Primary immunodeficiency associated with hypopigmentation: A differential diagnosis approach

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Abstract
Primary immunodeficiency diseases (PIDs) are a group of more than 400 disorders representing aberrant functioning or development of immune system. Hypopigmentation syndromes also characterize a distinguished cluster of diseases. However, hypopigmentation may also signify a feature of genetic diseases associated with immunodeficiency, such as Chediak-Higashi syndrome, Griscelli syndrome type 2, Hermansky-Pudlak syndrome type 2 and type 10, Vici syndrome, and P14/LAMTOR2 deficiency, all of which are linked with dysfunction in vesicular/endosomal trafficking. Regarding the highly overlapping features, these disorders need a comprehensive examination for prompt diagnosis and effective management. As an aid to clinician, distinguishing the pathophysiology, clinical phenotype, and diagnosis as well as treatment options of the six mentioned PID disorders associated with hypopigmentation are described and discussed in this review.

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Introduction

Primary immunodeficiency diseases (PIDs) are an extremely diverse group of disorders, resulting from insufficient or abnormal functioning of the immune system. There are more than 400 distinct disorders to date associated with 430 gene defects, classified as PID. However, the number of recognized disorders is increasing rapidly as a result of remarkable advancements in sequencing technology.\(^1\)

Predominantly, PIDs are due to monogenic defects with different inheritance patterns and variable penetrance, which result in a broad spectrum of, sometimes overlapping, symptoms, which may complicate the diagnosis.\(^2,3\) It is supposed that millions of people are living with PID worldwide, but a small proportion of them are identified. The delay in diagnosis may lead to longer hospitalization and higher morbidity.\(^4,5\)

These diseases are not limited to the conditions of susceptibility to infection. A wide spectrum of dysregulation, from immunodeficiency to autoinflammation, lymphoproliferation, and malignancy, gives rise to immunological manifestations of PID along with multi-organ involvement. Therefore, it is suggested to use the term “inborn errors of immunity” as a substitute.\(^6,7\)

Several organs and systems of the human body may be involved with these diseases. Gastrointestinal, pulmonary, and skin manifestations are among the most common phenotypes.

This article focuses on PIDs that also manifest with oculocutaneous hypopigmentation, including Chediak-Higashi syndrome (CHS), Griscelli syndrome type 2 (GS2), Hermansky-Pudlak syndrome type 2 (HPS2), Hermansky-Pudlak syndrome type 10 (HPS10; it has replaced HPS9), Vici syndrome (VIVIS), and P14/LAMTOR2 deficiency. Secretory lysosomes are the key to the linkage of albinism and immunity. Many studies support the hypothesis that LYST is a scaffold protein with 3801 amino acids, commonly known as LYST. The amino terminus of LYST consists of ARM/HEAT repeats, which are known to be involved in vesicular trafficking and membrane interaction. Mutation analysis of LYST revealed the involvement of ARM/HEAT domain in degranulation, while BEACH domain is necessary for granule movement and polarization at the immunological synapse.\(^15–18\) Many studies support the hypothesis that LYST is a scaffolding protein, while many others indicate that it may act as a cytoskeletal component. Mutations in LYST also alter cyclic nucleotide levels, suggesting that it may play a role in cell signaling pathways.\(^16,19\)

Compound heterozygous mutations, loss of heterozygosity, and homozygous mutations resulting from uniparental isodisomy are commonly reported in CHS patients.\(^22,23\) There may be a correlation between the type of mutation and the phenotypic presentation; a frameshift mutation isodisomy are commonly reported in CHS patients.\(^22,23\) There may be a correlation between the type of mutation and the phenotypic presentation; a frameshift mutation arising from deletions, or a nonsense mutation giving rise to severe early-onset CHS whereas missense mutations

Method

A search was conducted in Pubmed/MEDLINE, Scopus, and Google Scholar, using the following terms: “Inborn errors of immunity,” “Primary immunodeficiencies,” “Oculocutaneous albinism,” “Hypopigmentation syndromes” as well as specific terms for each disease and their equivalents. Only English documents were included (except for the original study which identified a disease, referred to in the “History” sections) and no time limit was applied.

Chediak-Higashi Syndrome (CHS)

History

This disease was originally described by Cuban pediatrician Antonio Béguez Caesar in 1943 as “Familial chronic malignant neutropenia with atypical granulations in the leukocytes,” and then by Steinbrinck in 1948.\(^10\) Alejandro Moisés Chédiaik in 1952 and Otokata Higashi in 1954 defined this disease as “new leucocytal anomaly” and “congenital gigantism of peroxidase granules,” respectively.\(^11,12\) Sato noticed the consistency between these two papers and suggested the name “Chédiaik and Higashi’s Disease or Chédiak-Higashi’s Leuco-anomaly” for this condition.\(^13\)

Pathophysiology

Chediak-Higashi (OMIM 214500) is an autosomal recessive disease caused by mutations in Lyssosomal Trafficking Regulator gene (LYST), also called CHS or CHS1. LYST is mapped to a five-centimorgan sequence in chromosome segment 1q42.1–42.2.\(^14\) This gene encodes a cytosolic protein with 3801 amino acids, commonly known as LYST. The structural analysis of LYST protein points to its probable functions; carboxyl terminus residues form a pleckstrin homology (PH)-like domain followed by a BEACH domain and WD-40 repeats (Figure 1). While WD-40 repeats are known to be associated with protein–protein interactions, little is known about the function of BEACH domains. They may play a role in vesicular trafficking and are identified in eight other human proteins, named BEACH Domain Containing Proteins (BDCPs), all associated with well-known diseases such as cancer, common variable immunodeficiency (CVID), autism, and systemic lupus erythematosus (SLE). The amino terminus of LYST consists of ARM/HEAT repeats, which are known to be involved in vesicular trafficking and membrane interaction. Mutation analysis of LYST revealed the involvement of ARM/HEAT domain in degranulation, while BEACH domain is necessary for granule movement and polarization at the immunological synapse.\(^15–18\) Many studies support the hypothesis that LYST is a scaffolding protein, while many others indicate that it may act as a cytoskeletal component. Mutations in LYST also alter cyclic nucleotide levels, suggesting that it may play a role in cell signaling pathways.\(^16,19\)

Compound heterozygous mutations, loss of heterozygosity, and homozygous mutations resulting from uniparental isodisomy are commonly reported in CHS patients.\(^22,23\) There may be a correlation between the type of mutation and the phenotypic presentation; a frameshift mutation resulting from deletions, or a nonsense mutation giving rise to severe early-onset CHS whereas missense mutations

Figure 1 The LYST gene encodes various known protein domains: ARM-HEAT repeats (Armadillo-Huntingtin, elongation factor 3, protein phosphatase 2A, and the yeast kinase T0R1), pleckstrin homology (PH)-like domain, Beige and Chediak-Higashi (BEACH), and a few WD-40 repeats (containing tryptophan-aspartic acid dipeptide). The presence of concanavalin A-like lectin and perilipin domains are also proposed, but the exact locations are not known yet.\(^15,18,20\) Burgess et al. suggested that the concanavalin A-like lectin domain may be enclosed by two ARM repeats.\(^21\)
result in mild late-onset atypical CHS without hemophagocytic lymphohistiocytosis (HLH) manifestations.⁴⁴

Cellular presentation of CHS is the presence of giant ring-shaped granules, with normal enzyme activity and pH, but impaired ability of polarization at the immunological synapse and exocytosis along with mixed identity. The distance of granules to the immunological synapse (IS) and microtubule-organizing center (MTOC) and the polarization of MTOC itself toward the immunological synapse are affected by CHS. Miscaloration of molecules specific to different cellular compartments, such as lysosome-associated membrane protein, late lysosomal markers (LAMP1 and LAMP2), early endosome antigen 1 (EEA1), and cat ion-independent mannose 6-phosphate receptor, transport vesicle marker (CI-M6PR), suggests that giant granules are made from a wide range of vesicle subtypes. Rab14, another lysosome size regulator, was also found to be increased in CHS NK cells. After silencing this molecule, the granule size and cytotoxicity were restored.⁵⁵-⁶⁶ The mechanism responsible for the formation of giant granules is not well established; fusion inhibition and fission activation are proposed as two possible functions for LYST, each of which is supported by several studies. The actual mechanism may be a combination of these two hypotheses.⁶⁷,⁶⁸ The impaired ability of CHS granules to fuse with the cell membrane and degranulate may be due to the structure of cortical actin meshwork, blocking the exocytosis pathway for large compartments.⁶⁹ This impaired exocytosis also results in defective membrane repair and delayed MHC class II antigen-presenting.⁷⁰,⁷¹

The presence of giant granules is reported in nearly all cell types of CHS patients. In addition to defective cytotoxicity of the immune system, giant granules are responsible for neurological symptoms caused by defective degranulation or membrane repair,⁷² and defective platelet aggregation because of abnormal shape or number of dense bodies, decreased serotonin and calcium as well as increased ATP-to-ADP ratio.⁷³⁻⁷⁵

**Sign and symptoms**

Chediak-Higashi syndrome patients are usually presented with silvery hair, skin hypopigmentation, recurrent infections, and neurological manifestations. Skin hypopigmentation is not complete as it is associated with hyperpigmentation in exposed areas; which may be more likely to be noticed compared with the general hypopigmentation.⁷⁴ Reduced iris pigmentation is another commonly reported presentation along with age-dependent visual loss, visual field constriction, and/or nystagmus.⁷⁵

Defective chemotaxis and microbicidal activity of immune cells result in increased susceptibility to infection. Recurrent infections of skin, respiratory tract, or, less commonly, gastrointestinal (GI) tract with pyogenic staphylococcus or streptococcus species are likely to occur. Viral and fungal infections are also reported in CHS patients. Otitis media, periodontitis, dental and subcutaneous abscess, oral ulcers, pneumonia, and enteritis are among the most commonly reported manifestations. However, in patients with atypical CHS, recurrent infections may be insignificant or absent.⁷⁶-⁸⁰

Neurological presentations, varying from intellectual disability to tremor or paraplegia, occur in all patients, even in those who have received stem cell transplants, and can start in any age. Neurological findings may include developmental delay, attention deficit disorder, learning difficulties, ataxia, seizures, defective tendon reflexes, extensor plantar response, L-dopa-responsive parkinsonism, dystonia, vibration sense deficits, rapid eye movement (REM) sleep behavior disorder (RBD), amyloid deposits, balance abnormalities, and paraparesis caused by cerebral or cerebellar atrophy, neuronal degeneration, endoneurial lymphohistiocytic infiltrates, and, probably, demyelinating polyneuropathy. There are also cases presented with involvement of peripheral nervous system. Neurological manifestations, years after undergoing bone marrow transplantation (BMT), are probably due to long-term progression of lysosomal defect.⁸¹,⁸²-⁸⁴

The bleeding diathesis observed in CHS is a result of coagulopathy related with defective platelet function and occasionally thrombocytopenia. Bleeding tendency of variable severity includes mucosal bleeding, easy bruising, epistaxis, and petechiae.⁸⁵

Most of the CHS patients develop a potentially fatal HLH, known as the accelerated phase. This hyperinflammatory condition can manifest as prolonged fever, hepatosplenomegaly, lymphadenopathy, neutropenia, thrombocytopenia, anemia, hypertriglyceridemia, hypofibrinogenemia, hyperferritinemia, and high levels of proinflammatory cytokines accompanied by edema and neurological findings.⁸⁶-⁸⁸ Phagocytosis of blood cells by macrophages contributes to the diffused lymphohistiocytic infiltrate, which can be seen in bone marrow, spleen, lymph nodes, skin, liver, and central nervous system (CNS). Defective NK cell and cytotoxic T lymphocyte activity may account for the clinical phenotype of HLH. It is suggested that the onset of accelerated phase can be triggered by an uncontrolled Epstein-Barr virus (EBV) infection.⁸⁹,⁹⁰

Patients with atypical phenotype present a milder form of the above-mentioned symptoms and they may be diagnosed late due to their insignificant manifestations. Neurological findings, if present, can be a key to diagnose atypical CHS.⁹¹

**Diagnosis**

The suspicion of CHS can be made when a child is presented with partial albinism and hyperpigmentation in exposed areas, along with pyogenic infections, or occasionally in the accelerated phase. A definitive diagnosis is established only after laboratory analyses; presence of giant granules in the cytoplasm of neutrophils, lymphocytes, eosinophils, and NK cells is a hallmark of CHS.⁹²,⁹³ The distribution of giant melanin granules in the hair shaft can also help in diagnosing CHS; melanin granules are larger in size and fewer in number compared with normal individuals. This method can distinguish between CHS and other hypopigmentation or silvery hair syndromes such as GS².⁹⁴-⁹⁶ The same distribution of melanin granules in skin biopsy can also lead to the diagnosis of CHS.⁹⁷

Genetic analysis of the LYST gene further confirms the diagnosis; next-generation sequencing is the most
efficient method because of the large size of the gene. A homozygous or compound heterozygous mutation in LYST determines CHS. We can identify carriers using mutation analysis, unlike hair shaft microscopy.\textsuperscript{55}

Neurological manifestations can be detected by magnetic resonance imaging (MRI) and computed tomography (CT) examination, which help a neurologist to suspect CHS when these presentations are accompanied by ocularcutaneous albinism (OCA). Prenatal diagnosis is possible using genetic testing of chorionic villus cells, amniotic fluid sample, or examining fetal white blood corpuscle (WBC) count.\textsuperscript{46}

**Treatment**

The only option to cure hematopoietic and immunological manifestations is allogenic hematopoietic stem cell transplantation (HSCT) from a human leukocyte antigen (HLA)-matched donor. This treatment is considerably effective in preventing recurrence of disease and death. However, there was a higher rate of mortality in patients who had developed the accelerated phase at the time of transplantation.\textsuperscript{30} To overcome this problem the patient must undergo HLH treatment prior to the transplantation procedure.\textsuperscript{35,52} Although stem cell transplantation reduces the probability of recurrent infections, it cannot prevent neurological manifestations.\textsuperscript{45} Therefore, rehabilitation should be considered to reduce neurological dysfunction. Parkinsonism, if present, can be cured with L-dopa therapy. Refractive errors can be corrected by lenses and/or rehabilitation and adaptive therapy prescribed by an ophthalmologist. Eyes and skin protection from sunlight is also critical in order to prevent further complications.\textsuperscript{38}

Administration of inactivated vaccines along with antiviral and antiviral treatments decreases the risk and fatality of infections.\textsuperscript{48,51}

It is suggested that granulocyte-colony stimulating factor (G-CSF) can increase WBC count and neutrophil function, which, in turn, reduces the probability of further infections.\textsuperscript{54,55} IL-2 may also restore NK cell activity and cytotoxicity.\textsuperscript{56}

Annual evaluation of neurological, dermatological, immunological, and ophthalmological presentations is necessary in all patients to avoid disease recurrence. Monitoring hematological statuses is beneficial in patients with atypical CHS.\textsuperscript{38}

**Griscelli Syndrome type 2 (GS2)**

**History**

In 1978, Griscelli et al. first described this condition in two patients with partial albinism and immunological manifestations.\textsuperscript{37} In 2000, GS2 was distinguished from GS1 after the responsible gene was identified by Menasche et al.\textsuperscript{48}

**Pathophysiology**

Griscelli syndrome type 2 (OMIM 607624), an autosomal recessive disease, commonly occurs in families with consanguineous parents. Three types of this syndrome are identified to date, all of which presented with OCA. GS1 is a result of mutations in MYO5A gene, encoding Myosin-Va, and is associated with neurological symptoms. GS2 results from mutations in RAB27A gene and is presented with immunological symptoms. Griscelli syndrome type 3 (GS3) is restricted to hypopigmentation and is caused by mutation in MLPH gene, which encodes melanophilin. These three proteins are involved in vesicular trafficking by connecting melanosomes to the actin cytoskeleton and are considered to form a tripartite complex.\textsuperscript{59} Different expressions of these molecules in tissues may account for distinctive presentations of these mutations; while RAB27A is expressed in hematopoietic immune cells and not in CNS, MYO5A expression in brain tissue is well established and there is no evidence of melanophilin expression in cytotoxic cells.\textsuperscript{58,60} RAB27A is mapped to the region 15q15-21.1, which is close to MYO5a locus.\textsuperscript{61} RAB27A encodes a member of Rab GTPases family, RAB27a. This protein is a key component of vesicular trafficking in a variety of cell types such as blood leukocytes, platelets, and melanocytes. RAB27a is known to mediate transport and docking of vesicles. A defect in this protein results in impaired exocytosis and cell killing in immune cells as well as abnormal pigmentation of skin because of the accumulation of melanosomes.\textsuperscript{62} In addition to nonsense, missense, and frameshift mutations, affecting gene products’ stability and/or activity, next-generation sequencing methods have revealed the role of copy number variations as a cause of GS2.\textsuperscript{58,61}

**Signs and symptoms**

Patients present with OCA, similar to CHS and occasionally in a subtle form. They may develop HLH or the accelerated phase within months after birth. Neurological involvement is seen in approximately two-thirds of the patients and is predominantly a result of HLH, rather than RAB27a defect in the nervous system.\textsuperscript{64} Hyperreflexia, hypertension, seizures, intracranial hypertension, developmental delay, nystagmus, ataxia, cerebral hypodense areas, and degenerative white matter disease are among the reported neurological findings. Absent or impaired cutaneous delayed-type hypersensitivity, hepatosplenomegaly, and impaired NK cell functioning are also reported in these patients.\textsuperscript{65}

**Diagnosis**

Silvery-gray hair can lead to the suspicion of GS2. This disease can be distinguished from CHS by the absence of large granules in blood cells or microscopic examination of hair and skin.

In GS2, there are uneven clusters of pigments in hair along with melanosome accumulation in melanocytes and poor pigmentation of keratinocytes, whereas in CHS, large melanosomes are present in both melanocytes and keratinocytes and hair pigment distribution is even and granular.\textsuperscript{66} Analysis of RAB27A mutation confirms the diagnosis.
Treatment

The only effective treatment of GS2 is allogenic HSCT. Median time of neutrophil engraftment was 13 days in a study of 10 patients with a survival rate of 80% following HSCT. Full or almost full donor chimerism is expected; however, it can decrease during the follow-up. Similar to CHS, GS2 patients presenting with accelerated accelerated phase at the time of transplantation have a higher death risk; therefore, HLH therapy is suggested prior to HSCT. Supportive treatment of symptoms must be considered.

Hermansky-Pudlak syndrome type 2 (HPS2)

History

This condition was initially described by Frantisek Hermansky and Paulus Pudlakin 1959 in two unrelated patients presented with prolonged bleeding time and albinism. The gene responsible for HPS2 was detected by Dell’Angelica et al. in 1999, which led to the definition of different subtypes of HPS.

Pathophysiology

Hermansky-Pudlak syndrome type 2 (OMIM 608233) is an autosomal recessive disease caused by mutations in AP3B1 gene, which encodes the β3A subunit of the Adaptor Protein-3 (AP-3). This ubiquitously expressed heterotrameric complex is known to mediate cargo proteins trafficking from intracellular compartments to lysosomes by recognition of target signals. Mutated β3A results in degradation of the whole AP-3 complex and thus defective lysosomal trafficking and accumulation of proteins in plasma membrane. Defective lytic granule exocytosis in cytotoxic T lymphocytes as well as defective conjugation of NK cells with target cells and impaired cytokine and chemokine secretion (e.g., TNFa and IFNγ from NK cells) may account for immunological manifestations in HPS2 patients. Again, localization of lytic enzymes remains intact in this disease, except for perforin, which undergoes a partial decrease in freshly isolated NK cells. Defective cytotoxicity is due to abnormal trafficking of transmembrane proteins such as CD63 to lysosomes and impaired microtubule-mediated polarization of lytic granules at the MTOC and therefore immunological synapse as well as defective degranulation of few correctly polarized granules. Presence of enlarged lysosomal organelles is also reported in some of the HPS2 cell types (e.g., cytotoxic T lymphocytes [CTLs]).

According to Benson et al., mislocalization of proteins such as neutrophil elastase and/or gelatinase to the plasma membrane may be responsible for neutropenia observed in HPS2 patients. AP-3 is also involved in the formation of vesicles containing tyrosinase, which, in turn, fuse with premelanosomes. Absence of functional AP-3 complex therefore results in abnormal melanosome maturation resulting in OCA. Tyrosinase-related protein 1 (Tyrp1) localization appears to be normal in HPS2 cells, suggesting that this molecule is transported using an alternative pathway independent of AP-3 complex.

It is demonstrated that protein mistrafficking affects surfactant secretion and lung tissue repair. Together with lamellar bodies’ dysfunctioning, it gives rise to the pulmonary disease in HPS2 patients.

Endothelial secretion of von Willebrand factor during primary hemostasis is affected by AP-3 deficiency according to the recent data presented by Karampini et al. In this study, the authors demonstrated an impaired trafficking of CD63 to Weibel–Palade bodies as well as defective Ca2+ and cAMP-mediated exocytosis in HPS2 endothelial cells. Depletion of v-SNARE VAMP8 suggests that defective VAMP8 recruitment is responsible for impaired exocytosis.

Signs and Symptoms

Clinical findings of HPS2 include albinism, bleeding diathesis, and neutropenia. Ocular hypopigmentation may be visible at birth, resulting in gradual visual loss. Hair and skin color vary from white to brown and may change over time. Horizontal nystagmus, hearing loss, hepatosplenomegaly, developmental delay, and episodes of epistaxis are reported among HPS2 patients. Other manifestations are mild facial dysplasia, including a broad nasal root, coarse face, mild epicanthal folds, a long philtrum, low-set posteriorly rotated ears, and dysplastic hip. Susceptibility to bacterial infections of upper respiratory tract and pneumonia, as well as viral infections, is a well-known feature of this disease. Paucity of NK and invariant natural killer (NKT) cells has also been reported in two cases of HPS2. A higher incidence of Hodgkin lymphoma is reported in HPS2 patients and is suggested to be a result of NK and NKT cell defect.

Unlike other subtypes, pulmonary phenotype of HPS2, HPS pulmonary fibrosis (HPSPF), starts in childhood and progresses until early adulthood. Severe chronic lung fibrosis is a common symptom in children with HPS2, associated with dyspnea, clubbing, and oxygen demand. The occurrence of potential comorbidities such as pneumothorax or scoliosis exacerbates the pulmonary disease. Recurrent infections because of immunodeficiency are other common complications, usually presented with tachypnea and wet coughing.

Interstitial lung disease (ILD) affects children and young adults with HPS2 and is thought to have a correlation with genotype, given that patients with complete absence of β3A show more severe manifestations comparing to those with a reduced concentration of the protein, a result of compound heterozygosity. Radiographic findings of ground glass opacifications, thickening of interlobular septa, interstitial reticulations on HRCT scans of the chest, and high plasma concentrations of TGF-81 and IL-17A are known associations of ILD in HPS2 patients. Presence of foamy alveolar macrophages and type II pneumocyte hyperplasia, along with interstitial fibrosis, suggests the involvement of these two cell types in the pathogenesis of the pulmonary phenotype.
Differential diagnosis of primary immunodeficiency associated with hypopigmentation

Among more than 30 patients of HPS2 described in the literature, only few are reported to develop hemophagocytic lymphohistiocytosis, two of which were carriers of mutations in loci associated with increased risk of HLH (e.g., RAB27A) and many presented with incomplete episodes of HLH lacking one or more of the criteria of the condition.79,82 Therefore, the risk of hemophagocytic lymphohistiocytosis in HPS2 cannot be measured to date, but it seems to be lower than in CHS or GS2. Analysis of development of HLH in mouse, murine model of HPS2, after infection with lymphocytic choriomeningitis virus (LCMV) revealed that the risk of HLH is related to the degree of defect in cytotoxicity, which is, in turn, related to genotype, and that an extra RAB27A mutation probably does not contribute to an increased risk of HLH.83

**Diagnosis**

Tyrosinase positive OCA, neutropenia, abnormal bleeding, decreased visual acuity can help to suspect HPS, but definitive diagnosis and subtyping are only possible through genetic examination and analysis of mutation.84 Since skin hypopigmentation is variable and may be subtle in some cases, comparing skin tone with other family members should be considered. Platelet dysfunctioning can be examined by electron microscopy of fresh plasma where the absence of delta granules points to a diagnosis of HPS. This is the most sensitive method; however, it is not available in many laboratories.85

Pulmonary disease in HPS2 patients is not specific to this disease and can be mixed up with a few other etiologies of ILD. However, since pulmonary fibrosis is rare in childhood, accompanying partial albinism, it can help to suspect HPS2. HPSPF can be diagnosed using high-resolution computed tomography (HRCT) of the chest looking for ground-glass infiltrates, honeycombing, reticular opacities, and thickened interlobular septa.86

Finally, amolecular analysis of AP3B1 is necessary to establish the diagnosis of HPS2.

**Treatment**

To limit the occurrence of recurrent infections, which in turn aggravates the pulmonary disease, proper immunization is helpful. Skin and eye protection from sunlight is highly important to prevent skin damage and malignancies. Bleeding diathesis should be managed by platelet transfusion in the case of severe bleeding or surgical procedures. Desmopressin (DDAVP) can help reduce bleeding complications. Nutritional and developmental management, orthopedic treatment for scoliosis, screening for secondary complications, and pain treatment are important during the follow-up.84

Granulocyte-colony stimulating factor treatment is proposed to cause immunological improvement in HPS2 patients. Respiratory distress can improve using oxygen therapy and mechanical ventilation. Antibiotic prescription can prevent secondary infections and further complication of the respiratory disease.77

**Hermansky-Pudlak syndrome type 10 (HPS10)**

**History**

The gene related to this disease, AP3D1, was initially identified in 1998 in a mouse model,87 but it was not until 2016 that the presence of a similar gene mutation was reported in a patient. Ammann et al. described a patient with HPS2-like manifestation but with epileptic episodes.88 They proposed the acronym HPS10. In 2018, three other patients were described with the same condition, further establishing the link between AP3D1 gene and HPS10.89

**Pathophysiology**

Hermansky-Pudlak syndrome type 10 (OMIM 617050) is an autosomal recessive disease due to mutations in AP3D1 gene, encoding δ subunit of AP-3 complex. This subunit is crucial for the formation of both ubiquitous and neuron-specific isoforms of AP-3, explaining the neurological manifestations of HPS10. An AP3D1 mutation was initially reported in *mocha* mouse, a null allele of δ subunit. In the absence of a functional AP-3δ, the whole AP-3 complex (comprising subunits δ, ε3B, μ3B, and ε3) is degraded.87 In addition to ubiquitous AP-3 functions in many cell types, neuron-specific isoform is involved in trafficking of neurotransmitters, synaptic membrane proteins, and zinc transporter (ZnT3). Zinc deficiency, membrane protein mis-sorting, and defective cargo transport to neurotransmitter vesicles may be the key to epileptic presentations of HPS10; however, no more detailed pathophysiological explanations are available to date.88,90

Similar to HPS2, impaired cytotoxicity of CTLs and freshly isolated NK cells is detected in HPS10 cells. Absence of platelet delta granules and increased collagen/epinephrine ratio are also demonstrated in AP3D1 mutant cells. Other effects of AP-3 deficiency in HPS10 is expected to be similar to those of HPS2.88

So far, the only genotype identified to be responsible for this disease is a homozygous frameshift deletion of AP3D1, resulting in δ subunit loss of function and therefore AP-3 instability. Introducing the wild-type AP3D1 gene into HPS10 T cells restores the impaired cytotoxicity, clarifying that AP3D1 mutation solely accounts for the cytotoxic abnormalities observed in this disease.88,89

**Signs and Symptoms**

To date, four patients are described with HPS10; three of them were siblings, and all four had consanguineous parents. Common phenotypes include OCA, developmental delay, facial dysmorphism, feeding difficulties, microcephaly, febrile episodes associated with neutropenia, hepatosplenomegaly, and susceptibility to infection.

Neurological manifestations include horizontal nystagmus, head lag, brisk reflexes, hearing loss, tonic self-limited seizure episodes, and generalized hypotonia. Brain MRI of one of the patients revealed mild atrophy, enlarged ventricles, and delayed myelination.88,89
Symptoms such as susceptibility to airway infections, pneumonia, bronchitis and sepsis, respiratory distress, and pulmonary collapse point to potential pathophysiological similarities with HPS2 (e.g., defective surfactant secretion).89 In spite of platelet functional defects, no bleeding abnormalities are reported in these patients. Although there was no evidence of hemophagocytosis in these patients, the probability cannot be excluded regarding the presence of HLH-associated findings.

Two patients (twin sisters) died a few days after birth, their brother died at the age of 2.4 years, and the other subject at the age of 3½ years. Causes of death include pneumonia, sepsis, seizure, hemodynamic instability, or a combination of these.

Diagnosis

A clinical picture consisting of epileptic episodes, OCA, and recurrent infections can be indicative of HPS10, particularly in the case of consanguineous parents. However, to establish a definitive diagnosis, molecular analysis of AP3D1 gene may be necessary.88,89

Treatment

No certain treatments are proposed until now, but management of complications can have significant effects on the prognosis. Monitoring the patient for neutropenia and hepatosplenomegaly is helpful along with pulmonary disease assessment and considering mechanical ventilation if needed.88,89

Vici Syndrome (VICIS)

History

This disease was originally described in 1988 by Carlo Dionisi Vici et al. in two brothers presented with agenesis of the corpus callosum, cutaneous hypopigmentation, bilateral cataract, cleft lip and palate, combined immunodeficiency, and a history of recurrent infections and neuropsychological abnormalities.91 The gene responsible for this disease was initially identified in 2007 as a breast cancer-related gene, but its link to VICIS was first discovered in 2013.92,93

Pathophysiology

Vici syndrome (OMIM 242840) is caused by recessive mutations in EPG5 gene, which encodes ectopic P granules protein 5 homolog (EPG5). This protein is crucial for autophagy pathway, probably by regulating autophagosome-lysosome fusion and cargo degradation. Multisystemic manifestations of VICIS highlight the role of EPG5-dependent autophagic process in a variety of organs and systems of human body.94 Transport of foreign nucleic acid to acidic endosomes also depends on EPG5; therefore, reduced susceptibility to viral infections such as influenza is expected. EPG5 is also involved in toll-like receptor-9 (TLR9) signaling through trafficking of its ligand, CpG, from early endosomes to late endosomes and lysosomes. Defective termination of TLR signaling, upstream to NF-κB nuclear translocation, is a probable underlying cause of increased cytokine secretion. TLR9 takes part in IgM memory B cell differentiation and also in recognition of incoming cargo in the autophagic pathway, explaining the link between immune dysregulation and autophagy defects in VICIS. EPG5 deficiency results in abnormal memory B cell differentiation, and thus hypogammaglobulinemia and susceptibility to bacterial infections.95–97

Defective autophagy and recycling of material result in the accumulation of autophagic compartments and lack of material. Therefore, it is suggested to be the cause of neurodegeneration in VICIS.98,99

Signs and symptoms

The most common findings in patients with VICIS are corpus callosum agenesis, recurrent infections, and profound developmental delay. Cataract, cardiomyopathy, and albinism are also proposed as parts of VICIS clinical picture but may be absent in a minority of patients. Failure to thrive (FTT) and progressive microcephaly are highly consistent findings of VICIS, in some cases associated with epilepsy. Radiological findings include pontine hypoplasia, delayed myelination, white matter paucity, and ventricular dilation.100 Muscle pathologies are nonspecific, including fiber abnormality and hypotonia, as well as increased glycogen storage. Sensorineural hearing loss is another manifestation of VICIS.101

In addition to ocular hypopigmentation, other ophthalmologic manifestations, such as optic nerve hypoplasia, visual impairment, nystagmus, and fundus hypopigmentation, are also reported in patients with VICIS.102 Combined immunodeficiency, mainly involving humoral immunity, is associated with lymphopenia, neutropenia, leucopenia, hypogammaglobulinemia, and defective memory B cell function. Respiratory infections are the most common results of immune dysfunction, followed by mucocutaneous candidiasis, sepsis, urinary tract infections, gastroenteritis, bacterial conjunctivitis, and perineal abscesses.103 Thyroid agenesis, thymus hypoplasia, renal dysfunction, hepatomegaly, and dysmorphic face are less frequently reported findings in these patients.103

Diagnosis

Vici syndrome should be suspected in every child with absent corpus callosum, immune dysfunction, profound developmental delay, cataracts, hypopigmentation, cardiomyopathy, progressive microcephaly, and failure to thrive. The diagnosis can be confirmed by genetic testing using one or more techniques to identify a recessive mutation in EPG5 gene.100
**Treatment**

There is no definitive treatment for VICIS and management includes reducing the effects of multisystem involvement.

Patients with VICIS may not respond properly to immunization because of defective memory B cell function; therefore, immunoglobulin infusion and antimicrobial prophylaxis must be considered. Epilepsy, cataract, cardiomyopathy, renal dysfunction, and thyroid abnormalities may also need supportive treatment considering the condition of each patient.103,104

**P14/LAMTOR2 deficiency**

**History**

In 2006, four offspring of a Mennonite family were described by Bohn et al. to have a previously unknown inborn error of immunity. The gene responsible for the condition was identified and mapped in the same study.105

**Pathophysiology**

A recessive mutation in the autosomal gene P14 results in P14 deficiency. P14, also called LAMTOR2, is one of the five molecules forming the late endosomal/lysosomal adaptor and MAPK and mTOR activator/regulator (LAMTOR) complex. LAMTOR assembly is essential for extracellular-signal-regulated kinase-mitogen-activated protein kinase (ERK-MAPK) and mTOR cascades by localizing a scaffold protein, mitogen-activated protein kinase, and ERK kinase 1 partner (MP1), to late endosomes, and therefore taking part in endosomal traffic and cell proliferation.106 Loss of P14 results in the absence of epidermal Langerhans cells (LCs, skin-residing dendritic cells) because of apoptosis.107 Furthermore, P14 deficiency results in reduced expression of TGFβRII, a TGFβ receptor on LCs. Taken together with the fact that TGFβ inhibits apoptosis through MAPK pathway, this can be a possible explanation for cell cycle arrest in P14 gene depletion.107 The exact pathophysiology behind immune dysfunction is unknown yet; however, reduced CTL cytotoxicity is observed in P14-depleted cells and is reconstituted upon P14 gene transfer. G-CSFR-dependent intracellular signaling cascade includes ERK phosphorylation, which is reduced in the absence of P14, proposing a possible explanation for neutropenia observed in these patients. Reduced B cell maturation, class switching, and memory cell formation are also identified in P14-depleted cells, as well as impaired ability of neutrophils to kill bacteria, despite unaffected phagocytosis.109 Defense against intracellular pathogens requires proper localization of the pathogen to lysosome, a P14-dependent process. In P14-deficient cells, the pathogen particles are able to escape from the endolysosomal system and antimicrobial effectors.108

**Signs and symptoms**

Clinical findings of P14 deficiency are similar to those of CHS or HPS2, except for the short stature seen in P14 deficiency. Patients are presented with partial albinism, congenital neutropenia, coarse facial features, short stature, and immunodeficiency. The latter includes reduced CTL cytotoxicity, reduced ability of humoral immune system to recall antigens, neutropenia, low serum IgM levels, and reduced IgG levels in adolescence, associated with recurrent bronchopulmonary infections.105

**Diagnosis**

A combination of the mentioned clinical findings may be suggestive for P14 deficiency, but since the symptoms are highly identical to other inborn errors of immunity associated with albinism, and the number of cases in the literature is not enough to propose a complete list of possible findings, definitive diagnosis can only be based on genetic testing and/or expression analysis of P14.

**Treatment**

The only treatment for congenital neutropenia is allogeneic BMT. There is a single case report of this treatment, in which the patient developed severe graft versus host disease (GvHD) after receiving an allograft from an HLA-identical sibling due to increased TNFα production. Therefore, a more careful approach in treatment is recommended until the effects of BMT in this disease are investigated at a preclinical stage.109 Each manifestation must be managed using proper supportive treatment to achieve a better survival.

**Conclusion**

We described six immunodeficiency syndromes presenting with hypopigmentation, all of which related to dysfunction in vesicular/endosomal trafficking. With highly overlapping symptoms and findings, these diseases require careful examination and diagnosis. Except of treatment with HSCT in some cases, the disease cannot be eliminated completely from the body. Supportive treatment and routine check-up must be considered in order to prevent exacerbation of the condition, for example, HLH development. Further studies on pathophysiology, manifestations, and treatment options are needed to increase the acuity and efficiency of management.

In Figure 2, we present an algorithm based on most common manifestations and differential diagnosis criteria as well as treatment options for the mentioned disorders; this would help to approach to differential diagnosis and management of patients with PID and hypopigmentation.
Figure 2. Differential diagnosis flowchart to approach primary immunodeficiencies associated with hypopigmentation. HLH: hemophagocytic lymphohistiocytosis; ILD: interstitial lung disease; PID: primary immunodeficiency; EPG5: ectopic P granules protein 5; LYST: lysosomal trafficking regulator; AP3B1,D1: adaptor related protein 3 subunit beta 1, delta 1; HSCT: hematopoietic stem cell transplantation; G-CSF: granulocyte colony-stimulating factor.
References


