Elejalde Syndrome—A Melanolysosomal Neurocutaneous Syndrome

Clinical and Morphological Findings in 7 Patients

Carola Duran-McKinster, MD; Rodolfo Rodriguez-Jurado, MD; Cecilia Ridaura, MD; M. A. de la Luz Orozco-Covarrubias, MD; Lourdes Tamayo, MD; Ramon Ruiz-Maldonando, MD

Background: Silvery hair and severe dysfunction of the central nervous system (neuroectodermal melanolysosomal disease or Elejalde syndrome) characterize this rare autosomal recessive disease. Main clinical features include silver-leaden hair, bronze skin after sun exposure, and neurologic involvement (seizures, severe hypotonia, and mental retardation). Large granules of melanin unevenly distributed in the hair shaft are observed. Abnormal melanocytes and melanosomes and abnormal inclusion bodies in fibroblasts may be present. Differential diagnosis with Chédiak-Higashi syndrome and Griscelli syndrome must be done.

Observations: We studied pediatric patients with silvery hair and profound neurologic dysfunction. Immune impairment was absent. Age of onset of neurologic signs ranged from 1 month to 11 years; the signs included severe muscular hypotonia, ocular alterations, and seizures. Mental retardation since the first months of life was noted in 4 cases. Psychomotor development was normal in 3 cases, but suddenly the patients presented with a regressive neurologic process. Four patients died between 6 months and 3 years after the onset of neurologic dysfunction. One patient showed characteristic ultrastructural findings of Elejalde syndrome.

Conclusions: Elejalde syndrome is different from Chédiak-Higashi and Griscelli syndrome and is characterized by silvery hair and frequent occurrence of fatal neurologic alterations. Psychomotor impairment may have 2 forms of presentation: congenital or infantile. Although Elejalde syndrome and Griscelli syndrome are similar, the possibility that they are 2 different diseases, although probably allelic related, is suggested.

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Silvery hair was first recognized as a pathologic feature in Chédiak-Higashi syndrome (CHS). Oculocutaneous hypopigmentation and silvery-gray hair, a marked defective chemotaxis of neutrophils, and an apparent association with lymphoid malignancy characterize this rare autosomal recessive disorder. The diagnosis is usually based on the presence of pathognomonic, anomalous giant cytoplasmic granules in neutrophils and in a wide variety of other granule-containing cells. Melanin in the hair shaft is abnormally distributed in multiple small clumps with a regular pattern. Death occurs at an early age, following an “accelerated phase” after which infections and/or lymphomalike organ infiltration occurs.

In 1979, Elejalde et al first described 3 consanguineous families as having neuroectodermal melanolysosomal disease (NEMLD). The main features were an autosomal recessive heredity characterized by silvery hair, profound dysfunction of the central nervous system, abnormal melanocytes and melanosomes, and abnormal inclusion bodies in fibroblasts and other cells. Apparently ignoring Elejalde’s description, in recent years several articles have been published describing patients with the combination of silvery hair and neurologic involvement without giant cytoplasmic granules or immunologic dysfunction and classifying them as having the following diseases: CHS, Griscelli disease with cerebral involvement, and Griscelli disease with neurologic involvement. Unlike CHS and...
PATIENTS AND METHODS

From February 1971 to January 1997, all clinical records of patients with silvery hair seen at the Department of Dermatology of the National Institute of Pediatrics were reviewed. Clinical and pathological findings of our patients were compatible with CHS in 6 cases, GS in 2 cases, and Elejalde syndrome in 7 cases. Patients with silvery hair and neurologic involvement were selected for this study. The following data were collected: sex, age, parental consanguinity and family history, age of onset of neurologic alterations, ophthalmologic examination, clinical and neurologic features, and follow-up. Data from the following laboratory tests were recorded: complete peripheral blood cell count from the 6 patients and bone marrow aspirate from 3. Immunologic studies in all patients included serum IgG, IgA, and IgM. Antinuclear antibodies, complement, and phagocytic function were tested with nitroblue tetrazolium. Cell-mediated immunity was evaluated by delayed hypersensitivity skin tests with phytohemagglutinin, concanavalin A, C. albicans, and purified protein-derivative (tuberculin) antigens as well as with T-lymphocyte subsets. Isohemagglutinin antibody titers against blood groups were obtained in patients 1 and 2.

A complete neurologic examination was performed by an experienced pediatric neurologist in all of the patients. Specific studies included the following: electroencephalogram, cerebrospinal fluid analysis, and visual- and auditory-evoked potentials. Cerebral tomographic scan and magnetic resonance imaging were performed for 5 patients. Skin biopsy specimens from the arm or leg were obtained from each patient, and sections were made for light microscopy in all patients and for transmission electron microscopy in 2 (patients 3 and 6). Samples of hair were obtained from all of the patients and parents for light microscopic examination.

RESULTS

The results of the general features are summarized in Table 1. The patients’ age at onset of neurologic signs ranged from 1 month to 11 years (mean age, 3 years). All patients were born at term after an uneventful pregnancy and normal delivery. Consanguinity of the parents (first or second cousins) was reported in 3 patients. Three patients had other family members (2 cousins in patient 3, a brother in patient 4, and 2 sisters in patient 7) with silvery hair. They had died in the first decade of life following a regressive neurologic process.

In all patients, the physical examination revealed a lighter skin color in covered areas that contrasted with the patient’s bronzed skin on sunlight-exposed areas. The scalp and body hair, eyebrows, and eyelashes had a silvery color (Figure 1). Skin and hair color of the patients contrasted with the dark skin and black hair of family members. Samples of the hair observed by light microscopy showed the same characteristics in the 7 patients, consisting of an abnormal distribution of melanin in small and large clumps, irregularly distributed along the hair shaft with no other abnormalities. A complete ophthalmologic examination showed a wide spectrum of abnormalities (Table 1).

Chédiak-Higashi syndrome and GS were excluded in the analysis of our patients for the following reasons: there was no clinical or laboratory evidence of immunologic impairment and abnormal giant intracytoplasmic granules in neutrophils could not be found in peripheral blood smears or in bone marrow aspirates in patients 5, 6, and 7. Patient 6 had the only blood cell count with persistent leukopenia. Humoral and cellular immunologic test results were within normal limits in all cases. Neurologic alterations were the most striking features (Table 2). The 4 youngest patients (patients 1, 4, 5, and 7) were severely mentally retarded since the first months.

Griscelli syndrome (GS), NEMLD does not exhibit defects in cellular or humoral immunity but a severe impairment of the central nervous system.

Herein, we describe 7 patients with NEMLD (Elejalde syndrome) seen in the National Institute of Pediatrics of Mexico.

Table 1. Clinical Features*

<table>
<thead>
<tr>
<th>Patient No./Sex</th>
<th>Age at Onset of First Signs</th>
<th>Parents’ Consanguinity</th>
<th>Ophthalmological Examination Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M</td>
<td>1 mo†</td>
<td>Negative</td>
<td>Nystagmus, esotropia</td>
</tr>
<tr>
<td>2/F</td>
<td>3 y</td>
<td>Negative</td>
<td>Nystagmus, hypopigmented retina</td>
</tr>
<tr>
<td>3/F</td>
<td>11 y†</td>
<td>Positive</td>
<td>Diplopia, papilledema</td>
</tr>
<tr>
<td>4/M</td>
<td>2 mo†</td>
<td>Positive</td>
<td>Congenital amaurosis, hypopigmented papilla</td>
</tr>
<tr>
<td>5/M</td>
<td>1 mo</td>
<td>Negative</td>
<td>Pupilar areflexia</td>
</tr>
<tr>
<td>6/F</td>
<td>6 y</td>
<td>Positive</td>
<td>Diplopia</td>
</tr>
<tr>
<td>7/F</td>
<td>1 mo†</td>
<td>Negative</td>
<td>Congenital amaurosis</td>
</tr>
</tbody>
</table>

*All patients had bronzed skin color and silver-gray hair color.
†With other family members affected.

Figure 1. Characteristic bronzed skin color and silvery hair in scalp, eyelashes, and eyebrows in Elejalde syndrome (patient No. 4).
Table 2. Neurologic Features

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Neurologic Alterations</th>
<th>Mental Development</th>
<th>Seizures</th>
<th>Electroencephalogram</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Hypotonia</td>
<td>Spastic quadripareis</td>
<td>Yes</td>
<td>Severe retarded</td>
</tr>
<tr>
<td>2</td>
<td>Hypotonia</td>
<td>Flaccid quadriplegia</td>
<td>Yes</td>
<td>Regressive</td>
</tr>
<tr>
<td>3</td>
<td>Hemiplegia</td>
<td>Flaccid hemiplegia</td>
<td>Yes</td>
<td>Regressive</td>
</tr>
<tr>
<td>4</td>
<td>Hypotonia</td>
<td>Flaccid quadriplegia</td>
<td>Yes</td>
<td>Severely retarded</td>
</tr>
<tr>
<td>5</td>
<td>Hypotonia</td>
<td>Spastic quadriplegia</td>
<td>Yes</td>
<td>Severely retarded</td>
</tr>
<tr>
<td>6</td>
<td>Hypotonia</td>
<td>Ataxia</td>
<td>Yes</td>
<td>Regressive</td>
</tr>
<tr>
<td>7</td>
<td>Hypotonia</td>
<td>Flaccid quadriplegia</td>
<td>No</td>
<td>Severely retarded</td>
</tr>
</tbody>
</table>

* For all patients, the visual and auditory evoked potentials were abnormal, except where indicated otherwise.

COMMENT

Pigmentary abnormalities characterized by hypopigmented skin and silvery hair at birth are shared by CHS, G5, and Elejalde syndrome, and they have been responsible for the erroneous classification of these conditions as partial albinism. Tanning of the skin is evident after sun exposure and is long lasting. A defective transfer of melanin from melanocytes to the surrounding keratinocytes provoking a heavily pigmented basal layer explains the persistent bronze skin. The phenotype of these patients is not reminiscent of albinism, a condition in which cutaneous melanocytes are almost absent and erythema and sunburn without tanning is frequent after sun exposure.

Analysis of hair samples by light microscopical examination is of great diagnostic value. An abnormal dis-
tribution of melanin in clumps in the hair shaft leaves spaces free of melanin and impairs the refraction and absorption of light. As a result, the hair shaft is light colored with a silver-leaden shine. Small melanin granules regularly distributed in both cortical and medullar zones are characteristic of CHS, while GS and Elejalde syndrome share the same pattern, consisting of small and large melanin clumps irregularly distributed along the hair shaft (Figure 5).

Four of our patients were severely retarded almost from birth. The remaining 3 patients seemed to develop normally until neuromuscular alterations started in the form of a regressive neurologic process. Clinical manifestations of neurologic impairment in Elejalde syndrome may have 2 different forms of presentation: (1) congenital, as observed in our youngest patients (patients 1, 4, 5, and 7) and in the first known cases of Elejalde syndrome, or (2) infantile, first developing during childhood (patients 2, 3, and 6). The noncongenital or infantile form of the onset of Elejalde syndrome was not previously reported. The sudden presentation of central nervous system dysfunction in Elejalde syndrome can be compared with the “accelerated phase” described in CHS in which recurrent episodes of infections and death are observed. A triggering factor for the sudden dysfunction has not been identified.

Our patient 6 presented with persistent leukopenia and died of a neurologic regressive process. This patient's condition raises the question of the possible existence of cases of Elejalde syndrome with immune compromise.

The histopathological findings of the cerebellar biopsy specimen (patient 6) were nonspecific, but these abnormalities can be contained within chronic necrotizing/inflammatory lesions, which are observed in diverse viral diseases or immunoallergic conditions. Some viral infections can be excluded because none were found in the studied specimen. The presence of numerous T lymphocytes in the lesions suggests that these cells are responsible for the tissue damage. Unfortunately, we could not perform T-cell subset detection studies to determine if the lymphocytes were cytotoxic T cells. Furthermore, it is important to consider angiocentric immunoproliferative lesions as they have been observed in immunocom-
promised patients as benign lymphocytic infiltrations, eg, lymphomalic in CHS or real lymphomas. ¹⁰

Melanin in the skin and hair and neuromelanin in the brain probably play an important role in the pathologic alterations found in Elejalde syndrome. The skin pigmentation and the characteristic silvery hair are due to a distribution of melanin in clumps. It is not known if the abnormal distribution of melanin is due to a structural melanocytic anomaly or to a biochemical defect in melanin composition. The relation between melanin and neuromelanin and the role of neuromelanin in neurologic alterations are not known. Perhaps the distribution of melanin in clumps that in the skin causes only a color change is responsible for serious neurologic alterations in the brain. We do not know the characteristics of neuromelanin in the central nervous system of our patients, but the clinical picture of a severe neuromuscular dysfunction could be related to its abnormal quantity or quality.

Elejalde syndrome should be identified as an independent entity, different from CHS and GS. The CHS gene product has been identified and mapped on chromosome 1q42-1q43. This gene was designated “LYST” (lysosomal trafficking regulator) and is believed to be involved in lysosomal transport. ¹¹ Pastural et al ¹² recently studied 4 patients with GS, including the first case reported by Griscelli: 2 of their patients mapped to chromosome 15q21 and were associated with mutations in the myosin-Va, a molecular motor protein. Mutations were in different functional domains of the gene in each patient. This mutation caused a complete loss of function of the myosin protein, and 1 patient had a severe degenerative neurologic disorder, similar to those described in all of our patients with Elejalde syndrome, supporting the idea of 2 different diseases, although probably allelic related.

Elejalde syndrome does not have an immune-gross defect as GS, and a different molecular pathogenesis in the regulation of the human hematopoietic system is suggested. Further studies are needed to support this hypothesis.

The possibility of a late onset in Elejalde syndrome should be kept in mind. In view of the failure of the current therapeutic measures, new approaches should be sought. For the time being, only the genetic counseling may be offered to families with affected children. Our patients and those described in the literature suggest an autosomal recessive mode of inheritance. Differential diagnosis with another condition associated with light and sometimes silvery hair include the infantile form of sialic acid–storage disease, a lysosomal storage disorder characterized by coarse facial features, hepatosplenomegaly, and development delay. Histological evidence of lysosomal storage and vastly increased tissue and urine levels of free sialic acid are present. ¹³ ¹⁴ No microscopic description of the hair shaft has been made.

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Reprints: Carola Duran-McKinster, MD, Apartado Postal 101-16, Mexico City, 04530 Mexico.

REFERENCES