Case report

Ichthyin (NIPAL4)-autosomal recessive congenital ichthyosis with atopic diathesis: Case report and literature review

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Abstract

Autosomal recessive congenital ichthyosis (ARCI), is a rare form of ichthyosis with multiple mutations identified. Ichthyin (NIPAL4) gene mutation is identified in about 18% of cases. In addition to the usual ichthyosis phenotype we are presenting a new association between ARCI and atopic diathesis with multiple allergies. To the best of our knowledge this is the second case to report such an association between ARCI and atopic diathesis.

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Keywords: Ichthyosis; Atopic dermatitis; Ichthyin mutation

1. Introduction

Autosomal recessive congenital ichthyosis (ARCI) is an uncommon form of congenital ichthyosis. The prevalence of ARCI is 1:200,000–300,000 in the United States while it is more common in certain regions such as Norway (1:91,000) (Bale and Doyle, 1994; Pigg et al., 1998).

ARCI is caused by different gene mutations, including transglutaminase-1 (TGM1), ALOX12B, ALOXE3, CYP4F22, ABCA12, SLC27A4/FATP4, and ichthyin (NIPAL4) (Li et al., 2012; Alavi et al., 2012). Germline mutation in TGM-1 gene is the most common cause of ARCI (Li et al., 2013; Akiyama and Shimizu, 2008). Patients with ARCI are sharing the common features of large polygonal scales all over the body with mild erythema without blisters. Presence of ectropion, eclabium and keratoderma are variables. The association between ARCI and atopic dermatitis has been reported only once in the English literature by Wajid et al. (2010). Hereby, we are reporting the second case with such association.

2. Case report

An 8 year-old Saudi girl was brought to our dermatology clinic accompanied by her parents and her 18-year older brother, who has the same skin problem. Both complained of diffuse scales all over the body with mild erythema and severe itching, since birth, no history of blisters. Nails, teeth, hair and sweating are normal. They were born at full term without a collodion membrane with uneventful pregnancy and delivery. Both have multiple allergies to sea food, peanut, and eggs which caused anaphylaxis in few occasions. They have itching all over
the body with accentuation over flexural areas. Parents are first degree relative and have another three healthy siblings.

On physical examination both have fine large scales covering the body, more pronounced on extremities with mild redness. Lichenified plaques over antecubital and popliteal fossae were also noted. Mild keratoderma was identified but no blisters. Teeth, nails and hair are all normal. They have mild redness of the eyes without ectropion. Hair examination under microscope was normal. Scalp shows thin layer of scales. Excoriations over arms and legs were also noticed. (Figs. 1 and 2).

Taking into consideration the presentation with diffuse scales, mild redness without blister with an autosomal recessive inheritance pattern, ARCI was diagnosed.

Therefore, TG-1 was done and it was negative. Hence, other known mutations have been requested, ALOXE3, ALOX12B, and ichthyin (NIPAL4). Ichthyin was identified as homozygous for a partial deletion in the exon 3–4. Both of them were treated with mild topical keratolytics, antihistamine and mild topical steroid. They were provided with Epi-Pen for anaphylaxis episode. Parents gave a history of peanut allergy without atopic dermatitis. Therefore; the presence of peanut allergy cannot be attributed to underlying genetic condition solely.

3. Discussion

Autosomal recessive congenital ichthyosis (ARCI) is an uncommon form of ichthyosis. The prevalence of ARCI is 1:200,000–300,000 in the U.S.A. but it is more common in certain regions such as Norway (1:91,000) (Bale and Doyle, 1994; Pigg et al., 1998).

ARCI is caused by mutations in several different genes, including transglutaminase-1 (TGM1), ALOX12B, ALOXE3, CYP4F22, ABCA12, SLC27A4/FATP4, and NIPAL4 (Li et al., 2012; Alavi et al., 2012). The most common identified mutation is TGM-1, however, in 20% of cases the gene is not identified (Fischer, 2009).

Eckl et al. reported the result of direct sequencing of 520 patients from 520 independent families. 32% of them have mutations in TGM1, 16% in ichthyin, 12% in ALOX12B, 8% in CYP4F22, and 5% in ALOXE3 and in 22% of the patients, no mutations could be detected (Eckl et al., 2009). The majority of patients with ichthyin-ARCI present with fine large brown scales on erythrodermic background (a nonbullous congenital ichthyosiform erythroderma-like phenotype). However, larger brown scales and a classic lamellar ichthyosis-like phenotype can be present as well. The presence of collodion membrane at birth is variable and can be absent in up to 60% of patients (Lefèvre et al., 2006). One of the classic features of ichthyin-ARCI

Fig. 1. Wide spread large scales with background of erythema. Inset: mild keratoderma.

Fig. 2. The brother shows mild involvement while it is more extensive in his sister, after starting therapy.
is the presence of keratoderma. Lefèvre et al. reported the presence of keratoderma in 23 patients and 60% of them were born without collodion membrane (Lefèvre et al., 2006). Based on this observation as well as others it was suggested that the presence of diffuse yellowish keratoderma may be indicative of a phenotype–genotype correlation. However, keratoderma can be mild as in our patient. Atopic dermatitis association with ichthyin-ARC1 was reported once by Wajid et al. (2010). Hence, our case is the second case reporting such an association.

Mutations in ichthyin (NIPAL4) gene should be differentiated from other genes causing ARC1, such as the ALOXE3, ALOX12B and CYP4F22 genes. In general, patients with ALOX gene mutations, mainly those with ALOX12B gene mutations are born with a collodion membrane, but later on they improve markedly, most of them achieving complete healing of their skin and others having only a mild NBCIE phenotype (Kurban et al., 2010). On the other hand, patients with CYP4F22 are not born with collodion membranes, but later on the patients start developing the ARC1 phenotype (Lefèvre et al., 2006) while patients with ichthyin-ARC1 are born with or without a collodion membrane with fine brown scales on erythematous background with keratoderma and possible atopic diathesis.

We are here reporting the second case of possible association between atopic diathesis and ARC1. The association can be added to the list of other ichthyosis which can cause atopic diathesis and itching; Netherton syndrome and Sjögren–Larsson syndrome. This association can be explained by the interaction between filaggrin and ichthyin genes, mutation in ichthyin gene will lead to loss of function of filaggrin and this will lead to atopic diathesis (Li et al., 2013).

Conflict of interest

None.

References