. Thus, the parental JIA prevalence in our study was approximately 4-fold.

The exact prevalence of DM1 in Finnish children in the whole country is not known, although the incidence of pediatric DM1 is considered to be the world's highest and seems to increase all the time (Harjutsalo et al 2008, Myers and Zimmet 2008). In a recent study, the prevalence of DM1 was 3.7/1000 in children in the Helsinki region (Oilinki et al 2012). The estimate made over ten years ago in the USA was 2/1000 (Jacobsson et al 1997). The combined DM1 prevalence in first- and second-degree relatives of JIA patients was only 2-fold in the US study (Prahalad et al 2002). Compared with these figures, the prevalence of pediatric DM1 in the present study was 3.3- to 5.7-fold when only siblings were included, and 4.2- to 8.3-fold, when both siblings and index patients with JIA were included.

In some earlier studies, the prevalence of JIA was increased in the first-degree relatives of CD patients (Neuhausen et al 2008). Contrary to expectations, the prevalence of CD in the present study did not exceed the prevalence in Finnish adults (14/1000 vs. 20/1000; Lohi et al 2007) or children (11/1000 vs. 10/1000; Mäki et al 2003). Unlike in the population studies, the present study subjects were not screened and the diagnoses were made on clinical grounds only. In Sweden, the prevalence of CD was 7/1000 among the 3004 non-screened children (Carlsson et al 2001). When

this figure was used as a reference, the prevalence of CD in JIA families was 1.9-fold in the present study.

The estimated MS prevalence in Finland is 1.0/1000, with pronounced regional variations (Sumelahti et al 2001). In the UK, the respective figure was 1.5 (Hirst et al 2009) and considered to be higher than in most other countries. In the USA, the prevalence of MS was 4/1000 among first- and second-degree relatives of JIA patients (Prahalad et al 2002). In the present study, the prevalence of MS in first-degree relatives was 3.1/1000 when adults and children were combined, which is 3- to 4-fold compared to the Finnish population data (Sumelahti et al 2001).

As expected, mothers had AIDs more often than fathers (96/1000 vs. 68/1000). This is due to a higher prevalence of AIDs in females (Jacobsson et al 1997, Zeff et al 2008, de Vries et al 2009).

In conclusion, the most distinctive differences between the present and literature data were seen in the presence of JIA in siblings and DM1 in JIA children.

4. Simultaneous occurrence of JIA and DM1 in the same patient

Four conclusions can be drawn from the study on simultaneous occurrence of JIA and DM1. First, the number of patients increased between years 1975-2005. Second, the prevalence of seropositivity was high. Third, the occurrence of uveitis was low. And fourth, almost 25% had a third AID and 16% had psychiatric problems.

The increase of DM1 incidence in Finnish children is well-known (Harjutsalo et al 2008), and there may also be a slight increase in JIA incidence (Kunnamo et al 1986, Kaipiainen-Seppänen and Savolainen 1996 and 2001, Berntsson et al 2003). Between 1965-1996, the average annual increase of DM1 incidence was calculated to be 3.4% (Tuomilehto et al 1999). If there is an increase in JIA incidence, their number must be small compared to DM1.

The distribution of JIA subtypes corresponds to that seen in JIA in general, with two

exceptions: more (15% vs. 2.6%) seropositive and fewer (1% vs. 4.6%) systemic cases (Kaipiainen-Seppänen and Savolainen 1996 and 2001, Berntson et al 2003). Some patients with systemic JIA might be missing here if they were treated with NSAIDs and systemic glucocorticoids only.

Chronic uveitis was present in only 7% of patients with JIA and DM1. In line with this, uveitis was present in only 8% of children with JIA and another AID. In earlier Finnish studies, the proportion has been 21% (Kunnamo et al 1986) and 24% (Kotaniemi et al 2001). The results suggest that the mechanisms of uveitis and AIDs are different. Although 22% of the JIA patients were ANA-positive, the few patients with chronic uveitis did not have ANAs.

A fifth of our study patients had a third AI disease, in line with some earlier studies on clustering of AIDs in individuals with JIA and in their families (Andersson-Gäre and Fasth 1995, Prahalad et al 2002 and 2004 and 2010). In contrast, no association was found between the third AID and ANA- or RF-positivity, as previously observed for simultaneous JIA, DM1 and HT (Rudolf et al 1981, Aggarwal and Meena 2003).

In the recent studies from western countries, JIA patients seem to have a fairly normal psychosocial outcome, as shown in the UK study in 60 polyarthritis patients aged 7-18 (Ding et al 2008) and in the Finnish study regarding 123 patients aged 21-26 (Arkela-Kautiainen et al 2005). In the Netherlands, 4.7% of 233 DM1 patients aged 9-19, had received psychological care (de Witt and Snoek 2011). In a large Finnish birth cohort, 12% of the boys and 4% of the girls born in 1981 had used child mental health services by 2005 (Sourander et al 2008). In another study in over 5000 subjects from Finland, 5.2% had been treated in psychiatric hospital between 13-24 years of age (Gyllenberg et al 2010).

Compared with these figures, the 16% occurrence of serious psychiatric problems was almost 3-fold in the JIA patients in the present study. Depression was the most frequent diagnosis. The large number of patients with serious psychiatric problems was an unexpected surprise, and emphasizes the importance of multiprofessional

care, including the psychosocial aspect.

There were only minor differences in glucocorticoid consumption between the groups constructed by the presence of JIA and DM1. The 49 patients with DM1 preceding JIA had been on systemic glucocorticoids at some stage of their arthritis just as frequently as those 33 who had JIA before DM1, but they had been treated more often (53% vs. 27%) with intra-articular corticosteroid injections. These observations are against the common practice to avoid glucocorticoids, especially systemic glucocorticoids, for diabetic patients. These observations raise the suspicion that JIA is more severe when presenting with DM1. The aim of this more aggressive intra-articular corticosteroid injection -treatment could also have been to cut down inflammation to stabilize the glucose balance.

A case report from year 2000 describes the onset of DM1 only 5 months after the introduction of the etanercept therapy to a patient with systemic JIA (Bloom 2000). At least in theory, DM1 could be drug-induced. In our study, 17 JIA patients with DM1 received biologic agents (11 etanercept, 6 infliximab), they had all got diabetes prior to therapy with biologic agents.

This nationwide study used the SII registers which included patients who had reimbursement for drugs for JIA and DM1. After 1994, when the reimbursement for NSAIDs was withdrawn, a few mild oligoarthritis may have been missed, as well as systemic JIA cases which were treated with NSAIDs and/or glucocorticoids only. The treatment of JIA has become more aggressive over the last decades. The use of effective, reimbursable drugs has increased, and more patients therefore, have been included in the database. However, considering the current medication practices in Finland, their number must be low. On the other hand, salicylates were the only NSAIDs in the 70s and because they are cheap it may be that in some cases reimbursement was not even applied for. This could explain the lower numbers in the early years of our study.

5. Trends in the medical treatment practice of JIA in years 2000-2007

The present study covers the entire population of incident-JIA patients in the country and documents the trends in the drug treatment modalities during eight consecutive years. The most accurate method to examine the drug use is to collect data on the actual intake. Since this approach is difficult, counting the purchases of the medication rather than the number of prescriptions is the next-best estimate of the use of medicines.

The use of mtx during both the first 3 and the first 12 months increased steadily during the follow-up period. Mtx became the most common early-phase drug whereas glucocorticoid consumption diminished. If the first DMARD was not efficient enough, the tendency in the first study years was to add prednisolone into the regimen, whereas later, the practice of adding another DMARD was preferred.

The treat to target with DMARDs is, besides gaining a remission, also administering glucocorticoids shorter periods at lower doses. Ample evidence shows that the earlier the treatment with DMARDs is started, the better the long-term outcome will be (Albers et al 2009b). That is why an effective early treatment is emphasized. In line, the present study revealed how an early use of mtx diminished the consumption of glucocorticoids.

The impact of adult RA treatment, and also the impact of the FIN-RACo study can be seen in the present study (Möttönen et al 1999). Both have emphasized an early treatment with multiple drugs. Therefore, the use of e.g. sulphasalazine did not decrease, since it was often part of combination therapy. Likewise, hydroxychloroquine was used as combined with mtx (Haapasaari et al 2005).

Patients with no DMARDs or oral glucocorticoids during the first 3 months covered almost 20% of all patients. We assume that many of these had mild oligoarthritis or Still's disease, which was treated with NSAIDs and intra-articular/intra-venous glucocorticoids, but compliance problems cannot be excluded. The Finnish system to treat is to actively inject the inflamed joints with glucocorticoids. The child is then

often symptom-free the next morning and the parents may think it is unnecessary to start any other treatment e.g. mtx, and so they do not purchase the medicines.

There was a restricted supply of etanercept in Finland during the first study years until summer 2003, which explains the limited use of TNF-inhibitors. Among the JIA patients 4.6% have Still's disease in this country (Kunnamo et al 1986, Kaipiainen-Seppänen and Savolainen 2001). The treatment is often introduced with non-reimbursable NSAIDs and glucocorticoids. In addition, the ICD-10 diagnoses in the SII certificates are not necessarily in line with the ILAR classification.

In an earlier prospective Finnish incidence study on arthritis in 161 children, 28 (17.4%) had CA, and all but one (3.6%) of them met the ARA criteria for JRA (Kunnamo et al 1986). By applying this figure, 70 or fewer of the present 1970 JIA patients might get another diagnosis if they were to be examined later.

To summarize, we identified several major changes in Finnish JIA patients' drug treatment in years 2000-2007. A lengthy follow-up is needed to see if the patients have benefitted from an early introduction of DMARDs and the use of combination therapy.

6. The effect of simultaneous DM1 on the drug treatment for JIA

When evaluating the drug treatment of JIA patients nationwide (IV), it was interesting to compare the difference in drug treatment between JIA patients in general and JIA patients with another AID (DM1).

In order to save on the use of glucocorticoids with patients who already had DM1, systemic drug treatment must be used aggressively for a maximum effect. During the first three disease months mtx was introduced to 83% of JIA patients who already had DM1. The difference was significant ($p=0.002$) when we compared the drug treatment of patients with both JIA and DM1 to the drug treatment of JIA patients in the whole country. The earlier mtx is introduced the better a chance a patient has of reaching remission, especially patients with two simultaneous but different AIDs.

METHODOLOGICAL ASPECTS

The main strength of the study on AIDs in children with JIA is the large number, over 400, of patients and a long follow-up of 5.5-9.5 years. Moreover, the SII registers cover all children with certain chronic diseases in the country and allow population-based comparisons of the occurrence of DM1, CD and HT in JIA patients. The main limitation of the study was that the JIA patients were selected, i.e. admitted to a tertiary centre due to moderate or severe JIA. In addition, subclinical CD or HT was not actively screened. Since autoimmune diseases associated with JIA may develop later, very long monitoring times until adulthood are needed to find all patients.

The study on AIDs in the JIA patients' relatives was retrospective and the data were collected by questionnaires only. On the other hand, patients in Finland are well aware of their chronic diseases and exact diagnoses, since chronic diseases are registered in the nationwide files of the SII for reimbursement of the drugs and other treatment costs for certain diseases like DM1, MS and CA. The epidemiology of CD has been under active study in Finland, and the prevalence figures are well known. Since the data were collected from the files of the tertiary hospital and with the RFH providing services in child rheumatology for the whole country, the number of our study subjects was high: 362 index cases with JIA in families and 1238 family members.

The study on patients with simultaneous JIA and DM1 was a nationwide, epidemiological study, again based on the SII reimbursement registers. It is most likely that the identified 82 patients represent all or a great majority of eligible patients, and the information even allowed us to establish which disease had started first.

Our study regarding the entire population of incident JIA patients documented the general trends in the drug treatment during 8 consecutive years and covered as many as 1970 patients.

Despite of the large number of study subjects and the modern statistics used, several outcomes were so rare (e.g. 23 patients with JIA and DM1, years 2000-2007) that the analyses were under-powered.

CONCLUSIONS AND CLINICAL RECOMMENDATIONS

1. AIDs tend to accumulate in children with JIA. AIDs also cluster in families with JIA in a child. Therefore, clinicians who treat JIA patients should be aware of the increased risk of other AIDs not only in their patients but also in the patient's family members.
2. The number of patients with simultaneous JIA and DM1 has increased in Finland, in line with the increase of DM1. Patients with multiple AIDs need multi-professional care and substantial support. Psychological support especially, is necessary not only for the patients but also for the parents. In addition, JIA may be more severe in children with DM1.
3. When we evaluated JIA patients' drug treatment nationwide, several major changes were identified between years 2000-2007. However, a long follow-up until adulthood is needed to see how much the patients will benefit from an early introduction of DMARDs and a combination therapy.
4. If a JIA patient already had DM1, he/she needs a more aggressive drug treatment – partly in order to avoid corticosteroids.

The treatment of JIA patients has undergone major changes during the last decades. It has become more challenging and the demands for the treatment keep on growing. Patients' problems are not just medical. Patients need ample high-quality treatment and support to cope with the numerous of problems they have to face.

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Autoimmune diseases in children with juvenile idiopathic arthritis

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Juvenile idiopathic arthritis (JIA) is an autoimmune (AI) disease with a genetic background. Studies on comorbidity of JIA and other AI diseases are scarce. In the USA, the prevalence of diabetes mellitus (DM1) was reported to be 6-fold in 443 children with JIA (1). Studies on clinical coeliac disease (CD) or hypothyroidism (HT) are not available, but an Italian study on subclinical CD in screened JIA patients reported a 7- to 10-fold (2, 3) prevalence, and a 3.7-fold prevalence for subclinical HT (2).

We evaluated retrospectively the occurrence of the common AI diseases DM1, CD, and HT as diagnosed by clinical criteria, in children with JIA, and compared their occurrence with that in the general population. The results are expressed as prevalence rate ratios (PRRs) and 95% confidence intervals (CIs).

In Finland, the incidence of DM1 was 42/100000 children aged < 15 years in 1996, and the incidence is still increasing (4, 5). DM1 is more common in Finland than in any other country (5). The prevalence of CD was 1% in Finnish schoolchildren (6). No prevalence studies are available on AI thyroiditis; the incidence has shown variation between 3 and 12/1000 children (7, 8), leading to HT in about 70% of the cases (8).

For the present study, we recruited 417 children aged < 16 years (283 girls, 135 boys), who were consecutively admitted to the Rheumatism Foundation Hospital (RFH) between 1 January 1996 and 30 September 2001, with a diagnosis of JIA by the Edmonton criteria. Clinical data (age at JIA diagnosis, course type of JIA, and presence of uveitis) were collected from the hospital registers. The follow-up lasted either until the patients' 16th birthday (191 patients) or until 31 January 2006 (226 patients).

The prevalence of DM1, CD, and HT in the age-matched population was calculated from official registers: the whole-population data were retrieved from the Official Statistics of Finland and the number of children with DM1, CD, and HT at < 16 years (at the end of 2003, 2004, 2005, and 2006, respectively) from the registers of the National Social Insurance Institute.

Nine JIA patients had DM1 [2.2% (95% CI 1.0–4.1)] and PRR for DM1 was 5.0 (95% CI 2.3–9.5). DM1 preceded JIA in 7/9 cases. Three patients had

biopsy-proven symptomatic CD [0.7% (0.1–2.1)]. PRR for CD was 5.6 (95% CI 1.2–16.5). CD was diagnosed before JIA in 1/3 cases. Three patients had HT [0.7% (0.1–2.1)] and were on thyroxine substitution. PRR for HT was 5.6 (95% CI 1.2–16.5). HT preceded JIA in 2/3 cases (Table 1).

To conclude, we found that 13/417 [3.1% (95% CI 1.7–5.3)] children with JIA had at least one additional AI disease, such as DM1, CD, or HT, the risk being about 5-fold compared to that in the general population. Two patients had two additional AI diseases.

All patients who developed DM1, CD, or HT while already treated for JIA were on methotrexate and were given occasional intra-articular glucocorticoid injections.

The 2.2% prevalence of DM1 means a 2-fold risk compared with the population, which is lower than the 6-fold figure in the USA (1). Among screened Italian and Israeli JIA children, 9.3% and 12%, respectively, were identified with subclinical HT, which is 13 to 17 times our 0.7% clinical HT cases (2, 9). As regards these comparisons, it should be pointed out that the RFH is a tertiary centre for children with chronic arthritis, especially those with more severe disease. Furthermore, our patients were classified according to the course type of JIA while others mainly use the onset type.

An untreated AI disease, such as CD, which often remains non-symptomatic for years, may predispose the patient to another AI disease (3). However, a gluten-free diet may reduce joint symptoms in patients with CD (10). Our CD diagnoses were based on histological findings in symptomatic patients, thus representing an end-stage AI process. Therefore, perhaps a gluten-free diet, although carefully followed, had no effect on arthritis.

The fact that only one patient (7.7%) with an additional AI disease had uveitis as compared with 90 (22%) without suggests that the predisposing factors to AI disorders and uveitis are different. As AI diseases often develop in adulthood, our figures probably underestimate the real frequency of AI diseases in JIA patients.

This study was approved by the Ethical Committee of Päijät-Häme Hospital District.

Table 1. Distribution of autoimmune diseases between the different course types of 417 patients with juvenile idiopathic arthritis.

Variable	All	Autoimmune disease		
		Diabetes mellitus	Coeliac disease	Hypothyreosis
Number	417	9	3	3
Age at diagnosis (years), mean (range)	7 (1–15)	6.9 (0.8–10.8)	6.6 (1.8–10.8)	7.9 (5–9.9)
Diagnosis (course type), n (%)				
Oligoarthritis	92 (22)	4	0	0
Extended oligoarthritis	150 (36)	2	0	1
Polyarthritis, seronegative	137 (33)	2	3	2
Polyarthritis, seropositive	18 (4)	1	0	0
Systemic arthritis	11 (2.5)	0	0	0
Psoriatic arthritis	7 (2)	0	0	0
Enthesitis-related arthritis	2 (0.5)	0	0	0
Uveitis present at any time during the follow-up, n (%)	91 (22)			

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Rheumatoid arthritis (RA) remains a threat to work productivity: a nationwide register-based incidence study from Finland

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Some reports suggest that the incidence of rheumatoid arthritis (RA) is declining and that people contract RA at an older age than before (1–3). We wanted to explore whether these trends are present during the new millennium.

For case identification we used the registry of the Social Insurance Institution (SII). In Finland, all permanent

residents are covered under the National Health Insurance since 1973, and patients with certain chronic and severe diseases, including chronic inflammatory rheumatic disorders such as RA, are entitled to special reimbursement of medications.

Regarding RA, a patient must file a medical certificate based on an examination performed in a rheumatology

REGULAR ARTICLE

Diabetes, coeliac disease, multiple sclerosis and chronic arthritis in first-degree relatives of patients with juvenile idiopathic arthritis

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Keywords

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ABSTRACT

Aim: To evaluate the occurrence of autoimmune diseases in first-degree relatives of children with juvenile idiopathic arthritis (JIA) and to compare the figures with published population data.

Materials and methods: Families of the 362 children with recently diagnosed JIA admitted to Rheumatism Foundation Hospital, Finland, from 1996 to 2001 were contacted by questionnaires regarding autoimmune diseases in family members. Data were collected on type 1 diabetes, coeliac disease, multiple sclerosis and chronic arthritis, consisting mainly of JIA, rheumatoid arthritis, spondyloarthropathy or psoriatic arthritis.

Results: In all, 21.4% of the 355 families with a patient with JIA had members with type 1 diabetes, coeliac disease, multiple sclerosis or chronic arthritis. Thirty-three mothers and 23 fathers had type 1 diabetes, coeliac disease, multiple sclerosis or chronic arthritis in 15.2% (95% CI 11.6–19.4) of the families, and 23 mothers and 15 fathers had chronic arthritis in 10.7% (95% CI 7.7–14.5) of the families. When compared with available research data, the prevalences of rheumatoid arthritis, spondyloarthropathy, psoriatic arthritis, paediatric type 1 diabetes and JIA (in siblings) were increased in JIA families. Coeliac disease was as prevalent as in the population.

Conclusion: Autoimmune diseases cluster in families with a child with JIA.

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is considered as an autoimmune disease, with the exception of systemic subtype, which is currently considered as an autoinflammatory disease. Autoimmune diseases seem to cluster in children with JIA (1,2), and shared susceptibility genes have been identified during the recent years (3). In fact, observations that chronic arthritis clusters in families of patients with JIA have been published since the 1950s (4–7). In addition, JIA has a tendency to cluster in families (5–7); in a recent study, familial factors had a 13% attributable risk for JIA (7).

In the Netherlands, the prevalence of spondyloarthropathy was 40/1000 in parents of children with JIA, compared with the population prevalence of 2.5/1000 (8). In Taiwan, the prevalence of autoimmune diseases was 45/1000 in families of patients with JIA, but the population prevalence was not reported (9). Two previous, controlled studies from the United States in 2002 and 2004 documented clustering of autoimmune diseases in families with JIA in children (2,6). The prevalence of autoimmune diseases was 161/1000 in first-degree relatives (2), when the population prevalence was estimated to be 50/1000 (10). In the case-

control setting, autoimmune diseases were more common in JIA families than in control families, but the difference was significant only for chronic arthritis and thyroiditis (2). The relatives of patients with JIA had an increased risk for JIA (5). The prevalence of type 1 diabetes among patients with JIA was sixfold compared with the population prevalence (6).

Key notes

- In a nationwide study, 21.4% of families with JIA patients had members with type 1 diabetes, coeliac disease, multiple sclerosis or chronic arthritis.
- The prevalences of rheumatoid arthritis, spondyloarthropathy and psoriatic arthritis were, but the prevalence of coeliac disease was not, higher than in the population.
- The prevalence of type 1 diabetes in children was 4.2-fold compared with recent child population data from Finland.

The aim of this article is to evaluate the clustering of autoimmune diseases in families of children with JIA. The occurrences of type 1 diabetes, coeliac disease, multiple sclerosis and chronic arthritis in first-degree relatives are compared with other studies.

MATERIAL AND METHODS

Rheumatism Foundation Hospital in Heinola, Finland, was until 2010 a tertiary centre for juvenile patients with chronic arthritis, especially for the more serious cases. Rheumatism Foundation Hospital provided diagnostic, therapeutic and rehabilitation services in paediatric rheumatology nationwide. The families of all new patients with JIA admitted in 1996–2001 were retrospectively identified from the hospital registers. All diagnoses were revised according to the ILAR Edmonton 2004 criteria (11), using the available information registered in patient records.

In winter 2003–2004, a questionnaire was sent by post to the identified 432 patients. In case they did not reply, a new questionnaire was sent within a year. Finally, 46 patients did not respond, 15 letters were returned owing to an unknown address, and nine patients were excluded because required information was incomplete (e.g. adoption, paternal information unavailable). Complete data were obtained from the parents and siblings of 362 (84%) patients with JIA, and they belonged to 355 families. The number of siblings was 528, and thus the total number of children was 890. There were 710 parents, and the number of family members (index JIA cases excluded) was 1238.

The questions concerned the diagnoses of chronic arthritis, coeliac disease, type 1 diabetes and multiple sclerosis in family members (first-degree relatives) of the index JIA patients. The families were asked whether patients or their first-degree relatives (mothers, fathers or full siblings) were entitled to special reimbursement for diabetes or arthritis treatment from Social Insurance Institute, and if entitled, which was the exact diagnosis. The duration of arthritis was not enquired about, but Social Insurance Institute grants reimbursement only for chronic diseases. The diagnoses (recorded according to the ICD-10 classification) were collected and had to be made by a physician.

Statistics

Statistical comparison between groups was made by *t*-test or chi-square test, when appropriate. The prevalence were expressed with 95% confidence intervals (95% CI).

Ethics

The study was approved by the Ethics Committee of Päijät-Häme District Central Hospital.

RESULTS

Description of the families and index cases

The 355 families included 24 (5.8%) multiple-JIA families; 6 JIA cases in siblings were diagnosed during the study period in Rheumatism Foundation Hospital and 18 elsewhere or

outside the study period in Rheumatism Foundation Hospital. The mean age of mothers was 45 years (range 28–66) and that of fathers 47 years (31–74). The mean child count per family was 2.6 (range 1–18), with the index JIA patients included.

Of the 362 index JIA patients, 241 (66.6%) were girls and 121 (33.4%) boys, and 331 belonged to single-JIA and 31 to multiple-JIA (24) families. At the end of the study, the mean age of girls was 15.5 years (range 7–27) and that of boys 15.7 years (range 7–26). The course types of JIA in the index patients are given in Table 1.

Autoimmune diseases in the families and family members

Type 1 diabetes, coeliac disease, multiple sclerosis or chronic arthritis were present in 76 families [21.4% (95% CI 17.3–26.0)], with no significant difference between multiple-JIA and single-JIA families (Data not shown). Thirty-three mothers [9.3% (95% CI 6.5–12.8)] and 23 fathers [6.5% (95% CI 4.2–9.6)] had type 1 diabetes, coeliac disease, multiple sclerosis or chronic arthritis (Table 2). As both parents had autoimmune diseases in no case, there were 56 families [15.8% (95% CI 12.1–20.0)] with autoimmune disease in the father or mother (Table 2).

Chronic arthritis formed 62.5% of the autoimmune diseases in fathers and 71.9% in mothers (Table 2). Fathers and mothers did not differ for the different types of chronic arthritis, but JIA was the only chronic arthritis diagnosis in siblings (Table 3). JIA in at least one sibling was present in 6.8% of the families.

Autoimmune diseases were present in 2.7% (95% CI 1.8–3.7) of the 1238 family members of the children with JIA when chronic arthritis was not included, and in 7.0% (95% CI 5.6–8.5) when chronic arthritis was included (Table 2).

Results that are not shown

The numbers of autoimmune diseases of patients were too small for statistical tests by the course types of JIA in the index patients and in relation to the presence of autoimmune diseases or a specific autoimmune disease in the family.

When the data on age, sex and course type of JIA were compared between the 70 eligible families who did not

Table 1 Course type* of juvenile idiopathic arthritis (JIA) in 362 index patients

Course types	Girls (N = 241) n (%)	Boys (N = 121) n (%)	All (N = 362) n (%)
Oligoarthritis, persistent	47 (19.5)	32 (26.5)	79 (21.8)
Oligoarthritis, extended	84 (34.8)	42 (34.7)	126 (34.8)
Polyarthritis seronegative	88 (36.5)	33 (27.3)	121 (33.4)
Polyarthritis seropositive	15 (6.2)	2 (1.6)	17 (4.7)
Systemic onset JIA	4 (1.7)	4 (3.3)	8 (2.2)
Juvenile psoriatic arthritis	1 (0.4)	4 (3.3)	5 (1.4)
Enthesitis-related arthritis	1 (0.4)	4 (3.3)	5 (1.4)
Undefined arthritis	1 (0.4)	0 (0)	1 (0.3)

*The International League Against Rheumatism (ILAR) Edmonton 2004 criteria.

Table 2 Autoimmune diseases in families of index juvenile idiopathic arthritis (JIA) patients

Autoimmune disease diagnosis	Fathers (N = 355) n (%)	Mothers (N = 355) n (%)	Siblings (N = 528) n (%)	Family members* (N = 1238) n (%)	Index JIA patients (N = 362) n (%)
Type 1 diabetes	3 (0.8)	2 (0.6)	6 (1.1)	11 (0.9)	8 (2.2)
Coeliac disease	4 (1.1)	6 (1.7)	7 (1.3)	17 (1.4)	3 (0.8)
Multiple sclerosis	2 (0.6)	3 (0.8)	0 (0)	5 (0.5)	0 (0)
Total (chronic arthritis excluded)	9 (2.5)	11 (3.1)	13 (2.5)	33 (2.7)	11 (3.0)
Chronic arthritis	15 (4.2)	23 (7.0)	18 (3.0)	56 (4.5)	–
Total (chronic arthritis included)	23 (6.5)	32 (9.7)	31 (5.9)	86 (7.0)	–

There were two autoimmune diseases in two mothers (coeliac disease + chronic arthritis, type 1 diabetes + multiple sclerosis), in one father (coeliac disease + chronic arthritis) and in two siblings (type 1 diabetes + coeliac disease in both). There were two index JIA patients in one family.

*Index JIA patients not included.

Table 3 Chronic arthritis by specific diagnoses in family members of index juvenile idiopathic arthritis (JIA) patients

Diagnosis	Fathers (N = 355) n (%)	Mothers (N = 355) n (%)	Siblings (N = 528) n (%)	Family members (N = 1238) n (%)
Rheumatoid arthritis	6 (1.7)	10 (2.8)	0 (0)	16 (1.3)
Spondylarthropathy	4 (1.1)	2 (0.6)	0 (0)	6 (0.5)
Psoriatic arthritis	2 (0.6)	2 (0.6)	0 (0)	4 (0.3)
JIA	2 (0.6)	4 (1.1)	18 (3.4)	24 (1.9)
Reactive arthritis	1 (0.3)	4 (1.1)	0 (0)	5 (0.4)
Others*	0 (0)	1 (0.3)	0 (0)	1 (0.1)

*Arthritis with non-specified collagenosis.

Prevalences of autoimmune diseases – a comparison with literature

The prevalence of autoimmune diseases in this study and in the other studies available is given in Table 4. In this study, the parental prevalence of rheumatoid arthritis was 22.5/1000, that of spondyloarthropathy 8.5/1000, that of psoriatic arthritis 5.6/1000 and that of multiple sclerosis 3.1/1000. In children, the JIA prevalence was 34.1/1000 (only siblings included) and the type 1 diabetes prevalence was 15.7/1000. Except multiple sclerosis, the prevalences of this study exceeded the published population figures (Table 4). The prevalence of coeliac disease has been well studied both in Finland and elsewhere, and our figures were quite similar to the published prevalence (Table 4).

attend the study and the 355 families who attended, no statistically significant differences were found (Data not shown).

DISCUSSION

There are three main results in the present retrospective study on the prevalence of autoimmune diseases in 355

Table 4 Prevalence (per 1000) of autoimmune diseases in the present and other available studies

Disease	Present study prevalence (95% confidence interval) in first-degree relatives	Prevalence (year; reference) in the population Finland	Prevalence (country, year; reference) in the population Other countries
Chronic arthritis (parents)	45.2 (34.3–58.3)	NA	NA
Rheumatoid arthritis (parents)	22.5 (12.9–36.3)	8.0 (1993; ref. 13)	6.6 (Sweden, 2010; ref. 27)
Spondylarthropathy (parents)	8.5 (3.1–18.3)	1.5 (1997; ref. 14)	2.1 (Norway, 2005; ref. 28)
Psoriatic arthritis (parents)	5.6 (1.5–14)	NA	1.3 (Norway, 2009; ref. 15)
JIA (parents)	8.5 (3.1–18.3)	NA	NA
JIA (children*)	34.1 (20.3–53.3)	0.8 (1985; ref. 16) [†]	0.9 (Sweden, 1988; ref. 17) [‡] 1.5 (Norway, 1994; ref. 17) [‡] 1.2 (USA, 2010; ref. 17) [‡]
Type 1 diabetes (parents)	7.0 (2.3–16.4)	NA	NA
Type 1 diabetes (children [§])	15.7 (8.6–26.3)	3.7 (2011; ref. 20)	1.9 (USA, 1996; ref. 10)
Coeliac disease (parents)	14.1 (6.8–25.7)	19.9 (2001; ref. 22)	9.5 (USA, 2003; ref. 29) 4.8 (Sweden, 2001; ref. 30)
Coeliac disease (children [§])	11.2 (5.4–20.6)	10.0 (2001; ref. 23)	3.1 (USA, 2003; ref. 29) 1.3 (Sweden, 2001; ref. 24)
Multiple sclerosis (parents)	3.1 (1.0–7.3)	1.0 (1993; ref. 25)	1.5 (UK, 2005; ref. 26)

NA, not available.

*528 siblings included.

[†]ARA criteria.

[‡] European League Against Rheumatism criteria.

[§]528 siblings and 362 index juvenile idiopathic arthritis (JIA) children combined.

families with JIA in a child. First, as many as 21.4% of the JIA families had at least one member with type 1 diabetes, coeliac disease, multiple sclerosis or chronic arthritis. This figure is high when compared with the 4.5% occurrence of autoimmune diseases in JIA families Taiwan (9) but not far from the 16.1% occurrence in JIA families in the United States (2). We did not collect data on thyroiditis, which has been a major autoimmune disease in many previous JIA studies with 5.5–11.2% prevalence in family members (1,2,9,12). Second, when compared with previously published population data, the prevalence of rheumatoid arthritis, spondyloarthropathy and psoriatic arthritis in parents, and the prevalence of JIA and of type 1 diabetes in children, was increased. And third, there were no significant differences in the occurrence or distribution of autoimmune diseases between the single-JIA and multiple-JIA families, which disagreed with the previous US study (2).

Chronic arthritis formed two-thirds of autoimmune diseases in parents. In them, the 9.7% occurrence in single-JIA and 25% occurrence in multiple-JIA families are in line with the previously found 18% occurrence in Finnish multiple-JIA families (5). In the present study, rheumatoid arthritis was the most common specific diagnosis, especially in mothers. The 22.5/1000 prevalence of rheumatoid arthritis was 3.5-fold (13) and the 8.5/1000 prevalence of spondyloarthropathy was 6.7-fold compared with national population data (14). Surprisingly, the parents with spondyloarthropathy had no sons with juvenile spondylarthropathy, and three of the four index JIA patients with a parent with spondylarthropathy were girls. The prevalence of psoriatic arthritis in Finnish adult population is not known; in our study, the 5.6/1000 prevalence was 4.6-fold compared with the prevalence in Norway (15).

The prevalence of JIA was 0.8/1000 in Northern Finland by American Rheumatism Association (ARA) criteria in 1985 (16). The 34.1/1000 prevalence of JIA in siblings in the present study was 42.6-fold, but the true difference must be lower because ARA criteria excluded spondylarthropathy. In addition, the study population was less selected than the subjects of the present study collected from the specialized tertiary hospital. The prevalence in the present study was 22.7- to 28.4-fold when compared with the figures by European League Against Rheumatism (EULAR) criteria from the United States, Sweden and Norway (17). The JIA prevalence in parents was 8.5/1000, but no population data are available for JIA in adults.

In a recent study from Finland, autoimmune diseases clustered in children with type 1 diabetes and also in their first-degree relatives (18). In that study, the overall prevalence of autoimmune diseases was 22.0% in the families with a child with type 1 diabetes. Although the incidence of type 1 diabetes in Finland is highest in the world (19), the exact prevalence figures are not known. In a very recent study, the prevalence was 3.7/1000 in Finnish children at Helsinki region (20). An old, more than 10 years ago published estimate from the United States was 1.9/1000 (10). Compared with these Finnish and American figures, the prevalence of paediatric type 1 diabetes in the present study

was 4.2- to 8.3-fold when both siblings and children with JIA were included. Compared with the Finnish population data alone (20), the prevalence was about threefold in siblings and about sixfold in the children with JIA.

In an earlier study, the prevalence of JIA was increased in the first-degree relatives of patients with coeliac disease (21). Contrary to expectations, the prevalence of coeliac disease in the present study did not substantially exceed the 20/1000 prevalence in Finnish adults (22) or the 10/1000 prevalence in Finnish children (23). Unlike in population studies, the present study subjects were not screened; the diagnoses were carried out on clinical grounds only. In Sweden, the prevalence of coeliac disease was 7/1000 among 3004 non-screened children (24), and using this figure as a reference, the prevalence of coeliac disease in JIA families was 1.9-fold in the present study.

The estimated multiple sclerosis prevalence in Finland is 1.0/1000, with pronounced regional variations (25). In the UK, the respective figure was 1.5 (26) and considered to be higher than in most other countries. In the United States, the prevalence of multiple sclerosis was 4/1000 among first- and second-degree relatives of patients with JIA (2). In the present study, the prevalence of MS in the first-degree relatives was 3.1/1000 when adults and children were combined, which seems to be higher than in the Finnish population (25).

In the present study, mothers were affected 1.4-fold more often than fathers, as expected owing to the higher prevalence of autoimmune diseases in women (10). In the United States, the difference was larger, threefold, obviously because of the high frequency of thyroiditis (12).

The study data were collected by questionnaires only. The patients in Finland are well aware of their chronic diseases and exact diagnoses, because chronic diseases are registered in nationwide files of the Social Insurance Institute for imbursement of the drugs and other treatment costs for certain diseases like type 1 diabetes, multiple sclerosis and chronic arthritis. The epidemiology of coeliac disease has been under active investigation in Finland, and the prevalence figures are well known. As the study subjects were identified from the files of a tertiary hospital specialized for rheumatic diseases and providing services for the whole country, the number of study subjects was high: 362 index cases with JIA and 1238 family members. On the other hand, the study was not population-based, and obviously, serious cases were overrepresented, as was seen, for example, in the high number of extended oligoarthritis cases. Only 2% had systemic onset JIA, which may rather be considered as an autoinflammatory than autoimmune disease. In line, no autoimmune co-diseases were found in the family members of systemic onset patients with JIA.

In conclusion, autoimmune diseases cluster in families with JIA in a child. This conclusion is justified, although the present prevalence figures were compared with figures from other studies with varying ways of data collection and prevalence estimation. Despite of obvious clustering, autoimmune diseases are so rare that prospective population-based well-matched studies are extremely laborious,

expensive and time-consuming. When treating patients with JIA, vigilance for further autoimmune diseases is warranted not only for the patients but also for their family members.

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CONFLICTS OF INTEREST

None of the author has any conflicts of interests regarding this study.

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Simultaneous Juvenile Idiopathic Arthritis and Diabetes Mellitus type 1 - a Nationwide Study.

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Abstract

Objective: To describe the occurrence and main clinical and laboratory findings of patients having both Juvenile Idiopathic Arthritis (JIA) and Diabetes Mellitus type 1 (DM1) in a period of thirty years.

Materials and methods: Eighty-two patients having simultaneous JIA and DM1 were identified in the reimbursement registers of National Institute of Insurance during 1976-2005. Data on their clinical history were collected from patient files.

Results: Occurrence of simultaneous JIA and DM1 increased 4,5fold between the first

(1976-85) and the last (1996-2005) decade. Prevalence of uveitis was 7%, of RF-seropositivity 15%; 22% of patients had a third autoimmune disease (AID), 16% had serious psychiatric problems.

Conclusion: The occurrence of patients with the two diseases, JIA and DM1, increased in three decades. The prevalence of uveitis was low, the number of seropositive patients was high and further AIDs were frequent. Patients had multiple additional problems and necessitated multiprofessional care.

Key words: Juvenile idiopathic arthritis, diabetes mellitus type 1, autoimmunity, uveitis, psychiatric problems

Introduction

Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease in children, and the incidence in Finnish children is rather similar to other western populations (1). Instead, the incidence of diabetes mellitus type 1 (DM1) in Finland is the highest in the world, and still increasing (2). Different autoimmune (AI) diseases seem to cluster in the same children (3).

The few reports on patients having both JIA and DM1 are mostly case reports (4,5,6,7). The first pediatric patient with arthritis and diabetes we were able to find was a seven-year-old girl reported in 1968 (4). Thereafter, ten patients with JIA and DM1 have been reported, nine of whom also had thyroiditis (5,6,7,8).

Rudolf et al. in 1986 identified seven patients with JIA among 200 diabetic children. Six of them had polyarthritis with rheumatoid factor (RF) and/or antinuclear antibodies (ANA) and evidence on thyroid problems. The seventh one was a boy with HLA B27 positive oligoarthritis and family history of ankylosing spondylitis (8).

When 66 Italian JIA patients were screened for pre-diabetic autoantibodies only 3% showed any positivity at all, and no clinical evidence for DM1 could be verified (9).

We identified from national registers all patients with both JIA and DM1 covering a period of 30 years (1976 to 2005), and a population of about five million. In Finland according to an established practice certain chronic diseases in children, like DM1 and JIA, are all taken care of at the secondary level (central hospitals).

The aim of the present paper is to describe the occurrence and the main clinical and laboratory findings in the patients with both DM1 and JIA, during the 30 years.

Material and methods

The Social Insurance Institution (SII) in Finland maintains registers on individuals granted with a special reimbursement for medication for defined chronic diseases. From 1966 SII has provided reimbursement for the prescription of drugs for chronic rheumatic diseases including JIA, and from 1975 for DM. In 1994, non-steroidal anti-inflammatory drugs (NSAIDs) were excluded from the reimbursed drugs for chronic arthritis. Injectable drugs e.g. intra articular glucocorticoids are not reimbursed for and so not registered, since they are administered in inpatient and outpatient clinics and paid by them. Biologic agents are applied for with specific certificates, which we did not check.

We analyzed patients identified in the SII register on the basis of reimbursement for medication both for chronic arthritis and DM granted for the first time between January 1st, 1976 and December 31st, 2005. The register files of the SII provide basic data like birth date, gender and residential area of the patients and date of the reimbursement decision.

During the 30-year surveillance period, in all 240 patients were reimbursed for both chronic arthritis and DM. We excluded 112 patients who were reimbursed for arthritis at >21 years and for DM <30 years of age. The age limit of 20 for JIA was chosen because of the possibility that reimbursement was applied for with delay, which for DM is unlikely. The files of the remaining 128 patients were further checked to ascertain the diagnoses and the exact age at the onset of the diseases. Twenty had adult onset RA, three had DM secondary to glucocorticoids and five had DM type 2. Thirteen patients had been rediagnosed as something else than JIA. Three potential patients were excluded because their files could not be located.

The remaining 82 patients fulfilling the study criteria were classified according to the ILAR criteria (10). Data on laboratory markers, radiological changes, uveitis, and the use of intra articular and systemic glucocorticoids, were collected by charting the hospital records of the study subjects.

The study patients were divided into two groups based on which disease, JIA or DM1, started first. The activity of JIA was assessed on the basis of inflammatory parameters (sedimentation rate, ESR; C-reactive protein; CRP) at disease onset, the presence of erosions in native radiology and the use of glucocorticoids. The need of systemic glucocorticoids or the need of >6 annual intra articular injections were set as criterions of an active disease.

Patients were considered having serious psychiatric problems, if they were forwarded after regular psychological consultation to psychiatrists and had psychiatric medication (usually anti-depressants), long-term therapy, and/or psychiatric hospital admission.

Ethics. All data were collected from patient files, without contacting the subjects concerned. The study was done by the permission of The Ministry of Social Affairs and Health.

Statistical methods. The data are presented as means with standard deviations (SD), medians with interquartile range (IQR) or counts with percentages. Statistical comparison between the groups was made by permutation test (Monte Carlo p-value), Chi-Square test or Fisher exact test, when appropriate. Estimates of occurrence rate ratios (ORR) were calculated by using Poisson regression models. Gender- and age-matched samples of the general population were obtained from data in the Official Statistics of Finland.

Results

Subclassification of JIA:

All 82 patients having JIA and DM1 (55 girls, 27 boys) were classified according to ILAR criteria. See Table 1.

Occurrence:

Simultaneous JIA and DM1 occurrence during the 30 year period is shown in Figure 1A. Occurrence increased statistically significantly (age and sex adjusted p for linearity <0.001): 4.49fold (95% CI: 2.32 to 8.69) when comparing the first (76-85) and last (96-05) period.

JIA or DM1 first:

Forty-nine patients (35 girls, 14 boys) had DM1 prior to JIA and 33 (20 girls, 13 boys) had JIA prior to DM1 (Figure 1B).

Age of onset:

The mean onset age of JIA of all 82 patients was 8.5 years (SD 5,2) and that of DM1 8,1 years (SD 6,4) (p=0.61). The age at the onset of the diseases stayed rather constant

during the three surveillance decades.

Laboratory findings:

There were no significant differences between ESR and CRP at disease onset between the DM-first and JIA-first groups. ANA were found in 18 (22%) patients, with no difference between the groups. With one exception, RF was positive only in those who presented with DM first (Table 2).

Erosions:

Erosions in native radiographs were present in 21(43%) in the DM-first and in 13(39%) in the JIA-first group ($p=0.75$).

Corticosteroid use

Nine (27%) of the 33 patients with JIA first had been on systemic glucocorticoids at some time and similarly, nine (27%) had received six or more intra articular injections in some year. The respective figures for the 49 children with DM first were 14 (29%) (systemic glucocorticoids) and 26 (53%) (six or more intra articular injections/year). Among DM first- 53% and JIA first-group 27% had six or more intra articular glucocorticoid injections per year ($p=0,021$).

Use of biologic agents

According to patient files 17 of our patients received biologic agents (etanercept was first introduced to 11patients and infliximab to 6 patients); all the 17 had DM1 prior to biologic agent introduction.

Uveitis

Six patients (7%) had chronic uveitis. Five of them had JIA before DM1, four had oligoarthritis (one extended arthritis), and one had seronegative polyarthritis. The patient with seronegative polyarthritis had DM1 before JIA. Five patients with chronic uveitis were ANA negative, only one being ANA positive. A seventh patient, a boy with oligoarthritis (ANA -/HLAB27+), had experienced several bouts of acute uveitis.

Additional autoimmune diseases

Eighteen out of 82 patients (22%) had a third AI disease, which in 12 cases was hypothyreosis; 3/11 were RF-seropositive, all were ANA negative (RF and ANA unknown of the patient who developed psoriatic arthritis). Six had celiac disease.

Psychiatric diseases

Thirteen (16%) patients, three (11%) male, ten (18%) female, had psychiatric disorders demanding regular, longstanding therapy or medication and/or psychiatric hospital

admittance (five depressions, necessitating drug therapy and psychiatric therapy, one psychosis and drug abuse, one alcohol abuse, one had severe compliance problems in his teens, two anorexias and one bulimia with depression, one ADHD and compliance problems).

Discussion

There are five major findings in this study: (1) an increase in the number of patients in the three study decades, (2) high prevalence of seropositivity, (3) low proportion of uveitis, (4) a third AI disease in almost a quarter of patients, (5) serious psychiatric problems in almost 20% of patients.

The increase in occurrence.

The reason for this, in the first hand, must be the increase in DM1 incidence (11). If also the incidence of JIA has risen, remains to be proved. The analysis of Finnish DM1 incidence between 1965-96 showed an absolute average increase of 0,67 (3,4%) per year (12). If there is increase in JIA incidence, its magnitude must be modest, compared to that of DM1. Various studies point to a slight increase in the incidence of JIA in Finland during the last decades (1,13,14,15).

JIA subclassification

The distribution of JIA subtypes corresponds to that seen in JIA in general, with two exceptions: there seems to be more (15%) seropositive and less (1%) systemic cases. Normally, the proportion of seropositive cases is 2,6%, and of systemic disease 4,6%, calculated from earlier studies (1,3,14,15). The studies of Rudolf and Agrawal show a similarly high quantity of patients with seropositive JIA (6,8); the cause remains to be elucidated. Some patients with systemic JIA might be missing, if treated with NSAIDs and systemic glucocorticoids only, because reimbursement for such medication is not applied for (intravenous treatment is paid by institutions and oral glucocorticoid preparations are cheap).

Uveitis

Chronic uveitis was present in six (7%) patients only; five of them had JIA prior to DM1. The low incidence is in line with our previous report, in which 8% of JIA patients with another AI disease had uveitis (3). In previous Finnish studies the percentage has been 21 (13) and 24 (16). Are predisposing factors to uveitis and AI diseases different? Five of the six patients with chronic uveitis did not have ANA, which is against numerous previous studies. In spite of this, a 22% ANA positivity was registered in 80 patients, in line with earlier reports. Mean age stayed constant, in accordance with previous Finnish studies (1,15,17)

Additional autoimmune diseases

A fifth of our study patients had a third AI disease. There are plenty of previous studies on the accumulation of AI diseases in individuals with JIA and in their families (3,18,19,20,21). In disaccordance with Rudolf and Agrawal (6,8) no clear association with ANA or RF-positivity could be shown in our twelve patients with simultaneous JIA, DM1 and hypothyreosis. In six patients the third disease was celiac disease, five of them had DM1 prior; no clear connection to ANA- or RF-positivity could be seen among them either.

Psychiatric problems

As early as in 1974 McAnarney et al. in USA found children with chronic arthritis having more psychological difficulties than their healthy peers (22).

In the latest studies from Western countries, JIA patients seem to have a quite normal psychosocial outcome, as in a study from the UK on 60 polyarthritics aged 7 to 18 (23), and in a Finnish one on 123 21 to 26-olds (24).

In Netherlands 4,7% of 233 DM1-patients, aged 9 to 19, had received psychological care (25).

In a large Finnish birth cohort 12% of boys and 4% of girls born in 1981 had used child mental health services by 2005 (26). In a cohort of 5 346 children born that year 5,2% (6,2% of males and 4,1% of females) had been admitted to psychiatric hospital treatment between 13 and 24 years of age (27).

Reflecting the above results to our patients, the number of serious psychiatric problems was almost threefold, 16%. The problems were considered serious because treatment by a psychologist alone was insufficient and the patients had to be remitted to a psychiatrist. Depression was the most frequent diagnose and could be seen underlying also some other cases. The high number of patients with serious psychiatric problems was unanticipated and emphasizes the follow up of the psychological function of the patients as well as the importance of multiprofessional care.

Glucocorticoid consumption between the two groups

There were only minor differences in glucocorticoid consumption between the groups. To our surprise those 49 patients with DM1 preceding JIA had been on systemic glucocorticoids at some phase of their arthritis as frequently as those 33 who had JIA before DM1 (28% and 27%, respectively), which is against our common JIA treatment protocol. Normally, we try to avoid systemic glucocorticoids in diabetic patients. Could it be that their disease was more serious, even if no further evidence (number of erosions, laboratory parameters) to support such a supposition was found? Among those 49 patients, 53% had more than six intra articular glucocorticoid injections, compared to 27% of patients from JIA prior DM-group ($p=0.021$). The aim might have been to avoid

systemic glucocorticoids in diabetics.

A case report in 2000 describes onset of DM1 5 months after introduction of etanercept therapy in a patient with systemic JIA (28). This could, theoretically, be drug induced. In our study 17 patients received biologic agents (11 etanercept, 6 infliximab); however, all had their DM1 prior to the biologic agent therapy.

Due to accumulating reports it is obvious that, AIDs in general, and these two diseases specifically, must have common genetic features. Becker et al. discovered in 1998 that in some cases clinically distinct AIDs may be controlled by a common set of susceptibility genes (29). After that a number of different single genes have been shown susceptible both for JIA and DM1 (30,31,32,33,34).

This is the first nationwide study on patients having DM1 and JIA simultaneously. Finland is an appropriate country for epidemiological studies, because of the structure of the health care system and the homogeneity of the population. It is unlikely that many patients are missing in the SII register, keeping the costs of the diseases in mind, and equally unlikely that a patient with these diseases would have been treated outside the national health care system, although after 1994 we may have missed a few cases of mild oligoarthritis or systemic disease, treated with NSAIDs and/or glucocorticoids only. Treatment of JIA has become more aggressive during the last decades. There has been increasing use of reimbursable medication, and more patients thereby appearing in the database. However considering the prevailing medication practices in Finland their number must be low. On the other hand salicylates were the only NSAIDs in the 70s and because these are cheap it may be that in some cases reimbursement was not applied for. This could explain the lower numbers in the early years of the register.

Conclusion

The number of patients with simultaneous JIA and DM1 has clearly increased in Finland. Patients with multiple AI diseases need well co-operating multiprofessional care, and support is necessary not only for patients but for parents as well (23). Vigilance for further AI diseases is warranted. Several questions call for further studies: how to best provide psychosocial support? Why do these patients have so much seropositivity? Why so little uveitis?

Competing interests: None

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Table 1.

Subtypes of juvenile idiopathic arthritis (JIA) in 82 patients with both JIA and diabetes mellitus.

JIA	Onset type N (%)	Course type N (%)
Systemic onset arthritis	1 (1.2)	1 (1.2)
Oligoarthritis	45 (55)	33 (40)
Oligoarthritis, extended		11 (13)
Polyarthritis, seropositive	12 (15)	12 (15)
Polyarthritis, seronegative	22 (27)	22 (27)
Enthesitis related arthritis	2 (2)	2 (2)
Psoriatic arthritis	0 (0)	1 (1,2)

Table 2. Laboratory findings at disease onset in two patient groups.

	DM first (N=49)	JIA first (N=33)	p value
ESR, median (IQR)	26 (12, 45)	27 (12, 45)	0.62
CRP, median (IQR)	7 (3, 26)	10 (5, 16)	0.90
ANA+ (%)	11 (22)	7 (21)	0.97
RF+(%)	11(22)	1(3)	0,023

Figure 1A. Simultaneous occurrence of JIA and DM1 during 30 years, in ten year episodes. The year of onset of the second disease as end point. The error bars give 95 per cent confidence intervals.

Figure 1B. Cumulative distribution of difference between onset age of DM and JIA. Gray band shows the 95 per cent confidence intervals.

