SILVER HAIR SYNDROMES: CHEDIAK-HIGASHI SYNDROME (CHS) AND GRISCELLI SYNDROMES (GS)

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Normal pigmentation is a complex biological process and in the human, at least 127 different genes have been identified (Bennett and Lamoreaux 2003). Colour loci are the genetic loci in which mutations can affect pigmentation of the hair, skin, and/or eyes.

Differences in skin and hair colour are basically genetically determined and depend on the uniform distribution of melanin polymers produced by melanocytes and secreted into keratinocytes. The movement of melanosomes from post-Golgi compartments to the periphery of melanocytes is known to be regulated by motor proteins, e.g. myosin -V and Rab27, interacting with each other and functioning by means of vesicle trafficking. Motor proteins play a critical role in transporting melanosomes within melanocytes as well as neurosecretory vesicles within neurons. Therefore, mutations in these proteins can produce a dilute or silvery hair colour and various neurologic defects (Lambert et al. 1998).

The so-called *silver hair syndromes* have misleading been referred to as partial albinism syndromes. Oculocutaneous albinism comprises a group of congenital hypopigmentation disorders related to mutations in genes interacting in melanin formation pathway, resulting from aberrant processing of tyrosinase, the enzyme critical to pigment production in mammals. In contrast, the phenotype of patients with silver hair syndrome is characterized by a silver-grey sheen hair (Fig. 1) and hypopigmented skin at birth followed by a prolonged bronzed skin after sun exposure (Fig. 2a and b). This phenotype is associated to the following clinical conditions:

- **Chediak-Higashi syndrome (CHS):** associated to defective chemotaxis secondary to impaired synthesis and/or maintenance of storage/secretory granules;
- **Griscelli syndromes (GS):** (1) with primary and severe neurological disorder (**GS1** also known as *Griscelli/Elejalde syndrome*); (2) with severe disturbed B-cell and T-cell immunity (**GS2**, as originally described by Griscelli); and (3) without extracutaneous abnormalities (**GS3** or *GS restricted to hypopigmentation/pigment dilution*).

Skin/hair hyperpigmentation is the result of a failure to transfer melanine to keratinocytes which provokes a hyperpigmented epidermal basal layer. Light microscopic examination of a skin biopsy shows the same characteristics in the four conditions, making it difficult to distinguish between each other. An accumulation of melanin in basal melanocytes contrasting with an extremely scant pigment in adjacent keratinocytes is observed, especially with Fontana-Masson stain. Electron microscopy examination reveals accumulation of mature melanosomes in the cytoplasm around the nucleus of a melanocytes or melanocytes with different stages of melanosomes formation.

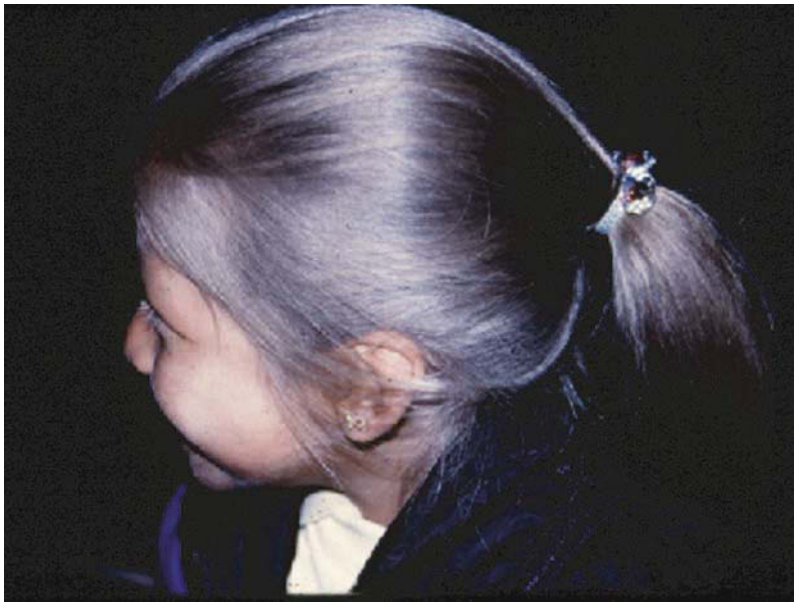

Fig. 1. Silver shine of hair and bronzed skin characteristic of silver hair syndromes.

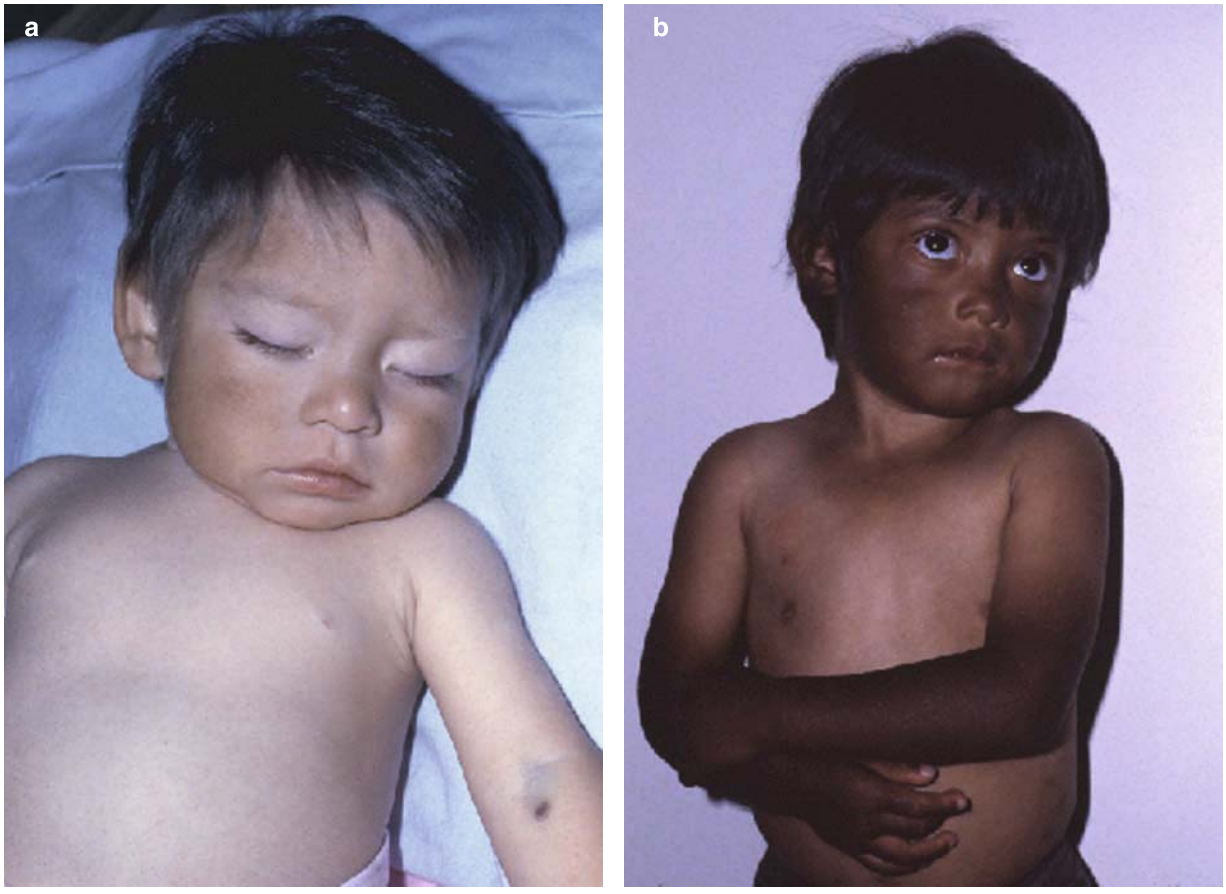

Fig. 2. (**a**) and (**b**) Chediak-Higashi syndrome. Characteristic hypo and hyperpigmented skin after sun exposure.

The silver-grey sheen (Fig. 1) of the scalp and body hair, eyebrows and eyelashes is the result of an abnormal distribution of pigment in clumps in the hair shaft leaving spaces free of melanin that impairs the refraction and absorption of light.

The natural course of the diseases and outcome is dictated by the site of involvement and the type of genetic mutation.

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CHEDIAK-HIGASHI SYNDROME (CHS)

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Introduction

This is a rare autosomal recessive immunodeficiency disorder (OMIM # 214500) where silvery hair was first recognized as a pathological feature (Beguez-Cesar 1943, Chediak 1952, Higashi 1954, Steinbrinck 1948). The hallmark of the disorder are the pathognomonic giant inclusion bodies seen in all granule-containing cells, including granulocytes, lymphocytes, melanocytes, mast cells and neurons (see below). CHS is a special lysosomal disorder in that it is not due to a specific enzyme deficiency but to a fusion defect of primary lysosomes.

The features of CHS are decreased pigmentation of hair and eyes, photophobia, nystagmus, large eosinophilic, peroxidase-positive inclusion bodies in the myeloblasts and promyelocytes of the bone marrow, neutropenia, abnormal susceptibility to infection, enterocolitis, and peculiar malignant lymphoma. Various neurological abnormalities have been described including clumsiness, abnormal gait, peripheral neuropathy, cranial nerve palsies and a variable degree of cognitive impairment with imaging evidence of diffuse atrophy of the brain, cerebellum and spinal cord (Ballard et al. 1994, Farah and Rogers 2004, Misra et al. 1991, Pettit and Ballard 1984, Tardieu et al. 2005, Uyama et al. 1994).

Most patients eventually enter a usually fatal "*accelerated phase*" of accelerated reaction manifested by fever, pancytopenia and non malignant lymphohistiocytic lymphoma-like organ infiltrates (Farah and Rogers 2004, Nowicki and Szarmach 2006). This lymphoma-like stage is precipitated by viruses, particularly by infection by the Epstein-Barr virus. It is associated to anaemia, bleeding episodes, and overwhelming infections (mostly of the skin, lungs, and respiratory tracts) often leading to early death without appropriate treatment (i.e., bone marrow transplantation).

The CHS locus has been mapped to chromosome 1q42.1–42.2 (Barrat et al. 1996, Fukai et al. 1996). The defective gene is the lysosomal trafficking regulator gene (**LYST**) currently termed **CHS1** gene which encodes a clue protein to regulate the secretory processes of intracellular lysosomal vesicles and melanosomes. An increased susceptibility to recurrent infections secondary to an impaired phagocytosis and a lack of natural killer cell function is characteristic.

Historical perspective and eponyms

This syndrome was first described in 1943 by a Cuban pediatrician in three siblings (Beguez-Cesar 1943). Steinbrink reported 1 case in 1948. In 1952, **Alexander Moisés Chédiak**, a Cuban physician and serologist, born in 1903, reported 4 cases in 13 Cuban siblings, and in 1954 **Otokata Higashi**, a Japanese pediatrician, graduated from Tohoku University, Sendai, Japan, who later was Professor of pediatrics at Akita University, described 4 cases in 7 Japanese siblings. In these cases the parents were related; however, subsequent cases have not necessarily involved related parents (Van Hale 1987). Sato (1955) recognized the similarity between Chediak and Higashi's cases (Chediak 1952, Higashi 1954) reporting the probable identity of a "new leucocyte anomaly" (Chediak) and "congenital gigantism of peroxidase granules" (Higashi) and first named the disease Chediak-Higashi syndrome along with Donohue and Bain (1957) (Farah and Rogers 2004).

Incidence and prevalence

CSH has been described in all ethnic groups and is usually rare except for a cluster of cases that has been described in an isolated area of the Venezuelan-Andes (Ramirez-Duque et al. 1983). A similar syndrome has been described in numerous animal species including the Aleutian mink, partial albino Hereford cattle, blue foxes, albino whales and the beige mouse (the latter used as an animal model for the disease) (Farah and Rogers 2004, Windhorst and Padgett 1973).

Clinical manifestations

CHS commonly affects the skin, eyes, and central nervous system. The age at diagnosis ranges from 1 month to 39 years (median age, 5.6 years). The disease is usually first suspected either because of coexistent hypopigmentation (Fig. 2) (infants born with CHS have non pigmented skin – similar to albinos but in a patchy distribution – blonde hair, and blue eyes) and a history of recurrent pyogenic infections, or on the basis of a sibling in whom the diagnosis has been previously made, or after incidental observation of giant peroxidase-positive intracellular granules on a peripheral blood smear (Fig. 3) or bone marrow examination. Signs and symptoms that usually appear soon after birth include adenopathy, aphthae, gingivitis, hyperhidrosis, malaria, jaundice, severe and extensive pyoderma, recurrent sinopulmonary infections and fever usually unrelated to recognizable infections (Nowicki and Szarmach 2006).

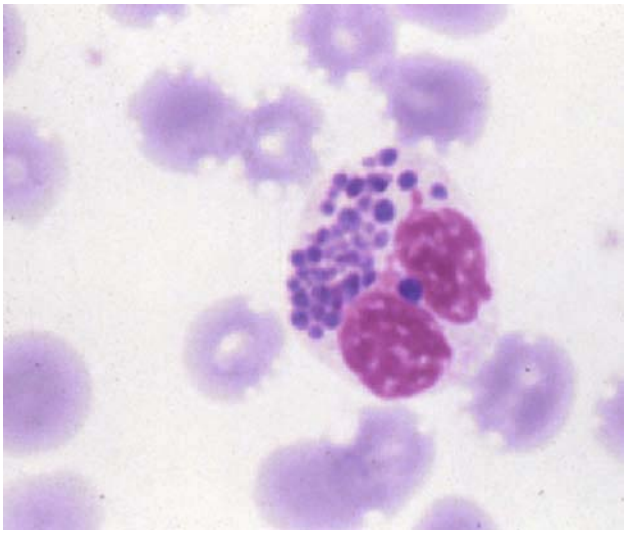

Fig. 3. Giant cytoplasmic granules in neutrophils pathognomonic of Chediak-Higashi syndrome.

Skin manifestations

Most patients with CHS exhibit oculocutaneous albinism in at least one of three sites: the skin, the hair, or the eyes. Hair are sparse and colour varies from blonde to dark brown, bur always has a silvery tint that is particularly noticeable in strong light. CHS patients also have less skin pigmentation that their siblings and are susceptible to sunburns. This lack of pigmentation is also noticeable in the areolas and genitals. The pigmentary disturbance is not due to absence of melanin, but to its abnormal aggregation into giant melanosomes (Farah and Rogers 2004, Zhao et al. 1994).

Eye involvement

The albinism in CHS is often more evident in the eyes than in the skin. Ocular alterations include a lack of pigmentation in the iris and the retina, pigmentary degeneration of the peripheral retina with progressive visual loss (Sayanagi et al. 2003). Overall, in CHS the skin is fair, the retinae are pale, and the irides are translucent. Ocular involvement can also be manifested clinically by photophobia, rotatory nystagmus, and an increased red reflex. Abnormal giant melanosomes have been found in the optic cup and neural crest derived melanocytes (Farah and Rogers 2004): therefore the ocular hypopigmentation in patients with CHS is related to an ultrastructural melanosomal defect.

Recurrent infections

Recurrent infections affect mainly the skin, respiratory tract and mucous membranes. The most commonly involved organisms are Staphylococcus aureus, beta-haemolytic streptococci, Streptococcus pneuomniae, and other bacteria, fungi, and viruses. Recurrent skin

infections range from superficial pyoderma to deep subcutaneous abscesses and ulcers that heal slowly and result in atrophic scars. Deep ulcerations resembling pyoderma gangrenosum have been also described.

This increased susceptibility has been attributed to the various immunologic defects observed in CHS including cellular immune deficiency, absent natural killer (NK) cytotoxic activity, altered neutrophils and monocytes numbers, diminished chemotactic responses, and delayed degranulation and intracellular killing of microorganisms (Farah and Rogers 2004, Gallin et al. 1975, Merino et al. 1983, Root et al. 1972).

Neurological abnormalities

CHS may present with neurological dysfunction and should be considered in the differential diagnosis of children and young adults first seen with symptoms of spinocerebellar degeneration or movement disorders. In many persons with CHS, neurological changes appear in the lymphoproliferative phase. Progressive neurological deterioration is common in patients who survive early childhood. The adult form of CHS manifests during late childhood to young adulthood and is marked by various neurological sequelae (see below).

The various neurological abnormalities of CHS have been mainly described in young adult patients (Ballard et al. 1994, De Freitas et al. 1999, Farah and Rogers 2004, Fukuda et al. 2000, Hauser et al. 2000, Jacobi et al. 2005, Lockman et al. 1967, Misra et al. 1991, Pettit and Berdal 1984, Sheramata et al. 1974, Tardieu et al. 2005, Uyama et al. 1994, Van Hale 1987). Among the most common are signs of spinocerebellar degeneration such as clumsiness and abnormal gait, progressive parkinsonian syndrome (e.g., bradykinesia, resting tremor and oculogyric crises), dystonia, and peripheral neuropathy which is manifested by dysesthesias and paresthesias, transitory pareses (including cranial nerve palsies), and sensory deficit of the glove-stocking type (Van Hale 1987). The sensorineural neuropathy may begin early in childhood and progress to complete loss of muscle stretch reflexes, weakness, atrophy, and sensory deficits. Ataxia, with broad-based gait and dysdiadochokinesia, seizures, and behavioural abnormalities also occur. Headaches or emotional lability may occur occasionally in a setting of cognitive deterioration. The patient may become bedridden and totally incapacitated. Mental retardation or progressive intellectual decline have been also associated with CHS and appear to be independent of other neurological signs. The intellectual limitation may progress even after cure of the haematological manifestations with bone marrow transplantation (Uyama et al. 1994). Tardieu et al. (2005) reported on 3 CHS patients who underwent successful allogenic bone marrow transplantation in childhood with sustained mixed chimerism and no subsequent recurrent infections or haemophagocytic syndrome. At the age of 22–24 years, each patient developed a neurological syndrome combining difficulty walking, loss of balance and tremor. Examination revealed cerebellar ataxia and signs of peripheral neuropathy. Electrophysiology studies showed motor-sensory axonal neuropathy, there was moderate axon loss and rarefaction of large demyelinated fibres on peripheral nerve biopsy, and cerebellar atrophy was detected on brain MRI in two patients. Tardieu et al. (2005) reviewed also the neurological status of other 8 patients with CHS who had survived the initial bone marrow post transplantation period: 2 manifested neurological lesions immediately after transplantation; 1, aged 24 years, began having gait abnormality, falls when walking, and decreased cognitive abilities at the age of 21; 3 other patients, aged 2, 14 and 17 years, had borderline IQ scores but normal neurological examination. Tardieu et al. (2005) noted that the neurological signs/symptoms observed were identical to those in adults with mild CHS who did not undergo bone marrow transplantation, and concluded that the neurological syndrome including the low cognitive abilities most likely resulted from steady long-term progression, despite bone marrow transplantation, of the lysosomal defect in neurons and glial cells.

Coagulation defects

There is usually a mild bleeding diathesis associated with CHS (Farah and Rogers 2004). Coagulation

studies usually show a prolonged bleeding time, a normal platelet count, and impaired platelet aggregation with epinephrine and collagen (Buchanan and Handin 1976). This results form a platelet storage pool dense granule deficiency (Apitz-Castro et al. 1985). Patients usually experience increased cutaneous bruising during the chronic phase, even though thrombocytopenia and severe hemorrhage can occur during the accelerated phase.

Imaging

Nonspecific radiological manifestations are hilar and mediastinal lymphadenopathy, hepatosplenomegaly; lymphangiography with a reticular pattern of enlarged inguinal and para-aortic lymph nodules. Oral radiographs reveal extensive loss of alveolar bone, leading to tooth exfoliation in most cases (Taiby 1996).

CT and/or MRI may show marked temporal dominant (or diffuse) brain atrophy and diffuse spinal cord atrophy (Uyama et al. 1991, 1994); periventricular decreased density (CT); increased signal intensity on T2-weighted images and lack of enhancement on T1-weighted images in periventricular and coronal radiated regions (Ballard et al. 1994). The overall pattern is quite similar to that seen in other lysosomal disorders (e.g., GM2 gangliosidosis) with extensive, diffuse white matter disease (probably a combination of hypomyelination and demyelination), showing an antero-posterior gradient and abnormalities in the deep cerebral grey matter (Patay 2005).

Pathology

The hallmark of CHS is the occurrence of giant lysosomal inclusion bodies and organelles in all granule-containing cells (Fig. 3), including granulocytes, lymphocytes, monocytes, erythroid precursors, histiocytes, mast cells, platelets, melanocytes, Schwann cells, neurons and fibroblasts (Farah and Rogers 2004, Windhorst et al. 1966). Electron microscopy and histochemical staining have demonstrated that these are abnormal giant lysosomes. These contain lipoidal material in varying stages of degradation (Barak and Nir 1987). Ultrastructural studies by means of immunogold electron microscopy have suggested that the giant granules are derived from azurophilic granules containing myeloperoxidase and CD63 and not from specific and gelatinase granules (Kjeldsen et al. 1998).

Histological studies support the association between peripheral neuropathy and the cellular infiltrates of the accelerated phase of the disease. Giant lysosomes are present in the cytoplasm of the Schwann cells of myelinated peripheral nerve axons.

Pathogenesis and molecular genetics

Chediak-Higashi syndrome is inherited as autosomal recessive and is caused by mutation in the lysosomal trafficking regulator gene (**LYST**), currently named **CHS1** gene, located on chromosome 1q42.1–42.2 (Barrat et al. 1996, Fukai et al. 1996). The defective gene encodes a clue protein to regulate the secretory processes of intracellular lysosomal vesicles and melanosomes. The CHS protein is expressed in the cytoplasm of cells of a variety of tissues and may represent an abnormality of organelles protein trafficking. The CHS gene affects the synthesis and/or maintenance of storage/secretory granules in various types of cells: lysosomes of leukocytes and fibroblasts, dense bodies of platelets, azurophilic granules of neutrophils, and melanosomes and melanocytes which are generally larger in size and irregular in morphology, indicating that a common pathway in the synthesis of organelles responsible for storage is affected in patients with CHS. In the early stages of neutrophils maturation, normal azurophilic granules fuse to form megagranules, whereas in the later stage (i.e., during myelocyte stage), normal granules are formed. The mature neutrophils contain both populations. A similar phenomenon occurs in monocytes. The impaired function in the polymorphonuclear leukocytes may be related to abnormal microtubular assembly (Nowicki and Szarmach 2006). The mechanism of peripheral nervous system damage in CHS has not completely elucidated: both the axonal and demyelinating types of peripheral neuropathy associated to CHS have been reported. Defective melanisation of melanosomes

occurs in hypopigmentation associated to CHS: in melanocytes autophagocytosis of melanosomes occurs. The increased susceptibility to recurrent infections is likely secondary to an impaired phagocytosis and a lack of natural killer cell function.

The pathophysiology of the so-called accelerated phase (see above and below) seems related to an immune dysregulation (similar to what occurs in the haemophagocytic lymphohistiocytosis syndromes) (Rubin et al. 1985, Kinugawa 1990) with uncontrolled activation of lymphocytes and macrophages, possibly secondary to the lack of NK cell function.

Karim et al. (2002) performed mutation analysis of 21 unrelated patients with the childhood, adolescent, and adult forms of CHS: in patients with severe childhood CHS, they found only functionally null mutant CHS1 alleles, whereas in patients with the adolescent and adult forms of CHS they also found missense mutant alleles that likely encode CHS1 polypeptides with partial function.

Animal model

Disorders similar to CHS occur in many mammalian species besides man, including mouse, cattle, mink, and killer whale. Kahraman and Prieur (1990) stated that this disorder has been identified in at least 10 species including humans. They succeeded in prenatal diagnosis of CHS in cats by demonstrating abnormally large lysosomes (stained for acid phosphatase) in cultured amniotic fluid cells. In mink and cattle the disorder is autosomal recessive (Padgett et al. 1964).

The beige mouse has been used as an animal model for the disease (Windhorst and Padgett 1973). The mouse *beige (bg)* locus consists of a s series of seven mutant alleles of a gene located on chromosome 13. The human CSH1 (LYST) gene was mapped to a chromosome region (1q42.1–42.2) homologous to the position of the mouse *beige* gene (Barrat et al. 1996). When the mouse *beige* gene was positionally cloned (Barbosa et al. 1996; Perou et al. 1996a, b) cDNAs were used to isolate the human gene (Nagle et al. 1996) and to demonstrate the homology between mouse beige and humans (Barbosa et al. 1997). Thus far the pathologic mutations identified all resulted in lack of expression of the normal CHS protein (Spritz 1998, Farah and Rogers 2004).

Kunieda et al. (2000), by using a bovine/murine somatic cell hybrid panel, demonstrated linkage between the CHS locus and marker loci on the proximal end of bovine chromosome 28. CHS in Japanese black cattle is a hereditary disease with prolonged bleeding time and partial albinism.

Natural history

The disease typically proceeds along with an indolent course, with relapsing febrile episodes and infections, usually of the upper respiratory tract and skin. Intercellular vesicle formation is deficient, resulting in giant granules in many cells with deposition of lymphohistiocytes in the liver, spleen, lymph nodes and bone marrow, resulting in hepatosplenomegaly, bone marrow infiltration, bleeding tendency and haemophagocytosis. Most patients develop progressive neurologic deterioration, as a secondary event with a heterogeneous clinical picture (Silveira-Moriyama et al. 2004).

Accelerated phase

Viral infection, particularly due to Epstein-Barr virus, has been associated to the so-called "accelerated phase". Spritz (1998) stated that about 85–90% of CHS patients eventually develop this strange *lymphoproliferative syndrome* which is characterized by generalized lymphohistiocytic infiltrates, fever, jaundice, hepatosplenomegaly, lymphadenopathy, pancytopenia, and bleeding. This in turn leads to worsening of the neutropenia and increases the risk of infections (Farah and Rogers 2004). Thrombocytopenia ensues which intensifies the bleeding disorder. Onset of this phase may occur shortly after birth or may be delayed of years. It usually leads to death from infection or hemorrhage. This phase can resemble some lymphoma but it is not a true malignancy.

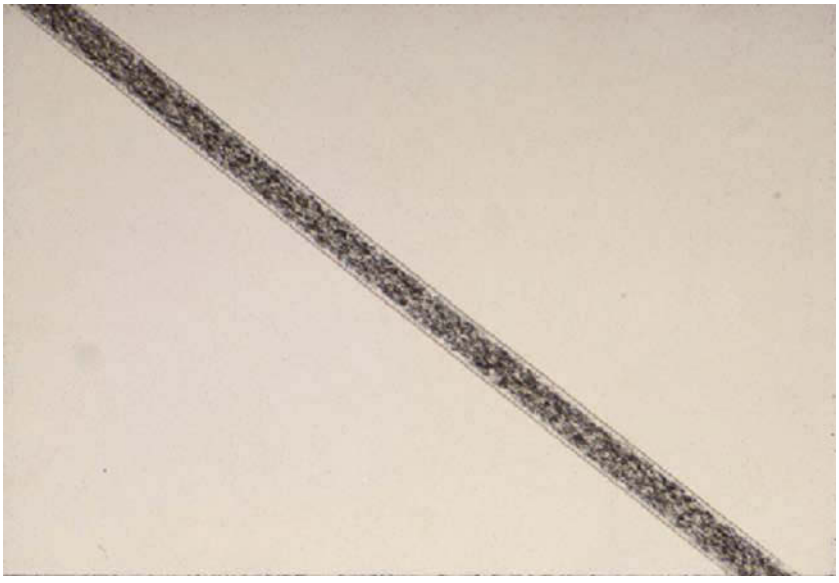

Fig. 4. Light microscopy of hair in Chediak-Higashi syndrome. Small granules regularly distributed are pathognomonic.

Diagnosis

With simple methods, light microscopy of the hair and a peripheral blood smear the diagnosis of CHS can be confirmed based on the presence of pathognomonic anomalous giant cytoplasmic granules in neutrophils (Fig. 3) or in leukocyte precursor cells (bone marrow smears) and multiple small clumps of melanine along the hair shaft distributed in a regular pattern (Fig. 4). Fluorescent cytometric analysis reveals the characteristic leukocyte dysfunction, the cellular granularity and surface molecules.

Light and electron microscopy examinations of biopsy specimens of periodontal tissues reveal massive bacterial invasion of epithelial tissue, epithelial cells and connective tissue.

Prenatal diagnosis can be made by examination of the hair from foetal scalp biopsy and from leukocytes from foetal blood samples.

Differential diagnosis

It should include albinism, bacterial mouth infections, cutaneous T-cell lymphoma, Griscelli syndrome (see below) and pyoderma gangrenosum.

Treatment and prognosis

The prognosis of CHS is generally poor: early death occurs without treatment from infections, hemorrhage, or complications of the accelerated phase. However, there is significant clinical heterogeneity among patients with CHS, and some patients may survive into adulthood with few or even no severe infections, although they may develop progressive neurological deterioration (Tardieu et al. 2005, Uyama et al. 1994).

Current treatment protocols for CHS include prophylactic trimethoprim-sulphamethoxazole and aggressive parenteral antibiotic treatment of infections. Ascorbic acid (vitamin C) at doses of 20 mg/Kg or 0.2–6 grams per day has been shown to improve neutrophils function in vitro, although there is no proof that this provides clinical benefit (Malech and Nauseef 1997).

High dose of methylprednisolone and splenectomy in the accelerated phase may improve significantly the clinical, radiological and haematological findings (Aslan et al. 1996).

Allogeneic bone marrow transplantation from an HLA-matched sibling is the therapy of choice and should be performed early. In absence of a family donor, an unrelated donor or a placental blood graft is a good alternative (Mottonen et al.

2003): cure of the accelerated phase can be achieved even when transplantation results only in mixed chimerism, suggesting that even a small fraction of donor cells are sufficient to suppress this phase. Conversely, ocular and skin pigmentary disturbances are not corrected by the bone marrow transplantation and neurological complications can still develop or progress after the transplant (Haddad et al. 1995, Tardieu et al. 2005, Uyama et al. 1994).

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GRISCELLI SYNDROMES (GS)

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Introduction

Griscelli syndrome (GS) is a rare autosomal recessive disorder (OMIM # 214450, 607624 and 609227) characterized by pigmentary dilution of the skin, due to abnormal melanosomal transport which result in abnormal accumulation of end-stage melanosomes in the centre of melanocytes, and by silvery grey hair, due to pigment clumping in hair shafts. While most patients also develop an *haemophagocytic syndrome*, characterized by uncontrolled activation of T lymphocytes and macrophages leading to death if not treated by bone marrow transplantation (OMIM # 607624) (Menasche et al. 2000), some show *severe primary neurological impairment* early in life without apparent immune abnormalities (OMIM #214450) (Anikster et al. 2002) and other have *hypomelanosis only with no immunologic or neurological manifestations* (Menasche et al. 2003) (OMIM # 609227). Recently, all these phenotypes (see Figs. 5–8) have been grouped under the same umbrella name (i.e., Griscelli syndrome/GS) because of shared biological mechanisms, but divided into three different subtypes (GS1–GS3), as they result from defects in three separate genes, located on chromosome 15q21 and 2q37 (Anikster et al. 2002; Menasche et al. 2000, 2002, 2003; Pastural et al, 1997, 2000):

- Myosin VA (MYO5A) gene, located on chromosome 15q21 (OMIM # 160777), causing GS with neurological impairment without haemophagocytic syndrome or **GS1** (OMIM # 214450);
- Ras-associated protein RAB27A gene, located on chromosome 15q21 (OMIM # 603868), causing GS with haemophagocytic syndrome or **GS2** (OMIM # 60764);
- Slac2-a/melanophilin (SLAC2A/MLPH) gene, located on chromosome 2q37 (OMIM # 606526), causing GS with no immunologic or neurological involvement or **GS3** (OMIM # 609227).

The protein products of the three genes are functionally closely linked one to each other as interacts in the same molecular pathways, resulting in melanosome transport of actin filaments to dock at the plasma membrane (i.e., in melanosome movement): defects in each gene result in pigmentary dilution because of defective release of melanosome content to neighbouring cells, such as keratinocytes in the skin (Menasche et al. 2002). In some body and cellular sites, however, MYO5A and RAB27A are expressed differently: for example, MYO5A is expressed in the brain, whereas RAB27A is not. Defects in MYO5A cause primary neurological dysfunction, whereas defects in RAB27A do not cause neurological abnormalities (unless as secondary effects of lymphocyte infiltration of central nervous system) (see GS2). Unlike myosin Va (the protein product of MYOVA), the GTP-binding protein (the protein product of RAB27A) appears to be involved in the control of the immune system thus causing the haemophagocytic syndrome. Melanophilin (Mlph) links the function of myosin Va and the GTP-Rab27a protein in the melanosome without additional functions: this explains why expression is restricted to the characteristic hypopigmentation in the third form of GS. In the protein complex *Rab27a-Mlph-MyoVa*, Mlph interacts with Rab27a through its N-terminal part (SHD) and with MyoVa through its C-terminal part (F-exon) (Fig. 9).

It is now accepted that the GS form caused by mutations in the MYOVA gene (GS1) and the so-

called **Elejalde syndrome** (OMIM # 256710) (see below) are allelic or better represent the same entity. The GS form caused by mutations in the Slac2-a/melanophilin (SLAC2A/MLPH) gene (GS restricted to hypopigmentation) represents the so-called "**silvery hair syndrome restricted to pigment dilution**" (OMIM # 609227) (see below).

Historical perspective and eponyms

Historically, Griscelli and co-workers (Griscelli et al. 1978), who worked at the Hospital Necker pour les enfants maladies in Paris, France, and his colleague Siccardi first described a condition characterized by partial albinism, frequent pyogenic infections and acute episodes of fever, neutropenia and thrombocytopenia. The pigmentary dilution was characterized by large clumps of pigment in the hair shafts and an accumulation of melanosomes in melanocytes. Despite an adequate number of T and B lymphocytes, the patients were hypogammaglobulinemic, deficient in antibody production, and incapable of delayed skin hypersensitivity and skin graft reaction. Their leukocytes did not stimulate normal leukocytes. A defect of helper T-cells was postulated. One patients was an 11-year-old North African girl with unrelated parents with a brother and sister with silvery hair who had died at 30 and 18 months of age, respectively. The morphological normality of polymorphonuclear leukocytes and lack of giant granules distinguished the disorder form Chediak-Higashi syndrome. The morphologic characteristics of hypopigmentation also distinguished the disorder from Chediak-Higashi syndrome, as well as from other pigmentary anomalies. These original cases (Griscelli et al. 1978) fit with the GS2 phenotype.

In 1977, Elejalde and co-workers described a new pigment mutation in two males and one female each from a consanguineous marriage in an inbred Columbian kindred. Elejalde et al. (1979) described this condition as neuroectodermal melanolysosomal disease (NEMLD). Dr. Elejalde (Elejalde et al. 1977, 1979) is credited for having first recognized a (primary) neurological impairment in patients with a silver hair syndrome. His original observation (Elejalde et al. 1977) credited to him the name of his own syndrome and an entry in the McKusick catalogue (OMIM # 256710) (OMIM 2006). This syndrome however is currently regarded as the same entity of GS1 (because both entities are caused by mutations in the MYOVA gene, see also above) and some authors continue to use only the eponym Griscelli syndrome type 1 (GS1) to characterize the Elejalde syndrome (Menanche et al. 2002). According to other authors (Duran-McKinster et al. 1999, Huizing et al. 2002, Ivanovich et al. 2001) the absence of immunological defects allows Elejalde syndrome to be distinguished from GS (at least from GS1). We believe that perhaps Dr. Griscelli should be (at least) credited for the accuracy of his ascertainment in recognizing a primary neurological involvement in the GS spectrum and the term *Griscelli/Elejalde syndrome* could be used as an alternative eponym for GS1.

Incidence and prevalence

GS is a rare disease in all populations. Male and female are equally affected. Most reported cases are from Turkish and Mediterranean populations; however, in 2004, Manglani et al. (2004) and Rath et al. (2004) reported several cases from India. In the US is rare with fewer than 10 cases reported (Scheinfeld and Johnson 2006). The largest series of patients with GS1 (Griscelli/Elejalde syndrome) have been reported in Mexico (Duran-McKinster et al. 1999).

Clinical manifestations

Often the first manifestation of GS that is noted is silvery hair. Not long after the immunologic effects of GS caused by mutations in the Rab27A gene (GS2) are noted. These immunologic defects resemble those of the haemophagocytic lymphohistiocytosis (HLH) and the X-linked lymphoproliferative syndrome. The neurological effects of GS caused by defects in MYOVA gene usually manifest early in life closer to birth.

Mutations in both MYO5A and RAB27A genes cause pigmentary dilution and other internal organ abnormalities. Skin manifestations of both GS12 and

GS2 include granulomatous skin lesions, partial albinism, and generalized lymphadenopathy. The skin is usually pale, but the hypopigmentation is not complete. Liver manifestations include hepatosplenomegaly and jaundice as a result of hepatitis. Patients can present with pallor as a result of pancytopenia. Partial ocular hypopigmentation has been observed in some patents but retinal degeneration has not been reported.

We will describe the main clinical features, the pathogenesis and molecular genetic aspects and the natural history of GS according to the three different subtypes.

Griscelli syndrome type 1 (GS1) or Griscelli/Elejalde syndrome [GS with neurological involvement]

GS1 (OMIM # 214450) represents hypomelanosis with a primary neurological deficit and without immunologic impairment or manifestations of haemophagocytic syndrome (Menasche et al. 2002). Neuromuscular disorders are the hallmark of the disease. Psychomotor impairment may have two forms of presentation: congenital or infantile, first developing during childhood (Fig. 6). The sudden presentation of central nervous system dysfunction can be compared with the "accelerated phase" described in CHS and GS2 (see below). A severe regressive psychomotor process develops rapidly with loss of normal skills until patients die. A triggering factor for this sudden dysfunction has not yet been identified. Severe migraine status followed by hemiparesis has also been described. In general, normal humoral and cellular immunity is observed and recurrent infections are not the rule as in CHS and GS3. Ocular abnormalities are quite frequent. Patients may present congenital amaurosis or progressive loss of vision, nystagmus, diplopia as well as hypopigmented retina.

The natural history in GS1 is characterized by initial referred because of hypotonia, marked motor developmental delay, and mental retardation, with

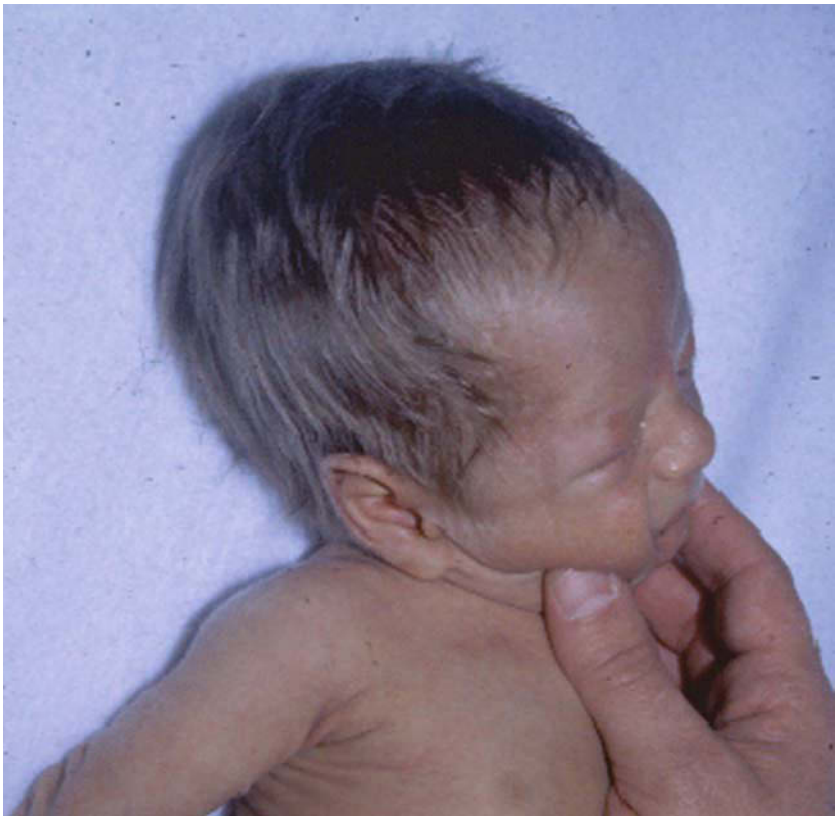

Fig. 5. Patient with Griscelli syndrome. Silvery hair is evident in hair scalp, eyelashes and eyebrows.

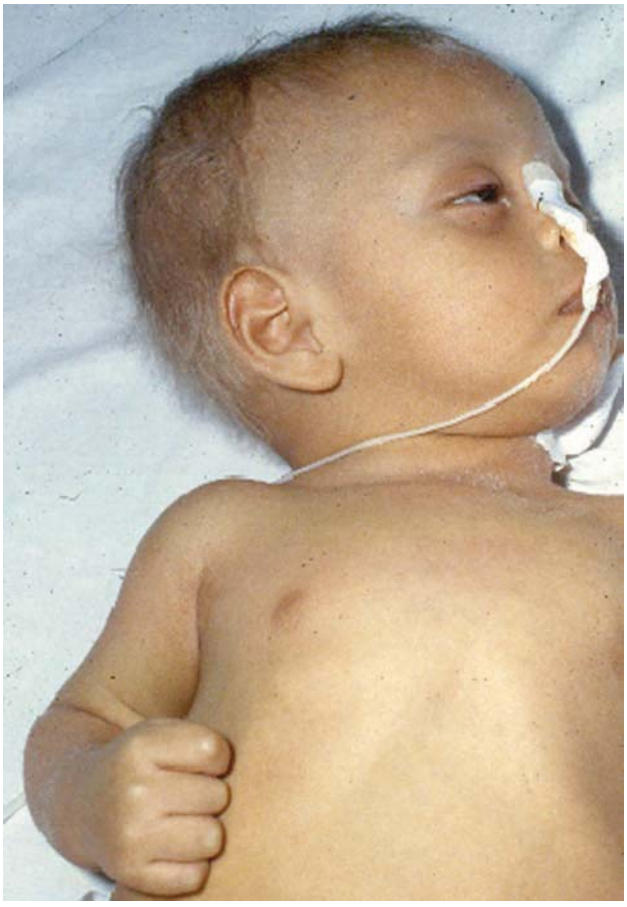

Fig. 6. Characteristic silvery hair in scalp in a patient with Elejalde syndrome with spastic quadriplegia.

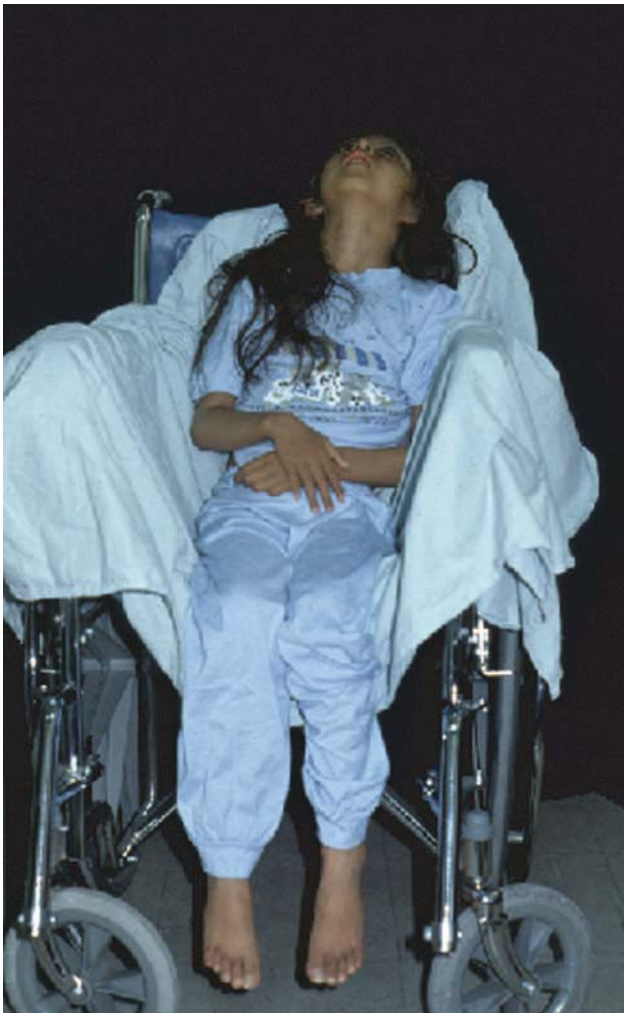

Fig. 7. Flaccid quadriparesis in a 6-year old patient with Elejalde syndrome.

no history of infections or "accelerated phase". Psychomotor development may be normal early in life but suddenly the patients present with a regressive neurological process. One typical manifestation at onset include recurrent vomiting, acute febrile illness and/or lethargy after which patients typically deteriorate neurologically as indicated by regression of cognitive and motor function. Central nervous system disorder is stable and never regresses with time. The age of onset of neurological signs ranges from 1 month to 11 years. Clinical features include also periodic episodes of ocular alterations (e.g., exotropia and nystagmus), ataxia, brainstem signs, hemiparesis, peripheral facial palsy, spasticity, and seizures (Fig. 7). In addition to the silver-leaden hair, bronze skin with diffuse freckling may develop after sun exposure. Large granules of melanin unevenly distributed in the hair shaft are observed. Usually, the long-lasting bronzed skin in patients with ES is not as darker as in patients with CHS or GS2. Death usually occur within the first decade of life when the patients are not treated.

Electroencephalogram usually reveals a diffuse and severe encephalopathy. Magnetic resonance imaging and computed tomography have demonstrate abnormal non-specific findings. Isolated congenital cerebellar atrophy was observed in a patient with the MYO5A defect. No evidence of infiltration of lymphocytes is present in these patients. MRI can reveal

areas of increased T2 signal intensity and focal areas of abnormal enhancement in the subcortical white matter.

GS1 is caused by mutations in the gene encoding myosin Va (or myosin 5a) (MYO5A) located on chromosome 15q21 (Pastural et al. 1997). MYO5A is a motor molecule, one of the large family of unconventional class myosin V, involved in melanosome movement as well as neurosecretory vesicles. Mutation in MYO5A has been found in synaptic terminals in the retina and brain. It is required for normal photoreceptor signalling, suggesting that it might function in central nervous system synapses in general, with aberrant synaptic activity. Bahadoran et al. (2003a, b) characterized GS1 as comprising hypomelanosis and severe central nervous system dysfunction, corresponding to the "dilute" phenotype in the mouse.

Anikster et al. (2002), Huizing et al. (2002), Menasche et al. (2002) and Bahadoran et al. (2003a, b) suggested that *Elejalde syndrome* and GS1 may represent allelic conditions or (at least) in some patients the same entity (see below). Sanal et al. (2000) suggested that ashen is a mouse model of Elejalde syndrome: however, in 2000 Wilson et al. showed that a mutated Rab27a gene, not the MYOVA gene, causes the pathology of Mouse. Anikster et al. (2002) suggested also that neurological involvement in some patients with GS occurred secondarily to the haemophagocytic syndrome and that patient with primary central nervous system complications and MYOVA mutations (i.e., with the GS1 form) have Elejalde syndrome. Several other reports established that neurological manifestations in patients with GS caused by RAB27A (i.e., the GS2 form) were related to lymphocyte infiltration of the central nervous system (De Saint Basil and Fisher 2001, Menasche et al. 2000, Pastural et al. 2000), whereas patients with GS caused by MYO5A mutations (i.e., the GS1 form) exhibited a primary neurological disease, potentially described as Elejalde syndrome.

Griscelli syndrome type 2 (GS2) [GS with haemophagocytic syndrome]

GS2 (OMIM # 607624) is characterized by hypomelanosis with immunologic abnormalities with or without neurological impairment. The GS2 phenotype currently corresponds to the original patients reported by Griscelli et al. (1978) (see above "historical perspective and eponyms"). GS2 patients exhibit various degrees of skin hypopigmentation and a silvery-gray sheen of the hair with large pigment aggregates in hair shafts. In most patients at least one episode of haemophagocytic syndrome (HS) or haemophagocytic lymphohistiocytosis (HLH) (the so-called "accelerated phase"), which is a lymphohistiocytic proliferation of unknown origin consisting of multivisceral infiltration, haemophagocytosis, pancytopenia, hypertriglyceridaemia, hypofibrinogenaemia, and hypoproteinaemia (Fig. 5) occurs. It is triggered by infectious episodes (usually viral but also bacterial) and is associated with a poor prognosis. When a remission is obtained, recurrent, accelerated phases with increasing severity are seen. The immunodeficiency is characterized by absent delayed-type cutaneous hypersensitivity and impaired natural killer cell function. No abnormal cytoplasmic granules are present in leukocytes. Patients with GS2 have immunologic abnormalities during the course of the haemophagocytic syndrome leading to leukocyte brain infiltration that sometimes result in secondary neurological involvement with diffuse white matter abnormalities seen at MRI (Anikster et al. 2002, Aksu et al. 2003): main signs include hyperreflexia, seizures, signs of intracranial hypertension, (e.g., vomiting or altered consciousness), strabismus, dysartrhia, ataxia, or regression of developmental milestones. The primary clinical differentiation between GS2 and GS1 is that the former has no primary neurological features. Occasionally, neurological problems may be the first sign of the accelerated phase.

CT and MRI findings are usually normal at birth. When the disease manifests, imaging findings are abnormal: CT can shoe areas of coarse calcification in the globus pallidus bilaterally, left parietal white matter, periventricular and left brachium pontis. Patients with GS2 can manifest unilateral hypodense signals in the genu and posterior limb of the internal capsulae (compatible with inflammatory changes), as well as posterior aspects of both thalami, together with minimal generalized atrophy. CT scanning can also suggest cell infiltration of the

brain. The subcortical white matter can be affected as occurs in the GS1 variant.

GS2 is caused by mutations in the RAB27A gene which encodes a GTP-binding protein (rab27) that functions in the targeting and re fusion of transport vesicles with their appropriate acceptor membranes (Mamishi et al. 2008). Like other rab proteins, rab27 requires geranylgenarylation of two consensus C-terminal cysteine residues in order to be anchored to membranes. Truncation of the carboxy-terminal part of rab27 would render it inactive (Westbroek et al. 2008). To date all patients with GS and mutations in RAB27A have developed the haemophagocytic syndrome.

Mutations in Munc 13-4 cause *familial haemophagocytic lymphohistiocytosis subtype 3* (FHL3), a syndrome that resembles GS2. Neeft et al. (2005) have shown that Munc 13-4 intimately interacts with the Rab27 protein: both proteins are intensely expressed in cytolytic T lymphocytes and mast cells and co-localize on secretory lysosomes.

Griscelli syndrome type 3 (GS3) [GS restricted to hypopigmentation]

The third form of GS, GS3, is characterized by the fair skin at birth of CHH and the other forms of GS followed by bronzed skin after sun exposure. Children can be referred because of unspecific complaints of failure to gain weight or recurrent tonsillitis and then noticed to have silver-gray hair, eyebrows, and eyelashes. Clinically, GS3-associate albinism is indistinguishable from that described in the other forms of GS. Skin biopsy and light microscopic examination reveals the same pattern as GS1 and GS2. Microscopic analysis of hair shafts show the characteristic features of GS, i.e., the presence of large clumps of pigment in the hair shaft. Most importantly, longitudinal follow-up reveals that phenotypic presentation is restricted to hypopigmentation, without any immune or neurological manifestation.

GS3 is caused by mutations in the gene that encodes melanophilin (Mlph) (SLAC2A/MLPH gene), the orthologue of the gene mutated in leaden mice. It has also been shown that an identical phenotype can result from the deletion of the MYOVA F-exon, an exon with a tissue-restricted expression pattern. The protein Mlph links the function of myosin Va and the GTP-Rab27a protein in the melanosome without additional functions: this explains why expression in GS3 is restricted to the characteristic hypopigmentation. In GS3 the Mlph is unable to associate with Rab27a, either transiently over expressed or endogenously expressed in melanocytes.

Diagnosis

As silver hair syndrome present four different clinical and genetic patterns, in view of the restricted or failure of current therapeutic measures, a correct diagnosis is mandatory to offer a correct genetic counseling to the families with affected children. Skin biopsy and light microscopic examination in all the three forms of GS reveals the same pattern (Fig. 8). Light microscopy of the hair reveals a different distribution of melanin in small and large clumps irregularly arranged along the hair shaft. MYOVA and RAB27A interact in the same molecular pathway, resulting in melanosome transport. Menasche et al. (2002) suggested that patients with partial (albinos-like) hypopigmentation and manifestations of haemophagocytic syndrome, with or without neurological involvement, should be screened for mutation in RAB27A, and patients with partial (albinos-like) hypopigmentation and primary neurological disease without haemophagocytic syndrome should be screened for MYO5A mutations.

Characteristic laboratory features in GS2 include pancytopenia, hypofibrinogenaemia, and hypoproteinaemia.

Treatment and prognosis

Medical treatment for patients with GS is difficult. For patients with defects in RAB27A (GS2), antibiotics and antiviral agents are used with mixed effects. Similarly medications may not control the neurological signs/symptoms of the disease. In GS related to MYO5A mutations (GS1), no specific treatment exists because the defect is in the brain rather than in the blood cells as in cases caused by

Fig. 8. Light microscopy of hair showing clumped pigment in small granules regularly distributed in CH syndrome (above) and small and large granules irregularly distributed characteristic of GS1 and GS2 patients without abnormalities, restricted to pigment dilution (middle) contrasting with normal hair (below).

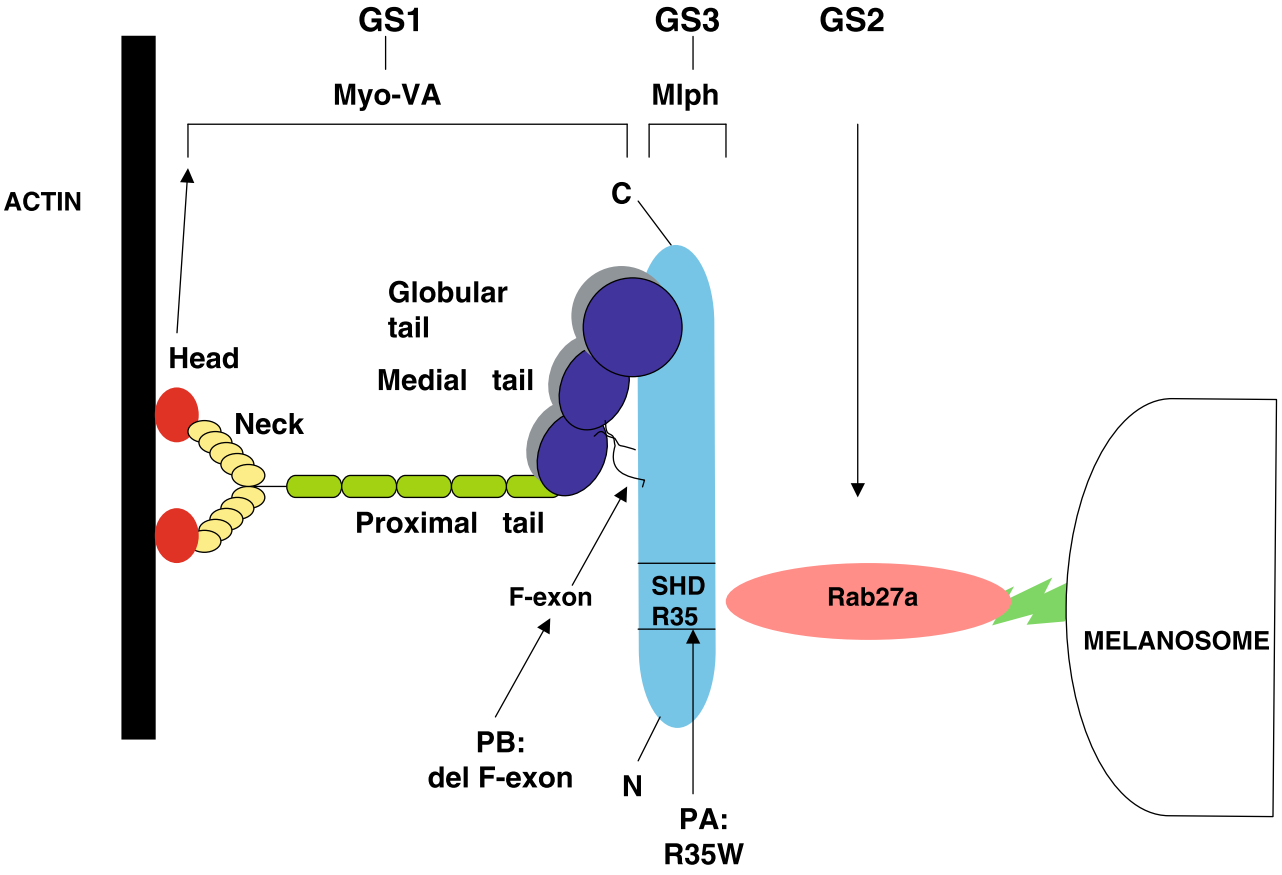

Fig. 9. Scheme of the heterotrimeric protein complex involved in human melanosome transport. A defect in any of the proteins, MyoVa, Rab27a, or Mlph, leads to identical pigmentary dilution, found in the three forms of GS (see text for further explanation). The F-exon of MyoVa is required for MyoVa-Mlph interaction and the SHD of Mlph for Mlph-Rab27a interaction (adapted from Menasche et al. 2000).

mutations in the RAB27A mutations (GS2). The severe neurological impairment and retarded psychomotor development do not improve with time.

Only allogeneic bone marrow transplantation is the treatment of choice in the early period of the disease (Arico et al. 2002). In preparation for a transplant, particularly in patients with GS caused by mutations in RAB27A (GS2), various immunosuppressive regimens have been used to attenuate the accelerated phase. Even a low number of donor cells in the patient's bone marrow can be sufficient to control symptoms of GS in cases caused by mutations of the RAB27A gene (GS2).

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