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Novel insights from adaptor protein 3 complex deficiency

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Hermansky-Pudlak type 2 is an autosomal recessive disorder characterized by oculocutaneous albinism, bleeding disorders, recurrent infections, and moderate/severe neutropenia. The disease is caused by mutations in the *AP3B1* gene encoding for the β3A subunit of the adaptor protein 3 (AP-3) complex. Because the expression of the β3A subunit is normally ubiquitous, its deficiency leads to a precise phenotype in cells with a large number of intracellular granules, such as neutrophils, natural killer cells, cytotoxic T lymphocytes, platelets, and melanocytes. Given the AP-3 deficiency, the lysosomal membrane proteins are not appropriately sorted to the granules but are delivered to plasma membrane with subsequent effects on cell development and differentiation. Missorting of proteins (eg, tyrosinase) in melanocytes and platelets accounts for oculocutaneous albinism and bleeding disorders, respectively. Absence of AP-3 leads to low intracellular content of neutrophil elastase and consequently to neutropenia. Abnormal movement of lytic granules and reduced perforin content in cytotoxic T lymphocytes and natural killer cells account for their respective defects in cytolytic activity. It is likely that the investigation of the physiopathology of Hermansky-Pudlak type 2 syndrome will reveal nonredundant functions of this adaptor protein in the intracellular trafficking of membrane proteins. (J Allergy Clin Immunol 2007;120:735-41.)

Key words: *Hermansky-Pudlak syndrome, NK cells, neutropenia, cytotoxicity, albinism, platelets*

Abbreviations used
AP: Adaptor protein
CTL: Cytotoxic T lymphocyte
GS: Griscelli syndrome
HLH: Hemophagocytic lymphohistiocytosis
HPS: Hermansky-Pudlak syndrome
NE: Neutrophil elastase
NK: Natural killer
NKT: Natural killer T
SCN1: Severe congenital neutropenia
TGN: Trans-Golgi network

Oculocutaneous albinism and immunodeficiency constitute the common clinical manifestations of a heterogeneous group of genetically inherited disorders that includes Hermansky-Pudlak syndrome (HPS) type 2, Chediak-Higashi syndrome, Griscelli syndromes (GSs) 1 and 2, and the endosomal-adaptor protein p14 deficiency (Table I).[1-5] HPS2 is an autosomal-recessive disease caused by mutations of the *AP3B1* gene encoding for the β3A subunit of the heterotetrameric adaptor protein (AP) 3 complex. Immunologic studies of these genetic defects have revealed the essential role of a set of genes and of the related proteins for formation of secretory lysosomes.[6,7] These intracellular granules, which are also known as lysosome-related organelles, are essential constituents of melanocytes, platelets, natural killer (NK) cells, cytotoxic T lymphocytes (CTLs), and polymorphonuclear cells. Because lysosome-related organelles have important functions in the maintenance of cell homeostasis, their abnormal formation has a profound effect on the correct functioning of immune system. Abnormal granule formation in these cell types leads to hypopigmentation, impaired NK cell and CD8 cell cytotoxicity, neutropenia, and/or neutrophil dysfunction.[8]

In addition to oculocutaneous albinism and immunodeficiency, HPS2 is also characterized by hemorrhagic diathesis and prolonged bleeding time caused by impaired platelet aggregation. In this respect, HPS2 resembles the

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TABLE I. Comparison of HPS2 with other causes of partial albinism and immunodeficiency

	HPS2 (AP-3 complex deficiency)	Chediak-Higashi syndrome	GS1	GS2	p14 Deficiency	HPS1
Oculocutaneous albinism	+	+	+	+	+	+
Absent platelet dense bodies	+	+	–	–	–	+
Giant intracellular granules	–	+	–	–	–	–
Neutropenia	+	+	+	+	+	–
CTL and/or NK cell dysfunction	+	+	–	+	+	–
Hemophagocytosis syndrome	+/–	+	–	+	–	–

typical manifestations of the heterogeneous groups of disorders known as Hermansky-Pudlak syndromes.[9]

CLINICAL MANIFESTATIONS OF AP-3 DEFICIENCY

Although HPS2 syndrome is characterized by oculocutaneous albinism, recurrent infections, and hemorrhagic diathesis, the same clinical signs are also observed in other inherited diseases of the immune system that are characterized by skin hypopigmentation (eg, Chediak-Higashi syndrome, GSs) or platelet functions (HPSs 1, 3-8; Table I).[9-12]

The first manifestations of HPS2 are detectable already at birth, when the affected children present horizontal nystagmus, sparse white hair that may darken over time, and the typical signs of ocular hypopigmentation, including iris transillumination and hypopigmentation areas of fundus.[3,13,14] In contrast, other features such as dysmorphic face and marked pectus deformity of anterior ribs may not be evident until childhood. At that stage, the distinctive facial features of children with HPS2, such as epicanthal folds, posteriorly rotated ears, broad nasal root, and retrognathia, will become manifest. Despite the normocephalic cranium, children with HPS2 may show mild development delay. In some of the patients, poor balance and intentional tremor have been described, but they usually achieve major milestones on time. Some other symptoms are inconsistently observed in all patients with HPS2. Variable symptoms of the disease include pulmonary fibrosis developing in childhood, dysplastic acetabulae, liver and spleen enlargement, and moderate thrombocytopenia.[3,15]

From infancy, patients with HPS2 present numerous episodes of upper respiratory infections, otitis media, and pneumonia, which are usually responsive to antibiotic therapy. They also display an increased susceptibility and severity course of viral infections caused by cytomegalovirus, EBV, respiratory syncytial virus, influenza A, and parainfluenza viruses.[3,13-16] Despite that, all patients with HPS2 have shown good tolerance for live vaccines including varicella and measles/mumps/rubella and normal antibody production after immunization.[13] However, in one 3-year-old patient with HPS2, an upper airway infection, probably caused by parainfluenza virus, rapidly progressed to respiratory failure and subsequently to hepatosplenomegaly, pancytopenia, and bone marrow hemophagocytosis, which are clinical signs of hemophagocytic lymphohistiocytosis (HLH). This severe disease complication was unresponsive to chemotherapy treatment, according to the HLH-2004 protocol, and led to the child's death before bone marrow transplantation could be attempted.[15] Although HLH is observed in other primary immunodeficiencies characterized by oculocutaneous albinism and impairment of NK cell cytotoxicity, such as Chediak-Higashi syndrome and GS2, this child is the first patient with HPS2 to develop this life-threatening condition (Table I).[10,11] On the basis of our current knowledge of the disease, it is impossible to know whether this event is related to the partial impairment of NK cell cytotoxicity and whether it might recur in other patients with HPS2. Alternatively, the development of HLH in this child affected by HPS2 might be related to his peculiar genotype. Besides being homozygous for a mutation of *AP3B1*, this patient had an heterozygous mutation of *RAB27A*, which is the causative gene of GS2,[15] thereby increasing the risk of HLH. However, the low number of subjects with HPS2 reported to date is insufficient to rule out either 1 of the 2 alternative hypotheses.

Laboratory investigation of patients with HPS2 usually reveals neutropenia and severely impaired CTL and NK cell cytotoxicity, whereas lymphocyte subpopulations and proliferative response to mitogens are normal.[3,13-18] Neutropenia (neutrophil counts from 0 to 1600 cells/μL) is associated with incomplete maturation arrest at the stage of promyelocytes. However, neutrophil numbers usually increase during infectious episodes and show a good response to treatment with granulocyte stimulating factor.[13,15,16]

Recurrent epistaxis and prolonged bleeding after teeth extraction is observed in most patients with HPS2, but some patients may not experience any obvious episode. Investigation of platelets in patients with HPS2 demonstrates reduction of dense bodies as shown by electron microscopy, prolonged bleeding time (>15 minutes), and abnormal response to collagen and adenosine diphosphate, but normal response to ristocetin in platelet aggregation studies.[3,13]

All 9 patients with HPS2 described to date are homozygous or composite heterozygous for mutations in the gene *AP3B1* encoding for the β3A subunit of the heterotetrameric AP-3 complex (Table II).[19] The majority of mutations described result in complete absence of β3A protein expression; moreover, in most of cases, the