

Myoclonus and Angiokeratomas in Adult Galactosialidosis



Galactosialidosis is an autosomal recessive lysosomal storage disorder characterized by a combined deficiency of β -galactosidase and α -neuraminidase, due to a defect of another lysosomal protein, cathepsin A. The latter, forms a complex with β -galactosidase and neuraminidase, and protects them against excessive proteolytic degradation. Three clinical phenotypes had been described: a severe early infantile form; a milder late infantile type with minor mental deterioration; and a juvenile/adult form, mainly found in Japan, which is characterized by slowly progressive neurological symptoms, skeletal and eye abnormalities, dysmorphism, angiokeratomas, and long survival.¹ Herein, we report a case of galactosialidosis of the juvenile-adult form in a Peruvian girl with angiokeratoma corporis diffusum (ACD) and myoclonus.

A 24-year-old woman presented a 5-year history of involuntary movements. At age 19, she developed a progressive myoclonic disorder that started in the lower limbs and caused frequent falls. The myoclonus subsequently spreads to other body regions. Five years into the disease, she was almost wheelchair bound, and other activities such as eating and speaking were considerably affected. There were, however, no seizures or cognitive decline.

She was the third child of nonconsanguineous Peruvian parents and had two older sisters, one of which had skin lesions but no abnormal movements. There was no family history of neurological disorders. Further information about ancestor's origins couldn't be obtained, although some oriental features seemed to be present in distant relatives. The patient's developmental milestones were normal and she had a history of anemia and irregular menstrual cycles.

Physical examination revealed densely peppered red macules ranging from 1 to 3 mm on palms (Fig. 1), elbows, knees, oral mucosa, lips, and on thighs and loins in a bathing suit distribution. She had distal transverse reddish bands on her nails and few naevi on her soles. She was short (146 cm) and had course facial features and hypertrichosis. Neurological examination showed mild intellectual dysfunction (IQ, 68), mild sensorineural hearing impairment, and decreased visual acuity. Deep tendon reflexes were brisk.

Tone and muscle strength were slightly reduced. She had multifocal, stimulus sensitive myoclonus triggered by action. She had a wide-based-bouncing gait and needed help to walk because of negative myoclonus.

The laboratory tests were all normal except for a mild microcytic anemia. Cerebrospinal fluid examination (including lactate levels) and copper metabolism were normal. She had subclinical hypothyroidism but no elevated antithyroid antibodies. Serum gluten antibodies were within normal range. Ophthalmologic examination revealed myopia, mild optic atrophy, reduced visual acuity but no macular cherry-red spots. The electroencephalogram was normal. Needle electromyography showed myopathic changes with normal nerve conduction velocities. Muscle biopsy was nonspecific. Median nerve somatosensory evoked potentials were enlarged (P25-N33(left/right) = 16/20 μ V), but C reflexes were absent. No visceromegaly was found on abdominal ultrasound. Brain MRI revealed no abnormalities except vermian atrophy. Basal ganglia spectroscopy was normal. Histopathological examination of skin lesions showed telangiectasias and angiokeratomas. Angiokeratomas are vascular lesions that can be found isolated in normal individuals, but when they are wide spread, the term ACD is used. ACD constitutes the dermatological hallmark of several inherited lysosomal disorders.² In a Giemsa-stained peripheral blood smear, small cytoplasmic vacuoles were observed in the lymphocytes, suggesting a storage disorder. Electron microscopic examination revealed numerous cytoplasmic vacuoles with electron-lucid granular deposits in the endothelial cells of blood vessels, in pericytes (Fig. 2) and fibroblasts. The same characteristic vacuoles were found in the naevus melanocytes. Assays of enzymatic activities in leukocytes showed a marked decrease in β -galactosidase (3.1 μ mol/l/h; normal range: more than 15). Biochemical



FIG. 1. Telangiectasias on palms.

Additional Supporting Information may be found in the online version of this article.

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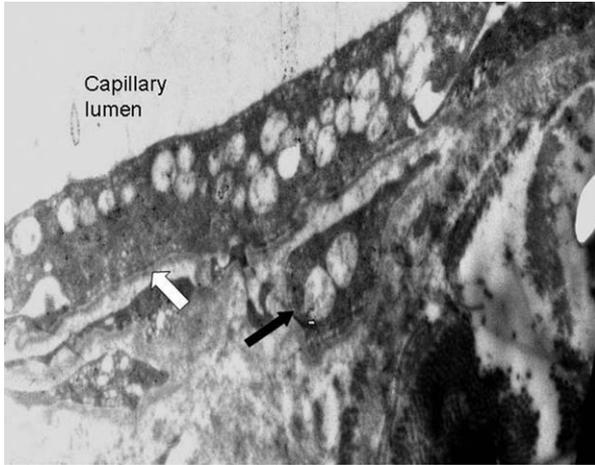


FIG. 2. Electron-microscopic examination showing numerous cytoplasmic vacuoles with electron lucid granular deposits in the endothelial cells and pericytes (arrows).

analysis showed elevated urinary sialyloligosaccharides characteristic for galactosialidosis.¹

This case was diagnosed as a juvenile/adult form of galactosialidosis based on biochemical and enzymatic tests. This patient presented with typical features, but so far, she had no epilepsy or macular cherry-red spots also described in this disease.^{1,3-5} She was treated with levetiracetam 2,000 mg/day with improvement of myoclonus. Specific therapy in humans is not available at present.¹

In galactosialidosis, sialyloligosaccharides accumulates in lysosomes of different tissues and are excreted in body fluids. Previous neuropathological studies have demonstrated neuronal swelling and the accumulation of heterogeneous inclusions and cytoplasmic vacuoles in anterior horn cells, spinal ganglia, sympathetic ganglia, myenteric plexus, hippocampus, and Meynert nucleus. Endothelin-1, a substrate of cathepsin A, was more recently identified as one of the storage materials in the cerebellum, hippocampus, and spinal cord.⁶

To date, most of the patients with juvenile galactosialidosis were Japanese^{1,3-5} and we think this is the first case reported from Latin America. Conceivably, this young woman has the

same genetic mutation as the Japanese subjects perhaps explained by ancient or more recent migration waves arriving in Peru. Alternatively, this patient has a different molecular defect from that seen in the Japanese variant.

Legends to the Video

Segment 1. Action and stimulus sensitive myoclonus is demonstrated. Negative myoclonus interfering with gait improves after treatment. Course facial features can be observed.

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