Kreyden OP, Böni R, Burg G (eds): Hyperhidrosis and Botulinum Toxin in Dermatology.
Curr Probl Dermatol. Basel, Karger, 2002, vol 30, pp 178–187

Rare Forms of Hyperhidrosis

Oliver P. Kreyden

Department of Dermatology, University Hospital of Zurich, Switzerland

A distinction is made between the essential or primary form of hyperhidrosis, which is in most cases focal and located in the axilla, on the palms of the hands or the soles of the feet, and the mostly generalized secondary form of hyperhidrosis. While the essential form is triggered by emotional factors, the secondary one is due to an underlying neurological or endocrinological disease. Beside these quite common hyperhidroses, there are several rare forms of focal hyperhidrosis. Some of them are associated with syndromes, other forms are distinct dermatological diseases such as localized unilateral hyperhidrosis (LUH), Ross syndrome or granulosis rubra nasi. Many neurological diseases are associated with focal hyperhidrosis. In the following, only syndromes with dermatological symptoms will be discussed and I will not go into the details of the different neurological syndromes due to their multifariousness.

Rare Syndromes Associated with Hyperhidrosis

POEMS Syndrome (Crow-Fukase Syndrome, Takatsuki Syndrome)

POEMS syndrome [1, 2] has been defined as an association of polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes. The most frequent skin changes beside hyperhidrosis are hyperpigmentation sparing the mucosae, hypertrichosis, scleroderma-like skin thickening and capillary angiomas. None of these abnormalities is pathognomonic, but their predominance at the extremities may be suggestive and leads to a search for other elements of the syndrome, notably gammopathy. The syndrome is mostly described in Japanese patients and is therefore also called Crow-Fukase syndrome or Takatsuki syndrome. Seen in men twice as often as in women, usually between the ages of 40 and 50 years, all five clinical features are not

always presentor may be accompanied by other signs. The neurological deficit is usually severe and 50% of the patients become unable to walk. Liver, spleen and lymph node enlargement are observed. The most frequent signs of an endocrinopathy are gynaecomastia, atrophy of the testicles, impotence and amenorrhoea. Testosterone levels are low and oestrogen levels are increased in men together with luteinizing hormone, follicle-stimulating hormone and prolactin. Hypothyroidism is frequent and diabetes mellitus is observed in 50% of the patients. POEMS syndrome is often associated with a myeloma. When bone lesions are minor, radiotherapy or surgery can improve the neuropathy and resection of a solitary plasmacytoma can lead to total remission. Chemotherapy or corticosteroids may improve the polyneuropathy in certain cases. Plasma exchange has not been successful.

Pachyonychia congenita

Pachyonychia congenita [3, 4] is a rare ectodermal dysplasia with variable expression. The condition is usually inherited as an autosomal dominant trait. The leading symptom is a discoloration and thickening of the nails (fig. 1), usually beginning within the first month of life. There are four clinical types of pachyonychia congenita. From type I (Jadassohn-Lewandowsky syndrome) to type II (Jackson-Lawler syndrome) and types III and IV, the severity of the disorder increases. Except type I all other forms of pachyonychia congenita show palmoplantar hyperhidrosis beside palmoplantar bullae. Depending on the severity of the pachyonychia congenita, other symptoms may be associated such as natal teeth in addition to the main findings of pachyonychia, palmoplantar hyperkeratosis and follicular keratosis (type II), cheilitis and eye symptoms (type III) and hardness of hearing, mental retardation and hair anomalies (type IV).

Apert Syndrome

Apert syndrome, also known as acrocephalosyndactyly, is a rare type of premature craniofacial synostosis characterized by the clinical triad of cranial and facial malformations along with syndactyly of the hands and feet. It is thought to occur as a result of androgen end-organ hyperresponse affecting the epiphyses and sebaceaous glands [5]. This produces early epiphysial fusion resulting in short stature, short and fused digits and acrocephaly. Most cases also have subnormal intelligence. The severe acne vulgaris involving atypical sites such as the upper extremities constitutes the dermatological hallmark of this rare genodermatosis and is often resistant to treatment requiring oral isotretinoin [6]. A report of a patient who demonstrated the classic findings of Apert syndrome combined with severe hyperhidrosis could represent a new clinical finding not previously reported in association with this syndrome [7].

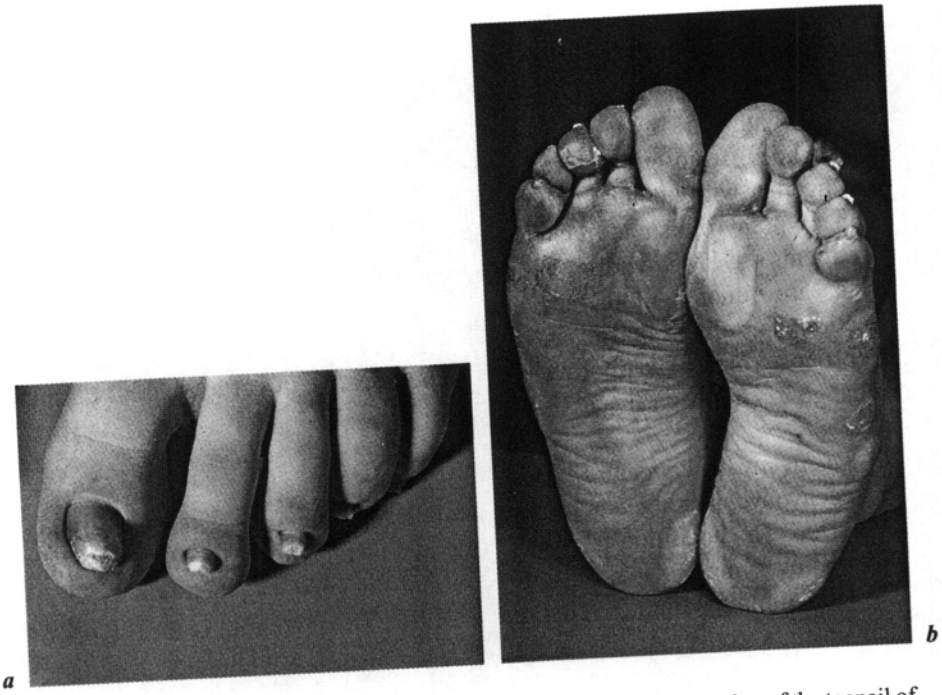

Fig. 1. ***a*** Pachyonychia congenita. Typical discoloration and thickening of the toenail of a 16-year-old girl. ***b*** Pachyonychia congenita. Palmoplantar hyperkeratosis of the same patient with pachyonychia congenita type II (Jackson-Lawler syndrome).

Pachydermoperiostosis (Touraine-Solente-Gole Syndrome, Friedreich-Erb-Arnold Syndrome)

Pachydermoperiostosis [8, 9] is a rare disease with an autosomal dominant mode of inheritance (fig. 2). Classically, pachydermoperiostosis is characterized by a triad of finger clubbing, periosteal new bone formation and skin and soft tissue changes, giving an acromegaloid look. Although rare, it is important to recognize this condition as misdiagnosis may subject the patient to unnecessary investigations and worry. Primary (idiopathic, hereditary) pachydermoperiostosis should be distinguished from secondary (symptomatic) forms of the disease, which are often associated with lung tumours. In a Japanese review, 121 cases of pachydermoperiostosis were reported. Most of them were male (94.1%), about one fourth had a family history. The principal features were clubbing of the digits (88.4%), periosteal new bone formation (94.1%), coarsening of the facial features with furrowing of the skin of the face (72.7%) and cutis verticalis gyrata (59.5%). Arthralgia (40.5%), hyperhidrosis of the feet and hands (44.6%), gastric hypertrophy (8 cases), gastric ulcers (5 cases) and endocrine abnormalities (17 cases) were also reported [10].

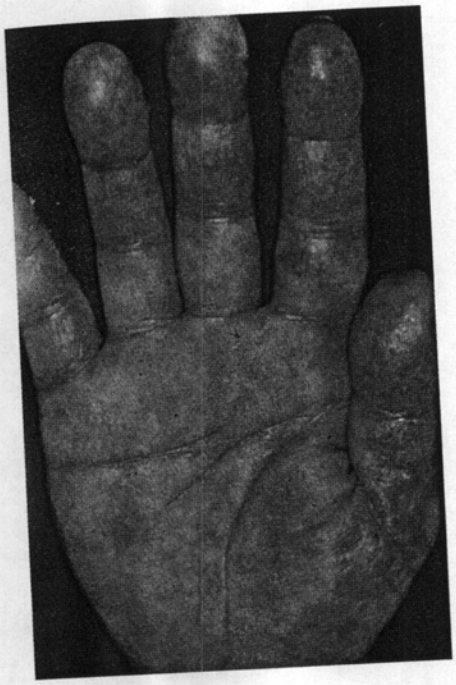

Fig. 2. Sweating palm with the characteristic clubbed digits and thickening of the skin from a 31-year-old man with pachydermoperiostosis [9].

Papillon-Lefèvre Syndrome (Palmoplantar Keratoma with Periodontitis)

In 1924, Papillon and Lefèvre [11] reported the coexistence of palmoplantar keratoma and severe dental anomalies in a brother and sister. This condition is inherited as an autosomal recessive trait [12]. The causative gene has been mapped on chromosome 11q14 [13]. Papillon-Lefèvre syndrome is characterized by a diffuse transgressing palmoplantar keratosis (fig. 3) and premature loss of both the deciduous and permanent teeth [11]. In addition, many patients show scaly erythematous lesions over the knees and elbows, often misdiagnosed as psoriasis. Furthermore some patients manifest excessive sweating (hyperhidrosis), the growth of fine body hair and the development of dirty-coloured skin on the affected parts. Calcification of the falx cerebri of the dura mater, as well as other areas of the brain, have been reported [14].

Nail-Patella Syndrome

Nail-patella syndrome (NPS) is an autosomal dominant genetic defect characterized by nail hypoplasia in association with bone and kidney abnormalities. The nail abormalities may be limited to the thumb or affect all fingers. The bone abnormalities include an absent or hypoplastic patella, radial head abnormalities and iliac crest exostosis [15]. In a clinical review of a family with NPS involving six generations, Pechman and Bergfeld [16] could show

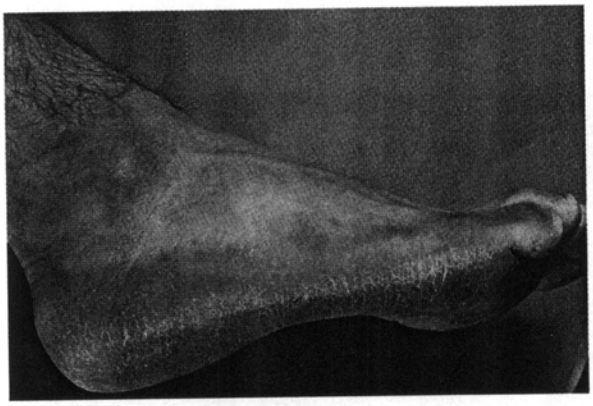

Fig. 3. Papillon-Lefèvre syndrome (palmoplantar keratoma with periodontitis). Characteristic diffuse transgressing palmoplantar keratosis from a 21-year-old man.

that 33 of 68 members of the extended family were affected with NPS and 9 members suffered from hyperhidrosis. The incidence of hyperhidrosis indicated a direct inheritance because it occurred only in members affected with NPS. They concluded that hyperhidrosis occurred as a spontaneous mutation transmitted as an autosomal dominant trait closely linked to NPS or that hyperhidrosis represents a previously unrecognized associated disorder [16].

Distinct Dermatological Disorders or Syndromes Associated with Hyperhidrosis

Idiopathic Localized Unilateral Hyperhidrosis

Only a few cases of LUH or localized segmental hyperhidrosis have been described in the literature [17–27]. LUH is a rare but well-defined form of localized hyperhidrosis (fig. 4) with unknown pathogenesis that occurs in otherwise healthy individuals [17, 20]. LUH has been attributed to either neurological factors [28–31], underlying tumours [32–39] or diverse unknown causes. Lesions can affect any part of the body, although hyperhidrosis is usually located mainly on the forearm or the forehead and is restricted to an area of less than 10×10 cm [18, 21]. Beside the unusual localization the major difference to essential hyperhidrosis is that LUH has no typically triggering factor and occurs even during the night while patients are asleep [20]. Some authors have identified an eccrine hamartoma as a cause of LUH [40–42]. Sweat eccrine gland hamartomas, however, are extremely rare. Severe localized

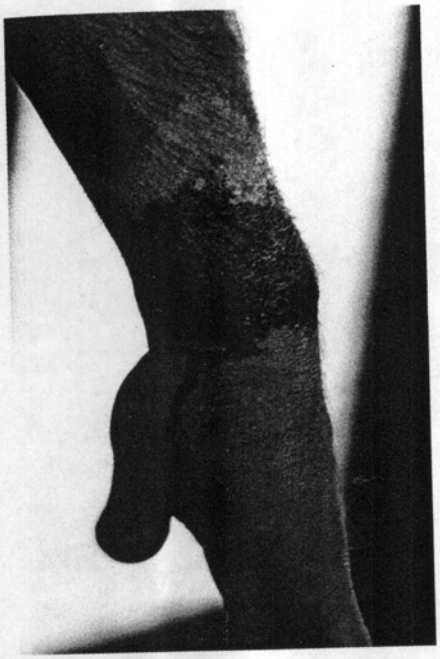

Fig. 4. Patient with LUH on his right wrist showing the dripping hyperhidrosis after application of the iodine-starch test (Minor test).

hyperhidrosis can be associated with a glomus tumour [43]. Other organoid hamartomas have been reported to cause localized hyperhidrosis. These include eccrine pilar angiomatous hamartoma, seborrhoeic naevus and naevus sudoriferus and the blue rubber bleb naevus syndrome [44]. If the spread of the disorder is more extensive than 10 cm^2 or the localization is not typical (i.e. thorax), an underlying neurological disorder or intrathoracic neoplasm has to be excluded. None of these cases are LUH in the strict sense but rather examples of segmental secondary hyperhidrosis. In 1 case of LUH, a subclinical increase in evaporative water loss from other areas of the body with a left-right gradient in the sweating rate was found. Because of the widespread sweat gland dysregulation, a more central involvement of the autonomous nervous system was concluded in this case [23]. Another theory of the aetiology of LUH is that the hyperhidrotic area arises from traumatic injuries as a result of misdirected reconnection of the sympathetic nerve fibre network after injury, similar to the Frey syndrome [20].

Ross Syndrome

Ross syndrome is characterized by the following triad: unilateral tonic pupils, generalized areflexia (Holmes-Adie syndrome) and progressive segmental anhidrosis with a compensatory band of excessive perspiration [45]. Patients suffering from Ross syndrome usually do not perceive the hypohidrosis; instead,

it is the compensatory segmental hyperhidrosis that is bothersome. In addition, many patients suffer from several symptoms of vegetative dysfunction such as palpitation, stenocardia, orthostatic hypotonia and irritable colon [46, 47]. As a consequence of the progressive anhidrosis, patients with Ross syndrome often suffer from xerosis (exsiccation eczema). Dry skin or an unusual, strictly localized eczema can be an initial symptom and lead to the diagnosis of Ross syndrome even if the compensatory hyperhidrosis has not yet developed [46]. Because pilo-erection and vasomotor control in patients with Ross syndrome are normal, the sympathetic dysfunction involves only the sudomotor fibres [48]. The pathogenesis of Ross syndrome is unknown. Multiple neuropathies of the autonomous nervous system [45] or a failure in the synthesis or release of neurotransmitters have been suggested as possible causes. Because histologically intact nerve fibres are found, Ross postulated that the defect lay in the acetylcholine cholinesterase activity rather than in a degeneration of the sweat glands. In addition, the fact that the anhidrosis occurred within a dermatome instead of developing in patches suggested that the site of the defect was in the ganglion cells themselves rather than peripheral. Recently, immunofluorescence studies showed a selective reduction of the nerve fibres that innervated the sweat glands in the anhidrotic areas, whereas epidermal innervation remained normal [49].

Granulosis rubra nasi

Granulosis rubra nasi, a heritable papular red lesion of the nose associated with hypersudation (fig. 5), is an uncommon dermatosis usually seen in children which begins to resolve at puberty. It was first described by Jadassohn in 1901 [44]. The hyperhidrosis is the most conspicuous feature of the disease and small beads of sweat and erythema on the tip of the nose may often occur. This erythema can later spread to the rest of the nose and at times to the cheeks, upper lip and chin. Vesicles have also been seen, and small cystic lesions may be present. Because of these acneiform findings, the disorder was also called 'acne papulo-rosacea of the nose' [50]. Histologically the epidermis, pilosebaceous apparatus and connective tissue elements are normal in appearance. The pathogenesis is unknown. A special form of sweat retention is discussed. Heid et al. [51] found a phaeochromocytoma in a 19-year-old girl with granulosis rubra nasi, hyperhidrosis and tachycardia. They also concluded that granulosis rubra nasi could be a complication of hyperhidrosis [51].

Treatment of the Rare Forms of Focal Hyperhidrosis

Aluminium salts can help in mild cases of focal hyperhidrosis and should be tried in any case. Systemic treatments like sedatives or tranquillizers in

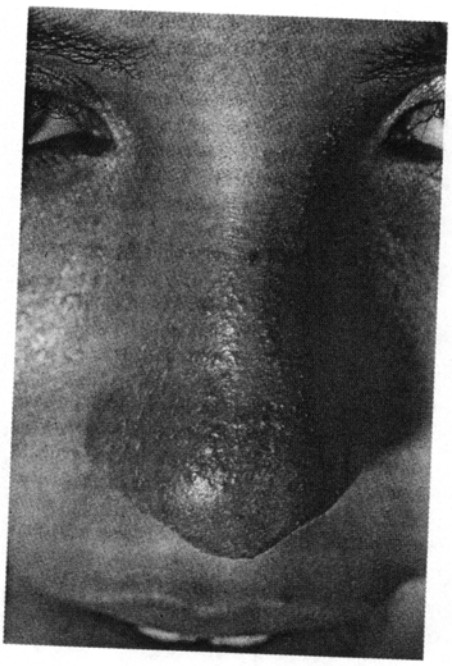

Fig. 5. 11-year-old girl with granulosis rubra nasi showing erythematous papular lesions of the nose and small drops of sweat on the tip of the nose.

combination with β-blockers are usually neither very effective nor, due to the side-effects, well tolerated by patients [52]. In 2 cases of Ross syndrome, iontophoresis was very effective [48]. However, this regimen is rather complicated because it has to be adapted individually for each patient, and, furthermore, it is not applicable in every case. Bergmann et al. [49] were the first to try the focal application of botulinum toxin in a therapy-resistant case of Ross syndrome. The therapy was tolerated well by the patient and was continued for a period of half a year [49]. We also obtained excellent results with botulinum toxin in 1 case of LUH in which local therapy with aluminium chloride (30%) had not provided adequate relief of hyperhidrosis [20]. Thus, botulinum toxin A may prove to be a successful new treatment option not only for essential focal hyperhidrosis of the axilla, palms or soles, but is to be recommended in the treatment of rare forms of focal hyperhidrosis as well, provided that the underlying disease responsible for the hyperhidrosis is treated first.

References

1 Dereure O, Guillot B, Dandurand M, et al: Cutaneous lesions in POEMS syndrome: A propos of 3 case reports and a review of the literature. Ann Dermatol Vénéréol 1990;117:283–290.

2 Masson C, Krespi Y: POEMS syndrome. Presse Méd 1994;23:646–648.