

# Editorial

## Shabbir's syndrome: the nosological status elucidated

Jameel Ahmad Shaheen, Mohammad Khalid

Dermatology Department, Quaid-e-Azam Medical College, Bahawalpur

Professor Syed Ghulam Shabbir (1923-2002), an eminent Pakistani dermatologist, while working at Mayo Hospital, Lahore, observed a new, distinctive, recessively inherited disease which exclusively occurred in Muslim children of Punjab Province of Pakistan. For the first time in 1986, Shabbir *et al.*<sup>1</sup> published a series of 22 children in 12 Punjabi families, who presented with chronic ulcers over the skin with involvement of nails and larynx. The disease usually started within 2 weeks after birth. The presenting complaints were hoarseness, dystrophic changes in the nails, chronic bleeding, and crusted lesions of the periorificial skin of the face. In addition, the teeth were deformed. The ulcers did not respond to any drugs, including antibiotics, antituberculous therapy, corticosteroids, and dapsone. Shabbir *et al.*<sup>1</sup> named this disorder "The Laryngo-Onycho-Cutaneous (LOC) syndrome (LOCS)". However, this entity was not known to dermatologists of the Western hemisphere until Ainsworth *et al.*<sup>2</sup> from Glasgow, Scotland, reported laryngeal and ocular granulation tissue formation in two children of Punjabi descent who had similar features affecting their skin, nails and teeth. In 1992, this disease was published as Shabbir's syndrome in the 5<sup>th</sup> edition of Rook's Textbook of Dermatology, one

of the most widely used reference books available on the subject.<sup>3</sup> However, the nosological status of the disease was still not clear because of lack of ultrastructural and genetic findings.

Later, Ainsworth *et al.*<sup>4</sup> examined 27 affected children in 18 families suffering from similar disorder. This rare multisystem disorder was characterized by dermal and submucosal granulation with voice defects due to vocal cord thickening and/or nodules which clinically manifested as hoarse cry. In some children a weak cry was noted at birth. The disease, according to authors, had been reported only in Muslim families of Punjabi origin, though they were born and living in UK, belonged to Punjab Province of Pakistan or India. Manifestations appeared during the early few months of life and included skin ulcerations, loss of toenails and fingernails, and conjunctival scarring and pterygium formation. Other epithelial surfaces were later involved. Some of the affected persons had amelogenesis imperfecta. No impairment of immune function was detected. Death in early childhood was common due to respiratory tract infection, although among those who survived, remission occurred during the second decade. Ainsworth *et al.*<sup>4</sup> proposed the designation LOGIC syndrome for 'laryngeal and ocular granulation' in such children.

In 1995, Phillips *et al.*<sup>5</sup> from Melbourne, Australia, described 3 children of Pakistani ancestry. All of them presented with laryngeal

---

### Address for correspondence

Dr. Jameel Ahmad Shaheen,  
Associate Professor of Dermatology,  
Department of Dermatology,  
Quaid-e-Azam Medical College /  
Bahawal-Victoria, Bahawalpur  
Email: drshaheenjg@yahoo.com

involvement, chronic skin granulation, nail dystrophy, and conjunctival disease. All showed hypoplastic dental enamel and increased susceptibility to trauma. The parents were known to be consanguineous in 2 of the 3 cases. The disease progressed to life-threatening respiratory obstruction in 2 patients and to blindness and fatal respiratory obstruction in the third child. Laser therapy was to some extent successful in alleviating laryngeal manifestations. The two children with the severest clinical disease showed abnormal hemidesmosomes on ultrastructural examination. Phillips *et al.*<sup>5</sup> also reported abnormally weak immunoreactivity with antibodies directed against basal cell proteins, caused by an inherited defect in the lamina lucida of the skin basement membrane zone. It suggested that the syndrome might represent a distinctive form of junctional epidermolysis bullosa, the first attempt to resolve the enigma of Shabbir's syndrome.

The mystery was further unraveled in 2003 when McLean *et al.*<sup>5</sup> successfully localized the gene for LOCS to a 2-Mb region on chromosome 18q11.2 using genomewide homozygosity mapping. They observed mutations in a candidate gene within the region, laminin alpha-3 (LAMA3); causing junctional epidermolysis bullosa, a lethal skin blistering disorder (Herlitz-Pearson subtype). The gene encodes 3 distinct proteins, designated laminin alpha-3a, alpha-3b1 and alpha-3b2, which are produced by alternative splicing. A causative LAMA3 mutation was identified in 15 consanguineous Punjabi families with Shabbir's or LOC syndrome, consisting of a frameshift mutation predicting a stop codon in an exon that is specific to laminin alpha-3a. This specific protein is secreted only by the basal keratinocytes of stratified epithelia especially of

skin, respiratory tract and eye. It suggests that LOCS may be due to dysfunction of keratinocyte-mesenchymal communication. The authors opened a new field of research by giving a hypothesis that the laminin alpha-3a N-terminal domain may be a key regulator of the granulation tissue response.

Now the nosological status of Shabbir's syndrome has been finally established as a subtype of junctional epidermolysis bullosa (JEB),<sup>7,8</sup> since it is associated with mechanical fragility of the skin, ultrastructural features of the hemidesmosomes consistent with junctional EB, and mutations in the laminin 5 gene; however, it has distinct clinicopathological features and molecular findings which differentiate it from other variants of JEB. Shabbir's syndrome, Shabbir disease, laryngo-onycho-cutaneous syndrome (LOC), JEB-LOC, LOGIC, JEB-other (JEB-O),<sup>8</sup> affects mainly the offspring of consanguineous Muslim families originating in the Punjabi region of Pakistan and India, although cases have been reported in the absence of consanguineous coupling. It is inherited in an autosomal recessive pattern. In contrast to the excessive erosions and bulla formation described in other JEB subtypes, patients with Shabbir's syndrome have minimal blistering and extensive granulation formation.<sup>9,10</sup> The conjunctival lesions start in the lateral portion of the eye and result in symblepharon. The conjunctival granulation tissue often leads to total palpebral occlusion and blindness. Conjunctival granulation tissue is rare in other variants of JEB.<sup>9,10</sup>

Regarding the pathogenesis, most cases of Shabbir's syndrome show a homozygous recessive mutation in LAMA3 gene, leading to the foreshortening of a critical portion of the N terminus of the  $\alpha$ 3 chain laminin-5 trimer. The tissue localization of the laminin  $\alpha$ 3A

corresponds to the clinical manifestations of Shabbir's syndrome i.e. with LM332 variant. This applies to the skin, nail, and mucous membrane fragility while with LM311 variant, which is present in the lungs, these patients are also susceptible to pneumonia.<sup>6</sup> Similarly, missense mutations in the tumor suppressor gene encoding p63 protein result in reduced p63 expression in Shabbir's syndrome which might be related to the corneal granulation overgrowth and ocular changes in these patients.<sup>11</sup> Immunofluorescence mapping reveals type IV collagen in the floor and bullous pemphigoid 180 antigen in the roof of blister i.e. cleavage occurs in the lamina lucida.<sup>9</sup>

Patients of Shabbir's syndrome are managed on the same lines as other subsets of JEB. The disease is refractory to pharmacotherapy and often surgical interventions like tracheostomy, suprapubic catheterization are required. Vascular laser therapy showed encouraging results in laryngeal lesions in one case. Similarly, thalidomide and amniotic membrane transplantation were successfully used to reduce corneal scarring. The majority of patients succumb to the disease during childhood; nevertheless, in those who survive the condition remits in the second decade.<sup>8,9</sup>

## References

1. Shabbir G, Hassan M, Kazmi A. Laryngo-onycho-cutaneous syndrome: a study of 22 cases. *Biomedica* 1986; **2**: 15-25.
2. Ainsworth JR, Spencer AF, Dudgeon J *et al*. Laryngeal and ocular granulation tissue formation in two Punjabi children: LOGIC syndrome. *Eye* 1991; **5**: 717-22.
3. Harper J. Genetics and genodermatosis. In: Champion RH, Burton JL, Ebling FJG, eds. *Rook's Textbook of Dermatology*, 5<sup>th</sup> edn. Oxford: Blackwell Scientific Publications; 1992. P. 305-72.
4. Ainsworth JR, Shabbir G, Spencer AF, Cockburn F. Multisystem disorder of Punjabi children exhibiting spontaneous dermal and submucosal granulation tissue formation: LOGIC syndrome. *Clin Dysmorph* 1992; **1**: 3-14.
5. Phillips RJ, Atherton DJ, Gibbs ML *et al*. Laryngo-onycho-cutaneous syndrome: an inherited epithelial defect. *Arch Dis Child* 1994; **70**: 319-26.
6. McLean WHI, Irvine AD, Hamill KJ *et al*. An unusual N-terminal deletion of the laminin alpha-3a isoform leads to the chronic granulation tissue disorder laryngo-onycho-cutaneous syndrome. *Hum Molec Genet* 2003; **12**: 2395-2409 Erratum in: *Hum Molec Genet* 2004; **13**: 365.
7. Fine J-D, Burge SM. Genetic blistering diseases. In: Burns T, Breathnach S, Cox N, Griffiths C, eds. *Rook's Textbook of Dermatology*, 8<sup>th</sup> edn. Oxford: Willey-Blackwell; 2010. P. 39.1-39.37.
8. Cohn HI, Murrell DF. Laryngo-onycho-cutaneous syndrome. *Dermatol Clin* 2010; **28**: 89-92.
9. Fine JD, Eady RA, Bauer EA *et al*. The classification of inherited epidermolysis bullosa (EB): report of the Third International Consensus Meeting on diagnosis and classification of EB. *J Am Acad Dermatol* 2008; **58**: 931-50.
10. Figueira EC, Crotty A, Challinor CJ *et al*. Granulation tissue in the eyelid margin and conjunctiva in junctional epidermolysis bullosa with features of laryngo-onycho-cutaneous syndrome. *Clin Experiment Ophthalmol* 2007; **35**: 163-6.
11. Atkinson SD, Moore JE, Shah S *et al*. P63 expression in conjunctival proliferative diseases: pterygium and laryngo-onycho-cutaneous (LOC) syndrome. *Curr Eye Res* 2008; **33**: 551-8.