Exploring the development and long-term outcomes of SJIA-related lung disease in pediatric patients

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Introduction

Overview of Systemic Juvenile Idiopathic Arthritis (SJIA)

- Chronic autoinflammatory disease of childhood onset, representing 10-15% of the total juvenile idiopathic arthritis (JIA) population
- Characterized as arthritis accompanied by daily spiking fevers, a fleeting erythematous rash, and various extrarticular features
- Standard treatment utilizes a combination of NSAIDS, corticosteroids, immunosuppressants (i.e. methotrexate), and more recently, biologics targeted at the neutralization of key inflammatory cytokines interleukin-1 (anakinra and canakinumab) and interleukin-6 (tocilizumab) elevated in SJIA

Complications of SJIA

- Macrophage Activation Syndrome (MAS)
- Chronic interstitial lung disease (SJIA-LD)
- Pulmonary artery hypertension
- Hypertension

Clinical Findings and Features of SJIA-LD

<table>
<thead>
<tr>
<th>Number of patients with SJD-LD</th>
<th>Suspected SJD-LD</th>
<th>Probable SJD-LD</th>
<th>Definite SJD-LD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age at SJD diagnosis</td>
<td>1.7 years</td>
<td>3.6 years</td>
<td>3.6 years</td>
</tr>
<tr>
<td>Median age at SJD-LD diagnosis</td>
<td>16</td>
<td>16</td>
<td>13</td>
</tr>
</tbody>
</table>

Chest CT Findings

<table>
<thead>
<tr>
<th>Features on Baseline Chest CT</th>
<th>Proportion of total patients</th>
<th>Proportion requiring O2 supplementation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleural thickening</td>
<td>0.353</td>
<td>0.33</td>
</tr>
<tr>
<td>Septal thickening</td>
<td>0.647</td>
<td>0.45</td>
</tr>
<tr>
<td>Bronchopulmonary/vascular</td>
<td>0.382</td>
<td>0.46</td>
</tr>
<tr>
<td>Thickening</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tree-in-bud opacities</td>
<td>0.118</td>
<td>0.50</td>
</tr>
<tr>
<td>Ground-glass opacities</td>
<td>0.382</td>
<td>0.62</td>
</tr>
<tr>
<td>Pleural thickening</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary artery enlargement</td>
<td>0.235</td>
<td>0.38</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>0.412</td>
<td>0.43</td>
</tr>
<tr>
<td>Pulmonary artery enlargement</td>
<td>0.059</td>
<td>0.56</td>
</tr>
</tbody>
</table>

Objectives

This study aims to look at the following:

- Treatment/intervention strategies for SJIA patients after lung disease diagnosis
- Prognostic predictors for patients who exhibit poor outcomes
- Long-term outcomes for SJIA-LD patients in terms of morbidity and mortality

Study population and design

- Prospective cohort study of 34 patients were identified based on the following criteria:
  - Suspected SJD-LD: either of the following, not due to lung disease that predated SJIA diagnosis, infection, or other identifiable cause: (1) objective findings on clinical exam (including but not limited to tachycardia, cough or shortness of breath, abnormal findings on chest imaging)
  - Probable SJD-LD: both clinical findings and chest imaging findings as above; OR pulmonary hypertension as measured by echocardiogram
  - Definite SJD-LD: chronic illness consistent with interstitial lung disease, pulmonary arterial hypertension, and/or pulmonary artery hypertrophy
- Clinical data were abstracted from patient medical records
- Study was approved by CCHMC IRB, and written informed consent was obtained from all patients and their legal guardians

Conclusions

- Median age at SJIA diagnosis is 1.7 years and median age at SJIA-LD diagnosis is 3.6 years
- Most prevalent clinical features of SJIA patients at lung disease diagnosis are clubbing, dyspnea, cough, tachycardia, and supplemental oxygen requirement
- Overall use of the three main biologics for SJIA treatment (AN, TCZ, CAN) decreased post SJIA-LD diagnosis, while use of the JAK inhibitor tofacitinib increased post SJIA-LD diagnosis. Use of methotrexate, cyclosporine, A, corticosteroids, and tacrolimus post SJIA-LD remained comparable to use prior to lung disease diagnosis
- Usage of medications primarily used in the treatment of lung disease increased post SJIA-LD diagnosis
- Most common feature seen on baseline chest CT for patients diagnosed with SJIA-LD is septal thickening. However, the features with the greatest proportion of patients requiring O2 supplementation are ground-glass opacities, tree-in-bud, and PA enlargement
- While overall survival is ~90%, there is a steady increase in the proportion of patients requiring home oxygen in the first 500 days. In total, 15 out of the 34 patients required supplemental oxygen, with all but 1 patient requiring supplemental oxygen within the first 500 days

Future Directions

- To track long-term disease outcomes by sending out periodic follow-up surveys for patients who were referred to CCHMC for consultation or secondary opinion and are regularly followed by an outside primary rheumatologist and/or pulmonologist
- To elucidate the underlying biological mechanism and pathogenesis of SJIA-LD. Previous studies showing differences in the cytokine profile of children with SJIA-LD compared to those without lung disease, such as elevated E- and IFN-γ pathway activation, and T cell function, suggest that there exist distinct activated cell subsets and cell states associated with SJIA-LD.
- Further characterization of the specific activated immune subsets in patients with SJIA-LD will help better define patients at risk for this LD as well as establish strategies to screen for early onset

Acknowledgements

- Thank you to the patients and families for their participation in this study and the clinicians who have referred patients for evaluation.
- Special thanks to the SMURRF program and the Schulert lab for this wonderful experience
- This project is supported by the Systemic Juvenile Idiopathic Arthritis Foundation, the NIH (National Institute of Arthritis and Musculoskeletal and Skin Diseases grant R03-AR-07677), and a Cincinnati Children's Research Foundation ARC grant.