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I n 1902 Brocq first described a case of bullous congenital ichthyosiform erythroderma, a phenotype characterized by congenital erythroderma, intermittent blistering and dark or greyish hyperkeratosis predominantly involving the flexor areas such as knees and the elbows as well as the dorsal aspects of hands and feet [1]. Thirty-five years later Siemens reported on a considerably less severe ichthyosis characterized by bulla formation [2]. All of these phenotypes showed an autosomal dominant mode of inheritance [1-3].

In contrast to bullous congenital ichthyosiform erythroderma (BCIE), however, patients affected with IBS do not have a history of post-neonatal erythroderma. The hyperkeratosis is milder, and the blistering mostly involves the upper part of the legs. As a characteristic feature, IBS patients show denuded areas on a hyperkeratotic background, the so-called “Mausering” phenomenon [2, 4, 5]. During the past decade, further cases of IBS have been reported, but the question of nosological classification has so far not been settled. Some authors describe IBS as a distinct entity [4-7], but others favor the concept that this phenotype merely represents a clinical variant of bullous ichthyosiform erythroderma of Brocq [8, 9], whereas a third group of authors believes that their cases represent new entities [10]. The lumen was filled with erythrocytes and neutrophils as well as eosinophils. A diagnosis of ichthyosis bullosa of Siemens was unequivocally established by molecular analysis demonstrating a mutation in the K2e gene. This keratin is expressed in the upper layers of the epidermis. In the present family, six individuals belonging to four successive generations were affected. Remarkably, all of them showed in addition, a syndactyly of the second and third toes whereas this anomaly was absent in family members with a healthy skin. If this finding should be more than a chance association, it may represent an example of genetic linkage. (Key words: ichthyosis bullosa of Siemens, bullous ichthyosiform erythroderma of Brocq, epidermolytic hyperkeratosis, K2e mutation, zygodactyly.)

Case report

The patient was a 21-year-old man who suffered from blistering of the skin since his third year of life. His father and his 24-year-old sister were similarly affected but had noticed some improvement of the disease during adulthood. During childhood intermittent periods of superinfection had occurred to a degree that the family believed they were especially prone to an infectious skin disease. The mother of the patient reported that a first-born child, a boy, had died some days after birth from a “burned skin syndrome”. The patient’s grandfather and great-grandmother were likewise affected (Fig. 1). All of the infected individuals showed, in addition, a zygodactyly of their second and third toes. The proband consulted us because he had developed blistering on the dorsal aspect on his upper legs after having marched in boots over a distance of 12 km.

On physical examination, his shanks were swollen and showed bruising and multiple erosions with superinfection. Brownish hyperkeratosis was present in the axillary, gluteal and periumbilical region (Figs. 2 to 4) and resulted in a rippled appearance especially on the flexural aspects of his elbows and knees. Superficially denuded areas of 2 cm diameter were noted (Fig. 3). The patient showed, in addition, bilateral zygodactyly of his second and third toes. Histopathological examination of a biopsy obtained from the right upper leg revealed orthohyperkeratosis and acanthosis. In the upper layers of the epidermis, a granular degeneration of keratinocytes with perinuclear halo formation was noted (Fig. 5). Electron microscopical examination of a biopsy obtained from a blistering area (right shank) showed intra-epidermal cleavage resulting in a blister reaching from the basal layer to the stratum granulosum. The lumen was filled with erythrocytes and neutrophils as well as a granular degeneration of keratinocytes.
as cellular debris. The roof of the blister consisted of a broad granular layer and a keratotic horny layer containing some neutrophils. Neither clumping nor thickening of tonofilaments could be detected.

**Mutation analysis**

The results of mutation analysis have been published in detail elsewhere [13]. A mutation was found in the keratin 2e gene, a type II keratin expressed on chromosome 12q. In the sequence coding for the helix termination peptide of the rod domain, the transition of T102 to C leads to the substitution of proline for leucine90. The mutation creates a restriction site in the DNA. Because of the nature of the amino acid substitution, and because none of the 50 control subjects showed this mutation, this is most likely the gene defect responsible for this skin disease. As no blood samples from other family members were available, a segregation analysis was not possible.

**Treatment**

Antibiotic treatment resulted in clearing of the superinfection of the shanks. Subsequently an ointment preparation containing Excipial® creme with 10% urea, 1% NaCl and 25% aqua dem. was used with a satisfactory response. In addition, oral treatment with acitretin, 35 mg/day, was initiated but discontinued after some days by the patient because of oral dryness and gastrointestinal problems.

**Discussion**

Recent molecular studies have provided proof that ichthyosis bullosa of Siemens (IBS) is a distinct skin disease to be separated from congenital bullous ichthyosiform erythroderma of Brocq [13]. The delineation of IBS provided further support for the notion that epidermolytic hyperkeratosis (EH) does not represent a clinical entity but is merely a histopathological phenomenon found in many different skin diseases. The term epidermolytic hyperkeratosis was introduced by Frost and van Scott [14] and further delineated by Ackerman [15]. In contrast to BCIE, EH of IBS is limited to the upper level of the spinous layer and to the granular layer. Perinuclear halo formation and clumping of keratohyalin granules are found at this level [2, 4, 5]. As proposed by Traupe [7], a biopsy should be taken from an area of maximal clinical involvement in order to make sure that the histopathological and ultrastructural features of IBS are found. Electron microscopical examination shows a marked edema of keratinocytes of the granular and upper spinous layer. Thickened bundles of tonofilaments as well as clumping of tonofilaments forming a V-shape or shell around the nuclei are present [4, 5].
The concept that IBS represents a distinct entity within the spectrum of phenotypes characterized by EH, has now been confirmed at the molecular level. EH of the Brocq type, either with congenital erythroderma (BCIE) or without erythroderma reveals mutations in the type II keratins K1 and K10 that are localized on chromosome 12q [16-20]. These keratins are expressed in the basal and suprabasal layers of the epidermis [18]. By contrast, the mutation causing IBS was found in keratin 2e which is likewise localized in the granular and upper spinous layer [13, 21-23]. This finding demonstrates that IBS is an entity to be distinguished from BCIE [13].

Because of the varying nomenclature and variable clinical appearance of this phenotype, it is difficult to determine how many cases of IBS have previously been reported in the literature. For example, McGregor et al. [10] have proposed, even in 1991, the name “bullous ichthyosis” as a unifying term for all cases of ichthyosis showing the histopathological of EH. Their familial observation can now be categorized as IBS. Other case reports [9, 11] are more difficult to categorize. For example, a patient observed by Murdoch and Leigh [9] had typical features of IBS but showed, in addition, “a background erythroderma, albeit variable”. On the other hand Gaser [3] has pointed out that clinical signs of blistering may be absent in BCIE although histological features of blistering can be documented.

Vakilzadeh and Kolde [12] described a family affected with “autosomal dominant ichthyosis exfoliativa”. The clinical feature were similar to IBS, but electron microscopical examination failed to reveal any defect of tonofilaments. According to recent data, however, this family observation has been recognized as a case of IBS because a mutation in the keratin 2e gene has been documented. A second ultrastructural examination could show tonofilament clumping focally in the upper spinous layer [13]. In the present case, ultrastructural features of a tonofilament defect were likewise absent, although a K2e mutation has been demonstrated [13]. Possibly in this case the lack of tonofilament clumping also depended on the biopsy site.

Because keratins are major structural proteins of the epidermis, the identified keratin mutation may be regarded as the cause of the disease. The blistering observed in EH results from a disturbed architecture of keratin filaments [24, 25]. Letal et al. [25] pointed out that the degree of severeness of blistering, resulting in either epidermolysis bullosa simplex or bullous ichthyosis, depends on the nature of the mutation. They found a correlation between severe BCIE and mutations within the highly conserved rod domains of major keratin genes [25]. By contrast, milder cases of this phenotype are mapped to less conserved regions either within or outside the rod domain [16]. In the present case, the underlying mutation was found in a highly conserved region, namely in the 2B rod domain. We can speculate that a point mutation in K2e always implicates a mild clinical picture because of the nature of the keratin which is expressed in the granular and upper spinous layer. It would be interesting to know which mutations were at the origin of some previously published cases that are difficult to classify [9, 11]. In the present case, a brother of the proband died some days after birth from an alleged “burned skin syndrome”. It is difficult to evaluate this point of the case history because congenital erythroderma is typical of BCIE but not of IBS [3-5]. Moreover, congenital erythroderma present in BCIE is not usually a lethal disorder.

Remarkably, all affected individuals of the present family showed zygodactyly of their second and third toes whereas family members with a healthy skin did not show this trait. If this phenomenon is not a mere coincidence, it can be best explained as an example of linkage inheritance. The mutation responsible for zygodactyly would be present on a gene locus neighbouring the IBS gene. If this concept holds true, the present family observation could be taken as a first step in gene mapping of a rather frequent trait, zygodactyly.

Topical treatment is, so far, more important than administration of oral drugs. In order to ensure a keratolytic effect, urea, propylene glycol or vitamin A acid may be applied whereas sodium chloride or lactic acid exert a beneficial effect by hydration of the horny layer [7]. A first report on oral treatment of IBS with acitretin given at a low dosage appears to be promising [6]. A dosage of 35 mg/day resulted in a marked decrease of hyperkeratosis without any increase of blistering. From the oral retinoid treatment of BCIE patients it is known that increased blistering may occur even at a dosage of 0.7 mg/kg/day [26] but some authors have reported a substantial improvement with 0.6 mg/kg/day [27]. The clinical, histopathological and molecular delineation of IBS is important for a precise diagnosis and appropriate genetic counselling. The demonstration of a K2e mutation allows the prediction that the skin involvement should be milder than in that observed in BCIE. Furthermore, a prenatal diagnosis no longer depends on morphological analysis of a fetal skin biopsy [28]. If the underlying mutation is known, a diagnosis of IBS can be established or excluded by obtaining fetal cells through amniocentesis or at an earlier stage by chorion villus sampling [16, 20].

References


