Generalized dystonia and striatal calcifications with lipoid proteinosis

H.A.G. Teive, MD; E.R. Pereira, MD; J.A.A. Zavala, MD; M.C. Lange, MD; L. de Paola, MD; S. Raskin, MD, PhD; L.C. Werneck, MD, PhD; T. Hamada, MD; and J.A. McGrath, MD

Abstract—Lipoid proteinosis (LP) is an autosomal recessive disease that typically presents with papular, verrucous, poxlike, or acneiform scars and lesions and hoarseness. LP was recently mapped to the 1q21 locus and shown to result from mutations in the extracellular matrix protein 1 gene (*ECM1*). Epilepsy, mental retardation, and hippocampal calcifications can occur. The authors describe a patient with generalized dystonia caused by striatal calcifications.

NEUROLOGY 2004;63:2168–2169

Lipoid proteinosis (LP; OMIM 247100) was described in 1929 by Urbach and Wiethe.[1] It is autosomal recessive and is also known as hyalinosis cutis et mucosae because of the progressive deposition of hyaline-like material (glycoprotein) that occurs in the skin, mucosae, and other tissues.[2] Approximately 250 cases have been reported.[2]

Typically, clinical manifestations first appear in early childhood with hoarseness, followed by poxlike and acneiform scars, along with infiltration and thickening of the skin and other mucous membranes.[2] In many affected individuals, intracerebral calcifications (particularly involving the hippocampi) are present. Neurologic and psychiatric manifestations include epilepsy and memory deficits, social and behavioral changes, paranoid symptoms, mental retardation, and aggressiveness.[2-7]

LP was recently mapped to the 1q21 locus and has been shown to result from mutations in the extracellular matrix protein 1 gene (ECM1).[6,7]

In this report, we describe a patient with LP who had skin lesions, mental retardation, and intracerebral calcifications—all typical for the disease—but in whom there was also severe generalized dystonia, a previously unrecognized and unreported clinical manifestation of LP.

Case report. A 24-year-old man was evaluated for mental retardation and dystonia. He was the product of an unremarkable full-term pregnancy, and there was no history of consanguinity. The patient was asymptomatic until age 2 years, at which time he developed hoarseness and yellowish skin papules over the body. Psychomotor and mental retardation was evident by age 6 years. Hoarseness worsened, and the patient became unable to speak during his teens. Bilateral foot dystonia then began in an ascending way, with axial, upper limb, oromandibular, and cervical compromise (anterocollis). Biperiden, 16 mg/d, and diazepam, 10 mg/d, were given with a slight response, but the dystonia progressed, and the patient became disabled and dependent on a caregiver.

Family history was positive for a 34-year-old sister diagnosed with LP and having epilepsy, mild mental retardation, and skin, mucous membrane, and eyelid infiltration. Her CT scan showed bilateral symmetric hippocampal calcifications, and a skin biopsy was consistent with LP.

Our patient had beaded eyelid papules (moniliform blepharosis) and diffuse acneiform scars over his face, torso, and limbs. The oral mucosa had a cobblestone appearance, and the tongue had a rubber-like texture. Neurologic examination showed profound mental retardation, mutism, and severe generalized dystonia, affecting predominantly the oromandibular region (i.e., a jaw-closure dystonia), cervical dystonia (anterocollis), and limb dystonia (affecting the upper limbs and lower limbs, with sustained and fixed postures) associated with truncal dystonia (with lordosis).

Blood workup was unrevealing, and a brain CT scan showed bilateral symmetric hippocampal and striatal calcifications (figures 1 and 2). A routine (awake and sleep) EEG recording was slightly irregular, but no epileptiform activity was demonstrated. A CT scan of the larynx showed no gross changes. A skin biopsy showed epidermal and dermal changes with acanthosis, irregular hyperkeratosis, and deposition of periodic acid-Schiff–positive, homogeneous, hyaline, eosinophilic material around dermal blood vessels and adnexal structures, consistent with LP. Direct sequencing of the proband's genomic DNA identified a homozygous frameshift mutation, 541del3ins16, in exon 6 of the *ECM1* gene. This mutation, which has not previously been reported in LP, leads to a premature termination codon 22 bp downstream and is predicted to ablate all isoforms of *ECM1*.[2,8] Sequencing of exon 6 in 60 control chromosomes did not detect this sequence change in any sample.

Discussion. LP is a genetic disorder resulting from mutations in the *ECM1* gene.[6-8] This gene encodes an 85-kDa protein, and alternative splicing gives rise to three distinct isoforms (ECM1a, ECM1b, and ECM1c) with functions that are not fully understood. ECM1a and ECM1b are expressed in the skin and upper respiratory tract, but the former can be more widely distributed.[6-9] ECM1c has only been detected in two cancer cell lines.[8] In patients with LP, the molecular pathology usually involves loss-of-function mutations (nonsense or frameshift changes on both alleles) with the majority of mutations occurring in exons 6 and 7. Mutations

From the Movement Disorders Unit (Drs. Teive, Pereira, Zavala, Lange, de Paola, and Werneck), Neurology Service, Hospital de Clínicas, Federal University of Paraná, Curitiba, PR, Brazil; Genetika Laboratory (Dr. Raskin), Curitiba, Paraná, Brazil; Department of Dermatology (Dr. Hamada), Kurume University School of Medicine, Kurume, Fukuoka, Japan; and Genetic Skin Disease Group (Dr. McGrath), St. John's Institute of Dermatology, The Guy's, King's College and St. Thomas' Hospitals' Medical School, London, UK.

Received March 9, 2004. Accepted in final form July 16, 2004.

Address correspondence and reprint requests to Dr. Hélio Teive, Rua General Carneiro 1103/102, Centro, Curitiba, PR, 80060-150, Brazil; e-mail: hagteive@mps.com.br

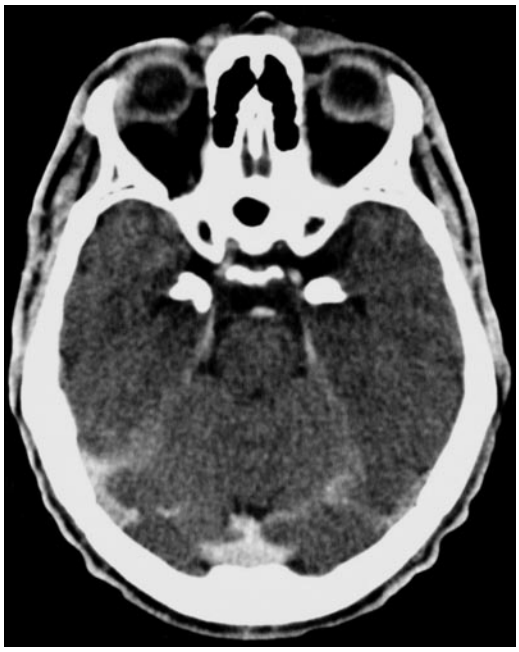

Figure 1. Axial brain CT showing symmetric mesial temporal lobe (hippocampal) calcifications.

in exon 7, which is spliced out in the ECM1b isoform, can result in a slightly less severe skin and respiratory tract phenotype, but specific correlation between genotype and phenotype for neurologic manifestations has not been found.[7]

Epilepsy, particularly temporal lobe epilepsy, has been described as a common manifestation of LP. Our patient had no seizure history and a nonepileptiform EEG. The patient's sister had epilepsy and hippocampal calcifications; her brain imaging study (CT scan) did not reveal the presence of striatal calcifications, unlike the findings described in our patient.

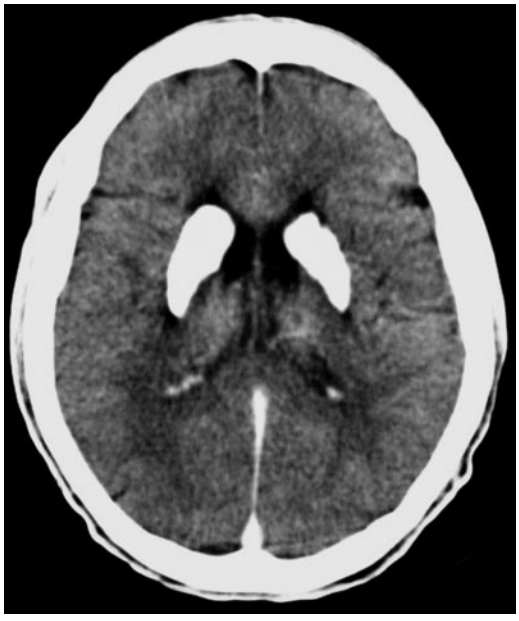

Figure 2. Axial brain CT showing symmetric striatal calcifications.

Bilateral temporal lobe calcifications within the amygdala, periamygdaline gyrus, and anterior and anteroposterior temporal horn may appear in up to 75% of the patients. These imaging patterns are highly suggestive of LP.[3-5] Autopsy material shows dense amorphous masses of calcium and bone and multiple, haphazardly arranged small blood vessels with calcified walls and gliotic adjacent tissue. The cortex and white matter show isolated blood vessels completely occluded by fibrin, partial calcification, small perivascular areas of infarction, and demyelination.[4]

Mental retardation and memory deficits may be seen in patients with LP. Amnestic syndromes seem to be related to hippocampal calcifications.[3] Our patient had severe mental retardation; thus, formal memory testing did not apply.

Our case is classified as heredodegenerative dystonia, with childhood onset and generalized dystonia. There is no evidence of primary and secondary dystonia or dystonia-plus syndromes. In the group of autosomal recessive heredodegenerative dystonias, other diseases could be considered, such as familial basal ganglia calcifications and mitochondrial encephalopathies, but their clinical picture is rather different. Finally, Fahr disease, hypoparathyroidism, and pseudohypoparathyroidism could be hypothetically considered in the differential diagnosis; however, we believe in our case they were efficiently ruled out by complementary tests as demonstrated.[10]

Our patient also has the unique clinical feature of dystonia and unreported imaging findings of bilateral symmetric striatal calcifications. These observations extend the possible clinicopathologic abnormalities that may occur in this inherited disorder and demonstrate that LP should be remembered as a possible cause of dystonia.

Acknowledgment

The authors thank Professor José Fillus Neto, MD (Department of Dermatology of Federal University of Paraná), for his evaluation of skin biopsies and Arnolfo de Carvalho, MD (Department of Radiology of Federal University of Paraná), for his analysis of CT scans.

References

1. Urbach E, Wiethe C. Lipoidosis cutis et mucosae. Wirchows Arch A Pathol Anat 1929;273:285–319.
2. Hamada T. Lipoid proteinosis. Clin Exp Dermatol 2002;27:624–629.
3. Newton FH, Rosenberg RN, Lampert PW, O'Brien JS. Neurologic involvement in Urbach-Wiethe's disease (lipoid proteinosis). Neurology 1971;21:1205–1213.
4. Yakout YM, Elwany S, Abdel-Kreem A, Abou-Seif S. Radiological findings in lipoid proteinosis. J Laryngol Otol 1985;99:259–265.
5. Staut CCV. Lipoid proteinosis: CT and MRI features. Int J Neuroradiol 1998;4:199–207.
6. Hamada T, McLean WH, Ramsay M, et al. Lipoid proteinosis maps to 1q21 and is caused by mutations in the extracellular matrix protein 1 gene (ECM1). Hum Mol Genet 2002;11:833–840.
7. Hamada T, Wessagowit V, South AP, et al. Extracellular matrix protein 1 gene (ECM1) mutations in lipoid proteinosis and genotype-phenotype correlation. J Invest Dermatol 2003;120:345–350.
8. Chan I. The role of extracellular matrix protein 1 in human skin. Clin Exp Dermatol 2004;29:52–56.
9. Mongiat M, Fu J, Oldershaw R, et al. Perlecan protein core interacts with extracellular matrix protein 1 (ECM1), a glycoprotein involved in bone formation and angiogenesis. J Biol Chem 2003;278:17491–17499.
10. Fahn S, Bressman SB, Marsden CD. Classification of dystonia. In: Fahn S, Marsden CD, DeLong MR. Dystonia 3: advances in neurology, vol 78. Philadelphia: Lippincott-Raven, 1998:1–10.

Generalized dystonia and striatal calcifications with lipoid proteinosis

H. A.G. Teive, E. R. Pereira, J. A.A. Zavala, et al.

Neurology 2004;63;2168-2169
DOI 10.1212/01.WNL.0000145602.64073.C2