Chapter 11

Immunologic Complications in Dyskeratosis Congenita and Hoyeraal-Hreidarsson Syndrome

Fabien Touzot, MD, PhD (Fabien.touzot@nck.aphp.fr)
Sainte-Justine Hospital, University of Montreal, Montreal, QC, Canada

Soma Jyonouchi, MD (jyonouchi@email.chop.edu)
Children's Hospital of Philadelphia, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA

Patrick Revy, PhD (partick.revy@inserm.fr)
INSERM UMR 1163, Laboratory of Genome Dynamics in the Immune System, Paris Descartes – Sorbonne Paris Cité University, Imagine Institute, Paris, France

Introduction

Immune cells are highly proliferative upon stimulation by antigens. Hence, lymphocytes are particularly vulnerable to the effects of telomere dysfunction. An accelerated decline in the number and function of peripheral mature immune cells, a phenomenon known as immune senescence, also contributes to the pathophysiology of DC/HH [1, 2]. Additionally, it is possible that the dysfunction of

the hematopoietic environment, from which immune cells originate, contributes to immune dysfunction in these disorders [3]. Individuals with DC and HH can exhibit a progressive immune deficiency manifesting as increased susceptibility to life-threatening infections, the severity of which worsens with age. Immunologic complications are one of the common features of DC and HH and contribute to the premature mortality seen in these disorders [4]. This chapter summarizes the main immunologic complications observed in individuals wiht DC/HH and the recommendations to evaluate and manage them. Each patient requires their own treatment plan, managed in collaboration with immunologists, hematologists, and other specialists.

Immunological Features of Individuals with DC and HH

Lymphopenia (low numbers of lymphocytes) is the most common immunological abnormality observed in patients with DC and HH (70 % of patients) [1, 2]. A decreased count of B cells and NK cells are the most remarkable signs of these syndromes. In particular, a virtual absence of B lymphocytes is often observed in HH from birth [5-12]. B lymphocytes produce antibodies (immunoglobulins known as IgG, IgM, or IgA) and are part of what is known as the humoral immune system. Low numbers of B lymphocytes is one of the most consistent immunological features of DC/HH and results in hypogammaglobulinemia that can affect all immunoglobulin subtypes (IgG, IgM, or IgA). The antibody response toward specific antigens is sometimes impaired, which may reduce the response to vaccinations. The marked involvement of B lymphocytes in DC and HH is likely due to the additional cell proliferation which B lymphocytes undergo during their development (thus resulting in accelerated telomere shortening) coupled with a shorter life span than T lymphocytes [13]. The T cell compartment is less frequently affected as T cells subsets' absolute number and function is often normal in

DC and HH. However, some patients exhibit a decrease in T cell counts (CD4 and/or CD8 counts), inversion of CD4/CD8 ratio, and a prematurely advanced naive to memory (CD45RA/CD45RO) T cell transition [9]. Abnormality of T cell proliferation to specific antigens (candida and tetanus), and less frequently to mitogens, indicating reduced T cell function, has also been observed [14].

Clinical Presentation of the Immunodeficiency

Individuals with DC or HH often have markedly variable clinical features of immunodeficiency – from severe combined immunodeficiency (SCID)–like presentation in infancy to much milder presentation in adolescents mimicking common variable immunodeficiency (CVID). Opportunistic infections (e.g., Pneumocystis Jirovecii infection or CMV infection) are seen in individuals with T cell dysfunction. The antibody deficiency is associated with recurrent sinus and/or lung infections. The most prominent immune-mediated clinical feature of infant-onset DC or HH is a severe, chronic, non-infectious enteropathy. The histopathological hallmark of the intestinal involvement is the presence of mucosal inflammation and apoptosis (similar to what is observed in gut graft versus host disease) associated with intractable diarrhea. It is unclear if this enteropathy results only from a defect in the renewal of the digestive epithelium or if gut mucosal immune dysfunction also participates in the pathophysiology of this feature. Strikingly, some patients presenting with such enteropathy have benefited from anti-TNF-alpha monoclonal antibody (infliximab or adalimumab).

Immune Evaluation of Individuals with DC and HH

As immune abnormalities can precede the development of clinically significant pancytopenia in individuals with DC/HH, they might be underdiagnosed, undertreated, and lead to premature mortality because of severe infections. Thus, all newly diagnosed patients would benefit from a complete immunological evaluation consisting of

complete blood cell counts as well as a numeration of lymphocyte subsets performed by flow cytometry: CD3+CD4+ and CD3+CD8+ T cells (with naive and memory subsets based on the expression of CCR7 or CD62L and CD45RA), CD56+CD3+ NK cells, CD19+ B cells and CD27+CD19+ memory B cells. Assessment of lymphocyte proliferative responses to the mitogens (mainly phytohemagglutinin) should be performed if the patient's clinical features include a severe combined immunodeficiency (i.e., CD3+ cells below 500 per mm3). Serum immunoglobulin levels (IgG, IgA, and IgM) should be evaluated as well as tetanus, diphtheria, and pneumococcal antibody titers.

Management of the Immune Deficiency

Treatment of patients depends on the clinical presentation and degree of immune dysfunction. Antimicrobial prophylaxis with trimethoprim-sulfamethoxazole (5-6 mg/kg TMP component three times a week) may be recommended for patients at risk for opportunistic infection due to severe T cell lymphopenia. Intravenous (IV) or subcutaneous (SC) immunoglobulin replacement (400 to 600 mg/kg monthly for IV and 100 to 150 mg/kg weekly for SC) is indicated in case of recurrent bacterial infections resulting from low antibody levels. The annual influenza vaccination is recommended, especially in case of pulmonary involvement, even for patients with immunoglobulin substitution, as cellular immunity plays an important role in the resolution of influenza virus infection, and new strains of influenza are typically not represented in the antibody repertoire of immunoglobulin substitution [15].

Immunologic Improvement by Hematopoietic Cell Transplantation

As mentioned above, the immunologic complications observed in DC/HH patients mainly stem from bone marrow failure that compromise the development of a functional immune system. Thus, hematopoietic cell transplantation (HCT, see Chapter

13, Hematopoietic Stem Cell Transplant) is a treatment that can improve the immunological status of the patients. The clinical benefit of a partial reconstitution of the immune system in bone marrow failure syndromes, including DC, has been demonstrated in rare patients who experienced a spontaneous genetic reversion (i.e., the correction of the genetic mutation) in cells from the immune/hematopoietic compartment [16-18]. In these cases, the genetic reversion confers a strong selective advantage of the corrected cells that can, at least in part, reconstitute an efficient immune system and protect patients. This rare phenomenon of genetic reversion appears to be highly beneficial for the patients in terms of immunologic complications. Therefore, by analogy, the severe immunodeficiencies observed in DC-HH patients can be cured by HCT. However, as described in Chapter 13, Hematopoietic Stem Cell Transplant, HCT can be associated with significant complications and long-term concerns and does not correct the non-hematopoietic abnormalities seen in this disease.

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