

Eczema herpeticum in a patient with atopic dermatitis, carrying r501x and 2282del4 filaggrin null mutations

Rodrigo Valdés-Rodríguez¹, Víctor M. Saavedra-Alanís², Mario A. Islas-Aguilar² and Bertha Torres-Álvarez³

¹Department of Dermatology, Temple University, School of Medicine, Philadelphia, USA; ²Department of Biochemistry, Faculty of Medicine, Universidad Autónoma de San Luis Potosí, San Luis Potosí, S.L.P.; ³Department of Dermatology, Hospital Central "Dr. Ignacio Morones Prieto", Universidad Autónoma de San Luis Potosí, San Luis Potosí, S.L.P., México

Abstract

Eczema herpeticum is an acute dermatoses caused by herpes simplex virus type 1 in atopic dermatitis patients, and is considered a dermatology emergency. Eczema herpeticum occurs in less than 3% of atopic patients. We report a patient with a history of atopic dermatitis who presented to an emergency department with eczema herpeticum. He was admitted and treated with antiviral medications with good outcome. We investigated filaggrin null mutations in the patient and his family and correlate them with the severity of the disease. We present the first Mexican patient with eczema herpeticum, atopic dermatitis and the presence of R501X and 2282del4 filaggrin null mutations. (Gac Med Mex. 2015;151:236-9)

Corresponding author: Bertha Torres-Álvarez, torresmab@yahoo.com.mx

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Introduction

Eczema herpeticum is an acute, disseminated dermatosis, most commonly caused by herpes simplex virus type 1, which affects patients with an underlying dermatosis. Acute dermatosis (AD) is the most common predisposing dermatosis; eczema herpeticum occurs to 3% of patients with AD¹, causing dermatosis with vesicles, pustules and hemorrhagic crusts, accompanied with fever and general discomfort².

In our country, AD is the most common cause of pediatric dermatology consultation³ and one of the more common in adults worldwide⁴. It is an inflammatory, chronic and intermittent disease of the skin that

usually starts in childhood, characterized by intense pruritus, eczematous plaques, xerosis and lichenification⁵. The most important risk factor for the onset and severity of AD reported in literature is the filaggrin gene⁶; additionally, the presence of mutations in this gene predisposes to a larger number of skin infections⁷.

However, whether the most common mutations identified in Europeans, R501X and 2282del4⁸, are related to clinical presentation of the disease and their possible complications in Mexican patients is not known; therefore, we decided to study a patient and his family.

We present the first case of a Mexican patient with eczema herpeticum and AD, who was analyzed for the presence of mutations in the filaggrin gene and their correlations with clinical expression of the disease.

Correspondence:

*Bertha Torres-Álvarez
Departamento de Dermatología
Hospital Central Dr. Ignacio Morones Prieto
Av. Venustiano Carranza, 2395
C.P. 78240, San Luis Potosí, S.L.P., México
E-mail: torresmab@yahoo.com.mx

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Figure 1. Physical appearance of the patient in the Emergency Department.

Clinical case

Eighteen-year male with a history of AD who came to the Emergency Department of the Hospital Central “Dr. Ignacio Morones Prieto” due to non-quantified fever and dermatosis with two days’ evolution, which started in the face and neck and then spread to other parts of the body. On physical examination he had widespread dermatosis with predominance in the face, characterized by erythematous papules with central umbilication, vesicles and pustules, mostly with painful hemorrhagic crusts (Fig. 1). The patient was admitted with an eczema herpeticum diagnosis. In his laboratory tests, only slight leukocytosis was noticeable. Treatment was started with intravenous acyclovir and hot compresses with potassium permanganate at 0.01%; consultation was requested to the Ophthalmology Department, which prescribed hydrating ophthalmic solutions. Evolution was favorable and, thus, the patient was discharged. History and physical examination was obtained from the patient’s direct relatives with regard to signs and symptoms of AD based on the American Academy of Dermatology diagnostic criteria⁹ (Table 1).

After informed consent was obtained, blood was drawn from four of the five family members and DNA was purified from whole blood samples using the WIZARD[®] purification kit (Promega[®]). Then, 200-300 ng

Table 1. Clinical characteristics of the patient and his family

	R501X/wt	2282del4/wt	R501X/2282del4	wt/wt
Main characteristics				
- Pruritus	+		+	
- Classical distribution			+	
- Recurrent dermatitis			+	
- Personal history of atopy	+		+	
Other characteristics				
- Xerosis	+	+	+	
- Palmar hyperlinearity/Keratosis pilaris	+	+	+	
- Early onset age	+		+	
- Cutaneous infections			+	
- Infraorbital fold	+		+	
- White dermographism			+	
- Dennie Morgan fold			+	
- Periorbital hyperpigmentation	+	+	+	
Aggravating factors				
- Sweat			+	
- Situations of stress			+	

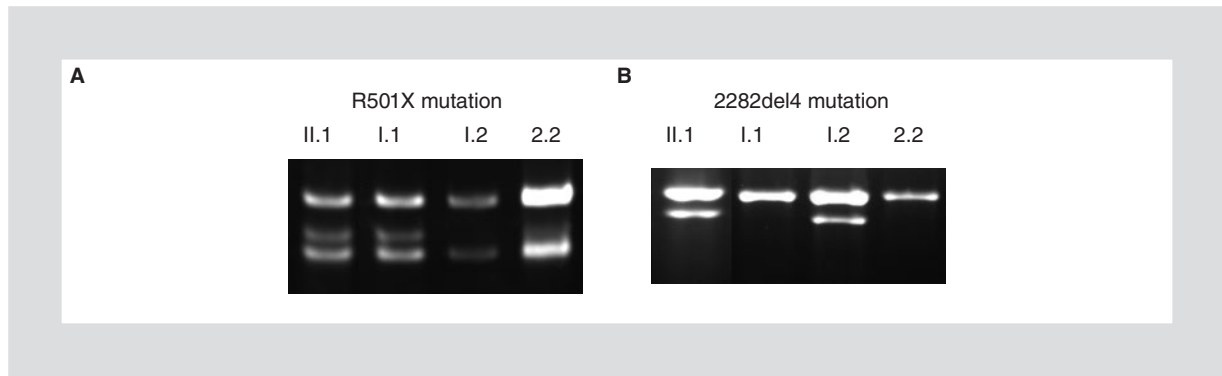


Figure 2. A: analysis of the R501X mutation by PCR-RFLP with the N1aIII enzyme; II.1 and I.1 individuals are heterozygous and I.2 and 2.2 individuals are normal homozygous. **B:** analysis of the 2282del4 mutation by PCR-RFLP with the DraIII enzyme; II.1 and I.2 individuals are heterozygous and I.1 and 2.2 individuals are normal homozygous.

of DNA of each patient were used to perform standard PCR based on the sequences published by Smith, et al.¹⁰, where the regions corresponding to the involved mutations (2282del4 and R501X) in exon 3 of the filaggrin gene were amplified in separate samples with the PTC-100TM MJ Research Inc. equipment. To analyze the R501X mutation, the product of the PCR was incubated overnight with five units of restriction enzyme N1aIII (NEB®) at 37 °C and the product was analyzed by means of polyacrylamide electrophoresis at 11% in Tris-Borate-EDTA (TBE) standard buffer. The 2282del4 mutation was similarly analyzed by incubating with the DraIII enzyme (NEB®) and separating the products in agarose gel at 2% in TBE (Fig. 2).

Results and discussion

The presence of null mutations produces lower amounts of protein and that which is expressed is truncated¹¹, which directly affects the epidermal barrier of the skin and the natural moisturizing factor, resulting in an inadequate barrier that allows the penetration of foreign agents, including viruses and bacteria; in addition, loss of natural moisturizing of the skin occurs¹².

Although different mutations in the filaggrin gene have been detected⁶, we decided to study the most common mutations in Europeans, R501X and 2282del4, for two reasons: first, 93% of the Mexican population belongs to the Mestizo ethnic group with an important part of its ancestry being European¹³, and second, in a previous study in Mexican population we identified both these mutations to be present¹⁴. Additionally, these mutations have been reported to be a risk factor for the occurrence of eczema herpeticum, and out of these, R501X increases the risk up to 3-fold¹⁵.

We found our patient to be compound heterozygous for both mutations. It is important knowing if mutations are at *cis* or *trans* and, therefore, we were interested in studying the family and trying to correlate the mutational status of this gene with clinical manifestations of AD. In effect, the father and the mother are carriers of the R501X and 2282del4 mutations, respectively, and, therefore, we considered this patient to be compound heterozygous with both alleles mutated (*trans*), which would imply lower filaggrin expression and processing¹¹.

According to the genetic map of the family (Fig 3.) and clinical characteristics (Table 1), the R501X mutation appeared to show higher expression than 2282del4; however, only our patient showed AD important features and the eczema herpeticum complication, probably due to double haploinsufficiency caused by both mutations.

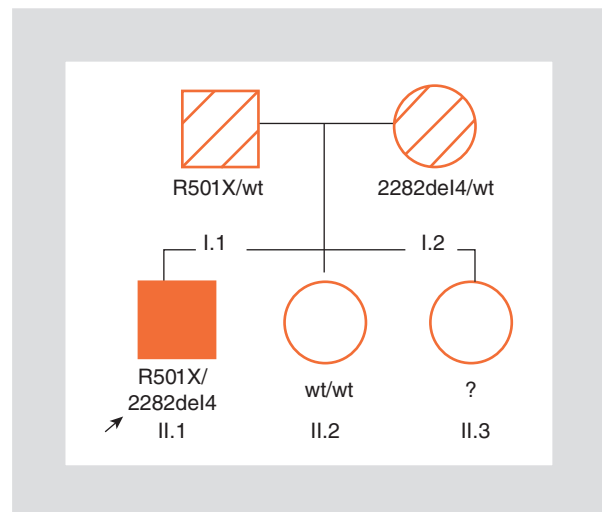


Figure 3. Genetic map of the family.

To conclude, this is the first case of a Mexican patient where AD severity and complications are positively related to the presence of the R501X and 2282del4 mutations and thus, analyzing more numerous groups of the Mexican population, both with and without AD, will allow for the prevalence of mutations in this disease and their relationship with AD to be known, which would help to establish the clinical course of AD in the Mexican population and offer better treatment.

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