Simultaneous Juvenile Idiopathic Arthritis and Diabetes Mellitus Type 1 — A Finnish 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 (DM-1) in a period of 30 years.

Methods. Eighty-two patients having simultaneous JIA and DM-1 were identified in the reimbursement registers of the Finnish National Institute of Insurance during the period 1976-2005. Data on their clinical histories were collected from patient files.

Results. Occurrence of simultaneous JIA and DM-1 increased 4.5-fold between the first (1976-85) and the last (1996-2005) decade. Prevalence of uveitis was 7%, of rheumatoid factor seropositivity 15%; 22% of patients had a third autoimmune disease [autoimmune disease (AID)], and 16% had serious psychiatric problems.

Conclusion. The occurrence of patients with the 2 diseases, JIA and DM-1, increased over 3 decades. The prevalence of uveitis was low, the number of seropositive patients was high, and further cases of AID were frequent. Patients had multiple additional problems necessitating multiprofessional care. (J Rheumatol First Release Dec 15 2011; doi:10.3899/jrheum.110654)

Key Indexing Terms:
JUVENILE IDIOPATHIC ARTHRITIS DIABETES MELLITUS TYPE 1
AUTOIMMUNITY UVEITIS PSYCHIATRIC PROBLEMS

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]. But the incidence of diabetes mellitus type 1 (DM-1) in Finland is the highest in the world, and still increasing[2]. Different autoimmune diseases (AID) seem to cluster in the same children[3].

The few reports on patients having both JIA and DM-1 are mostly case reports[4,5,6,7]. The first pediatric patient with arthritis and diabetes we were able to find was a 7-year-old girl reported in 1968[4]. Thereafter, 10 patients with JIA and DM-1 have been reported, 9 of whom also had thyroiditis[5,6,7,8]. Rudolf, *et al*[8] in 1986 identified 7 patients with JIA among 200 diabetic children. Six of them had polyarthritis with rheumatoid factor (RF) and/or antinuclear antibodies (ANA) and evidence of thyroid problems. The seventh was a boy with HLA-B27-positive oligoarthritis and family history of ankylosing spondylitis. When 66 Italian patients with JIA were screened for prediabetic autoantibodies, only 3% showed any positivity at all, and no clinical evidence for DM-1 could be verified[9].

We identified from Finnish national registers all patients with both JIA and DM-1, covering a period of 30 years (1976 to 2005), within a population of about 5 million. In Finland, according to an established practice, certain chronic diseases in children, such as DM-1 and JIA, are all treated at the secondary level (central hospitals).

Our aim was to describe the occurrence and the main clinical and laboratory findings in the patients with both DM-1 and JIA during those 30 years.

MATERIALS AND METHODS

The Social Insurance Institution (SII) in Finland maintains registers on individuals granted a special reimbursement for medication for defined chronic diseases. From 1966, the SII has provided reimbursement for the prescription of drugs for chronic rheumatic diseases including JIA, and from 1965 for DM. In 1994, nonsteroidal antiinflammatory drugs (NSAID) were excluded from the drugs reimbursed for chronic arthritis. Injectable drugs, e.g., intraarticular glucocorticoids, are not reimbursed for and so are not registered, since they are administered in inpatient and outpatient clinics and are paid for by them. Reimbursement for biological agents is 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 for both chronic arthritis and DM paid for the first time between January 1, 1976, and December 31, 2005. The register files of the SII provide basic data such as birth date, sex, and residential area of the patients and date of the reimbursement decision.

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During the 30-year surveillance period, 240 patients were reimbursed for drugs to treat both chronic arthritis and DM. We excluded 112 patients who were reimbursed for drugs to treat arthritis at age > 21 years and for DM drugs at < 30 years of age. The age limit of 20 years for JIA was chosen because of the possibility that the reimbursement application was delayed, 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, 3 had DM secondary to glucocorticoids, and 5 had DM type 2. Thirteen patients had been rediagnosed with something other 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 International League of Associations for Rheumatology (ILAR) criteria[10]. Data on laboratory markers, radiological changes, uveitis, and the use of intraarticular and systemic glucocorticoids were collected by charting the hospital records of the study subjects.

The study patients were divided into 2 groups based on which disease, JIA or DM-1, started first. The activity of JIA was assessed on the basis of inflammatory measures [erythrocyte sedimentation rate (ESR), C-reactive protein (CRP)] at disease onset, erosions demonstrated by radiology, and the use of glucocorticoids. The need for systemic glucocorticoids or the need for > 6 annual intraarticular injections were set as criteria of active disease.

Patients were considered to have serious psychiatric problems if they were referred to psychiatrists after regular psychological consultation and took psychiatric medication (usually antidepressants), had longterm therapy, and/or were admitted to a psychiatric hospital.

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

Statistical methods. The data are presented as means with 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's exact test, as appropriate. Estimates of occurrence rate ratios were calculated using Poisson regression models. Sex- 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 DM-1 (55 girls, 27 boys) were classified according to ILAR criteria (Table 1).

Occurrence. Simultaneous JIA and DM-1 occurrence during the 30-year period is shown in Figure 1. Occurrence increased statistically significantly [age- and sex-adjusted p for linearity < 0.001; 4.49-fold (95% CI 2.32 to 8.69) increase comparing the first (1976-85) and the last (1996-2005) period].

JIA or DM-1 first. Forty-nine patients (35 girls, 14 boys) had DM-1 prior to JIA and 33 (20 girls, 13 boys) had JIA prior to DM-1 (Figure 2).

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)

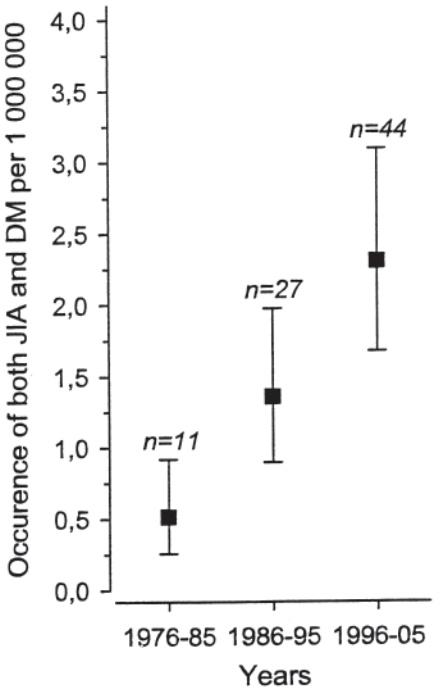

Figure 1. Simultaneous occurrence of juvenile idiopathic arthritis (JIA) and diabetes mellitus type 1 (DM-1) over 30 years, in 10-year episodes. The year of onset of the second disease is the endpoint. Error bars mark the 95% CI.

Age of onset. The mean onset age of JIA of all 82 patients was 8.5 years (SD 5.2) and that of DM-1, 8.1 years (SD 6.4; p = 0.61). The age at the onset of the diseases stayed rather constant during the 3 surveillance decades.

Laboratory findings. There were no significant differences between ESR and CRP at disease onset between the DM-first and the JIA-first groups. ANA were found in 18 patients (22%), with no difference between the groups. With 1 exception, RF was positive only in those who presented with DM first (Table 2).

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

Corticosteroid use. Nine (27%) of the 33 patients with JIA first had been receiving systemic glucocorticoids at some time, and similarly, 9 (27%) had received 6 or more intraarticular injections in some year. The respective numbers for the 49 children with DM first were 14 (29%; systemic glucocorticoids) and 26 (53%; ≥ 6 intraarticular injections/year).

In the DM-first group, 53% had ≥ 6 intraarticular glucocorticoid injections per year, and in the JIA-first group, 27% (p = 0.021).

Use of biological agents. According to patient files, 17 of our patients received biological agents (etanercept was first introduced to 11 patients and infliximab to 6 patients); all of the 17 had DM-1 prior to introduction of a biological agent.

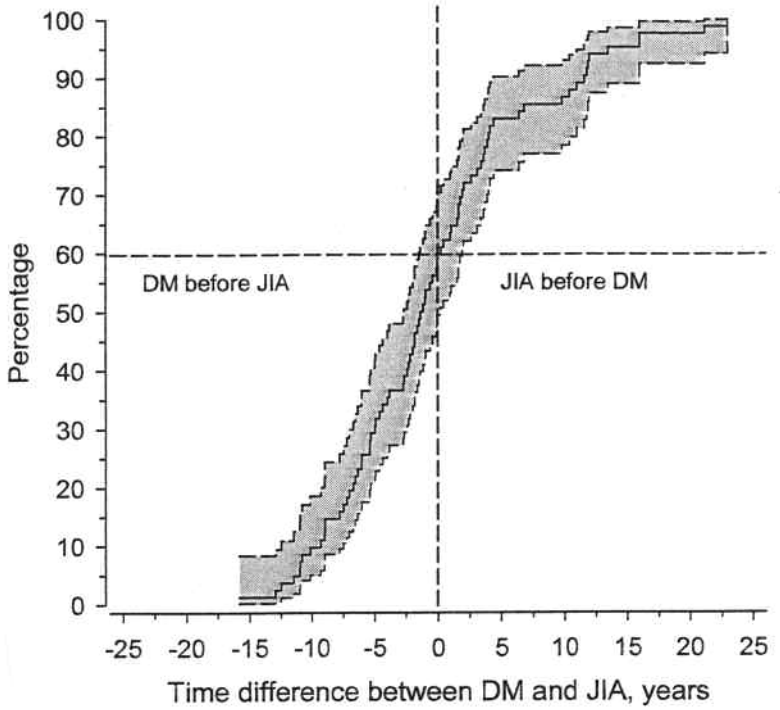

Figure 2. Cumulative distribution of difference between onset age of diabetes mellitus (DM) and that of juvenile idiopathic arthritis (JIA). Gray band shows the 95% CI.

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

Measure	DM First, n = 49	JIA First, n = 33	p
ESR, median (IQR)	26 (12, 45)	27 (12, 45)	0.62
CRP, median (IQR)	7 (3, 26)	10 (5, 16)	0.90
ANA+, n (%)	11 (22)	7 (21)	0.97
RF+, n (%)	11 (22)	1 (3)	0.023

DM: diabetes mellitus; JIA: juvenile idiopathic arthritis; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; IQR: interquartile range; ANA: antinuclear antibodies; RF: rheumatoid factor.

Uveitis. Six patients (7%) had chronic uveitis. Five of them had JIA before DM-1, 4 had oligoarthritis (1 extended arthritis), and 1 had seronegative polyarthritis. The patient with seronegative polyarthritis had DM-1 before JIA. Five patients with chronic uveitis were ANA-negative, only 1 being ANA-positive. A seventh patient, a boy with oligoarthritis (ANA–/HLA-B27+), had several occurrences of acute uveitis.

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

Psychiatric diseases. Thirteen patients [16%; 10 female (18%) and 3 male (11%)] had psychiatric disorders demanding regular, longstanding therapy or medication and/or admittance to psychiatric hospital (6 depressions necessitating drug therapy and psychiatric therapy, 1 psychosis and drug abuse, 1 alcohol abuse, 1 severe compliance problems as a teenager, 2 cases of anorexia and 1 of bulimia with depression, 1 case of attention deficit hyperactivity disorder and compliance problems).

DISCUSSION

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

Increase in occurrence. The reason for the increase in occurrence must be the increase in incidence of DM-1[11]. It remains to be proved whether the incidence of JIA also has risen. The analysis of incidence of Finnish DM-1 between 1965 and 1996 showed an absolute average increase of 0.67 (3.4%) per year[12]. If there is an increase in incidence of JIA, its magnitude must be modest, compared to that of DM-1. 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 2 exceptions: there seems to be more (15%) seropositivity and fewer (1%) sys-

temic 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 Agrawal and Rudolf show a similarly high quantity of patients with seropositive JIA[6,8]; the cause remains to be elucidated. Data for some patients with systemic JIA might be missing, if they were treated with NSAID and systemic glucocorticoids only, because reimbursement for such medication was not applied for (intravenous treatment is paid for by institutions, and oral glucocorticoid preparations are inexpensive).

Uveitis. Chronic uveitis was present in 6 patients (7%) only; 5 of them had JIA prior to DM-1. 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 factors predisposing to uveitis and AI diseases different? Five of the 6 patients with chronic uveitis did not have ANA, which contrasts with numerous previous studies. In spite of this, a 22% ANA positivity was registered in 80 patients, in agreement with earlier reports. Mean age stayed constant, in accord 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 contrast with data from Agrawal, *et al*[6] and Rudolf, *et al*[8], no clear association with ANA or RF positivity could be shown in our 12 patients with simultaneous JIA, DM-1, and hypothyroidism. In 6 patients the third disease was celiac disease, and 5 of them had DM-1 previously; no clear connection to ANA positivity or RF positivity could be seen among them either.

Psychiatric problems. As early as 1974, McAnarney, *et al* found children with chronic arthritis having more psychological difficulties than their healthy peers[22]. In the latest studies from Western countries, patients with JIA seemed to have a quite normal psychosocial outcome, as in a study from the United Kingdom of 60 children aged 7 to 18 years with polyarthritis[23], and in a Finnish study of 123 patients 21 to 26 years old[24].

In the Netherlands 4.7% of 233 patients with DM-1, aged 9 to 19 years, 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 5346 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].

By comparison, the number of serious psychiatric problems in our patients was almost 3-fold (16%) greater. The problems were considered serious because treatment by a psychologist alone was insufficient and the patients had to be referred to a psychiatrist. Depression was the most frequent diagnosis and could be seen underlying some other cases. The high number of patients with serious psychiatric problems was unanticipated and emphasizes the importance of followup of the psychological function of the patients as well as the importance of multiprofessional care.

Glucocorticoid use. There were only minor differences in glucocorticoid consumption between the groups. Surprisingly, those 49 patients with DM-1 preceding JIA had been taking systemic glucocorticoids at some phase of their arthritis as frequently as those 33 who had JIA before DM-1 (28% and 27%, respectively), which is against our common JIA treatment protocol. Normally, we try to avoid use of systemic glucocorticoids in diabetic patients. It is possible that their disease was more serious, even if no further evidence (number of erosions, laboratory measures) to support this was found. Among those 49 patients, 53% had > 6 intraarticular glucocorticoid injections, compared to 27% of patients from the group that had JIA prior to DM ($p = 0.021$). The treatment aim might have been to avoid systemic glucocorticoids in diabetic patients.

A case report in 2000 describes the onset of DM-1 five 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 biological agents (11 etanercept, 6 infliximab); however, all had their DM-1 prior to the start of biological agent therapy.

According to accumulating reports, it is obvious that AID in general and these 2 diseases specifically must have common genetic features. Becker, *et al* discovered in 1998 that in some cases clinically distinct AID may be controlled by a common set of susceptibility genes[29]. After that, a number of different single genes have shown susceptibility for both JIA and DM-1[30,31,32,33,34].

This is the first nationwide Finnish study of patients having DM-1 and JIA simultaneously. Finland is an appropriate country for epidemiological studies because of the structure of the healthcare 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 healthcare system, although after 1994 we may have missed a few cases of mild oligoarthritis or systemic disease, treated with NSAID 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 appear in the database. However, considering the prevailing medication practices in Finland, their number must be low. On the other hand, salicylates were the only NSAID in the 1970s and because these are inexpensive, 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.

The number of patients with simultaneous JIA and DM-1 has clearly increased in Finland. Patients with multiple AI diseases need well-coordinated multiprofessional care, and support is necessary not only for patients but for parents as well[23]. Vigilance for further AI diseases is warranted. Several ques-

tions call for further studies, such as how to best provide psychosocial support, the reason these patients have so much seropositivity, and the reason for so little uveitis.

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