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WORD COUNT 2763
TIME SUBMITTED 08-FEB-2024 11:41AM
PAPER ID 106755925

Name of Journal: *World Journal of Clinical Pediatrics*
Manuscript NO: 88912
Manuscript Type: ORIGINAL ARTICLE

Retrospective Cohort Study

Systemic Juvenile Idiopathic Arthritis–Associated Lung Disease: A Retrospective Cohort Study

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Abstract

BACKGROUND

Lung damage in systemic juvenile arthritis (sJIA) is one of the contemporary topics in pediatric rheumatology. Several previous studies showed the severe course and fatal outcomes in some patients. The information about interstitial lung disease (ILD) in the sJIA is scarce and limited to a hundred of the cases.

AIM

To describe the features of sJIA patients with ILD in detail.

METHODS

In the present retrospective cohort study information about the five patients less than 18 years old with sJIA and ILD was included. The diagnosis of sJIA was made according to the current 2004 and new provisional International League of Associations for Rheumatology (ILAR) criteria 2019. ILD was diagnosed with chest computed tomography with the exclusion of other possible reasons for concurrent lung involvement. Macrophage activation syndrome (MAS) was diagnosed with HLH-2004

and 2016 EULAR/ACR/PRINTO Classification Criteria and HScore were calculated during the lung involvement.

RESULTS

The onset age of sJIA ranged from 1 to 10 years. The time interval before ILD ranged from 1 month to 3 years. The disease course was characterized by the prevalence of the systemic features above articular involvement, intensive rash (100%), persistent and very active macrophage activation syndrome (Hscore ranging 194-220) with transaminitis (100%), and respiratory symptoms (100%). Only three patients (60%) developed a clubbing phenomenon. All patients (100%) had pleural and four patients (80%) had pericardial effusion at the disease onset. Two patients (40%) developed pulmonary arterial hypertension. Infusion-related reactions to tocilizumab were observed in three (60%) of the patients. One patient with trisomy 21 had a fatal disease course. Half of the remaining patients had sJIA remission and two patients had improvement. Lung disease improved in three patients (75%), but one of them had initial deterioration of lung involvement. One patient who has not achieved the sJIA remission had the progressed course of ILD. No cases of hyper-eosinophilia were noted. Four patients (80%) received canakinumab and one (20%) tocilizumab at the last follow-up visit.

CONCLUSION

ILD is a severe life-threatening complication of sJIA that may affect children of different ages with different time intervals since the disease's onset. Extensive rash, serositis (especially pleuritis), full-blown MAS with transaminitis, lymphopenia, trisomy 21, eosinophilia, and biologic infusion reaction are the main predictors of ILD. The following studies are needed to find the predictors, pathogenesis, and treatment options, for preventing and treating the ILD in sJIA patients.

INTRODUCTION

Juvenile idiopathic arthritis with systemic onset (sJIA) is the most life-threatening form of JIA due to macrophage activation syndrome and internal organ involvement [1,2]. The lung disease is a rare, severe, potentially fatal manifestation of sJIA. Its prevalence has still grown last 20 years from single cases at the beginning of 2000 to 5% nowadays [1]. Lung involvement in sJIA includes pulmonary arterial hypertension, interstitial lung disease, presenting with pulmonary alveolar proteinosis, and lipoid pneumonia [1,2]. Patients may have a combination of ILD and pulmonary arterial hypertension. The mechanisms of lung involvement in sJIA are still unclear. It is known that hyperproduction of interleukine-1, interleukine-18, and γ-interferon pathway signaling are the main key points of the pathogenesis of lung involvement in sJIA. Several risk factors, associated with lung involvement in sJIA were proposed: onset age <2 years, prevalence of systemic features, chronic or recurrent or poor controlled macrophage activation syndrome (MAS), persistent and progressed lymphopenia, anaphylaxis to interleukine-6 and interleukine blockers, trisomy on 21 chromosomes [3]. The outcomes of the patients with sJIA with lung diseases (sJIA-LD) are extremely serious. In the first case series of 25 patients published with Y. Kimuro *et al* (2013) 68% died in 8.8±11.4 months after the lung involvement appeared [4]. Several recent studies showed better outcomes with a mortality rate near 4.6% which is 7.5 times more than in sJIA patients without lung involvement [5]. There are no approved pathogenic medications for the treatment of lung involvement in sJIA patients. Treatment with γ-interferon direct blocker (emapalumab), indirect blockers (JAK-inhibitors), and anti-interleukine-18 blockers (IL-18 binding protein) seems to be promising but requires approval [6-8]. Additional treatment options might include corticosteroids (GCS), anti-interleukine-1 (IL1) and anti-interleukine-6 biologics (IL6), cyclosporine A (CSA) and tacrolimus, mofetil mycophenolate, intravenous immunoglobulin (IVIG), and pulmonary arterial hypertension (PAH) specific treatment for control the pulmonary blood pressure and oxygen supplementation. [1, 2, 9] Children with sJIA with chronic lung involvement are more susceptible to lung infections and require specific profilaxis [4].

The information about patients with lung involvement is scarce and related to patients whose chronic lung disease has already been diagnosed.

Our study aimed to describe the patients with sJIA-LD with a focus on the initial clinical and laboratory features.

MATERIALS AND METHODS

Population

In the present retrospective cohort study, we included available information about five pediatric patients (onset age less than 18 years) with sJIA-LD. The diagnosis of sJIA was made according to the current 2004 [10] and new provisional International League of Associations for Rheumatology (ILAR) criteria 2019 [11]. If the patient didn't fit one of the major criteria he/she was diagnosed with sJIA-like disease (probable"/"possible" sJIA).

Interstitial lung disease was diagnosed with chest computed tomography with the exclusion of other possible reasons for concurrent lung involvement.

Macrophage activation syndrome (MAS) was diagnosed with HLH-2004 [12] and 2016 EULAR/ACR/PRINTO Classification Criteria for Macrophage Activation Syndrome Complicating Systemic Juvenile Idiopathic Arthritis [13] and HScore was calculated during the lung involvement [14]

Statistics: The sample size was not calculated initially. We included all available cases in our center. We used only descriptive statistics (quantitative and categorical data).

RESULTS

Common symptoms at onset of SJIA

Diagnosis of sJIA was established in all patients. Two patients did not meet the current ILAR criteria in 2004, because Pt1 and Pt2 hadn't got arthritis, at onset. All patients corresponded to new provisional criteria for sJIA 2019. Pt2 developed severe polyarthritis two years after the disease onset. The correspondence of the patients to current (2004) and new provisional (2019) ILAR criteria is shown in Table 2. Serositis

was presented by pericarditis in three cases (Pt1, Pt2, Pt4), pleurisy in four cases (Pt1-4), and peritonitis in Pt2. One patient (Pt5) developed leucopenia at onset due to MAS. The demographic characteristics of patients are in Table 1.

Lung involvement

All patients had dyspnoe, but the cough had only one patient (Pt2). Clubbing (figure 1) of the fingers was in three (60%) patients. Respiratory failure was diagnosed in four (80%) patients. They were admitted to the intensive care unit (ICU) for respiratory support.

In two cases lung disease was diagnosed at the SJIA onset (Pt3-4) and in three cases lung disease developed later in Pt1, Pt2, and Pt5 (figure 2).

Two patients developed PAH, Pt1 had persistent PAH and required PAH-specific treatment, and Pt2 had temporary PAH at the lung disease onset and successfully resolved in one month after high-doses systemic GCS treatment.

MAS and ILD development

All patients have met the abovementioned MAS criteria. Severe full-blown MAS had all five (100%) patients at the onset with a score range of 194-220 points. All patients had persistent/relapsed courses of MAS. In all cases, ILD was detected in patients with features of MAD. Interestingly, MAS was more aggressive and hardly controlled in patients with early onset (Pt1 and Pt2) and patients with trisomy 21 syndrome (Pt5).

Assessment of the known risk factors of LD-SJIA

We observed the risk factors which were previously described [1, 3]. Infusion reaction on tocilizumab had three (60%) patients. Trisomy 21 syndrome had one patient (Pt5). Four patients developed SJIA at the age of two or younger, and Pt3 developed sJIA at the age of ten years. All patients had severe MAS

Treatment:

All patients received corticosteroids. High doses of intravenous corticosteroids patients received at the onset and major flare, including MAS. Inhalated corticosteroids (budesonid and fluticasone) were used in one case with lipoid pneumonia. All five patients have experience of tocilizumab treatment, and as we've already pointed out

infusion reaction was diagnosed in 3 cases (Pt1, Pt2, and Pt4). In 4/5 (80%) cases, tocilizumab was changed to canakinumab; abatacept was added to canakinumab therapy in Pt1. Patient 1 with PAH has received sildenafil with positive dynamic and stabilization in PAH.

Outcomes

The outcomes of our cases were different. Patient 5 with trisomy of 21 syndrome has a fatal outcome. The girl developed a flare of sJIA with respiratory and heart failure. Two patients (Pt2 and Pt3) achieved sJIA remission with the improvement of ILD, but Pt2 initially had deterioration with the following improvement. Two patients had incomplete sJIA remission (Pt 1 and Pt4) with ILD improvement in Pt4, but Pt1 despite the combination treatment of canakinumab and abatacept has not achieved ILD improvement. His PAH is under the control of sildenafil. Patients with early onset had more severe ILD. Demographic characteristics, clinical with ILAR criteria radiological features, and treatment outcomes are in Table 1-4.

DISCUSSION

Systemic juvenile idiopathic arthritis (sJIA) is an autoinflammatory disease that is characterized by fever, rash, arthritis, and damage to other organs. [1]

Macrophage activation syndrome (MAS) is a life-threatening complication in children with sJIA, related to the hyperproduction of proinflammatory cytokines, especially: interleukin 1 (IL-1), interleukin 6 (IL-6), interleukin 18 (IL-18), interferon γ (IFN-γ). [2,9,15,16] Systemic Juvenile Idiopathic Arthritis–Associated Lung Disease (sJIA-LD) is a troupe of nosology that is characterized by chronic lung disease in patients with sJIA. [1] Now, it is clear, that lung involvement in sJIA patients is associated with persistent systemic inflammation, especially with macrophage activation syndrome. [1-3]

Clinical symptoms, associated with interstitial lung disease

Unfortunately, typical respiratory symptoms at the beginning of the disease are usually absent or poorly expressed, and because of this, sJIA-LD occurs unexpectedly in many

patients. For example, the cough was present in 33-43%, tachypnea - in 33-38%, auscultative changes in the lungs - in 30%, while hypoxemia was already registered in 43% of patients, and symptomatic PAH - in 30% [1,3].

Sometimes the main clinical symptoms indicating lung lesions are distal phalangeal dilation or the so-called clubbing symptom (61%) and erythema of the distal phalanges (34%)

Despite, the diagnosis of sJIA patients with lung involvement had unusual clinical presentations, as itchy rash (56%), eosinophilia (37%), and unexplained intense abdominal pain (16%) [3].

In our group, Pt2 one year before the lung involvement had a severe sJIA flare with aseptic peritonitis that required diagnostic surgery.

Another important feature is the development of a hypersensitivity reaction (anaphylaxis) to 2-3 injections of tocilizumab in many children with JIA with lung damage [1,3,9] The estimated probability of a hypersensitivity reaction during treatment with tocilizumab is up to 9.1% [17-19]. Three (60%) of our patients had tocilizumab anaphylaxis. Hypersensitivity to biological agents was found to be a risk factor for interstitial lung disease [1,3].

Laboratory symptoms, associated with interstitial lung disease

Lymphopenia (<60% of the lower normal limit for age) was detected in sJIA patients with lung involvement. This could not be explained by the current MAS and was found in 42%. The combination of hyperferritinemia and severe lymphopenia serves as a marker of the risk of lung involvement in patients with sJIA [3]. Another important laboratory symptom is eosinophilia, associated with ILD in sJIA patients [3].

Interstitial lung involvement

Pulmonary alveolar proteinosis (PAP) is a poorly studied disease manifested by the accumulation of lipid substances in the alveoli due to ineffective excretion of lipid substances by macrophages. [20] Macrophage dysfunction in sJIA-LD is not associated

with congenital defects of macrophages, as in primary lung disease. [1, 20-22]. Patients with MAS have a highly active systemic inflammation that contributes to macrophage differentiation disturbances [1]. Similar cytokine transmission pathways in MAS and sJIA-LD explain the close similarity between both conditions. Several cytokines, such as IFN-γ and IL-18 now are the focus of MAS pathogenesis. [23-24].

The persistence of high levels of IL-18 in patients with sJIA receiving canakinumab may explain the development of lung damage in children being in remission under the biological treatment [25].

In interleukin-18-dependent diseases, specific therapy with interleukin-18-binding protein is required, since other treatments may be ineffective [7].

It is known that the lungs are the main source of physiological production of interleukin 1ß and interleukin-6. These proinflammatory cytokines, as well as the levels of the endogenous antagonist of interleukin-1 receptors, are higher in children under the age of 4 years, which may explain the higher frequency of ILD in younger children. [26-29]

Interleukin-1β, interleukin-6, and interferon-γ are the main cytokines involved in the pathogenesis of sJIA and MAS.[1] The same cytokines play a key role in lung tissue damage, in particular, due to activation and/or dysfunction of macrophages in the pulmonary interstitium. [20-22] Hyperinfection and increased regulation of innate immunity lead to an increase in the production of interleukin-1β, which stimulates the levels of granulocyte-macrophage colony-stimulating factor (GM-CSF), as well as hyperproduction of surfactant and its accumulation in tissues and impaired clearance. Elevated levels of interleukin-6 inhibit the production of type II bone morphogenetic protein receptors, which control cell growth and differentiation. Interleukin-18, associated with the interferon-γ signaling pathway, is also associated with severe forms of MAS and ILD in patients with sJIA. The level of this cytokine remains elevated, despite the control of systemic inflammation by interleukin-1 or interleukin-6 blockade. This may explain lung damage in patients with sJIA who are in remission with interleukin-1 and interleukin-6 blockade. [23-25] Chronic lung inflammation with accumulation of surfactant and lipoproteins in the alveoli leads to interstitial

pulmonary fibrosis, decreased elasticity of the pulmonary artery with the formation of pulmonary hypertension. [1] A brief pathogenesis of lung damage in sJIA is shown in Figure 3.

Pulmonary arterial hypertension

The pathogenesis of PAH is a result of systemic inflammation with proinflammatory cytokine dysbalance. It's known, that the low expression of *BMPR2* (bone morphogenic protein receptor type II) associated with potential endothelial dysfunction and PAH, in turn, one of the central cytokines in the pathogenesis of systemic arthritis (IL-6) *in vitro* BMPR reduced its activity. [30-32]

Radiological findings of the interstitial lung involvement

In clinical practice, radiological methods are often used to diagnose lung lesions. SJIA-LD is characterized by compaction/infiltration of lung tissue, thickening of the interlobular septa, and damage to the peripheral parts of several lobes, mainly basal, para mediastinal, or anterior parts of the upper lobes in combination with the symptom of frosted glass, as well as the detection of enlarged lymph nodes with increased density in CT of the chest with contrast [1,3].

Outcomes of the patients with LD-sJIA

The most alarming problem of SJIA-LD is high mortality and short life expectancy since the development of lung damage. According to available data, 68% (n = 17) of patients died after 8.8±11.4 months. from the onset of lung damage. [4] Unfortunately, mortality was about 40 times higher in the group of people with SJIA-LD [3] In males, hypoxia at the beginning of lung damage, and neutrophilia in bronchial lavage (more than 10 times higher) were considered the main predictors of death. [3,32]

Management of the patients with LD-sJIA

In managing children with interstitial lung disease, a multidisciplinary approach is required with the participation of specialists in various fields, including a

rheumatologist, pulmonologist, infectious disease specialist, rehabilitation specialist, psychologist, transplant surgery, as well as comprehensive laboratory and instrumental support, including, in particular, spirometry, pulse-oximetry, assessment of diffusion ability lung, computed tomography of the chest, echocardiography with assessment of pressure in the pulmonary artery, electrocardiography, assessment of SJIA and MAS laboratory activity. Sometimes, with chronic progressive hypoxemia, lung transplantation is the only method that can prolong the patient's life. Knowledge of the pathogenesis of this condition is important for the formation of potential prediction markers, targeted therapy, and prognosis. The following studies are needed to find the predictors, pathogenesis, and treatment options, for preventing and treating the ILD in sJIA patients.

Limits of the study

The main limitations of this study are related to the retrospective analysis and the very small sample size. The authors could not influence the treatment and could not if the treatment chosen in the past could influence the development of the complication and its severity or not. The absence of molecular studies decreased the value of this study.

CONCLUSION

ILD is a severe life-threatening complication of sJIA that may affect children of different ages with different time intervals since the disease's onset. Extensive rash, serositis (especially pleuritis), full-blown MAS with transaminitis, lymphopenia, trisomy 21, eosinophilia, and biologic infusion reaction are the main predictors of ILD.

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