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Lipoid proteinosis or Urbach-Wiethe disease: description of a new case with cerebral involvement☆,☆☆

Lipoidoproteinosis o enfermedad de Urbach-Wiethe: a propósito de un nuevo caso con afectación cerebral

Dear Editor:

Lipoid proteinosis (LP), also known as hyalinosis cutis et mucosae or Urbach-Wiethe disease (OMIM: 247100), is a rare recessive autosomal disorder. The disease follows a slow, benign course. To date, some 250[1] to 300 cases[2,3] have been reported. LP is characterised by intracellular deposition of periodic acid-Schiff—positive (PAS-positive) hyaline material in the skin, mucous membranes, and internal organs.[4—6]

This type of genodermatosis results from loss-of-function mutations in the gene coding for extracellular matrix protein 1 (ECM1) on chromosome 1q21.[1,7—9] *ECM1* contains 10 exons with 3 isoforms (ECM1a, the most frequent; ECM1b; and ECM1c), whose functions remain to be determined. EMC1 is expressed in the dermis, keratinocytes, endothelial cells, and developing bones. It is linked to keratinocyte differentiation, basement membrane regulation, collagen composition, and growth-factor binding (skin homeostasis).[1,9]

Clinical manifestations of LP are secondary to protein abnormalities and vary greatly among individuals.[5] The disorder affects multiple systems, especially the skin and mucosa of the upper aerodigestive tract.[7] Nearly pathognomonic for LP, the disease typically presents in childhood with a weak cry and hoarse voice due to laryngeal infiltration.[10] At the age of 3, infiltration and diffuse thickening of the skin occurs, resulting in papules and chickenpox-like scars. Around 50% to 60% of the cases

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☆☆ The genetic part of this study has been published previously (J Clin Neurol. 2014;10:64—8).

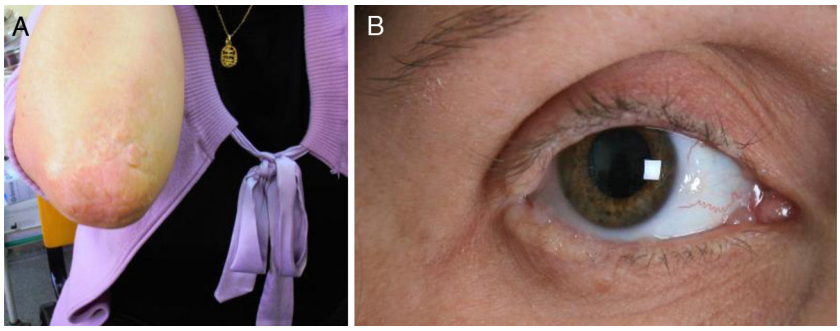

Figure 1 (A) Hyperkeratotic plaques on the skin covering the elbows. (B) Moniliform blepharosis.

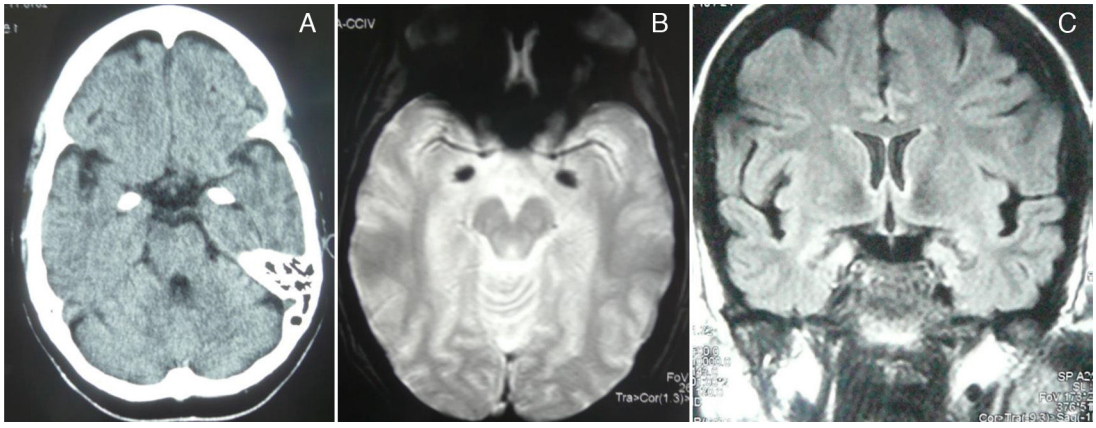

Figure 2 Non-contrast CT displaying bilateral symmetrical hyperdensity, axial T2*-weighted gradient-echo MRI (hypointensity), and coronal FLAIR MRI (hyperintensity) in the amigdalae and unci. Findings were compatible with calcifications.

present moniliform blepharosis resembling a string of pearls; this finding is almost pathognomonic.[11] In 50% to 70% of the cases, cranial CT and MRI scans display bilateral, symmetrical calcifications in the medial region of the temporal lobes, including the hippocampus (unci) and the amygdalae[12]; other findings include epileptic activity, memory alterations, social/behavioural anomalies, paranoid symptoms, and mental retardation.[1,8,12,13]

We present the case of a 35-year-old woman whose parents were not consanguineous. At the age of 9 months she displayed a hoarse, dysphonic voice and has visited our department since 1997 for numerous reasons: headache, memory loss, a feeling that she was experiencing things that were not real, difficulty recognising places, dizziness, instability, anxiety, and depression. She had a history of hypothyroidism. The physical examination revealed a dysphonic, low-pitched voice. The skin covering her joints displayed numerous yellowish hyperkeratotic verrucous papules in a paving-stone pattern; the lingual, labial, and jugal mucosae were also affected, and she displayed moniliform blepharosis (Fig. 1). The neurological examination was normal. The neuropsychological assessment revealed a slight decrease in information processing speed and mild alterations in episodic memory and recall processes.

A complete analysis including hormone, antibody, immunity, and serology tests yielded no significant results. Cranial CT and MRI scans (T2*-weighted gradient-echo sequences) displayed bilateral, symmetrical hyperdense/hyperintense lesions in the unci and amigdalae, which were compatible with calcifications (Fig. 2). A sleep-deprived EEG revealed no abnormalities. Cognitive evoked potentials (P300) pointed to delayed reaction time in the Posner task and normal P3 latency in the oddball task.

A skin biopsy revealed dermal and epidermal changes with irregular acanthosis, hyperkeratosis, and deposition of homogeneous eosinophilic PAS-positive diastase-resistant hyaline material around the blood vessels of the dermis and adjacent structures; these glycoprotein alterations were consistent with LP.

Sequencing the protein-coding region of the *ECM1* gene revealed a nonsense mutation at exon 7 of *ECM1*, c.1076G>A, which resulted in a premature stop codon, p.Trp359*, affecting isoform ECM1a.

Further studies are necessary to establish a more specific connection between genotype and phenotype; in our case, we hypothesised that the new mutation may have resulted in a more extensive phenotype with skin, mucosa, and brain involvement. Likewise, mutations outside exon 7 (such as those affecting the ECM1b isoform, which lacks exon 7) have been associated with a more severe mucocutaneous phenotype but no neurological involvement.[14]

To the best of our knowledge, this is the first case of genetically confirmed LP with brain calcifications to be published in the Spanish-language literature.

Conflicts of interest

The authors have no conflicts of interest to declare.

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Multiple vascular malformations in a patient with microcephalic osteodysplastic primordial dwarfism type II☆

Múltiples malformaciones vasculares en un paciente con enanismo primordial osteodisplásico microcefálico tipo II

Dear Editor:

Microcephalic osteodysplastic primordial dwarfism (MOPD) is a syndrome characterised by intrauterine growth retardation, impaired postnatal growth, microcephaly, and a phenotype similar to that of Seckel syndrome.[1] MOPD type II, the most distinctive type of MOPD, is a rare disorder with a recessive autosomal inheritance pattern. We recently published the case of a Colombian carrier of a new mutation of the *PCNT* gene with a nucleotide change in exon 10, c.1468C>T, resulting in a premature stop codon at amino acid position 490, p.Q490X, which is predicted to generate a truncated protein.[2]

When the case was reported, the patient was 5; he was extremely small (below the third percentile for his age), with delayed psychomotor development and microcephaly, downward-slanting palpebral fissure, a prominent nose, amelogenesis imperfecta, ulnar deviation, a high narrow pelvis, unusually short arms and legs, coxa vara, a high-pitched voice, and an outgoing personality.[2] Complementary tests performed when he was 4 included a simple brain CT scan and an angiography. The CT scan showed no alterations in the fourth ventricle and posterior fossa, closure of the metopic and sagittal sutures, and permeability of the coronal and lambdoid sutures, whereas the angiography revealed no aneurysms or signs of moyamoya disease. We requested a molecular study to confirm the diagnosis.

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