Mal de Meleda – Through History and Today

Ana Bakija-Konsuo

"Cutis" Clinic for Dermatovenerology, Dubrovnik, Croatia

SUMMARY Meleda disease is an indigenous dermatological disease classified as a hereditary palmoplantar keratoderma. The disease was first described on the island of Mljet, Croatia, by Luko Stulli in 1826. We present a historical review of the literature data throughout the centuries till today. Recently, the gene responsible for the disease has been identified on chromosome 8qter within the cluster of Ly-6 homologous human genes. Various mutations in the secreted LY6/PLAUR-related protein1 gene (SLURP1) located on the aforementioned chromosome were identified as the cause of the disease. Due to similarity between the islands of Malta and Mljet, we are proud of the fact that, to the credit of Croatian researchers and scientists, Mal de Meleda entered the international scientific literature under that very name and has preserved it until today.

KEY WORDS: Mal de Meleda, keratoderma, SLURP-1.
overstepped over the course of time, nor by character differences, and neither by the influence of effective ancillary circumstances. It appears both in men and in women. Any suspicion of infectious spreading would be inopportune. The very appearance of the disease is repulsive; ability of action in hands is reduced, with fingers, ring and baby fingers in particular, in the position of strengthened and constant bend.” (1-5).

According to legend, the first case of the disease happened in a respectable family when a family elder, because of some local feud – the issue was allegedly the familial and local prestige regarding the selection of the seat of the new parish – witnessed by an entire procession, desecrated the eucharist sacrament by grabbing it and smashing it on the ground and trampling it underfoot. As of that moment, he and his descendants were permanently branded. Members of his family bear on their hands an indelible mark, visible to everyone as the lasting symbol of God’s punishment. Even today, in the deserted chapel there is a silver platelet on the Baroque altar painting of the Madonna showing an arm with visible skin lesions (6,7).

The island of Mljet itself was used by the Dubrovnik Republic as a quarantine. Interestingly enough, Hansen’s disease, brought to Dubrovnik from Rome in 1500, was eradicated by the Republic within two weeks, since all suspicious patients were promptly sent to Mljet. Today’s settlement of Korita was, according to legend, named “korota”, which means “mourning”, following one such pestilence when the village was catastrophically desolated (7,8). The locals called the disease “guba” (leprosy), which was traditionally said to have arrived from Herzegovina to the village of Maranovići. It was known among the people that it was not directly passed from parents to children, and that the diseased gave birth to the healthy and the healthy gave birth to the diseased, so it occurred in the third and in the fourth generation (2,4,9).

During the 19th and 20th centuries, Meleda disease, named after one of the most beautiful Croatian islands located to the north-east of Dubrovnik, was of scientific interest to numerous physicians of that age, particularly to dermatovenerologists. As early as 1839, Behrend calls the disease “Morbo di Melada” (“Melada” is the Italian name for the island of Molat, near Zadar, therefore Behrend’s naming is incorrect) (3,10). More than half a century later, in 1896, a municipal doctor from Janjina, Dr Oscar Hovorka pl. Zderas created confusion by claiming that he had discovered the endemic source of Hansen’s disease. Hovorka described several cases from the settlement of Maranovići, two from Babino polje, and two from Blato (11). This was at the time when leprosy was be-

![Figure 1](image1.jpg)

**Figure 1.** Clinical appearance of changes of the upper extremities in a patient with Mal de Meleda.

![Figure 2](image2.jpg)

**Figure 2.** Clinical appearance of changes of the lower extremities in a patient with Mal de Meleda.
Unlike Vohwinkel who claimed the opposite (14), Siemens energetically advocated the separate status of the Mljet disease, calling it *Keratosis palmoplantaris transgrediens*, from palmoplantar keratosis of the Unna-Thost type (15,16).

In 1931, Moncorps, in his monographic narrative “Keratosen” found in Jadassohn’s extensive “Handbuch der Haut- und Geschlechtskrankheiten”, again blurred the boundaries which had been created around Meleda disease as a separate entity, and this despite Siemens’ claim of the transgrediency of skin lesions (from palms and soles) and the assumption of its non-dominant inheritance (17). Niles and Klump strongly advocated that Meleda disease was an independent entity, and so the disease entered the global literature mostly thanks to the research and works of Kogoj, as emphasised by Hoede in his writings in 1941 (18,19). Kogoj stayed in Mljet during 1930 and twice more, in 1946 and 1960, along with his student Bošnjaković (20,21). Bošnjaković described the clinical features in detail and inferred the recessive manner of inheritance (2,6,22). Kogoj named Meleda disease *Keratosis extremitatum hereditaria progrediens*, in order to emphasize the main features of the disorder, primarily the location of pathological changes extending to the upper and lower extremities, the hereditary character, and the expansion of lesions from distal parts of limbs, i.e. palms and soles to underarms, knees, and thighs up to the inguinal and gluteal region (20). He argued in favor of the term *progrediens*, which indicates the dynamics of the pathological process, as opposed to Siemens’ term *transgrediens*, which indicates a present state and is static (21). According to the works of Kogoj and Bošnjaković, patients at the beginning of the past century complained of painful cracks onto which they poured tallow; in this way they would heal in two days (4).

During 1969 and 1970, Schnyder et al. determined that brachyphalangia is an obligatory symptom of Meleda disease (23,24). The monitoring of radiological changes during ten years in patients with Meleda disease was described by Kaćić et al. in 1981, who confirmed the conclusions of a research conducted by Kaćić et al. in 1969 which showed that osteoporosis, cystiform osteolysis, and acroosteolysis were characteristic, but still facultative symptoms of the Meleda disease. The authors established that phalangeal changes, such as bilateral brachymesophalangy of the fifth finger of the hand and the second, third, and fourth finger of the foot, as well as the bilateral brachihypophalangy of the fifth finger, are obligatory anomalies and thus can be considered pathognomic (25,26). In 1983, Topić and Salamon found that the inflammation of the corner of the lips (chelitis an-
high allele frequency in the island’s population, and probably even its increase over time (41-44).

Meleda disease is still being investigated today, as can be seen from the genetic research of Fisher et al., who managed to localize the gene responsible for the disease on the 8qter chromosome within the cluster of Ly-6 homologous human genes (45). Mutations in the secreted LY6/PLAUR-related protein1 gene (SLURP-1) located on aforementioned chromosome were identified as the cause of Mal de Meleda (46). Mapping to this region has been confirmed by Bouadjar et al. and by Pate et al. (47,48).

SLURP-1 (previously known as ARS Component B) regulates keratinocyte proliferation, apoptosis, and differentiation, and is involved in the regulation of cutaneous inflammation (49,50). The amino acid composition of SLURP-1 is homologous to that of the single domain frog cytotoxin and snake venom neurotoxins, such as α-bungarotoxin (46). Keratinocytes secrete SLURP-1 protein, which is detectable in plasma and urine where it was first isolated (51). The physiological role of SLURP-1 remained to be discovered, so further investigation will be needed in order to fully elucidate its effect on keratinocytes (50,52).

Favre et al. have demonstrated that SLURP-1 is a late marker of epidermal differentiation and is present in all analyzed biological fluids (saliva, sweat, tears, and urine). They showed that SLURP-1 is almost undetectable in the skin or sweat of patients with Mal de Meleda. The presence of SLURP-1 in several biological fluids suggests that an immunologic Mal de Meleda pre-diagnosis could be performed without any invasive procedures. Whether SLURP-1 has a specific function in these biological fluids is still unknown (51).

SLURP-1 potentiates the human α7 nicotinic acetylcholine receptors (nAchR) that are present in keratinocytes, and plays an important role in the differentiation of stratified squamous epithelium (50,53). It is a secreted epidermal neuromodulator which is likely essential for both epidermal homeostasis and inhibition of TNF alpha release by macrophages during wound healing. This explains both the hyper proliferative as well as the inflammatory clinical phenotype of Mal de Meleda (52).

Three different homozygous mutations (a deletion, a nonsense, and a splice site mutation) were detected in 19 families of Algerian and Croatian origin, suggesting founder effects. Moreover, one of the common haplotypes presenting the same mutation was shared by families from both populations. Secreted and receptor proteins of the Ly-6/uPAR superfamly have been implicated in transmembrane signal transduction, cell activation, and cell adhesion. This is the first instance of a secreted protein being involved in a palmoplantar keratoderma (46). So far, a total of 11 mutations associated with the inception of Mal de Meleda disease have been found in the gene encoding SLURP-1, and with a few exceptions, all the mutations induce the same clinical features, regardless of differences in age or geographical origin (54-58).

**CONCLUSIONS**

The writers of classical antiquity called this island Melite, Meleta, Melada, or Malta, the meaning of which in Greek language corresponds the Latin word mell, which means honey. Once numerous honeybee swarms in Mljet’s forests gave the island its name, just as with the larger and much more famous island of Malta (59). It is Malta that, due to the similarity between the two toponyms, took and still lays claim to the two most important legends of Mljet – the legend of Odysseus and the nymph Calypso and the legend of St Paul’s shipwreck on his journey to Rome. This makes us even prouder that, to the credit of Croatian researchers and scientists, Mal de Meleda entered the international scientific literature under that very name and has preserved it until today (3,9,10,20,23, 24,37,39,46).

**References:**