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Pulmonary function in children with juvenile idiopathic arthritis and effects of methotrexate therapy

Lungenfunktion bei Kindern mit einer juvenilen idiopathischen Arthritis und der Einfluss einer Methotrexattherapie

Summary *Objective* To evaluate impairment of lung function as an adverse effect associated with methotrexate therapy in patients with juvenile idiopathic arthritis (JIA). *Methods* We performed pulmonary function testing including diffusion capacity for carbon monoxide as measured by the single breath method (DLCO-SB) in 89 children with juvenile idiopathic arthritis. Forty (45%) were treated with methotrexate for a median of 24 months (range 3 to 120 months). Except for the presence of asthma in two children, there was no clinical or radiological evidence of pulmonary disease. *Results* Pulmonary function testing demonstrated moderate airway obstruction in two children with known bronchial asthma. Neither obstructive nor restrictive alteration of ventilation was found in any other patient. Two juvenile idiopathic arthritis patients showed a reduced CO diffusion capacity of 64 and 67%. One of them was treated with methotrexate. *Conclusions* With regard to lung function impairment treatment with low dose methotrexate appears to be safe even when performed for several years reaching a total amount of up to 3.5 g. In contrast to studies performed in adult rheumatoid arthritis patients, in children with juvenile idiopathic arthritis impairment of lung function is a rare event.

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Zusammenfassung *Einleitung* Bei Kindern mit juveniler idiopathischer Arthritis kann eine Lungenbeteiligung im Rahmen der Grunderkrankung sowie aufgrund der immunsuppressiven Therapie mit Methotrexat erfolgen. *Methoden* Untersucht wurde die Lungenfunktion einschließlich der Lungendiffusionskapazität mit der CO-single-breath-Methode (DLCO-SB) bei 89 Kindern mit einer juvenilen idiopathischen Arthritis. 40 (45%) wurden mit einer durchschnittlichen Dauer (Median) von 24 Monaten (3–120 Monate) mit Methotrexat behandelt. Außer bei zwei Kindern mit einem bekanntem Asthma bronchiale war weder klinisch noch radiologisch eine pulmonale Manifestation erkennbar. *Ergebnisse* Bei zwei Kindern mit bekanntem Asthma bronchiale zeigte sich eine mäßiggradige obstruktive Ventilationsstörung. Weder obtruktive noch restriktive Ventilationsstörungen fanden sich bei den anderen untersuchten Kindern. Zwei Patienten wiesen eine verminderte CO-Diffusionskapazität von 64 und 67% auf, von denen einer mit Methotrexat behandelt wurde. *Zusammenfassung* Hinweise auf eine Methotrexat bedingte Lungenfunktionseinschränkung fanden sich selbst bei Therapie über einige Jahre mit einer kumulativen MTX-Dosis bis zu 3,5 g nicht. Im Gegensatz zu Studien bei erwachsenen Patienten mit einer rheumatoiden Arthritis finden sich bei Kindern mit einer juvenilen idiopathischen Arthritis nur selten Lungenfunktionseinschränkungen.

Key words Juvenile idiopathic arthritis – methotrexate – diffusion capacity

Schlüsselwörter Juvenile idiopathische Arthritis – Methotrexat – Diffusionskapazität

Introduction

Juvenile idiopathic arthritis (JIA) is an chronic inflammatory joint disease. Several subgroups have been defined according to the number of involved joints during the first six months of the disease and the occurrence of extra-articular manifestations (12). Numerous reports have documented the association of rheumatoid arthritis and pulmonary abnormalities. Caplan syndrome, pulmonary rheumatoid nodules, pulmonary vasculitis, diffuse interstitial fibrosis and pleuritis have been described in adult patients and children with JIA (4, 10). In addition, lung function parameters characteristic of restrictive lung disease, e.g., reduced total lung capacity and diminished diffusing capacity, have been described in JIA patients without pulmonary symptoms and radiological findings indicating pulmonary involvement. The prevalence of lung involvement in JIA is thought to be lower than in adult RA.

In 1991 methotrexate was shown to be effective in the treatment of JIA in a double blind placebo-controlled trial and became the drug of choice for treatment of active, severe JIA resistant to non-steroid anti-inflammatory drugs (7). However, initiation of effective antirheumatic therapy with methotrexate is delayed because physicians worry about side effects on lung or liver. Methotrexate-induced pulmonary disease is well documented in adult RA-patients, with an estimated prevalence of 2 to 5% (3, 9, 13). The main pulmonary side effects of methotrexate are interstitial pneumonitis and lung fibrosis. Methotrexate-induced impairment of lung function in children with JIA is still controversial. Alterations of pulmonary function in JIA may be a complication of the underlying disease or related to treatment with methotrexate.

In this study we evaluated the effect of methotrexate treatment on lung function parameters in children with JIA.

Patients, materials and methods

Patients

Pulmonary function tests were performed in 89 children who met the ILAR criteria for the diagnosis of JIA (12). The patient characteristics are outlined in Table 1. Patients were subdivided into six groups, systemic onset JIA (type 1), polyarticular onset JIA (type 2 and type 3), oligoarticular onset JIA (type 4), JIA with arthritis and enthesitis (type 5) and JIA with arthritis and psoriasis (type 6). As only children of at least 6 years were able to perform lung function tests, the distribution of subtypes does not reflect the usual subgroup distribution in JIA, where nearly 50% of patients show an oligoarticular onset occurring predominately in females before the age of six. A thorough clinical examination was carried out in all children and the disease activity was evaluated based on the presence or absence of joint swelling, pain, heat, limitation of motion and morning stiffness. Patients and/or parents were asked to answer a complete respiratory questionnaire, requesting information about dry or productive cough, dyspnea on exertion, chest pain, cyanosis. Two patients of the oligoarticular group (JIA type 4) met the diagnostic criteria for asthma. None of the other patients had any history of chronic pulmonary disease.

Forty patients were treated with weekly oral methotrexate (weekly dose 10 to 15 mg/m^2, median cumulative dose of methotrexate 920 mg [range 120–3505 mg], median treatment period 24 months [range 3–120 months], Table 1).

Pulmonary function tests

Pulmonary function measurements were performed with a body plethysmograph (Masterscreen, Jäger GmbH, Würzburg, Germany) and included measure-

Table 1 Patients characteristics (total patient number: 89)

Subgroup JIA	No. Female/ Male	Age at time of study (years) Mean/ Range	Disease duration (months) Average/ Range	No. (%) patients treated with MTX
Type 1 Systemic onset	3/7	11.6 6–16	60 19–109	6 (60)
Type 2 and 3 Polyarticular onset	25/8	13.8 7–19	76 10–195	20 (61)
Type 4 Oligoarticular onset	14/5	11.5 7–17	68 3–194	8 (42)
Type 5 Arthritis and enthesitis	1/18	13 9–18	43 6–128	3 (16)
Type 6 Arthritis and psoriasis	6/2	14.2 12–18	38 6–84	3 (38)

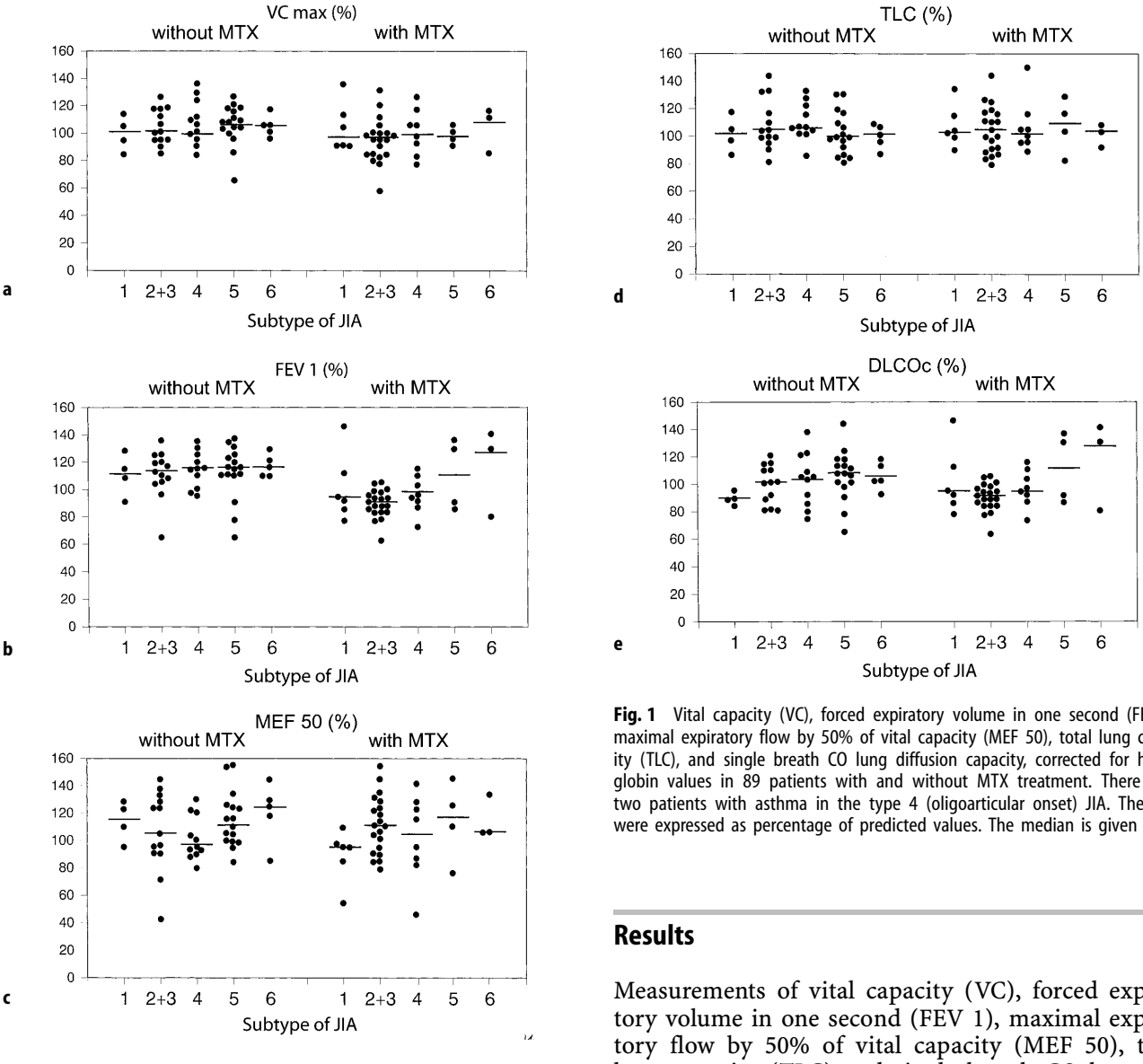

Fig. 1 Vital capacity (VC), forced expiratory volume in one second (FEV 1), maximal expiratory flow by 50% of vital capacity (MEF 50), total lung capacity (TLC), and single breath CO lung diffusion capacity, corrected for hemoglobin values in 89 patients with and without MTX treatment. There were two patients with asthma in the type 4 (oligoarticular onset) JIA. The data were expressed as percentage of predicted values. The median is given

ment of vital capacity (VC), forced expiratory volume measured at one second (FEV 1), maximal expiratory flow at 50% of vital capacity (MEF 50), total lung capacity (TLC), and single breath CO lung diffusion capacity calculated according to Zapletal et al. (15). The DLCO measurements were corrected for hemoglobin levels. Values are expressed as a percentage of the predicted value adjusted for age, sex, height and weight.

Statistics

Statistical analysis was performed using the SPSS software (SPSS Inc. USA). Parameters were analyzed by nonparametric testing (Mann-Whitney U-Test).

Results

Measurements of vital capacity (VC), forced expiratory volume in one second (FEV 1), maximal expiratory flow by 50% of vital capacity (MEF 50), total lung capacity (TLC) and single breath CO lung diffusion capacity are presented in Fig. 1. At the time of investigation, two children with known asthma (both in the JIA type 4 subgroup) showed MEF 50 values of 41% and 47% of predicted, indicating a peripheral airway flow limitation. In one additional patient, MEF 50 was reduced to 57% without clinically significant disease. Two JIA patients showed a reduced diffusion capacity of 64 and 67%, respectively. One child was treated with MTX for 2 years, the other one never received cytotoxic drugs. No abnormalities of pulmonary function parameters were observed in any other patient.

Functional respiratory parameters were independent of different JIA subtypes, disease duration, or disease activity. We were not able to demonstrate a relevant effect of methotrexate treatment on lung

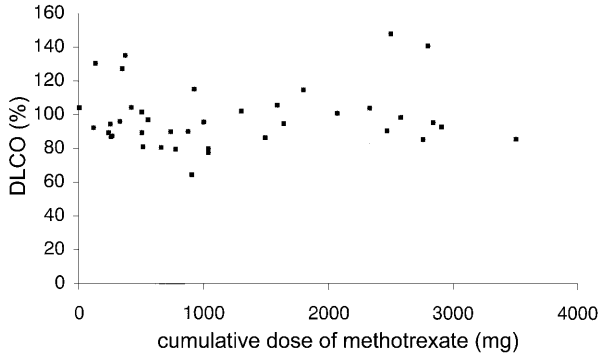

Fig. 2 Relationship between diffusing capacity, corrected for hemoglobin values and cumulative dose of MTX in 40 children with JIA: there was no correlation of total dosage of methotrexate and single breath DLCO

function parameters. Likewise, no correlation of cumulative dose (median: 920 mg, range: 120–3505 mg) or duration (median: 24 months, range: 3 to 120 months) of MTX therapy and pulmonary function was found (Fig. 2).

Discussion

The prevalence of pleuro-pulmonary involvement of JIA is still controversial. Prevalence reported by different investigators range from 4% to 62% (4,14).

Graham et al. (8) investigated pulmonary function tests in 46 patients before beginning methotrexate treatment and during the course of therapy to determine whether preexisting pulmonary impairment would preclude pulmonary side effects of methotrexate.

Neither reduction in diffusing capacity, development of restrictive indices nor clinical signs of lung fibrosis or acute pneumonitis were observed in any child before or during the treatment with methotrexate.

Pelucchi et al. (11) measured lung function including DLCO in 61 patients with juvenile arthritis between 5 and 33 years of age (27 patients treated with methotrexate). A moderate reduction of maximal mid expiratory flow was found in 14 patients (22.9%). In addition, the mean DLCO value and the DLCO value corrected for the hemoglobin value were reduced (67% and 80%, respectively).

Camiciottoli et al. (2) performed pulmonary function tests in 27 patients with juvenile arthritis (14 patients treated with methotrexate), and found respiratory function abnormalities in 51.8% of the patients. In this study the most frequently altered parameters were FVC and TLC (6 patients); reduced DLCO values were found in 1 patient only. MTX in combination with NSAIDs did not seem to affect lung function at one year more than NSAIDs alone.

In 85 of our 89 JIA patients there was no impairment of lung function. Two children with bronchial asthma and two additional patients without prior pulmonary symptoms showed a weak limitation of diffusion capacity. We therefore conclude that lung involvement is rare in JIA patients. Since asthma is a common disease with a prevalence of up to 20% in childhood, it is surprising to find only two children presenting with asthma symptoms. A lower incidence of atopic diseases in eastern Germany may be one possible explanation. However, it may be interesting to investigate the incidence of atopic diseases in children with disease of T-helper subtype 1 predominance. T-helper 1 cells predominately produce cytokines including interferon-γ, which show inhibitory effects on T-helper 2 cells, predominately producing cytokines like interleukin-4 and interleukin-10. Interleukin-4 plays a major role in enhancing immunoglobulin switching to IgE and production of IgE.

Interstitial lung disease represents one of the most common features in adult connective tissue disease and may also occur in adult RA patients (10). Lung involvement is frequently observed in children with systemic autoimmune disease like SLE. In 5 out of 11 consecutive children with systemic lupus erythematosus, an isolated decrease in DLCO values was found ranging from –20 to –50% of suspected DLCO. Treatment of lupus nephritis with cyclophosphamide improved DLCO as well as systemic disease activity. Therefore it seems likely that pulmonary involvement is related to the activity of the systemic inflammatory process. Since JIA is diagnosed after thorough exclusion of other diseases including SLE, lung involvement may possibly contribute to a so far unrecognized systemic autoimmune disease. Therefore, JIA patients with lung involvement should be monitored very carefully.

Treatment with methotrexate is associated with pneumonitis and interstitial fibrosis in adult RA patients (1, 5). Involvement of lung parenchyma with interstitial damage is supported by the reduction in VC and DLCO. The prevalence of hypersensitivity pneumonitis in adult RA patients has been estimated to range from 0.3% to 11.6%. In the literature one case of hypersensitivity pneumonitis in childhood has been reported, occurring after one month of therapy with methotrexate (6). No other pulmonary side effects of chronic low dose methotrexate therapy in children have been reported. In conclusion, airway toxicity seems apparently low.

Since JIA patients with a systemic or polyarticular onset show a more severe course of the disease, they received methotrexate therapy more frequently. In

our study 40 JIA patients treated with methotrexate were investigated; 19 patients have been treated for at least 2 years. No restrictive or obstructive pulmonary dysfunction could be observed and DLCO was normal in all but one patient. Since the frequency of impaired DLCO in JIA patients treated with methotrexate is similar to those without methotrexate, we conclude that there is no evidence of a deleterious effect of methotrexate treatment on lung function tests. No relationship was found between the cumulative dose and/or duration of methotrexate therapy and lung function parameters. These data further suggest that either the prevalence of impaired lung function is higher in adult RA patients than in JIA patients or methotrexate may be better tolerated in childhood. Since the rheumatoid factor, associated with more severe course of RA, was present only minority of the JIA patients investigated, they may suffer from a less severe disease. Since pulmonary investigation of pre-school children was impossible, these conclusions are limited to children above the age of six.

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