

Short communication

STAT 3 mutations, Giardia infection and the IL-17 pathway

Abstract:

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

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Comment [d3]: Immunoglobulin E (IgE)

The Hyper-IgE syndromes as a group of distinct primary immune disorders should be considered in the differential and treatment of parasitic disease.

Key Words:- HIES, *Giardia*, Job's syndrome

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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 gene. The defects result in Th-17 related impairment of host defenses against *Giardia* and other infections including *Staphylococcus* (1).

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Other mutational defects associated with Hyper-IgE include those in DOCK8 (Dedicator of cytokinesis8) 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).

Comment [d6]: Dedicator of cytokinesis 8

Specifically, the presence of STAT3 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* infection of the gastrointestinal tract.

25 Clinical Considerations:

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

Comment [d7]: Staphylococcus spp.

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33 Giardia Infection and Host Defense:

34 Giardia spp. is a protozoan parasite **found globally** that causes the disease giardiasis. Clinical symptoms
35 of abdominal pain and watery diarrhea are common. Immune responses involve CD4 T cells that
36 generate anti-Giardia antibodies. B cell independent CD4 regulated responses include the IL-17 pathway
37 (3).

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38 AD-HIES is a primary defect with Gastrointestinal and multi-system disease manifestations. Among these
39 **include** the presence of a prominent forehead, retention of primary teeth and scoliosis. The
40 Gastrointestinal disorders associated with AD-HIES include GI lymphoma, dysmotility, and eosinophilic
41 esophagitis. **The patients afflicted with this disease** are more prone to Salmonella and Giardia infections
42 (2).

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

46 Laboratory findings and immune profiling:

47 One of the hallmark laboratory results for patients with AD-HIES is an extremely elevated serum IgE
48 level. The differential of this finding includes parasitic disease and allergic pulmonary
49 bronchoaspergillosis (ABPA). The serum IgE in childhood is typically greater than 2000 IU/ml. The levels
50 of IgA, M and G are normal and specific antibody responses may be lower or normal. Cellular profiles
51 may include neutropenia (2).

52 Lymphocyte profiling reveals low memory B and T cells. Further analysis reflects a defect in the IL-17
53 responses with very low numbers of IL-17 producing Th-17 cells. STAT 3 is a key transducer protein for
54 many cytokines, including IL-17. STAT 3 is required for the differentiation of naïve T cells into Th-17 cells.
55 Th-17 responses have been found to be aberrant even among HIES patients without STAT 3 mutations
56 (3, 4).

57 Conclusions:

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

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