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Elejalde Syndrome: Report of a Case and Review of the Literature

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Abstract: Elejalde syndrome is a rare autosomal recessive condition, with only 10 reported cases through 2001. It is characterized by silvery hair, pigment abnormalities, and profound central nervous system dysfunction. The differential diagnosis includes Griscelli and Chediak-Higashi syndromes, which present with silvery hair, pigment abnormalities, central nervous system alterations, and severe immunologic dysfunction. We report a 6-year-old girl with Elejalde syndrome and review Elejalde, Griscelli, and Chediak-Higashi syndromes.

Neuroectodermal melanolysosomal disease (NEMLD), also known as Elejalde syndrome, is an autosomal recessive condition presenting with silvery hair, pigment abnormalities, profound central nervous system dysfunction, and normal immunologic function (1). The disorders that resemble this disease are Chediak-Higashi and Griscelli syndromes, which also feature silvery hair (2,3), but are associated with severe immunologic dysfunction (1).

CASE REPORT

A 6-year-old girl was referred to us for evaluation of hyperpigmentation in sun-exposed areas and silvery gray hair. On physical examination, her hair, eyebrows, and eyelashes were silvery gray, but normal in pattern and texture. The lighter skin color in covered areas contrasted with the patient's bronze skin on sunlight-exposed areas (Fig. 1).

Neuromuscular alterations were remarkable. She was severely mentally retarded and had convulsive episodes that had begun at age 7 months, controlled by anticonvulsants. She also had hyperactive deep tendon reflexes and spastic quadriparesis. Her parents were nonconsanguineous.

She had no history of recurrent infections or illnesses. Ophthalmologic examination of the conjunctiva, cornea, pupils, lenses, optic disc, and retina did not show any abnormalities. The pupils were equal and reactive to light bilaterally.

Light microscopy of the hair revealed melanin in small and large clumps, irregularly distributed along the hair shaft, predominantly within the medullary zone, with no other abnormalities (Fig. 2). Skin biopsy specimens subjected to light microscopic examinations showed irregular distribution of melanin granules in the basal layer and melanophages, with no giant melanosomes (Fig. 3). Electron microscopy study of the skin showed melanocytes with an abundance of melanosomes of various sizes and in various stages of development and adjacent keratinocytes with only sparse melanosomes (Fig. 4). CD68 staining was positive in the melanocytes.

The electroencephalogram was abnormal, with generalized encephalopathy. Magnetic resonance imaging (MRI)

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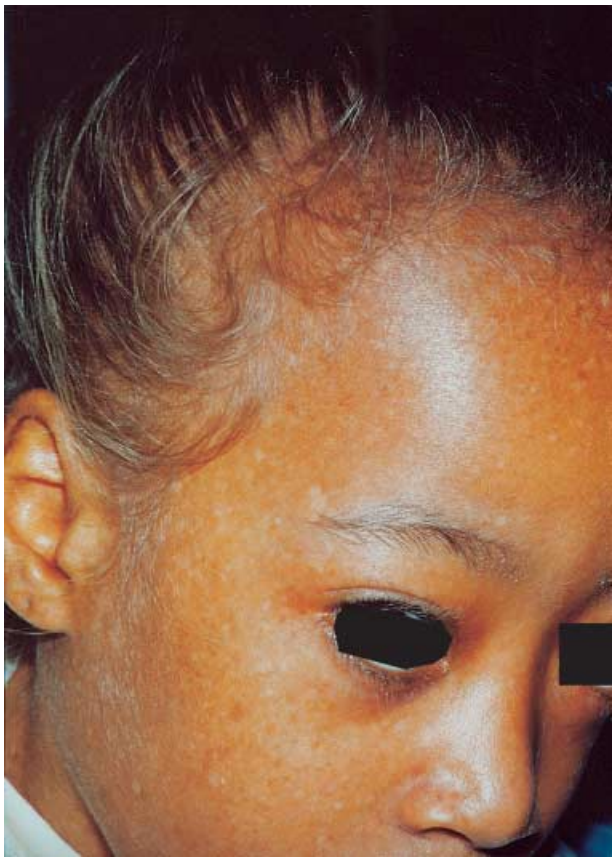

Figure 1. The patient at the age of 6 years had silvery scalp hair, eyelashes, and eyebrows as well as bronze skin.

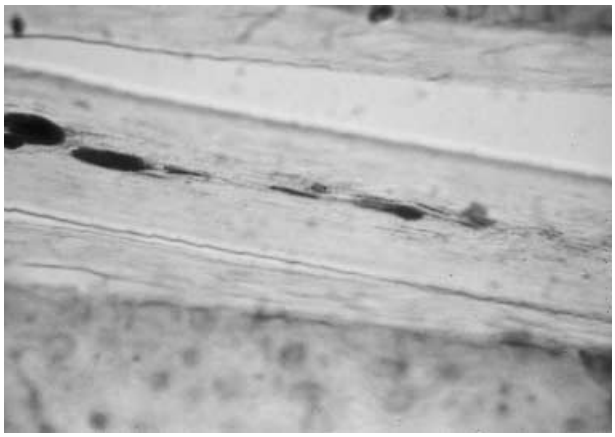

Figure 2. Light microscopy of the hair shaft shows small and large clumps of pigment irregularly distributed (original magnification 400×).

of the brain revealed abnormal cerebellar atrophy with no evidence of cellular infiltration in the central nervous system. The chromosome analysis demonstrated no alterations.

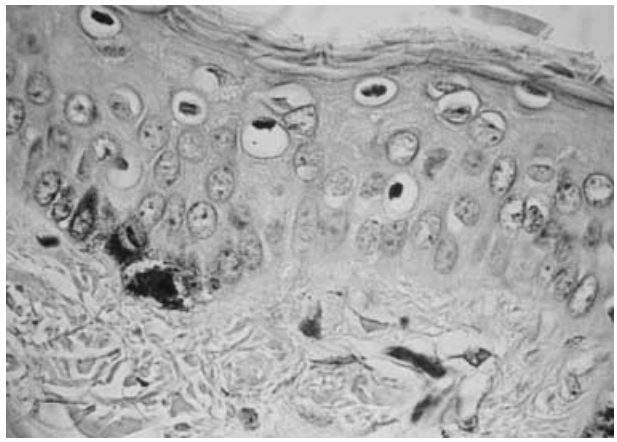

Figure 3. A skin biopsy specimen shows increased pigment in the basal melanocytes (original magnification 400×).

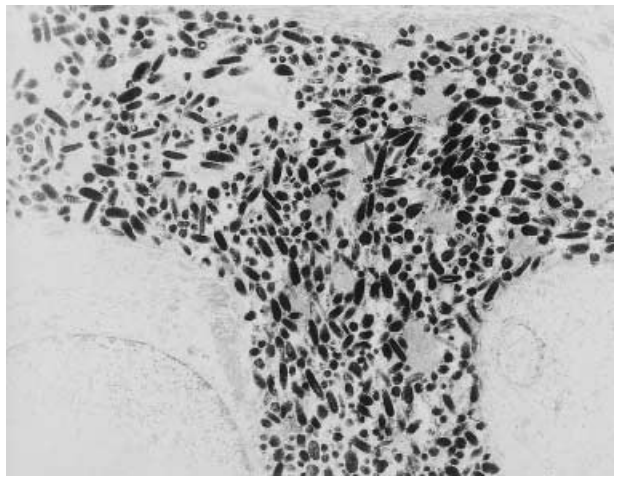

Figure 4. Ultrastructural appearance of the melanocytes, with different stages of melanosome formation (original magnification 8000×).

Laboratory evaluations, including hematocrit, hemoglobin level, white blood cell count, cholesterol, triglycerides, aspartate aminotransferase, alanine aminotransferase, platelets, prothrombin time, and partial thromboplastin time, were normal. Humoral and cellular immunologic test results were within normal limits. Immunologic studies included serum immunoglobulin levels, specific antibody responses, lymphocyte subsets, and proliferation to mitogens and antigens. Abnormal giant intracytoplasmic granules in neutrophils could not be found in peripheral blood or bone marrow. Bone marrow aspiration revealed no evidence of an infiltrative or malignant process. Cerebrospinal fluid tests were normal.

On the basis of the combination of clinical presentation, light microscopy of the hair, and normal immunologic studies, a diagnosis of Elejalde syndrome was made.

DISCUSSION

The silvery hair syndromes have misleadingly been referred to as partial albinism syndromes. They resemble albinism, but hypopigmentation is the result of a failure to transfer melanin to keratinocytes as a result of impaired melanosome transport (4).

Elejalde syndrome was first described in 1978 by Elejalde et al (5), with only 10 reported cases until 2001 (1). It is a quite rare autosomic recessive disorder (5), characterized by silvery hair, pigment abnormalities, profound central nervous system dysfunction of early onset, and normal immunologic function (1). The underlying molecular basis for Elejalde syndrome remains unknown (2).

The hair, eyelashes, and eyebrows have a silvery color (1). Tanning of the skin is evident after sun exposure and is long lasting (5).

Neurologic dysfunction includes severe hypotonia, hyporeflexia or hyperreflexia, spastic hemi- or quadriplegia, flacid hemi- or quadriplegia, seizures, ataxia, profound developmental delay, and convulsive episodes (1,5). Ophthalmologic findings include nystagmus, diplopia, congenital amaurosis, and pupilar areflexia (1,5).

Light microscopy of the hair shows small and large melanin clumps irregularly distributed along the hair shaft, predominantly in the medulla (5,6). Skin biopsy specimens observed under light microscopy show a normal number of melanocytes with irregular distribution and irregular size of melanin granules in the basal layer (5).

Electron microscopic studies of the skin reveal melanocytes with melanosomes of various sizes and various developmental stages (3). Melanization of melanosomes is incomplete due to a maturation defect (2,3), but humoral and cellular immunity are normal (3).

The differential diagnosis of this disease includes Griscelli and Chediak-Higashi syndromes (1–5). The main differences are listed in Table 1.

Griscelli syndrome is a rare, lethal, autosomal recessive disorder (7,8) characterized by silvery hair, pigmentary dilution, variable cellular and humoral immunodeficiency, recurrent infections, neurologic dysfunction, and an "accelerated phase," that is an acute activation of lymphocytes and macrophages (3), with lymphohistiocytic infiltration of many organs (2). Dermatologic findings in patients with Griscelli syndrome may be limited to the pigmentary abnormalities of the hair, although cutaneous pigmentary dilution has occasionally been noted (2). Light microscopic examination of the hair shows irregular small and large aggregations of melanin pigment, accumulated mainly in the medulla (7), while histopathologic evaluation of skin biopsy specimens shows hyperpigmented oval melanocytes with poorly pigmented adjacent keratinocytes (2).

Patients with Griscelli syndrome are predisposed to develop a lymphohistiocytic proliferation of unknown origin consisting of multivisceral infiltration, leading to fever and hepatosplenomegaly. These episodes have been associated with viral infections, most notably Epstein-Barr virus (2).

The other silvery hair syndrome, Chediak-Higashi, is a multiorgan, autosomal recessive disorder (9) characterized by immune defects, oculocutaneous hypopigmentation, silvery gray hair, neurologic dysfunction, lymphoproliferative syndrome, and a marked defective chemotaxis of neutrophils (5,9–12). Giant organelles and giant inclusion bodies in all granule-containing cells are hallmarks of this disease (1,13,14). Most patients with Chediak-Higashi

TABLE 1. *Differentiation of Syndromes with Silvery Hair*

	Elejalde	Griscelli	Chediak-Higashi
Age at onset	Infancy/early childhood	Infancy/early childhood	Infancy/early childhood
Inheritance	Autosomal recessive	Autosomal recessive	Autosomal recessive
Melanin in the hair	Small and large clumps, irregular pattern	Small and large clumps, irregular pattern	Small clumps, regular pattern
Leukocytic granules	None	None	Yes
Recurrent infections	None	Yes	Yes
Neurologic impairment	Yes	Yes	Yes
Immune defects	None	Humoral and cell-mediated immunity disturbed	Diminished chemotaxis of neutrophils, decreased natural killer function, decreased antibody dependent cellular cytotoxicity
Skin light microscopy	Irregular distribution and irregular size of melanin granules in the basal layer	Hyperpigmented basal melanocytes with sparse pigmentation in adjacent keratinocytes	Large melanin granules in melanocytes and keratinocytes
Skin electron microscopy	Melanocytes with different stages of melanosomes formation	Accumulation of normal-size, mature melanosomes in melanocytes, few melanosomes in keratinocytes	Giant melanosomes in melanocytes and keratinocytes
Accelerated phase	None	Yes	Yes

syndrome exhibit hypopigmentation of the skin, hair, and eyes, ranging from relatively mild pigmentary dilution to oculocutaneous albinism (10). The eyes may show pigmentary dilution of the iris, nystagmus, photophobia, strabismus, and reduced visual acuity (10,15,16).

Affected individuals have frequent pyogenic infections due to immunologic deficits (1,11), primarily with *Staphylococcus aureus*, β-hemolytic streptococci, and common fungi (9). Most important of these immunologic defects are neutropenia and lack of natural killer (NK) cytotoxicity activity (1,9,10). About 85% of children with Chediak-Higashi syndrome eventually progress to the "accelerated phase" (10,16).

Melanin in the hair shaft is abnormally distributed in multiple, small clumps with a regular pattern (4). Light and electron microscopy of the skin show giant abnormal melanosomes in melanocytes and keratinocytes with an aberrant maturation pathway (7,10). Most children with Chediak-Higashi syndrome die during the first decade of life from pyogenic infections, hemorrhage, or complications of the "accelerated phase" (10).

Our patient had silvery hair, pigment abnormalities, profound central nervous system dysfunction, and irregular distribution of melanin in the hair shaft, but no immunologic disturbances. Light and electron microscopic examination showed irregular pigmentation in the basal keratinocytes and melanocytes, with no giant melanosomes. The giant cytoplasmic granules in polymorphonuclear cells typical of Chediak-Higashi syndrome were not found. Based on this, the diagnosis of Elejalde syndrome was made.

In conclusion, the differential diagnosis for children with silvery hair, pigment abnormalities, and neurologic dysfunction includes Elejalde, Griscelli, and Chediak-Higashi syndromes. The examination of a patient with these characteristics should include light microscopic analysis of the hair shafts, study of skin biopsy samples, evaluation of immune function, and examination of peripheral blood.

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