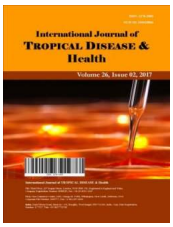

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STAT 3 Mutations, *Giardia* Infection and the IL-17 Pathway

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Author's contribution

The sole author designed, analyzed and interpreted and prepared the manuscript.

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Short Communication

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ABSTRACT

Parasitic infections may be common in endemic areas. *Giardia* spp. infections are widespread and not endemic to one region. The combined presence of parasitic infections and high serum immunoglobulin level E (IgE) levels, can be found in isolation or as a clinical manifestation of certain immune defects.

The Hyper-IgE syndromes (HIES) as a group of distinct primary immune disorders should be considered in the differential and treatment of parasitic disease. The aim of this study was to highlight the importance of recognizing underlying immune defects in the clinical setting of parasitic infection, including HIES.

Keywords: HIES; Giardia; job's syndrome.

1. INTRODUCTION

Hyper IgE syndromes are characterized by immune defects leading to recurrent infections and abscesses, based on diminished immune and inflammatory responses. Patients with the Autosomal Dominant form of HIES have heterogeneous mutations in the Signal Transducer and Activator of Transcription factor 3 (STAT 3) gene. The defects result in T helper

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cell population 17 (Th-17) related, impairment of host defenses against *Giardia* spp., and against other infections including *Staphylococcus* species [1].

Other mutational defects associated with Hyper-IgE include those in DOCK 8 (Dedicator of cytokinesis 8) and PGM3 (Phosphoglucomutase 3). Hyper-IgE responses are important in host defense against parasitic infections, but these infections may be related to underlying immune defects [2].

Specifically, the presence of STAT 3 mutations which lead to dysregulation of IgE production, and are associated with clinical features such as atopic dermatitis and recurrent lung infections, should be considered in the presence of parasitic *Giardia* spp. infection of the gastrointestinal tract.

2. CLINICAL CONSIDERATIONS

In the evaluation of patients with parasitic disease, the anticipated elevation of serum IgE in the presence of certain features may lead to the diagnosis of an underlying primary immune defect. The infections caused by a variety of fungi and *Staphylococcus* bacteria, leading to skin and lung abscesses can be important in recognition of the diagnosis. The gastrointestinal disease is variable among these patients, but may be associated with eosinophilia. Thus, physical examination and pattern of microbiologic signatures are useful in identifying those patients with parasitic disease who may have an underlying primary immune defect.

3. GIARDIA INFECTION AND HOST DEFENSE

Giardia spp. is a protozoan parasite that causes the disease giardiasis. Clinical symptoms of abdominal pain and watery diarrhea are common. Immune responses involve CD 4 T cells that stimulate the production of antibodies by B cells. B cell independent CD 4 regulated responses include the IL-17 pathway [3]. The recognition of the role of the Th-17 mediated immune response to the infection is important clinically, since patients with IL-17 pathway defects may present with protracted gastrointestinal infections.

Autosomal Dominant (AD)-HIES is associated with gastrointestinal and multi-system disease manifestations. Among these are the presence of a prominent forehead, retention of primary teeth and scoliosis. The gastrointestinal disorders associated with AD-HIES include GI lymphoma, dysmotility, and eosinophilic esophagitis. The patients afflicted with this disease, are more prone to Salmonella and *Giardia* spp. infections [2].

In the evaluation of a patient with *Giardia* spp. an immune defect in the production of IL-17 can be considered in the context of the patient's history, physical examination findings and patterns of prior infections.

4. LABORATORY FINDINGS AND IMMUNE PROFILING

One of the hallmark laboratory results for patients with AD-HIES is an extremely elevated serum IgE level. The differential diagnosis of this finding includes parasitic disease and allergic pulmonary broncho-aspergillosis (ABPA). The serum IgE in childhood is typically greater than 2000 IU/ml. The serum levels of IgA, IgM and IgG are normal, and specific antibody responses may be lower or normal. Cellular profiles may include neutropenia [2].

Lymphocyte profiling reveals low memory B and T cells. Further analysis reflects a defect in the IL-17 responses with very low numbers of IL-17 producing Th-17 cells. STAT 3 is a key transducer protein for many cytokines, including IL-17. STAT 3 is required for the differentiation of naïve T cells into Th-17 cells. Th-17 responses have been found to be aberrant even among HIES patients without STAT 3 mutations [3,4].

Primary immune defects in general, may have susceptibility to infection with protozoan *Giardia* spp., and in one study of 115 primary immunodeficiency -related hospital admissions, over a 14 year time period, there were 23 cases of gastroenteritis [5]. The most common cause was related to *Giardia* spp. infection. Parasitic disease may cause atypical and severe infections among patients with primary immune defects.

Common variable immunodeficiency or CVID is characterized by impaired B-cell differentiation, and is associated with defective production of immunoglobulins. In addition, CVID patients have variable T cell defects such as deficient T helper cell function. The prevalence of diarrhea among patients with combined variable immunodeficiency (CVID) varies. In one retrospective study of 37 CVID patients, there were 23 patients with diarrhea. *Giardia* spp. was

the causative agent in 53.8% of these cases [6]. In a French study of the DEFI group, 252 patients with CVID were studied. Among these patients, 118 had a report of chronic diarrhea. *Giardia* spp. was the most common cause identified, and occurred among 35 patients. While respiratory tract infections are the most common, and 240 patients in this cohort experienced respiratory difficulty, the presence of a protozoal gastrointestinal infection may signify T cell impairment [7].

5. CONCLUSIONS

The Hyper-IgE syndromes comprise a group of primary immune defects with distinct genetic mutational defects. Patients may be prone to parasitic disease based on defects affecting the IL-17 pathway. Upon presentation of patients with parasitic disease, particularly in non-endemic areas, evaluation for HIES may be indicated. Further studies can be conducted to elucidate the immune mechanism of gastrointestinal parasitic disease among these patients.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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