127 Miscellaneous Immunodeficiencies

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Ataxia-Telangiectasia

This syndrome is characterized by telangiectasia, a progressive ataxia, sinopulmonary infections, hypersentivity to ionizing radiation, and combined immunodeficiency.

Clinical features: Clinical presentation is variable and may be of early or late onset. The ataxia is cerebellar but may become generalized. Apraxia is almost always present. Patients are normal until they start walking with an ataxic, unsteady gait with frequent falls. The face may appear expressionless and may give the impression of stupidity. The speech becomes slurred and handwriting is characteristic as the child becomes severely ataxic. Strabismus, drooling, and weakness are common features in older children. Mental retardation occurs in some patients.

Extrapyramidal and posterior column signs are common. Telangiectasia begins in the palpebral conjunctiva between 1 and 6 years. It may become generalized and visible on the earlobes, nose, and antecubital areas. Some patients have little or no telangiectasia. Other cutaneous manifestations may include premature graying, hypertrichosis, hyperpigmentation, hypopigmentation, atopic dermatitis, and pyoderma.

Infections are usually in the form of sinusitis and pneumonia. Bronchiectasis and chronic lung damage will eventually lead to right-sided heart failure. These patients are usually small and retarded in growth. Many may not develop secondary sex characteristics. Mitral valve prolapse may develop in some patients.

Malignancy is a real threat that interrupts the lives of many patients. It has been estimated that, in about 38% of those who die, the direct cause of death is malignancy. Such malignancies include lymphosarcoma, Hodgkin disease, leukemia, adenocarcinoma, gonadoblastoma, reticulum cell carcinoma, medulloblastoma, dysgerminoma, and T- and B-cell lymphomas. Family members are at an eightfold higher risk of developing breast cancer, compared to the general population.

Those who survive long enough into adulthood become wheelchair bound and, later on, bedridden.

Pathology: There is cerebellar atrophy with loss of Purkinje cells. Peripheral nerve cells have malformed nuclei of Schwann cells. The thymus is hypoplastic with absent Hassall corpuscles.

Genetics and immunopathogenesis: The syndrome of ataxia-telangiectasia (A-T) is inherited as an autosomal recessive disorder. The ATM gene is located on the 11q22–23 chromosome. There is lack of nuclear DNA repair that leads to extensive and wide-ranging cellular damage in different organs. Some of the organs affected include the central nervous system, endothelium of blood vessels, T- and B-lymphocytes, and thymus. There is increased production of alpha-fetoprotein (A-FP). There are both cellular and humoral immune defects.

Epidemiology: Carriers of defective AT gene are more common in Caucasians and is in the range of 1.4–2%. The incidence of the disease is around 1 in 20,000–100,000 live births.

Diagnosis: The clinical and phenotypic features are characteristic. Signs and symptoms of immunodeficiency with recurrent infections may not develop early. Laboratory diagnosis may reveal lymphopenia and eosinophilia. Immunologic abnormalities include one or more of the following: IgA deficiency (in about 70%); high IgA and low IgG; decreased IgG; decreased IgA and IgM; decreased IgG, IgA, and IgG2; decreased IgG and IgG4; depressed specific antibody response; increased autoantibodies; depressed T-cell number and function; and very high A-FP. There is excessive chromosomal breakage. Endocrine abnormalities include decreased 17-ketosteroids and high urinary follicle-stimulating hormone; also, these patients have abnormal response to insulin-induced hypoglycemia. Magnetic resonance imaging of the brain shows atrophy and dilated ventricles.

Treatment: There is no curative therapy. Propranolol can be used to decrease tremors. IVIG is not beneficial, and the prognosis is very gloomy.

Caution: Radiologic examinations should be avoided as much as possible. Exposure to ionizing radiation increases the chromosomal breakage and, hence, development of malignancy.

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Cartilage-Hair Syndrome

The syndrome is characterized by short stature, with short limbs, fine sparse hair, and immune deficiency mostly cellular. It is inherited in an autosomal recessive mode.

The immune deficiency is characterized by lymphopenia, defective delayed immune response, and markedly decreased T-cell response to mitogens. These patients are susceptible to fungal, bacterial, and viral infections. Antibody response is also poor in more than one third of the patients. Fatal varicella infections have been reported. Some of the patients may have severe anemia, Hirschsprung disease, and increased incidence of cancer. The phenotypic features, however, are variable with some patients having immunodeficiency with normal hair, and normal skeletal system. Others may have normal hair and intact immune system. Mutations in RNA processing (RMRP) gene have been reported in patients with immunodeficiency. The treatment is supportive with antibiotics in patients with immunodeficiency. Bone marrow transplant may cure some patients with immunodeficiency.

Partial Albinism, Immunodeficiency, and Progressive Neurologic Disease (PAID Syndrome/Griscelli Syndrome)

Some features of the syndrome were partially reported (Griscelli) in 1978 in two Tunisian girls.

Since then sporadic cases have been reported from different countries. The largest number of cases is reported from Saudi Arabia with new features of the syndrome being described. The syndrome is characterized by partial albinism, recurrent fever, and accelerated phase with pancytopenia and hemophagocytic lymphohistiocytosis. In the majority of cases the final course is characterized by organomegaly, with neurological involvement which progresses into coma and death.

Clinical features: The syndrome is so characteristic it can be recognized at birth especially in dark-skinned patients. The salient features of the syndrome are silvery tint to golden gray hair with a "dead ash" appearance especially on the eye brows (see ❯ *Fig. 127.1*); hypopigmented skin, recurrent fever, hepatosplenomegaly; CNS involvement with demyelination of the white matter, and early death, in the majority.

The syndrome is inherited in an autosomal recessive mode. Recently three mutations have been described with three different clinical presentations:

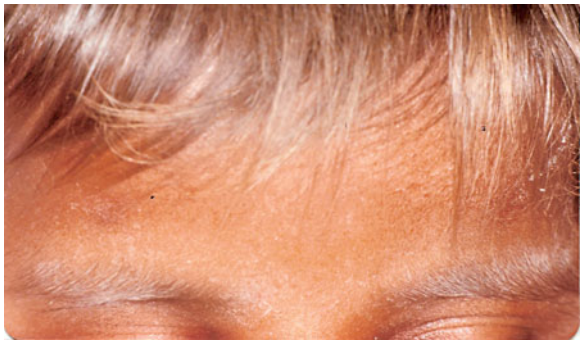

Figure 127.1
Close-up to show the typical hair and skin color in Griscelli syndrome

Type 1 Griscelli (GS1) is characterized by the presence of CNS disease with no hemophagocytic abnormalities and immunodeficiency.

Type 2 patients have hemophagocytic abnormalities, immunodeficiency, and variable neurological involvement.

Type 3 has abnormal melanin pigment distribution with partial albinism but no immunological, hematological, or neurological abnormalities. This type is more compatible with longer longevity.

Cutaneous manifestations: The skin is light in color, with areas of normal pigmentation and others without pigmentation giving freckled appearances. In some patients the skin is bronzy in color. The hair is grayish to silvery, or even golden gray, especially on the eyebrows. This is more apparent in brown or dark-colored skin and black hair. The parents usually make the diagnosis of the abnormality very early.

Recurrent fever: The clinical course in the majority of patients is characterized by frequent episodes of fever. Most febrile episodes yield negative cultures, but some may be indications of sepsis, pneumonia, or otitis media.

Neurological abnormalities: Neurological involvement is variable; some patients have hypotonia, or hyper reflexia in the lower extremities, others have seizures, coma, and death. Some patients may be mistakenly diagnosed as aseptic meningitis. The main lesion of the CNS is demyelination process that starts initially in the posterior fossa and spreads to the rest of the white matter (❯ *Fig. 127.2a, b*). CNS findings in 18 of our patients are summarized in the ❯ *Table 127.1*. Among the 18 patients (index cases) and their 16 affected siblings, 95% had CNS involvement. Four of the 18 patients had optic neuritis and visual loss. The

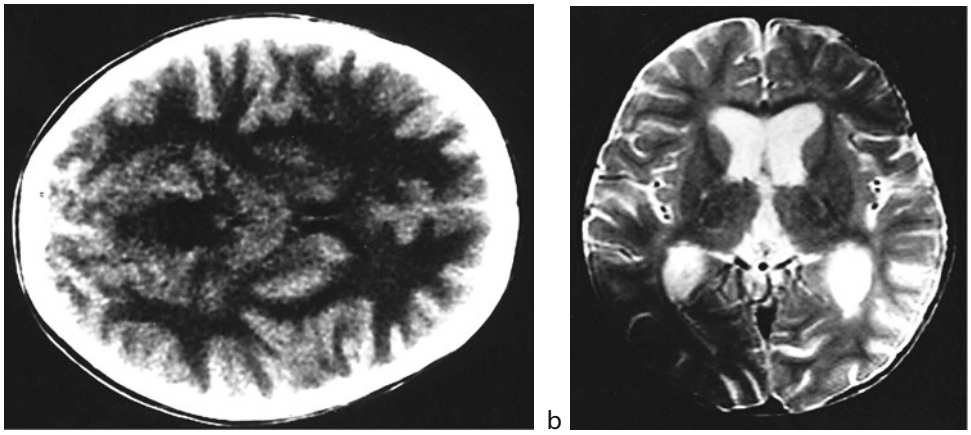

Figure 127.2
(a) CT of the brain of pt. with Griscelli syndrome. (b) MRI of the brain of pt. with Griscelli syndrome

Table 127.1
Clinical Findings in PAID (Griscelli disease)

		Findings
Total patients	18	Hypertonocity, ataxia-hyper reflexia, hemiparesis, facial palsy, coma, retinitis, mental retardation
Male/female	9/9	
CNS involvement	11(61%)	High protein mononuclear cells (50% B-cells, 50% CD4)
CFS involvement		
Abnormal EEG	11(61%)	Mild brain atrophy (two patients)
CT scan and MRI		White matter demyelination (11 patients)
Abnormal CT scan	11	Cerebellum alone (three patients)
Abnormal MRI	8	Generalized (four patients)

CNS involvement is at least partially reversible when treated early with a combination of immunosuppressive drugs.

Hematologic features: Very often these patients are anemic and they develop a picture reminiscent of the accelerated phase of Chediak–Higashi Syndrome. They develop pancytopenia, hepatosplenomegaly, and infiltration of the spleen, liver, bone marrow, and lungs with histiocytic mononuclear, atypical lymphocytes. CNS infiltration is evident by the presence of mononuclear cells in the CSF. Liver enzymes are elevated in all symptomatic patients.

Immunologic abnormalities: All patients with recurrent fever and infections have poor primary antibody response with very low isohemagglutinin antibody titer. They are anergic to recall antigens by skin test. As they become older, they develop a picture of combined immunodeficiency with low T- and B-cell count and defects in their function. Some patients had defective leukocyte chemotaxis.

Radiological findings: Computerized tomography (CT) and magnetic resonance imaging (MRI) may be normal in asymptomatic patients. Once the patient develops even mild neurologic manifestations, white matter changes will be detected. The early demyelination changes start in the cerebellum. As the disease progresses, the whole white matter disappears and the ventricles become dilated. This process is reversible when patients are treated early.

Histopathology findings: There is characteristic distribution of melanin pigment. The hair when examined under a high power lens shows areas of clumped pigment alternating with areas of no pigment. Skin biopsy shows melonocytes with short dendrites packed with mature pigment but very little pigment released in the epidermis. Langerhans cells may

be normal, decreased, or absent. The CSF cytology is 50% B-lymphocytes and 50% T-helper (CD4) lymphocytes. Over 78% of patients have high CSF proteins. Lungs, liver, and spleen and bone marrow are infiltrated by hemophogocytic histiocytes in symptomatic patients.

Epidemiology: The syndrome has been reported in case reports from different countries including Turkey, Mexico, Jordan, Kuwait, USA, and Europe but more than two thirds of the cases came from Saudi Arabia. Males and females are equally affected.

Pathogenesis and genetics: Consanguinity of parental marriages – usually first cousin – is the rule in all patients reported from the Arabian Peninsula. Mutations that have been identified are in MYO5A that encodes an unconventional myosin (GS1), mutation in RAB27A that encodes a GTP-binding protein of the Ras family (GS2), and MYO5A gene or gene that encodes for melanophilin (MLPH) in GS3.

Natural course: Untreated, patients die early in life, usually in the first decade of their lives. Before their demise patients become lethargic and stuporous followed by coma and death. They may develop septicemia or hepatitis with jaundice before they die. None of our patients survived beyond 6 years of age without BMT.

Diagnosis: Is made easy by the presence of the typical features confirmed by microscopic exam of the hair. The diagnosis can be made at birth.

Treatment: The disease is fatal if untreated. Rarely do patients survive beyond age 6–8 years. When patients are in accelerated phase with CNS involvement, chemotherapy with prednisolone, VPI6, with cyclosporine A, or antithymocyte immunoglobulins leads to temporary remission. If CNS is involved, intrathecal methotrexate can totally reverse the white matter changes, though partial response in relapse is the rule. The only curative treatment is allogeneic BMT or hematopoietic stem cell from a matched donor.

Prenatal diagnosis: Prenatal diagnosis can be achieved by examination of the fetal hair or and gene mutation of MYO5A or RAB27A in families with defined history.

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