Pneumonia in children with juvenile idiopathic arthritis in Finland 1999-2014: a nationwide retrospective register linkage study

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Abstract

Objective

To compare the incidence of pneumonia in children with juvenile idiopathic arthritis (JIA) to the aged-matched general population and to evaluate the use of anti-rheumatic medication among children with JIA and pneumonia.

Methods

The National Hospital Discharge Register collects data on ICD-diagnoses of hospital patients in Finland. From this register, patients with JIA under 18 years of age with pneumonia from 1999 through 2014 were identified. The control group consisted of age-matched patients derived from the general population with a diagnosis of pneumonia made in the same calendar year as the pneumonia of the JIA patients. The patient records of the children with JIA were scrutinised for the use of anti-rheumatic medication.

Results

We identified 223 pneumonias among the JIA patients (56,161 patient-years) and 53,058 pneumonias in the control group (17,546,609 person-years). The incidence of pneumonia in children with JIA was 386 (annual range 131–639) and in the control group 303 (annual range 225–438) per 100,000 person-years. The incidence of pneumonia increased significantly over time among JIA patients ($p=0.013$) and in the control group ($p<0.001$). Through 2007-2014 the rate of pneumonia was significantly higher among children with JIA ($p<0.001$) than control children. We found 150 JIA patients with pneumonia confirmed by positive chest radiograph. Altogether 47% of the JIA patients had combination medication. The use of methotrexate and biologic agents increased significantly over time ($p=0.016$ and $p<0.001$, respectively).

Conclusion

The incidence of pneumonia increased in children with JIA and in the general population from 1999 to 2014. During 2007–2014 JIA patients had a significantly higher rate of pneumonia than age-matched controls. The use of active anti-rheumatic medication was common.

Key words

juvenile idiopathic arthritis, pneumonia, disease-modifying anti-rheumatic drugs, biologic agents

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Introduction

The risk of infections among children with juvenile idiopathic arthritis (JIA) is increased because of the JIA itself and the immunomodulatory medication used for treatment (1). The increasing use of biologic agents in the treatment of JIA raises concern about an increased risk of infections further (2). Among adults, the risk of serious infections associated with rheumatoid arthritis is increased (3) and this risk is doubled by the use of biologic agents (4, 5). In children with JIA, with or without anti-rheumatic medication, mild infections, *e.g.* upper respiratory tract infections have been described most frequently, but the risk of serious infections in JIA patients on biologic agents may also be increased (1, 6-8).

The most common serious infection among JIA patients is pneumonia (7-9). The rates of all-cause pneumonia are higher for patients with certain chronic medical conditions, like rheumatoid arthritis, and for patients on immunosuppressive medication compared to healthy controls (10). Pneumonia is one of the most common indications for hospitalisation of children (11) and, despite pneumococcal vaccination, children on immunosuppressive medication are prone to all-cause and pneumococcal pneumonia (12).

We have previously shown that the incidence of bloodstream infections among children with recent-onset JIA is 3-fold compared to the general population, although not statistically significantly so (13). The aim of this retrospective national register study was to determine the incidence of pneumonia among JIA patients under 18 years of age in Finland during 1999–2014 and to compare the incidence to the general child population. We evaluated the trends of the incidence of pneumonia in this population during this follow-up period in the both groups and took into account the changes in the treatment of JIA. In addition to national register data, we retrieved the pneumonia cases and recorded the data on the level of individual patients as presented in the patients' health records.

Materials and methods

Register

We collected the register data for this national retrospective study from the National Hospital Discharge Register (HILMO) maintained by the National Institute for Health and Welfare. This register includes both outpatient and inpatient visits, including admission and discharge dates from ward care, individual identity codes, principal and secondary diagnoses (International Classification of Diseases 10th revision, ICD-10), procedures, age, gender and hospital identificatory codes.

The coordinating ethics committee of Helsinki and Uusimaa Hospital District approved the study protocol.

Study population

The data on children diagnosed with JIA from 1999 through 2014 were identified from the HILMO register and used for this study. We sought first children younger than 16 years with a diagnosis of JIA (M08.0-M08.9, M32-M35 and M45). The follow-up period lasted until the day children were 18 years or to the end of year 2014. After this search, we linked the identity codes of the JIA patients to the diagnosis of pneumonia (J13-J18.9) of the hospital discharge registries. Pneumonias occurring after the diagnosis of JIA had been established were included.

The reference population consisted of the general population matched for age, gender and calendar year. The incidence of pneumonia in the general population younger than 18 years was compared to the incidence of pneumonia among JIA patients of the same age.

We used the patient's first pneumonia in a calendar year as the baseline estimate and definition for incidence. Changing the definition of incidence to include pneumonia episodes separated by three months as distinct cases did not markedly affect the incidence estimates. The difference to baseline figures was less than 3%.

Patient records

Using the HILMO register we determined the group of JIA patients with the diagnosis of pneumonia. We received permissions to collect data from the patient health records from all the Finnish hospitals. An experienced pediatrician reviewed the records in

detail and confirmed that the data on JIA and pneumonia was compatible with the respective clinical diagnoses. Only JIA patients whose pneumonia was verified by chest radiographs were included. The patient records included the subtype and the time of JIA diagnosis, medication history, comorbidities, date of the pneumonia, inpatient and outpatient visits at the hospital and examinations before the diagnosis of pneumonia.

Statistical analyses

We calculated the crude pneumonia rates of children with JIA and the control group during the study period per 100,000 person-years. Poisson's regression model was used to analyse the incidence trend separately in the study and the control group and also for comparing the differences of the incidence trends between these groups during the follow-up. The χ^2-test was used to calculate the difference of incidences separately by 8-year intervals (1999-2006 and 2007–2014). The trends in the use of anti-rheumatic medication were calculated using the function "prop.trend.test" in R (Software environment for statistical computing and graphics, v. 3.3.0, The R Foundation for Statistical Computing).

Results

There were 477 children younger than 18 years with JIA and pneumonia; this included the cases of pneumonia before the JIA diagnosis was set. The incidence of pneumonia was 990 per 100,000 (annual range 790–1437) patient-years. This is 3-fold compared to the general population at the same age. When the pneumonias diagnosed before the diagnosis of JIA was set were excluded, there were 223 pneumonias in 56,161 JIA patient-years during 1999–2014. This yielded an incidence of 386 (annual range 131–639) per 100,000 patient-years in patients with JIA. In the control group, there were 53,058 pneumonias in 17,546,609 person-years, which yielded an incidence of 303 (annual range 225–438) per 100,000 person-years.

Through the follow-up the incidence of pneumonia increased significantly in JIA patients (p=0.013) and in the control group (p<0.0001). The incidence of pneumonia was on average 1.3-fold (annual range 0.6–1.9) higher in children with JIA compared to the control group throughout the entire follow-up. During the first half of the follow-up period (1999–2006) there was a slight variability in the incidences between the study and the control groups, but during the latter half (2007–2014) the incidence of pneumonia was significantly higher (p<0.0001) in the study group than in the control group (χ^2-test). There was no statistically significant difference when the trend of the incidences of pneumonia in the two groups was assessed (Poisson's regression) (Fig. 1).

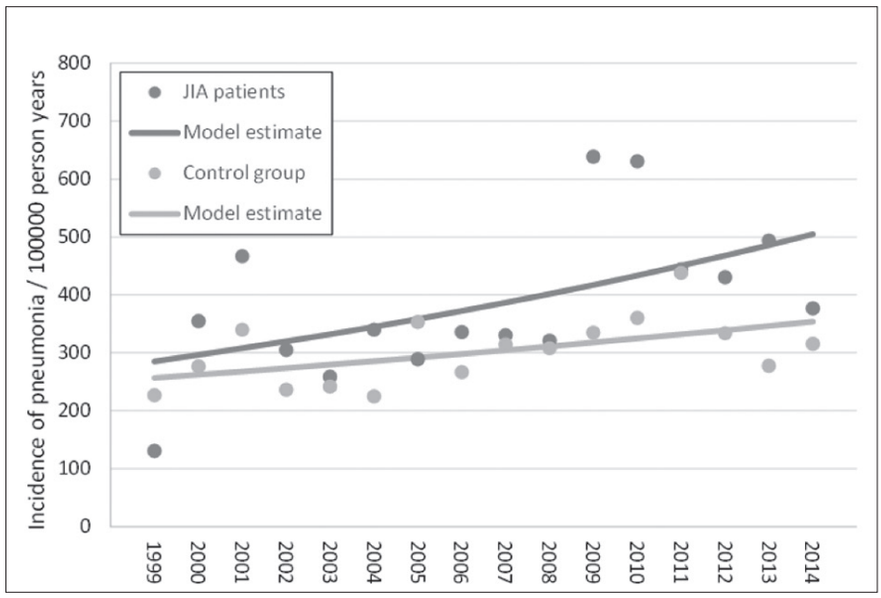

Fig. 1. Incidence of pneumonia in JIA patients and in control group.

We analysed the records of patients with JIA and pneumonia. In this detailed clinical part of the research we included only patients whose pneumonia was confirmed with an appropriate finding by chest radiography. Thus, of the 223 pneumonias in patients who had a diagnosis of JIA at the time of the pneumonia, 150 were confirmed by radiography (131 children) in 1999–2014. This data included both inpatient and outpatient visits. Of these 150 pneumonia episodes 111 (74%) were treated in the hospital and the rest were treated at home.

At the time of the pneumonia, the mean age of JIA patients was 9 years and 57% were girls. The most common JIA diagnoses were oligoarthritis and rheumatoid-factor negative polyarthritis. The mean duration of JIA before the pneumonia was 4 years (Table I).

Table I. Characteristics of children with JIA at the time of pneumonia (n=150).

Age (mean ± SD)	9.2 ± 4.8
JIA duration (years, mean ± SD)	4.1 ± 3.1
Age (%)	
< 5 years	35 (23.3)
5–9 years	49 (32.7)
10–14 years	43 (28.7)
15–17 years	23 (15.3)
Female (%)	86 (57.3)
JIA subgroups (%)	
Systemic arthritis	14 (9.3)
Oligoarthritis persistent	40 (26.7)
Oligoarthritis extended	22 (14.7)
Polyarthritis, RF-	60 (13.3)
Polyarthritis, RF+	10 (6.7)
Psoriatic arthritis	3 (2.0)
Enthesitis-related arthritis	1 (0.7)

Altogether 126 of the radiography-verified pneumonia patients with JIA (84%) received disease modifying anti-rheumatic drugs (DMARDs) at the time of the pneumonia diagnosis (Table II); 70 patients (47%) had two or more DMARDs. The use of combination medication remained unchanged during the follow-up. The most common DMARD was methotrexate (MTX) and its use increased significantly (p=0.016) during the study period. Tumour necrosis factor inhibitors (TNFi) were the most common biologic agents (bDMARD). Fourteen of the bDMARD

Table II. Anti-rheumatic medication before pneumonia in JIA patients (n=150).

Medication	n (%)
Methotrexate	92 (61.0)
Biologic agents	47 (31.0)
TNFi	38 (25.3)
Etanercept	20 (13.3)
Adalimumab	6 (4.0)
Infliximab	12 (8.0)
Tocilizumab	5 (3.3)
Certolizumab	1 (0.7)
Abatacept	1 (0.7)
Anakinra	2 (1.3)
≥1 prior biologic agent	14 (9.3)
Hydroxychloroquine	36 (24.0)
Glucocorticoids any dose	23 (15.0)
≥10 mg dose of prednisolone	6 (4.0)
Sulfasalazine	13 (8.7)
Leflunomid	12 (8.0)
Combination medication	70 (46.7)
Without medication	24 (16.0)

TNFi: Tumour necrosis factor inhibitor.

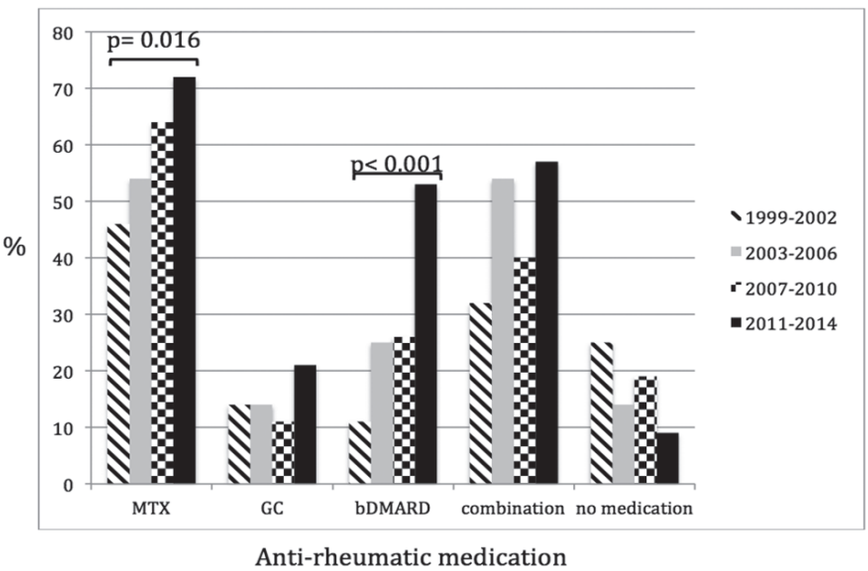

Fig. 2. Anti-rheumatic medication before pneumonia in JIA patients (n=150).
MTX: methotrexate; GC: glucocorticoids; bDMARD: biologic disease-modifying anti-rheumatic drugs.

users (30%) had received two or more TNFi:s. The proportion of patients treated previously with biologic agents increased significantly (p<0.001) during the study. The use of glucocorticoids (GC) was stable throughout the study period (Fig. 2). Only six patients (4%) had a prednisolone dose of more than 10 mg per day. A total of 24 children (16%) took no anti-rheumatic medication at the time of the pneumonia either because the JIA diagnosis was so recent or because the disease was in remission.

Discussion

This retrospective national register study revealed that the incidence of hospital visits requiring pneumonia increased significantly through 1999–2014 in children with JIA but also in the general population of the same age. In the first half of the follow-up (1999–2006) there were only slight differences between the groups but in 2007–2014 the JIA patients had a significantly higher rate of pneumonia. Still, the trends of the incidence of pneumonia between the study and the control group were similar throughout the entire study period.

In the developed countries, the incidence of pneumonia is 3400 to 4000 per 100,000 patient-years among children under five years of age. The incidence of pneumonia requiring hospitalisation of children has varied between 200 and 2300 per 100,000 patient-years in the same age group (14). In our study, the incidence of pneumonia among JIA patients was 3-fold compared to the general population, when pneumonias before the JIA diagnosis are also taken into account. However, the difference was smaller when only the pneumonias diagnosed before the diagnosis of JIA were considered. This finding supports previous evidence that JIA patients are susceptible to infections (1, 15) and raises the question of the possible protective role of the treatment of JIA by means of better control of inflammation. In a very recent study, however, hospitalisation due to infection has not been associated with the risk of JIA in the first year of life (16).

The annual variation in the incidence of pneumonia was substantial in the study group and control group. The incidence of pneumonia peaked twice in the JIA group, in 2001 and 2009–2010. The occurrence of pneumonia must be viewed against the concurrent epidemics: In 2001, there was moderate influenza epidemic in Finland, in 2009 an H1N1 influenza pandemic and in 2010 respiratory syncytial virus infections affected the child population (17).

Hospitalisations for pneumonia, especially in children under 2 years, have decreased after introduction of pneumococcal vaccination in the general population (18-20). In a Finnish prospective study on the aetiology of pneumonia (21), bacterial infection was diagnosed in half of the cases and *Streptococcus pneumoniae* was the most common bacteria (28%). Pelton *et al*. pointed out that immunocompromised persons of all ages suffer from pneumonia despite pneumococcal vaccination (12). Vaccination of children against pneumococcal infections started in Finland in 2010 and the vaccination uptake is about 95% (17). Despite the introduction of pneumococcal vaccination, there was no decreasing trend in the incidence of pneumonia (Fig. 1). Immunisation against the influenza virus of children aged 6–36 months was started in Finland in 2007 but the vaccination coverage is only 20% (17). Consequently, the increasing trend of pneumonias in JIA patients must be explained by healthcare patterns and improved, active diagnostics of infections of immunocompromised patients. General practitioners may refer patients on immunosuppressive treatment who fall ill with infections for hospital treatment and radiological examinations with a lower threshold than patients not on immunosuppressive treatment. Also, families are advised to contact the hospital without delay in the case of infection.

According to a US register study, children with JIA have a 2-fold increase in the rate of hospitalisation because of

bacterial infections when not treated with methotrexate or TNFi; there was no connection between infection risk and anti-rheumatic medication (1). According to the literature, however, the risk of lower respiratory tract infections and soft tissue infections does increase in children with JIA treated with TNFi (22). A Finnish study pointed out serious adverse effects in one third of the children with JIA treated with biologic agents (23), the most common of which were infections which occurred at a rate of 4000 per 100,000 patient-years (23). A British register study showed that the use of TNFi increases the risk of medically significant infections as defined by the treating physician but there was no difference in the occurrence of serious infections, the most common of which were pneumonia and varicella (24). Beukelman and colleagues (9) reported that since the introduction of biologic agents, including TNFi (etanercept, adalimumab, infliximab, golimumab, certolizumab), abatacept, anakinra, canakinumab and tocilizumab, only anakinra has been associated with an increase in the risk of infections. The risk factors for hospitalisation due to infections (pneumonia, urinary tract and soft tissue infections) were recent infection and high-dose oral GC, according (9). Also in adult studies the risk of pneumonia was related to the use of high dose prednisone in RA patients (26). In our study only 4% of the patients were treated with high doses of GC.

In Finland, there has been increasing trend in the use of biologic agents, especially etanercept since 1999 (27), and almost one-third of adolescents and young adults with JIA use biologic agents (28). In the present study, JIA patients with pneumonia had been treated at an increasing rate with biologic agents but oral GC use remained quite stable throughout the study period. Anti-rheumatic combination medication was common. Mannion and colleagues (2) also reported that from 2005 to 2012 the use of TNFi in children with JIA increased 2- to 3-fold while and GC use was relatively unchanged. According to the CARRA registry, 45% of JIA patients had ever received biologic agents and 28% of TNFi users had received >1 anti-TNF agent during the course of their disease (29). This registry includes selected patients collected by paediatric rheumatologists.

To our knowledge this is the first study on the incidence of pneumonia in JIA patients. The strength of our study is the considerable size of the study population and the long follow-up time of 16 years. In addition, this national register data covers all the entire hospital network in Finland. Paediatric rheumatologists manage all JIA children treated in hospitals and comprehensive data on inpatient and outpatient discharge diagnoses are available in the HILMO register. This study comprises the entire population of JIA patients with pneumonia in Finland.

This register study, as many others, has its limitations. The retrospective study design may cause bias because of incomplete data. From the HILMO register it is not possible to extract data on JIA treatment, disease activity or the etiology of pneumonia. Nor were we able to obtain reliable data on comorbid diagnoses from the register. Because the data of the registry is limited and evaluation of all patient records and controls would have been a momentous task, it was not feasible to compare JIA patients with and without pneumonia. Rather, we decided to include only patients with radiologically confirmed pneumonia for a detailed evaluation of the anti-rheumatic medication.

The data of the HILMO register was used to assess the incidence of pneumonia among JIA patients. Although children with serious infections are treated at hospitals, milder cases of pneumonia not visible in this data are treated by open-care physicians. Logistically, there may be some errors in the registry data, *e.g.* ICD-10 coding and changes in the coding practices might affect final incidence figures over the long time span of this study (1999–2014) but such deviations would be similar in both study groups.

Conclusion

The incidence of pneumonia increased significantly in children with JIA and in the general age-matched population in 1999–2014. The incidences varied slightly between these groups and during the latter half of the study period the incidence was higher in JIA patients.

Active treatment of JIA with the use of several immunosuppressive drugs concomitantly was common. The use of methotrexate and biologic agents became significantly more common among children with JIA and pneumonia during the study period. This trend of intensifying immunosuppressive therapy of JIA may increase the risk of pneumonia, but the difference in relation to the general population was not big. Modern intensive and effective anti-rheumatic treatment may improve the condition of the JIA patients and thus at least partly compensate for the slightly increased infection risk caused by the immunosuppressive effect of the drugs.

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