Seizure (2007) **16**, 465—468

ELSEVIER

SEIZURE

www.elsevier.com/locate/yseiz

CASE REPORT

Epilepsy and migraine in a patient with Urbach—Wiethe disease

Kristl G. Claeys [a,b,*,1], Lieve R.F. Claes [a,1], Johan W.M. Van Goethem [c], Sandy Sercu [d], Joseph Merregaert [d], Julien Lambert [e], Eric A. Van Marck [f], Paul M. Parizel [c], Peter De Jonghe [a,b]

[a] *Neurogenetics Group, Department of Molecular Genetics, Flanders Interuniversity Institute for Biotechnology (VIB), University of Antwerp, Universiteitsplein 1, B-2610 Antwerpen, Belgium*
[b] *Department of Neurology, University Hospital Antwerp, Wilrijkstraat 10, B-2650 Antwerpen, Belgium*
[c] *Department of Radiology, Neuroradiology Section, University Hospital Antwerp, Wilrijkstraat 10, B-2650 Antwerpen, Belgium*
[d] *Laboratory of Molecular Biotechnology, Department of Biomedical Sciences, University of Antwerp, Universiteitsplein 1, B-2610 Antwerpen, Belgium*
[e] *Department of Dermatology, University Hospital Antwerp, Wilrijkstraat 10, B-2650 Antwerpen, Belgium*
[f] *Laboratory of Pathology, Faculty of Medicine, University of Antwerp, Universiteitsplein 1, B-2610 Antwerpen, Belgium*

Received 28 October 2006; received in revised form 2 February 2007; accepted 20 February 2007

KEYWORDS
Epilepsy;
Migraine;
Cerebral calcifications;
Partial seizures;
Topiramate

Summary We report the clinical, neuroradiological, and molecular genetic findings in a patient with lipoid proteinosis or Urbach—Wiethe disease. Interestingly, in this patient epilepsy and migraine were the symptoms leading to the diagnosis of the disease, contrary to most patients in whom skin abnormalities are the first recognized symptoms.

Introduction

Lipoid proteinosis (LP) or Urbach—Wiethe disease,[13] is a rare autosomal recessive disorder, characterized by laryngeal infiltration leading to hoarseness, generalized thickening of skin and mucosae, and extracutaneous features including epilepsy and psychiatric abnormalities.[2—4,9] LP is caused by mutations in the extracellular matrix protein 1 (*ECM1*) gene.[2] ECM1 is involved in epidermal differentiation, binding of several extracellular matrix components, in regulation of angiogenesis and in bone

* Corresponding author at: Department of Neurology, University Hospital Antwerp, Wilrijkstraat 10, B-2650 Edegem, Antwerpen, Belgium. Tel.: +32 3 821 34 28; fax: +32 3 821 43 12.
E-mail addresses: kristl.claeys@ua.ac.be (K.G. Claeys), godelieve.claes@ua.ac.be (L.R.F. Claes), johan.van.goethem@uza.be (J.W.M. Van Goethem), sandy.sercu@ua.ac.be (S. Sercu), joseph.merregaert@ua.ac.be (J. Merregaert), julien.lambert@uza.be (J. Lambert), eric.van.marck@uza.be (E.A. Van Marck), paul.parizel@uza.be (P.M. Parizel), peter.dejonghe@ua.ac.be (P. De Jonghe).
[1] These authors contributed equally to this work.

1059-1311/$ — see front matter
doi:10.1016/j.seizure.2007.02.014

formation. Thus far, 25 different pathogenic mutations have been described in individuals with LP. In most LP patients, skin abnormalities are the first and most prominent symptom. Here we report clinical, neuroradiological, and molecular genetic findings in a patient in whom mild skin changes were overlooked and diagnosis was made only in adulthood as a result of the occurrence of migraine and epilepsy.

Case report

A 39-year-old Belgian woman presented at our neurology clinic with temporal lobe epilepsy since 5 years, and migraine without aura, fulfilling the criteria of the international headache society (IHS),[12] since 2 years. The headache occurred almost daily, in attacks with very rapid onset and lasting 1 day. Her headaches were characterized by a unilateral localization, severe pain intensity causing the patient to stay in bed, and were associated with photo- and phonophobia. There was a positive response to acute treatment with tryptans. She experienced complex partial seizures and less frequently secondary generalized tonic-clonic seizures. The partial seizures were characterized by reduced consciousness without automatisms or other symptoms, and were not preceded by an aura. After multiple trials with several anti-epileptic drugs (AED), including valproate, lamotrigin, carbamazepin, phenobarbital, gabapentin and levetiracetam, she became seizure-free and experienced no more headache attacks with a daily treatment of topiramate 200 mg per day in monotherapy, after one and a half year follow up. She had mild mental retardation (total IQ = 71; Standard Progressive Matices of Raven). Cognitive decline and neuropsychological functioning were not investigated in this patient, which is a limitation of the study. She experienced recurring major depressions with suicide attempts at the age of 36 and 38 years, and severe affective disorder causing relational and social problems since 5—10 years. Clinical neurological examination was normal. Skin examination showed thickened skin at the hands, elbows and face (Fig. 1A) resulting in a limited mouth opening, sparse hair, beaded papules along the eyelid margins and partially missing eyelashes (Fig. 1B). These skin changes were mild and previously unnoticed by the patient and her environment. She had a coloboma iridis at her left eye. She experienced hoarseness since infancy. There was no known consanguinity in her family and all relatives originated from Belgium. She had four sisters, three brothers, and two sons, all of them healthy. There was no family history of epilepsy or migraine.

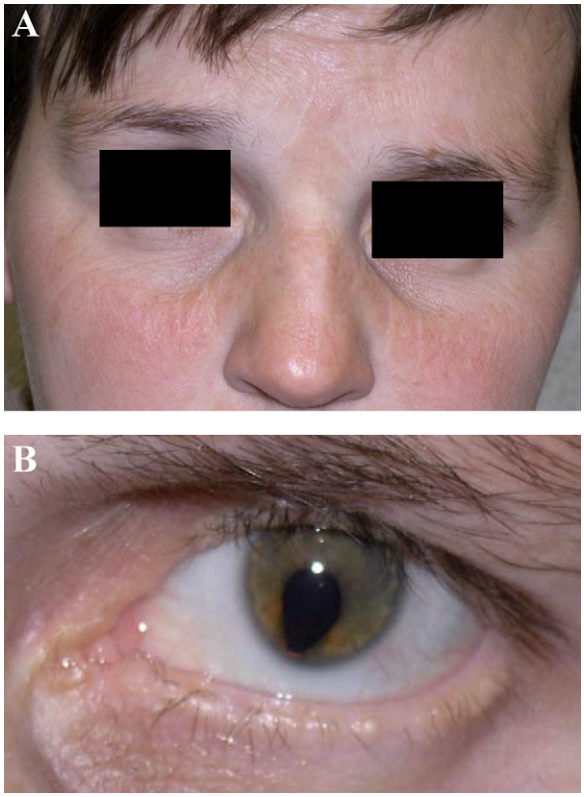

Figure 1 Photographs of the patient showing: (A) thickened skin of the face, and (B) beaded papules along the eyelid margins and partially missing eyelashes. The patient also had a coloboma iridis at her left eye.

Blood workup was unrevealing. A brain CT showed bilaterally symmetric horn-like calcifications within the medial temporal lobes involving the hippocampus and parahippocampal gyrus and amygdalae (Fig. 2A). Gradient-echo T2*-weighted MRI showed these lesions as bilaterally symmetric hypointense areas immediately anterior to the temporal horns of the lateral ventricles (Fig. 2B and C). Multiple interictal EEGs demonstrated frequent epileptiform activity (sharp waves and spike wave complexes) in the left temporal lobe.

We extracted DNA from peripheral blood of the patient and her parents, after written informed consent and local Ethical Committee's approval. Sequence analysis of the 10 coding exons and flanking intron sequences of *ECM1* in the patient revealed a mutation in exon 7, leading to a homozygous substitution of a C to a T at cDNA position 727 (c.727C > T), predicting a truncated protein of 242 amino acids (p.R243X). The patient's parents were both heterozygous for the mutation. A pyrosequencing assay confirmed the sequencing results, and the mutation was absent in 92 healthy Belgian control individuals. Paternity was confirmed. Mutations were numbered relative to the ATG initiation codon and described according to the MDI/HGVS

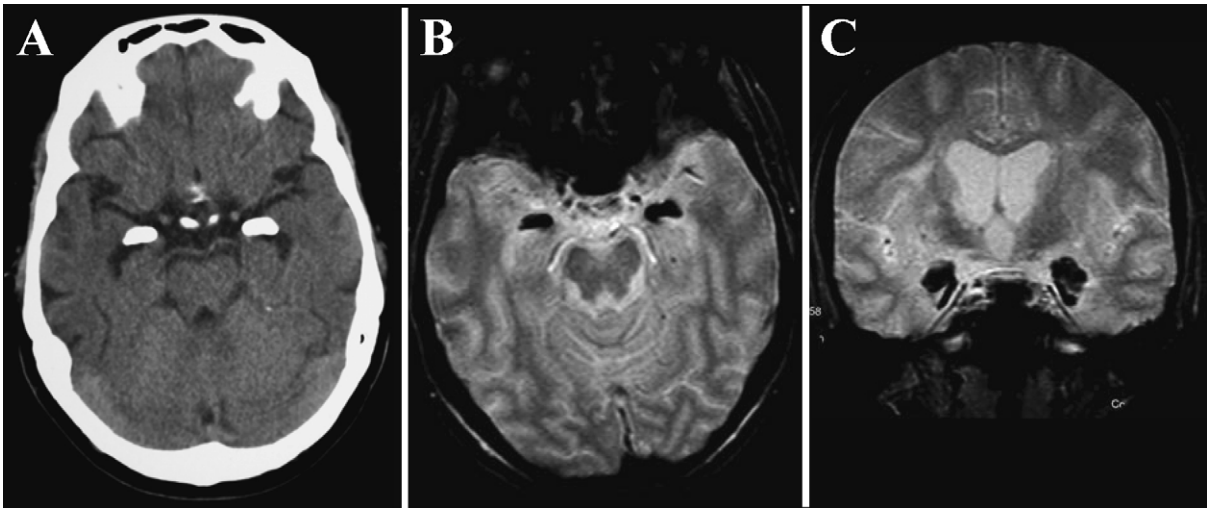

Figure 2 (A) Axial non-contrast CT scan at the level of the midbrain. There are bilaterally symmetric horn-like calcifications within the medial temporal lobes involving the amygdaloid complex. (B and C) Axial (B) and coronal (C) gradient echo T2*-weighted MRI (FLASH, TR 800 ms, TE 15 ms) reveal bilaterally symmetric hypointense areas immediately anterior to the temporal horns of the lateral ventricles. On the coronal image, the downward extension of the calcifications into the parahippocampal gyrus and the uncinate process is clearly seen.

mutation nomenclature recommendations (http://www.hgvs.org/mutnomen/). Because ECM1 has several splice variants, we used the longest mRNA transcript (NCBI accession number NM_004425).

Discussion

This case report illustrates that LP may show diverse clinical features and yet remain undiagnosed for many years, until neuropsychiatric problems and especially epilepsy occur. This adult LP patient presented with temporal lobe epilepsy and migraine without aura, whereas her skin abnormalities had not been noticed before.

In LP patients, seizures can occur as a visual or olfactory aura, followed by loss of consciousness with or without automatisms such as lip smacking and facial grimacing, as déjà-vu sensations, rage attacks, or behavioral disturbances, compatible with temporal lobe epilepsy.[10,11] Both partial and, less frequently, secondarily generalized seizures can occur, which can present at adult age or in childhood. The true incidence of seizures in LP is unknown. Seizures in LP patients are reported to be often therapy-resistant. However, after many trials with different AED including valproate, lamotrigin, carbamazepin, phenobarbital, gabapentin and levetiracetam, our patient became seizure-free on topiramate 200 mg per day in monotherapy, which should be considered as a possible therapy in LP patients. In most LP cases with epilepsy, as in our patient, EEG changes are observed. However, these may also be present in LP patients without clinical signs of epilepsy. Characteristic bilaterally symmetrical calcifications are found in the anteromedial temporal lobes, especially of the amygdalae, in 50—75% of LP cases over 10 years of age.[10,11] Bilateral mesial temporal lobe calcifications involving the hippocampus and surrounding structures (including amygdalae) have been described previously in LP patients with and without epilepsy.[10,11] The amygdalae are engaged in processing affective stimuli and emotional long-term memory.[8,10] Our patient suffered from a severe affective disorder causing relational and social problems, which might be related to dysfunction of the amygdalae. Our patient did not experience obvious memory deficits, however, neuropsychological tests were not performed, due to refusal of the patient, which is a limitation of the study.

Recently, it was shown that ECM1 interacts with the matrix metalloproteinase 9 (MMP9).[5] MMP9 is a factor related to the development of epilepsy and neuropsychiatric disease.[14] Thus, loss of functional interaction between ECM1 and MMP9 or other proteins may play a role in the process leading to the neuro-cerebral abnormalities observed in our LP patient.

Epilepsy, particularly temporal lobe epilepsy, has been described as a common manifestation of LP, especially in combination with intracerebral calcifications, particularly in the anteromedial temporal lobe. Clinically, our patient experienced temporal lobe epilepsy, and epileptic activity has been observed on EEG in the left temporal lobe, both corresponding to the location of the calcifications in our patient. Thus, it seems very likely that the epilepsy in our patient is part of the Urbach—Wiethe

disease. To the contrary, migraine without aura as observed in our patient has not been described before in LP patients. It remains undetermined whether migraine is part of the LP syndrome, or rather a co-incident finding in our patient. However, migraine and epilepsy are linked by their comorbidity and by an underlying mechanistic similarity, neuronal hyperexcitability, which is common to both disorders.[1,6] This supports the suggestion that migraine could be part of the clinical symptoms in our LP patient.

We identified a homozygous nonsense mutation p.R243X in exon 7 of ECM1 which has been reported previously.[3] However, their patient was a compound heterozygote for this mutation and an insertion mutation (c.542insAA/p.R243X). Interestingly, their patient experienced hoarseness and skin abnormalities without any neurological symptoms. The majority of mutations in *ECM1* have been identified in exons 6 and 7. Seven of 25 reported mutations were located elsewhere in the gene. Mainly nonsense, frameshift and deletion mutations have been found, except for one patient who was a compound heterozygote for the nonsense mutation p.W160X and the missense mutation p.F167I in exon 6,[3] and another patient who was homozygous for the missense mutation p.F167L in exon 6.[7] Mutations in exon 7 are usually associated with a slightly milder mucocutaneous LP phenotype, as was the case in our patient. However, neurological symptoms such as epilepsy do not show a clear specific genotype–phenotype correlation.[3]

To conclude, lipoid proteinosis has to be considered in patients with temporal lobe epilepsy and temporal calcifications, especially when other symptoms like skin changes are overlooked.

Acknowledgements

This study was supported by the Fund for Scientific Research Flanders (FWO-F, G.0096.04, G.0133.05), the Interuniversity Attraction Poles (IUAP) program P5/19. LRFC is a postdoctoral fellow of the FWO-Flanders, Belgium.

References

1. Aurora SK, Cao Y, Bowyer SM, Welch KM. The occipital cortex is hyperexcitable in migraine: experimental evidence. *Headache* 1999;**39**:469–76.
2. Hamada T, McLean WH, Ramsay M, Ashton GH, Nanda A, Jenkins T, 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**:833–40.
3. Hamada T, Wessagowit V, South AP, Ashton GH, Chan I, Oyama N, et al. Extracellular matrix protein 1 gene (ECM1) mutations in lipoid proteinosis and genotype–phenotype correlation. *J Invest Dermatol* 2003;**120**:345–50.
4. Hofer PA. Urbach–Wiethe disease (lipoglycoproteinosis; lipoid proteinosis; hyalinosis cutis et mucosae). A review. *Acta Dermatol Venereol Suppl (Stockholm)* 1973;**53**: 1–52.
5. Jourquin J, Tremblay E, Decanis N, Charton G, Hanessian S, Chollet AM, et al. Neuronal activity-dependent increase of net matrix metalloproteinase activity is associated with MMP-9 neurotoxicity after kainite. *Eur J Neurosci* 2003;**18**:1507–17.
6. Koch UR, Musshoff U, Pannek HW, Ebner A, Wolf P, Speckmann EJ, et al. Intrinsic excitability, synaptic potentials, and short-term plasticity in human epileptic neocortex. *J Neurosci Res* 2005;**80**:715–26.
7. Kowalewski C, Kozlowska A, Chan I, Gorska M, Wozniak K, Jablonska S, et al. Three-dimensional imaging reveals major changes in skin microvasculature in lipoid proteinosis and lichen sclerosus. *J Dermatol Sci* 2005;**38**:215–24.
8. Markowitsch HJ. Differential contribution to right and left amygdala to affective information processing. *Behav Neurol* 1998;**11**:233–44.
9. Newton FH, Rosenberg RN, Lampert PW, O'Brien JS. Neurologic involvement in Urbach–Wiethe's disease (lipoid proteinosis). A clinical, ultrastructural, and chemical study. *Neurology* 1971;**21**:1205–13.
10. Siebert M, Markowitsch HJ, Bartel P. Amygdala, affect and cognition: evidence from 10 patients with Urbach–Wiethe disease. *Brain* 2003;**126**:2627–37.
11. Teive HA, Pereira ER, Zavala JA, Lange MC, de Paola L, Raskin S, et al. Generalized dystonia and striatal calcifications with lipoid proteinosis. *Neurology* 2004;**63**:2168–9.
12. The Headache Classification Committee of the International Headache Society. The international classification of headache disorders: 2nd edition. Cephalalgia 2004;24 (Suppl. 1):1–160.
13. Urbach E, Wiethe C. Lipoidosis cutis et mucosae. *Wirch Arch Pathol Anat* 1929;**273**:285–319.
14. Wang X, Jung J, Asahi M, Chwang W, Russo L, Moskowitz MA, et al. Effects of matrix metalloproteinase-9 gene knock-out on morphological and motor outcomes after traumatic brain injury. *J Neurosci* 2000;**20**:7037–42.