Griscelli Syndrome

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Abstract
Griscelli syndrome, a rare, autosomal recessive disorder, results in hypopigmentation of the skin and the hair, the presence of large aggregates of pigment in hair shafts and the accumulation of mature melanosomes in melanocytes. It is caused by mutations in either the myosin-VA (MYO-VA) or RAB27A encoding gene. Patients with a RAB27A mutation also exhibit a cytotoxic defect and the appearance of an uncontrolled T-lymphocyte and macrophage-activation syndrome also known as hemophagocytic syndrome. In contrast, patients with myosin-Va defect associate hypopigmentation with an early primary and severe neurological impairment, without immune abnormalities. RAB27A and myosin-5a genes have been localized to the same chromosomal 15q21 region and encode for proteins, which are key effectors of intracellular vesicular transport. RAB27A, specifically regulates the cytotoxic granule exocytosis. The cytotoxic defect caused by RAB27A mutations is responsible for triggering the hemophagocytic syndrome which is often fatal, and for which the only cure is bone-marrow transplantation.

Keywords
partial albinism, exocytosis, defective cytotoxicity, intracellular trafficking, RAB27A, MYO-VA.

Disease name and synonyms
Griscelli syndrome (GS) (MIM 214450) or partial albinism with immunodeficiency, is an autosomal recessive genetic disorder which may have two different molecular causes: a defective member of the family of monomeric GTPases, RAB27A or a myosin VA (MYO-VA) function. Recent data suggest that one of the two hereditary forms of this disease (defective RAB27A) is similar to the partial albinism with immunodeficiency, termed "PAID syndrome" (MIM 604228), described by Harfi *et al.* (1) and that the other form (defective MYO-VA), is similar to the neuroectodermal melanolysosomal syndrome reported by Elejalde (MIM 256710) (2).

Diagnostic criteria/ definition
Clinically, Griscelli syndrome is characterized by partial pigmentary dilution or albinism with silvery gray hair, frequent infections, cellular immune deficiency, neurologic abnormalities, and fatal outcome caused by an uncontrolled T lymphocyte and macrophage activation

syndrome, the so-called accelerated phase of the disorder.

Differential diagnosis

GS differs from the Chediak-Higashi syndrome (MIM 214500), which also associates partial albinism with immunodeficiency but with the presence of giant organelles inclusion bodies in virtually all granulated cells, a hallmark of this disease. In familial hemophagocytic lymphohistiocytosis (MIM 603553), X-linked lymphoproliferative syndrome (MIM 308240) and virus-associated hemaphagocytic syndrome, patients develop an accelerated phase identical to the one observed in GS (3). However, those disorders do not involve partial albinism and thus microscopic examination of the hair shaft enables GS to be easily differentiated from them.

Prevalence

GS was first described in 2 patients in 1978 by Griscelli and al (4). Since then, more than 40 cases have been described in the literature (1, 5-11). GS is very rare in almost all populations, although most cases reported are from Turkish and Mediterranean populations.

Clinical description

The age at diagnosis of 20 reported cases of GS ranged from 1 month to 8 years with a mean of 17.5 months. The single most consistent dermatoskeletal expression of albinism in GS patients is a silvery gray sheen to their hair (5, 12). Patients generally have lighter hair than their unaffected family members. Some patients present with subtle pigmentary dilution of the skin and iris but this is not a common feature.

Hyperpigmentation in sun-exposed areas has also been noted in a few cases. Both molecular defects responsible for GS lead to the same pigmentary dilution expression. In contrast, immunological and hematological manifestations are observed only in the patients with the RAB27A defect and include : anemia, neutropenia and lack of natural killer (NK) cell function, with development of an accelerated phase of the disease with fever, jaundice, hepatosplenomegaly, lymphadenopathy, pancytopenia and generalized lymphohistiocytic infiltrates of various organs including the central nervous system (CNS).

This lymphoproliferative syndrome is similar to that observed in the Chediak-Higashi syndrome, familial hemophagocytic lymphohistiocytosis (FHL), X-linked lymphoproliferative (XLP) syndrome and the virus-associated hemophagocytic syndrome (3). Onset of the accelerated phase seems to be associated with a virus infection (Epstein-Barr virus, hepatitis A virus, herpes virus 6...) (5, 10) or sometimes a bacterial infection. When a remission is obtained, recurrent accelerated phases with increasing severity will be observed.

Neurological manifestations in GS are frequent and observed either in association with immunological features or alone. During the accelerated phase, patients frequently develop progressive symptoms, caused by activated lymphocytes and macrophages, involvement of CNS (8, 11), including hyperreflexia, seizures, signs of intracranial hypertension (vomiting, altered consciousness), regression of developmental milestones, hypertonia, nystagmus and ataxia. Psychomotor development is normal at onset and regression of the CNS signs, at least in part, can be observed during remission although some sequelae may be irreversible. Neurological manifestations may be the first sign of an accelerated phase. In contrast, in the patients with defective myosin 5a function, severe neurological symptoms are noticeable as of birth without any sign of an accelerated phase, and consist of hypotonia, absence of coordinated voluntary movements and severe retarded psychomotor development (2, 13) similar to that observed in the syndrome described by Elejalde. CNS disorder is stable and never regresses with time.

Light microscope examination findings of patients hair are characteristic, constantly observed and identical in both groups of patients (with MYO-VA or with RAB27A defect). Hair shafts contain a typical pattern of uneven accumulation of large pigment granules, instead of the homogeneous distribution of small pigment granules in normal hair (4, 5, 11, 14).

A variety of immunological abnormalities have been described in GS. They appear to be restricted to the patients with RAB27A defect. The capacity of lymphocytes and NK cells from these patients to lyse target cells is impaired or absent. These T and NK cells cytotoxicity dysfunctions, which result from the inability to secrete cytotoxic granules when RAB27A is not functional, is a constant feature in these patients, and is responsible for accelerated-phase onset (12, 15).

Patients have normal numbers of T, B and NK cells, and normal B and neutrophil functions, although decreased chemiluminescence and chemotactic responses have been reported for some patients (5). Biological features of the accelerated phase are not specific to GS and include pancytopenia, hypertriglyceridemia, low fibrinogen level, cerebrospinal fluid pleocytosis and the presence of activated macrophages and T lymphocytes, mainly CD8, which infiltrate the various organs which show signs of of hemophagocytosis (3). So far, no immunological abnormalities have been observed in GS patients with the MYO-VA defect. T lymphocytes and NK cells from these patients have a normal

cytotoxic activity. Myosin Va defect does not affect cytotoxic granule secretion and these patients never develop an accelerated phase (12).

Similarly, cranial CT scanning and MRI are different in the two groups of GS patients. Isolated congenital cerebellar atrophy was observed in a patient with the MYO-VA defect (13). In contrast, in patients with defective RAB27A, cerebellar hypodense areas, ventricular dilatation, or hyperdense areas compatible with inflammatory changes were observed. Additional findings included generalized white matter changes and periventricular calcifications (1, 8, 16). When performed, biopsy specimens showed cerebral lymphohistiocytic infiltration, sometimes associated with hemophagocytosis.

Management and treatment

The prognosis for long-term survival of GS patients is relatively poor. In the form caused by the RAB27A defect, GS is usually rapidly fatal within 1 to 4 years without treatment at onset of an accelerated phase. Chemotherapy (VP16) or more recently antithymocyte globulins (ATG, 10mg/kg x 5 days) and cyclosporin A (CsA) have achieved remissions and the use of intrathecal methotrexate injections transiently help treat the neurocerebral involvement (5, 9, 16-18). However, chemotherapy is sometimes ineffective for the treatment of the primary disease and frequently fails to control relapses. Allogenic bone-marrow transplantation (BMT) remains the only curative treatment in this disease. Even a low number of donor cells in the patient's bone marrow are enough to control the disease. In the form with MYO-VA defect, no specific treatment can be proposed. The severe neurological impairment and retarded psychomotor development do not improve with time. Recurrent infections presented by some of these patients were easily improved with positional changes and antibiotic treatment.

Etiology

Genetic linkage analysis localized GS to chromosome 15q21 in a region containing the human gene for myosin-5a (MYO-VA), as well as the gene coding for RAB27A. Mutations in RAB27A were detected in all the GS patients analyzed who did not have the mutated MYO5A (12). Thus, mutations in either MYO5A or RAB27A, two genes separated by less than 1.6 cM at 15q21, can lead to the GS.

Myosin Va and RAB27A co-localize in part with melanosomes in melanocytes and their respective defects lead to the abnormal melanosome distribution observed in GS (20). In addition, RAB27A was shown to be necessary for cytotoxic granule exocytosis and thus the cytotoxic activities of T and NK cells, which were shown to be defective in this group of patients (12). Thus, in GS, MYO5A and RAB27A anomalies lead to the same defective transport of melanosomes which are not properly transferred to surrounding keratinocytes, accounting for the pigmentary dilution characteristic of this disorder. Pigmentary dilution is indistinguishable between these two molecular defects. However, because of the role of myosin Va in brain tissue, only patients with the myosin VA defect develop primary and severe neurological impairment in the absence of any immunological expression. In contrast, defective RAB27A expression is always associated with abnormal lymphocytotoxic activity which results in the occurrence of a lymphoproliferative syndrome as recently demonstrated in the case of the FHL caused by a genetically determined perforin deficiency (15). Neurological signs in these patients are the consequence of an accelerated phase, and appear secondary to perivascular lymphohistiocytic organ infiltration.

Diagnostic methods

The diagnosis of GS must be considered for any child with hypopigmentation accompanied by neurological abnormalities or signs of the accelerated phase, such as hepatosplenomegaly, jaundice or pancytopenia. Microscopy examination of the hair shaft provides strong support for the diagnosis of GS. The characteristic neurological symptoms and analysis of lymphocyte cytotoxic activity of patient tend to incriminate one of the two molecular causes. Confirmation can be provided by mutation analysis of the patient's DNA.

Prenatal diagnosis

Prenatal diagnosis of GS was first accomplished by light microscopy examination of the hair shaft (21). With the recent identification of the GS genes, direct mutation-based carrier detection and prenatal diagnosis are now possible in families with defined MYO5A or RAB27A gene mutations. In addition, given the proximity of the two genes responsible for GS, polymorphic markers linked to the GS locus in the 15q21 region can be used for this purpose even if the precise mutation has not yet be identified in a family.

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