The mortality rate and causes of death among juvenile idiopathic arthritis patients in Finland

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Abstract

Objective

To explore mortality rates and causes of death in juvenile idiopathic arthritis (JIA) patients in Finland compared with the general population.

Methods

All incident patients with JIA (age <16 years at the index day) during 2000-2014 were collected from the nationwide register maintained by the Social Insurance Institution of Finland and The National Population Registry identified three age-, sex- and residence-matched controls for each case. They were followed up together until 31st Dec 2015.

Results

Altogether 4,180 JIA patients (62% females) were identified. Mean age at diagnosis was 8.3 years. The average follow-up time was 6.6 years (IQR 3.1–10.5). The patients were compared with 12,511 controls. During 28,941 follow-up years, 11 JIA patients (6 females, 5 males) and 23 controls (12 females, 11 males) died. The mean age at death was 20.3 (range: 11–30) in JIA patients and 23.1 (range: 9–29) years in the control group, (p=0.17). Cumulative mortality in JIA was 0.6% (95% Cl 0.3–1.2) compared to 0.6% (95% Cl 0.4–1.0) in the controls; (hazard ratio 1.44, 95% Cl 0.70–2.95). Accidents were the most common (54%) cause of death in JIA, whereas suicide (39%) in the controls. Substance abuse and depression contributed more to deaths in the controls (39%) than in the JIA patients (10%), (p=0.053).

Conclusion

The mortality rate was not elevated in patients with juvenile idiopathic arthritis.

Key words

arthritis, juvenile, mortality, accidents, suicide

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Introduction

Juvenile idiopathic arthritis (JIA) is a heterogenous inflammatory rheumatic disease with onset before the age of 16 years. It is classified into seven categories according to the criteria of ILAR (International League of Associations for Rheumatology) (1). Along with progress in disease management (*e.g.* biologic medications) during the last two decades, the outcome of JIA has greatly improved (1). Permanent invalidity is nowadays rare and mortality rate low (2, 3). The causes of deaths have changed over the decades (4). In the 1960s, the main causes were amyloidosis and infections, whereas the number of suicide and accident deaths increased in the 1990s (4). In this study, we explore the mortality rate and causes of death after the turn of the millennium among all Finnish incident patients with JIA.

Material and methods

In Finland, patients with JIA are eligible for a special (higher rate) reimbursement for the costs of disease-modifying anti-rheumatic drugs, and these individuals are recorded in a register maintained by the Social Insurance Institution of Finland.

From this nationwide register, we collected all the incident cases with JIA from 1st Jan 2000 to 31st Dec 2014. The date of reimbursement decision was defined as the index day. For each case, the National Population Registry identified three controls matched for age, sex and residence. The individuals were followed up until 31st Dec 2015. Information from death certificates was obtained from the Statistics Finland, and the data were linked by the personal identity codes. Causes of deaths were classified according to the International Classification of Diseases 10th Edition (ICD-10) codes.

The characteristics of the study population were presented as means with standard deviations (SD), as medians with interquartile range (IQR), or as counts with percentages. Survival analysis was based on the product limit estimate (Kaplan-Meier) of the cumulative survival function. Cox proportional Hazard Model was used to estimate the mortality risk for the JIA patients and for the control population. The results were presented as hazard ratio with 95% confidence intervals (Cl). For all the analyses $p<0.05$ was considered significant. Stata 14.1 (Stata Corp LP, College Station, TX, USA) was used for the analyses.

Permission to use databases was obtained from the SII (the Social Insurance Institution of Finland). By the Finnish legislation, no approval by an ethical committee nor patient's informed consent is required for register-based studies done without contacting study subjects.

Results

Patient characteristics

A total of 4,180 patients with JIA (1,577 females, 2,603 males) were identified (Table I). The patients were compared with 12,511 matched controls, 7,793 females and 4,718 males.

Mortality rate

During 28,941 follow-up years 11 patients with JIA (0.3%; 6 females, 5 males) died. The number of deaths in the control group was 23 (0.2%; 12 females, 11 males). The mean age at death was 20.3 years (range: 11–30) in the JIA patients and 23.1 years (range 9–29) in the control group ($p=0.17$).

The ten-year cumulative mortality of the JIA patients was 0.4% (95% Cl 0.2–0.8) *vs.* 0.3% (95% Cl 0.2–0.5) of the controls and at the end of the follow-up 0.6% (95% Cl 0.3–1.2) *vs.* 0.6% (95% Cl 0.4–1.0), respectively.

The relative risk of death in the JIA group was not elevated (Fig. 1). Hazard ratio was 1.44 (95% Cl 0.70–2.95; $p=0.32$), in females 1.50 (95% Cl 0.56–4.00; $p=0.42$) and in males 1.36 (95% Cl 0.47–3.93; $p=0.56$).

Causes of death

In the patients with JIA about half of the deaths happened due to accidents including two poisonings, one drowning, one skating, one motor vehicle, and one riding accident. Seven accidental deaths occurred in the control group, mainly in motor vehicle accidents. Suicide was the most common (39%) cause of death in the controls, whereas only two (18%)

Table I. Caracteristics of the incident juvenile idiopathic population in Finland 2000-2014.

	Males	Females	Total
N	1,577	2,603	4,180
Mean age on the index day, years (SD)	8.3 (4.6)	8.4 (5.0)	8.3 (4.8)
Follow-up, person years	10,962	17,979	28,941
Median follow-up time, years (IQR)	6.7 (3.1,10.7)	6.5 (3.1,10.5)	6.6 (3.1,10.5)
Age at the end of follow-up, years (SD)	14.8 (6.3)	14.8 (6.4)	14.8 (6.4)

SD: standard deviation; IQR: interquartile range.

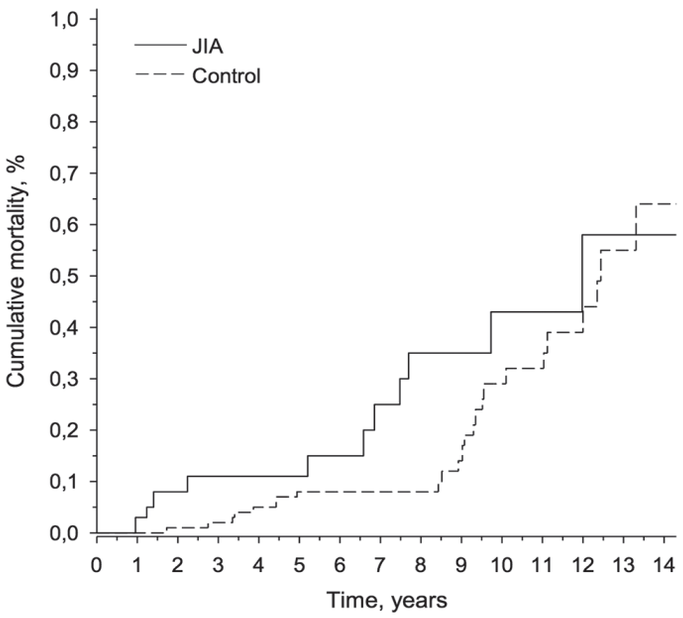

Fig. 1. Cumulative mortality of the patients with incident juvenile idiopathic arthritis (JIA) and the control group.

patients with JIA committed a suicide. Infection was involved in deaths of two JIA patients (meningitis and pneumonia) and one control (encephalitis). Cancer caused three deaths in the control group. The reason for one death in the control group remained unclear.

JIA itself was recorded as the primary (underlying) cause of only one death. This patient had systemic JIA and viral gastroenteritis and pneumonia as other causes. Seronegative JIA was a contributing cause of death for two patients. One of them had Down syndrome and diabetes and the other had meningitis and colitis ulcerosa.

There was no statistical difference in the primary causes of death in the patients with JIA compared to the controls.

Psychiatric disorders (mainly substance abuse diagnoses) were the most common contributing causes of death in the controls (39%), whereas in the patients with JIA that was the case only in one person (9%), (p=0.053).

Discussion

This register study covering the whole Finnish population showed that since the turn of the millennium contracting JIA does not translate into a higher risk of death. Our rates are parallel with the data from recent years (Table II), although some studies have been small (5, 6). In the USA a register study including all new patients from 62 paediatric rheumatology centres between 1992 and 2001 observed a mortality rate of 0.2% during 7.9 years of follow-up (3). Earlier studies reported higher and varying mortality rates (7-11). The variation between studies can be explained by differences in follow-up times (7, 11), study populations (6, 8-11) and decades (9-11).

The decrease in the mortality of JIA patients since the 1960s has happened simultaneously with the increase in more intensive anti-rheumatic drug treatment and the decrease in the incidence of secondary amyloidosis (4, 12). Amyloidosis was not an infrequent cause of death at the Rheumatism Foundation Hospital in Finland during 1951–1961, but in the 1980s its incidence was reduced by more than 50% (4). The advent of anti-tumour necrosis factor alpha therapy in the early 2000s further contributed to the disappearance of amyloidosis (4). Some concern has risen considering the safety of biologic agents. Beukelman *et al*. (2016), however, found no difference in serious infections between biologics (mostly anti-TNF-alpha therapy) and methotrexate (13). Horneff *et al*. (2016) did not find any difference between these drugs in malignancies either (14). The active rheumatic disease is more likely to increase the risk for infection and malignancies than medication (13, 14).

Table II. Studies reporting mortality in juvenile idiopathic arthritis patients over the last decades.

Author, country	Year Published	Number of patients	Follow-up, mean (years)	Number of deaths	Annual mortality/1000 patients
Laaksonen (11), Finland	1966	544	16	25	2.87
Baum and Gutowska (9), Europe, USA, Pacific area	1977	6,290	9.2	184	3.17
Koivuniemi and Leirisalo (10), Finland	1999	30	7.8	1	4.27
French *et al*. (7), USA	2001	57	25.6	4	2.74
Minden *et al*. (5), Germany	2002	215	16.5	0	0
Hashkes *et al*. (3), USA	2010	9,604	7.9	20	0.26
Krause *et al*. (6), USA	2016	71	7.5	0	0

In our study infection caused only two immediate deaths in the JIA group, but we found no death due to malignancies in this group. Nor were deaths related to disease and treatment complications in contrast to some previous studies (3, 11).

The main cause of death among the JIA patients was accidents. This was already shown in 1993 in a Finnish study, in which trauma deaths were doubled from the period 1969–1979 to 1980–1990 (4). This result was explained by better general conditions and scarce invalidity among JIA patients (4). During the same period, accident-related deaths also increased in general among Finnish children and became the most common cause of death (15). This increase has been a worldwide trend (16). The elevated accident risk has been attributed to children's incomplete mental and physical development (16).

From 1969 to 1980 in Finland, suicide deaths increased among people aged 15–19 in general and they doubled among JIA patients (4). This increase in suicide was thought to be due to a greater exposure of young people to drugs and alcohol (17). Since the 1990s, there has been a decline in youth suicide rates (17). At the same time, the use of antidepressants and mental health services has increased (17). In our JIA group, only two young people ended up committing suicide.

Active treatment with disease-modifying anti-rheumatic drugs and remission of JIA positively affect patients' mental health and quality of life (18), which has improved even further with biological treatments (19). This also applies to the mental health of systemic JIA patients, even though general health, physical and social well-being are lower than in the general population (20).

The strength of this study lies in it being nationwide. Further, the causes of death are based on a fully comprehensive death certificate statistics. In all cases of death, health officials immediately inform the cause of death to magistrates, who file the death certificates in the population information system. If the cause of death is or is suspected to be resulting from an accident, a suicide, a crime, a poisoning, or if the reason is unknown, an autopsy will be performed. The data is then forwarded to the Statistics Finland.

A study based on official registers has some limitations. No clinical data was available, and the patients could not be accurately divided into the categories of JIA. Patients with a severe disease may have died before applying for reimbursement for drug treatment. Mild cases of JIA with no need for disease-modifying anti-rheumatic drugs may not have been included in our cohort. The date of the reimbursement decision defined the index day, but the disease may have started much earlier. In our study, the average follow-up time was shorter than in the previous studies (Table II).

In summary, patients with JIA do not have an elevated risk of death. Even if a chronic disease can be a burden to its carrier, it is comforting that suicides are rare. We can assume that in the treatment of JIA patients the health care system works quite well.

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