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Epidermolysis bullosa Associated with Type 1 Diabetes Mellitus - Case Report of a Lethal Disease

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Abstract

We present a rare lethal case of a dystrophic form of epidermolysis bullosa (EB) associated with type 1 diabetes mellitus in a 5-year-old boy diagnosed with EB at birth. This association has not been reported before. Two well-known mutations in the collagen *COL7A1* gene (compound heterozygous: c.425A>G in exon 3 and c.2005C>T in exon 15) were determined as cause of EB. Whether the association with diabetes mellitus type 1 was causally related remained undetermined. We also discuss the therapeutic difficulties resulting from this association.

Keywords: Epidermolysis bullosa; Diabetes mellitus; *COL7A1* gene

Introduction

Epidermolysis bullosa (EB) is a heterogeneous group of diseases characterized by blisters of the skin and mucosal membranes ranging from mild to lethal [1]. It results from an anchoring defect between the epidermis and dermis, resulting in friction and skin fragility [2]. About 30 genetically different types share, as a common feature, this mechanical fragility of epithelial tissues, most notably the skin [3]. Based on electron microscopy, EB is classified into three categories according to the level where blisters are formed: simplex EB - blisters formed on the basal layer; junctional EB - blisters formed in the lamina lucida; dystrophic EB (DEB) - blisters formed in dense lamina [4]. Aside from various degrees of severity of blistering other complications can also occur, including pain, anemia, esophageal stenosis or cardiomyopathy. Patients with missing collagen protein are at risk of cutaneous malignancies at adult age. The majority of patients with dystrophic EB will

develop cutaneous squamous carcinoma by the age of 40 years [5].

Genetically, two forms of DEB have been described: an autosomal recessive form (OMIM 226600) and an autosomal dominant form (OMIM 131750).

Type 1 diabetes mellitus (DM1) is a polygenic multifactorial disorder resulting from autoimmune destruction of pancreatic beta cells producing insulin. Multiple genes and environmental factors such as viruses, some dietary factors, certain chemicals or drugs have been implied in its etiology [6]. The association of these EB and type 1 diabetes mellitus has very rarely been described in the literature [7].

Patient and Methods

The patient was referred to our genetics service on the 7th day of life in May 2009 by, family doctor, primary care physician. The diagnosis of EB was based on the characteristic clinical signs present at birth: bullous blistering formation occurring immediately after birth, in areas exposed to mechanical and even minor trauma. Electronic microscopy examination failed to yield results. Peripheral blood (EDTA) for genetic testing was obtained from the patient as well as his parents after informed consent. DNA was extracted using a DNA isolation kit according to the manufacturer protocol (Omega, Georgia, USA). Mutation detection and screening of exons 1-48 and exons 72-118 of the *COL7A1* gene of the index patient was performed using the "priority strategy." The coding region and adjacent intron/exon boundaries specific for the *COL7A1* gene of the patient were amplified by PCR, sequenced by Sanger and compared to the database (reference for exons and mRNA: NM000094; CDS 2-8836). At the age of 16 months the patient was suspected to have developed type 1 diabetes mellitus based on suggestive clinical signs: thirst, weight loss, polyphagia, polyuria and frequent urination. The diagnosis was confirmed by biochemical tests: increased blood glucose levels

of 134-615 mg/dl (reference values 60-99 mg/dl), glycosuria (2+), ketonuria (2+), metabolic acidosis pH 7.22 (ref. pH 7.35-7.45), glycated hemoglobin (14%); islet cells antibodies and insulin antibodies were present.

Results

The patient, born on May 2009, presented from the first days of life with congenital multiple cutaneous forms of blisters on the limbs, trunk, face and on the buccal mucosa. The blisters size differed from 1-2 cm to 10 cm diameter. They broke open and involved broad epidermal areas of erosion, ulceration, and purulent secretions.

The patient was the first child in a family of unrelated *healthy parents*. There are no other known cases of illness or other significant diseases in the family. The pregnancy had a normal course. Delivery was normal without signs of hypoxia. During the course of the disease multiple new blisters appeared over the entire skin, seemingly spontaneous or caused by minor trauma. This caused multiple wounds and scars deforming areas of skin. Subsequently atrophy of the nails and multiple scars developed some retractile, with a tendency of synechiae and abnormal semi-flexion position of the fingers. The lesions were intensely painful and pruritic. Blistering also involved the eyes and mucosa of the mouth. The patient manifested retardation of the gross motor skills because of pain and blistering. Tentative skin biopsy and electron microscopy examination failed technically.

At the age of 16 months, he was diagnosed with diabetes mellitus type 1 requiring insulin substitution using an insulin pump initiated with an adequate dietary regime. Patient compliance to treatment was appropriate, diabetes remains under control in clinical and biological balance.

Molecular analysis identified a compound mutation in the *COL7A1* gene (Collagen VII, alpha-1 polypeptide): c.425A>G, p.K142R, exon 3 of maternal origin and c.2005C>T, p.R669X, exon 15 of paternal origin (**Figure 1**).

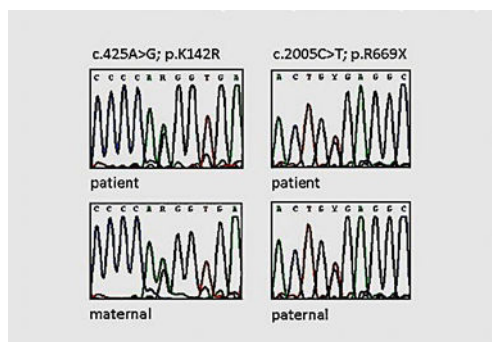


Figure 1: Molecular analysis revealed the same mutation c.425A>G in the mother and son (described first time by Gardella in 1996) and the mutation c.2005C>T in the father and son (described first time by Cserhalmi-Friedman in 1998).

Discussion

Our observation refers to two different genetic entities not known to be causally related. The dystrophic form of EB described here is an autosomal recessive disease caused by mutations in the gene *COL7A1* located on chromosome 3p21.31 (Gene MIM number 120120). Christiano et al. described the entire intron/exon organization of *COL7A1* in 1994 [8]. This gene has 118 exons, one of the genes with the highest number of exons [9]. In the DEB register (<https://www.deb-central.org/>) 659 mutations are listed whereas in the Human Gene Mutation Database (HGMD) professional 2017 a total of 773 mutations are registered (<http://www.hgmd.cf.ac.uk/ac/gene.php?gene=COL7A1>). These mutations alter the structure or disrupt the production of type VII collagen, which impairs the ability of anchoring fibrils to connect the epidermis to the dermis [10,11]. Of the two mutations in *COL7A1* in our patient, c.425A>G in exon 3 has been described previously by Gardella et al. in 1996 [12]. This splice site mutation, 425A→G, has been observed repeatedly in Italian and Central European populations [13,14]. Varki et al. in 2007 analyzed *COL7A1* gene mutations in 310 patients with the referral diagnosis of DEB on the basis of clinical observations, evidence for sublamina densa blistering, negative or attenuated immunofluorescence for type VII collagen or ultrastructural abnormalities in the anchoring fibrils. They found a mutation in one or both alleles in 243 (78.4%) of patients. The mutation most frequently detected was c.425A>G in 3.9% as occurred in our patient. As with other splice-site mutations in *COL7A1* causing a premature codon termination, the phenotypic expression is similar to our patient, namely, a severe clinical type of EBD.

Mutation c.2005C>T, exon 15 was described for the first time by Cserhalmi-Friedman et al. in 1998 [15]. This rare heterozygous variant is associated with different phenotypes: short stature, syndactyly of fingers and toes, and palmo-plantar blistering. Our patient had no growth delay, no finger and toe syndactyly, and the blistering was generally distributed.

Our patient is compound heterozygous, each of the two parents contributing a different mutation in the same gene. The inheritance pattern corresponds to autosomal recessive inheritance. Dystrophic forms of EB, even if it is not proved by electron microscopy, can be established by the clinical aspects and the mutations identified.

Hirsch et al. described recently a considerable success in somatic gene therapy in a 5-year-old patient with junctional epidermolysis bullosa due to a homozygous mutation in the *LAMB3* gene (OMIM 150310). Cultured keratinocytes from a 4 cm² biopsy of unaffected skin were transfected with a retroviral vector carrying the normal *LAMB3* gene, grown to 0.85 cm², grafted to the patient. The transgenic skin transplantation restored normal skin function [16].

Diabetes mellitus type 1 is a polygenic multifactorial disease involving multiple genes and environmental factors. The most important insulin-dependent (type I) diabetes mellitus (IDDM1 gene) is located on chromosome 6p21 within MHC, class II

region (histocompatibility system). Most DM1 susceptibility alleles are in MHC class II DR and DQ genes, located very close to each other, forming the DR-DQ haplotype. Increased risk for DM1 is attributed to the DR3-DQ2 and DR4-DQ8 haplotypes. The two haplotypes present together are found in 30-50% of patients with DM1 versus 2-3% in the general population [17]. Among the protective DR-DQ haplotypes, the DR7 haplotype bearing DQB1 is significantly more protective than the one bearing DQB1.

At the current level of knowledge of the human genome the combination of the two entities described here have to be considered as coincidental. Klausegger communicated 4 patients (3 patients from Bosnia and Herzegovina and 1 patient from Serbia) with the same mutation combination: c.425A>G, p.K142R, exon 3 and c.2005C>T, p.R669X, exon 15 (personal communication). All 4 patients did not show any signs of associated DM1. However, a causal relationship of the two diseases cannot be excluded. There are few factors that could be involved in this case: e.g. different bacterial and fungal germs causing prolonged and repeated infections, the use of many and different antibiotics or diverse and massive use of antiseptic substances [18].

The association of the two disorders raises other complicated issues related to the use of insulin and the diet. The usage of the insulin pump, however, is abrogating all its drawbacks related to cost and accessibility. In addition, it is recommended to use especially soft foods avoiding causing oral-esophageal mucosal injury, which can create difficulties to establish this sick menu [19].

The clinical course in our patient was unfavorable, with multiple, generalized bullous lesions, scars, constrictions, major difficulties with food intake, need for gastrostomy. Gradual worsening of symptoms and persistent complications (severe malnutrition, hydroelectrolytic imbalance, hypoproteinemia, infections) led to death at the age of 5 years and 6 months.

Conclusion

An association of dystrophic epidermolysis bullosa and type 1 diabetes mellitus as described here is a rare event. It is most probably a non-causal coincidence. Dystrophic EB associated with diabetes mellitus type 1 requires a particular therapeutic concept ensuring both continuous administration of insulin and an optimal dietary program.

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